An Investigation of the Psycho-Social Risk Factors and Associated Outcomes of Psychotic Experiences in Early Adolescence

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AN INVESTIGATION INTO THE PSYCHO-SOCIAL RISK FACTORS AND ASSOCIATED OUTCOMES OF PSYCHOTIC EXPERIENCES IN EARLY ADOLESCENCE.

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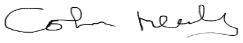
A thesis submitted to the School of Post Graduate Studies, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland in fulfilment of the degree of Doctor of Philosophy.

29/06/2020

Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed: 

Student Number: 17134293

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Table of Contents

Abbreviations

ABD: Adolescent Brain Development Study

APSS: Adolescent Psychotic Symptoms Screener

AUC: Area Under the Curve

C-GAF: Current Global Assessment of Functioning

C-GAS: Children's Global Assessment Scale

CI: Confidence Interval

CIDI: Composite International Diagnostic Interview

DAWBA: Development and Well-Being Assessment

DIA-X/M-CIDI computerized version of the Munich-Composite International Diagnostic Interview

DIS: Diagnostic Interview Schedule

DIS-C: Diagnostic Interview Schedule for Children

DSM: Diagnostic and Statistical Manual

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, revised third edition

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition

GUI: Growing Up in Ireland

GWAS: Genome wide association Study

ICD: International Classification of Disease

ICD-10: International Classification of Disease tenth edition

K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia

MSP-GAF: Most Severe Past Global Assessment of Functioning

OR: Odds Ratio

PAF: Population Attributable Fraction

PCG: Primary Care Giver

PEs: Psychotic Experiences

PLSI: Psychosis-Like Symptom Interview

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PTSD: Post-Traumatic Stress Disorder

ROC: Receiver-Operating Characteristic

SCAN: Schedules for Clinical Assessment in Neuropsychiatry.

SCL-90: Symptom Checklist-90

SD: Standard Deviation

SDQ: Strengths and Difficulties Questionnaire

YSR: Youth Self-Report Questionnaire

List of Tables

List of Figures

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Lastly, possibly most importantly, I would like to thank the participants from the **Growing Up in Ireland study** and **Adolescent Brain Development study**. Without their dedication, and the dedication of millions of other participants like them around the world, our understanding of psychiatric phenomena would stagnate and research would grind to a halt. Their trust and honesty in the research community is to be respected and treasured.

Dedication

I dedicate this thesis to my parents Michael and Helen, and to my brother Ciaran.

It is a privilege to have such a loving family.

“Think and Wonder, Wonder and Think”

Theodor Geisel, (1990)

Abstract

Background: Psychotic experiences (PEs) are common in adolescence and are associated with poorer psychiatric outcomes. The nexus between PEs, mental disorder and psychosocial outcomes is poorly understood. The aims of this thesis were three-fold. Firstly, I investigated if psychosocial data predicts adolescent PEs (Study-I) and if changes in self-concept alters the risk of PEs (Study-II). Secondly, I examined the published literature investigating the relationship between childhood PEs and mental disorder (Study-III), investigated if PEs improved the prediction of subsequent psychopathology (Study-IV) and investigated if children who report PEs have poorer functioning into adulthood (Study-V). Lastly, I examined whether malleable psychosocial variables mediate the relationship between PEs and subsequent psychopathology (Study-VI).

Method: I conducted five secondary analyses of longitudinal observational data and one systematic review. I used data from the Adolescent Brain Development (ABD) Study and Cohort 98' from the Growing-Up in Ireland (GUI) study. The ABD study (ages:12-18) included clinical interview and self-report data. The GUI (ages:9-18) included survey questionnaire data. The systematic review was conducted by two reviewers. Statistical analyses included machine learning methods, logistic regression, mixed-model analysis and traditional and counter-factual mediation.

Results: Psychosocial characteristics adequately predicted subsequent PEs (Area Under the Curve:0.61, Study-I). Changes in self-concept vastly altered the odds of adolescent PEs (Study-II). Children reporting PEs had a 4-fold increased odds of a psychotic disorder (Population Attributable Fraction: 23%) and a 3-fold increased odds of non-psychotic disorders (Study-III). PEs improved the prediction of subsequent externalising problems beyond established markers (Study-IV). Children reporting PEs had persistently poorer functioning into adulthood (Study-V). Self-concept and parent-

child conflict mediated between 13-52% of the longitudinal relationship between PEs and non-psychotic psychopathology (Study-VI).

Discussion: PEs are interconnected with poorer psychiatric and psychosocial outcomes. Based on the evidence, PEs appear to be a marker of global vulnerability to psychiatric distress that occurs in the context of psychiatric and psychosocial hardship. Assessing PEs improves the prediction of subsequent psychopathology. Finally, our evidence suggests that, in the presence of early adolescent PEs and non-psychotic psychopathology, interventions targeting self-concept and parent-child conflict may reduce the incidence of subsequent psychiatric outcomes.

List of Scientific Papers for Consideration in this Thesis

Table 1. List of papers included in this thesis

No.	Reference	Impact Factor	Quartile*
I.	**Healy, C.,** Coughlan, H., Williams, J., Clarke, M., Kelleher, I., & Cannon, M. (2019). Changes in self-concept and risk of psychotic experiences in adolescence: a longitudinal population based cohort study. *Journal of Child Psychology and Psychiatry.* 60(11), 1164-1173.	**6.12**	**Q1**
II.	**Healy, C.,** Brannigan, R., Dooley, N., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychological Medicine.* 49 (10), 1589-1599.	**5.64**	**Q1**
III.	**Healy, C.,** Gordon, A. A., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Do childhood psychotic experiences improve the prediction of adolescent psychopathology? A longitudinal population - based study*. Early Intervention in Psychiatry.* 13(5), 1245-1251.	**3.32**	**Q1**
IV.	**Healy, C.,** Campbell, D., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2018). Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood. *Acta Psychiatrica Scandinavica,* 138(1), 26-34.	**4.69**	**Q1**
V.	**Healy, C.**, Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). What mediates the bidirectional relationship between psychotic experiences and non-psychotic psychopathology: A longitudinal cohort study. *Journal of Abnormal Psychology* (In Press).	**5.52**	**Q1**
VI.	**Healy, C.**, Kenney, J., Jollans, L., Clarke, M., Whelan, R., Kelleher, I., & Cannon, M. Predicting adolescent psychotic experiences from psychosocial characteristics: a machine learning approach using a longitudinal cohort study. *Lancet Psychiatry* (Submitted).	**5.64**	**Q1**

VII.	* **Healy, C** & Cannon, M. (2020). Psychotic-Like Experiences in the general population and psychosis risk. In Risk Factors for Psychosis. Ed. A, Thompson & M, Bromme. Elsevier.	**N/A**	**N/A**

Note: *Book Chapter: Extracts from this book chapter were used as part of the introduction chapter of the thesis. N/A = None applicable. Quartile were based on *Scrimago Journal Ranking* in the field of *Medicine* under the category of *Psychiatry and Mental Health* (see https://www.scimagojr.com/journalrank.php).

Table 2. Other related scientific studies published during the time thesis but for consideration.

No.	Reference	Impact Factor	Quartile*
I.	**Healy, C.** & Cannon, M. (2020) We need to talk about prevention. *American Journal of Psychiatry*. 177 (4), 285-287.	**13.66**	**Q1**
II.	Cannon, M., **Healy, C.,** Clarke, M. & Cotter, D (2020) Prenatal and perinatal risk factors for psychosis: canaries in the coalmine. *Lancet Psychiatry*. (In Press). doi: 10.1016/S2215-0366(20)30095-X	**18.33**	**Q1**
III.	McMahon, E., Corcoran, P., Keeley, H., Clarke, M., Coughlan, H., Wasserman, D., ... & Cannon, M. (2020). Risk and protective factors for psychotic experiences in adolescence: a population-based study. *Psychological Medicine*. (In Press) doi: 10.1017/S0033291719004136	**5.64**	**Q1**
IV.	Carey, E., Gillan, D., **Healy, C.,** Dooley, N., Campbell, D., McGrane, J., ... & Cannon, M. (2020). Early adult mental health, functional and neuropsychological outcomes of young people who have reported psychotic experiences: a 10-year longitudinal study. *Psychological Medicine.* (*In Press*) doi: 10.1017/S0033291720000616	**5.64**	**Q1**
V.	O' Neill, A., Carey, E., Dooley, N., **Healy, C.,** Coughlan, H., Whelan, R., … & Cannon, M. (2020) Multiple Network Dysconnectivity in Adolescents with Psychotic Experiences: a longitudinal population-based study. *Schizophrenia Bulletin* (In Press).	**7.29**	**Q1**
VI.	Mongan, D., Focking, M., **Healy, C.,** Raj Susai, S., Heurich, M., … Cotter, D. & McGuire, P. (2020). Development of proteomic prediction models for transition to psychotic disorder in the	**15.92**	**Q1**

	clinical high-risk state and psychotic experiences in adolescence. *JAMA Psychiatry*. (Under Review)		
VII.	Coughlan, H., **Healy, C.,** Clarke, M., & Cannon, M (2019). Early risk and protective factors and young adult outcomes in a longitudinal sample of young people with a history of psychotic-like experiences. *Early Intervention in Psychiatry. (In press)* doi: *10.1111/eip.12855*	**3.32**	**Q1**
VIII.	Dhondt, N., **Healy, C.,** Clarke, M., & Cannon, M. (2019). Childhood adversity and adolescent psychopathology: evidence for mediation in a national longitudinal cohort study. *The British Journal of Psychiatry*. 215 (3), 559-564.	**7.23**	**Q1**
IX	Dooley, N., O'Hanlon, E., **Healy, C.,** Adair, A., McCandless, C., Coppinger, D., ... & Cannon, M. (2019). Psychotic experiences in childhood are associated with increased structural integrity of the left arcuate fasciculus–A population-based case-control study. *Schizophrenia Research.* 215, 378-384.	**4.57**	**Q1**
X	Sabherwal, S., Föcking, M., English, J. A., Fitzsimons, S., Hryniewiecka, M., Wynne, K., ... & Zammit, S. (2019). ApoE elevation is associated with the persistence of psychotic experiences from age 12 to age 18: Evidence from the ALSPAC birth cohort. *Schizophrenia Research*. 209, 141-147.	**4.57**	**Q1**
XI	Carey, E., Dooley, N., Gillan, D., **Healy, C.,** Coughlan, H., Clarke, M., ... & Cannon, M. (2019). Fine motor skill and processing speed deficits in young people with psychotic experiences: A longitudinal study. *Schizophrenia Research*, 204, 127-132.	**4.57**	**Q1**
XII	Cotter, S., **Healy, C.,** Cathain, D. N., Williams, P., Clarke, M., & Cannon, M. (2019). Psychopathology and early life stress in migrant youths: an analysis of the 'Growing up in Ireland' study. *Irish Journal of Psychological Medicine.* 36(3), 177-185.	**0.53**	**Q3**

Note: Quartile were based on *Scrimago Journal Ranking* in the field of *Medicine* under the category of *Psychiatry and Mental Health (see* https://www.scimagojr.com/journalrank.php).

Table 3. Conference Presentations

Date	Conference
Oral Presentations	
April 2019	College of Psychiatrists in Ireland (Dublin) –10th Anniversary Conference. Irish Psychosis Network Symposia. *Changes in self-concept and risk of psychotic experiences*
Nov 2018	Growing up in Ireland Conference (Dublin) – *Changes in self-concept and risk of psychotic experiences.*
Oct 2018	IEPA - Early Interventions in Psychiatry (Boston) – Symposia - Exploring the nexus between functional disengagement and mental illness in adolescents and young adults. Presentation: *Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood.*
May 2018	Life History Research Society Conference (Paris) – *Sticks And Stones May Break My Bones But Words Increase The Risk Of Psychotic Experiences.*
April 2018	Schizophrenia International Research Society (Florence) – *Sticks And Stones May Break My Bones But Words Increase The Risk Of Psychotic Experiences.*
Poster presentation	
March 2019	Royal College of Surgeons Research Day (RCSI Internal) – *Predicting adolescent psychotic experiences from psychosocial characteristics: a machine learning approach with a national representative longitudinal cohort study.*
Nov 2018	Beaumont Hospital Translational Research Awards 2018 (Beaumont Internal) – *Predicting adolescent psychotic experiences from psychosocial characteristics: a machine learning approach with a national representative longitudinal cohort study.*
March 2018	Royal College of Surgeons Research Day (RCSI Internal) – *Child and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis.*
March 2017	Royal College of Surgeons Research Day (RCSI Internal) – *The divergent effect of different childhood psychotic experiences on adolescent psychopathology and functioning.*

Chapter 1.

Introduction

Chapter Overview.

This chapter contains extracts from the author's book chapter 'Psychotic-Like Experiences in the General Population'. This chapter can be found in Risk Factors for Psychosis: Paradigms, Mechanisms, and Prevention, edited by Dr Andrew Thompson and Dr Matthew Broome. Mr Healy is the first author of the book chapter and contributed to all aspects of its conception.

Reference: Healy, C & Cannon, M. (in press). Psychotic Like Symptoms in the general population and psychosis risk. In Risk Factors for Psychosis. Ed. A, Thompson & M, Bromme. Elsevier. ISBN: 9780128132012. Doi: https://doi.org/10.1016/B978-0-12-813201-2.00007-7

1.1 Introduction

Over the past two decades a growing body of literature has challenged the dichotomous conceptualisation of psychotic phenomena. This literature has assisted in re-shaping the perception of such phenomena and their meaning within psychiatry. Below this chapter focuses on a number of areas, including prevalence and measurement, risk factors and clinical/psycho-social outcomes associated with having had such experiences.

1.2 Evolving Conceptualisations of Psychotic Phenomena

Hallucinations and delusions, two of the most recognisable features of psychosis (Andreasen, 1997, Kelleher and Cannon, 2016), capture a range of qualitatively diverse experiences. The former is characterised by anomalous perceptual experiences and the latter by unusual and intractable thought content and beliefs (Oyebode, 2015).

Historically, these phenomena were thought to be primary features that distinguished a patient with a psychotic disorder from those with a neurotic disorder (Kelleher & Cannon, 2016) and were considered clearly beyond the realm of 'normal' experience. To our knowledge, the seminal investigation of psychotic phenomena in the general population dates back to 1894. Sidgewick and Colleagues' investigation of hallucinations was conducted in 17,000 members of the general population (Sidgwick et al., 1894). Roughly, 10% of the sample reported hallucinations, the majority of which were visual. Although promoted by certain prominent figures of the time such as William James, there is little evidence of follow up investigations (James, 1895; Powers, 2019).

A number of studies scattered throughout the latter half of the 20th century also noted that psychotic phenomena were reported by a substantial minority of non-clinical individuals in the general population (Bentall & Slade, 1985; Chapman & Chapman, 1980; Claridge, 1987; Romme & Escher, 1989). However, since the turn of the millennium, the number of epidemiological investigations into the presence of psychotic symptoms in the general population has dramatically increased (Van Os et al; 2000; Bak et al., 2005; Brugha et al., 2005; Johns et al., 2002; Laurens et al., 2007; Poulton et al., 2000). These investigations have found that psychotic symptoms were not

incomprehensible as had been historically proposed (Frith, 2004), nor were they exclusive to those with severe mental disorder. In fact, they are relatively common phenomena.

1.3 Renewed Interest

Renewed interest in psychotic symptoms within the general population was sparked by a pivotal report by Poulton and colleagues (Poulton et al., 2000). Using the Dunedin birth cohort they demonstrated that children (age 11) who report psychotic symptoms had a 16-fold increased risk of developing a schizophreniform disorder by age 26. Such findings were highly important for understanding the aetiology of psychotic disorders and were thought to present a real window of opportunity for the early identification of those at-risk.

Subsequently, Van Os and colleagues expanded Strauss' (1969) observation which suggested that psychotic symptoms, reported by patients, were not uniform and were more accurately conceptualised a multi-dimensional continua (Van Os et al., 2000; Johns & Van Os, 2001; Strauss, 1969). Expanding on Struss's observations, they suggested that psychotic symptoms were evident within the general population and proposed the concept of an extended psychosis phenotype (Van Os et al., 2000; Johns & Van Os, 2001). This proposed that psychotic phenomena reported by the general population and by patients with a psychotic disorder lay on different ends of the same continuum.

By their very nature, experiences within the general population should reflect some degree of intact reality testing and should not be accompanied by clinical levels of impairment. However, as I shall argue, sub-clinical does not mean that they are not clinically meaningful. There is now a wealth of research indicating the relevance of these phenomena in a range of concurrent and subsequent psychiatric conditions. For simplicity, I have referred to these sub-clinical psychotic symptoms as psychotic experiences (PEs). They have also been referred to in the literature as psychotic-like experiences/symptoms or subclinical/sub-threshold psychotic experiences/symptoms (Lee et al., 2016).

1.4 The Prevalence of Psychotic Experiences

Current estimates suggest between 5-7% of adults in the general population have PEs (McGrath et al., 2015; van Os et al., 2009). The prevalence in children and adolescents is higher with 17% and 7.5% reporting PEs, respectively (Kelleher et al., 2012; Majier et al., 2018). For most individuals (~80%) PEs are transient and 64% of those who have PEs will have less than five such experiences in their life time (McGrath et al., 2015). Roughly 20% of those who report PEs will have re-occuring (also known as 'persistent') experiences (Linscott & van OS., 2013; Sullivan et al., 2020), and these tend to be individuals who have greater PE endorsement and poorer functioning on first examination (Calkins et al., 2017).

1.5 Measuring and Definition of Psychotic Experiences

PEs have been generally measured by clinical interview and self-report questionnaires. Within these two methods, there is a wide variety of assessment tools. Lee and colleagues reported that across 76 studies, three definition types and 41 different assessment types were used (Lee et al., 2016).

There is converging evidence from both questionnaires and interviews reporting PEs regarding prevalence and their associations with mental disorder (Kelleher et al., 2012). There is some suggestion that questionnaires may generate more false-positive ratings (van Os et al., 2009; and Schultze-Lutter et al., 2014). However, even 'false positive ratings' have been associated with subsequent interview-validated PEs and other psychiatric outcomes, possibly suggesting that they may in fact represent a weaker expression of the psychosis phenotype (van der Steen, 2018).

A question on auditory hallucinations appears to be the most valid single item measure of PEs within child and adolescent populations (Kelleher et al., 2011; Laurens et al., 2012; Horwood et al., 2008; and Granö et al., 2016). However, given the variety of phenomena that can be reported, a single item endorsement may result in false negatives. Additionally, endorsement alone may in fact ignore other potentially important PE characteristics such as frequency, conviction on reality testing, or

associated distress/impairment (Sullivan et al., 2020). Mixed-method investigations incorporating quantitative and qualitative information may shed more light on what additional features are important for PEs beyond a binary measurement or cumulative count (Coughlan et al., 2019).

Other investigations have opted for approaches that resemble a continuum. These included factor analysis (Capra et al., 2015; Shevlin et al., 2017; Therman & Ziermans, 2016; Yung et al., 2009) or latent constructs analysis/SEM (Laurens, Downs, Cullen, Barragan, & To, 2012; Sullivan et al., 2015). These approaches capture the dynamic complexities of a continuum better than dichotomous grouping and provide a useful framework for how PEs may vary in severity and interact with symptoms of psychiatric disorders. However, their utility can be difficult to translate into something that can be applied to a 'real world' setting.

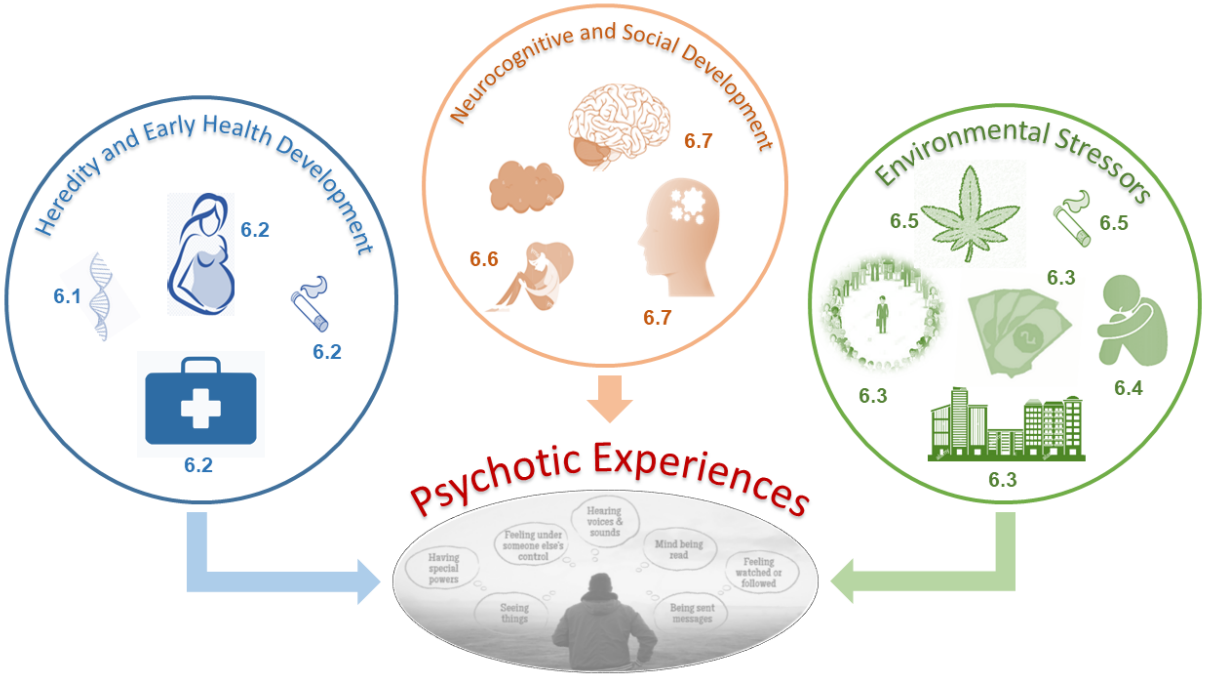
1.6 Known Risk Factors and Correlates of PEs?

There appears to be an overlap between the risk factors for psychotic disorders and PEs (Linscott & Van Os, 2013; Kelleher & Cannon, 2011). This overlap is apparent over a range of factors including heritability and early life, neurocognitive and social development and environmental stressors. Below I highlight some of the most commonly reported findings. A visual schematic of these findings can be found in Figure 1.1.

1.6.1 Heritability and Genetics. Polanczyk and colleagues reported that genetic effects account for 43% of the variance in PE expression (Polanczyk et al., 2010). Genetic variance expression appears to be almost twice as high in men compared to women (Nesvåg et al., 2016). Young adolescents with PEs are 2.5 times more likely to have a mother with a psychosis-spectrum disorder (Polanczyk et al., 2010). The genetic origins of PEs are still unclear (Kelleher & Cannon, 2011) but our understanding is improving. For example, initially, it was thought that there was not a relationship between polygenic risk score for schizophrenia and PEs (Jones et al, 2016; Owrutsky et al., 2017; Zammit et al., 2013). However recent evidence from the largest biobank study to-date suggested that PEs are weakly associated with the polygenic risk score for

schizophrenia, depression and bi-polar disorder and are genetically correlated with autism spectrum disorder and the psychiatric genomic consortium cross-disorder GWAS (Legge et al., 2019). Additionally they found that four specific loci were associated with PEs in a genome-wide analysis and distressing PEs were associated with an increased copy number variation related with schizophrenia and neurodevelopmental disorders more broadly.

Figure 1.1. Risk Factors for Psychotic Experiences.



Note: Numbering corresponds to the section in the chapter detailing the evidence for each risk factors contribution to psychotic experiences.

1.6.2 Early Development and Health Factors. There appear to be increased rates of pre/peri natal complications and childhood infection in individuals with PEs. Increased rates of maternal infections and smoking during pregnancy have been associated with risk of PEs (Zammit et al., 2009). Higher birth weight has been associated with a reduced risk of PE (Thomas et al., 2009). Early childhood infection has also been associated with PEs. Exposure to Epistein-Barr Virus by age four resulted in a five-fold

increased risk of adolescent PEs (Khandaker et al., 2014). Atopic conditions in childhood have been shown to increase risk of adolescent PEs (Khandaker et al., 2014). These results suggest a role for the early-life immune system in development of vulnerability to PEs which is consistent with the literature on psychotic disorders (Cannon, Clarke, & Cotter, 2014). Proteomic studies suggest that complement pathway dysregulation may be one of the biological mechanisms that underpin the relationship between immune system and PEs (English et al., 2017; Focking et al., 2019).

1.6.3 Social Environment. Ethnic minority status (particularly in those of African-Caribbean origin) has been associated with an increased risk of PEs (Laurens et al., 2008; Morgan et al., 2009). Individuals living in 'urban' areas have a higher risk of PEs (Krabbendam & Van Os, 2005; Spauwen et al., 2004) and this association has been linked with the prevalence of one's own ethnic group within the local population, social adversity and victimisation by violent crime (Das-Munshi et al., 2012; Newbury et al., 2017).

Another common social risk factor for PEs is lower income status (Kaymaz et al., 2012). However, a recent World Health Organization world mental health survey found that there is a higher prevalence of adults reporting PE in middle- and high-income countries compared with low income countries (7.2% and 6.8% v's 3.2%, respectively; McGrath et al., 2015). One possible explanation for this is that the magnitude of the income inequality within a country (or local region) may be contributing to the likelihood of PEs, however this remains to be explored.

1.6.4 Trauma and victimisation. There is now a wealth of evidence linking adverse experiences to PE (Croft et al., 2019; McGrath et al., 2017; Arseneault et al., 2011; Bentall et al., 2012; Fisher et al., 2013; Kelleher et al., 2013; Peters et al., 2016; Trotta, Murray, & Fisher, 2015; van Dam et al., 2015). Some studies have demonstrated a dose response rate between traumatic experiences and PEs (Shevlin et al., 2011). Others have linked specific types of traumas events such as sexual abuse (Bentall et al., 2012), physical abuse (Fisher et al., 2013) and emotional abuse (Daalman et al., 2012) to risk of PEs. The most recent evidence indicates that all types of trauma

experienced in childhood or adolescence increase the risk of PEs, with exposure to trauma accounting for just under half of the PEs reported by young people (population attributable fraction: 45%, Croft et al., 2019).

There is now a lot of interest in the dynamic relationship between bullying and PEs (Fisher et al., 2013; Kelleher et al., 2013; Moffa et al., 2017). Within a longitudinal study of adolescents, Kelleher et al (2013) observed that even after controlling for baseline PEs, there is a relationship between bullying and new incidence of PEs. Interestingly, cessation of bullying was associated with a reduction in PEs indicating the potential for a causal relationship.

1.6.5 Cannabis and Tobacco Use. Cannabis use/abuse has been linked to both psychotic disorders (Moore et al., 2007; Arseneault et al., 2004) and PEs (Linscott & van Os, 2013; Van Gastel et al., 2014). Kuepper and colleagues demonstrated that incidence of cannabis use is associated with an increased risk of subsequent PEs and continued cannabis use is associated with a greater risk of persistent-PEs (Kuepper et al., 2011). Similar results were observed using elegant statistical modelling in Bourque et al (2018). The genetic under-pinning of this relationship has been explained by a shared genetic and environmental factors as well as a causal role of cannabis use (Nesvåg et al., 2016). Smoking tobacco has also been associated with an increased risk of PEs, even after adjustment for cannabis use (Bhavsar et al., 2018). This associations has been shown to be independent of and equally as strong as cannabis use (van Gastel et al., 2013).

1.6.6 Psychopathology. Emotional and behavioural problems in childhood have been shown to increase risk of subsequent PEs (Scott et al., 2009) and those with persistent psychopathology have an exacerbated risk (Lancefield et al. 2016). The cross-sectional and longitudinal relationship between PEs and psychopathology will be discussed in a later section.

1.6.7 The Neuro-Developmental Correlates of PEs

1.6.7.1 Cognitive and Motor Dysfunction. Individuals who report PEs have subtle cognitive dysfunction in domains consistent with the dysfunction seen in psychotic disorders. These include intellectual quotient (Horwood et al., 2008) and focal domain deficits, such as speed of processing, psycho-motor speed, receptive language, emotional recognition processing, executive functioning and memory (Carey et al., 2019; Blanchard et al., 2010; Daalman et al., 2011; Dickson et al., 2014; Gur et al., 2014; Kelleher et al., 2013; Roddy et al., 2012; Mollen et al., 2016). While poorer receptive language abilities and IQ scores in the early childhood have been associated with PEs and psychotic disorder (Cannon et al., 2002; Mollon et al., 2018) more evidence is necessary evaluate to early cognitive development and subsequent risk of PEs. Moreover, given that most individual PEs are transient, it is unclear to date if the cognitive trajectories of those with reoccuring-PEs differ to those with transient-PEs and does the cognitive performance improve with cessation of PEs.

1.6.7.2 Early Neuro-anatomical Markers. Similar to cognitive dysfunction, neuro-anatomical difference have been observed between those reporting PEs and those not. These include, global differences in gray matter volume and white matter integrity (Satterthwaite et al., 2015), structural and functional differences in fronto-temporal regions (Jacobson et al., 2010; O'Hanlon et al., 2015 Bourque et al., 2017), default network disruption (Jacobson et al., 2014; Orr, Turner, & Mittal, 2014) and reductions in global network efficiency and density (Drakesmith et al., 2015). However, similar to cognitive dysfunction, it is unclear whether the differences in brain structure and functioning precede the onset of PEs and the same questions arise regarding typical/atypical trajectories with transient-PE. Further work is needed on the neuro-developmental underpinnings of PEs.

1.6.8 Risk Factors for Re-occuring Psychotic Experiences

While much has been done over the last decade to identify risk factors for PEs, less has been accomplished regarding the identification of risk factors associated with re-occuring PE. A recent meta-analysis identified only six studies that investigated differences in risk factors between those who report persistent and transient PEs

(Kalman et al., 2019). Unfortunately, none of the risk factors which were identified in the individual studies were replicated.

1.6.9 Overview of the Risk factors and Correlates.

The evidence to date highlights the overlap between risk factors for psychotic disorder and PEs. Some of these are stable biological characteristics or are general rather than individual characteristics (e.g. urbanicity or social class). Others, however, present an opportunity for intervention (such as victimisation, psychopathology, or psychosocial characteristics). Intervening early may reduce 'risk' in individuals who are known to be vulnerable to a wide variety of mental disorders. This is particularly important for individuals with re-occuring-PE whom we already know have more severe symptoms in their early years, and have a greater risk of eventually developing psychiatric disorders (De Loore et al., 2011; Dominguez, et al., 2011; Calkin et al., 2017).

Finally, while several studies have identified individual risk factors for PEs, it is likely that identified (and unidentified) factors interact on multiple-levels resulting in the dynamic and diverse expression of PEs. It is likely that higher-order statistical techniques such as network analysis (Wigman et al., 2016) or machine learning algorithms (Bourque et al., 2017) may model this type of interactive environment better than the current techniques. Moving towards these styles of investigation may be an important future step for psychiatric epidemiology.

1.7 Outcomes associated with PEs

The term "sub-clinical" psychotic experiences/symptoms is somewhat misleading. Sub-clinical does not mean that they are not clinically meaningful. Many individuals with PEs meet diagnostic criteria for common psychiatric conditions (Kaymaz et al., 2012; McGrath et al., 2016) and co-morbidities are evident from an early age (Bartels-Velthuis et al., 2011; Downs et al., 2013; Kelleher et al., 2012; Laurens et al., 2012). PEs, even when transient are associated with increased rates of subsequent suicidal behaviour (Yates et al., 2019) and poorer global functioning (Calkins et al., 2017). Thus, those with "sub-clinical" PEs should not be presumed to be as free from psychopathology and not help seeking (Calkins et al., 2017; Murphy et al., 2010; Bhavsar et al., 2017).

Conversely, for some, PEs are transient and/or benign phenomena. The relationship between PEs and poorer outcomes is probabilistic rather than deterministic (Linscott & Van Os, 2013) and for many they have limited effects (Johns et al., 2ld014; Peters et al., 2016). Below we discuss the associations between PEs and psychiatric disorders as well as their psycho-social associations (see Figure 2).

1.7.1 Psychotic Disorders. Unsurprisingly PEs have been investigated as a risk factor for psychotic disorders (Poulton et al., 2000; Sullivan et al., 2020). It has been reported that 7.4% of individuals who report early PEs go on to develop a psychotic disorder (Linscott & Van Os, 2013), and 60% of those who do develop a disorder have previously reported some degree of PEs (Sullivan et al., 2020). Persistence of PEs has an accentuated association with psychotic disorders. Those with persistent-PEs were 9.9 times more-likely than their peers to develop a psychotic disorder whereas those with only two reports of PEs were 5 times more-likely (Dominguez et al., 2011).

1.7.2 Non-psychotic disorders. PEs have been associated with a myriad of non-psychotic disorders. This relationship takes one of three forms; 1) psychopathology precedes the onset of PEs; 2) psychopathology and PEs co-occur; and 3) PEs precede the onset of psychopathology.

1) As addressed in the risk factor section, individuals who report non-psychotic disorder and general psychopathology have an increased risk of subsequent PEs (McGrath et al., 2016; Scott et al., 2009; Lancefield et al., 2016).

2) Multiple studies have demonstrated that PEs are associated with an increased risk of co-occurring common psychiatric conditions such as affective disorders, anxiety disorder and behavioural disorders (Armando et al., 2010; Kelleher et al., 2012; Laurens et al., 2012; Wigman et al., 2012; Yung et al., 2009). For example, Kelleher and colleagues, using four independent samples demonstrated that the majority of those with PE meet criteria for a non-psychotic disorders and had elevated risk of psychiatric multi-morbidity (Kelleher et al., 2012). Those with both PEs and co-occuring psychiatric

conditions have elevated levels of mental health services use and required a longer duration of care (Bhavsar et al., 2017). In fact, those PEs but without a co-occuring common psychiatric condition also have elevate levels of secondary mental health service use and use of psychological treatment services (Bhavsar et al., 2019).

3) The third relationship is that PEs, even when transient, are markers for vulnerability to subsequent psychiatric conditions. Fisher and colleagues reported that 92.3% of participants who reported PEs at age 11 had a diagnosable psychiatric condition by age 38 (Fisher et al., 2013). McGrath and colleagues, using a sample of 31,000 individuals, demonstrated a bi-directional temporal relationship between PEs and common mental disorders (OR range: 1.3-2, McGrath et al., 2016). A meta-analysis investigating longitudinal prospective studies demonstrated the relationship between PEs and non-psychotic disorder, however this relationship was weaker than the relationship with psychotic disorders (Kaymaz et al., 2012). Thus, it appears that PEs increase vulnerability to subsequent general psychopathology but also have a homotypic relationship with psychotic disorders. These associations are further elevated for those with re-occuring PEs (De Loore et al., 2011; Downs et al., 2013).

1.7.3 Suicidal Thoughts and Behaviour. PE have also been linked with suicidal ideation, attempts and death by suicide (Cederlof et al., 2017; DeVylder et al., 2015; Kelleher, Corcoran, et al., 2013; Sharifi et al., 2015; Sullivan et al., 2015). A meta-analysis has indicated that those with PEs were at a 2-3 increased risk of suicidal behaviours (Honings et al., 2016) and PEs had a 25% population attributable fraction for subsequent attempted suicide and death by suicide (Yates et al., 2019). Additionally, re-occuring PEs are associated with an even greater risk of suicide behaviour (Connell et al., 2016).

1.7.4 Negative psycho-social outcomes. Given the relationship between PEs and psychiatric disorders it is not surprising PEs have been associated with a range of poor psycho-social outcomes. For example, those who report PEs have poorer global functioning (Kelleher et al., 2015; Yung et al., 2009), lower quality of life (Svirskis et al., 2007), less social support (Saha et al., 2012), a more externalising locus of control

(Sullivan et al., 2017) and higher rates of perceived social stigma (Lien et al., 2015). Individuals who report PEs are less likely to marry/be divorced (Linscott & Van Os, 2013; Scott et al., 2006), have higher rates of unemployment (Scott et al., 2006; van Os et al., 2009), physical health problems (Moreno et al., 2013), hospitalisation for non-psychotic disorder (Werbeloff et al., 2012), higher rates of arrest (Honings et al., 2016) and a shorter lifespan (Sharifi et al., 2015).

Poorer outcomes are even evident in early life. Adolescents with PEs have lower optimism, low self-esteem, high avoidance coping and school misconduct (Dolphin, Dooley, & Fitzgerald, 2015), poorer functioning (Calkins et al., 2017b; Kelleher et al., 2015) and increased risk of sleep disturbances (Lee et al., 2012; Taylor et al., 2015).

1.7.5 Overview of outcomes

It is clear that there is a strong link between PEs and psychiatric disorders. Given that these phenomena are the sub-clinical manifestation of some of the most debilitating conditions, it is perhaps not surprising that they are associated with negative outcomes. However, what is surprising is the trans-diagnostic properties of these phenomena. Because the link between PEs and psychopathology varies by temporality and across psychiatric conditions it has been suggested that PEs may be a trans-diagnostic marker for general psychiatric vulnerability.

Specifically, PEs have been associated with the on-going psychiatric conditions, multi-morbidity, subsequent psychiatric conditions, suicidal behaviour and a variety of negative psycho-social outcomes. Such findings highlight the importance of screening for PEs as a non-specific risk marker. This may be particularly important in early life prior to psychiatric conditions becoming embedded. However, as previously stated, the relationship between PEs and psychiatric disorders is probabilistic rather than deterministic. It is likely that certain predisposing characteristics (family history of mental disorder, history of adversity) interact with PEs altering (likely increasing) the probability of a psychiatric outcome. Conversely, certain modifiable psycho-social characteristic may in fact lie on the causal pathway between PEs and subsequent psychiatric

outcomes. Identifying these characteristics would present an opportunity for intervention.

1.8 Thesis Outline, Aims and Structure

In this chapter, I have highlighted some of the major risk factors for PEs and their associated outcomes. Below I specify the aims of this thesis, as they relate to the risk factors and outcomes of PEs. Thus, the aims of this thesis fall into three distinct sections: prediction and preventative targets, outcomes associated with PEs and mediators of those outcomes.

1.8.1 Section I Prediction and Preventive Targets.

Aim I. To investigate the predictive value of childhood and adolescent psycho-social risk factors for adolescent PEs.

I have highlighted the accumulating evidence of risk factors for PEs. Given this wealth of evidence, across multiple domains (biological, psychological, social and environmental) it may be possible to identify young people at risk of PEs prior to reporting these phenomena. Additionally, there may be a specific cross-sectional sequela of demographic, clinical and psycho-social variables that distinguishes those with PEs from those without PEs. To-date only one study has attempted to predict PEs, with the primary focus on neuroimaging data (Bourque et al., 2017) and with limited success. I aim to focus on prediction based on demographic and psycho-social data as it is more feasible to acquire such data on a large scale and in a community setting.

Aim II. To investigate whether changes in self-concept between childhood and adolescence alter the risk of adolescent PEs.

The second aim of this section is to utilise modifiable psycho-social targets for PEs. The vast majority of risk factors for PEs are inflexible (such as family history of mental disorder, urbanicity or socio-economic status) or difficult to modify (trauma). I aimed to utilise the malleable nature of self-concept to investigate whether changes in self-concept (improvements or worsening) are associated with differential risk of incidence of PEs.

1.8.2 Section II Outcomes Associated with Psychotic Experiences.

Aim III. To synthesise the literature relating to childhood and adolescent PEs and risk of mental disorder; psychotic disorder and non-psychotic disorders.

There is a growing body of evidence that, in youth, PEs are associated with many different psychiatric disorders and it has been suggested that PEs may be an early trans-diagnostic pluripotent marker. However, only one study has attempted to synthesise the evidence of the relationship between PEs and psychiatric disorders (Kaymaz et al., 2012). Within this study, the majority of the baseline assessment of PEs were reported in adulthood rather than childhood. Given the prevalence of PEs in childhood and the potential for PEs to be an early pluripotent marker a thorough investigation of the relationship between childhood and adolescent PEs and mental disorder is warranted.

Aim IV. To investigate whether childhood PEs improve the prediction of mid-adolescent psychopathology.

One question that arises out of the relationship between PEs and mental disorders is whether assessing PEs adds clinically useful prognostic information about psychiatric vulnerability of the young person? Or do established markers already capture the information provided by PEs? I aim to establish whether assessing PEs improves the prediction of subsequent psychiatric outcomes.

Aim V. To examine the relationship between childhood PEs and subsequent global functioning throughout adolescence and into early adulthood.

There is a wealth of literature on the cross-sectional relationship between PEs and psycho-social dysfunction. However there is limited longitudinal research investigating if children who report PEs have functional problems beyond mental disorder? Thus, will those who report PEs require support for ongoing functional difficulties beyond the duration of the phenomena? I aim to examine the longitudinal relationship between PEs and subsequent functional outcomes.

1.8.3 Section III Mediator of the Outcomes.

Aim VI. To investigate if malleable psycho-social factors meditate the bi-directional relationship between adolescent PEs and non-psychotic psychopathology.
In Section II, I highlight the vulnerability that young people who report PEs have to mental disorders. However not all of those with PEs go on to report a psychiatric disorder. I proposed that a part of the reason for this is due to the mediating effect of psycho-social variables. Thus, I investigated whether certain malleable psychosocial variables mediate the bidirectional relationship between PEs and mental disorder, thus posing as a possible point for intervention for those already display psychiatric phenomena.

1.9 Data Sources and Methods

The specific methodology of each investigation is reported in each chapters. Below I provided an overview of the data sources and the rationale for PE measurement.

1.9.1 Data Sources. All of these investigations were conducted using three data sources: the literature to-date and two Irish datasets. The first Irish dataset was a large longitudinal nationally representative epidemiological study: *Cohort 98'* from the *Growing up in Ireland*. Interview were conducted on children and their families gathering primarily questionnaire data. In this thesis I present data from the first, second and third waves of the study when participants were aged nine, thirteen and seventeen. *Cohort 98'* were used in Study I ('Predicting early adolescent psychotic experiences from psycho-social characteristics'), Study II ('Changes in self-concept and risk of psychotic experiences in adolescence') and Study VI ('What mediates the longitudinal relationship between psychotic experiences and psychopathology?').

The second Irish dataset was a smaller longitudinal study of young people from general population; the *Adolescent Brain Development* study. Clinical interviews and cognitive assessment were conducted on the young people at ages twelve, fifteen and nineteen. The Adolescent Brain Development study was used in Study IV ('Do childhood psychotic experiences improve the prediction of adolescent psychopathology?') and Study V ('Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood').

In Study III (‘Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis’), the published literature was used as the data source.

1.9.2. Psychotic experiences In the adolescent brain development study PEs were assessed by clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia) with additional follow up questions for PEs using the SOCRATES assessment (Kelleher & Cannon, 2014). At each wave, the data was assessed by three experts in the field of psychosis. In the Growing up in Ireland study PEs were assessed at ages 13 and 17 using the *Adolescent Psychotic Symptoms Screener*. PE endorsement was classified based on validated clinical criteria (Kelleher et al., 2011).

SECTION I

PREDICTION AND PREVENTIVE TARGETS.

Chapter 2

STUDY I - PREDICTING ADOLESCENCE PSYCHOTIC EXPERIENCES FROM PSYCHOSOCIAL CHARACTERISTICS: A MACHINE LEARNING APPROACH

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search and statistical analysis. He was the first and corresponding author on the published manuscript.

Predicting adolescent psychotic experiences from psychosocial characteristics: a machine learning approach using a longitudinal cohort study.

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Abstract

Background: Psychotic experiences are commonly reported in early adolescence and are associated with an increased risk of psychiatric disorders and poor psycho-social outcomes. Despite the identification of risk factors for PEs, accurately predicting who will report the phenomena remains a major challenge. Several techniques have now been developed to improve prediction such as machine learning algorithms. In a large population based cohort we investigated the prediction of PEs at age 13 based on psychosocial data recorded at age 9 and classify those with PEs based on age 13 data.

Method: Data from the child cohort of the Growing up in Ireland study (n=7169) was used in this investigation. This comprised 174 psychosocial features collected at age 9 and 215 features collected at age 13 from children and their primary care giver. Psychotic experiences were measured using the Adolescent Psychotic Symptoms Screener at age 13. Penalized regression analysis was conducted on the data using elastic net model fitting and 10-fold cross-validation. Area under the Curve (AUC) were compared to random label modelling.

Results: 12.2% of participant reported PEs in adolescence. Age 9 psychosocial characteristic significantly predicted PEs in adolescence (AUC: 0.61, CI:0.60-0.62, $p<.001^{e-12}$) while age 13 characteristics accurately classifed 68.0% of those with PEs (AUC:0.76, CI:0.75-0.76, $p<.001^{e-12}$). Thirty-five age 9 features and 43 age 13 features significantly contributed to the models with themes centring on family dysfunction, parental characteristic, psychopathology, low self-concept, anti-social behaviour, neighbourhood characteristics and peer alienation. The same themes were evident at both time points.

Discussion: Childhood psychosocial characteristics were able to identify 55% of adolescent PEs while adolescent characteristics can classify 68% of children with PE from those without. Similar poly-thematic psychosocial profiles were evident in childhood and adolescence. Pre-emptive interventions targeting these themes may impact on the prevalence of psychotic experiences.

2.1. Introduction

Psychotic experiences (PEs) are commonly reported in early adolescence and are considered an early pluri-potent marker for severe psychiatric conditions (1). These phenomena share an etiological overlap with psychotic disorders; however, their origins to date remain unclear (2). Several risk factors for PEs have been identified, including early life trauma (3), psychopathology (4), cognitive dysfunction (5) and socio-economic factors (6). Identifying young people at risk of PEs and providing appropriate early intervention is an important goal for preventative psychiatry. However, our ability to predict the onset of PEs is very limited (7).

Machine learning algorithms, such as penalized regression and support vector machines, have been shown to improve diagnostics in several areas of medical science (8). However, their use in psychiatry to date has been relatively limited. (9). Machine learning is frequently coupled with neuroimaging data to allow for large quantities of data to be analyzed simultaneously while using advanced techniques to prevent overfitting, see *Jollans and Whelan* (10). Neuroimaging data alone has been shown to be predictive of major depressive disorder, psychosis, substance use and dementia and has proven useful in identifying the regional and functional correlates of such conditions (10).

One major limitation of prediction algorithms using neuroimaging data is the financial and logistical cost of using these techniques. An alternative approach would be to use the technique with psychosocial data. Psychosocial data is easy to obtain and more cost effective. Such data are now widely available in several longitudinal community samples (11, 12). To date only one study has attempted to predict the onset of PEs (7). *Bourque and colleagues* demonstrated that functional neuroimaging can be used to distinguish young people who go on to report PEs from those without albeit with limited predictive accuracy (7).

The aims of this study was to: 1) examine the predictive accuracy of childhood psychosocial data (age 9) to identify adolescents with PEs (age 13); and 2) examine the classification of adolescent PEs based on adolescent psychosocial data (age 13).

2.2. Method

2.2.1 Participants

Participant were members of the *Growing Up in Ireland* (GUI) study. The GUI is a longitudinal, sample of children from the general population in Ireland. We present data on the child cohort (Cohort '98) which comprised of 8658 children and their families who were recruited from national primary schools at age 9 (wave 1). Four years later, all 8658 were targeted for re-recruitment and 7423 were interviewed at age 13 (wave 2). For a further description of the cohort see *Healy et al.* (13).

2.2.2. Measurement

Age 9 features. At age 9, 174 individual features were used in the investigation. Data was obtained from the participating child and the primary care giver at wave 1. This included demographic characteristics (age, sex, handedness, nationality, ethnicity and socio-economic status), birth characteristics and complications, maternal drinking and smoking during pregnancy, general health, chronic or ongoing illness, contact with medical services (general practitioner or hospitalization), specific learning difficulties (dyslexia, speech and language difficulties e.t.c), reading and mathematics abilities, child-peer interaction (number of friends, amount of time spent with friends), bullying (type, severity), child-parent relationship, child hobbies and day to day activities, child's school achievements (expected and obtained), exposure to early life stressors (death of a parent/friend/close relative, moving home country, drug or alcohol use in the family e.t.c.), child psychopathology, temperament, and self-concept, parenting style, and parental criminality, parent smoking and drinking habits, parental depression, parental marital status, inter-parent conflict, parental religiosity, household income, urban environment factors (population level, vandalism in local area, safe space for children, child's perceived threats within the neighborhood e.t.c). A full list of feature, the features type (continuous or categorical) and the percentage of missing values can be found in supplementary materials 1.

Age 13 features. At age 13, 215 features were included in the investigation. Again, the data were obtained from the child and the primary care giver and included similar (age appropriate) features to those obtained at age 9. Such features comprised of

demographics, health and contact with medical services, bullying, child-parent relationship, child activities, school and cognitive factors, exposure to early life stressors, child psychopathology and urban environment factors. Additional features at this wave of the study include personality characteristics, anti-social behavior, smoking, drinking and recreational substance use, and child-peer relationship. A full list of features, the feature type (continuous or categorical) and the percentage of missing values can be found in supplementary 1.

Psychotic experiences. Psychotic experiences were only measured at age 13. Psychotic experiences were measured using the *Adolescent Psychotic Symptoms Screener* (APSS) (14). The APSS is a self-report questionnaire comprising of seven questions pertaining to hallucinatory and delusional experiences. Six of these were included in the GUI survey instrument.

1) Have you ever heard voices or sounds that no-one else can hear?
2) Have you ever seen things that other people could not see*?*
3) Have you ever thought that people are following you or spying on you?
4) Some people believe that their thoughts can be read by another person. Have other people ever read your mind?
5) Have you ever felt that you were under the control of some special power?
6) Have you ever felt that you have extra-special powers*?*

The participating children were required to respond by circling “No” (0 points), “Maybe” (0.5 points) or “Definitely” (1 point) to each question. To be categorized as having experienced PEs participants were required to score two or more points on the APSS or to respond “definitely” to the question about auditory hallucinations. Both of these scoring criteria have been validated against clinical interview and have been shown to have good sensitivity and specificity for PEs (two or more points: 70% and 86%; and auditory hallucination: 70% and 100%, respectively). PEs were only measured in the GUI at age 13.

Feature pre-processing.

To be included in the study participants had to have data pertaining to psychotic experiences at age 13 (n=7169). All continuous data was transformed to z-scores. Winzorising was applied to extreme values (replacement value: 3 standard deviations either side of the mean value). Mean replacement was applied to missing variables. All binary variables were coded as 0 or 1. All nominal variables were dummy coded. Mode replacement was applied to binary and nominal outcomes.

2.2.3. Statistical Analysis.

Two investigations were conducted. The first, investigated the predictive value of age 9 features to identify participants with PEs at age 13. The second, investigated the used of age 13 features to classify those with PEs from those without PEs.

Models were fitted using logistic regression with elastic net regularization (15, 16), and 10-fold cross-validation. Elastic net combines least absolute shrinkage and selection operator (LASSO) and ridge regularization. This allows the model to include relevant but correlated coefficients in the same spare model fit by automating variable selection and continuous shrinkage simultaneously (17). Nested cross-validation was used to identify the optimal hyper-parameters: for the weight of the LASSO versus the ridge (α) and the regularization coefficient (λ). 15 linearly spaced values ranging from 0.01 to 1 were explored for both α and λ. The mode of α and the median of λ across sub-folds were selected as parameters for the main fold. Prediction accuracies for binary outcomes (PEs or no PEs) were trained on the area under the curve (AUC) and we additionally report the overall accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Confidence intervals were calculated using Stata 15.

Finally for each investigation, 10 null sub-fold models were also investigated using the same methodology with the same dataset but participants were randomly assigned an outcome label (participants were randomly assigned to report PEs or not report PEs). The accuracy of the models with the real data (real models) were compared to the accuracy of the models with the randomly assigned data (null models) using t-tests. The null models were also used to calculate a minimum beta threshold of the 95th percentile. This was used to identify which features should be included in the real model across iterations.

2.3. Results

Demographic characteristics of the sample and prevalence of PEs

At baseline the participants mean age was $\bar{X}$ = 9.0 years (SD: 0.1) and 51.2% of the sample were female. At follow up the participants mean age was $\bar{X}$ = 13.0 years (SD: 0.1). Psychotic experiences were reported by 12.2% of the participants in adolescence (n=876, unweighted sample). The average APSS total score was $\bar{X}$ = 0.6 (SD: 0.9, range 0-6) in the overall sample and $\bar{X}$ = 2.7 (SD: 0.9, range 1-6) in the PE group.

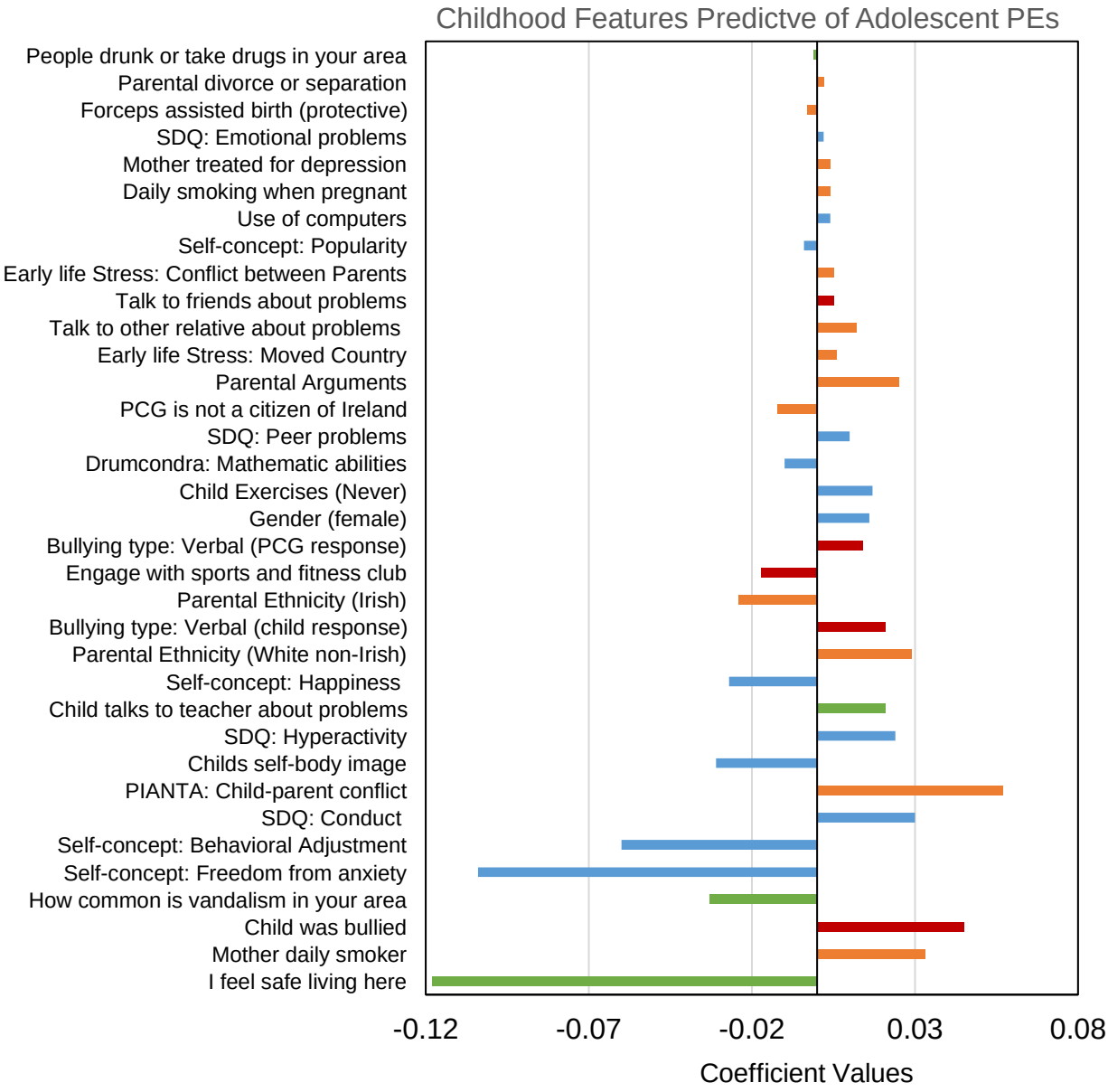
Aim One. Prediction of adolescent psychotic experiences.

The model of childhood psychosocial characteristics returned an AUC= 0.61 (95% CI: 0.60 - 0.62). 100% of the real model sub-folds significantly out-performed the null model sub-folds (t (18) = 19.37, p <.001^{e-12}). The average accuracy of the real models were 59.7% (95% CI: 58.5-60.8) with a sensitivity of 55.3% (95% CI: 51.9-58.6) and a specificity of 60.3% (95% CI: 59.1-61.5). The PPV was 16.2 % (95% CI: 14.9-17.6) and the NPV was 90.6 % (95% CI: 89.7-91.5). 35 features surpassing the 95th percentile threshold are included in Figure 2.1 in order of importance based on mean frequency choice in the sub-folds (from bottom to top). “Feeling safe living in their neighbourhood” was the most prominent feature with two other neighbourhood features surpassing the 95th percentile. Additionally 11 parent-child relationship or parent only features, four psychopathology features, four self-concept features, four child lifestyle features and three features related to bullying all surpassed the 95th percentile threshold.

Aim Two. Classification analysis of adolescent psychotic experiences.

The model performed well with an AUC= 0.76 (95% CI: 0.75 - 0.76). 100% of the real model sub-folds significantly out-performed the null model sub-folds (t (18) = 60.22, p <.001^{e-21}). The average accuracy of the models were 70.7% (95% CI: 69.6-71.7) with a sensitivity of 68.0% (95% CI: 64.8-71.1) and a specificity of 71.0% (95% CI: 69.9-72.1). The PPV was 24.6 % (95% CI: 22.9-26.4) and the NPV was 94.1% (95% CI: 93.4-94.8). 43 features surpassing the 95th percentile are included in Table 2.1 in order of importance. The most prominent feature was depression score. 12 features were related to the child-parent relationship or were parent only features, 9 related to anti-social behaviour and externalising behaviour.

Figure 2.1 Coefficient values for the significant childhood psycho-social features associated with the prediction of adolescent PEs.



Note. Thematic Colouring: Orange = Family and Parent Characteristics; Blue = Individual Characteristics; Red = Child-Peer Relationship; and Green = Neighbourhood Characteristics.

Table 2.1 The adolescent features beyond the 95th percentile and their coefficient values.

Adolescent Features	Coefficient Values	Adolescent Features Continued	Coefficient Values
Depression Score	0.340	Amount of time spent alone on a school day	0.031
PCG tells me their ideas and I shouldn't question them	0.079	Amount of time at a homework club	0.056
PCG really doesn't like me to tell them my troubles	0.049	Written things/sprayed paint things that was not theirs	0.040
Self-concept: Popularity	-0.099	Have you spoken to your child about sexual orientation	0.041
Self-concept: Freedom from anxiety	-0.114	Child has sniffed glue or aerosols	0.055
Self-concept: Behavioural Adjustment	-0.147	How common is it for people to be drunk in your local area	-0.031
Childs computer use	0.084	Taken something from a shop or store without paying for it	0.028
IPPA: Alienation	0.058	Parent with ongoing chronic condition	0.026
Verbal reasoning Score	-0.116	SDQ: Hyperactivity	0.025
PCG is not a citizen of Ireland	0.104	Early life Stress: Conflict between Parents	0.030
Punched someone on purpose in order to hurt or injure them	0.047	Not having an specific learning disability (protective)	-0.027
Taken money or something else that did not belong to them from your home	0.061	Child bullied	0.024
Child carried a knife/weapon in case it was needed in a fight	0.135	Mum lets me get away with things	0.019
Bullying type: Gossip or Rumours	0.098	Not paid the correct fare on a bus or train	0.012
Exercise to lose weight or avoid weight gaining	0.075	Mum points out what I could do better	0.026
We do not intend to continue living in this area	0.039		

Note: SDQ: Strengths and Difficulties Questionnaire; PIANTA: Child-parent relationship quality scale; PCG: Primary Care Giver; IPPA: Inventory of Parent and Peer Attachment

2.4. Discussion.

To our knowledge, this is the largest longitudinal epidemiological study to date using machine learning to predict adolescent PEs based on psychosocial data. This study has the advantage of using a longitudinal sample of adolescence, a large number of psychosocial features and PEs were based on clinically validated screening measure.

Our results indicated that age nine psychosocial characteristic were able to distinguish between adolescents with PE verses those without PEs. The predictive accuracy for adolescents with PEs was adequate (~60%). AUC values are known to decrease as sample size increases (18). Thus, despite low accuracy, this value is likely to be a relatively precise estimate of the predictive value of adolescent PEs based on childhood psychosocial characteristics. *Bourque et al,* using neuroimaging and clinical characteristics, report a similar prediction accuracy for PEs with mood symptoms from controls on a two year follow-up period (7). The strongest predictive childhood feature was whether the child felt safe living in their neighbourhood, which is in line with evidence suggesting that a young person's perception of local environment significantly influence their risk of PEs (19).

Secondly, our results indicated that adolescent psychosocial characteristics were able to classify adolescents with PEs from those without PEs with a reasonably degree of accuracy (71%) with similar sensitivity (68%) and specificity (71%). Adolescent depression score was the strongest feature to distinguish PEs from controls with externalizing behaviour and the child parent relationship also featuring prominently. This aligns with recent meta-analytical evidence indicating that young people with PEs have a four-fold odds of reporting co-occuring depression and a two-fold odds of reporting co-occuring behavioural disorders (20).

In both models there was a high NPV (91% and 94%, respectively), indicating that most individuals who test negative no not have adolescent PEs. However there was limited PPV in both models indicating a high degree of false positives. This is possibly because

the majority of those who are exposed to the most predictive features in either model do not go on to report PEs.

Features and associated themes.

Despite the difference in prediction accuracy, the themes identified from the features in childhood were similar to the themes identified in adolescence. Four main themes emerged: family and parent characteristic, individual characteristics, neighbourhood characteristics and the child-peer relationship. Importantly, these themes emerged in an unbiased manner. Some of the emerging features are commonly reported in the literature such as urbanicity and psychopathology (4, 20-23) while others point to factors that have been underappreciated to date.

Family and Parent Characteristics. Familial conflict was evident at both ages generally taking two forms: conflict between parents and conflict between the child and the PCG. Conflict between parents was associated with PE at both time point, albeit exacerbated in adolescence. Parental divorce and separation also significantly featured in the childhood model. Interestingly, in childhood, talking to individuals outside of the family nucleus about problems was associated with adolescent PEs again suggesting a strained family relationship. Increased family conflict has previously been associated with PEs, including exposure to parental conflict and divorce (3). Our results are in line with such observations, stressing the importance of these features as a predictor of PEs.

Additionally three features were specifically associated with the primary care giver: parental ethnicity, smoking, and maternal health. Being from an ethnic minority group is commonly associated with an increased risk of PEs (6) however, this is normally a characteristic of the participants themselves. Our results suggest that the PCG has an important role in determining the child's risk of PEs possibly due to integration factors such social cohesion (24). Previous research has demonstrated that maternal smoking during pregnancy increases the risk of PEs (25). We extend these observations by suggesting that current maternal smoking is associated with an increased risk of PEs.

Finally, maternal health, such as being treated for depression was associated with an increased risk of PEs. This may suggest a predisposed risk for such phenomena, as has been observed in previous studies (6).

Individual Characteristics. Several individual characteristics emerged, such as psychopathology self-concept and anti-social behaviour specifically in adolescence. Psychopathology was an important predictor and classifying characteristic. While the spectrum of psychopathological symptoms were evident at both time points, greater weight was given to externalizing symptoms in childhood and internalizing symptoms in adolescence. Psychopathology is a known risk factor for PEs (4, 20, 22). Our results are in line with these observations, which suggests that childhood PEs have a close relationship with non-psychotic psychopathology.

Three self-concept sub-scales in childhood and adolescence were associated with PEs: freedom from anxiety, behavioural adjustment and popularity. The evidence indicated that the higher the scores on each of these three subscales, the lower the risk of PEs. Previous research has highlighted that self-concept is associated with PE (26-28). Our results suggest that the particular sub-components of self-concept may be useful targets for reducing PEs.

Anti-social behaviour was only thoroughly investigated in adolescence and prominently featured in the model. All severities of anti-social behaviour and alcohol use were associated with PEs. Previous investigations have demonstrated that PEs are associated with externalizing behaviours (4, 29), anti-social behaviour (30, 31) such as violence (32) as well as increased rates of recreational substances use (33). Our results indicate that these characteristics are evident even in early adolescence.

Neighbourhood Characteristic. Several researchers have noted an increased prevalence of PEs in urban areas (6). Recent evidence has suggested that this may be due to the higher rates of adverse exposures in these areas such as low social cohesion and criminal victimization (34). As already stated, within our predictive model feeling unsafe in one's own neighbourhood was the most consistent predictor of

adolescent PEs with parental reported vandalism also scoring highly. Our results are in line with these observations indicating that security and safety in the neighbourhood is associated with and increased risk of PEs, particularly in childhood (19).

Child-Peer Relationship. Poor relationship between the child and his/her peers at both time points were associated with PEs. Child-peer problems such as bullying (particularly verbal bullying), alienation, isolation and increased amount of time on single user activities (time on the computer) were all associated with an elevated risk of PEs. Previous observations have indicated that bullying and low peer status are associated with an increased risk of PEs (35, 36). Our results support these observations while also suggesting that adolescents with PEs also report great isolation.

Machine learning approaches are important under-used techniques in epidemiology (37). The use of these techniques may improve the prediction of children likely to report complex phenomena such as PEs. These techniques are not without scepticism and limitations (38). Nevertheless, they may become useful identification tools and aid in the prevention of psychiatric disorders. Combining these tools with large epidemiological studies using psychosocial data may improve the prediction any number of poor outcomes. Thus, with enhancements they may allow for the development of an adequate screening to tool to identify young people at risk of poor outcomes. This would align with global challenge of selective and indicated prevention for mental health outcomes (39). Moreover, because psycho-social data is easy to collect with limited cost, it is possible to implement findings into community service or school settings.

2.4.1. Strengths and Limitations.

As previously stated, this is the largest longitudinal cohort study to use machine-learning techniques to investigate PEs. PEs were based on a clinically validated screening tool and a wide variety of childhood features were used based on both child and PCG reports. It is possible that a multi-modal approach (including biological data) may improve the prediction of PE; however, biological data was not available with the current study. Alternative supervised learning algorithms, such as deep learning or ensemble algorithm stacking, may improve the prediction of PE. However, we opted not

to use such approaches as the greater the complexity of the algorithm the more difficult it is to interpret the results. This interpretation cost, diminishes understanding and prevents the likelihood of translation into a real world setting (clinical or community). PEs were not measured in childhood, limiting our ability to measure persistent PEs.

Finally, given that the data came from a community sample, it likely was comprised of some individuals whose psychotic experiences are both distressing and associated with psychopathology and others for whom these phenomena are relatively benign experiences. Unfortunately, we do not have data on the degree of distress associated with the experiences and, as such, do not distinguish these two groups.

2.4.2. Conclusion

Overall, it is possible to identify 55% of those who go on to have adolescent PEs based on childhood psychosocial characteristics and to classify 68% of those with PEs based on adolescent characteristics. The poly-thematic psychosocial profile of adolescents with psychotic experiences points toward family dysfunction, psychopathology, low self-concept, anti-social behaviour, feeling unsafe in own neighbourhood, peer alienation and parental characteristics (smoking and immigration) as relevant factors. The majority of these themes are evident in childhood as well as adolescence. As such, pre-emptive interventions targeting these themes may prove to have an impact on the incidence of adolescent psychotic experiences.

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Chapter 3

STUDY II - CHANGES IN SELF-CONCEPT AND RISK OF PSYCHOTIC EXPERIENCES IN ADOLESCENCE

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search and statistical analysis. He was the first and corresponding author on the published manuscript.

Note: The study below is the final copy of the published manuscript. The document appears in the *Journal of Child Psychology and Psychiatry (Q1, Impact Factor: 6.1)*. The content of the article has not been altered.

Changes in self-concept and risk of psychotic experiences in adolescence: a longitudinal population based cohort study.

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Abstract

Background: Psychotic experiences (PEs) are commonly reported in adolescence and are associated with a range of negative outcomes. Few targets for intervention for PEs have been identified. One potential target is self-concept: an individual's beliefs about his/her personal attributes. Improvements in self-concept have been shown to reduce psychotic symptoms in patients with schizophrenia but no study has investigated the relationship between changes in self-concept and risk of PEs in the general population. We aimed to investigate:(1) the relationship between child and adolescent self-concept and adolescent PEs; and (2) whether changes in self-concept between childhood and adolescence were associated with risk of adolescent PEs.

Method: Using data from age-9 and age-13 (n=7423) of the child cohort (Cohort'98) from the Growing Up in Ireland study we investigated the relationship between self-concept at age-9 and-13 and PEs at age-13. PEs were measured using the Adolescent Psychotic Symptoms Screener and self-concept was measured using the Piers Harris-II. Using a stratified analysis, we investigated the relationship between change in self-concept between age-9 and age-13 and the risk of PEs at age-13. Additionally we investigated changes across the six self-concept subscales.

Results: PEs were reported by 13% of participants at age-13. "Very-low" self-concept at age-9 was associated with an increased risk of PEs at age-13 (Adjusted-OR:2.74,CI:1.80-4.19), and "High" self-concept at age-9 was associated with a decreased risk of PEs at age-13 (Adjusted-OR:0.77,CI:0.60-0.97). The stratified analysis indicated that improvements in self-concept reduced the odds of adolescent PEs and decline in self-concept increased the odds of adolescent PEs. This effect was noted across the majority of the self-concept subscales.

Conclusion: There is a strong relationship between self-concept and PEs. The antecedents of low self-concept may be a useful target for preventative psychiatry. Broad-spectrum interventions targeting self-concept in childhood may help to reduce the incidence of PEs in adolescence.

Keywords: Psychotic experiences, Self-concept, Child Development, Preventative Psychiatry.

Abbreviations: PEs**:** Psychotic Experiences

3.1 Introduction

Psychotic experiences (PEs) are commonly reported in early adolescence (Kelleher, Connor, et al., 2012) and are associated with a wide range of adverse outcomes, including increased risk of mental disorder, suicidal behaviour and psychosocial dysfunction (Kelleher, Keeley, et al., 2012; Linscott & van Os, 2013; Scott, Chant, Andrews, & McGrath, 2006; Svirskis et al., 2007).

A wide range of risk factors for PE have been identified, see *Kelleher and Cannon* for summary (Kelleher & Cannon, 2011). However, to date there has been limited attention given to early life psychosocial risk factors for PEs. One early psychosocial characteristic that emerges during childhood is self-concept (Montemayor & Eisen, 1977). Self-concept is an organised, a multi-faceted construct (Shavelson, Hubner, & Stanton, 1976), that refer to the sum of an individual's beliefs and knowledge about his/her personal attributes and qualities (Mann et al., 2004). Self-esteem is the evaluative and affective dimension of self-concept (Harter, 1999) and these terms are frequently used inter-changeably (Piers & Herzberg, 2002). Low self-concept has been linked with vulnerability to common mental disorder (Mann, Hosman, Schaalma, & de Vries, 2004) and meta-analytic data suggests that school based intervention targeting self-concept improves symptoms of common mental disorder and academic performance (Haney & Durlak, 1998).

Within the context of psychosis, limited available data suggest that self-concept is reduced amongst individuals who report psychotic phenomena across the psychosis continuum. In clinical populations, patients with schizophrenia report more negative self-concepts (Close & Garety, 1998) and this has been strongly associated with positive symptoms (hallucinations and delusions) (Barrowclough et al., 2003). Similar findings have also been observed in individuals at ultra-high risk for psychosis (Carol & Mittal, 2015; Morrison et al., 2006). Within the general population, it has been reported that low self-concept is a risk factor for PEs (Krabbendam et al., 2002) and within adolescence, those with PEs were four times more likely to have concurrent low self-concept (Dolphin, Dooley, & Fitzgerald, 2015).

Two pilot randomised control trials using cognitive behavioural therapy aimed at improving self-concept in individuals with psychotic disorders suggested that improving self-concept successfully reduced positive symptoms and improved social functioning (Hall & Tarrier, 2003; Lecomte et al., 1999). Given these findings in patient populations, it is possible that improving self-concept may reduce the risk of PEs in the general population and conversely the decrease in self-concept may increase the risk of PEs. To-date, no study has investigated the relationship between changes in self-concept between childhood and adolescence and the risk of PEs in young people within the general population.

The main aims of this study were to, using a longitudinal nationally representative population sample, investigate: 1) the longitudinal relationship between self-concept at age-9 (childhood) and PEs at age-13 (adolescence); 2) the cross-sectional relationship between self-concept and PEs in adolescence; 3) if changes in self-concept (improvement or a decline) between childhood and adolescence are associated with risk of adolescent PEs; and 4) if changes in the subscales of self-concept between childhood and adolescence are associated with risk of adolescent PEs.

3.2 Method

3.2.1 Participants.

Participants were members of the Child cohort (Cohort ’98) of the *Growing Up in Ireland* (GUI) study. The GUI study is a longitudinal, nationally representative sample of children from the general population in Ireland. Participants were 8,658 children and their families who were recruited from over 900 national primary schools at age 9 years. Four years later, at age 13, all 8,658 were targeted for re-recruitment and 7423 were interviewed (88% retention). A frequency weight was applied to the data to ensure that the sample was representative of the general population. The frequency weight was calculated using parameters from the 2006 Census of the Irish Population. A minimum information algorithm that fits the population marginal was used in a regression framework and the sample estimates were adjusted so that they match the population parameter (for further information Thornton et al., 2016).

To account for demographic difference between those who took part at wave two and who did not the sample was reweighted. This reweighting took into account differences in attritions in: study child gender, family structure, primary care giver age, primary and secondary care givers economic status, primary and secondary care givers social class, ethnicity and accommodation tenure status. Additional adjustments were made for wave one variable associated with wave two attritions. These include primary care giver smoking, drinking and depression, size of the household and wave one income quintile. The final reweighting adjustment reflected the population level of children who were living in Ireland at nine years and who continued to residence in Ireland at 13 years (Thornton et al., 2016).

Ethical Considerations. The GUI received ethical approval from the Health Research Board's Research Ethics Committee in Ireland. Ethical Approval for this secondary analysis was granted by the Research Ethics Committee of the Royal College of Surgeons in Ireland's.

3.2.2 Measurement

Outcome variable. Psychotic experiences (PEs) were measured using the *Adolescent Psychotic Symptoms Screener* (APSS) (Kelleher, Harley, Murtagh, & Cannon, 2011). The APSS is a self-report questionnaire comprising of seven psychotic symptoms including questions pertaining to hallucinatory and delusional experiences, six of which were included in the GUI survey instrument (listed below). The one item not included in the GUI study ("Have you ever had messages sent to you through TV or Radio") was shown to have 0% positive predictive value for that particular type of phenomena and only 40% positive predictive value for any type of psychotic experience (Kelleher, Harley, Murtagh, & Cannon, 2011).

1) Have you ever heard voices or sounds that no-one else can hear?
2) Have you ever seen things that other people could not see*?*
3) Have you ever thought that people are following you or spying on you?
4) Some people believe that their thoughts can be read by another person. Have other people ever read your mind?

5) Have you ever felt that you were under the control of some special power?
6) Have you ever felt that you have extra-special powers*?*

The participating children were required to respond by circling “No” (0 points), “Maybe” (0.5 points) or “Definitely” (1 point) to each item. PEs were measured as a dichotomous variable and were defined as scoring two or more points on the APSS or a response of “definitely” to the question about auditory hallucinations. Both of these measurements have been validated against clinical interview and have been shown to have good sensitivity and specificity for PEs (two or more points: 70% and 86%; and auditory hallucination: 70% and 100%, respectively). The APSS was administered in the GUI at age 13 only.

Exposure variables. Self-concept was measured using the Piers Harris-II (Piers & Herzberg, 2002), which was administered at both age 9 and age 13. The Piers Harris II is a 60 item self-report questionnaire which is designed to assess self-concept in young people aged between seven and eighteen. It is comprised of six subscales comprising:

1) *Behavioural Adjustment:* 14 items, e.g. “I cause trouble to my family”; and “I am a well behaved in school”.
2) *Intelligence and School Status:* 16 items, e.g. “I am an important member of my class”; and “I forget what I learn”.
3) *Physical Appearance and Attributes:* 11 items, e.g. “My classmates in school think I have good ideas”; and “My looks bother me”.
4) *Freedom from Anxiety:* 14 items, e.g. “I worry alot”; and “I like being the way I am”.
5) *Popularity:* 12 items, e.g. “I feel left out of things”; and “I have many friends”.
6) *Happiness and Satisfaction:* 10 items, e.g. “I am a good person”; and “I wish I were different”.

The participating children were asked to respond “yes” or “no” to each statement regarding their perceptions of themselves. Total scores were transformed into t-scores and divided into categories in accordance with Piers Harris (2002). Total Score categories were: Very Low (<2nd percentile), Low (3rd-14th percentile), Low Average

(15th-28th percentile), Average (29th-71st percentile), Above Average (72nd-83rd percentile), High (84th-97th percentile) and Very High (>98th percentile).

Confounding variables. Adjustments were made for a number of confounding variables which might have influenced the relationship between self-concept and PEs (see Table 3.1). These included: a) demographic variables; b) family history of psychiatric disorder, c) childhood and adolescent psychopathology; and d) exposure to early life stress. Each of these variables have been shown to increase the risk of PEs (Linscott & van Os, 2013; Lancefield et al., 2016; McGrath et al., 2017) and have also associated with self-concept (Piers & Herzberg, 2002; and Harter, 2012).

a) Demographic Variables. The participating child's age, gender, handedness, nationality (Irish or non-Irish nationality), the primary care givers ethnic background (White Irish, White non-Irish, Black or Asian/Other) and urbanicity (living in a rural or urban area) were investigated. Urban areas were defined as living in an area with a population density of >10,000 people. Additionally, two proxies of socio-economic status were investigated; the Primary Care Givers (PCG) highest educational attainment (None/Primary education only to Post-graduate education) and annual Income in quintiles (Lowest quintile to highest).

b) Family history of psychiatric disorder. Family history of psychiatric disorder was reported by the PCG at age 13.

c) *Psychopathology.* Psychopathology was defined as scoring above the 'Abnormal' cut-off on the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001). Item responses on the SDQ were reported by the PCG at age 9 and 13.

d) Exposure to a high number of early life stressors. The GUI investigated 13 specific early life stressors to which the child may have been exposed to. These included death of a parent, death of a close family member, death of a friend, divorce/separation of parents, moving house within Ireland, moving country, staying in foster home, serious illness/injury, serious illness/injury of a family member drug taking or alcoholism in the

immediate family, conflict between parents, parent in prison, other disturbing event. These were reported by the PCG. We used a binary cut off of three or more stressors (8.2% of the total sample) reported at age 13.

3.2.3 Statistical analysis

All statistical analyses were conducted using Stata 15.

Prevalence and demographics characteristics of participants with or without Psychotic Experiences.

T-tests and logistic regressions were used to examine the difference in the demographic and clinical characteristic between participants with and without PEs. Subsequent analyses were adjusted for variables where differences were observed between the two groups (see Table 3.1). A supplementary analysis was conducted investigating the relationship between self-concept and psychopathology (above the abnormal cut off of the SDQ scale) at both waves of the study. This was conducted using logistic regression and the results are depicted in supplementary materials.

Aim 1. The longitudinal association between child self-concept and adolescent psychotic experiences.

The relationship between childhood self-concept and adolescent PEs was investigated using binary logistic regression with PEs as the outcome variable and childhood self-concept as the exposure variable. We investigated total self-concept score (as a categorical and continuous variable). Adjustments were made for differences in the confounding variables that were observed between those with and without PEs.

Aim 2. The cross-sectional association between child self-concept and adolescent psychotic experiences.

The relationship between adolescent self-concept scores and adolescent PEs was investigated using binary logistic regression with PEs as the outcome variable and childhood self-concept as the exposure variable. We investigated total self-concept score (as a categorical and continuous variable). Adjustments were made for differences in the confounding variables that were observed between those with and

without PEs. Additionally, we adjusted for childhood self-concept and we report adjusted and unadjusted odds ratios.

Aim 3. Change in self-concept between childhood and adolescence and risk of adolescent psychotic experiences.

To investigate the relationship between changes in self-concept and risk of adolescent PEs the self-concept scores were stratified into one of three groups (Low, Average and High). This was done for both the childhood and adolescent self-concept scores. The very low, low and low average categories were collapsed into a 'Low' category (childhood prevalence: 31%; adolescent prevalence: 29%). Average category remained 'Average' (childhood prevalence: 42%; adolescent prevalence: 43%). High average, high and very high categories were collapsed into a 'High' category (childhood prevalence: 27%; adolescent prevalence: 28%). We then investigated if increases in the self-concept between childhood and adolescent (i.e. reporting low self-concept in childhood and high self-concept in adolescence) was associated with a reduced risk for adolescent PEs and 2) if decreases in self-concept (i.e. high self-concept in childhood and low self-concept in adolescence) increased the risk of PEs. This analysis was conducted using logistic regressions. Again, adjustments were made for demographic and clinical differences between controls and PEs. We report the adjusted and unadjusted odds ratios.

Aim 4. Change in self-concept sub-scales between childhood and adolescence and risk of adolescent psychotic experiences.

Finally, we investigated the relationship between changes in the self-concept sub-scales scores and risk of adolescent PEs. This was conducted using the same approach described above in Aim 3. Self-concept sub-scale categories were stratified into three groups in childhood and adolescence (Low, Average and High). We then investigated if increases in the self-concept sub-scale between childhood and adolescent (i.e. reporting low popularity in childhood and high popularity in adolescence) was associated with a reduced risk for adolescent PEs and 2) if decreases in self-concept sub-scale (i.e. high popularity in childhood and low popularity in adolescence) increased the risk of PEs. This analysis was conducted using logistic regressions with adjustments

were made for differences in the confounders between controls and PEs. Additionally adjusting for all other self-concept sub-scale scores at adolescence.

3.3 Results

Prevalence and Demographic Characteristics of Adolescents Who Reported Psychotic Experiences.

PEs were reported by 13% (n=934) of adolescents at age 13. Demographic characteristics are presented in Table 3.1.

Participants with PEs were significantly less likely to be male and Irish. They were significantly more likely to live in an urban area, have a family history of mental disorder, have had psychopathology in childhood and have psychopathology in adolescence and to have experienced three or more stressful life events (see Table 3.1). In terms of self-concept, 33% of those with childhood psychopathology and 29% of those with adolescent psychopathology report self-concept scores below the 14th percentile (low or very low) in childhood. Thirty-four percent of those with adolescent psychopathology reported-self-concept scores below the 14th percentile in adolescence.

Aim 1. The longitudinal association between child self-concept and adolescent psychotic experiences.

***Childhood Self-Concept and Adolescent PEs*.** There was a significant relationship between childhood self-concept and adolescent PEs (see Table 3.2 and Figure 3.1). Twenty-five percent of individuals who reported PEs in adolescence scored below the 14th percentile for self-concept in childhood, compared with 13% of those who did not report PEs in adolescence. Those who reported PEs in adolescence were three times more likely to have scored within the poorest self-concept category in childhood (see Figure 3.1). Additionally, those who reported PEs in adolescence were over 30% less likely to have had high self-concept in childhood. The results indicated a linear dose-response relationship such that for every unit increase in childhood self-concept the odds of adolescent PE reduced by 1.04 (see Table 3.2). Adjusting for confounders had some effect in low and very categories but had a limited effect on all other categories.

Table 3.1. The prevalence and odds ratios for the characteristics of participants with and without adolescent PEs.

CHARACTERISTICS	CONTROLS	PSYCHOTIC EXPERIENCES	OR (CI)
DEMOGRAPHIC			
AGE (MEAN, SD)	13.01 (0.11)	13.02 (0.15)	**0.015**[a]
GENDER (% OF MALES)	51.99	42.88	**0.69** (0.60-0.80)
HANDEDNESS (% LEFT HANDED)	13.32	14.05	1.06 (0.87-1.29)
NATIONALITY (% OF IRISH)	89.78	86.81	**0.75** (0.61-0.92)
URBANICITY (% LIVING IN URBAN AREA)	12.76	15.87	**1.29** (1.06-1.57)
PRIMARY CARE GIVERS CULTURAL BACK GROUND (%)			
· **WHITE IRISH**	91.55	88.41	Ref
· **WHITE NON-IRISH**	6.18	8.31	**1.58** (1.22-2.04)
· **BLACK**	1.40	1.85	**1.81** (1.07-3.04)
· **ASIAN/OTHER**	0.86	1.44	1.07 (0.58-1.98)
SOCIO-ECONOMIC STATUS (PRIMARY CARE GIVERS HIGHESET LEVEL OF EDUCATION %)			
· **NONE/PRIMARY**	3.46	3.94	1.03 (0.58-1.83)
· **LOWER SEC**	16.23	18.82	1.16 (0.90-1.48)
· **HI SEC/TECH VOC/UPPER SEC**	39.19	38.11	Ref
· **NON DEGREE**	19.53	17.98	0.97 (0.80-1.17)
· **PRIMARY DEGREE**	12.92	12.36	0.91 (0.73-1.13)
· **POST GRAD**	8.67	8.79	0.96 (0.76-1.21)
ANNUAL INCOME QUINTILE (FAMILY %)			
· **LOWEST**	20.84	19.99	1.14 (0.82-1.42)
· **2ND**	19.51	24.6	1.19 (0.94-1.52)
· **3RD**	19.22	21.64	-
· **4TH**	21.34	14.35	0.83 (0.65-1.05)
· **HIGHEST**	19.09	19.43	1.01 (0.81-1.26)
FAMILY HISTORY OF PSYCHATRIC DISORDER (%)	2.96	4.66	**1.84** (1.30-2.61)
CHILDHOOD PSYCHOPATHOLOGY (%)	6.28	12.06	**2.18** (1.69-2.79)
ADOLESCENT PSYCOPATHOLOGY (%)	5.31	10.99	**2.42** (1.86-3.14)
THREE OR MORE STRESSFUL LIFE EVENTS BY ADOLESENCE (%)	7.69	11.59	**1.55** (1.22-1.97)

Note: Emboldened metrics denote significant differences ($p < .05$). [a]: p-value report instead of odds ratio.

Aim 2. ***The cross-sectional association between child self-concept and adolescent psychotic experiences.***

Adolescent Self-Concept and Adolescent PEs**.** There was a strong relationship between adolescent self-concept and PEs (see Table 3.2). Almost 40% of participants with PEs scored below the 14th percentile on self-concept in adolescence (13% of controls). Those who reported very low self-concept were six times more likely to have reported PEs. Additionally, those who reported above average to high self-concept were 2-3 times less likely to report PEs. Similar to childhood, the results indicated a dose-response relationship such that every unit increase self-concept was associated with a 1.08 reduced odds of adolescent PE (see Table 3.2).

Aim 3 and 4. Change in self-concept (total and subscale scores) between childhood and adolescence and risk of adolescent psychotic experiences.

A stratified investigation was conducted to investigate if an increase or decrease in self-concept between age 9 and age 13 was associated with risk of PEs at age 13. Participants were stratified into three groups using self-concept data from their wave one (age 9) reports: Low self-concept, Average self-concept and High self-concept. We investigated if changes in self-concept (improvement or a decline) between childhood and adolescence are associated with risk of adolescent PEs.

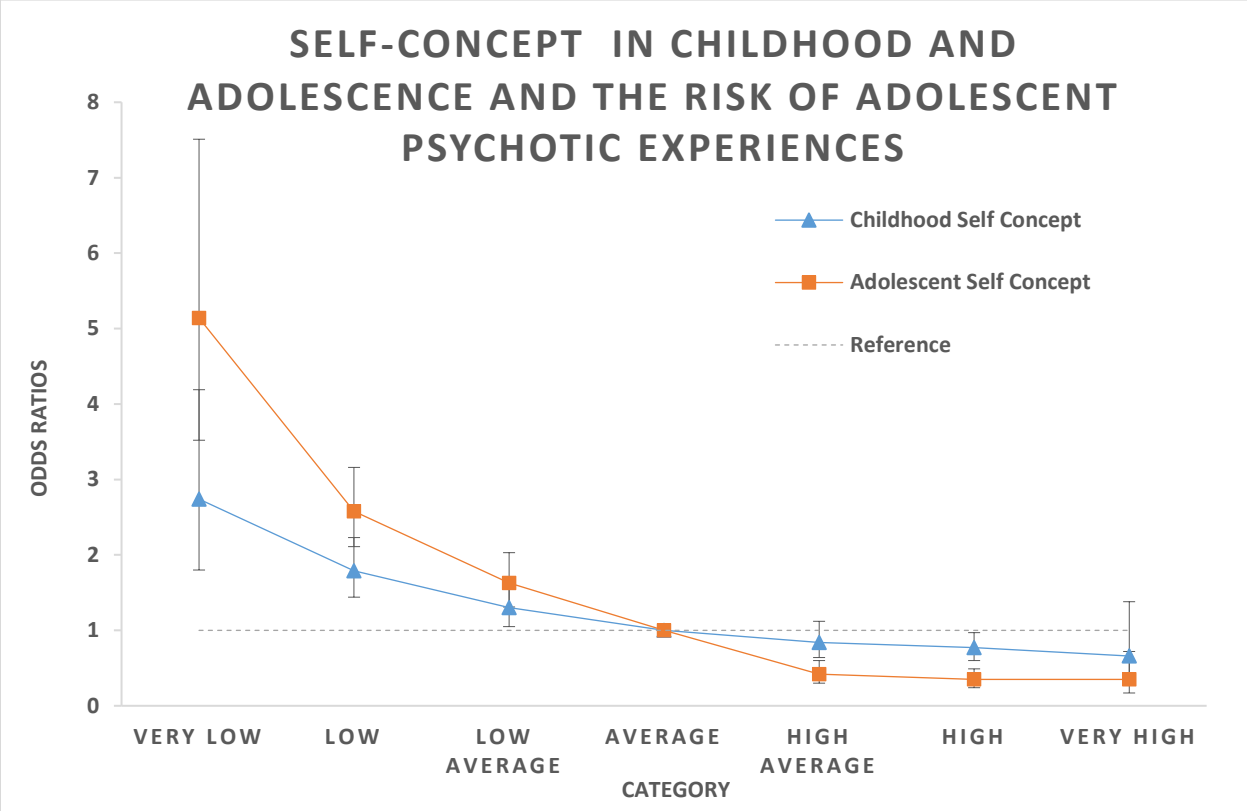
Low Self-concept reported in Childhood. In total, 42% of the participants with low self-concept scores at age 9 also reported low self-concept scores at age 13 (see Table 3.3). Twenty-seven percent of those with persistently low self-concept had PEs at 13. Forty-two percent of those with low childhood self-concept improved to average by adolescence while 16% improved to high. Improvement in self-concept was associated with an incremental reduction in the likelihood of PEs, such that those whose self-concept improved to within the average range by adolescence were 2.3 time less likely to report PEs than those who had persistently low self-concept. Those whose self-concept improved to within the high range were 5.5 time less likely to report PEs than those who had persistently low self-concept. Improvements in all subscale categories with the exception of ‘Physical Appearance and Attributes” were associated with reduction in a risk of PEs (see Table 3.4).

Table 3.2. The relationship between childhood (Wave 1) and adolescent (Wave 2) self-concept and PEs.

	CHILDHOOD SELF CONCEPT AND ADOLESCENT PES (AGE 9)				**ADOLESCENT SELF CONCEPT IN ADOLESENCE PES (AGE 13)**				
TOTAL SELF CONCEPT SCORES CATEGORY (%)	Controls	Children who report PEs in adolescence	Unadjusted Odd Ratio (CI)	Adjust 1 Odds Ratio (CI)	Controls	Participants reporting PEs	Unadjusted Odd Ratio (CI)	Adjust 2 Odds Ratio (CI)	Adjust 3 Odds Ratio (CI)
VERY LOW (≤2ND %ILE)	2.18	4.69	**3.10 (2.05-4.68)**	**2.74 (1.80-4.19)**	1.31	7.95	**6.62 (4.65-9.42)**	**5.96 (4.15-8.57)**	**5.14 (3.52-7.51)**
LOW (3ND-14TH %ILE)	11.05	21.90	**1.92 (1.55-2.38)**	**1.79 (1.44-2.23)**	11.34	29.58	**2.84 (2.36-3.44)**	**2.71 (2.24-3.28)**	**2.58 (2.11-3.16)**
LOW AVERAGE (15TH-28TH %ILE)	15.62	16.65	**1.34 (1.09-1.66)**	**1.30 (1.05-1.62)**	12.74	17.77	**1.71 (1.39-2.11)**	**1.65 (1.34-2.04)**	**1.63 (1.31-2.03)**
AVERAGE (29TH-71TH %ILE)	43.38	37.64	Ref	Ref	43.77	34.29	Ref	Ref	Ref
ABOVE AVERAGE (72TH-83TH %ILE)	10.16	8.46	0.84 (0.63-1.10)	0.84 (0.64-1.12)	12.74	5.34	**0.41 (0.29-0.57)**	**0.41 (0.29-0.58)**	**0.42 (0.30-0.60)**
HIGH (84TH-97TH %ILE)	16.02	9.04	**0.75 (0.59-0.95)**	**0.77 (0.60-0.97)**	14.69	4.08	**0.35 (0.25-0.49)**	**0.35 (0.25-0.49)**	**0.35 (0.24-0.49)**
VERY HIGH (≥98TH %ILE)	1.60	1.61	0.60 (0.29-1.25)	0.66 (0.32-1.38)	3.41	0.99	**0.31 (0.15-0.63)**	**0.32 (0.15-0.66)**	**0.35 (0.17-0.72)**
CONTINIOUS VARIALBE (X̄, SD)	46.78 (8.39)	43.43 (10.02)	**0.96 (0.95-0.97)**	**0.96 (0.95-0.97)**	48.51 (7.81)	41.65 (10.19)	**0.92 (0.91-0.93)**	**0.92 (0.91-0.93)**	**0.92 (0.91-0.93)**

Note: Emboldened metrics denote significant differences (p <.05).
Adjust 1: Adjusting for age, gender, nationality, cultural background and urbanicity, family history of mental disorder, child psychopathology and exposure to three or more stressful life events.
Adjust 2: Adjusting for age, gender, nationality, cultural background, urbanicity, family history of mental disorder, child and adolescent psychopathology, exposure to three or more stressful life events.
Adjust 3: Adjusting for age, gender, nationality, cultural background, urbanicity, family history of mental disorder, child and adolescent psychopathology, exposure to three or more stressful life events and childhood self-concept.

Figure 3.1. Odds-ratios for the relationship between the self-concept and PEs.



Note. Childhood self-concept score are adjusted for age, gender, nationality, cultural background and urbanicity, family history of mental disorder, child psychopathology and exposure to three or more stressful life events. Adolescent self-concept score are adjusted for age, gender, nationality, cultural background, urbanicity, family history of mental disorder, child and adolescent psychopathology, exposure to three or more stressful life events and childhood self-concept.

Average Self-concept reported in Childhood. Of those who reported average self-concept at in childhood, 45% continued to score in the average self-concept category in adolescence. Self-concept worsened in 28% of participants and 24% of those whose self-concept worsened report PEs. Children whose self-concept scores declined from average to low by adolescence were significantly more likely to report PEs (see Table 3.3). Scoring in a lower category on 'Happiness and Satisfaction', 'Behavioural Adjustment', 'Freedom from Anxiety' and 'Popularity' sub-scales were associated with an increased risk of PEs (see Table 3.4). Self-concept improved in 27% of participants and children whose self-concept improved were significantly less likely to have PEs. Specifically, improvements

in ‘Behavioural Adjustment’ and ‘Freedom from Anxiety’ subscales significantly reduced the odds of PEs.

Table 3.3. The Prevalence and odds ratios of the change in self-concept score by adolescence for children who reported low, average and high self-concept in childhood.

CHANGE IN SELF-CONCEPT BY ADOLESCENCE	CONTROLS %	PES %	ODDS RATIO (CI)	ADJUST 1 ODDS RATIO (CI)
LOW SELF-CONCEPT IN CHILDHOOD	***N = 1,659***	***N = 367***		
REMAINED LOW	37.86	62.93	Ref	Ref
IMPROVED AVERAGE	44.26	31.72	**0.43 (0.33-0.55)**	**0.47 (0.36-0.61)**
IMPROVED TO HIGH	17.88	5.35	**0.18 (0.11-0.29)**	**0.22 (0.13-0.37)**
AVERAGE SELF CONCEPT IN CHILDHOOD	**N = 2,498**	**N= 322**		
DROPPED TO LOW	24.07	57.86	**3.74 (2.87-4.87)**	**3.67 (2.80-4.80)**
REMAINED AVERAGE	46.65	29.98	Ref	Ref
IMPROVED TO HIGH	29.28	12.16	**0.64 (0.44-0.94)**	**0.65 (0.44-0.96)**
HIGH SELF CONCEPT IN CHILDHOOD	**N= 1,604**	**N= 164**		
DROPPED TO LOW	13.63	33.47	**5.72 (3.62-9.04)**	**5.95 (3.72-9.53)**
DROPPED TO AVERAGE	39.58	46.47	**2.73 (1.79-4.17)**	**2.74 (1.78-4.22)**
REMAINED HIGH	46.79	20.06	Ref	Ref

Note: Emboldened metrics denote significant differences (p <.05).
Adjustment 1: Adjusting for age, gender, nationality, cultural background, urbanicity, family history of mental disorder, child and adolescent psychopathology, exposure to three or more stressful life events.

High Self-concept reported Childhood. In total, 44% of those with high self-concept in childhood continued to report high self-concept in adolescence. Self-concept declined from high to average in 40% of participants and decline to low in 15% of participants. Twenty percent of participants whose self-concept declined from high to low reported PEs. Those participants whose self-concept scores worsened between childhood and

adolescence were significantly more-likely to report PEs in adolescence such that there was an incremental increase in the odds of PEs with each drop in self-concept category (see Table 3.3). Adjusting for confounders had a limited effect on these values. Declines in ‘Happiness and Satisfaction’, ‘Behavioural Adjustment’, ‘Intelligence and School Status’ and ‘Popularity’ sub-scales were associated with an increased risk of PEs (see Table 3.4).

Table 3.4. Odds ratios of the change in self-concept subscale category by adolescence for children who reported low, average and high scores in childhood.

CHANGE IN SELF-CONCEPT BY ADOLESCENCE		HAPPINESS OR (CI)	POPULARITY OR (CI)	ANXIETY OR (CI)	BEHAVIOUR OR (CI)	INTELLECT OR (CI)	PHYSICAL OR (CI)
LOW IN CHILDHOOD							
ADOLESCENT CATEGORY	**Low**	Ref	Ref	Ref	Ref	Ref	Ref
	Average	**0.61 (0.43-0.87)**	**0.59 (0.43-0.80)**	**0.72 (0.52-0.99)**	**0.52 (0.38-0.72)**	**0.72 (0.53-0.97)**	**1.77 (1.24-2.52)**
	High	**0.63 (0.42-0.94)**	**0.50 (0.28-0.88)**	**0.30 (0.18-0.50)**	**0.30 (0.21-0.43)**	1.00 (0.62-1.60)	**2.31 (1.32-4.01)**
AVERAGE IN CHILDHOOD							
ADOLESCENT CATEGORY	**Low**	**2.02 (1.33-3.29)**	**1.54 (1.17-2.02)**	**1.93 (1.38-2.72)**	**1.59 (1.15-2.21)**	0.94 (0.68-1.28)	**0.56 (0.39-0.80)**
	Average	Ref	Ref	Ref	Ref	Ref	Ref
	High	1.54 (0.96-2.47)	0.84 (0.59-1.26)	**0.64 (0.43-0.95)**	**0.62 (0.44-0.87)**	0.98 (0.67-1.43)	1.30 (0.80-2.01)
HIGH IN CHILDHOOD							
ADOLESCENT CATEGORY	**Low**	1.31 (0.87-1.97)	**3.27 (1.72-6.22)**	1.44 (0.88-2.37)	**1.86 (1.18-2.93)**	**3.10 (1.70-5.64)**	0.61 (0.31-1.22)
	Average	**1.61 (1.13-2.29)**	1.53 (0.88-2.63)	1.22 (0.84-1.78)	1.18 (0.74-1.89)	**1.94 (1.18-3.20)**	0.91 (0.57-1.44)
	High	Ref	Ref	Ref	Ref	Ref	Ref

Note: Emboldened metrics denote significant differences (p <.05). Subscale titles: Happiness = Happiness and Satisfaction; Popularity = Popularity; Anxiety = Freedom from Anxiety; Behaviour = Behavioural Adjustment; Intellect = Intelligence and School Status; and Physical = Physical Appearance and Attributes;
Adjustment 1: Adjusting for age, gender, nationality, cultural background, urbanicity, family history of mental disorder, child and adolescent psychopathology, exposure to three or more stressful life events and all other subscales categories during adolescence.

3.4 Discussion

In a large nationally representative community sample, we demonstrated, for the first time to our knowledge, that there is a strong relationship between changes in self-concept between childhood and adolescence and risk of adolescent PEs. Self-concept in childhood and adolescence was associated with adolescent PEs and this relationship was beyond what could be explained by differences in the confounding variables. A change in self-concept between childhood and adolescence was robustly associated with risk of PEs, such that as self-concept declined the risk of PEs increased and as self-concept improved the risk of PEs decreased. These findings were evident in participants with low, average and high self-concept and were also evident across the different self-concept sub-scales.

Our results complement findings from other adolescent and adult general population studies, which indicate that PEs are associated with low self-concept (Dolphin et al., 2015; Krabbendam et al., 2002). Importantly, our results suggest that a proportion of those who report PEs in adolescence already have poorer self-concept in childhood and are potentially identifiable. For example, within this study 26% of those who report PE in adolescence had reported low or very low self-concept in childhood (13% in controls) and almost a third of those who persistently report low self-concept had PEs in adolescence. Persistent psychopathology has also been shown to increased likelihood of PEs (Lancefield, Raudino, Downs, & Laurens, 2016) and our results suggest that early psychosocial characteristic may also be useful in identifying those at risk of PEs and those who require intervention.

Importantly, our ‘change’ analysis supports the hypothesis that intervening in self-concept or maintaining high self-concept could reduce the incidence of PEs in adolescence. Meta-analysis has previously demonstrated that intervention in self-concept improves outcomes in common mental disorders (Haney & Durlak, 1998). Similar interventions have been effective in reducing positive clinical symptoms in patients with psychosis (Hall & Tarrier, 2003; Lecomte et al., 1999). Our results suggest that interventions aimed at improving self-concept may also have positive effects on the incidence of adolescent PEs in the general population. This effect can be achieved by

elevating any sub-components of self-concept. Further clinical research is necessary to directly test this hypothesis.

While it remains to be tested, it is plausible that the relationship between self-concept and PEs is in fact bi-directional, as has been previously demonstrated with non-psychotic psychiatric symptoms (Markowitz, 2001; Rosenberg, Schooler, & Schoenbach, 1989). It is conceivable there is a dynamic interplay between self-concept and any form of psychopathology, such that an improvement in how one thinks about oneself will be associated with a decline in psychopathology (psychotic or non-psychotic) and, conversely, an increase in psychopathology will be associated with a decline in how one thinks about oneself. Unfortunately, PEs were not investigated at the first wave of the study and, therefore, we cannot investigate the bi-directional relationship between PEs and self-concept. Future research should investigate the directionality of this relationship.

These results suggest that intervening in self-concept in childhood may have the potential to decrease the incidence of PEs in adolescence. Programmes focusing on improving and maintaining high self-concept would be a useful, broad-spectrum approach to improving well-being and symptomology in the general population (Mann et al., 2004). Such broad-spectrum interventions in childhood presents a real opportunity to investigate strategies in preventative psychiatry at the sub-clinical level before a severe mental disorder becomes embedded. Additionally, such interventions would aid in the early identification of those who will require support from psychiatric services. This may be particularly important for high-risk groups such as those reporting psychotic experiences as they are vulnerable to a wide range of adverse outcomes (Cederlof et al., 2017; Kaymaz et al., 2012; McGrath et al., 2016).

In addition to targeting self-concept itself, preventative psychiatry may also consider targeting the antecedents of low self-concept. It is plausible that self-concept in fact mediates the relationship between certain exposures such as childhood trauma or victimisation and PEs. For example, it has been reported that the clarity of one's self-concept mediated the relationship between psychosis group membership and total

childhood trauma score and specific individual traumas such as emotional and physical abuse (Evans et al., 2015). Such an investigation has yet to be conducted in a non-clinical sample.

While low self-concept has been associated with increased risk psychiatric outcomes, there is little research investigating the origins of low self-concept, particularly in childhood (Orth & Robins, 2014). Both traumatic experiences and attachment processes have been proposed to play a role in the formation of self-concept (Harter, 2012), however there is a little quantitative evidence directly investigating these claims and the evidence to date is inconsistent (Orth et al., 2010). Further research is necessary to fully establish the antecedents of low self-concept in childhood.

3.4.1 Strengths and Limitations

There were several strengths to the study: this is a large scale, nationally representative longitudinal cohort of children. There was an excellent sample retention rate (88%) and the reweighting of the data at age 13 ensured representation, therefore we are confident that there was minimal bias due to loss to follow-up. The Piers Harris II is a widely used validated measure of self-concept (Piers & Herzberg, 2002). Psychotic experiences were measured using a self-report instrument that was explicitly validated within this age range (Kelleher et al., 2011). However, self-report questionnaire measures of psychotic experiences are known to have a greater susceptibility to false positives then interview (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). One limitation is that PEs were not assessed at the first wave of the study and we were not able to investigate for a bi-directional relationship between self-concept and psychotic experiences.

3.4.2 Conclusion

There is a strong relationship between self-concept and psychotic experiences. This relationship is such that improvements in self-concept reduces the likelihood of adolescent PEs and decline in self-concept increases the likelihood of adolescent PEs. Self-concept and the origins of low self-concept may be a useful target for preventative psychiatry and these results suggest that intervening in self-concept between childhood

and adolescence may to reduce the incidence of PEs in adolescence. Future research should formally test the effect of self-concept interventions on PEs.

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Key Points:

What's known: Psychotic experiences (PEs) are commonly reported in childhood, associated with a wide range of adverse outcomes and few targets aimed at preventing these phenomena have been identified. One potential target is self-concept (a set of attitudes reflecting description and evaluation of one's own behavior and attitudes).

What's new: We demonstrate that improvements in self-concept reduces the odds of adolescent PEs and decline in self-concept increases the odds of adolescent PEs. This effect was robust across the self-concept sub-scales.

What's clinically relevant: Interventions targeting self-concept or the origins of low self-concept in childhood are likely to reduce the incidence of PEs in adolescence.

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SECTION II

OUTCOMES ASSOCIATED WITH PSYCHOTIC EXPERIENCES

Chapter 4

Study III - Childhood and Adolescent Psychotic Experiences and Risk of Mental Disorder: A Systematic Review and Meta-Analysis.

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search, data extraction and statistical analysis. He was the first and corresponding author on the published manuscript.

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

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Abstract

Background: Psychotic experiences (PEs) are common in childhood and adolescence and their association with mental disorders is well-established. We aimed to conduct a quantitative synthesis the literature on the relationship between childhood and adolescent PEs and i) any mental disorder; and ii) specific categories of mental disorder, while stratifying by study design.

Method: Three electronic databases (Pubmed, PsycInfo and Embase) were searched from inception to August-2017 for all the published literature on childhood and adolescent PEs and mental disorder (outcome) in non-help-seeking community samples. Study quality was assessed using a recognised quality assessment tool for observational studies. Two authors conducted independent data extraction. Pooled odds-ratios were calculated for mental disorders using random-effects models. Additional analyses were conducted investigating different categories of mental disorder while stratifying by study design.

Results: 14 studies from 13 community samples (n=29,517) were identified with 9.8% of participants reporting PEs. PEs were associated with a three-fold increased risk of any mental disorder (OR: 3.08, CI: 2.26-4.21,k=12). PEs were associated with four-fold increase risk of psychotic disorder (OR: 3.96, CI: 2.03-7.73, population-attributable-fraction: 23.2%, k=5). In addition, PEs were associated with an increased risk of affective disorders, anxiety disorders, behavioural disorders and substance-use disorders. Few longitudinal studies have investigated childhood and adolescent PEs and subsequent non-psychotic disorders which limited a meaningful synthesis and interpretation of these results.

Conclusion: This meta-analysis confirms that PEs are prevalent in childhood and adolescent community samples and are associated with a variety of mental disorders beyond psychotic disorders. Further longitudinal research is necessary to fully determine the longitudinal relationship between PEs and non-psychotic disorders.

4.1 Introduction

Research over the past two decades has highlighted that psychotic experiences (PEs) are far more prevalent in the population than psychotic disorders (Linscott and van Os, 2013). While approximately 5% of adults report PE phenomena (Linscott and van Os, 2013, McGrath et al., 2015, Maijer et al., 2018), the prevalence is higher in children and adolescents, with estimates ranging between 8-17% (Kelleher et al., 2012a, Maijer et al., 2018).

Initial research on the clinical significance of PEs focused on their association with future risk of psychotic disorders (Poulton et al., 2000, Zammit et al., 2013, Dominguez et al., 2011). Subsequent research found that individuals with PEs were also at risk of a range of non-psychotic disorders such as affective, anxiety and behavioural disorders (Kelleher et al., 2012b, McGrath et al., 2016, Calkins et al., 2014, Jeppesen et al., 2015), with findings identifying an association between PEs and both concurrent (Calkins et al., 2014) and later mental disorders (Dhossche et al., 2002). An existing meta-analysis confirmed the association between PEs and both psychotic and non-psychotic disorders (Kaymaz et al., 2012). However, that analysis was primarily focused on adult samples and did not specifically examine the association among children and adolescents.

Given that the prevalence of PEs in childhood is notably higher than adulthood (Kelleher et al., 2012a) and most individuals with lifetime PEs have their first onset by early adulthood (McGrath et al., 2016), clarifying if childhood and adolescent PEs are also associated with an increased risk of mental disorders (both psychotic and non-psychotic disorders) is therefore an important goal. With childhood and adolescent PEs being considered as an early pluripotent marker for subsequent psychiatric vulnerability (McGorry et al., 2018), it is also important to clarify any differences between cross-sectional and longitudinal relationships between PEs and mental disorders.

Specifically, the aims of this systematic review and meta-analysis are (i) to assess the association between childhood and adolescent PEs and mental disorder (any mental

disorder, any non-psychotic disorder and sub-categories of mental disorder) in non-help seeking individuals from the general population (2) to assess the effect of study design (cross-sectional or longitudinal design) on the relationship between childhood and adolescent PEs and mental disorders.

4.2. Method

4.2.1 Search Strategy

A systematic review was conducted investigating all of the published literature (from inception to August 2017) pertaining to childhood and adolescent PEs (≤ 18 years) and mental disorder in non-help-seeking community samples. Searches were carried out in August 2017 by CH using three electronic databases PUBMED, EMBASE and PsychINFO. A search strategy was devised with the assistance of a librarian. The search terms used were General population OR normal population OR normal healthy population OR healthy individuals OR community sample OR child and adolescent AND mental disorder OR psychiatric disorder OR psychopathology OR mental illness OR DSM* OR ICD* AND psychotic experience OR psychotic symptoms OR psychotic-like experiences OR psychotic-like symptoms OR auditory hallucinations OR hallucinat* OR delusion*. Additionally, the reference lists of all selected papers were searched for potential study inclusion.

4.2.2 Inclusion Criteria

Only studies published in a peer reviewed journal and written in English were included in the review.

Sample. Only non-help-seeking samples of children and/or adolescents were used in this investigation. We included samples if the majority of participants were aged 18 years or younger at the first enquiry of PEs.

Exposure. For the purpose of this investigation, childhood and adolescent PEs were considered as the exposure. Data on PEs reported by both questionnaire and interview format were included. Within the literature, PEs are reported either dichotomously (i.e.

as the presence or absence of any PE phenomena) or by sub-types (e.g. auditory hallucinations or paranoia). All studies that reported PEs dichotomously were included in this investigation. Where PEs were not reported in this way, and only data on sub-types of PEs were reported, only studies that reported on auditory hallucinations or hallucinations were included. The decision to include these two categories of PE as valid outcomes for this investigation was based on evidence that endorsement of auditory hallucinations on questionnaires has demonstrated predictive validity for the presence of PEs when subsequently assessed by clinical interview (Kelleher et al, 2011; Laurens et al, 2012; and Grauö et al, 2016). Where different 'strengths' or 'levels' of PEs were reported (e.g., 'weak' and 'strong' PEs or 'definite' and 'possible' PEs) only the strong or definite category was used to estimate the relationship with mental disorders (weak and possible PEs were combined with controls to improve community sample representation). If a study examined multiple reporting of PEs (for example participants were grouped into whether they had reported PEs never, once, twice or three times), these groups were combined (any PEs ever). Information on the criteria used for PEs in each selected study can be found on Table 4.1.

Outcome. For inclusion in this investigation, participants must have met criteria for a mental disorder in accordance with Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) standards (any edition). Diagnosed mental disorders were grouped into any mental disorder, any non-psychotic disorder and five specific categories of disorder: psychotic disorder, affective disorder (mania or depression), anxiety disorder (generalised anxiety, panic, obsessive-compulsive and phobias), behavioural disorder (conduct, oppositional defiant or attention-deficit/hyperactivity disorder) and substance use disorder (any).

4.2.3 Exclusion Criteria

Sample. Help-seeking, high-risk samples were excluded from the investigation. This was done to increase the representativeness of the pooled estimate relative to the general population. Inclusion of help-seeking samples is likely to bias the pooled estimates. Additionally, case-control studies were excluded from the investigation. While

pooled point estimates based on case-control studies are likely to be similar to cohort studies, the confidence intervals for these estimates are narrower than for cohort studies as the number of individuals within the exposure group are inflated relative to the general population. For this reason, case-control studies were excluded.

Non-Diagnostic Assessment of Psychopathology and Temporality. Any study that did not use ICD or DSM diagnostic criteria to determine rates of mental disorder was excluded from the review and meta-analysis. Additionally, as PEs were considered our exposure of interest and mental disorder our outcome, for cross-sectional studies PEs and mental disorder had to be assessed contemporaneously and for longitudinal studies PEs had to precede the assessment of mental disorder. If the temporal relationship between PEs and mental disorder explicitly stated that mental disorder preceded PEs, the study was excluded.

4.2.4 Study Selection and Data Extraction

Literature search was conducted by CH in August 2017 with studies reviewed by CH and RB. An assessment of study quality was conducted using the National Heart, Lung, and Blood Institute quality assessment tool for observational cohort and cross-sectional studies (see Supplement A, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The data extraction was conducted by two reviewers (CH and ND), with an initial reviewer consistency of 87.5%. Data extraction discrepancies between the two reviewers were resolved via joint discussion with a third reviewer (RB). We report the location of where the data was extracted from in each study in Supplement B.

Metrics. Unadjusted odds ratios were used when available. When odd ratios were not present but were calculable based on the information presented in the study (number of individuals were available) odds ratios were calculated. If the unadjusted odds ratios were not calculable or were not available within the text, adjusted odds ratios were used and the confounders documented in Table 4.1. If the study presented alternative metrics (Hazard Ratio or Risk ratio) relevant authors were contacted to request the information to calculate an odds ratios.

Disorder Grouping and Sub-categories. Mental disorders were grouped into two overall categories: (i) any mental disorder and (ii) any non-psychotic disorder. We also investigated five sub-categories of mental disorder: affective, anxiety, psychotic, behavioural and substance-use disorder. Affective disorders included both depressive disorders and mania. Anxiety disorders included generalised anxiety, separation anxiety, specific phobia, social phobia, panic, agoraphobia, obsessive compulsive disorder and post-traumatic stress disorder (PTSD). As the majority of studies reviewed use DSM-IV diagnostic criteria, PTSD was included under anxiety disorders classifications. Psychotic disorders included schizophrenia, schizophreniform disorder, non-affective psychosis and psychotic disorders not otherwise specified. Behavioural disorders included oppositional defiant, conduct and attention deficit/hyperactivity disorders.

When not explicitly reported in the text the 'any mental disorder' category and the 'any non-psychotic mental disorder' odds ratios were calculated by pooling the odds ratios of the disorders presented in the study. This was calculated by averaging the log odds for each disorder (i.e. logodds disorder X + the logodds disorder Y/ No of disorders) and averaging the standard error for each disorder (i.e. standard error of disorder X + standard error of disorder Y/ No of disorders). We used these metrics to calculate the odds ratio and 95% confidence interval for the 'any mental disorder' category for that study. We also used this approach if sub-categories of a disorder group were reported (i.e. reported on different types of anxiety disorders such as generalised anxiety disorder and panic disorder). This method reduced the likelihood of artificially narrowing the confidence intervals.

4.2.5 Data Analysis

All data analyses were conducted using Stata Version 15 (StataCorp, 2017).

Effects Model. We used random effects models as we expected heterogeneity in the distribution of the ORs. Heterogeneity was statically measured using the I^2 metric. Heterogeneity was expected for many reasons including differences in: the temporal relationship between PEs and mental disorders (concurrent or subsequent), the

methodology used to investigate PEs (questionnaire versus interview), the age of the participants, the manner of selection into each study and differences in diagnostic criteria. Model selection based on the heterogeneity estimates have been deemed inappropriate as the assumptions of the fixed and random models differ (Borenstein et al, 2010).

Analysis 1. Firstly, we investigated the association between childhood and adolescent PEs and both any mental disorder and any non-psychotic disorder. Random effects pooled odds ratios are reported with estimates of heterogeneity across studies. Funnel plots (see Supplement C and D) and the Egger regression test for publication asymmetry (Egger et al, 1997) were examined and trim and fill (Duval & Tweedie, 2000) adjustments were applied. Secondly, we stratified the results by study design to examine the effects design had on the relationship between PEs and mental disorder (any and any non-psychotic) separately. Finally, post-hoc meta-regressions were conducted on several variables that could explain the between-study variance in the relationship between PEs and any mental disorder (this was not conducted for any non-psychotic disorder as too few studies were available). The independent variables in these univariate regressions were PEs assessment type (interview or questionnaire), study design (cross-sectional or longitudinal), population size and follow-up time (longitudinal studies only). Bubble plots and non-descriptive results of this analysis are presented in Supplement E.

Analysis 2. In the second analysis we investigated the association between childhood and adolescent PEs with each sub-category of mental disorder: psychotic disorders, affective disorders, anxiety disorders, behavioural disorders and substance-use disorders. Similar to Analysis 1, we report the random effects pooled odds ratios and heterogeneity based on I^2. Again, we stratify by study design to investigate the relationship between PEs and the sub-categories of each mental disorder in separate cross-sectional and longitudinal analyses. Finally, for longitudinal studies we report the population attributable fraction (PAF) where this was calculable (psychotic disorders only).

4.3 Results

Study Selection

Based on the search terms, we extracted 3 092 studies from the three databases. 2 877 remained after removing duplicates. The titles and abstracts of all 2 877 were reviewed for relevance, which resulted in the identification of 186 for full text screening. Of those, 117 were excluded because the studies did not use a child or adolescent community sample. Based on the inclusion and exclusion criteria, 14 of the remaining 69 studies met criteria for inclusion in the review, 13 of which also met inclusion criteria for the meta-analysis. The specific reasons for exclusion are given in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (Figure 4.1).

4.3.1 Search Yield

The search yielded 14 studies from 13 (n=29 517) different community samples (Clemmensen et al., 2016, Jeppesen et al., 2015, Scott et al., 2009, Calkins et al., 2014, Kelleher et al., 2012b, Adriaanse et al., 2015, Poulton et al., 2000, Dhossche et al., 2002, Fisher et al., 2013, Dominguez et al., 2011, Bechtold et al., 2016, Zammit et al., 2013, Cederlof et al., 2017, McGrath et al., 2010). This included 6 cross-sectional studies from 6 different community samples and 8 longitudinal reports from 7 different community samples (average follow-up time of 10.5 years, range: 0.12-27 years). The characteristics of each study are presented in Table 4.1. Two community samples were represented in more than one investigation (the Cophenhagen and the Dunedin cohorts). The two studies presenting data from the Cophenhagen cohort examined different outcomes (see Table 4.1). We found an overlap between the outcomes in the two Dunedin cohort studies selected for review: Poulton et al (2000) investigated the longitudinal relationship between PEs and any disorder, non-psychotic disorder, psychotic disorder, affective disorder and anxiety disorder while Fisher et al (2013) investigated the longitudinal relationship between PEs and substance use disorder.

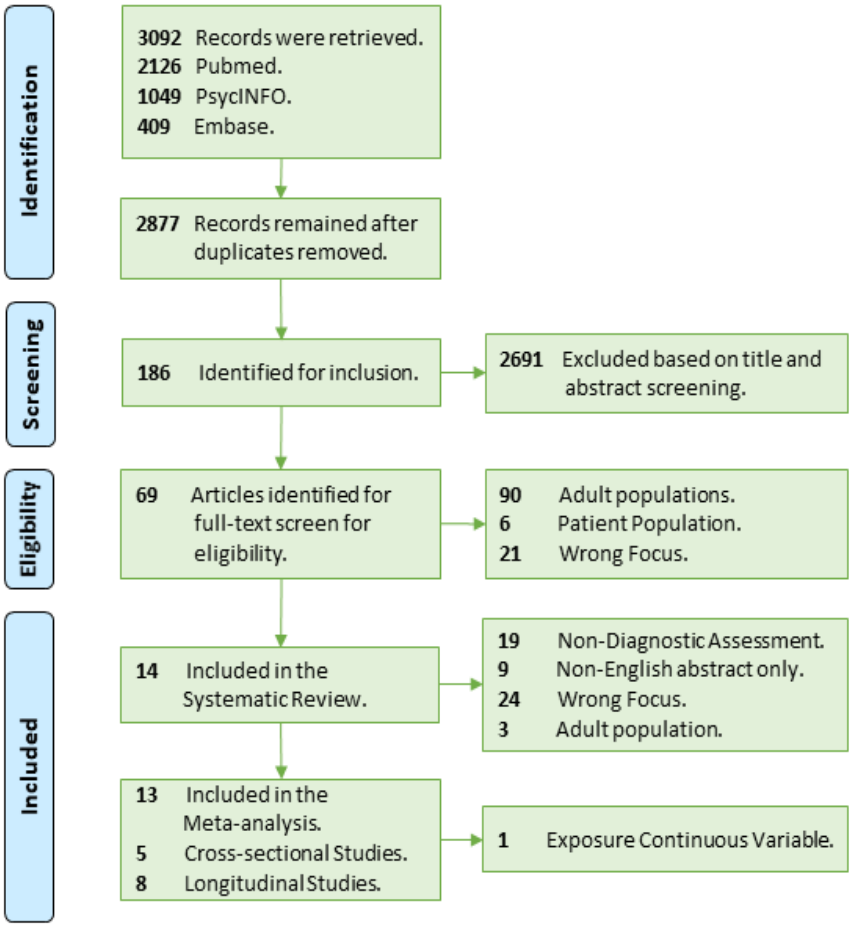
4.3.2 Prevalence of Psychotic Experiences

Data from 12 community samples (n=29 365) were used to calculate the prevalence of PEs (prevalence estimates could not be calculated from Adriaanse et al., 2015). The

point prevalence (defined as the prevalence at time point 1 in all longitudinal studies) of children and adolescents reporting PEs was 9.83% (n=2 886). The prevalence in cross-sectional studies was 16.11% (k=5; n=1 315) and the prevalence reported in longitudinal studies was 7.41% (k=7; n=1 571).

There was a minor discrepancy in the prevalence of PEs between the methods of reporting. In questionnaire-based studies the pooled prevalence of PEs was 11.83% (n=912; k=5). In interview-based studies the pooled prevalence was 9.12% (n=1 974; k=8).

Figure 4.1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Flow Diagram for Study inclusion



Multiple Reports of PEs

Two longitudinal studies reported PEs at multiple time points prior to the assessment of mental disorder (Dominguez et al., 2011, Bechtold et al., 2016). As so few studies (k=2) reported on PEs at multiple time points, statistical analyses were not carried out to investigate the relationship between persistent PEs and mental disorders. Both of these studies investigated the relationship between PEs and subsequent psychotic disorder and both indicated a greater risk in those who repeatedly reported PEs.

4.3.2 Meta-analysis

Analysis 1: PEs and any Mental Disorder and any Non-psychotic Disorder.

Twelve of the 13 samples were used to investigate the relationship between child and adolescent PEs and mental disorder. Adriaanse et al, (2015) was not included in this analysis because PEs were measured as continuous variable in the study. We found that PEs were associated with a 3-fold increased odds of any mental disorder (OR: 3.08, CI: 2.26-4.21, k=12, see Figure 4.2). When the investigation was narrowed to any non-psychotic disorder, those who report PEs had a 2.8-fold increase in the odds of meeting criteria for a mental disorder than their peers (OR: 2.82, CI: 1.86-4.28, k=8, see Figure 4.3).

Visual assessment of the funnel plots and Egger's regression test did not suggest an asymmetry in the published literature for any mental disorder or any non-psychotic disorder (any mental disorder: t=0.66, p=0.526, see Supplement C; and any non-psychotic disorder: t=0.98, p=0.364, see Supplement D). Statistical adjustment for one potentially missing study using a trim and fill method somewhat adjusted the odd ratio for any non-psychotic disorder in those with PEs (adjusted OR: 2.51, CI: 1.60-3.92, p <0.001). Significant between-study heterogeneity was evident for the relationship between PEs and both any mental disorder (I^2=58.7, p=0.005) and any non-psychotic disorder (I^2=54.5, p=0.031).

Table 4.1. Descriptive Summary of Studies Included in the Investigation

Author	Title	Population (N)	PE Assessment Type, PE criteria used, Age Range and Prevalence (%)	Mental Disorder Assessment Instrument, Diagnostic Criteria, Diagnosis Available and Age at Outcome (Longitudinal only)	Analysed Outcomes	Metrics and adjustment
Cross-sectional						
Clemmensen et al., 2016	Psychotic experiences and hyper-theory-of-mind in preadolescence–a birth cohort study	Copenhagen Child Cohort (n=1614)	K-SADS; PE Group; Age Range: 11-12; (10.5%)	DAWBA DSM-IV Any Mental Disorder	Any Mental Disorder	Unadjusted odds ratio and 95% confidence interval used
Kelleher et al., 2012b	Clinicopathological significance of psychotic experiences on non-psychotic young people: evidence from four population based studies	Adolescent Brain Development (n=212) Challenging times (n=211);	K-SADS; PE Group; ABD: Age Range: 11-13; 22.6%; CT: Age Range: 13-16; 7%;	K-SADS DSM-IV Any Mental disorder; Affective Disorder; Behavioural Disorders Anxiety Disorders	Any Mental disorder; Any Non-psychotic Mental Disorder; Affective Disorder; Behavioural Disorders Anxiety Disorders	Unadjusted odds ratio and 95% confidence interval used
Jeppesen et al., 2015	Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence	Copenhagen Child Cohort (n=1632)	K-SADS; PE Group; Age Range: 11-12; (10.5%)	DAWBA DSM-IV Anxiety; Obsessive-Compulsive Disorder; Depression; Oppositional Deficient Disorder;	Any Non-psychotic Mental Disorder; Affective Disorder; Anxiety Disorder; Behavioural Disorder	Unadjusted odds ratio and 95% confidence interval used

				Conduct Disorder; Attention Deficit Hyper-Activity Disorder;		
Scott et al., 2009	The prevalence and correlates of hallucinations in Australian adolescents: Results from a national survey	Australian National Survey of Mental Health and Well-Being (n=1261)	YSR; Hallucinations (Auditory or Visual); Age Range: 13-18; (8.4%)	DIS-C DSM-IV Depressive Disorder; Conduct Disorder; Attention Deficit Hyper-Activity Disorder	Any Mental Disorder; Any Non-psychotic Mental Disorder; Affective Disorder; Behavioural Disorder	Unadjusted odds ratio and 95% confidence interval used
Calkins et al., 2014	The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neuro-developmental Cohort	Philadelphia Neurodevelo-pmental Cohort (n=4665)	GOASSESS, K-SADS; PE Group; Age Range: 11-21; (19.7%)	GOASSESS/K-SADS DSM-IV Depression; Mania; Generalised Anxiety; Separation Anxiety; Specific Phobia; Social Phobia; Panic; Agorphobia; Obsessive Compulsive; Post-traumatic stress; Attention Deficit; Oppositional Defiant; Conduct; Eating disorder	Any Mental Disorder; Any Non-psychotic Mental Disorder; Affective Disorder; Anxiety Disorder; Behavioural Disorder;	Unadjusted odds ratio and 95% confidence interval used
Adriaanse et al., 2015	School-based screening for psychiatric disorders in Moroccan-Dutch youth	Dutch-Moroccan Cohort (n=152)	K-SADS; PE Group; Age Range: 9-16;	K-SADS DSM-IV Any Mental Disorder	Any Mental Disorder; Any Non-psychotic Mental Disorder;	Unadjusted odds ratio and 95% confidence

			Continuous PE score reported (x̄=3.4; SD=± 3.4)			interval used
Longitudinal						
Poulton et al., 2000	Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder	Dunedin (n=761)	DISC-C; PE Group (Strong only); Age:11; (1.8%)	DIS DSM-IV Schizohphreniaform Disorder; Mania Disorder; Depressive Disorder; Anxiety Disorder. Age: 26 x̄ Follow up: 15 Years	Any Mental Disorder; Any Non-Psychotic Mental Disorder; Psychotic Disorder; Affective Disorder; Anxiety Disorder	Unadjusted odds ratio and 95% confidence interval used
Dhossche et al., 2002	Diagnostic outcome of self-reported hallucinations in a community sample of adolescents	Erasmas (n=779)	YSR; Hallucinations (Auditory); Age Range: 11-18; (5%)	CIDI DSM-IV Any Mental Disorder; Depressive Disorder; Substance-Use Disorder; Specific Phobia; PTSD; Social Phobia. Age Range: 19-26 x̄ Follow up: 9 Years	Any Mental Disorder; Any Non-Psychotic Mental Disorder; Substance-Use Disorder; Affective Disorder; Anxiety Disorder.	Unadjusted odds ratio and 95% confidence interval used
Fisher et al., 2013	Specificity of childhood psychotic symptoms for predicting schizophrenia by 38	Dunedin (n=776)	DISC-C; PE Group (Strong only); Age:11;	DIS DSM-III-R and DSM-IV	Substance-Use Disorder	Unadjusted odds ratio and 95% confidence

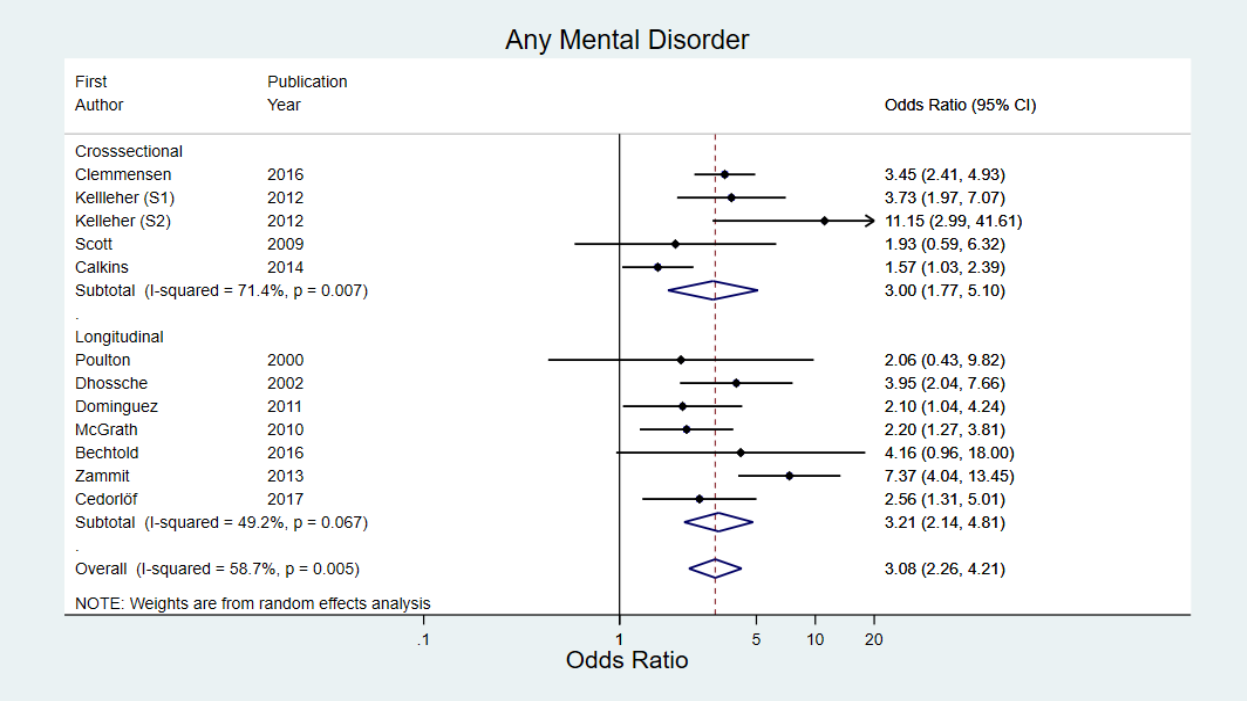
	years of age: a birth cohort study		(1.6%)	Schizophrenia; Persistent Anxiety; Persistent Depression; PTSD; Persistent Substance Dependence; Age: 38 x̄ Follow up: 27 Years		interval used
Dominguez et al., 2011	Evidence That Onset of Clinical Psychosis Is an Outcome of Progressively More Persistent Subclinical Psychotic Experiences: An 8-Year Cohort Study	Early Developmental Stages of Psychopathology (n=845)	SCL-90; PE Group; Age Range: 14-17; (21.18%)	DIA-X/M-CIDI DSM-IV and ICD-10 Psychotic Impairment x̄ Follow up: 4.9 Years from T2-T3	Any Mental Disorder; Psychotic Disorders	Unadjusted odds ratio and 95% confidence interval used
McGrath et al., 2010	Association Between Cannabis Use and Psychosis-Related Outcomes Using Sibling Pair Analysis in a Cohort of Young Adults	Mater-University Study of Pregnancy (n=3801)	YSR Hallucinations (Auditory or Visual) Age: 14 (15.8%)	CIDI ICD-10 Non-Affective Psychosis Age Range: 18-23 x̄ Follow up: 7 Years	Any Mental Disorder; Psychotic Disorder	Unadjusted odds ratio and 95% confidence interval used
Bechtold et al., 2016	Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms	Pittsburgh (n=908)	YSR; PE Group (Any sub-clinical); Age Range: 13-18;	DIS DSM-IV Psychotic Disorder Age Range: 26-36 x̄ Follow up: ~13 Years	Any Mental Disorder; Psychotic Disorder	Unadjusted odds ratio and 95% confidence interval used

			(24.1%)			
Zammit et al., 2013	Psychotic Experiences and Psychotic Disorders at Age 18in Relation to Psychotic Experiences at Age 12 in a Longitudinal Population-Based Cohort Study	Avon Longitudinal Study of Parents and Children (n=4724)	PLSI; PE Group (Definite); Age: 12 (4.9)	SCAN DSM-IV and ICD-10 Psychotic Disorder Age:18 x̄ Follow up: 6 Years	Any Mental Disorder; Psychotic Disorder	Unadjusted odds ratio and 95% confidence interval used
Cedorlöf et al., 2017	A longitudinal study of adolescent psychotic experiences and later development of substance use disorder and suicidal behaviour	Child and Adolescent Twin Study in Sweden (n=9242)	Seven Individual PE Items; Auditory Hallucinations; Age: 15 and 18 (5.6%)	National Patient Registry ICD-10 Substance Use Disorder; x̄ Follow up: 2.7 Years	Any Mental Disorder; Any Non-Psychotic Mental Disorder; Substance Disorder;	Hazard ratio presented. Authors contacted and unadjusted odds ratio used

Note: PE: Psychotic experiences; K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; DAWBA: Development and Well-Being Assessment; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; YSR: Youth Self-Report Questionnaire; DIS-C: Diagnostic Interview Schedule for Children; DIS: Diagnostic Interview Schedule; CIDI: Composite International Diagnostic Interview; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, revised third edition; SCL-90: Symptom Checklist-90;DIA-X/M-CIDI computerized version of the Munich-Composite International Diagnostic Interview; ICD-10: International Classification of Disease tenth edition; PLSI: Psychosis-Like Symptom Interview; and SCAN: Schedules for Clinical Assessment in Neuropsychiatry.

Study Design Stratification. When investigated separately, we found a 3-fold increase in odds of any mental disorder in children and adolescents who reported PEs among both cross-sectional (k=5) and longitudinal studies (k=7) (see Figure 4.2). Between study heterogeneity was evident across cross-sectional studies (I^2=71.4, p=0.007) and was somewhat suggested across longitudinal studies (I^2=49.2, p=0.067). When limited to non-psychotic disorders, both cross sectional (k=5) and longitudinal (k=3) studies indicated increased odds of any non-psychotic disorder in children and adolescents reporting PEs (see Figure 4.3). However, the number of studies available was limited in both design methods and there was significant heterogeneity across the cross-sectional studies (I^2=66.6, p=0.018).

Figure 4.2. Forest Plot of the Relationship between Child and Adolescent PEs and any Mental Disorder



Meta-regression Analysis. Given the significant between-study heterogeneity, we investigated whether a number of variables were likely to influence the relationship between PEs and any mental disorder. These included PE assessment type, study

design type, the total population of the study and follow up time in longitudinal studies. None of these variables had a significant effect on the relationship between PEs and any mental disorder (see Supplement E).

Analysis 2. PEs and Sub-categories of Mental Disorders.

There was a significant association between PEs and all sub-categories of mental disorder (see Table 4.2 and Supplements F and G). These results were particularly prominent for psychotic disorders (OR: 3.96, CI:2.03-7.73) affective disorders (OR: 3.83, CI:2.26-6.49, for depressive disorders only see Supplement H) and substance use disorders (OR: 3.41, CI:2.03-5.74). For example, analysis of data from the five longitudinal studies investigated the relationship between PEs and psychotic disorders found an approximate 4-fold increased risk of psychotic disorders in those with PEs. The population attributable fraction (PAF) was calculable from these five studies and indicated that childhood and adolescent PEs accounted for 23.2% of psychotic disorders. Heterogeneity was evident in the analysis investigating psychotic disorders and affective disorders.

Study Design Stratification. In studies using a cross-sectional study design, children and adolescents reporting PEs had an increased risk of affective and behavioural disorders. There was significant heterogeneity in the investigation of affective disorders. In those using longitudinal study designs, childhood and adolescent PEs were associated with over a 3-fold increased risk of substance use and psychotic disorders (Table 4.2). However very few studies (k=2) investigated the longitudinal relationship between child and adolescent PEs and subsequent affective disorders or anxiety disorders. No study included in this investigation had examined the longitudinal relationship between PEs and subsequent behavioural disorders.

Figure 4.3. Forest Plot of the Relationship between Child and Adolescent PEs and any Non-psychotic Disorder

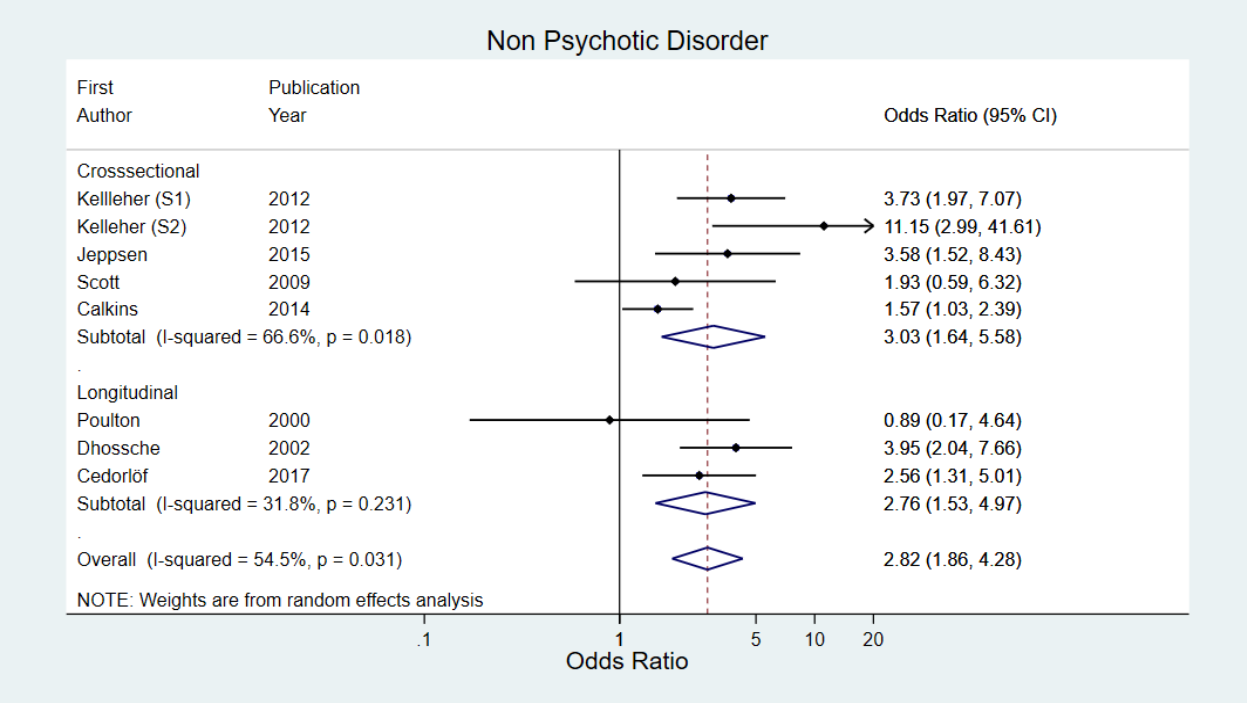


Table 4.2. The pooled odds ratios and the heterogeneity assessments of the relationship between childhood and adolescent PEs and each category of mental disorder (overall association and stratified by study design type).

Mental Disorder Categories	Overall			Longitudinal Study Design			Cross-Sectional Study Design		
	No of Samples	I^2	Pooled Odds Ratio (95% CI)	No of Samples	I^2	Pooled Odds Ratio (95% CI)	No of Samples	I^2	Pooled Odds Ratio (95% CI)
Psychotic	5	**70.1**	**3.96 (2.03-7.73)**	5	**70.1**	**3.96 (2.03-7.73)**	N/A	N/A	N/A
Affective	7	**59.1**	**3.83 (2.26-6.49)**	2	68.7	1.71 (0.23-12.52)	5	**62.7**	**4.35 (2.44-7.77)**
Anxiety	6	0.0	**1.45 (1.09-1.94)**	2	0.0	1.80 (0.71-4.55)	4	17.9	1.45 (0.98-2.14)
Behavioural	5	50.3	**2.09 (1.24-3.53)**	0	-	-	5	50.0	**2.09 (1.24-3.53)**
Substance Use	3	11.0	**3.41 (2.03-5.74)**	3	11.0	**3.41 (2.03-5.74)**	0	-	-

Note: I^2: Percentage of heterogeneity; CI: Confidence interval; N/A: Non-applicable; -=No study available; Emboldened values denote a probability of $p < .05$.

4.4 Discussion

This is, to our knowledge, the first systematic review of studies looking at risk of mental disorders in non-help-seeking children and adolescents who report PEs. Childhood and adolescent PEs were associated with increased odds of psychotic and affective, anxiety, behavioural and substance use disorders.

The prevalence of PEs in included studies was 9.3%, which is in keeping with meta-analytic estimates (Kelleher et al., 2012a, Maijer et al., 2018). It also is in keeping with the observation that PEs are more prevalent in early life than in adulthood (Linscott and van Os, 2013). Childhood and adolescent PEs were associated with a 3-fold increased odds of having any mental disorder or any non-psychotic disorder in both cross-sectional and longitudinal studies. Roughly a quarter of psychotic disorders were attributable to PEs in childhood or adolescence.

These results align with the suggestion that childhood PEs are an early stage pluripotent psychiatric marker (McGorry et al., 2018) and may therefore be considered as an early trans-diagnostic marker for vulnerability to subsequent mental disorder. This theory is empirically supported by follow-up research using a sub-sample of the Philadelphia cohort, which found that those with persistent PEs had increased rates of psychotic, affective and behavioural disorders while those with transient PEs had an increased rates of subsequent depressive disorders (Calkins et al., 2017). All three of their PE groups also had higher treatment history prevalence than controls at follow-up. Similarly, Fisher et al. (2013) found that, by age 38, 93.3% of those who reported PEs in childhood had met criteria for a mental disorder at some stage of their life. These results suggest that PEs may be a useful marker for identifying those at risk of subsequent mental disorder.

Our own research has highlighted that childhood PEs are not just a marker for subsequent risk but including PEs in assessments actually improves the prediction of subsequent psychopathology over and above the effects of a history of mental disorder, childhood functioning and traumatic experiences (Healy et al., 2018). While the meta-

analysis results from this investigation support the theory that those who report childhood and adolescent PEs have an increased risk of subsequent mental disorders (any and any non-psychotic disorder), there were very few longitudinal studies investigating the relationships between PEs and specific categories of non-psychotic disorders (Poulton et al., 2000; Fisher et al., 2013; Dhossche et al., 2002; and Cederlof et al., 2017). More research, specifically targeting the relationship between childhood PEs and subsequent non-psychotic disorder is therefore warranted.

In addition to the longitudinal outcomes, results from cross-sectional study design provided converging evidence suggesting that those who report childhood and adolescent PEs are more likely to have a co-occuring non-psychotic disorder. The synthesis of the cross sectional literature provides evidence that childhood and adolescent PEs are a potential feature of non-psychotic disorders. Research over the last two decades has challenged the homotypic nature of these phenomena, as those who report PEs have increased rates of a variety of different disorders (Calkins et al., 2014). However, similar to longitudinal research, the number of studies investigating the relationship between these phenomena and mental disorders is still relatively limited and subsequent research is necessary to fully examine the prevalence of each sub-category of mental disorder and PEs.

4.4.1 Heterogeneity

Most analyses revealed heterogeneity in the effects reported across studies. This was expected, given the variability between the studies in design characteristic such as PEs assessment type and follow-up time. These characteristics may affect the relationship between PEs and mental disorder. To investigate this, we ran four univariate meta-regressions (Supplement E). None of the variables we investigated had an effect on the relationship between PEs and any mental disorder. It is possible that other study or sample characteristics could have influenced this relationship. Such characteristics might include participant demographic characteristics or cross-study cultural differences, differences in diagnostic instrument or the interactive effects of a number of

features. Additionally, the number of studies available precluded an investigation of how study characteristics affect the relationship between PEs and specific mental disorders.

4.4.2 Strengths and Limitations

Strengths of the current study include investigation of both longitudinal and cross-sectional studies. A limitation is that some of the cross-sectional studies asked about lifetime (not current or recent) PEs. Interestingly, however, previous research has shown that, even when asked about lifetime experiences, most young people who report PEs have experienced these symptoms within the past year (Kelleher et al., 2012). The studies examined were restricted to published reports within peer-reviewed journals adding to the credibility of the findings; however, this also leaves open the possibility of publication bias. However, visual assessment of funnel plots and statistical assessment using Eggers regression test for the main analysis suggests that there minimal asymmetry in the overall investigation.

It was noted that there are a number of the studies that examine the relationship between PEs and psychopathology using non-diagnostic questionnaires, such as the *Strengths and Difficulties Questionnaire* (Goodman, 2001). While this investigation was restricted to the relationship between childhood and adolescent PEs and clinically defined mental disorder, we acknowledge that there is body of literature using these methods (Bartels-Velthuis et al., 2016, Dolphin et al., 2015, Bartels-Velthuis et al., 2010, Laurens et al., 2008). The majority of these studies have indicated an increased risk of internalising and externalising behavioural problems in those who report PEs. This, coupled with the results of the current study, suggests converging evidence across assessment tools in the relationship between childhood and adolescent PEs and psychopathology. However this remains to be confirmed. Only two of the studies in this investigation had examined PEs at multiple time points (Dominguez et al., 2011, Bechtold et al., 2016). This limited our ability to meaningfully assess the relationship between persistent PEs and mental disorder. It has been reported, using non-diagnostic questionnaires, that children with persistent PEs have an elevated risk of internalising and externalising problems relative to transient PEs and healthy participants (Downs et

al., 2013). Future research should investigate the relationship between persistent PEs and common mental disorder using diagnostic clinical assessments.

4.4.3 Conclusion

Children who report PEs are at increased risk of psychotic, affective, anxiety, behavioural and substance use disorders. Further research is necessary to understand why some young people with PEs go on to develop psychotic disorders while other young people with PEs go on to develop, for example, affective disorders (or, indeed, some young people with PEs do not develop any mental disorder at all).

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Conflict of Interest: None**.**

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Chapter 5

STUDY IV - DO CHILDHOOD PSYCHOTIC EXPERIENCES IMPROVE THE PREDICTION OF ADOLESCENT PSYCHOPATHOLOGY?

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search and statistical analysis. He was the first and corresponding author on the published manuscript.

Note: Below is a word document version of the study published in *Early Intervention in Psychiatry (doi: 10.1111/eip.12762)*. None of the content of the article has been altered.

Do childhood psychotic experiences improve the prediction of adolescent psychopathology? A longitudinal population-based study.

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Abstract Word Count: 249 (Max: 250)

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Conflicts of Interest: None

Abstract

Background: Early identification of individuals at risk of later mental disorders an important goal. A history of one or more psychotic experiences (PE) reported in childhood has been associated with subsequent psychopathology, but it remains unclear if it provides predictive information above beyond what is already captured by established clinical markers.

Aims: 1) To investigate the utility of childhood PE as a predictor of adolescent psychopathology while accounting for three known risk factors: childhood mental disorder; traumatic experiences; and poor childhood functioning; and 2) To investigate the additive effects of including childhood PE in predictive clinical model of adolescent psychopathology.

Method: The study sample comprised 86 Irish youth who completed two waves of the 'Adolescent Brain Development' study' (baseline x̄Age:11.7 and follow-up x̄Age:15.7). At baseline, participants completed a clinical interview assessing for PE, mental disorders, traumatic experiences and global functioning in childhood. The internalising and externalising problems sub-scales from the Youth Self Report questionnaire were used as follow-up outcomes variables in adolescence.

Results: Logistic regression analyses revealed that childhood PE was the only predictor significantly associated with both internalising (OR(Univariate): 7.58, CI: 2.59-22.15; OR(multivariate): 5.43, CI: 1.53-19.29) and externalising (OR(Univariate): 11.76, CI: 3.70-37.41; OR(Multivariate): 30.39 ,CI: 5.28-174.80) problems in adolescence. All predictive models with PE significantly predicted adolescent outcomes (AUC range: 0.70-0.81; all $p<.05$) and adding PE to the models improved the predictive value for externalising problems ($p=.02$).

Conclusion: Childhood PE is a powerful predictor of adolescent psychopathology, particularly externalising problems. Routine assessment of PE and targeted support for children who report PE may reduce the incidence of mental disorder in adolescence.

Keywords: Adolescence, Externalising Problems; Psychotic Experiences, Psychopathology,

Abbreviations: PEs: Psychotic Experiences; AUC: Area Under the Curve.

5.1 Introduction

Adolescence is widely acknowledged as a particularly vulnerable period for the development of mental disorder (Sawyer et al., 2012). The early detection of individuals who are likely to require intervention is an important goal for preventative psychiatry (Sourander et al., 2005). Several risk factors for adolescent mental disorder have been investigated and three of the most established are childhood mental disorder, childhood traumatic experiences and poor childhood global functioning. There is now a wealth of research indicating that childhood mental disorders are homo- and heterotypic predictors of later mental disorder (Copeland et al., 2009; Costello et al., 2003; Sounders et al., 2005; and Burke et al., 2005). Childhood trauma has a 28-32% of the population attributable risk for adolescent-onset mental disorders (Green et al., 2010; McLaughlin et al., 2012). Finally, global functioning has been shown to be predictive of adolescent mental disorder, adolescent suicidal behaviour and transition to psychosis (Lundh et al., 2016; King et al., 2010; Fusar-Poli et al., 2015).

A risk factor that has received increasing attention is childhood psychotic experiences (PE). PE are highly prevalent among young people, with 8-17% of children and adolescents reporting these experiences (Kelleher et al., 2012; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) and have been linked to an increased vulnerability to psychotic disorders, non-psychotic disorders and suicidal behaviour (Fisher et al., 2013; Kelleher, et al., 2012; McGrath et al., 2016; Poulton et al., 2000; Bartels-Velthuis, Wigman, Jenner, Bruggeman & van Os, 2016; Cederlof et al., 2017; Kaymaz et al., 2012; Kelleher et al., 2013). However, to-date it is unknown how well childhood PE predicts adolescent psychopathology relative to other childhood risk factors, and whether it provides additional predictive clinical information over and above what is already captured by other established clinical markers that present in childhood.

In the majority of cases, PE are a transient phenomena. It has previously been reported that PE, even when transient, is associated with increased risk of subsequent psychopathology (Calkins et al, 2017). However, there is also evidence that this relationship may be confounded by baseline psychopathology, and after accounting for

this, there is no longer a relationship between transient PE and subsequent psychopathology (Downs, Cullen, Barragan & Laurens, 2013). Further investigation into the predictive value of transient childhood PE is warranted.

Aims

The aims of this study were: (1) to investigate the predictive effect of childhood PE on adolescent psychopathology while taking into account three other potential predictors - childhood mental disorder, childhood traumatic experiences, childhood global functioning; (2) to investigate the additive effects of including PE in a childhood predictive model of adolescent psychopathology.

5.2 Method

5.2.1 *Participants*

The participants were drawn from the Adolescent Brain Development (ABD) study, an Irish population based study originally recruited from schools at age 11-13. The recruitment process for the baseline sample has been described in detail (Kelleher, Harley, Murtagh, & Cannon, 2011). Briefly, 212 participants aged between 11 and 13 years attended a clinical interview and cognitive assessment. Subsequently, 100 of these participants also agreed to take part in a neuro-imaging study (O'Hanlon et al., 2015). These 100 were invited back to take part in a follow-up study as adolescents (aged 14-16) and 86 agreed to take part.

Ethical Consideration: Ethical approval for the study was received from the Beaumont Hospital medical ethics committee.

5.2.2 Measurement

Childhood exposures (age 11-13)

Clinical Interview: At baseline (age 11-13), all participants were assessed using the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) (Kaufman et al., 1997). The K-SADS is a well-validated semi-structured diagnostic interview for the assessment of a wide range of mental disorders in children and

adolescents. A psychiatrist or psychologist interviewed both the participant and his or her parents separately. K-SADS guidelines were used when discrepancies between respondents were report. This interview examined information on a) PE; b) childhood mental disorder; c) traumatic experiences; and d) global functioning.

a) Psychotic Experiences: The psychosis subsection of the K-SADS is designed to assess a range of hallucinations and delusional thinking. Detailed notes were taken on any endorsed PE. All interviewers were given training on the assessment of any reported PE. In every case where a participant endorsed any PE, these were independently rated and classified based on criteria developed by *Kelleher & Cannon* (Kelleher & Cannon, 2014). In brief, PE was judged based on a number of qualities including: the content of the experience; the attribution of the experience (personal interpretation of the phenomena); the certainty of this attribution on reality testing (i.e. might have been my imagination/definitely wasn't my imagination); the clarity of the experience (degree of ambiguity in the description); and the degree of distress/impairment the experience caused (i.e. very/somewhat/not distressing). Endorsement of any PE was discussed and subsequently rated at a consensus meeting by three experts in psychosis. None met criteria for a psychotic disorder.

b) Childhood Mental disorder: Diagnosis of mental disorder was based on the K-SADS assessment for DSM IV disorders. Mental disorders were dichotomised such that participants with a diagnosis of at least one mental disorder up to the time of interview was coded as *present* while those without were coded as *absent.*

c) Childhood Traumatic experiences*:* Exposure to traumatic experiences during childhood was investigated during the clinical interview. This was examined using the post-traumatic stress disorder screening questions from the K-SADS. This section of the interview investigated exposure to ten potentially traumatic experiences: car accident; any other type of significant accident requiring medical attention; major fire-damage to property; being a witness to or victim of any violent event in a public setting; exposure to traumatic news (i.e. death in the family or other serious unexpected event); witnessing a

natural disaster; witnessing domestic violence; experiencing physical abuse; experiencing sexual abuse; and an open-ended question probing any other potentially traumatic events. If the participant or his/her parent responded that an event had been experienced by the participating child the response was coded as present. Each event was characterised as present or absent and the sum of these events were calculated for each participant to give a childhood trauma score. The childhood traumatic experiences variable was treated as an ordinal variable.

d) Global Assessment of Functioning: Global functioning was assessed using the Children's Global Assessment Scale (C-GAS) which was examined as part of the K-SADS (Shaffer et al., 1983). The C-GAS is a validated measure of global functioning adapted from the global assessment of functioning (GAF) scale for adults. The C-GAS is a 100-point scale which is divided into ten levels, with a lower score indicating more severe impairment. Scores between 1 and 10 indicate very severe impairment ('needs 24-hour care/supervision') while scores between 91 and 100 indicate superior functioning in all areas. The C-GAS score was treated as a continuous variable and current (past month) C-GAS was used in the analyses.

Adolescent Outcomes (age 14-16)

Psychopathology. Adolescent psychopathology was investigated using the Youth Self Report questionnaire (YSR) (Achenbach, 1991) at follow-up. The YSR is a 112 item questionnaire. Scales for both internalising problems and externalising problems were calculated. The *Internalising scale* is the composite of the Anxious/Depressed, Withdrawal/Depressed, Somatic Complaints subscales and the *Externalising scale* is the composite of the Aggressive Behaviour and Rule-Breaking Behaviour subscales. Internalising and Externalising problems were defined as endorsement >93rd percentile of the internalising and externalising scales, respectively, based on the Achenbach System of Empirically Based Assessment (Achenbach, 1991).

Psychotic Experiences. PE were investigated using the same format as in childhood. No participant met criteria for a psychotic disorder. For the purpose of this investigation,

transient PE was defined as PE reported in childhood but not in adolescence. Persistent PE was defined as PE reported in both childhood and adolescence.

5.2.3 Statistical Analysis

A previous investigation suggested a strong relationship between PE and mid-adolescent psychopathology (Kelleher et al., 2012). Based on these estimates, we expected roughly 85% statistical power based with the current sample size to detect an effect of PE.

Analysis 1. Childhood PE as a predictor of adolescent psychopathology.

Univariate and multivariate logistic regressions were used to investigate the relationship between childhood mental disorder, childhood traumatic experiences, childhood global functioning and childhood PE with adolescent internalising and externalising problems scales on the YSR. Odds ratios and confidence intervals are reported for each predictor.

Analysis 2. The additive predictive effects of including childhood PE in a clinical model of adolescent psychopathology.

Predictive models: We investigated the predictive effects of a childhood clinical model on adolescent outcomes with and without the inclusion of childhood PE as an additional predictor. The clinical model comprised of childhood mental disorder, childhood traumatic experiences and childhood global functioning. Model performance was evaluated using the area under the curve (AUC) of the receiver-operating characteristic (ROC), which quantifies the predicted sensitivity as a function of the false positive rate (1 –specificity). AUCs were based on each model's predicted probability values. To reduce overfitting, predicted probability values were calculated using a penalised logistic regression (the least absolute shrinkage and selection operator, or lasso penalisation method) with an automated optimum lambda selection process. Lambda search section ranging from 0-1 with an incremental increase of 0.5. This was conducted using the *plsearch* term in STATA 15 (StataCopr, 2017).

Model Comparison: We investigated the change in association between the childhood models of adolescent psychopathology by adding PE. Comparisons were based on the AUC using the *DeLong et al* method of AUC comparison for correlated receiver-operator characteristics (DeLong, DeLong, & Clarke-Pearson, 1988). Alpha-levels were set at .05.

5.2.4 Supplementary analysis. Transient childhood PE as a predictor of adolescent psychopathology.

It could be argued that persistent PE account for the relationship between childhood PE and adolescent psychopathology, thus undermining the use of childhood PE as a predictor of adolescent psychopathology. To account for this, we conducted the first analysis again, but with a restricted sample that excluded those who had persistent PE (PE were transient in 68.18% of cases, n=15).

5.3 Results

Comparison of baseline and follow-up samples

We compared the baseline demographic and clinical characteristics of those who attended baseline only (n=126) and those who attended baseline and follow-up (n=86). There was no significant difference between those who attended the follow-up and those who did not in the baseline socio-demographic variables or clinical variables (age, gender, years in education, PE prevalence, mental disorders prevalence, C-GAS scores and cumulative trauma, all p>.05).

Demographics of participants

Childhood clinical characteristics (age 11-13)

The childhood clinical characteristics are reported in Table 5.1. 22 (25.6%) children reported PE. There were no significant differences in age, gender and educational level between those who reported PE and those who did not (all p >.05). The most common disorders were generalised anxiety disorder (7%) and major depressive disorder (3.5%). 34.1% reported one traumatic experience, 9.4% reported two traumatic experiences and 4.7% reported three or more traumatic experiences.

Adolescent clinical characteristics (age 14-16)

Psychotic Experiences. PE were transient (childhood only) in 68.18% of cases (n=15). 31.81% of those with childhood PE also reported PE in adolescence. There was no significant difference in demographic or clinical characteristics between participants with transient PE and participants with persistent PE, at either time point (all p>.05).

Internalising and Externalising problems. There was no significant difference between male and female participants in the prevalence of internalising problems (30.0% and 30.4%, respectively; p>.05) and externalising problems (20% and 26.1%, respectively; p>.05).

Table 5.1. The demographic and clinical characteristic of the participants with and without adolescent PEs at follow up.

Characteristics	**Overall Sample (n =86)**	**Controls (n = 58)**	**Psychotic Experiences (n = 22)**
Demographic			
Gender (% of males)	46.51	42.19	59.09
Age (Mean, SD)	15.74 (1.35)	15.73 (1.41)	15.77 (1.19)
Secondary Education level (Mean, SD)	3.72 (1.39)	3.71 (1.41)	3.72 (1.35)
Childhood Clinical Characteristics			
Mental Disorder (%)	16.28	7.81	40.91***
Childhood Trauma (% two or more)	14.12	11.11	22.73
Childhood Global Functioning (Mean, SD)	78.35 (16.95)	82.53 (14.12)	66.42*** (18.94)
Adolescent Clinical Characteristic			
Internalising Problems	30.23	18.75	63.64***
Externalising Problems	23.25	10.94	59.09***
Persisting Psychotic Experiences	8.14	-	31.81

Note: ***: p <.001, SD = Standard Deviation.

Aim 1. Childhood PE as a predictor of adolescent psychopathology.

Internalising problems. Univariate analysis indicated that childhood PE (OR:7.58, CI:2.59-22.15, p<.001) and childhood functioning (OR:0.97, CI:0.94-0.99, p=.043) significantly predicted internalising problems in adolescence (see Table 5.2). When investigated in a multivariate model, childhood PE was the only predictor associated with an increased risk of internalising problems in adolescence. After accounting for PE, none of the other predictors were associated with problems (all p>.05).

Externalising Problems. Both the univariate and multivariate analyses indicated that childhood PE was the only significant predictor of adolescent externalising problems (OR:11.76, CI: 3.69-37.40, p <.001, see Table 5.2).

Table 5.2. Uni and multi-variate analysis of childhood predictors of adolescent internalising and externalising problems.

	Adolescent Outcomes			
	Internalising Problems OR (CI)		**Externalising Problems OR (CI)**	
Independent Predictors	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Childhood PEs	**7.58*** **	**5.43** **	**11.76*** **	**30.39*** **
	(2.59 - 22.15)	(1.53 - 19.29)	(3.70 - 37.41)	(5.28 - 174.8)
Childhood Mental	1.95	0.49	1.40	0.29
Disorder	(0.60 - 6.33)	(0.95 - 2.51)	(0.39 - 5.06)	(0.05-1.88)
Childhood Traumatic	1.53	1.44	1.37	0.92
Experiences	(0.89 - 2.64)	(0.75 - 2.76)	(0.78 - 2.44)	(0.40 - 2.12)
Childhood Functioning	**0.97***	0.98	0.98	1.02
	(0.94 – 0.99)	(0.95 - 1.01)	(0.96 - 1.02)	(0.97 - 1.06)

Note: 95% Confidence intervals are presented in parentheses; *: p <.05; **: p <.01; ***: p <.001.

Aim 2. The additive predictive effects of including childhood PE in a model of adolescent psychopathology.

Internalising Problems. Childhood PE alone predicted 76.7% of adolescent internalising outcomes (positive predictive value=63.6%, CI:40.7–82.8%; and negative predictive value=81.3%, CI:69.5-89.9%). Both models significantly predicted internalising outcomes (both p<.01; see Table 5.3 and Figure 5.1). However, there was no significant difference between the model clinical with and without PE (p > .05).

Externalising Problems. Childhood PE alone predicted 81.4% of adolescent externalising outcomes (positive predictive value=59.1%, CI:36.4–79.3%; and negative predictive value=89.1%, CI:78.8-95.5%). PE alone significantly outperformed the clinical model without PE (χ^2=5.23, p=.02, see table 3). Adding PE to the clinical model significantly improved predictability of externalising outcomes (χ^2=5.61, p=.02, Figure 5.1).

Table 5.3. The receiver operator characteristics for the three different predictive models of adolescent psychopathology with and without childhood PEs.

	Internalising Problems	**Externalising Problems**
Psychotic experiences alone	**.70****	**.76*****
	(.59-.80)	(.64-.87)
Clinical variables (without PEs)	**.71****	.60
	(.58-.83)	(.46-.74)
Clinical variables (with PEs)	**.75*****	**.816*****
	(.62-.87)	(.68-.93)

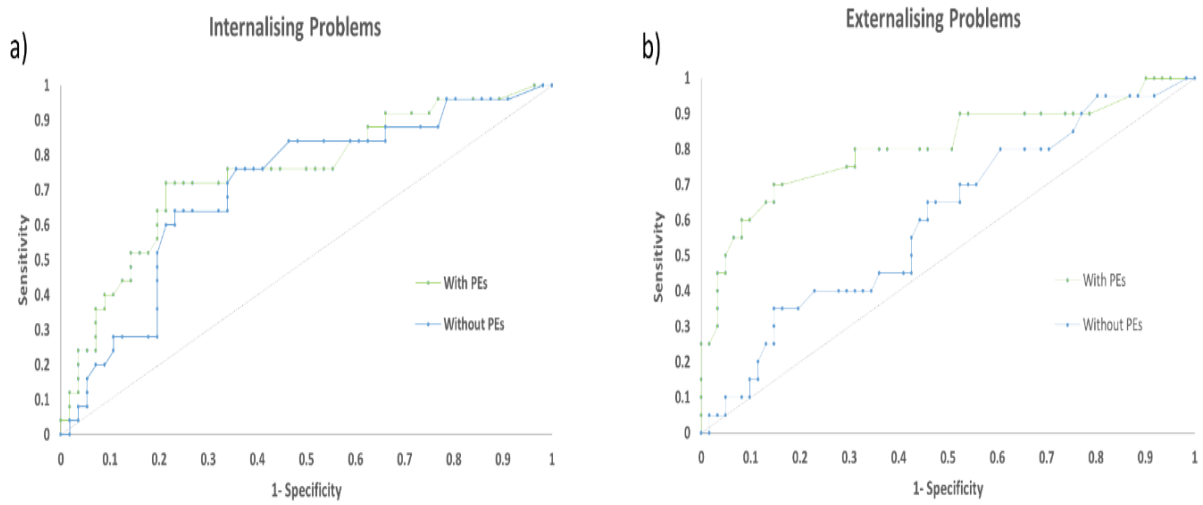
Note: 95% Confidence intervals are presented in parentheses; *: p <.05; **: p <.01; ***: p <.001

Supplementary analysis. The predictive effects of transient childhood PE on adolescent psychopathology.

Transient Psychotic experiences only. PE limited to childhood were significantly associated with an increased risk of adolescent internalising problems (univariate OR:6.50 CI:1.94-21.77, p=.002; multivariate OR:4.02 CI:1.03-15.64, p=.045) and adolescent externalising problems (univariate OR:9.31 CI:2.58-33.55, p=.001;

multivariate OR:20.24 CI:3.26-125.49, p=.001). After accounting for PE, none of the other predictors were associated with internalising or externalising problems (all p>.05).

Figure 5.1. Area under the curve for the childhood clinical model of adolescent outcomes with (green line) and without (blue line) the inclusion of childhood psychotic experiences in the model: a) adolescent internalising problems and b) adolescent externalising problems.



5.4 Discussion

Using a prospective longitudinal cohort sample our study demonstrated that childhood PE is a powerful predictor of adolescent psychopathology. When considered together with mental disorder, functioning and traumatic experiences, PE was the only childhood characteristic predictive of the adolescent internalising and externalising problems. Our secondary analysis reinforced these findings by indicating that adding PE into a childhood clinical model improved the prediction of adolescent psychopathology. This was particularly evident for externalising problems, where childhood PE alone was a better predictor of externalising problems than all other clinical variables combined. Finally, our supplementary analysis demonstrated that childhood PE, even when the phenomena are transient, are predictive of adolescent psychopathology even after accounting for childhood mental disorder, functioning and traumatic experiences.

PE are commonly reported in childhood (Maijer, Begemann, Palmen, Leucht, & Sommer, 2018; and Kelleher et al., 2012) and several studies have indicated their importance in concurrent and subsequent mental disorder (Kelleher et al., 2012; Fisher et al 2013; Zammit et al., 2013; and McGrath et al 2016). Few studies have considered the importance of accounting for other clinical predictors when investigating the relationship between PE and psychopathology, and those which have only adjusted for baseline psychopathology (Dhossche, Ferdinand, van der Ende, Hofstra, & Verhulst, 2002; Downs, Cullen, Barragan & Laurens, 2013; and Yung et al 2007) or concurrent psychopathology (Scott et al., 2009; and Varghese et al., 2009). Our results suggest that not only are childhood PE a valid predictor of subsequent psychopathology, but they also have additive predictive value even when several established clinical predictors have already been considered. This may be particular important for predicting adolescent externalising problems.

Externalising problems are known to increased risk of a range of difficulties in later life. For example, conduct problems, exhibited during adolescence, have been associated with an increased risk of adult mental disorder, poorer life satisfaction, marital/relationship difficulties, financial difficulties, substance abuse/dependence and criminality (Harley, Murtagh, & Cannon, 2008; Colman et al, 2009; Fergusson, Horwood, & Ridder, 2007; Erskine et al, 2016). Identifying those at risk of externalising problems and intervening early should assist in reducing the long-term burden on psychiatric services and improve the well-being of those who exhibit such behaviours.

Routine assessment of PE in childhood and utilising their predictive value may aid greatly in this process. Assessment of PE is logistically feasible. For example, most interviews provide screening questions for psychotic symptoms and short supplementary assessment tools are available (Kelleher & Cannon, 2014). Moreover, questionnaire assessments of PE are widely available and several studies have indicated that questions pertaining to auditory hallucinations have good predictive value for all PE (Kelleher, Harley, Murtagh, & Cannon, 2011 Laurens et al., 2012; and Granö

et al., 2016). Utilising these tools and embedding these practices in routine assessment may aid in the prediction of future psychiatric outcomes.

Finally, our supplementary analysis suggests that PE, even when transient, have predictive value for adolescent psychopathology. It has been reported that children with persistent PE have higher levels of psychopathology than those with transient PE and those without PE (Calkins et al., 2017; Downs, Cullen, Barragan, & Laurens, 2013). Downs and colleagues suggested that targeted intervention for individuals with persistent PE might reduce common childhood psychopathology. Our supplementary analysis indicated that children who report PE, even when the phenomena are transient, may also be at risk of adolescent psychopathology.

5.4.1 Strengths and Limitations

There are a number of strengths to this study. The data was obtained using longitudinal community sample with all childhood measures based on face-to-face clinical interviews. PE were based on defined criteria and transcripts of the notes taken during the clinical interviews were reviewed by experts in the field of psychosis. The YSR is a widely used, well validated measure that allows for a number of psychological constructs to be investigated efficiently. However, self-report measures are known to be less reliable than clinical interview. Within the sub-sample of participants who were re-recruited for follow-up, retention rate was high (86%). However, the overall sample size was small and sub-sampling limits the generalisability of the findings. This limitation was compounded in the supplementary analysis when participants with persistent PE were excluded. As such, external validation of these findings with a larger sample is warranted.

5.4.2 Conclusion

A report of PE in childhood is a powerful predictor of adolescent psychopathology. Routinely testing for PE within children's mental health services would provide additional valuable clinical information regarding the risk of future psychopathology, even when other known risk factors have been taken into consideration. This would

significantly improve the prediction of adolescent externalising problems and may assist in reducing the later burden on adolescent and adult mental health services.

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Chapter 6

Study 5: Childhood Psychotic Experiences Are Associated With Poorer Global Functioning Throughout Adolescence And Into Early Adulthood.

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search and statistical analysis. He was the first and corresponding author on the published manuscript.

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Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood.

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Abstract

Background: Psychotic experiences (PEs) are common in childhood and have been associated with concurrent mental disorder and poorer global functioning. Little is known about the effects of childhood PEs on future functioning. We investigated the effects of childhood PEs on global functioning from childhood into early adulthood.

Method: 56 participants from a community sample completed all three waves of the Adolescent Brain Development study (T1x̄Age: 11.69, T2x̄Age:15.80 T3x̄Age:18.80). At each phase, participants completed a clinical interview assessing for PEs, mental disorder and global function. Repeated measures models, adjusted for mental disorder and gender, were used to compare current (C-GAF) and most severe past (MSP-GAF) functioning in participants who had reported PEs in childhood and controls.

Results: Participants with a history of PEs had significantly poorer C-GAF ($p<.001$) and MSP-GAF scores ($p < .001$). Poorer functioning was evident in childhood (C-GAF: $p=.001$; MSP-GAF: $p<.001$), adolescence (C-GAF: $p<.001$; MSP-GAF: $p=.004$) and early adulthood (C-GAF: $p=.001$; MSP-GAF: $p =.076$).

Discussion: Children who report PEs have persistently poorer functioning through to early adulthood. The longitudinal association between childhood PEs and global functioning highlights the underlying global vulnerability in children reporting PEs, beyond what can be explained by mental disorder.

Keywords: Adolescent Development, Psychosis & Mental Disorders

Significant outcomes:

- Individuals who reported psychotic experiences in childhood had persistently poorer functioning into early adulthood.
- This association was above and beyond what can be explained by a diagnosed mental disorder.
- These results were also evident in young people whose psychotic experiences were transient.

Limitations:

- The data came from a relatively small longitudinal community sample.
- Attrition rates were high relative to the overall sample, although formal testing did not indicate an inherent bias.
- Global Assessment of Functioning scale is a composite metric and future research is necessary to fully determine the effects of psychotic experiences on symptomology, social and occupational functioning separately.

6.1 Introduction

Childhood psychotic experiences (PEs) are highly prevalent, with 17% of children reporting such phenomena[1]. PEs during childhood and early adolescence are associated with concurrent mental disorders [2-7]. Findings from longitudinal studies also suggest that children who report PEs have an increased vulnerability to subsequent psychotic and non-psychotic disorders [8-9]. For example, Fisher et al.[8] reported that more than 90% of those who had PEs in childhood had at least one mental disorder by age 38.

It has also been demonstrated that children with PEs exhibit poorer global functioning than their peers [2,10-12]. Global functioning is an important measure that is commonly used in research and clinical practice [13]. Shaffer and colleagues [14] state that assessment of functioning 'allows the rater to assimilate and synthesize his or her knowledge about many different aspects of the patient's social and psychiatric functioning, and condense it into a single clinically meaningful index of severity of disturbance' (p.1228) [14]. Functioning has been shown to be a valuable measure for identifying individuals in need of treatment [15-16], measuring the effectiveness of an intervention[17], and predicting transition to psychosis and outcomes in first-episode patients [18-19].

While PEs in childhood have been associated with concurrent poorer functioning [10-12], to date little is known about the longitudinal association between childhood PEs and global functioning later in life. To our knowledge, only Calkins et al. [20] have investigated this relationship - over a two-year follow up period. They demonstrated that participants who reported PEs displayed significantly poorer functioning than controls upon follow up. However, it is unclear whether the dysfunction seen in those who reported PEs reflects the impact of a co-occurring mental disorder, or if PEs are independently associated with poorer functioning. Moreover, it is yet to be established whether the poorer functioning associated with PEs is independent of baseline functioning.

Despite PEs being transient phenomena in roughly 80% of cases [21], few investigations have examined whether functional deficits persist once the experiences have ceased. To date only Calkins et al. [20] have reported that individuals with transient PEs still scored lower on global functioning measures at a two year follow up than those who had never experienced PEs; however co-occurring mental disorder was not accounted for. It remains to be established if PEs limited to childhood have an independent relationship with poorer functioning that extends into adolescence and early adulthood.

6.1.1 Aims

The aims of this study were: 1) to investigate the relationship between childhood PEs and global functioning during childhood, adolescence and early adulthood, independent of mental disorder and, additionally, independent of childhood functioning; and 2) to separately investigate if PEs reported in childhood only (transient PEs) and persistent PEs are associated with poorer functioning into early adulthood.

6.2 Method

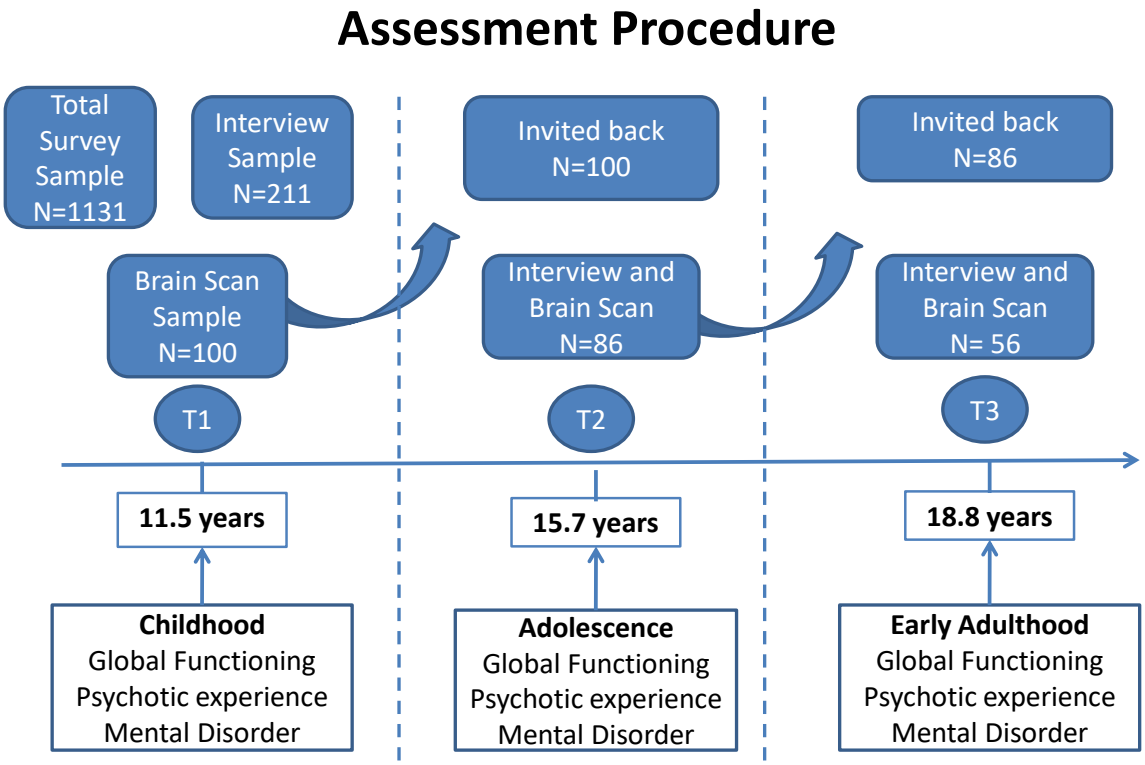
6.2.1 Participants

The participants were drawn from the Adolescent Brain Development (ABD) study - an Irish community sample who have completed three waves of assessment; once in childhood (T1: age 11-13 years), once in adolescence (T2: age 14-16 years) and once in early adulthood (T3: age 17-21 years). The recruitment process for the study has been described in detail [22]. The ABD study sample is comprised of 212 participants aged between 11 and 13 years, recruited from schools in the Dublin region. They attended a clinical interview and cognitive assessment at baseline. Additionally, 100 of these participants also had an MRI scan.

This subgroup of 100 were invited to take part in a follow up study (T2; aged 14-16) and 86 agreed to take part in another detailed clinical interview, cognitive assessments and MRI scan. All 86 were then invited to take part in a further follow up (T3; aged 17-21) with a similar procedure, and 56 (65%) agreed to take part (see Figure 6.1). Participants were divided into two groups based on whether they had reported PEs in childhood

(32.1% of the sample). For the secondary analysis participants who reported PEs were sub-divided into two groups; transient PEs (66.67%;those who reported PEs at T1 only) and persistent PEs (33.3; those who continued to report PEs at T2 and/or T3). Ethical approval for the study was received from the Beaumont Hospital medical ethics committee.

Figure 6.1. Flow chart of the assessment procedure for this investigation.



6.2.2 Measurement

Exposure measure

Clinical Interview. At all-time points (T1-T3), Axis-I disorders, and PEs were assessed using the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) [23]. The K-SADS is a well-validated semi-structured research diagnostic interview for the assessment of a wide range of mental disorders in children and adolescents. For consistency, a modified version of the K-SADS was re-administered at

T3. At T1 both the participant and his or her parents were interviewed separately by a psychiatrist or a psychologist. At T2 and T3 only the participants were interviewed.

Current and Past Disorder. At each interview participants were assessed for current and past mental disorder. The Axis I disorders investigated include affective disorders (such as depressive disorders, mania and bipolar disorder), anxiety disorders (including generalised anxiety disorder and panic disorder) and psychotic disorders (including schizophrenia spectrum disorders and other psychotic disorder). Additionally, during T1 behavioural disorders (such as conduct disorder, oppositional defiant disorder and attention deficit disorder) were investigated, and substance use disorder was investigated during T2 and T3. Participants who reported symptoms which met diagnostic criteria within the last month were classified as having a current mental disorder. For past mental disorder, participants had to meet diagnostic criteria at any time since the last assessments (T1 past disorder was the measure of disorder until the first assessment).

Psychotic experiences. PEs were defined based on the concept of the psychosis phenotype continuum. Psychotic 'experiences' incorporate a broader definition of psychotic phenomena than psychotic 'symptoms', such that the experiences do not have to be distressing (as has been described by Van Os et al. [24]). None of the participants met criteria for a psychotic disorder at any time point. The psychosis subsection of the K-SADS is designed to assess a range of hallucinations and delusional thinking. Detailed notes were taken of any endorsed PEs. All interviewers were given extensive training on the assessment of any reported psychotic phenomena. In every case where a participant endorsed any psychotic phenomena, these were independently rated and classified based on PE criteria developed by Kelleher & Cannon [25]. In brief, PEs were judged based on a number of qualities including: the content of the experience, the attribution of the experience (personal interpretation of the phenomena), the certainty of this attribution on reality testing (i.e. might have been my imagination/definitely wasn't my imagination), the clarity of the experience (degree of ambiguity in the description), and the degree of distress/impairment the experience

caused (i.e. very/somewhat/not distressing). Endorsement of any psychotic phenomena was discussed and subsequently rated at a consensus meeting by three experts in psychosis.

Outcome measures.

Global Assessment of Functioning. Global functioning was assessed using the Children's Global Assessment Scale at T1 and T2 [14] and the Global Assessment of Functioning scale at T3 [26]. The Children's Global Assessment Scale is a validated measure of global functioning adapted from the Global Assessment of Functioning (GAF) scale for adults [26]. Both are scored on a 100-point scale which is divided into ten levels, with a lower score indicating more severe impairment. Scores between 1 and 10 indicate very severe impairment ('needs constant supervision (24-hour care)') while scores between 91 and 100 indicate superior functioning in all areas. A descriptive vignette of each category is present in supplementary Table 1 (see supplementary materials). In-house training was provided to all interviewers in using the GAF. For the purpose of this investigation the current (C-GAF) and most severe past (MSP-GAF) scores at each time point were used in the investigation. The C-GAF is a measure of global functioning within the last month, while the MSP-GAF is a measure of the poorest level of functioning since the last assessment (T1 MSP-GAF measures the poorest level of functioning until the first assessment). These measures were treated as continuous variables.

6.2.3 Statistical Analysis

Demographics. Standard parametric testing was used to investigate differences in demographics between those with and without a history of PEs.

Primary analysis.

Association independent of mental disorder and childhood functioning. A full factorial fixed-effect repeated measures model was used to investigate the effects of childhood PEs on global functioning over time. C-GAF scores and MSP-GAF scores were investigated as dependent variables separately. Group (childhood PEs and

controls) and Time (T1-T3) were entered as independent variables in the model. The model was adjusted for gender and mental disorder (adjusting for current mental disorder when C-GAF was the dependent variable and past mental disorder when MSP-GAF was the dependent variable). Additionally, to investigate the temporal association between PEs and functioning, a second adjustment was made to account for childhood (i.e. baseline) functioning (T1 C-GAF and T1 MSP-GAF).

T1 C-GAF scores were accounted for when C-GAF was the dependent variable and T1 MSP-GAF scores were accounted for when MSP-GAF was the dependent variable. A restricted maximum-likelihood, auto-regressive model was used, accounting for repeated co-variance of participant and time. Additionally, post-hoc simple effects analyses were used to investigate the effects of childhood PEs on GAF scores at each time point with adjustments. Bonferroni correction was applied to the post-hoc simple effects analyses, which restricted the alpha level thresholds to $\alpha = .017$.

Secondary Analysis.

Relationship between transient and persistent PEs and functioning. A secondary analysis was conducted using the same methodology as the primary analysis, however the PE group was sub-divided to separately investigate the effects of transient PEs (reported only in childhood; 66.67% of participants) and persistent PEs (also reported during adolescence and/or adulthood; 33.33% of participants) on global functioning. Groups were defined as controls, transient PEs and persistent PEs.
All statistical analysis was conducted using SPSS 22 for windows.

6.3 Results

Missing data comparison

There were no significant differences in the demographic and clinical at baseline between those who attended all three waves of follow up and those who did not (gender, years in education, PEs prevalence, mental disorders prevalence, C-GAF and MSP-GAF scores, all $p < .25$). There was a significant difference in age which indicated that at baseline participants who attended all three waves were slightly older than those

who did not attend for follow up (attendees $\bar{x}$: 11.69, SD: 0.69; non-attendees $\bar{x}$: 11.47, SD: 0.57, p = .046).

Demographics of participants

56 participants took part in the all three waves of the study. 32.1% had a history of childhood PEs. Table 6.1 depicts the descriptive demographic information of those with and without a history of childhood PEs. There were no significant differences in the demographic variables between participants with and without a history of childhood PEs.

Primary analysis

Relationship between PEs and functioning.

C-GAF. Participants with a history of childhood PEs had significantly lower C-GAF scores than controls overall (F = 39.858, p < .001, see Figure 6.2 and Table 6.2). There was no significant effect of time, indicating that functioning scores were stable over time (F = 0.031, p = .969). There was no significant interaction between time and group (F= 0.230, p = .795).

Simple effects analysis. Simple effects analysis indicated that at each time point participants with a history of childhood PEs had significantly poorer C-GAF scores than controls (childhood: p = .001; adolescence: p < .001; and early adulthood: p = .001, see Table 6.2).

Covariates. Participants with current mental disorders had significantly poorer C-GAF scores than those without (F = 20.017, p < .001). There was no significant main effect of gender (F = 0.004, p = .951).

Accounting for childhood functioning: There was a significant main effect of group (F = 17.569, p < .001) which indicated that overall participants with a history of childhood PEs continue to have lower C-GAF scores than controls even after accounting for mental disorder and childhood functioning (T1 C-GAF). There was no significant effect of time (F = 0.011, p = .916). There was no significant interaction between time and group (F= 0.027, p = .869).

Table 6.1. Demographic results for participant with and without a history of childhood PEs.

Demographics	**Childhood Psychotic Experiences (n=18)**	**Controls (n=38)**	**p-value**
Gender (male/ female)	12/6	16/22	n/s
Age (years)			
T1	11.67	11.68	n/s
T2	15.83	15.82	n/s
T3	18.81	18.79	n/s
Education Level (years):			
T1. Primary Education	5.39	5.55	n/s
T2. Secondary Education	3.83	3.82	n/s
T3. Age of School Completion	17.86	17.80	n/s
T3. Currently Occupational Status (%)	17.6	15.8	
Still in School	70.6	73.7	
In 3rd Level Education	5.3	5.9	
Working	5.3	5.9	
Seeking Employment			
Mental Disorder (%)			
T1 Current	38.9	18.4	.099
T1 Past	61.1	31.6	.036
T2 Current	11.1	5.4	n/s
T2 Past	55.6	16.2	.003
T3 Current	12.5	9.7	n/s
T3 Past	56.3	22.6	.021

Note: n/s = non-significant ($p > .05$)

Simple effects analysis. Simple effects analysis indicated that participants with a history of childhood PEs had significantly poorer C-GAF scores than controls during adolescence ($p < .001$) and early adulthood ($p = .004$, see Table 6.2), even when accounting for gender, mental disorder and childhood functioning.

MSP-GAF. Participants with a history of childhood PEs had significantly lower MSP-GAF scores than controls ($F= 20.177$, $p < .001$, see Figure 6.2). There was a significant effect of time ($F = 9.941$, $p < .001$), with all participants on average having poorer MSP-GAF scores in mid-adolescence ($p < .001$) and early adulthood ($p = .005$) than in childhood. There was no significant interaction between time and group ($F= 0.219$, $p = .804$).

Simple effects analysis. Simple effects analysis indicated that those with a history of childhood PEs had lower MSP-GAF scores than controls (see Table 6.2) during childhood ($p < .001$), adolescence ($p = .004$) and somewhat in early adulthood ($p = .076$).

Covariates. Participants who met criteria for past mental disorder had significantly poorer MSP-GAF scores than controls ($F = 114.017$, $p < .001$). Male participants had significantly lower MSP-GAF scores than females ($F = 4.506$, $p = .038$).

Accounting for childhood functioning: There was no significant main effect of group ($F= 2.697$, $p = .106$), which indicated that after accounting for level of functioning (T1 MSP-GAF) in childhood and mental disorder participants with a history of childhood PEs did not differ from controls in adolescent and early adulthood MSP-GAF scores (see Table 6.2). There was no significant effect of time ($F = 0.700$, $p = .407$) and there was no significant interaction between time and group ($F= 0.007$, $p = .933$).

Secondary analysis.

Relationship between transient and persistent PEs and functioning.

C-GAF. There was a significant main effect of group ($F = 20.197$, $p < .001$) which indicated that overall participants with transient and persistent PEs had significantly poorer C-GAF scores than controls ($p < .001$ and $p < .001$, respectively, see Figure 6.2).

There was no significant difference between participants with transient PEs and participants with persistent PEs. There was no significant effect of time (F = 0.455, p = .636). There was no significant interaction between time and group (F= 0.525, p = .718).

Simple effects analysis.

Transient PEs vs. Controls: After controlling for gender and mental disorder participants with transient PEs in childhood had poorer C-GAF scores than controls during adolescence (p =.002), early adulthood (p = .005) and somewhat during childhood (p = .033).

Persistent PEs vs. Controls: Participants with persistent PEs had poorer C-GAF scores than controls during childhood (p = .002), adolescence (p < .001) and somewhat during early adulthood (p = .058).

Transient PEs vs. Persistent PEs: Participants with persistent PEs had significantly poorer C-GAF scores than participants with transient PEs in adolescence only (childhood: p = .192; adolescence: p = .004; and early adulthood: p = .896).

Covariates. There was a significant main effect of mental disorder (F = 27.864, p < .001) but no significant effect of gender on C-GAF scores (F = 0.162, p = .689).

MSP-GAF. There was a significant main effect of group (F= 9.207, p < .001) which indicated that overall participants with transient and persistent PEs had significantly poorer MSP-GAF scores than controls (p < .001 and p < .001, respectively). There was a significant effect of time (F = 6.145, p = .004) with participants having poorer MSP-GAF scores in mid-adolescence (p = .001) and early adulthood (p = .025) than in childhood. There was no significant interaction between time and group (F = 0.185, p = .945).

Simple effects analysis.

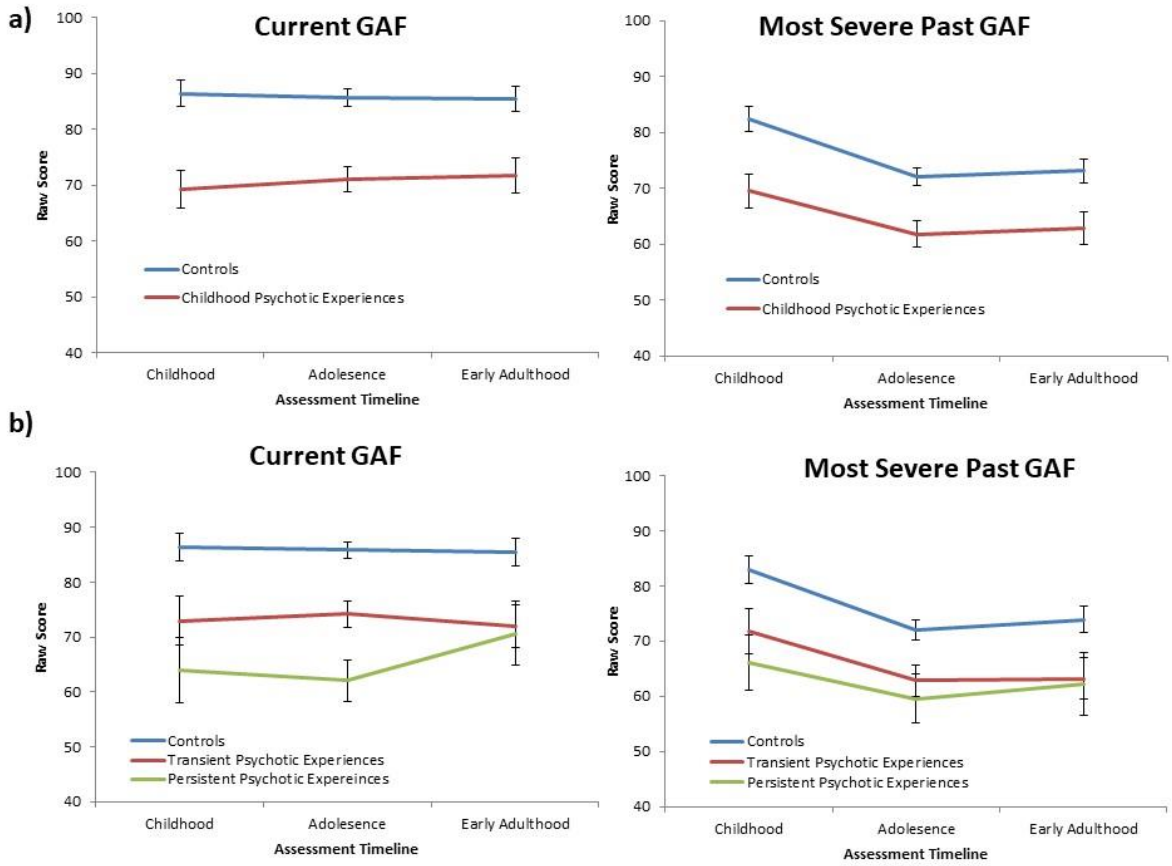
Transient PEs vs. Controls: Participants with transient PEs in childhood had poorer MSP-GAF scores than controls during childhood (p = .007) and somewhat during adolescence (p = .030). There was no significant difference between transient PEs and controls during early adulthood (p = .095).

Table 6.2. The mean and standard error GAF scores for each group through time for the primary analysis.

		Unadjusted	Adjusted for gender and mental disorder	Adjusted for gender, mental disorder and childhood functioning
Current - Global Functioning				
Childhood	*Childhood PEs*	66.86 (3.68)***	69.63 (3.58)**	-
	Controls	85.10 (2.68)	86.20 (2.56)	-
Adolescence	*Childhood PEs*	71.26 (2.38)***	70.73 (2.21)***	72.95 (2.32)***
	Controls	86.14 (1.69)	84.48 (1.59)	84.60 (1.57)
Early	*Childhood PEs*	71.56 (3.25)***	71.47 (3.27)**	73.51 (3.34)**
Adulthood	*Controls*	86.79 (2.30)	85.86 (2.51)	86.19 (2.52)
Most Severe Past - Global Functioning				
Childhood	*Childhood PEs*	62.77 (3.57)***	69.63 (3.17)***	-
	Controls	84.49 (2.76)	82.92 (2.40)	-
Adolescence	*Childhood PEs*	57.01 (3.26)***	61.83 (2.46)**	66.74 (2.41)
	Controls	76.73 (2.31)	72.01 (1.76)	70.10 (1.67)
Early	*Childhood PEs*	55.96 (3.89)***	62.89 (3.15)~*	68.22 (3.20)
Adulthood	*Controls*	77.41 (2.75)	73.92 (2.38)	72.73 (2.32)

Note: *** = *p <.001; ** = p <.01; * = p <.05; and ~*= p <.1*

Figure 6.2a. Current and most severe past global functioning scores for participants with and without childhood psychotic experiences. **6.2b.** Current and most severe past global functioning scores for participants with and without transient psychotic experiences (experiences reported in childhood alone). All scores are adjusted for the effects of mental disorder and gender.



Persistent PEs vs. Controls: Participants with persistent PEs had poorer MSP-GAF scores than controls during childhood ($p = .001$) and somewhat during adolescence ($p = .030$). There was no significant difference between persistent PEs and controls during early adulthood ($p = .391$).

Transient PEs vs. Persistent PEs: Participants with transient and persistent PEs did not significantly differ in MSP-GAF scores at any time point (childhood: $p = .374$; adolescence: $p = .517$; and early adulthood: $p = .735$).

Covariates. There was a significant main effect of mental disorder ($F = 96.030$, $p < .001$) but no significant effect of gender on MSP-GAF scores ($F = 2.451$, $p = .123$).

6.4 Discussion

In a community sample, we demonstrated for the first time that participants with a history of childhood PEs have persistently poorer global functioning throughout adolescence and into early adulthood. This effect was above and beyond what can be explained by mental disorder. This functional impairment was evident in both global functioning measures (current and most severe past), with highly significant and clinically relevant differences. The childhood PE group was characterised by scoring at least a one functional category lower than controls on the GAF at all-time points (average ~15 points).

The GAF scores of those with childhood PEs, while interpreted tentatively due to the small sample, formally constitute “probable to definite” functional impairment requiring intervention based on the definition employed by Bird et al.[15] and the Polanczyk et al.[27] meta-analysis. This significantly differs from those without a history of PEs were characterised by the GAF as having, at most, symptoms which were “transient and expectable reactions to psychosocial stressors” with “no more than slight impairment in social, occupational or school functioning” (see supplementary Table 1). The longitudinal association between childhood PEs and global functioning suggests an underlying global vulnerability in children reporting such experiences.

It is well established that PEs increase the risk of subsequent mental disorder. However, adjusting for mental disorder at each time point did not fully account for the relationship between PEs and functioning. The results suggest that the poorer functioning seen in children who report PEs cannot be wholly attributed to the presence of a diagnosable mental disorder. It is known that individuals with PEs have poorer psycho-social outcomes such as low self-esteem [7], lower educational attainment and are less likely to be in a romantic relationship [28]. Results from this study suggest that such negative psycho-social outcomes may have a relationship with PEs over and above what can be accounted for by co-occurring mental disorder.

Acknowledging the limitations of the small sample size, these results concur with findings from a larger longitudinal study with a two year follow up [20], which demonstrated that poorer functioning was evident even in participants with transient PEs. They also complement longitudinal studies indicating that those with PEs are vulnerable to subsequent mental disorder [8, 29-30].

Interestingly, after accounting for childhood functioning and mental disorder, we observed a relationship between childhood PEs and adolescent/early adulthood 'current' functioning, but not 'most severe past' functioning. One possible explanation for this is that the poorest level of functioning during any period ('most severe past' functioning) may be state dependent, indicating a reaction to psycho-social stressors present at the time. 'Most severe past', by definition, reflects a deviation from an individual's normal or 'trait' functioning. On the other hand, the association with current functioning suggests a trait characteristic. Most of the young people with a history of childhood PEs did not meet criteria for an on-going mental disorder at the time of interview, yet persistently poorer functioning was still evident. This adds additional support for the motion that children who report PEs have an underlying global vulnerability which extends beyond mental disorder.

The mechanisms behind the poorer functioning observed in those with childhood PEs are not known and few studies have investigated candidates. In a clinical sample of adolescent psychiatric patients, Wigman et al.[31] reported that those with PEs were more likely to adopt an avoidant coping strategy, and a sub-analysis tentatively suggests that this may be related to poorer functioning. Additionally, Kelleher et al.[12] reported that trauma, psychiatric disorder and certain cognitive domains, namely speed of processing/set shifting and visual working memory, moderate the relationship between childhood PEs and childhood functioning but do not fully mediate this relationship.

The results concur with findings suggesting that children presenting with PEs are a high risk group and should be monitored closely. Emerging adulthood is a crucial time for establishing the foundations of career aspirations as well as developing social and

romantic relationships [35]. Persistently poor social and occupational functioning during this period is likely to hinder an individual's progress towards such goals during this pivotal period of development. Moreover, mental disorders most often occur in the first two decades of life and are one of the greatest contributors to the global economic burden [32-34]. Projections of the economic cost of mental disorders do not include the costs associated with the unknown number of people who have functional difficulties but do not meet criteria for a diagnosable disorder. Utilising PEs as an early marker for functioning deficits as well as mental disorder and intervening accordingly may not only improve outcomes for those at risk but also benefit society by increasing global productivity.

6.4.1 Strengths and Limitations.

There were a number of strengths and limitations to this study. PEs, mental disorder and global functioning measures were all based on face-to-face clinical interviews, with characterised criteria for defining PEs. Transcripts of the notes on PEs from these interviews were also reviewed at a consensus meeting by three experts in psychosis. A well validated measure of functioning was used as the primary outcome. The sample used within this study is a community based sample, however attrition rates were only adequate and the ratio of those with PEs within this group is over-estimated relative to what is observed in the general population at this age range. Moreover, we advise caution when interpreting the effects of persistent PEs on global functioning.

The prevalence of persistent PEs within this sample was in keeping with the expected rate [21] , however, the sample size of this group hindered a more meaningful investigation into the functioning scores of this sub-set of participants. Nevertheless, the results are in line with previous observations [20]. Finally, recent research into the extended psychosis phenotype has been expanded to include sub-clinical negative symptoms [10,20]. Within this sample we do not have data pertaining to the negative symptoms of psychosis, therefore this facet represents a limitation of our investigation and an avenue to be explored in the future.

To conclude, children who report PEs continue to display poorer global functioning as they develop into early adulthood. Persistent global dysfunction suggests an underlying vulnerability which extends beyond diagnosable mental disorder. Despite the fact that most PEs are transient their associated effects can be long lasting.

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Declaration of Interest: None

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SECTION III

MEDIATORS OF THE OUTCOMES

Chapter 7

STUDY VI - WHAT MEDIATES THE LONGITUDINAL RELATIONSHIP BETWEEN PSYCHOTIC EXPERIENCES AND PSYCHOPATHOLOGY.

Thesis authors' role: Mr Healy was involved in all aspects of the investigation. He was involved in formulating the research question and drawing conclusions from the investigation. He conducted the literature search and statistical analysis. He was the first and corresponding author on the published manuscript.

Note: Below is a word document version of the study published in *Journal of Abnormal Psychology (In Press)*. None of the content of the article has been altered.

What mediates the longitudinal relationship between psychotic experiences and psychopathology?

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Abstract

Background: Psychotic experiences (PEs) are common in early adolescence and are associated with non-psychotic psychopathology. However, not all adolescents with PEs have subsequent psychopathology and vice-versa. To date, factors mediating the relationship between PEs and psychopathology have been under-studied.

Aims: To investigate the bidirectional relationship between PEs and psychopathology in adolescence, 2) to investigate potentially malleable mediators of these relationships.

Method: Data from two waves (age-13 and 17 years) of Cohort'98 of the Growing-Up in Ireland study were examined (n=6206). Using KHB-pathway decomposition, we investigated the following as potential mediators of the relationship between psychopathology and PEs: Parent-child relationship (conflict and positive), self-concept and child-peer relationship (alienation and trust). Supplementary counterfactual mediation and sensitivity analysis were conducted.

Results: Early adolescents with psychopathology had a two-fold increased odds of late adolescent PEs (Internalizing Problems: OR: 2.03, 95% CI: 1.56-2.62; Externalizing problems: OR: 1.99, 95% CI:1.51-2.60). Parent-child conflict explained between 23-34% of the associations between internalizing and externalizing problems and subsequent PEs. Early adolescents with PEs had an increased odds of late adolescent psychopathology (Internalizing Problems: OR: 2.01, 95% CI:1.61-2.50; and Externalizing Problems: OR:1.70,95%CI:1.25-2.31). Self-concept alone accounted for 52% of the relationship between PEs and subsequent internalizing problems.

Discussion: There is a bidirectional heterotypic relationship between psychopathology and PEs. Parent-child conflict and self-concept are important characteristics that mediate a proportion of the relationship between PEs and psychopathology. Interventions targeting parent-child conflict in the context of psychopathology and self-concept in the context of PEs may assist in reducing the incidence of poorer outcomes.

Keywords: Psychotic Experiences; Internalizing Problems; Externalizing Problems; Parent-Child Relationship; Self Concept;

General Scientific Summary: Psychotic experiences are common in adolescence and are frequently associated with other mental health problems. However, not all young people with psychotic experiences have mental health problems, and most with mental health problems do not have psychotic experiences. We found that psychotic experiences are bi-directionally associated with mental health problems. The relationship between psychotic experiences and subsequent mental health problems may partly be explained by the young person's self-concept. The relationship between mental health problems and subsequent psychotic experiences may partly be explained by conflict between the young person and their primary caregiver.

7.1 Introduction

Psychotic experience (PEs) are the sub-clinical expression of psychotic symptoms. They are reported by a substantial minority of the general population, with 17% of children and 8% of adolescents reporting PEs (Kelleher et al., 2012). PEs have been the subject of intense investigation because they have been shown to be associated with adverse outcomes. For example, a recent meta-analysis found that PEs in childhood are associated with a four-fold increase in odds for psychotic disorder and an almost three-fold increase in odds for a non-psychotic disorder (Healy et al., 2019a).

Psychotic experiences appear to have a bidirectional relationship with non-psychotic psychopathology (hereafter referred to as psychopathology) (McGrath et al., 2016). Children with psychopathology have been shown to have an increased risk of subsequent PEs (Scott et al., 2009), particularly those with persisting psychopathology (Lancefield et al., 2016). PEs in childhood and adolescence have also been associated with a range of both co-occuring and later mental disorders, including affective, anxiety, behavioral disorders as well as psychotic disorder (Bartels-Velthuis et al., 2010; Bartels-Velthuis et al., 2016; Healy et al., 2019a; Healy et al., 2019b; and Kelleher et al., 2012;).

It is possible that part of the reason for the bidirectional association between PEs and psychopathology is the result of a shared genetic liability (Legge et al., 2019). Additionally, environmental factors such as early life stress and trauma significantly increase the risk of both PEs and psychopathology (Coughlan and Cannon 2017; Arseneault et al., 2011; Kessler et al., 2010). These shared aetiological factors may partially explain or even compound the bidirectional association between PEs and psychopathology.

It has been reported that 57% of those who report PEs in early adolescence and 80% of those with PEs in mid-adolescence meet diagnostic criteria for any mental disorder (Kelleher et al., 2012). While this prevalence rate is much higher than that of the general adolescent population (Kessler et al., 2007), it also highlights that approximately two-fifths of early adolescents and one-fifth of mid-adolescents who report PEs do not meet

criteria for a mental disorder. This evidence supports the view that the relationship between psychotic experiences and mental disorder is “probabilistic not deterministic” (Linscott and van Os., 2013). Furthermore, it underlines the need to develop a more refined understanding of factors that mediate the association between psychopathology and PEs in childhood and adolescence. Ideally, these factors should be amenable to intervention so they can be targets to prevent subsequent psychosis or other psychopathology. This is particularly the case for individuals who may be at a high risk for mental disorder.

Traumatic experiences have been proposed as targets for intervention. However, in many cases, traumatic experiences are difficult or impossible to prevent and trauma interventions therefore often occur after the trauma has occurred.

One potentially promising area for preventative intervention is that of psychosocial factors; for example parent-child relationships, self-concept and child-peer relationships. These factors are easily identifiable and malleable. Parent-child relationship refers to the quality of the relational bond between parent and their children and is not simply equal to the sum of the exchanges between them (Driscoll & Pianta, 2010). Pianta (1997) divides this relational bond into three sub-constructs, positivity, dependency and conflict. Self-concept refers to the sum of an individual’s beliefs and knowledge about his/her personal attributes and qualities (Healy et al., 2019; Mann et al., 2004) and this term is frequently used inter-changeably with self-esteem (Piers & Herzberg, 2002). Finally, similar to parent-child relationship, child-peer relationship refers to the quality of the relational bond between children and their peers. Armsden and Greenberg (1987) describe three aspects of this relationship; trust, communication and alienation.

Encouragingly, evidence to date has already shown that even brief interventions targeting these factors are effective at reducing psychopathology (Haney & Durlak, 1998; Hall & Tarrier, 2003 Ewing et al., 2015; Piquero et al., 2016; Mikami et al., 2013). The three psycho-social factors above have all been linked to both PEs and psychopathology (child-parent relationship by Dhondt et al., 2019; Crush et al., 2018;

Boyda et al., 2018; self-concept by Dolphin et al., 2015; Hielscher et al., 2018; and Mann et al., 2004; and child-peer relations by El Bouhaddani et al., 2018; Kelleher et al., 2013; and Schreier et al., 2009).

Importantly, these factors have also been shown to mediate the homotypic and heterotypic trajectory of psychopathology. For example, Yong et al, (2014) has shown that parent-child conflict mediates the relationship between externalizing problems and subsequent internalizing problems. Johnson et al, (2016), demonstrated over six waves of data the reciprocal cross-lagged relationship between depression and self-esteem. This echoed the meta-analytical evidence for the bi-directional relationship between self-esteem with depression and anxiety over-time (Sowislo & Orth, 2013). Additionally, peer relationship, specifically peer rejection, has been shown to mediate the continuity of externalizing problems (Kim & Cicchetti, 2010). To-date however, no study has examined whether these variables mediate the bi-directional relationship between PEs and psychopathology.

The aim of the current study was two-fold. Firstly we examined the longitudinal bidirectional relationship between PEs and psychopathology, namely internalizing problems and externalizing problems. Secondly we explored the mediating role of the parent-child relationship, self-concept and child-peer relations on this bidirectional relationship. We hypothesized that PEs would increase the risk of subsequent psychopathology - and vice-versa - and that a proportion of these relationships would be explained by differences in the above psycho–social variables.

7.2 Method

7.2.1 Participants

Participants were members of the *Growing Up in Ireland* (GUI) study. The GUI is a longitudinal, nationally representative sample of children from the general population in Ireland. The GUI consists of two cohorts; an Infant cohort (also known as Cohort ’08) and a Child cohort (also known as Cohort ‘98). We present data on the Child cohort. The sample was generated from 910 randomly selected national primary schools of

which 82% agreed to participate in the study. Children aged 9 years were targeted for inclusion with 57% of families agreeing to participate. The child cohort comprises data from 8658 children and their families. This sample was weighted to ensure that study data were representative of the national population of 9-year olds in Ireland. The cohort was followed up in early adolescence (age 13 years, n = 7423, 88%) and again in late adolescence (age 17-18 years, n = 6216, 72%). Of the 6216 young people in the late adolescence sample, 6039 (97%) had data from all three time points.

To ensure national representation, the sample was reweighted to account for demographic differences between those who took part in the follow-ups and those who did not. Thus, this sample was representative of Irish children aged 9 who remained living in Ireland until age 17 or 18. Ethical approval for the GUI study was granted by the research ethics committee of the Health Research Board in Ireland. Ethical Approval for the secondary analysis was granted by the Research Ethics Committee of the Royal College of Surgeons in Ireland.

7.2.2 Measurement of exposures and outcomes

The exposures were measured in early adolescence (age 13). The outcomes were measured in late adolescence (age 17-18). The same questionnaires were used to measure both PEs and psychopathology at both time points.

Psychotic experiences. Psychotic experiences were measured using the *Adolescent Psychotic Symptoms Screener* (APSS) (Kelleher et al., 2011). The APSS is a self-report questionnaire comprising seven questions pertaining to hallucinatory and delusional experiences. Six of these were included in the GUI survey instrument. The six items included in the GUI study are listed below.

1) Have you ever heard voices or sounds that no-one else can hear?
2) Have you ever seen things that other people could not see*?*
3) Have you ever thought that people are following you or spying on you?
4) Some people believe that their thoughts can be read by another person. Have other people ever read your mind?

5) Have you ever felt that you were under the control of some special power?
6) Have you ever felt that you have extra-special powers*?*

The one item not included in the GUI study ("Have you ever had messages sent to you through TV or Radio") has previously been shown to have 0% positive predictive value for that particular type of phenomenon and only 40% positive predictive value for any type of psychotic experience (Kelleher, Harley, Murtagh, & Cannon, 2011). The participating adolescents were required to respond by circling "No" (0 points), "Maybe" (0.5 points) or "Definitely" (1 point) to each question. To be categorized as having experienced PEs participants were required to have a total score of two or more points on the APSS or to respond "definitely" to the question about auditory hallucinations. Both of these measurements have been validated against clinical interview and have been shown to have good sensitivity and specificity for PEs (two or more points: 70% and 86%; and definite auditory hallucination: 70% and 100%, respectively).

Psychopathology

Psychopathology was measured using the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001; Goodman & Goodman, 2009). Item responses on the SDQ were reported by the primary caregiver at age 13 and 17-18. The SDQ has four negative sub-scales (emotional problems, peer problems, conduct problems and hyperactivity). It does not have items on PEs. In line with Goodman ***et al's***, (2010) recommendations for epidemiology investigations into low risk populations, the SDQ was sub-divided into two commonly reported constructs, namely, internalizing problems and externalizing problems. Criteria for internalizing and externalizing problems were based on Goodman ***et al's***, (2001) original normative band suggestions for abnormal scores. The SDQ has been shown to have a reliability coefficient of $\alpha = 0.82$ within a community sample of children and adolescence (Goodman et al, 2001).

Internalizing problems. Internalizing scores were created by summing the emotional problems and peer problems sub-scales. Internalizing problems was defined as scoring seven or above on the internalizing scale (scoring above the summed borderline cut-off

for emotional problems and peer problems). This criteria was considered to be similar to those who have clinical levels of internalizing problems.

Externalizing problems. Externalizing scores were created by summing the hyperactivity problems and conduct problems sub-scales. Externalizing problems was defined as scoring nine or above on the externalizing scale (scoring above the summed borderline cut-off for hyperactivity problems and conduct problems). This criteria was considered to be similar to those who have clinical levels of externalizing problems.

Candidate Mediators

Our mediator variables were theorized to lie on the causal pathway between the exposure and the outcome. For the purpose of this investigation, candidate mediators had to be potentially malleable and amenable to intervention. These criteria resulted in us examining five mediator variables examined in the GUI study covering three themes.

Parent-child relationship. The parent-child relationship was measured using the Child-Parent Relationship Scale (Pianta, 1992). Two sub-scales were measured at age 13: a) Parent-Child Conflict and b) Parent-Child Positive. The Parent-Child Conflict sub-scale consists of statements assessing conflict between the child and the primary caregiver (higher scores indicates higher conflict). The Parent-Child Positive sub-scale consists of statements assessing the positive aspects of the relationship between the child and the primary caregiver (higher scores indicates more positive relationship). Each statement was rated by the primary caregiver on a five-point Likert scale ranging from “definitely does not apply” to “definitely applies”. Both scales were treated as continuous variables.

Child-peer relationship. Child-peer relationships were measured using the Inventory of Parent and Peer Attachment (Armsden & Greenberg, 1987). The Alienation and Trust subscales (peer subscales) were administered at age 13 (Gullone & Robinson, 2005). The reliability coefficient of these scales have been shown to be $\alpha = 0.69$ and $\alpha = 0.86$, respectively. The Trust subscale consists of 10 items (i.e. “My friends are fairly easy to talk to”) with higher score indicates greater trust and the alienation subscale consists of

7 items (i.e. “I feel alone or apart when I’m with my friends”) with higher scores indicate greater alienation. Each statement was rated by the participating child on a five point Likert scale ranging from “Almost Never or Not True” to “Almost Always or Always True”. Both scales were treated as continuous variables.

Self-concept. Self-concept (self-esteem) was measured using the Piers Harris-II (Piers and Herzberg 2002). The Piers Harris II is a 60 item self-report questionnaire, which is designed to assess self-concept in children aged between seven and eighteen years. The participating children were asked to respond “yes” or “no” to each statement regarding their perceptions of themselves (lower score indicating poorer self-concept). The Piers Harris II was administered at age 13. The Piers Haris II has been shown to have a reliability coefficient of $\alpha = 0.91$ within a community sample of children and adolescence (Piers and Herzberg 2002). The self-concept scale was treated as a continuous variable.

Confounding variables.

The proposed confounding variables were variables that had a known or a possible association with the exposure, mediator and the outcome. It was proposed that these variables did not lie on the causal pathway between the exposure and the outcome. These variables include demographic and family confounders and exposure to childhood adversity.

Demographic confounders. We investigated the participating child’s age, gender, handedness, nationality (Irish or non-Irish nationality), ethnic background (White Irish, White non-Irish, Black or Asian/Other) and urbanicity (living in a rural or urban area) and family history of mental disorder (reported by wave two) as demographic and family confounders. Urban areas were defined as living in an area with a population density of >10,000 people. Socio-economic status was investigated using the primary caregiver’s highest educational attainment (none/primary education only to post-graduate education). Family history of mental disorder was reported by the primary caregiver at waves 1 and 2 of the study.

***Exposure to Childhood adversity*.** The GUI investigated 13 specific early life stressors that the child may have been exposed to. These included the seven severe stressor (death of a parent, death of a close friend, parent in prison, drug abuse or alcoholism in the immediate family, serious illness/injury, mental disorder in family, stay in foster home) and six less severe events (moving home, moving country, serious illness/injury of a family member, conflict between parents, separation/divorce of parents, death of a close family member). These were reported by the primary caregiver. In line with our recent investigation into adversity (Dhondt et al., 2019), exposure was defined as experiencing to three or more minor events or at least one of the seven most severe events.

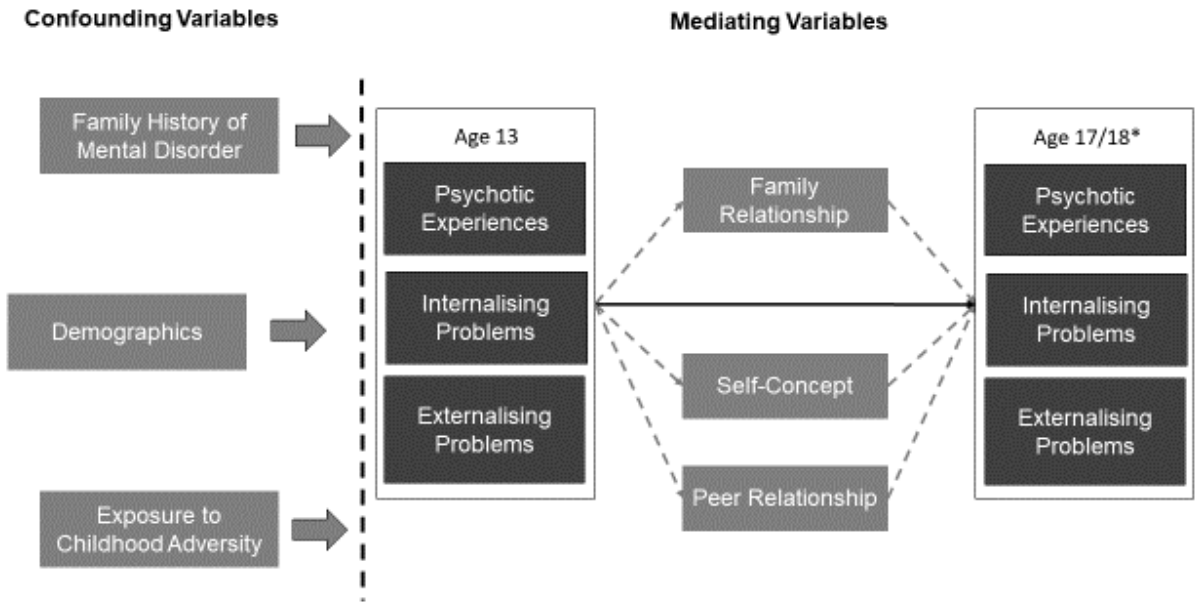
7.3 Statistical Analysis

All statistical analyses were conducted using Stata 15. T-tests and logistic regressions were used to examine the demographic characteristics of those who reported early adolescent PEs, internalising problems and externalising problems (see Table 7.1). All continuous variables were standardised using a z-score transformation. Exposure variables were PEs, internalising problems and externalising problems in early adolescence (age 13). Outcome variables were PEs, internalising problems and externalising problems in late adolescence (age 17-18). Logistic regression was used to investigate the heterotypic and homotypic relationships between early adolescent exposures and late adolescent outcomes (see Table 7.2). In addition to the confounders, in all analysis investigating heterotypic associations we additionally adjusted for early adolescent exposure to the outcome.

In line with mediation theory recommendations (Baron & Kenny, 1986), regression was used to investigate the relationship between the candidate mediator variables and each exposure and outcome variable (see Table 7.3). Linear regression was used to investigate the relationship between each exposure and the candidate mediators while logistic regression was used to investigate the relationship between mediators and outcomes. Variables found to be significantly associated with both exposures and

outcomes were investigated as mediators of the bidirectional relationship between PEs and psychopathology. This was investigated using three analytical styles. Firstly, data were analysed using KHB path-decomposition (Breen, Karlson & Holm., 2013), a method that allows for the nationally representative data weighting with an easy-to-interpret outcome metric: odds ratios and 95% confidence intervals for total, direct and indirect associations as well as the percentage mediated. Two additional counter factual mediation analyses were conducted as well as sensitivity analysis to estimate confounder bias (see supplementary materials). A visualisation of the investigation is presented in Figure 7.1.

Figure 7.1. The model of the pathway between early and late adolescent psychotic experiences and psychopathology.



7.3 Results

Prevalence and characteristics. In early adolescence, 12.8% of participants reported PEs, 8.5% had internalising problems and 8.0% had externalising problems. The demographic characteristics of adolescents with PEs, internalising problems and externalising problems are presented in Table 7.1.

There were significant differences between those with and without PEs in age, gender, nationality, cultural background, living in an urban area and a family history of mental disorder childhood adversity and early adolescent psychopathology. Internalising problems were significantly associated with being female, living in an urban area, lower socio-economic status, and a family history of mental disorder childhood adversity and early adolescence PEs and externalising problems. Externalising problems were significantly associated with being male, coming from an urban area, having a family history of mental disorder and lower socio-economic status childhood adversity and internalising problems. In late adolescence, 9.8% of participants reported PEs, 10.1% had internalising problems and 5.4% had externalising problems.

Longitudinal heterotypic and homotypic associations between psychotic experiences, internalizing problems and externalizing problems

Homotypic associations. As evident from Table 7.2, there were strong homotypic associations between early adolescent exposures and late adolescent outcomes for PEs and psychopathology. 33% of those who had externalizing problems in early adolescence also had externalizing problems in late adolescence. 26% of those with PEs in early adolescence also reported PEs in late adolescence. 31% of those with internalizing problems in early adolescence also reported internalizing problems in late adolescence. Strong associations were retained even after adjustment for the other exposures (OR range: 4.11 – 11.86)

Heterotypic associations. Strong heterotypic associations were also found between PEs, internalizing problems and externalizing problems (see Table 7.2). Odds ratios ranged in values from 1.70-3.64. These associations were bidirectional and were evident even after adjustment for the other exposures (with the exception of the early adolescent internalizing problems and late adolescent externalizing problems).

Table 7.1. Demographic characteristics of individuals with early adolescent psychotic experiences, internalizing problems, externalizing problems.

Sample characteristics	**Early Adolescence**						
	Overall	**Psychotic Experiences**	**Odds Ratio** (95% CI)	**Internalizing Problems**	**Odds Ratio** (95% CI)	**Externalizing Problems**	**Odds Ratio** (95% CI)
Adolescence Age (Mean, SD)	13.00	13.01	**0.09 (0.02–0.17)[a]**	12.98	**0.15 (0.05-0.25)[a]**	13.00	0.03 (-0.08-0.13)[a]
Gender (% of Males)	50.9	45.1	**1.28 (1.09-1.50)**	46.4	**0.82 (0.69-0.98)**	60.8	**1.55 (1.28-1.87)**
Handedness (% Left Handed)	12.8	13.4	1.09 (0.87-1.37)	12.4	0.96 (0.73-1.26)	15.5	1.28 (0.99-1.66)
Nationality (% of Non-Irish)	4.5	5.7	**1.41 (1.00-1.99**)	<7.0[b]	n/s[c]	<6.5[b]	n/s[c]
Urbanicity (% Living In Urban Area)	44.0	50.5	**1.35 (1.15-1.58**)	49.5	**1.28 (1.06-1.53**)	48.8	**1.23 (1.02-1.49**)
Primary Care Givers Cultural Background (%)							
White Irish	92.1	87.6	Ref	92.8	Ref	94.3	Ref
White Non-Irish	5.4	9.1	**1.87 (1.41-2.49)**	<7.0[b]	n/s[c]	<6.5[b]	n/s[c]
Black	1.1	<4.5[b]	n/s[c]	<7.0[b]	n/s[c]	<6.5[b]	n/s[c]
Asian/Other	1.3	<4.5[b]	**Sig [c]**	<7.0[b]	n/s[c]	<6.5[b]	n/s[c]
Socio-Economic Status (%)							
None/Primary	5.6	5.4	1.01 (0.71-1.46)	12.5	**2.95 (2.15-4.04)**	14.0	**2.83 (2.08-3.84)**
Lower Secondary	23.5	24.3	1.10 (0.90-1.35)	33.8	**1.75 (1.40-2.20)**	27.5	1.18 (0.93-1.49)
Tech Vocational/Upper Secondary	37.1	36.0	Ref	32.0	Ref	37.4	Ref
Non Degree	16.5	15.0	0.92	11.8	0.82	12.5	**0.74**

			(0.73-1.17)		(0.60-1.11)		**(0.55-0.99)**
Primary Degree	11.2	12.1	1.15	<7.0[b]	n/s[c]	<6.5[b]	**Sig [c]**
			(0.88-1.48)				
Post Grad	6.1	7.3	1.27	<7.0[b]	**Sig [c]**	<6.5[b]	**Sig [c]**
			(0.92-1.75)				
Family History Of Mental Disorder (%)							
Reported By Adolescence	6.1	7.8	**1.40 (1.04-1.88)**	14.5	**3.05 (2.32-4.00)**	17.8	**4.09 (3.15-5.32)**
Exposure To Adversity (%)							
Reported In Childhood	28.6	34.7	**1.39 (1.17-1.64)**	42.3	**1.91 (1.59-2.30)**	37.6	**1.53 (1.26-1.86)**
Early Adolescent Psychopathology							
Psychotic Experiences	12.8	-	**-**				
Internalising Problems	8.5	14.3	**2.15 (1.70-2.71)**	-	**-**	35.0	**8.11 (6.53-10.07)**
Externalising Problems	8.0	12.0	**1.78 (1.39-2.29)**	32.8	**8.11 (6.53-10.07)**	-	**-**

Note: Emboldened metrics denote significant differences (p <.05). [a] : Denotes Cohen's d effect size (absolute value) and the 95%ile confidence intervals. Socio-economic status was measured using the primary care givers highest level of education. [b] : Bottom-coded to preserve anonymity. [c]: Odds ratio and confidence intervals removed for statistical disclosure purposes. Sig : Significant finding but removed for statistical disclosure purposes. n/s: Non-significant finding but removed for statistical disclosure purposes.

Table 7.2. Prevalence of the exposures, outcomes, the positive predictive value and the adjusted odds ratio and 95th percentile confidence interval for the longitudinal association between the exposures and outcomes.

Early Adolescence		**Late Adolescence**								
		Psychotic Experiences			**Internalizing Problems**			**Externalizing Problems**		
Incidence (%)		9.8 (n=575)			10.1 (n=604)			5.4 (n=321)		
		PPV % 95% CI	**OR** 95% CI	**AOR** 95% CI	**PPV %** 95% CI	**OR** 95% CI	**AOR** 95% CI	**PPV %** 95% CI	**OR** 95% CI	**AOR** 95% CI
Psychotic Experiences	12.8 (n=725)	26.1 (22.8-29.5)	**4.29** (3.49-5.28)	**4.11** (3.34-5.06)	17.1 (14.3-20.1)	**2.01** (1.61-2.50)	**1.68** (1.33-2.13)	6.6 (4.9-8.8)	**1.70** (1.25-2.31)	**1.39** (1.00-1.95)
Internalizing Problems	8.5 (n=514)	15.7 (12.4-19.6)	**2.03** (1.56-2.62)	**1.56** (1.16-2.11)	41.2 (36.5-46.0)	**7.66** (6.18-9.48)	**6.35** (5.02-8.04)	13.6 (10.5-17.3)	**3.64** (2.74-4.83)	1.25 (0.87-1.80)
Externalizing Problems	8.0 (n=481)	18.4 (14.4-23.0)	**1.99** (1.51-2.60)	**1.57** (1.15-2.13)	22.9 (18.6-27.7)	**3.31** (2.59-4.23)	**1.94** (1.46-2.58)	32.8 (27.8-38.0)	**13.60** (10.51-17.61)	**11.86** (8.93-15.76)

Note: Reported incidence are weighted. PPV%: The positive predictive value and 95% confidence interval of the early adolescent exposure on the outcome. OR 95%CI: The odds ratio and 95% confidence interval for the exposure and the outcome adjusting for confounders. AOR 95%CI: The odds ratio and 95% confidence interval for the exposure and the outcome adjusting for confounders and the other exposures.

Table 7.3. The association between candidate mediators, exposures and outcomes.

	Candidate Mediators				
Psychopathology	**Parent Child Conflict**	**Parent Child Positive**	**Self-Concept**	**Peer Trust**	**Peer Alienation**
Early Adolescence (Age 13)[a]					
Psychotic Experiences	**0.17**	**-**0.03	**-0.75**	**-0.27**	**0.52**
	(0.10-0.25)	(-0.11- -0.04)	(-0.83- -0.68)	(-0.35- -0.19)	(0.44- 0.59)
Internalizing Problems	**0.95**	**-0.34**	**-0.69**	**-0.39**	**0.60**
	(0.86-1.04)	(-0.43- -0.25)	(-0.78- -0.59)	(-0.49- -0.30)	(0.51- 0.70)
Externalizing Problems	**1.41**	**-0.61**	**-0.43**	**-0.34**	**0.32**
	(1.33-1.50)	(-0.70- -0.52)	(-0.52- -0.33)	(-0.44- -0.24)	(0.23- 0.42)
Late Adolescence (Age 17//18)[b]					
Psychotic Experiences	**1.20**	**0.89**	**0.75**	0.92	**1.27**
	(1.10-1.31)	(0.81-0.97)	(0.70-0.83)	(0.84-1.00)	(1.16-1.39)
Internalizing Problems	**1.50**	**0.81**	**0.69**	**0.81**	**1.10**
	(1.38-1.64)	(0.75-0.88)	(0.63-0.74)	(0.75-0.88)	(1.01-1.20)
Externalizing Problems	**1.82**	0.93	**0.84**	0.91	1.12
	(1.62-2.04)	(0.83-1.04)	(0.75-0.94)	(0.81-1.01)	(0.99-1.27)

Note: Emboldened metrics denote significant differences (p <.05). [a]: The investigation between exposures and the mediators was investigated using linear regression. [b]: The relationship between mediators and exposure/outcome were investigated using logistic regression. All analysis are weighted.

Bi-directional mediation analysis between psychotic experiences and psychopathology

Early adolescent exposures association with the candidate mediators. As evident from Table 7.3, when we examined the relationships between our early adolescent exposures and our candidate mediators, PEs, internalizing problems and externalizing problems were all independently associated with parent-child conflict, self-concept, peer trust and peer alienation. Internalizing and externalizing problems were both associated with lower scores on the parent child positive scale.

However, no significant association was observed between PEs and the parent-child positive scale.

Candidate mediator association with the late adolescent outcomes. Our examination of the relationships between our candidate mediators and our late adolescent outcomes found that parent-child conflict and self-concept and peer alienation were each significantly associated with late adolescent outcomes (see Table 7.3). Higher positive-parent child relationship score were associated with significantly reduced risk of PEs and internalizing problems. Higher peer alienation scores were associated with late adolescent PEs and internalizing problems. Higher peer trust was associated with a decreased risk of internalizing problems.

Mediators of heterotypic relationship between early adolescent and late adolescent psychotic experiences and psychopathology

Early adolescent internalizing problems and late adolescent psychotic experiences. Parent-child conflict, self-concept and peer alienation mediated a significant proportion of the relationship between early adolescent internalizing problems and late adolescent PEs (percentage mediation range: 24-28%, see Table 7.4).

Multivariate path-decomposition demonstrated that parent-child conflict and self-concept combined mediated over 40% of the relationship between early adolescent internalizing problems and late adolescent PEs. After accounting for these indirect effects there was

no significant direct relationship between early adolescent internalizing problems and late adolescent PEs (OR: 1.26, CI (0.82-1.96), p = .293).

Table 7.4. Path decomposition of the heterotypic longitudinal relationships between internalizing problems, externalizing problems and psychotic experiences.

Mediator Variables	Univariate Path Decomposition				Multivariate Path Decomposition	
	Total Effect OR (95% CI)	**Indirect OR** (95% CI)	**Direct OR** (95% CI)	**Percentage Mediation Univariate**	**Multivariate Indirect OR** (95% CI)	**Percentage Mediation Multivariate**
Internalizing Problems and Subsequent Psychotic Experiences						
Parent Child Conflict	**1.76** (1.17-2.64)	**1.15** (1.02-1.30)	1.53 (0.99-2.64)	**24.7**	**1.13** (1.00-1.26)	**22.8**
Parent Child Positive	**1.86** (1.14-3.01)	1.04 (0.99-1.10)	**1.78** (1.09-2.89)	7.0	-	-
Self-Concept	**1.81** (1.21-2.70)	**1.18** (1.08-1.28)	**1.54** (1.02-2.30)	**27.6**	**1.12** (1.04-1.21)	**21.4**
Peer Alienation	**1.73** (1.03-2.88)	**1.14** (1.02-1.26)	1.51 (0.92-2.51)	**23.6**	1.07 (0.98-1.15)	12.6
Externalizing Problems and Subsequent Psychotic Experiences						
Parent Child Conflict	**1.78** (1.16-2.73)	**1.21** (1.00-1.46)	**1.47** (0.90-2.39)	**33.56**	1.15 (0.97-1.35)	24.6
Parent Child Positive	**1.77** (1.15-2.72)	1.06 (0.98-1.14)	**1.68** (1.09-2.59)	9.7	-	-
Self-Concept	**1.80** (1.16-2.78)	**1.12** (1.04-1.19)	**1.61** (1.04-2.51)	**18.6**	**1.08** (1.02-1.14)	**13.0**
Peer Alienation	**1.80** (1.17-2.79)	**1.07** (1.01-1.13)	**1.70** (1.10-2.62)	**10.7**	1.04 (0.99-1.08)	5.9
Psychotic Experiences and Subsequent Internalizing Problems						
Parent Child Conflict	**1.77** (1.29-2.45)	**1.05** (1.00-1.10)	**1.68** (1.22-2.31)	**9.0**	**1.05** (1.00-1.10)	**8.1**
Self-Concept	**1.64** (1.19-2.26)	**1.29** (1.17-1.44)	**1.27** (0.91-1.76)	**52.1**	**1.25** (1.13-1.36)	**38.5**
Peer Trust	**1.78** (1.30-2.42)	**1.05** (1.01-1.09)	**1.70** (1.25-2.31)	**8.2**	**1.02** (0.99-1.05)	3.4
Peer Alienation	**1.78** (1.31-2.41)	1.03 (0.97-1.10)	**1.72** (1.26-2.35)	5.9	**-**	-
Psychotic Experiences and Subsequent Externalizing Problems						
Parent Child Conflict	1.58 (0.94-2.67)	1.08 (1.00-1.16)	1.47 (0.87-2.47)	**16.2**	**-**	-
Self-Concept	1.45 (0.84-2.49)	1.12 (0.97-1.29)	1.30 (0.74-2.28)	30.1	**-**	-

Note: Emboldened metrics denote significant differences (p <.05). -: Not included in the multivariate path-decomposition.

Early adolescent externalizing problems and late adolescent psychotic experiences. Parent-child conflict, self-concept and peer alienation mediated a significant proportion of the relationship between early adolescent externalizing problems and late adolescent PEs . The percentage mediated ranged from 11–34%. Multivariate path-decomposition demonstrated that only self-concept was retained as a significant mediator of the relationship between early adolescent externalizing problems and late adolescence PEs.

Early adolescent psychotic experiences and late adolescent internalizing problems. Parent-child conflict, self-concept and peer trust mediated a significant proportion of the relationship between early adolescent PEs and late adolescent internalizing problems, with self-concept alone mediating over half of this relationship (percentage mediation range: 8-52%). Multivariate path-decomposition demonstrated that both parent-child conflict and self-concept combined mediated a proportion of the relationship between early adolescent PEs and late adolescent internalizing problems. After accounting for these indirect effects there was no significant direct relationship between of early adolescent PEs and late adolescent internalizing problems (OR: 1.03, CI (0.68-1.55), p = .880).

Early adolescent psychotic experiences and late adolescent externalizing problems. When accounting for early adolescent externalizing problems only parent-child conflict mediated a significant proportion of the relationship between early adolescent PEs and late adolescent externalizing problems. After accounting for this indirect effect there was no significant relationship between early adolescent PEs and late adolescent externalizing problems. There was no significant mediating effect of self-concept.

Mediators of homotypic relationship between early and late adolescent psychotic experiences internalizing problems and externalizing problems

Early and late adolescent psychotic experiences. Parent-child conflict, self-concept and peer alienation significantly mediated a proportion of the relationship between early

and late adolescent PEs (2-14%). Multivariate path-decomposition demonstrated that only self-concept was retained as a significant mediator of the relationship between early and late adolescent PEs (see Table 7.5). After accounting for these indirect effects there was still a strong significant direct relationship between early and late adolescent PEs (OR: 3.59, CI (2.70-4.78), p < .001).

Table 7.5. Path decomposition of the homotypic longitudinal relationship between internalizing problems, externalizing problems and psychotic experiences.

Mediator Variables	**Univariate Path Decomposition**				**Multivariate Path Decomposition**	
	Total Effect OR (95% CI)	**Indirect OR** (95% CI)	**Direct OR** (95% CI)	**Percentage Mediation Univariate**	**Multivariate Indirect OR** (95% CI)	**Percentage Mediation Multivariate**
Psychotic Experiences and Subsequent Psychotic Experiences						
Parent Child Conflict	**4.32** (3.29-5.66)	**1.03** (1.00-1.06)	**4.18** (3.19-5.49)	**2.14**	1.02 (0.99-1.05)	1.59
Self-Concept	**4.33** (3.30-5.69)	**1.23** (1.11-1.35)	**3.52** (2.65-4.68)	**14.1**	**1.16** (1.06-1.26)	**9.76**
Peer Alienation	**4.52** (3.44-5.93)	**1.13** (1.05-1.22)	**3.99** (3.03-5.26)	**8.25**	1.06 (0.99-1.14)	4.37
Internalizing Problems and Subsequent Internalizing Problems						
Parent Child Conflict	**8.20** (5.97-11.25)	**1.47** (1.29-1.67)	**5.58** (3.97-7.83)	**18.3**	**1.44** (1.29-1.59)	**17.36**
Parent Child Positive	**7.85** (5.78-10.63)	**1.07** (1.02-1.12)	**7.31** (5.37-9.95)	**3.39**	1.01 (0.97-1.06)	0.60
Self-Concept	**7.87** (5.69-10.88)	**1.30** (1.17-1.44)	**6.06** (4.39-8.36)	**12.64**	**1.24** (1.13-1.35)	**10.39**
Peer Trust	**7.34** (5.36-10.06)	**1.09** (1.03-1.15)	**6.76** (4.91-9.30)	**4.18**	1.03 (0.97-1.08)	1.24
Peer Alienation	**7.23** (5.28-9.91)	1.06 (0.98-1.14)	**6.83** (4.96-9.41)	2.88	-	-
Externalizing Problems and Subsequent Externalizing Problems						
Parent Child Conflict	**14.98** (9.81-22.88)	**2.33** (1.72-3.16)	**6.43** (3.81-10.87)	**31.25**	**2.33** (1.72-3.16)	**31.25**
Self-Concept	**13.69** (8.98-20.85)	1.08 (0.99-1.17)	**12.70** (8.22-19.63)	2.85	**-**	-

Note: Emboldened metrics denote significant differences (p <.05). -: Not included in the multivariate path-decomposition.

Early and late adolescent internalizing problems. Parent-child conflict, positive parent child relationship, self-concept and peer alienation significantly mediated a proportion of the relationship between early and late adolescent internalizing problems (2-14%). Multivariate path-decomposition demonstrated that combined parent-child conflict and self-concept mediated 28% of this relationship with parent-child conflict having the largest contribution. After accounting for these indirect effects there was still a strong significant direct relationship between early and late adolescent internalizing problems (OR: 4.38, CI (3.03-6.34), $p < .001$).

Early and late adolescent externalizing problems. Parent-child conflict mediated almost a third of the relationship between early and late adolescent externalizing problems (31%). After accounting for this indirect effect there was still a strong significant direct relationship early and late adolescent externalizing problems (OR: 6.43, CI (3.81-10.87), $p < .001$). There was no significant mediating effect of self-concept.

Supplementary analysis. Our supplementary analysis comparing counter factual analysis with KHB path-decomposition demonstrates that there were little differences in the estimated percentage mediation, total effect, direct effect and in-direct effect between the statistical approaches to mediation used (see supplementary materials Table 1-6). Additional, sensitivity analysis revealed that our findings relating to parent child conflict and self-concept were relatively robust to confounding. A confounder variable would have to explain between 10% and 40% of the residuals variance in both the mediator and the outcome to remove the effect of our mediator variables. For comparison, the percentage of the variance explained by three major observed confounders (family history of mental disorder, childhood adversity and socio-economic status) in the mediator-outcome relationship are reported in supplementary Table 7.

7.4 Discussion

From this large, longitudinal nationally representative study, we report two major findings. Firstly, we present evidence that there are strong homotypic and heterotypic associations between PEs and both internalizing and externalizing problems during the developmental period from early to late adolescence. The heterotypic associations were evident even after adjusting for the other exposures. All analyses were also adjusted for major known confounding variables. Findings from this study complement those found previously (McGrath et al., 2016; Scott et al., 2009; Lancefield et al., 2016; Dhosse et al., 2002) and provide confirmatory longitudinal evidence of a bidirectional relationship between PEs and psychopathology.

Secondly, we present evidence that both parent-child conflict and self-concept mediate the bidirectional relationship between PEs and psychopathology. The strength of the contribution of each of these factors differed depending on whether individuals presented with PEs or psychopathology in early adolescence. When individuals presented with psychopathology, the majority of the indirect effect on late adolescent outcomes were attributable to parent-child conflict. Self-concept was found to have a more secondary contribution. However, when participants reported PEs in early adolescence, the majority of the indirect effect on late adolescent outcomes was attributable to self-concept. This was particularly evident for internalizing problems where self-concept alone accounted for 52% of relationship between early adolescent PEs and late adolescent internalizing problems. Our findings suggest that self-concept may be a useful intervention target to reduce the incidence of later internalizing problems among young adolescents who report PEs.

The role of parent-child conflict in the association between early adolescent psychopathology and late adolescent outcomes

Similar to previous reports (Lancefield et al., 2016; and Scott et al., 2009), we found that young people who report early adolescent psychopathology are at higher risk of late adolescent PEs. Our analysis suggests that one-quarter of this association could be attributed to parent-child conflict. Parent-child conflict has previously been found to

mediate the heterotypic relationship between externalizing problems and subsequent internalizing problems (Yong et al., 2014). Parent-child conflict has been examined in relation to psychopathology and has been found to increase the risk of externalizing disorders (Burt et al., 2003). In line with Yong and colleagues (2014), we suggest that parent-child conflict may be a consequence of the early adolescent psychopathology. The consequence of this conflict may further lead to a broad range of psychiatric phenomena, including PEs, internalizing problems and externalizing problems.

Parent-child-conflict has not, however, been routinely examined in the field of PE research. Rather, PE research has tended to focus on other dimensions of family functioning, such as exposure to factors such as abuse, neglect, domestic violence or parent-parent conflict (Coughlan and Cannon 2017; McGrath et al., 2017). Conversely, living in a supportive family environment has been found to be protective against PEs (Crush et al 2018). These combined findings suggest that aspects of a young person's family environment and relationships can either place them at risk of or protect them against both psychopathology and PEs and highlight the importance of assessing family factors among young people with psychopathology. However, many of the family risk exposures that have been identified in PE research to date (such as trauma) are not readily amenable to intervention. In contrast, parent-child conflict may be amenable to intervention. Our results suggest that interventions aimed at decreasing parent-child conflict among early adolescents presenting with psychopathology could reduce the risk of PEs and psychopathology in late adolescence. These results warrant further non-observational investigations.

Self-concept and peer alienation were also identified as mediating the relationship between psychopathology and PEs. However, this role was considerably reduced when simultaneously considered with parent child-conflict. Positive parent-child relationship and peer trust were protective against early adolescent psychopathology and late adolescent PEs but did not mediate this relationship. This provides further support for providing interventions that focus on promoting positive social and family relationships among young people with psychopathology.

The role of self-concept in the association between early adolescent PEs and late adolescent psychopathology

In line with previous evidence (Downs et al., 2016; Healy et al., 2019) we found that early adolescent PEs were associated with late adolescent psychopathology. Our analysis suggested that self-concept alone accounted for half of the association between PEs and subsequent internalizing problems and a significant proportion of the association with subsequent PEs. PEs have previously been associated with poorer self-concept scores (Dolphin et al., 2015; Healy et al., 2019; Hielscher et al., 2018) and there is longstanding evidence that self-concept has a bidirectional relationship with psychopathology (Rosenberg et al., 1989).

Self-concept has been shown to mediate the relationship between internalizing and externalizing problems (Lee & Stone, 2012), between peer aggression and internalizing problems (Ybrandt et al., 2010), and between childhood maltreatment and well-being (Greger et al., 2017). Additionally, self-concept has been shown to mediate the pathway between trauma and psychosis (Evans et al., 2015). However to our knowledge, no other investigation has examined whether self-concept mediates the relationship between PEs and psychopathology. Our results suggest that self-concept may account for a large proportion of the pathway between early adolescent PEs and subsequent internalizing problems and this warrants further investigation. Interestingly, our path-decomposition analysis did not find a total, direct or indirect pathway between PEs and subsequent externalizing problems. This observation is similar to previous findings by Trotta and colleagues (Trotta et al., 2019). After accounting for childhood psychiatric exposure, there was no significant relationship between early adolescent PEs and subsequent conduct disorder or attention deficit hyper-activity disorder.

Parent-child conflict peer trust and peer alienation were identified as mediating a smaller proportion of the relationship between PEs and subsequent internalizing problems or PEs. These findings were not retained on multivariate investigations.

Our results highlight the importance of both internal (self-concept) and external (family based) perceived support structures in the face of psychopathology or PEs in adolescence. Differences in these support structures may alter the young person's ability to cope with current psychopathology, which may increase the risk of subsequent heterotypic negative outcomes. Maladaptive coping, such as increased emotion-orientated coping (i.e. worry and self-blame) has already been associated with transient and persistent PEs (Lin et al., 2011; and Wigman et al., 2014). Future research could investigate the interactive effects of differences in support structures and coping styles on the relationship between psychopathology and PEs.

7.4.1 Strengths and limitations

There were several strengths to the study. This is a large-scale nationally representative longitudinal cohort of children. Psychotic experiences were measured using a self-report instrument that has been explicitly validated with adolescents (Kelleher et al., 2009) and the prevalence estimates are in line with meta analysis estimates from the same age range (Kelleher, 2012b). The SDQ is a widely used instrument and we followed the authors' recommended guidelines for epidemiological studies (Goodman et al., 2009). Strict criteria were used to maximise the potential to examine directionality in our findings.

A major strength of the study is our use of counterfactual mediation to confirm our results. There was little difference in the percentage mediated, the direct or in-direct effects between the traditional mediation and the counterfactual mediation styles of analysis. We also ran sensitivity analysis to investigate potential confounder bias. Sensitivity analysis suggested that a confounder would have to explain between 10-40% of the unexplained variance in both the mediator and outcome to remove the effects of either parent-child conflict or self-concept. While this finding are relatively robust to a single omitted confounder, it is possible that this degree of variance could be achieved by several small unmeasured confounders.

Conversely, the fact that our mediating variables were measured at the same wave of the GUI study as our exposure makes it challenging to disentangle the direction of the relationship between the mediator and the exposure and it is possible that the relationships between our mediators and our exposures are bidirectional. This may be particularly important to consider given the large mediating effects of self-concept on the relationship between early adolescent PEs and late adolescent internalizing problems. Such a results should be interpreted with caution given observational nature of the data and cross-sectional pathway between the exposure and the mediator. We suggest that follow up investigation is required to fully establish the directionality of these relationships before our findings can be confirmed.

We also acknowledge a number of additional limitations to the study. The APSS questionnaire is limited by the the absence of additional data on factors associated with psychotic phenomena, such as distress or freqency. The SDQ was completed by the primary care giver and there is evidence that measures of self-report and parent reported psychopathology may differ (Van Roy et al., 2010). We acknowledge that this may be less reliable than report from both respondents and clinical interview. While we attempted to adjusted for known genetic (family history of mental disorder) and environmental (exposure to early life stress) risk factors that increase the risk of both PEs and psychopathology it is possible that residual confounding could have occurred. For example, the GUI does not have access to biological data and we cannot rule out residual effects of heritability beyond those who endorse a family history of mental disorder. Similarly, while we adjust for a number of known early life stressors the GUI does not have data on severe traumatic experiences such as abuse or neglect. Again, it is possible that there was residual confounding contributing to both PEs and psychopathology.

It is important to state that our results come from observational data and mediation analysis has strong causal assumptions which observational studies typically violate. We attempted to account for this using counter factual mediation which replicated our results. Nevertheless, we suggest that the mediating effects of self-concept and parent

child conflict on the relationship between PEs and psychopathology requires further investigation from non-observational data.

7.4.2 Conclusion

Findings from this study mark an important step in enhancing our understanding of some of the dynamics underlying the relationship between psychopathology and PEs in adolescents. They suggest that there is a strong and complex bidirectional relationship between adolescent psychopathology and PEs that can be best described as probabilistic rather than deterministic. The reasons why some young people with psychopathology go on to report PEs and others do not, and vice-versa, has heretofore been poorly understood. Our results provide the first observational evidence suggesting that these relationships can in part be explained by differences in parent-child conflict and self-concept. These variables are eminently amenable to clinical assessment and intervention and they offer a potential framework for developing clinical interventions to reduce the incidence and human impact of both psychopathology and PEs in youth populations.

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Chapter 8

Discussion

Chapter Overview.

This chapter provides a narrative review of the findings for the six studies which comprise this PhD and provides a context for the findings in the previous literature. We present the implications of the conducted research as well as suggestions for future research. The overall strengths and limitations of the research are also discussed.

Thesis authors' role: Mr Healy authored the discussion.

8. Discussion

8.1. Overview of Core findings

There were several core findings from this thesis. An overview of these findings are presented in tabular form in **Table 8.1** and in graphic form in **Figure 8.1**. For this PhD thesis I conducted six separate investigations using three data-sources. These investigations can be broadly broken down into three distinct areas:

Section 1: Prediction and Preventive Targets (Studies 1 and 2)

Section 2: Outcomes Associated with Psychotic Experiences (Studies 3, 4 and 5)

Section 3: Mediators of the Outcomes (Study 6).

Before discussing each of these sections, a brief summary of the findings from all six studies is provided.

8.1.1. Study 1: *Predicting Early Adolescent Psychotic Experiences from Psycho-social Characteristics.*

This study demonstrated that a significant proportion of those who reported PEs were identifiable from a number of psychosocial characteristics reported in childhood. Additionally, psychosocial characteristics measured in adolescence were useful in distinguishing those who reported PEs from those who did not. The themes of these characteristics were very similar in both investigations, only varying in their predictive accuracy. Four central themes emerged; individual characteristics, neighbourhood characteristics, family and parent characteristics and the child-peer relationship. The strongest predictive features included “Feeling unsafe in the local neighbourhood” and scoring highly on a depression scale. A number of the predictive features examined in this study have been previously investigated as risk factors in the published literature.

8.1.2. Study 2: *Changes in self-concept and risk of psychotic experiences in adolescence.*

This study demonstrated that there is a strong association between changes in self-concept and risk of psychotic experiences. As self-concept improves between childhood and adolescence, the associated risk of PEs reduces. Conversely, as self-concept worsens between childhood and adolescence, the risk of PEs increases.

Additionally, I explored whether certain components of self-concept were specifically associated with risk of PEs. Notably, I found that improvements in the most of the self-concept sub-scales were associated with a reduced risk of PE and that worsening in most of the self-concept sub-scales were associated with an increased risk of PEs.

8.1.3. Study 3: *Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis.*

I conducted a systematic review and meta-analysis on relationship between child and adolescent PEs and mental disorders. Using data from almost 30,000 children and adolescents, across 12 different community samples, I found that young people with PEs had a 3-fold increase in odds of meeting criteria for a mental disorder (any) and a 2.8-fold increase in odds of meeting criteria for a non-psychotic disorder. There was a 4-fold increase in the risk of psychotic disorder.

In terms of individual non-psychotic disorders, reporting PEs was associated with an increased risk of affective disorders, anxiety disorders, behavioural disorders and substance use disorders, although the strength of the association differed across the disorder categories. At the time of publication, there were a limited number of studies investigating the longitudinal relationship between PEs and risk of subsequent non-psychotic mental disorders.

8.1.4 Study 4: *Do childhood psychotic experiences improve the prediction of adolescent psychopathology?*

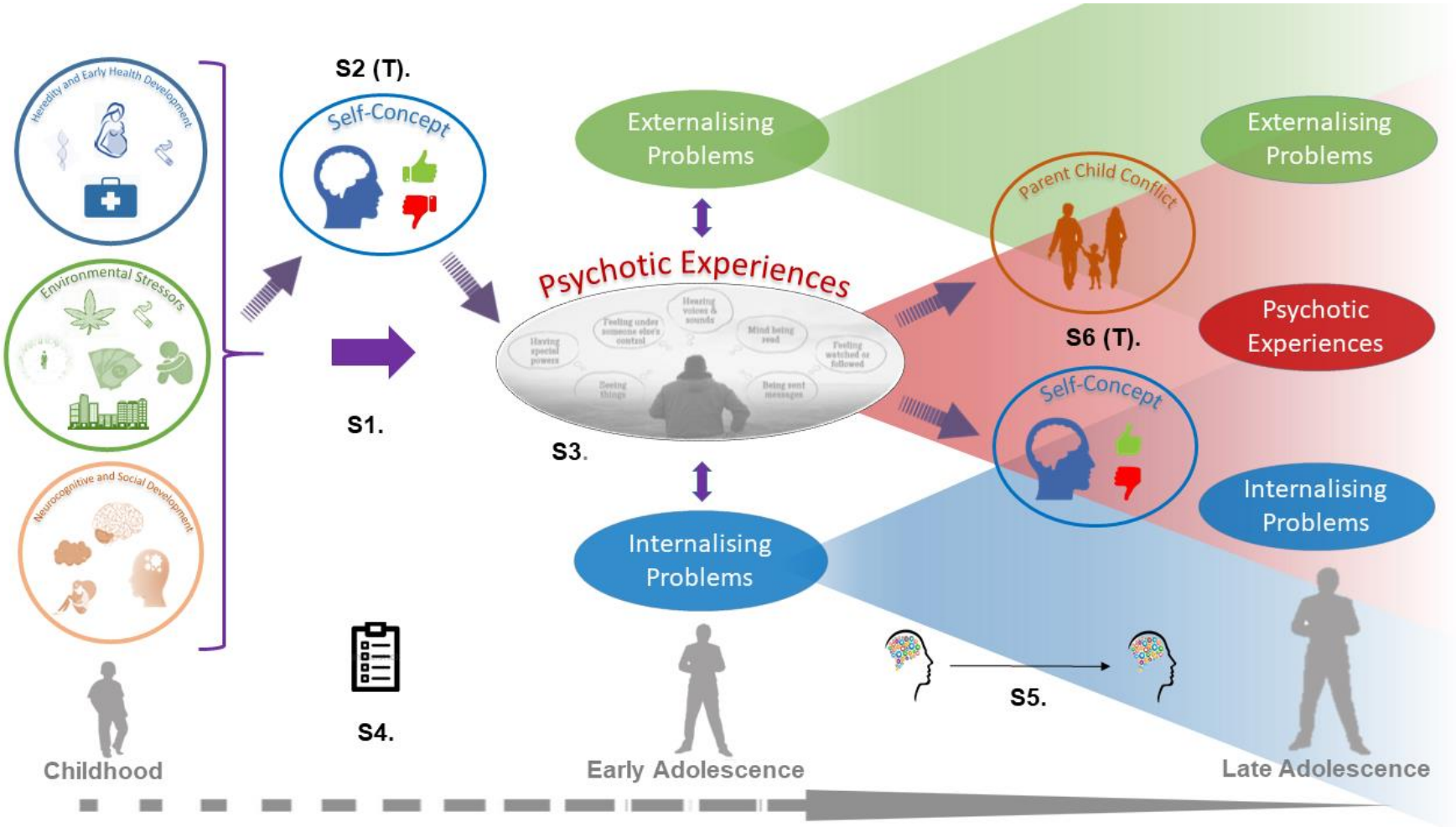
This study demonstrated that, in addition to increasing the risk of subsequent psychopathology, childhood PEs actually improve the prediction of later psychopathology. Data from the Adolescent Brain Development study, was used to demonstrate that PEs improve the prediction of subsequent psychopathology beyond what has been captured by traditional risk factors such as exposure to trauma, history of mental disorder and global functioning. This was particularly evident in the prediction of subsequent externalising problems.

Table 8.1 An overview of the core findings from the thesis.

Investigation	Sample	Core findings
Section 1. Prediction and Prevention Targets		
Study 1. Prediction of Psychotic Experiences: a machine learning approach.	Cohort 98' Growing Up in Ireland Study	• Childhood psychosocial characteristics were able to predict ~60% of those who reported PEs in adolescence. • Adolescent psychosocial characteristics were able to distinguish 71% of those with PEs from those without. • Similar poly-thematic psycho-social profiles were evident at both time points centred around four themes: individual characteristics, family/parent characteristic, neighbourhood characteristic and the child-peer relationship.
Study 2. Changes in Self-concept and risk of Psychotic Experiences.	Cohort 98' Growing Up in Ireland Study	• Improvement in self-concept from childhood to adolescence was strongly associated with a reduced risk of PEs. • Worsening self-concept from childhood to adolescence was strongly associated with an increased risk of PEs. • These patterns were observed across the majority of the self-concept subscales.
Section 2. Outcomes Associated with Psychotic Experiences		
Study 3. Psychotic Experiences and risk of Mental Disorder: Systematic Review and Meta-Analysis	Published Literature	• PEs were associated with a four-fold increased risk of Psychotic Disorder (PAF: 23%). • PEs were associated with three-fold increased risk of non-psychotic disorder. • Specifically, PEs were associated with an increased risk of affective disorders, anxiety disorders, behavioural disorders and substance Use Disorder.

Study 4. Clinical Utility of Assessing PEs.	Adolescent Brain Development Study	• Childhood PEs were independently associated with an increased risk of subsequent internalising and externalising problems. • Childhood PEs improved the prediction of externalising problems. • These results were retained even when the analysis was limited to those who only had transient PEs.
Study 5. Childhood PEs and subsequent global functioning**.**	Adolescent Brain Development Study	• Children reporting PEs had clinically relevant poorer functioning throughout adolescence and into early adulthood. • These results were evident even after adjusting for co-morbid mental disorder • These results were evident in both those who had transient PEs and those who had persistent PEs.
Section 3. Mediators of Outcomes		
Study 6. Mediators of the relationship between PEs and Psychopathology.	Cohort 98' Growing Up in Ireland Study	• There were bi-directional associations (increased risk) between PEs, internalising problems and externalising problem. • Self-concept mediated a significant proportion of the association between adolescent PE and risk of subsequent psychopathology. • Parent-child conflict mediated a significant proportion of the association between youth psychopathology and risk of subsequent psychopathology.

Figure 8.1 Visual Schematic of the overall findings from the thesis.



Note. S1-S6: Refer to each Study. T: Proposed targets for intervention.

8.1.5 Study 5: *Childhood psychotic experiences are associated with Poorer Global Functioning throughout Adolescence and into Early Adulthood*

This study demonstrates that children who reported PEs had significantly and clinically relevant poorer functioning during the developmental period from childhood, through adolescence and into early adulthood. Significant dysfunction was evident, even after controlling for mental disorders. In the case of current functioning, the deficits persisted into early adulthood even after additionally controlling for childhood functioning. Lower levels of functioning were evident in both those who had transient PEs as well as those who had reoccurring PEs.

8.1.6 Study 6: *What mediates the longitudinal relationship between psychotic experiences and psychopathology?*

This study reported on mediators of the longitudinal relationship between PEs and psychopathology. In the search for potential targets for intervention with young people, this study demonstrated that there were longitudinal homotypic and heterotypic associations between PEs, internalising problems and externalising problems. When a young person reported PEs, self-concept mediated over half of the relationship with subsequent internalising problems and 14% of the relationship with subsequent PEs. When a young person presented with non-psychotic psychopathology, parent-child conflict mediated between 18-34% of the relationship with subsequent PEs and non-psychotic psychopathology. This suggests that self-concept and parent-child relationships may be useful targets for intervention in the context of youth mental health.

8.2 Overall Discussion

In the following sections (8.2.1-8.2.3) I provide a narrative discussion of the findings from each of these studies in the context of evidence from the existing literature.

8.2.1 Section I – Prediction and Prevention Targets

Prevention has been cited as one of the “grand challenges” facing psychiatry this century (Arango et al., 2018). Within prevention there appears to be two core challenges: prediction and intervention.

Issues with prediction

The first challenge with prevention is that it requires a degree of “clairvoyance”. It requires that we are able to accurately distinguish those who are going to go on to have psychiatric problems in later life from those who will remain relatively free from psychiatric problems. This difficulty applies to almost all medical specialities and has remained a major struggle for the field of psychiatry. However recent advancements in statistical modeling has improved our ability to predict future outcomes. In Study 1 these advances are exploited to explore the predictive value of childhood psychosocial characteristics for adolescent PEs and their adolescent psychosocial sequelae’. Adolescent psychosocial features were accurately able to classify those with PEs (~70%), with features such as depressive symptoms and urban environment factors having the strongest discriminatory value. However, childhood psychosocial characteristics alone had only reasonable predictive accuracy (~60%) for adolescent PEs, even with advanced penalised regression techniques (Healy et al., submitted).

The predictive accuracy observed was similar to a previous investigation predicting PEs and mood symptoms based on psychosocial and functional neuroimaging features (Bourque et al., 2017). It is possible that the inclusion of other modalities of data, for example proteomics and genetic data, could improve the prediction of PEs beyond current estimates (Mongan et al., under-review). Alternatively, it is possible that for some individuals, PEs are a consequence of on-going adversity, such as bullying (Kelleher et al., 2013) and it may not be possible to identify these individuals based on childhood features. This would partially explain the discrepancy in the prediction accuracy between the childhood features from the adolescent features.

In addition to penalised regression techniques, other classification algorithms (Kessler et al., 2015; Pearson et al., 2019; Vieira et al., 2019) may aid in distinguishing those who report adolescent PEs from those who do not. Examples of such algorithms include support vector machines [*An algorithm that searched for the optimum classification of the data using hyperplanes. These hyperplanes attempt maximise the margin between*

the classification groups while accommodating some degree of misclassification.] decision tree algorithms [*An algorithm that builds a tree like structure which places the most predictive feature at the root and the training data is split into two subsets. These subsets are each search for their most predict features and an additional split is applied to the data. This process is iteratively completed until no further splits in the data are permissible.*] or *deep learning* [*A multi-layered computational models with multiple levels of abstraction, similar to neural networks, that can be optimised for classification.*]. However, more complex algorithms come at an interpretative cost. The greater the complexity of the algorithms the more difficult it is to interpret and potentially the less generalizable it may be to other datasets. Additionally, a complex algorithm which allows for limited user understanding. This may hinder user uptake in practical settings (such as clinical or community monitoring for those at high risk of psychiatric phenomena). To-date, too few investigations have examined the prediction of PEs. Further investigations are warranted.

Within the predictive models we identified, there were a number of recurring features that significantly contributed to the predictive value. These features clustered around four central themes: individual characteristics, family characteristics, the child-peer relationship and neighbourhood characteristics. Several of the significantly contributing features commonly appear in the literature. These include depressive symptoms (Kelleher et al., 2012), feeling unsafe within the neighbourhood (Newbury et al., 2016), minority status (Linscott & van Os., 2013) and familial conflict (McGrath et al., 2017).

Other features identified in this study have been rarely reported in the previous literature. For example, engaging in sports or fitness clubs and the child's willingness to discuss their problems with a teacher both had protective effects within the model. To our knowledge, sports participation has only been identified as a protective factor in one other investigation into PEs (McMahon et al., 2019). Sports participation in adolescence has been associated with fewer depressive symptoms, lower perceived stress and higher self-rated mental health in early adulthood (Jewett et al., 2014; McMahon et al., 2017). Willingness to discuss problems with a teacher echoes the findings of the

positive influence of “one good adult” (Dooley & Fitzpatrick, 2012). This findings suggest that young people who receive high support from at least one adult (parent, teacher, sports coach) have lower symptoms of depression and anxiety, and higher levels of life satisfaction, self-esteem and optimism. These external protective factors may be useful new avenue for research into PEs in young people.

Issue with intervention

The second core difficulty with prevention is that once we have identified those likely to struggle with psychiatric difficulties, what do we do next? Are there way of intervening to prevent/delay an outcome? What targets would be useful for preventing psychiatric difficulties in adolescence? In Study 2, I exploited a malleable psychosocial target, namely self-concept and examined if changes in self-concept were associated with differential risk of PEs.

The majority of the known risk factors for PEs are static, such as family history of mental disorder, or characteristics that are difficult to change, such as socio-economic status, or are events that are difficult to prevent (such as exposure to a traumatic event). This impedes our ability to reasonably intervene or prevent the onset of PEs. Thus, the need to identify targets for preventive interventions is essential.

A number of psycho-social characteristics are amenable to early detection and intervention, for example self-concept. In the second study, we investigated how changes in self-concept between childhood and adolescence altered the risk of PEs (Healy et al., 2019). We found that as self-concept improved the odds of PEs decreased and as self-concept worsened the odds of PEs increased. Improvement or maintenance of high self-concept was associated with a low incidence of adolescent PEs. These results were evident across the majority of the self-concept sub-scales, suggesting that there are multiple aspects of self-concept that could be targeted for intervention. These findings expand our understanding beyond the documented cross-sectional finding that those who report PEs have lower self-concept (Krabbendam et al., 2002; Dolphin et al., 2015; and Hielscher et al., 2018) and align with research highlighting the relationship

between self-concept and more severe psychotic phenomena (Close & Garety, 1998). For example, adolescents and adults at ultra-high risk of developing psychosis (Carol & Mittal, 2015; Morrison et al., 2006) and patients with schizophrenia (Barrowclough et al., 2003) have been reported to have lower self-concept and lower self-concept has been strongly correlated with positive symptoms. Our results suggest that self-concept may be a useful preventative target for reducing the incidence of PEs in early adolescence.

This may be a particularly useful target for children who have a predisposition to psychotic phenomena (for example those with a first degree family relative with psychosis or children with 22q11.2 deletion syndrome), or those who have been exposed to multiple environmental risk factors for psychotic experiences (such as trauma, live in an urban environmental and feel unsafe in their neighbourhood or who have a history of cannabis use). Interventions targeting self-concept may, potentially, reduce the incidence of PEs.

8.2.2 Section II - Outcomes Associated with Psychotic Experiences

There have been numerous investigations into PEs over the course of the past two decades (for review see, Healy & Cannon, 2020). These investigations have revealed two major findings. Firstly, PEs are common in childhood and adolescence. Secondly, those who report PEs are at an increased risk of mental disorder, psychopathology or general dysfunction (Kaymaz et al., 2012; Kelleher et al., 2012; Carey et al., 2020). These two observations lead to the hypothesis that PEs reported by young people are an early life pluripotent marker for psychiatric vulnerability (Van Os, 2013; McGorry et al., 2018). Synthesising this information suggests that it may be possible to identify those at an elevated risk of psychopathology even in early life (Healy & Cannon, 2020).

However, the evidence for this hypothesis is incomplete. For example, many of the investigations into the relationship between PEs and mental disorders have been cross-sectional. They also vary across the life span. To date, a thorough interrogation of literature on the relationship between childhood and adolescent PEs and mental disorder has not been conducted. Thus in Section II, I investigated the co-occuring and

subsequent psychiatric outcomes associated with PEs reported by young people and provided additional evidence for the hypothesis that PEs are an early life pluripotent marker.

Study 3, provided a review of the literature on the relationship between childhood and adolescent PEs and risk of mental disorder. This quantitative synthesis of the literature found that PEs in early life were associated with a four-fold increased odds of psychotic disorder and a three-fold increased odds of a non-psychotic disorders (Healy et al., 2019).

The results from both cross-sectional and longitudinal studies indicate that young people with PEs have an increased risk of mental disorder. PEs were specifically associated with an elevated risk of psychotic disorders, affective disorders, behavioural disorders, anxiety disorders and substance use disorders. These findings add to results from a recent meta-analysis indicating that PEs are associated with an increased risk of suicidal thoughts and behaviours (Yates et al., 2019). Combined, they support the hypothesis that PEs are a trans-diagnostic marker for psychiatric disorders (Van Os, 2013).

Possible mechanisms for the association between PEs and mental disorders include a shared genetic architecture (Legge et al., 2019) as well as shared environmental risk factors, such as trauma (Coughlan and Cannon 2017; Arseneault et al., 2011; Kessler et al., 2010). However, at the time of publication (Healy et al., 2019), there were a limited number of investigations reporting on the relationship between childhood and adolescent PEs and subsequent non-psychotic disorders.

Three recent studies have expanded this evidence. Trotta and colleagues demonstrated that early adolescent PEs are associated with an increased risk of subsequent PEs, psychotic symptoms, depression, anxiety, suicide attempts and self-harm (Trotta et al., 2019). Rimwall and colleagues, report that childhood PEs were associated with increased risk of subsequent mental disorder diagnosis and psychotropic medication

use (an effect that was exacerbated if the participant with PEs also reported a psychiatric diagnosis in childhood, suggesting a synergistic effect, see Rimwall et al., 2020). Additionally, Iorfino and colleagues (2019) demonstrated that baseline PEs were one of the few clinical variables that predicted upward transition in the clinical staging model (Stage 1a to 1b and Stage 1b to 2) to follow up (lorfino et al., 2019). [*Stage 1a to 1b implies a shift from non-specific symptoms with mild to moderate impact on functioning to an attenuated syndrome with moderate to severe specific symptoms and a moderate to severe impact on functioning. Stage 1b to Stage 2 implies that stage 1b symptoms have persisted worsened with a major impact on functioning*]. This additional evidence suggests that PEs are a useful prognostic marker of symptom progression as well as a marker for further risk of disorder.

One observation from the limited data available on the relationship between PEs and subsequent mental disorder is that it was unclear if assessing PEs was sufficient for the prediction of subsequent psychopathology. This raised an important question about the clinical utility of assessing PEs: Were PEs providing new information about a young person's subsequent risk, or were they capturing information that was already provided by established markers? Study 4 examined, not only if childhood PEs were associated with an increased risk of adolescent psychopathology, but whether assessing PEs actually improved the prediction of psychopathology over and above established risk factors (Healy et al., 2019).

Study 4 found that childhood PEs were associated with subsequent psychopathology and, adding to established knowledge, found that including PEs in the statistical model significantly improved the prediction of externalising problems. A subsequent investigation, using similar statistical methodologies found that early adolescent PEs significantly contributed to the prediction of late adolescent psychiatric disorders (any, internalising or externalising disorders) in victimised children (Meehan et al., 2020).

These findings reinforce the importance of assessing PEs in young people as they provide additional predictive information for subsequent psychiatric outcomes beyond

what is already captured by established markers, such as a history of psychiatric disorder, poorer global functioning and traumatic experiences. Moreover, assessing PEs is financially and logistically feasible as there are numerous, short, open-source instruments available that require little time to complete (Lee et al., 2016). Thus, assessing PEs aligns with the proposed preventive psychiatry model of 'indicated and selective prevention' (Arango et al., 2018) by assisting with the identification of young people with a trans-diagnostic risk (Healy & Cannon, 2020).

Study 5 examined whether childhood PEs were associated with adverse outcomes beyond mental disorder in early adulthood and observed that children who reported PEs had poorer global functioning from childhood, through adolescence and into early adulthood. Clinically relevant effect sizes (equating to roughly a 10 point difference in GAF scores) were evident into early adulthood even after stringent adjustment for mental disorder and childhood functioning. Calkins and colleagues also reported that young people with PEs had poorer functioning at two-year follow-up (Calkins et al., 2107). More recently, Carey and colleagues reported that young people with a history of PEs not only had a poorer global functioning at 10-year follow up but also had lower social function and role functioning scores (Carey et al., 2020). These results quantify the extent of the difficulties that a young person with a history of PEs may continue to have in daily psychosocial and occupational functioning even into early adulthood.

Early adulthood is considered a formative transitional period with heavy social investment (The Government Office for Science, 2008). The evidence suggests that pervasive difficulties during this period, have the potential to results in lasting human, relational, vocational and economic consequences for individuals and for society at large. Thus, it is important to consider that those who have reported PEs may require on-going support to help them reach their full potential (even if the PEs are transient phenomena). This support would be mutually beneficial to both the individual and broader society when the possible societal and individual gain is considered against the cost of supporting someone with mental illness.

8.2.3 Section III - Mediators of Outcomes

In spite of advances in prevention and intervention strategies, it is likely that a proportion of young people will experience psychopathology (psychotic or non-psychotic). This may be, in part, due to hereditary predisposition, environmental risk factors and the interaction between predisposition and environmental risk. To prevent on-going suffering in those with psychopathology, it is important to know which areas to target for intervention in the context of different psychopathological phenotypes. It is also important to distinguish those for whom poor mental health will be a pervasive problem and those for whom symptoms will subside.

Earlier, I have documented the significant relationship between PEs and risk of psychopathology. However, not all of those who report PEs will develop subsequent psychopathology. The relationship between PEs and psychopathology has best been described as probabilistic rather than deterministic (Linscott & van Os., 2013). This suggests that there may be factors on the pathway between PEs and subsequent psychopathology (and visa-versa) that are malleable and thus, amenable to intervention.

Study 6 explored the mediating role that selected malleable psychosocial characteristics play in determining the quality of this relationship. From this, there were three major findings. Firstly, there was a bi-directional heterotypic relationship between PEs and psychopathology. This aligns with the previous evidence that I have presented (McGrath et al., 2016).

Secondly, parent-child conflict was important for mediating the relationship between early adolescent psychopathology and late adolescent PEs. No other investigation to date has reported on the mediators of the bi-directional relationship between PEs and non-psychotic psychopathology. However, there is evidence that parent-child conflict mediates the relationship between externalising and internalising problems (Yong et al., 2014). This suggests that, in the context of non-psychotic psychopathology, parent-child conflict is a good target for intervention with the aim of preventing subsequent PEs.

Finally, I found that self-concept has an important role in mediating the relationship between early adolescent PEs and late adolescent psychopathology (Healy et al., In press). This was particularly the case for those who went on to have late adolescent internalising problems. Thus, if a young person reports PEs, and the aim is to prevent subsequent psychopathology (psychotic or non-psychotic), self-concept might be a good target for intervention.

In the supplementary materials (see page 281) I provided additional support for these findings through counter-factual mediation. This analytical style is based on the assumptions of conditional exchangeability and these investigations are considered an approximation of causal mediation. The results from these investigations mirrored the findings from the traditional mediation analysis, again highlight the effect of self-concept and parent-child conflict. Moreover, the sensitivity analysis estimated that an unmeasured confounder would have to explain roughly 20-40% of the residual relationship between the mediators and the outcome to eliminate the findings. For comparison some of the most widely cited observed confounders (family history of mental disorder, childhood adversity and socio-economic status), for the most part, only explained between 0-20% of the mediator outcome relationship. This suggest that the findings are robust to unmeasured confounding.

These observations highlight the important role that support structures in childhood and adolescence might play, whether internal (such as self-concept), or external (such as family support), in determining if young people with PEs or psychopathology go on to report subsequent psychiatric outcomes. It may be possible to develop interventions targeting these types of support structures in order to reduce the subsequent risk in those who already report psychiatric difficulties.

8.3 Conclusions and clinical Implications

Synthesising findings from these six studies, I conclude that there is a strong interconnected relationship between PEs, psycho-social characteristics and psychiatric outcomes. The nexus between these variables highlights the complexity of investigating

the aetiology and prediction of PEs in childhood and adolescence and the prognosis of young people who report PEs. These results suggest that a proportion of those who report early adolescent PEs may be identifiable in childhood based on psychosocial data. However, a significant proportion may not be identifiable based on these childhood factors. This poses a significant challenge for preventative psychiatry as it suggests that even when known risk factors for PEs are targeted for pre-emptive intervention, there are likely to be a number of false negative cases. False negative cases, in this context may be a specific sub-sample of young people who do not have a history of common risk factors for PEs but who are experiencing ongoing difficulties that are associated with phenomena, such as bullying (Kelleher et al., 2013) or psychiatric multi-morbidity (Kelleher et al., 2012). Multimodal research may be required to improve prediction. For example, biological data may be useful for improving prediction (Mongan et al., under review). However model complexity and implementation cost should be given serious consideration, as time and financial resources in clinical and community settings are limited. Prior to implementation on a large scale all screening tools used to create the predictive model should align with national or international criteria such as the Wilson & Jungner (1968) criteria for screening programs or the United Kingdom's National Screening Committee criteria (UK National Screening Committee, 2017). As a singular outcomes, PEs alone would not meet this threshold.

The results of the studies in this thesis highlight the importance of self-concept from a prevention and intervention perspective. Findings from sections I and III highlight the utility of self-concept as a "light touch" target for reducing the incidence of adolescent PEs in addition to reducing the risk of subsequent psychopathology in those who already report PEs. The bi-directional relationship between PEs and self-concept appears to mirror the long standing observed relationship between depression and self-concept (Haney & Durlak, 1998; Johnson et al, 2016; Sowislo & Orth, 2013). The evidence provides two overarching suggestions: 1) Self-concept may be a useful preventative target for children who have a high genetic (family history of psychotic disorder) or environmental susceptibility (past exposure to trauma) to PEs; and 2)

Targeting self-concept may reduce the risk of reoccurring PEs or heterotypic psychopathology.

There is a large body of evidence for the effectiveness of interventions targeting self-concept (O'Mara et al., 2006). In a meta-analysis of multiple self-concept interventions for children, using 145 primary studies O'Mara and colleagues reported medium to large effect sizes (mean Cohen's d: 0.51). The effectiveness of the interventions were in part moderated by the targeted nature of the intervention and the target population group. More recently, Katz and colleagues (2019) conducted a large multisite cluster randomised controlled trial investigating the effectiveness of a universal school based mental health literacy and dialectical behaviour therapy skills program on self-concept (Katz, Mercer & Skinner, 2019). The intervention had a large effect (all Hedge's g values: >1) on self-concept, coping skills and social support and these effects were evident at 12 month follow-up. It has yet to be established if these interventions have a downstream effect on PEs and psychopathology. Future non-observational research into those who already report PEs should be conducted to investigate the effectiveness of these approaches at reducing the incidence of subsequent PEs and psychopathology.

What is clear from the literature to date and the research presented in this thesis is that PEs are common in early adolescence, and that those reporting PEs are more vulnerable to a number of poorer outcomes than those not reporting PEs. We provide further evidence supporting the suggestion that PEs are an early pluripotent marker and strongly advocate that assessing PEs should be incorporated into routine clinical practice and broader assessments of mental health outcomes in community samples. Our results suggest that such assessments would significantly aid clinician and interested parties in improving the prediction of subsequent clinical outcomes. It would also assist in identifying those who are likely to have pervasive struggles with day-to-day social and occupational difficulties. PE endorsement may in fact be useful for triage, as a marker for early "high-risk", particularly when used in conjunction with other markers. This idea continues to gather support (Trotta et al., 2019; and Iorfino et al., 2019; Rimwall et al., 2020; Healy & Cannon, 2020).

8.4 Methodological considerations

Strengths. This work has a number of strengths. The investigations were conducted using three different data sources namely, the existing PE literature, a large nationally representative longitudinal study (GUI) using survey data and a smaller longitudinal sample (ABD) using clinical interview data. At every wave of the GUI and the ABD, a trained interviewer(s) conducted the session and recorded the data. In the GUI study, PEs were measured using clinically validated criteria (Kelleher et al., 2012) and in the ABD study, PEs were independently rated by three experts in the field of psychosis. In both the ABD and the GUI studies most of the scales (for example the Strengths and Difficulties Questionnaire and the Piers Harris II) have been validated and/or had their psychometric properties tested.

Our investigations also took advantage of advances in statistical techniques such as machine learning and counter factual analysis. Machine learning methodologies are beginning to gain notoriety in the field of psychiatry (see Dwyer et al., 2018) and with additional developments, may augment triaging by statistically identifying those at-risk of the poorest prognoses. This may improve the deployment of resources to those most in need. Moreover, if coupled with large scale community screening, they can similarly assist with the identification of those most at-risk within the community. This would provide a window of opportunity for early intervention, possibly before a psychiatric disorder becomes embedded.

In spite of its popularity in other fields, to my knowledge, few studies in the field of epidemiological psychiatry have used counter factual or causal analysis styles (for an overview see Hernán, 2004). Mostly, they have been limited to instrumental variable mendelian randomization studies (Vaucher et al., 2018). Counter factual theory can be considered a best approximation of the causal effect with observation data (provided confounding has been correctly specified). It is expected that the use of propensity scores, inverse probability weights and counterfactual regression adjustments will gain

in popularity and assist in identifying the ‘true’ estimation of the causal effect of environmental risk factors on psychiatric outcomes, including PEs.

Limitations. A number of limitations should also be considered.
The ABD study is a small interview based community sample and it is possible that the follow-up was affected by selection biases. To examine the possibility of bias, we analysed the baseline demographic and clinical characteristics between those who took part in the follow-up studies and those who did not in the ABD study. We did not find statistical differences in these characteristics but we cannot entirely rule out the possibility of selection and systematic bias in the data. However, the results reported here are supported by other evidence from similar studies using different samples (Meehan et al., 2020; Calkins et al., 2017).

The small sample size also precluded us from conducting a thorough investigation into individuals who have reoccurring PEs. These individuals have a greater risk of developing psychotic and non-psychotic disorder and have poorer functional outcomes (Bechtold et al., 2016; and Calkin et al., 2017). Further research on the factors that predict who goes on to have re-occuring PEs is warranted, particularly given that no predictors have been replicated to date (Kalman et al., 2019). Unfortunately, for logistical reason a specific investigation in re-occuring PEs using the data from the GUI was not part of this thesis. However, investigations into the predictors of re-occuring PEs using the GUI data are on-going.

A limitation of the GUI is that the primary care giver was the source of some of the psychological data for the young person (for example the Strengths and Difficulties Questionnaire was completed by the caregiver). While these instruments have been validated for use with caregivers, this is likely to add bias to our incidence estimates as parents and children can differ in response to psychological items, particularly in adolescence (Van Roy et al., 2010). Another limitation is that data was not collected on PEs at age 9.

For pragmatic reasons, our analysis of the literature to-date investigating the relationship between PEs and mental disorders, was conducted using unadjusted odds ratios. This may have resulted in bias in our results, as there are a number of shared environmental and biological confounders that could have given rise to both the exposures and the outcomes. For example, traumatic events have been shown to account for a proportion of the presentations of depression, anxiety and PEs (Bellis et al., 2019; Linscott & van Os., 2013; Croft et al., 2019). Thus, it is likely that there is a degree of confounding in the metrics between PEs and mental disorders. However, in spite of this potential bias, our own subsequent investigations (Healy et al., 2019) and the investigations of others (Trotta et al., 2019; Dhosshe et al., 2002) have demonstrated that there is a significant and clinically relevant relationship between PEs and mental disorder even after adjusting for major confounders. Additionally, even if the relationship between PEs and mental disorder is confounded by other factors, PEs can still be used as a marker for risk.

8.5 Concluding Remarks

PEs are common in early life and are associated with poor psychiatric and psychosocial outcomes. A proportion of those who go on to have adolescent PEs are identifiable from childhood psychosocial data. Furthermore, the manifestation of adolescent PEs appears to be related to changes in a young person's self-perception. Reporting PEs in youth should be considered a significant indicator for vulnerability to on-going and subsequent adverse psychiatric and psychosocial outcomes. As such, routine assessment of PEs in clinical and community settings is an important step towards selected and indicated prevention. Targeted prevention strategies are of paramount importance to offset the burden of mental disorder in young people.

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APPENDICES

Content List

Appendix – Study 1.

Supplementary Table 1. Missing data for the childhood features and replacement type

Childhood Features			
Variable	**Number of Missing values (out of 8565)**	**Replacement type or response**	**Percentage missing**
Demographic Characteristics			
Age	0	N/A	0.00
Sex	0	N/A	0.00
Mother is biologically related to the child	123	Yes	1.44
PCG describe yourself as religious	10	Quite	0.12
Are you a citizen of Ireland	9	YEs	0.11
Is the child a citizen of Ireland	8	Yes	0.09
PCG ethnic background (dummy coded)	8	Yes	0.09
Household income	626	Mean	7.31
Birth Characteristics			
Did you smoke during pregnancy (dummy coded)	334	No	3.90
Did you drink during pregnancy (dummy coded)	340	No	3.97
Childs Birth weight	118	Mean	1.38
Birth time	77	On time	0.90
Pregnancy Type (dummy coded)	76	Normal	0.89
Neonatal care after birth	76	No	0.89
Breast feeding	76	Yes	0.89
Child Health and Health Service Use Characteristic			
Child General Health (dummy Coded)	2	Very Healthy	0.02
Ongoing chronic illness	0	N/A	0.00
Long term medical Condition (child response)	68	No	0.79
Accident or Injury requiring medical treatment	3	No	0.04
Number of nights child spent in hospital Lifetime	8	Mean	0.09
In A& E in the last 12 months	1	No	0.01
Number of times contacted with GP	5	Mean	0.06
Hearing problems requiring correction	0	N/A	0.00
Concerns about child Speech	5	No	0.06
Child Body image (PCG response)	1	About right	0.01
Child Body image (Child response)	83	About right	0.97
Identified with Specific Learning Difficulty	6	No	0.07
Dyslexia	6	No	0.07
ADHD	6	No	0.07
ASD	6	No	0.07
Speech and Language Difficulties	6	No	0.07
Dyspraxia	6	No	0.07
Slow progress	6	No	0.07
Child Bullying Characteristics			

Bullying (PCG Response)	9	No	0.11
Physical Bullying (PCG Response)	9	No	0.11
Verbal Bullying (PCG Response)	9	No	0.11
Electronic Bullying (PCG Response)	9	No	0.11
Written Bullying (PCG Response)	9	No	0.11
Exclusion Bullying (PCG Response)	9	No	0.11
Cumulative Bullying (PCG Response)	9	No	0.11
Child was a bully	240	No	2.80
Physical Bullying (Child Response)	240	No	2.80
Verbal Bullying (Child Response)	240	No	2.80
Electronic Bullying(Child Response)	240	No	2.80
Written Bullying (Child Response)	240	No	2.80
Exclusion Bullying (Child Response)	240	No	2.80
Cumulative Bullying (Child Response)	240	No	2.80
Child was bullied	354	No	4.13
Physical Bullying (Child Response)	354	No	4.13
Verbal Bullying (Child Response)	354	No	4.13
Electronic Bullying(Child Response)	354	No	4.13
Written Bullying (Child Response)	354	No	4.13
Exclusion Bullying (Child Response)	354	No	4.13
Cumulative Bullying (Child Response)	354	No	4.13
Child Family and Peer Relationship			
Child talks to mom about problems	225	Yes	2.63
Child talks to dad about problems	248	Yes	2.89
Child talks to mom partner about problems	258	No	3.01
Child talks to dad partner about problems	258	No	3.01
Child talks to teacher about problems	251	No	2.93
Child talks to friend about problems	256	No	2.99
Child talks to other relative about problem	104	No	1.21
Days per week child spent with friends	4	2-3 day	0.05
CPRS conflict	31	Mean	0.36
CPRS Positive	25	Mean	0.29
CPRS dependence	25	Mean	0.29
Child Hobbies and School Activities			
Average hours watching tv/dvd	0	N/A	0.00
Average Hours reading	0	N/A	0.00
Average Hours using computer	4	Less then an hour	0.05
Playing video games	3	Less then an hour	0.04
Sports and fitness club	10	Yes	0.12
Cultural Activities	12	Yes	0.14
Youth Club	21	No	0.25
Child Exercise	53	Almost every day	0.62
Reading for fun	52	A few times a week	0.61

Child exercise last week	58	Seven days	0.68
Child is good at Maths (PCG response)	9	Average	0.11
Child is good at Reading (PCG response)	7	Average	0.08
How far do you expect the child to go in education	36	College	0.42
What do you think about school (dummy coded)	52	Sometimes	0.61
Drumcondra reading test	208	Mean	2.43
Drumcondra math test	119	Mean	1.39
Early Life Stressors			
Death of a parent	0	N/A	0.00
Death of a close family	0	N/A	0.00
Death of a close friend	0	N/A	0.00
Parents divorced/separated	0	N/A	0.00
Moving House	0	N/A	0.00
Moving Country	0	N/A	0.00
Stayed in foster care	0	N/A	0.00
Serious Illness or injury	0	N/A	0.00
Serious illness or injury of a family member	0	N/A	0.00
Drug or alcoholism in the immediate family	0	N/A	0.00
Mental disorder in the family	0	N/A	0.00
Conflict between parents	0	N/A	0.00
Parents in prison	0	N/A	0.00
Other disturbing event	0	N/A	0.00
No early life stress	0	N/A	0.00
Three or more early life stresses	0	N/A	0.00
Psychopathology, Temperament and Self Concept			
SDQ Emotionality subscale	8	Mean	0.09
SDQ Conduct subscale	17	Mean	0.20
SDQ Hyperactivity subscale	19	Mean	0.22
SDQ Peer Problems subscale	24	MEan	0.28
SDQ Prosocial subscale	15	Mean	0.18
EAS Shyness	12	Mean	0.14
EAS Emotionality	12	Mean	0.14
EAS Activity	18	Mean	0.21
EAS Sociability	40	Mean	0.47
Piers Harris Behavior	419	Mean	4.89
Piers Harris Intellectual	476	Mean	5.56
Piers Harris Physical	481	Mean	5.61
Piers Harris Freedom from Anxiety	381	Mean	4.45
Piers Harris Popularity	298	Mean	3.48
Piers Harris Happiness	371	Mean	4.33
Primary Care Giver Parenting			
Do you feel you have fun with child (PCG)	27	Yes	0.32
If PCG has a problem: Explain why behavior is wrong	6	Yes	0.07

If PCG has a problem: Ignore him/her	6	Never	0.07
If PCG has a problem: Smack him/her	9	Never	0.11
If PCG has a problem: Shout at him/her	10	Now and Again	0.12
If PCG has a problem: Send him/her to their room	10	Now and again	0.12
If PCG has a problem: Take away pocket money	10	Now and again	0.12
If PCG has a problem: Tell him/her off	10	Now and again	0.12
If PCG has a problem: Bribe him/her	10	Never	0.12
Mom encourages child at school (child response)	185	Always	2.16
Demandingness scale mum	465	Mean	5.43
Responsiveness subscale mom	449	Mean	5.24
Parenting style PCG (Dummy coded)	568	Authoritative	6.63
Primary Care Giver Health, Relationships and Demographics			
PCG Current smoker (dummy coded)	0	N/A	0.00
PCG Frequency of alcohol	0	N/A	0.00
PCG Treated for depression	257	No	3.00
CESD score	697	Mean	8.13
Marital Status (dummy coded)	158	Married	1.84
How often do you argue PCG-SCG	1260	Mean	14.71
How often do you argue about child PCG-SCG	1494	Mean	17.44
How often do you shout at each other PCG-SCG	1527	Mean	17.82
Have you ever been in trouble with the Garda (PCG)	195	No	2.28
Dyadic Adjustment score	1790	Mean	20.89
Child Religious denomination	4	Yes	0.05
Impression of the local Area			
How common is rubbish in your area	8	Not very common	0.09
How common in your area are poor hoses and gardens	9	Not common at all	0.11
How common is vandalism	10	Not very common	0.12
How common in your area are alcohol and drugs	16	Not very common	0.19
Is it safe to walk alone in this area after dark	32	Agree	0.37
Is it safe for children to play outside	11	Agree	0.13
There are safe parks and play areas	12	Agree	0.14
I like living around here	165	Yes	1.93
I have friends to play with here	174	Yes	2.03
There are good places to play here	198	Yes	2.31
Safe place to play	206	Yes	2.40
Adults are usually nice to you	192	Yes	2.24
I feel safe living here	168	Yes	1.96
Adults are nice to children	186	Yes	2.17

Note: PCG: Primary Care giver; CPRS; Child-Parent Relationship Scale; SDQ; Strengths and Difficulties Questionnaire; SCG: Secondary Care Giver.

Supplementary Table 2. Missing data for the adolescent features and replacement type.

Adolescent Variables			
Variable	**Number of Missing values (out of 7423)**	**Replacement type or response**	**Percentage missing**
Demographic Characteristics			
Age	0	N/A	0.00
Sex	0	N/A	0.00
Mother is biologically related to the child	75	Yes	1.01
Spirituality (PCG)	101	A little	1.36
Social Welfare payment	12	No	0.16
Primary Care Giver Education level	2	Tech Vocation	0.03
Are you a citizen of Ireland	91	Yes	1.23
Were you born in Ireland	91	Yes	1.23
Ethical Background (Dummy Coding)	91	N/A	1.23
Child Health			
Childs Overall Health (Dummy Coding)	1	N/A	0.01
Ongoing Chronic Illness	3	No	0.04
Accident in the last 12 months	3	No	0.04
Reluctant To Speak	0	N/A	0.00
Speech Developing Slowly	0	N/A	0.00
Description of Child Weight (PCG response)	11	About the Right Weight	0.15
Description of Child Weight (Child response)	95	About the Right Weight	1.28
Specific Learning Difficulty	9	No	0.12
Emotional or Behavioral Disorder	7	No	0.09
Autism Spectrum Disorder	5	No	0.07
Speech and Language Difficulties	5	No	0.07
Slow Progress	5	No	0.07
Physical Disability or Hearing and Visual Impairment	5	No	0.07
Mental Health Difficulty	5	No	0.07
An assessed Syndrome (e.g. Dow Syndrome or Tourette's)	5	No	0.07
None specific difficulty	5	Yes	0.07
Wheezing and Whistling	1	No	0.01
Exercised to lose weight	107	No	1.44
Substance Use			
Ever Smoked Cigarettes	386	No	5.20
Ever Drank Alcohol	360	No	4.85
Ever Smoked Weed	357	No	4.81
Ever Sniffed Glue	358	No	4.82
Any other Drug use	356	No	4.80
Cognition			

Verbal Reasoning	387	Mean	5.21
Numerical Abilities	387	Mean	5.21
Non-Verbal Reasoning	387	Mean	5.21
Peer relationship			
Number of Friends	8	4 or 5	0.11
Victim of bullying (PCG Response)	6	No	0.08
Physical Bullying (PCG Response)	6	No	0.08
Verbal Bullying (PCG Response)	6	No	0.08
Electronic Bullying (PCG Response)	2	No	0.03
Graffiti notes messages bullying (PCG Response)	1	No	0.01
Taking/Damaging Possession Bullying (PCG Response)	1	No	0.01
Sexual Comments (PCG Response)	6	No	0.08
Other Bullying (PCG Response)	6	No	0.08
Gossip Bullying (PCG Response)	2	No	0.03
Threatened or Forced to do thinks they didn't want to (PCG Response)	1	No	0.01
Bullying (Child Response)	107	No	1.44
Physical Bullying (Child Response)	108	No	1.45
Verbal Bullying (Child Response)	109	No	1.47
Electronic Bullying (Child Response)	110	No	1.48
Messages Bullying (Child Response)	110	No	1.48
Exclusion Bullying (Child Response)	110	No	1.48
Other Bullying (Child Response)	112	No	1.51
Taking/Damaging Possession Bullying (Child Response)	109	No	1.47
Gossip Bullying (Child Response)	109	No	1.47
Threatened or Forced to do thinks they didn't want to (Child Response)	110	No	1.48
Number of Friends the Child Hangs around with (Child Response)	98	Three to Five	1.32
Are you a year or younger than most of your friends	188	None	2.53
Are you about the same age	160	Most or all	2.16
Are you a year or two older than most of your friends	187	None	2.52
Are you two or more years older than most of your friends	187	None	2.52
IPPA Alienation sub scale	174	Mean	2.34
IPPA Trust sub scale	173	Mean	2.33
Child Hobbies and School Activities			
Watching Television	115	Mean	1.55
reading for Pleasure	112	Mean	1.51
Using a computer	115	Mean	1.55
Playing PlayStation e.t.c	101	Mean	1.36

Play sport with a coach	106	Mean	1.43
How often do you take drama or music	107	Mean	1.44
How often do you take clubs group	106	Mean	1.43
How often do you take homework club	108	Mean	1.45
How often do you play sports	113	Mean	1.52
I don't like team games	6	No	0.08
I am no good at games	4	No	0.05
I have no opportunity to play	5	No	0.07
I feel people laugh at me because of my size	5	No	0.07
I have a disability or a health problem that prevents me from playing	6	No	0.08
I prefer watching sports on TV	5	No	0.07
I do not fit in with the sporty crowd	5	No	0.07
I don't like getting dirty or sweaty	6	No	0.08
I am not competitive	4	No	0.05
I prefer to play computer games	5	No	0.07
On an average school day how much time in a day do you spend alone	99	Mean	1.33
Early life stress			
Death of a parent	0	N/A	0.00
Death of a close family	0	N/A	0.00
Death of a close friend	0	N/A	0.00
Parents divorced/separated	0	N/A	0.00
Moving House	0	N/A	0.00
Moving Country	0	N/A	0.00
Stayed in foster care	0	N/A	0.00
Serious Illness or injury	0	N/A	0.00
Serious illness or injury of a family member	0	N/A	0.00
Drug or alcoholism in the immediate family	0	N/A	0.00
Mental disorder in the family	0	N/A	0.00
Your house has been broken into	0	N/A	0.00
Conflict between parents	0	N/A	0.00
Parents in prison	0	N/A	0.00
Other disturbing event	0	N/A	0.00
No early life stress	0	N/A	0.00
Other Bullying	0	N/A	0.00
Other Moving (School e.t.c.)	0	N/A	0.00
Other Family member moving out	0	N/A	0.00
Other Damage to home	0	N/A	0.00
Childs Behavior			
Often starts fights bullies or threatens others (PCG Response)	7	Not at all	0.09
Has been physically cruel to other people (PCG Response)	7	Not at all	0.09

Deliberately destroyed or damaged property (PCG Response)	6	Not at all	0.08
Has lied to obtain favor (PCG Response)	11	Not at all	0.15
Has stolen items of value (PCG Response)	6	Not at all	0.08
Has run away from home over night (PCG Response)	4	Not at all	0.05
Has been a truant from school (PCG Response)	4	Not at all	0.05
Has used a weapon that could harm (PCG Response)	4	Not at all	0.05
Has been physically cruel to animals (PCG Response)	4	Not at all	0.05
Has broken into someone else's house (PCG Response)	4	Not at all	0.05
Has stayed out at night despite parental prohibition	4	Not at all	0.05
Not Paying bus Fair	349	No	4.70
Taken Something from a shop or store	345	No	4.65
Behaved badly in public so that people complained	345	No	4.65
Stolen or ridden in a stolen car or van	347	No	4.67
Taken money or something else that did not belong to you	346	No	4.66
Carried a knife or a weapon	346	No	4.66
Deliberately damaged property	347	No	4.67
Broken into a house or building	347	No	4.67
Written or sprayed painted on things that do not belong to me	347	No	4.67
Used Force, threats or a weapon to get money	347	No	4.67
Taken money or something else that from home	347	No	4.67
Broken into a car or van to steal	346	No	4.66
Deliberately set fire or tried to set fire to someone's property	345	No	4.65
Hit kicked or punched someone on purpose	347	No	4.67
Been involved in a serious physical fight	347	No	4.67
Number of days absent from school	31	No	0.42
How do you feel about school in general	151	I like it quite a bit	2.03
I was late for school	93	Never	1.25
I get in trouble for not following school rules	95	Never	1.28
I messed in class	93	Now and again	1.25
I had to do extra work	94	Never	1.27
I had to do detention	93	Never	1.25
I was suspended	94	Never	1.27
How many days were you absent from school	199	Mean	2.68
Have you ever discussed relationship issues with parents	365	No	4.92
Psychopathology, Self-Concept, Personality			

Short Moods and Feelings Questionnaire	105	Mean	1.41
Piers Harris Behavioral Score	116	Mean	1.56
Piers Harris Intellectual Score	129	Mean	1.74
Piers Harris Physical Scores	157	Mean	2.12
Piers Harris Freedom from Anxiety	111	Mean	1.50
Piers Harris Popularity	111	Mean	1.50
Piers Harris Happiness Score	115	Mean	1.55
SDQ Emotional Problems	2	Mean	0.03
SDQ Conduct Problems	2	Mean	0.03
SDQ Hyperactivity	2	Mean	0.03
SDQ Peer Problems	2	Mean	0.03
SDQ Prosocial	2	Mean	0.03
TIPI Extraversion	10	Mean	0.13
TIPI Agreeable	5	Mean	0.07
TIPI Conscientious	7	Mean	0.09
TIPI Emotional Stability	7	Mean	0.09
TIPI Openness	14	Mean	0.19
Parent-Child Relationship			
CPRS Conflict	12	Mean	0.16
CPRS Positive Relationship	13	Mean	0.18
PCG Monitoring	19	Mean	0.26
PCG Disclosure	20	Mean	0.27
PCG Stressor Scale	78	Mean	1.05
If I have a problem I Explain why the behavior is wrong	111	Always	1.50
If I have a problem I Ignore Him/Her	106	Never	1.43
If I have a problem I smack him/her	108	Never	1.45
If I have a problem I shout at him/her	105	Now and again	1.41
If I have a problem I send him/her to their room	107	Now and again	1.44
If I have a problem I stop treats or pocket money	113	Never	1.52
If I have a problem I give out to you	106	Now and again	1.43
IF I have a problem I offer treats to be good	112	Never	1.51
If I have a problem I ground him/her	108	Never	1.45
How well do you get on with mum	254	Very well	3.42
Mum expects me to follow rules	260	Agree	3.50
Mum really doesn't like me to tell her my troubles	264	Strongly disagree	3.56
Mum hardly ever praises me	250	Strongly disagree	3.37
Mum really lets me get away with things	254	Disagree	3.42
Mum will punish me if I don't behave	256	Agree	3.45
Mum I can count on her to help me out if I have a problem	251	Strongly Agree	3.38
Mum points out what I could do better	259	Agree	3.49
Mum spends time just talking to me	252	Agree	3.39
Mum does not punish me when I do things wrong	255	Disagree	3.44

Mum tells me that her idea are correct and shouldn't question them	271	Disagree	3.65
Mum respects my privacy	256	Agree	3.45
Mum gives me a lot of freedom	255	Agree	3.44
Mum makes most of the decision about what I should do	253	I'm in between	3.41
Mum believes I have the right to my own point of view	258	Agree	3.48
Demandingness sub-scale	280	Mean	3.77
Responsive Subscale	272	Mean	3.66
Autonomy	289	Mean	3.89
Has the child tried alcohol	78	I don't think so	1.05
Has the child tried cigarettes	77	I don't think so	1.04
Has the child tried weed	77	I don't think so	1.04
Have you spoken to the child about sexual intercourse	79	I don't think so	1.06
Have you spoken to the child about sexual feelings	77	I don't know	1.04
Have you spoken to the child about sexual orientation	81	I don't know	1.09
Primary Care Give Health			
Do you have any ongoing chronic conditions (PCG)	0	N/A	0.00
PCG current Smoking (Dummy Coding)	76	N/A	1.02
PCG drinking habits	77	1-2 a week	1.04
PCG treated for depression or anxiety	77	No	1.04
Total Depression score on the CES	75	Mean	1.01
Current Drug use	76	Not at all	1.02
Dyadic Adjustment Scale	1076	Mean	14.50
Have you ever been in trouble with the Garda	76	Never	1.02
Have you ever been to prison	76	Never	1.02
Home Life			
Does your child have clothes some new not secondhand	96	Yes	1.29
Does your child have two pairs of proper shoes	97	Yes	1.31
Does your child eat fresh fruit or vegetables	97	Yes	1.31
Does your child eat three meals a day	96	Yes	1.29
Does your child eat meat	96	Yes	1.29
Does your child have books at home	96	Yes	1.29
Does the child have outdoor leisure equipment	96	Yes	1.29
Does the child have indoor games	96	Yes	1.29
Does the child participate in leisure activities	96	Yes	1.29
Does the child have friends over to the house to play	96	Yes	1.29
Does the child participate in school trips	96	Yes	1.29
Does the child have suitable places to study e.t.c.	97	Yes	1.31

Neighborhood Characteristic			
Does the child have outdoor space in the neighborhood	97	Yes	1.31
How common is rubbish and litter in your local area	1	Not very common	0.01
How common is gardens and homes in a bad condition in your local area	1	Not at all common	0.01
How common is vandalism in your local area	7	Not at all common	0.09
How common is it for people to be drunk in public in your local area	7	Not at all common	0.09
Is it safe to walk home alone in you local area	18	Agree	0.24
Is there a safe area for my 13 year old	15	Strongly Agree	0.20
Is there an area for teenager to safely hangout	47	Agree	0.63
As a family we are happy living in this area	6	Strongly Agree	0.08
We as a family intend to continue living in this area	29	Strongly Agree	0.39

Note: PCG: Primary Care giver; CPRS; Child-Parent Relationship Scale; SDQ; Strengths and Difficulties Questionnaire; SCG: Secondary Care Giver.

Appendix – Study 2

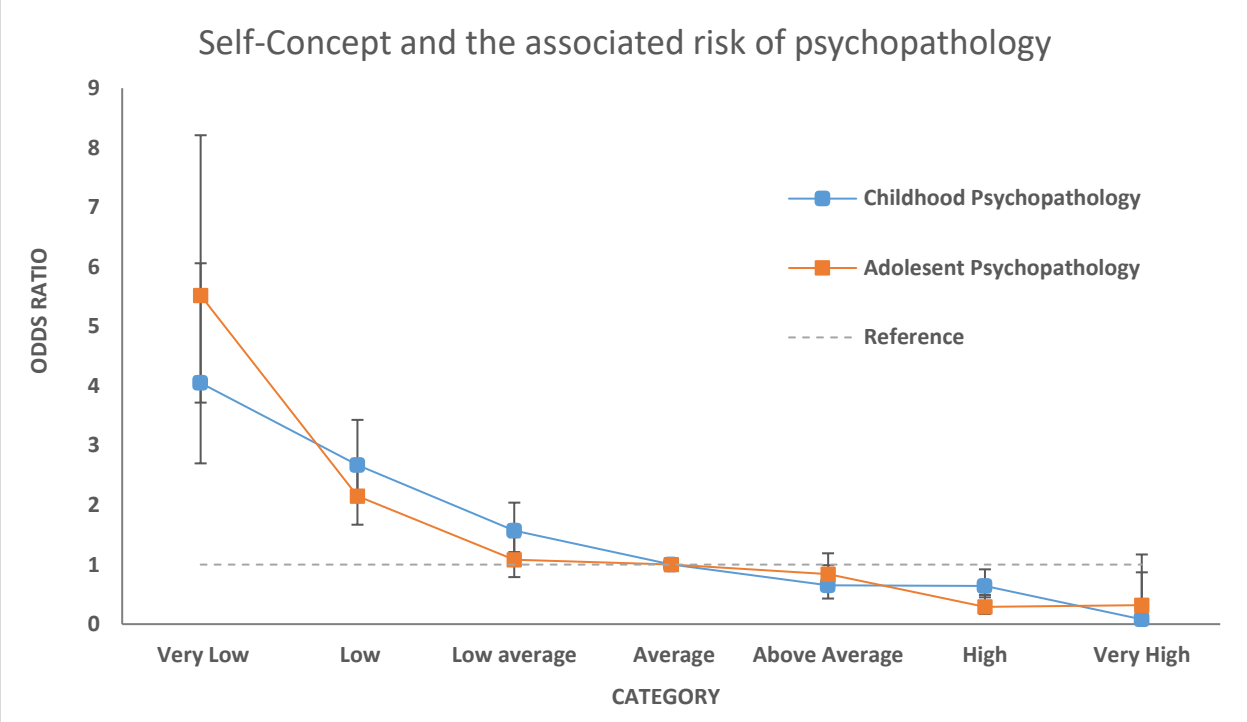
Supplementary Materials

Additional analysis. We have included an analysis, similar to the first aim of the study, investigating the relationship between self-concept and psychopathology at both waves. This allows the reader greater understanding of the relationship between self-concept and general psychopathology. We report the prevalence of psychopathology in those with low self-concept at both waves of the study. We also conducted two univariate logistic regressions to investigating the risk of psychopathology in those with differing levels of self-concept. The outcome variable was abnormal SDQ scores (scored >17) at each wave of the study. The reference category for self-concept was reporting average self-concept.

Results. In childhood 7.15% of individuals reported psychopathology. 33.68% of those with childhood psychopathology report self-concept scores below the 14th percentile (low or very low) and only 14.00% of those with childhood psychopathology report score above average (>71st percentile). Very low self-concept was associated with an four-fold increased risk of psychopathology (OR:4.05, CI:2.70-6.06) and low self-concept was associated with over a 2.5-fold increased risk of psychopathology (OR:2.60, CI:2.09-3.34).

In adolescence 6.35% of individuals reported psychopathology. 34.11% of those with childhood psychopathology report self-concept scores below the 14th percentile (low or very low) and only 13.72% of those with childhood psychopathology report score above average (>71st percentile). Very low self-concept was associated with an 5.5-fold increased risk of psychopathology (OR:5.52, CI:3.72-8.21) and low self-concept was associated with a two-fold increased risk of psychopathology (OR:2.15, CI:1.67-2.75).

Supplementary Figure 1. Odds-ratios for the relationship between the childhood self-concept and childhood psychopathology as well as the relationship between adolescent self-concept and adolescent psychopathology.



Note: Odds ratios are unadjusted.

Appendix – Study 3

Supplementary Materials

Supplement A: Assessment of Study Quality and for risk of bias.

Supplement B: Location within each of the study where the data were extracted from.

Supplement C: Funnel Plot for the overall association between of the relationship between child and adolescent PEs and any mental disorder.

Supplement D: Funnel Plot and Fill Funnel Plot for the overall association between of the relationship between child and adolescent PEs and any non-psychotic disorder.

Supplement E. Bubble plot for the effect of (a) PE definition, (b) study design, (c) population size and (d) Follow-up Time (Longitudinal studies only) on the relationship between child and adolescent PEs and any mental disorder.

Supplement F: Forest plot and Funnel Plot for the association between child and adolescent PEs and psychotic disorder.

Supplement G: Forest plots for the association between child and adolescent PEs and the subcategories of mental disorder (Affective Disorder, Anxiety Disorder, Behavioural Disorder and Substance use Disorder.

Supplement H: Forest plots for the association between child and adolescent PEs and Depressive Disorders and Post-Traumatic Stress Disorder.

Supplement I: A PRISMA checklist.

Supplement A: Assessment of Study Quality and for risk of bias using the National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Rating	Meta-analysis inclusion	Rational For Meta-analysis exclusion
Clemmensen	Y	Y	N	Y	NR	N/A	Y	N	Y	N/A	Y	CD	N/A	N	Fair	Y	N/A
Kellleher (sample 1)	Y	Y	N	Y	NR	N/A	Y	N	Y	N/A	Y	Y	N/A	Y	Good	Y	N/A
Kellleher (sample 2)	Y	Y	N	Y	NR	N/A	Y	N	Y	N/A	Y	Y	N/A	Y	Fair	Y	N/A
Jeppsen	Y	Y	N	Y	NR	N/A	Y	N	Y	N/A	Y	Y	N/A	N	Fair	Y	N/A
Scott	Y	Y	CD	Y	NR	N/A	Y	N	Y	N/A	Y	Y	N/A	Y	Fair	Y	N/A
Calkins	N	Y	Y	Y	NR	N/A	Y	N	Y	N/A	Y	CD	N/A	N	Fair	Y	N/A
Adriaanse	Y	Y	N	Y	NR	N/A	Y	Y	CD	N/A	Y	Y	N/A	N	Poor	N	Exposure continuous variable.
Poulton	Y	Y	Y	Y	NR	Y	Y	Y	Y	CD	Y	Y	Y	N	Good	Y	N/A
Dhossche	Y	Y	N	Y	NR	Y	Y	N	Y	Y	Y	CD	N	Y	Fair	Y	N/A
Fisher	Y	Y	Y	Y	NR	Y	Y	Y	Y	CD	Y	Y	Y	Y	Good	Y	N/A
Dominguez	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	CD	Y	N	Fair	Y	N/A
McGrath	Y	Y	Y	Y	NR	y	Y	N	Y	N	Y	Y	N	Y	Fair	Y	N/A

Bechtold	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	CD	Y	Y	Poor	Y	N/A
Zammit	Y	Y	N	Y	NR	Y	Y	Y	Y	N	Y	Y	N	N	Good	Y	N/A
Cedorlöf	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	CD	CD	Fair	Y	N/A

Reference: National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort. Accessed December 14, 2018.

Supplement B: Data extraction location within each study.

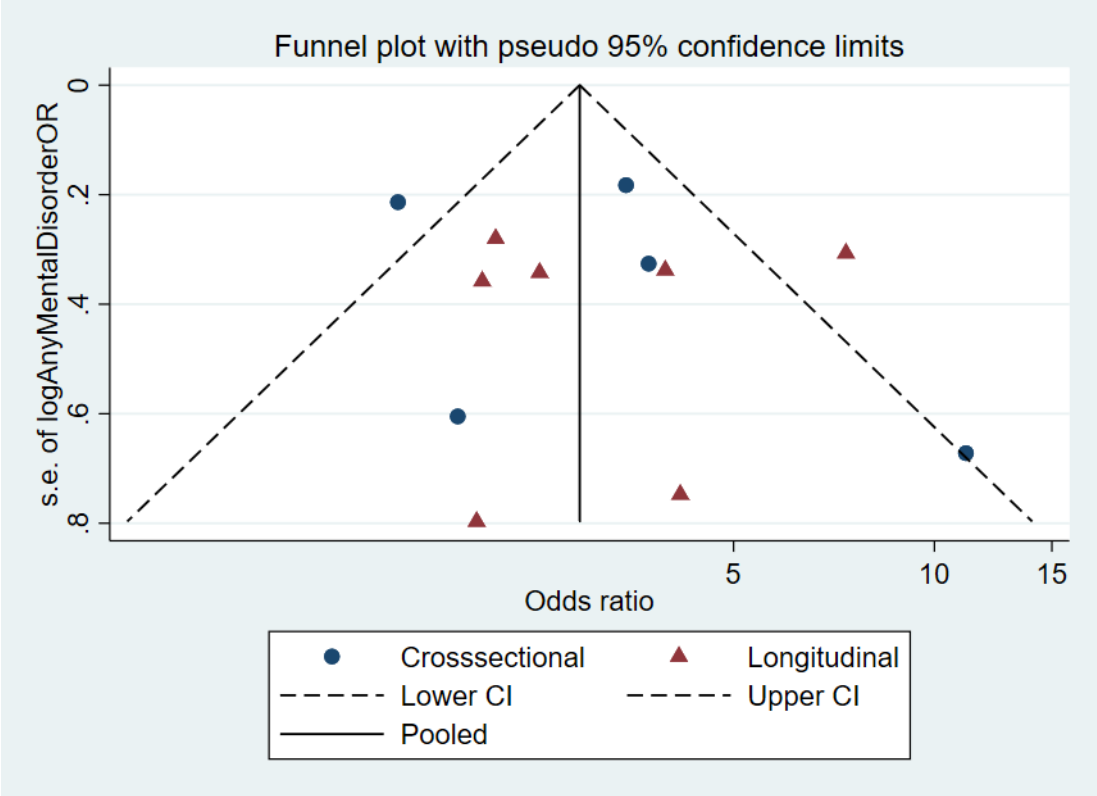
Sample	First Author	Publication Year	PE prevalence Data extraction	Data extraction on the relationship between PE and MD
1	**Clemmensen**	2016	Table 3. pp.96	Table 3. pp.96
2	**Kellleher (sample 1)**	2012	Access to the Data.	Table 3. pp29.
3	**Kelleher (sample 2)**	2012	Access to the Data.	Table 3. pp29.
4	**Jeppsen**	2015	N/C[a]	Table 1. pp.562.
5	**Scott**	2009	Table 1 pp.181	Table 2. pp. 182.
6	**Calkins**	2014	Results. Paragraph 1. pp.298	Table 3 pp. 302
7	**Adriaanse**	2015	N/C[b]	N/C[b]
8	**Poulton**	2000	N/C[c]	Table 2. pp. 1036.
9	**Dhossche**	2002	Prevalence of self-reported hallucinations pp.622	Table 5. pp. 623
10	**Fisher**	2013	Figure 1. pp.2081	Figure 1 pp. 2081
11	**Dominguez**	2011	Occurrence of psychotic experiences. Paragraph 2. pp.88.	Table 2. pp.89
12	**McGrath**	2010	Table 1 pp.442	Table 1.pp. 442
13	**Bechtold**	2016	Table 5. pp.787	Table 5. pp787
14	**Zammit**	2013	Figure 1. pp.744	Figure 1. pp.744
15	**Cedorlöf**	2017	Table 1. pp.14	Author contacted (Table 2 pp. 14)

Note: N/A[a]: Not calculated as the same cohort as Clemmensen (Sample 1); N/A[b]: Not calculated information on PEs is only present as a continuous variable; and N/A[c]: Not Calculated as the same cohort as Fisher (Sample 10).

Supplement B.

Supplementary Figure 1. Funnel plot (a) for the relationship between child and adolescent PEs and any mental disorder.

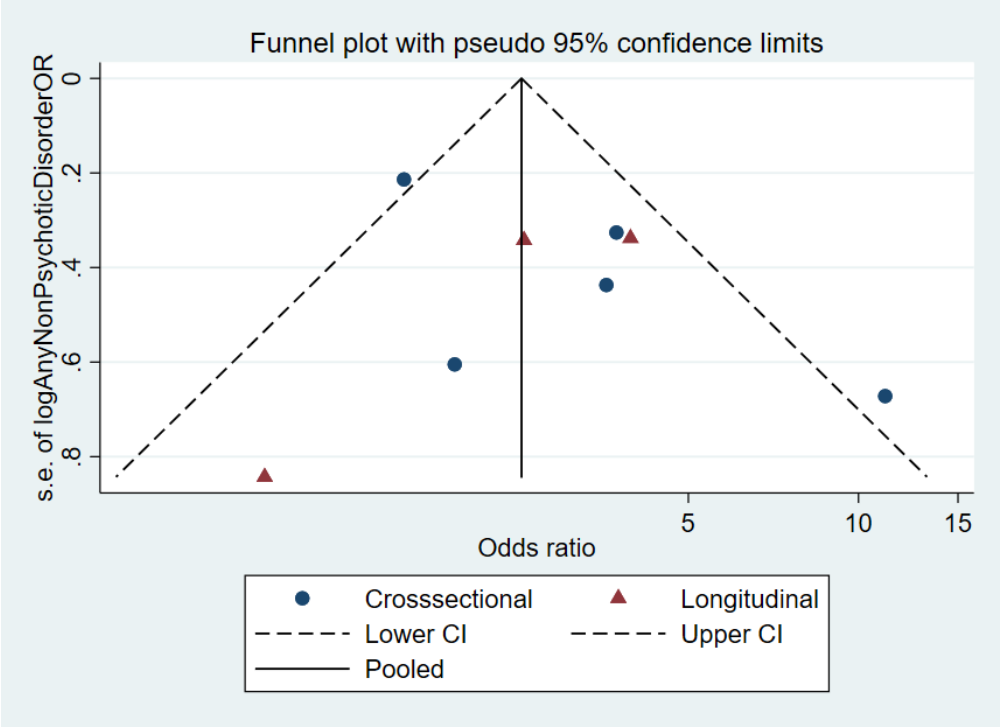
a)



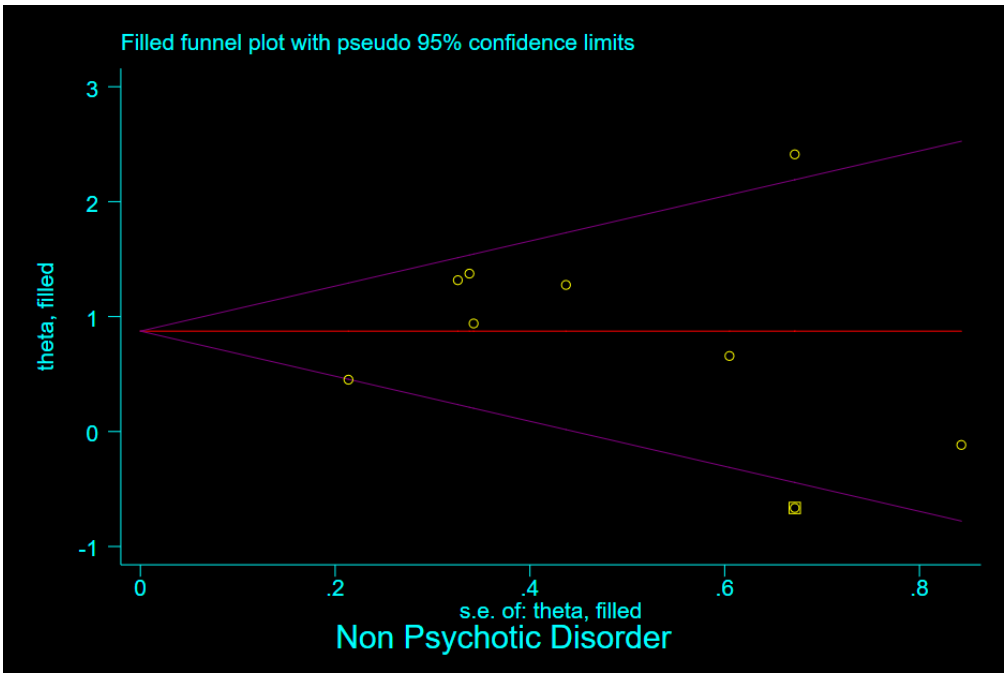
Supplement C.

Supplementary Figure 2. Funnel plot (a) and a Fill Funnel plot (b) for the relationship between child and adolescent PEs and any non-psychotic disorder.

a)



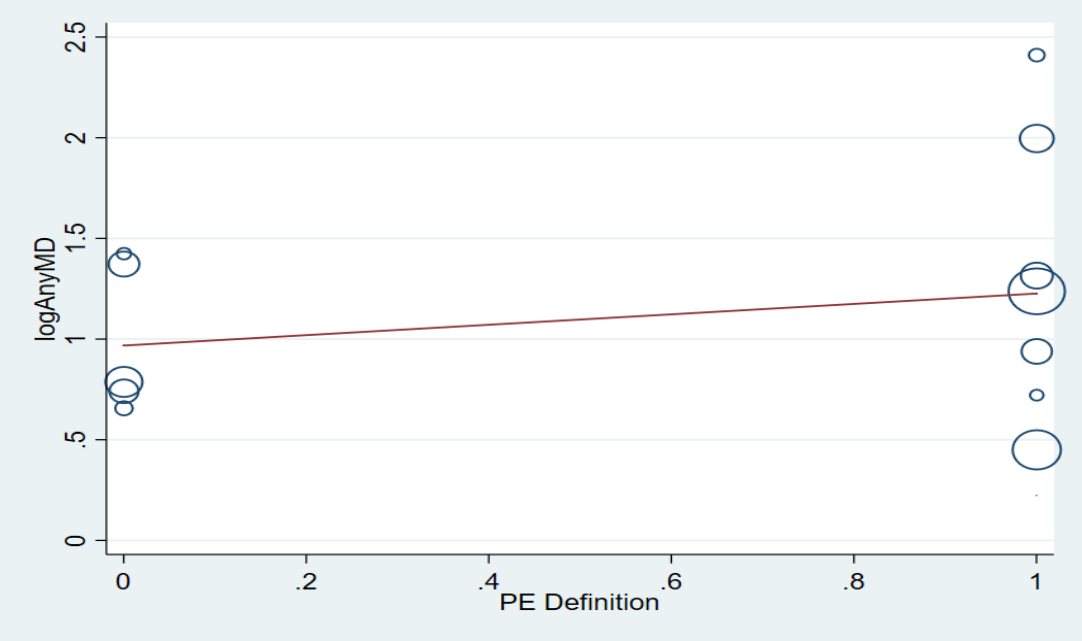
b)



Supplement D.

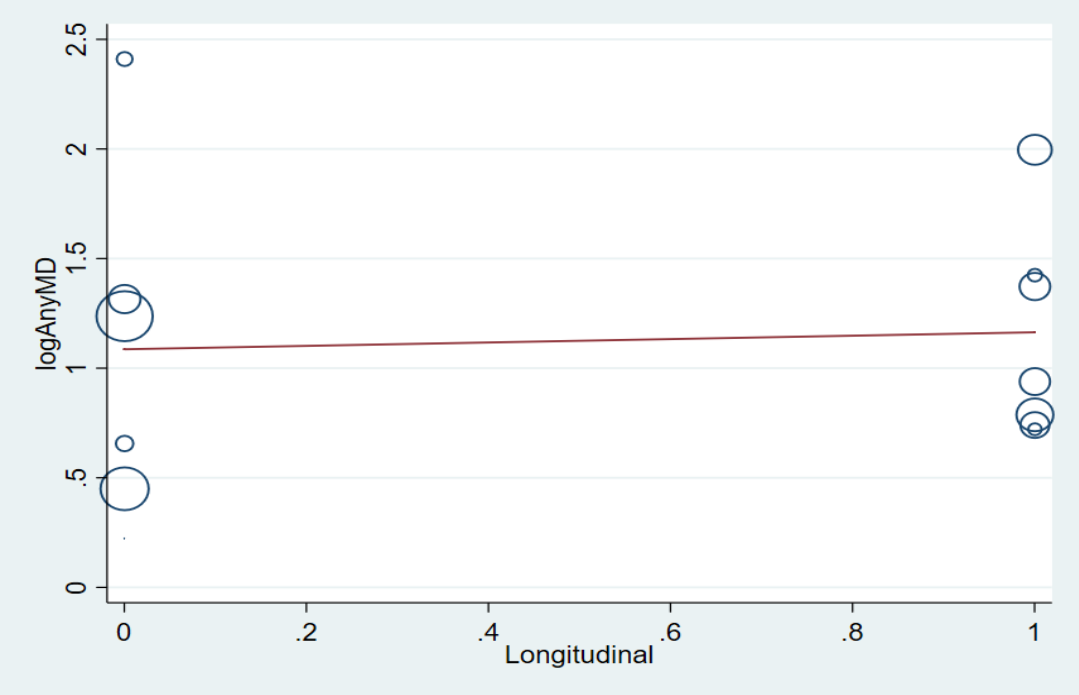
Supplementary Figure 3. Bubble plot for the effect of PE assessment type (a), study design type (b), population size (c), age at which PEs were investigated (d), gender (e) and Follow-up Time (Longitudinal studies – (f)) on the relationship between child and adolescent PEs and Any Mental Disorder.

a)



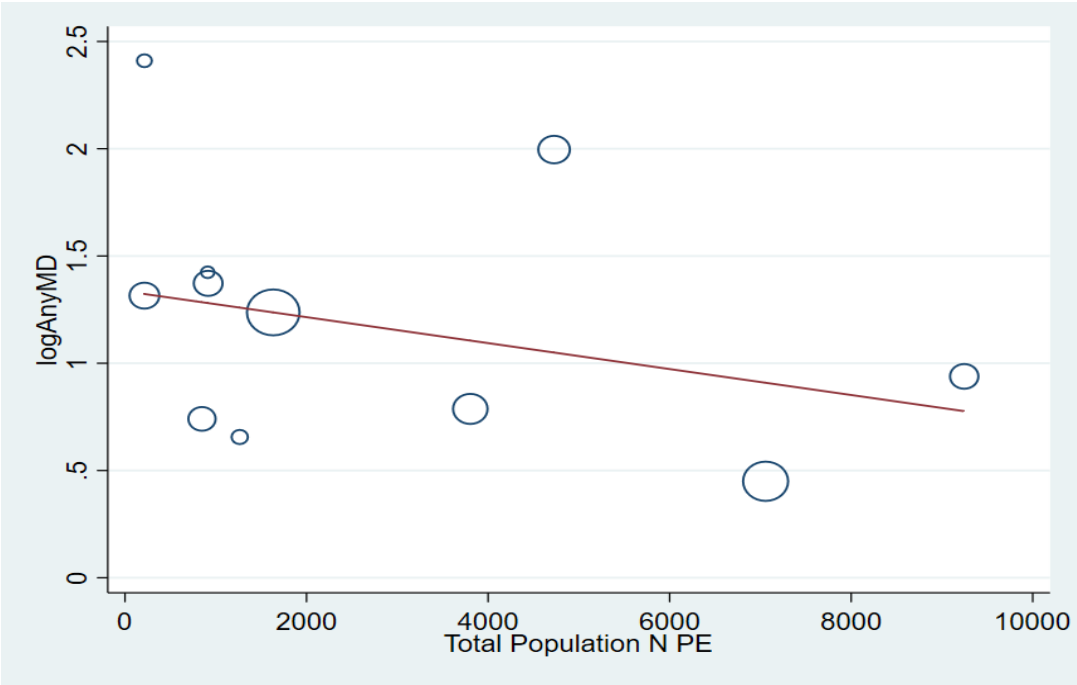
Assessment Type of PEs: Exp β: 1.29, 95%CI: 0.61-2.75, p =.46

b)



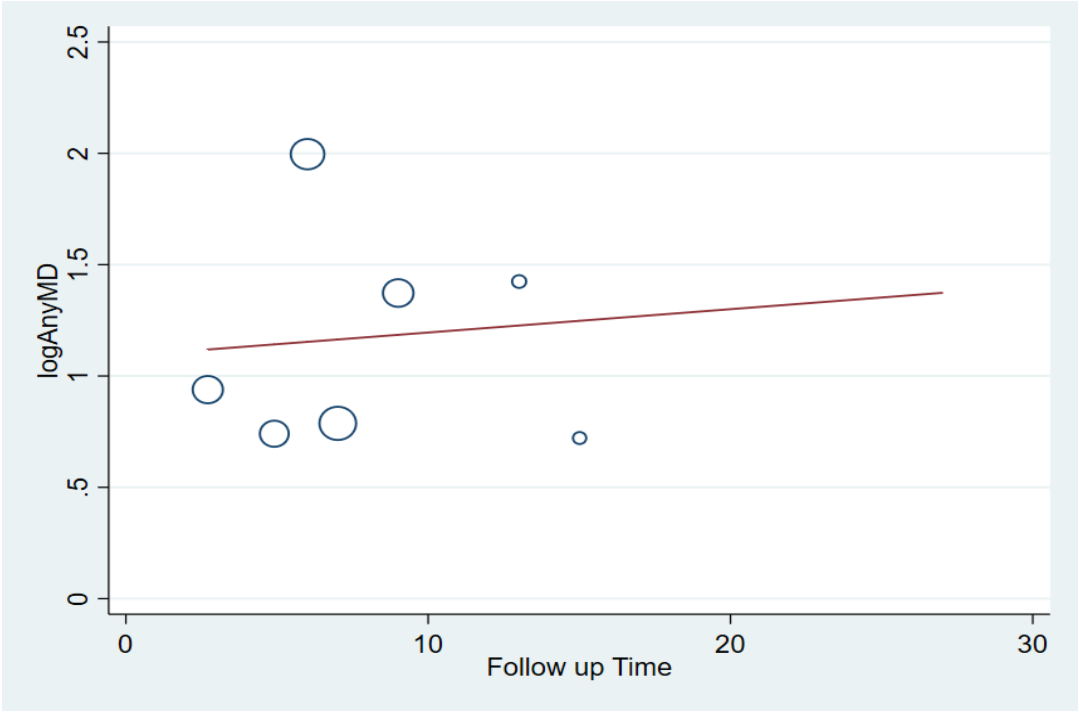
Study Design Type: Exp β: 1.08, 95%CI: 0.51-2.27, p =.82

c)



Total sample: Exp β: 1.0, 95%CI: 0.99-1.00, p =.30

d)

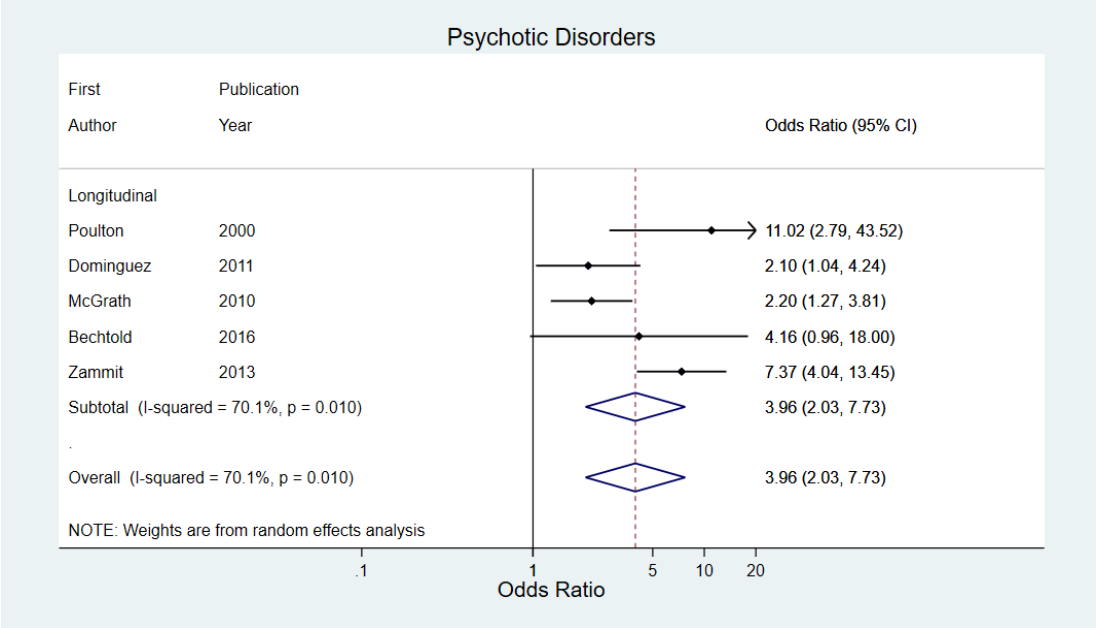


Follow-up Time: Exp β: 1.01, 95%CI: 0.85-1.20, p =.88

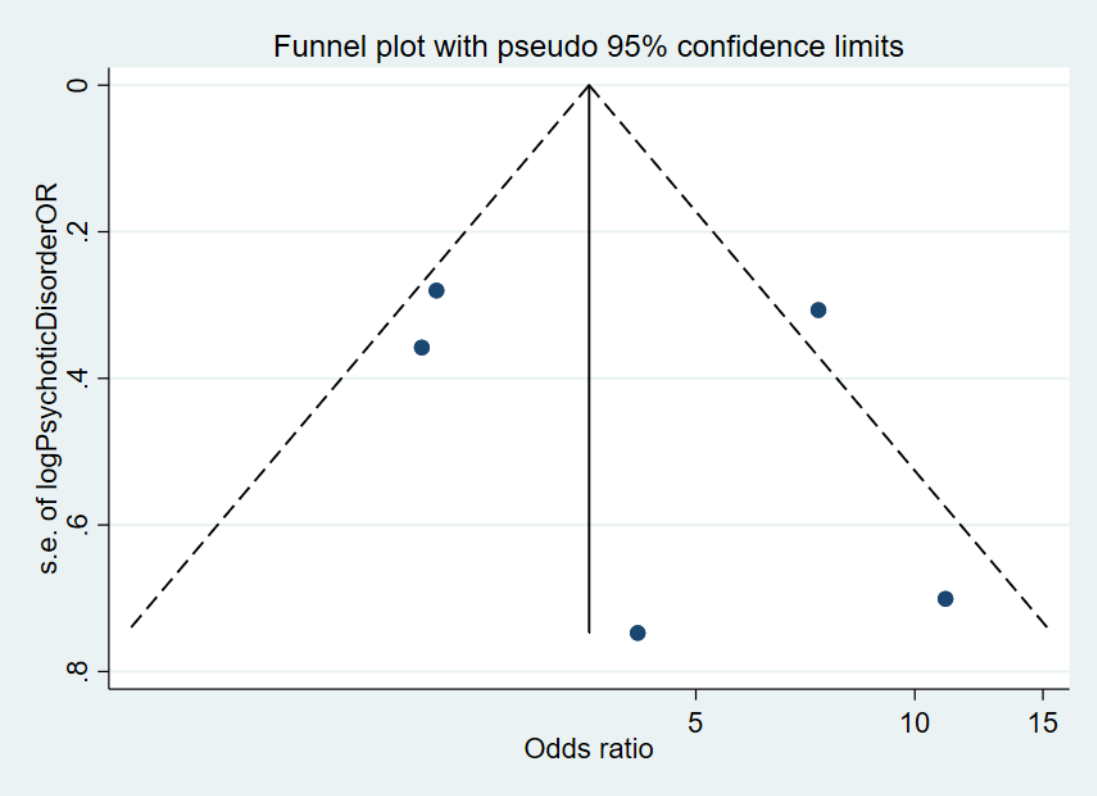
Supplement E.

Supplementary Figure 4. Forest plot (a) and Funnel plot (b) for the relationship between child and adolescent PEs and psychotic disorders.

a)



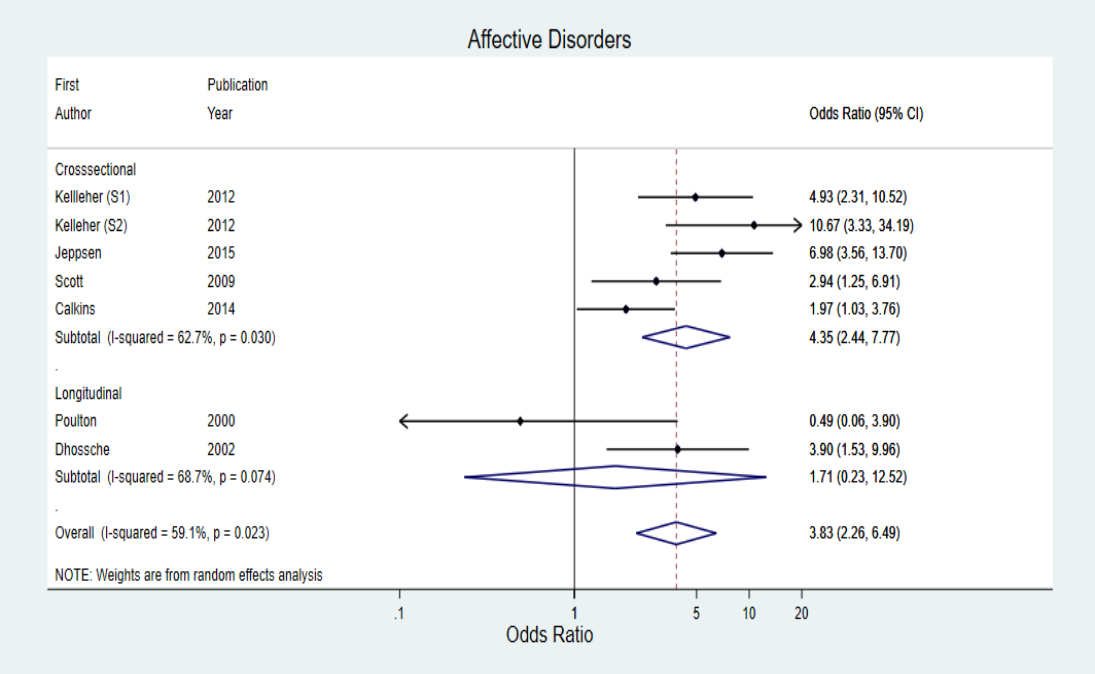
b)


Funnel plot with pseudo 95% confidence limits
s.e. of logPsychoticDisorderOR
0
.2
.4
.6
.8
5
10
15
Odds ratio

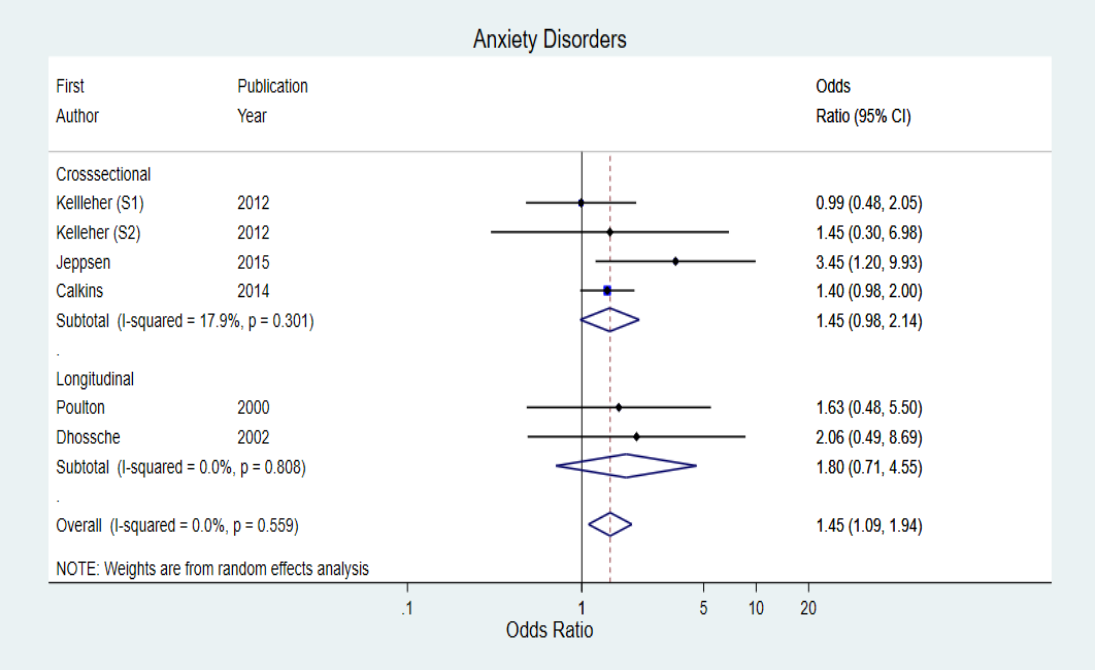
Supplement F.

Supplementary Figure 5. Forest plot for the association between child and adolescent PEs and Affective Disorders (a), Anxiety Disorders (b), Behavioural Disorders (c) and Substance use Disorder (d).

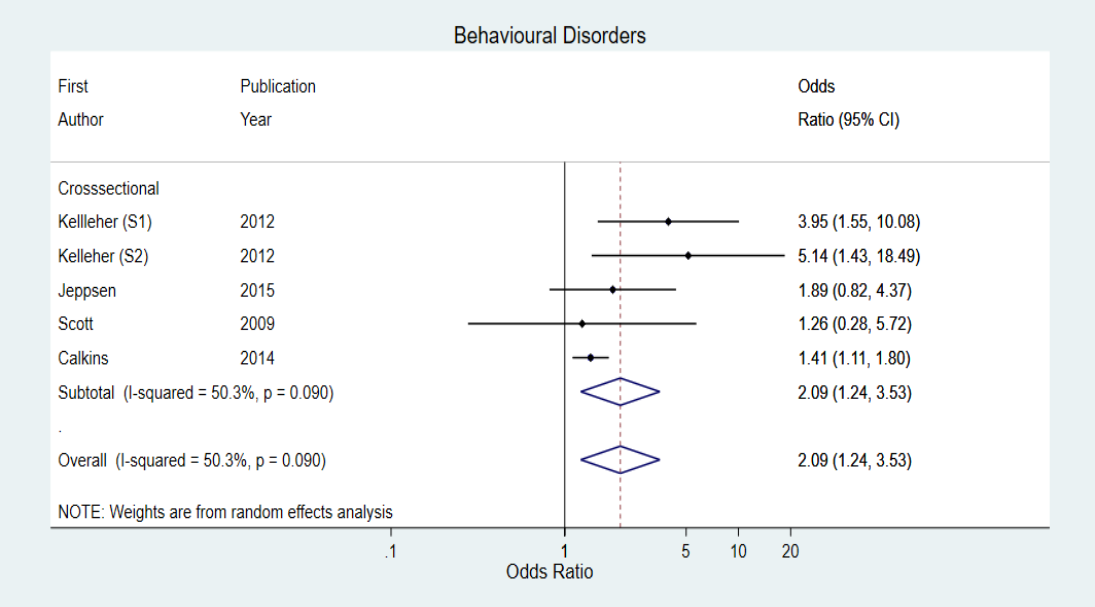
a)



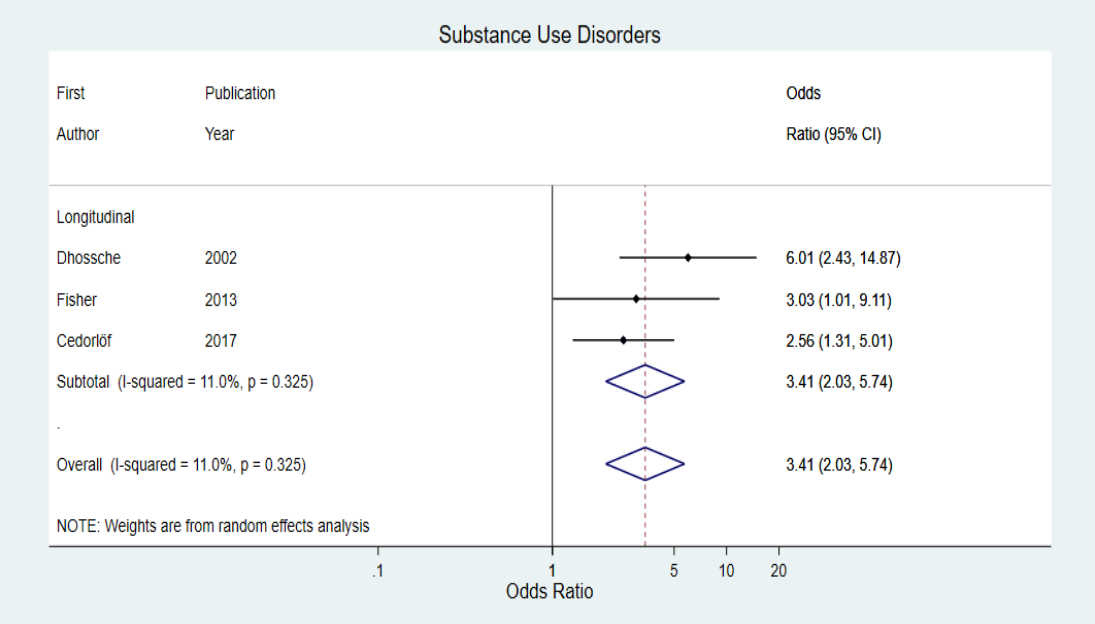
b)



c)


Behavioural Disorders
First Author
Publication Year
Odds Ratio (95% CI)
Crosssectional
Kellleher (S1) 2012 3.95 (1.55, 10.08)
Kelleher (S2) 2012 5.14 (1.43, 18.49)
Jeppsen 2015 1.89 (0.82, 4.37)
Scott 2009 1.26 (0.28, 5.72)
Calkins 2014 1.41 (1.11, 1.80)
Subtotal (I-squared = 50.3%, p = 0.090) 2.09 (1.24, 3.53)
Overall (I-squared = 50.3%, p = 0.090) 2.09 (1.24, 3.53)
NOTE: Weights are from random effects analysis
.1
1
5
10
20
Odds Ratio

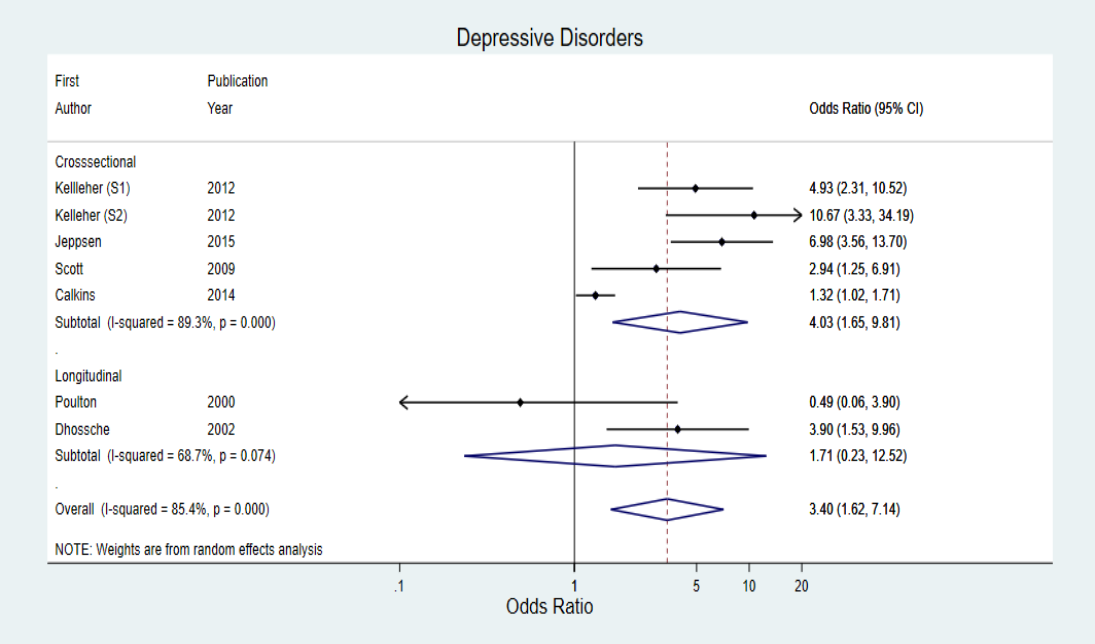
d)


Substance Use Disorders
First Author
Publication Year
Odds Ratio (95% CI)
Longitudinal
Dhossche 2002 6.01 (2.43, 14.87)
Fisher 2013 3.03 (1.01, 9.11)
Cedorlöf 2017 2.56 (1.31, 5.01)
Subtotal (I-squared = 11.0%, p = 0.325) 3.41 (2.03, 5.74)
Overall (I-squared = 11.0%, p = 0.325) 3.41 (2.03, 5.74)
NOTE: Weights are from random effects analysis
.1
1
5
10
20
Odds Ratio

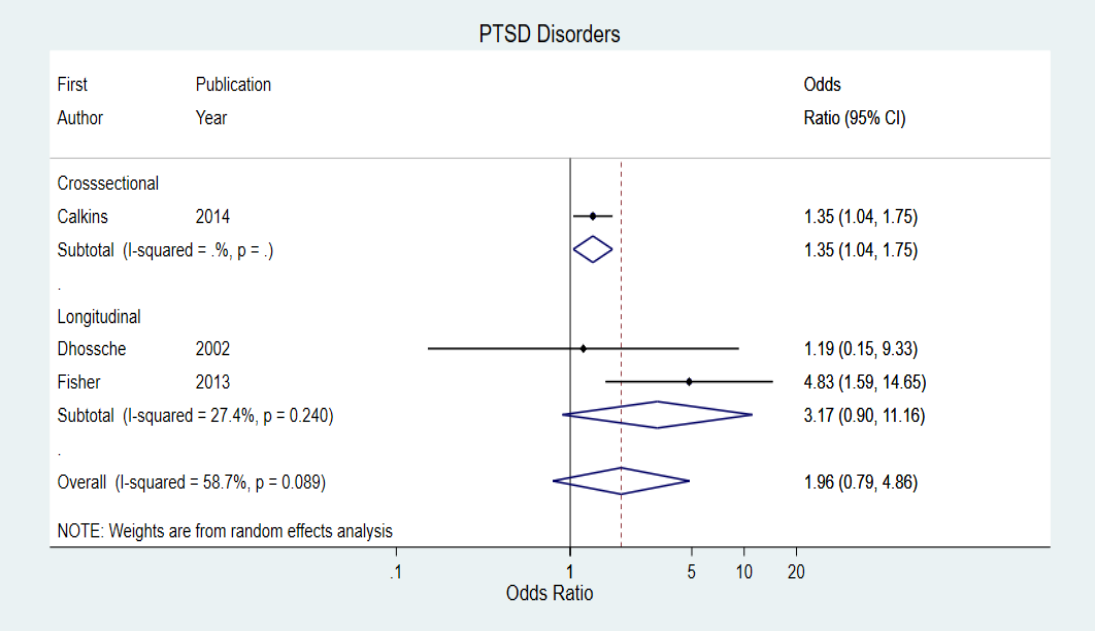
Supplement G.

Supplementary Figure 6. Forest plots for the association between child and adolescent PEs and Depressive Disorders (a) and Post-Traumatic Stress Disorder (PTSD) (b).

a)



b)



Supplement H.

Supplement H. A PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Fig 1,
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig 1, 4-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7, Sup B
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-7 Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Sup A
Summary	13	State the principal summary measures (e.g., risk ratio, difference	7

measures		in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Sup A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Sup A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 1-2 Table 2 Sup C-G
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 1-2 Table 2 Sup C-G
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Sup A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

Appendix – Study 5

Supplementary Table 1. Descriptive vignette of functioning for scoring the Global Assessment of Functioning (GAF) Scale (adapted from the *DSM-IV-TR,* pg. 34).

Score	Descriptive vignette of functioning
91 - 100	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
81 - 90	Absent or minimal symptoms (e.g., mild anxiety before exam), good functioning in all areas, interested and involved in a wide range of activities. Socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g. an occasional argument with family members).
71 – 80	If symptoms are present, they are transient and expectable reaction to psychosocial stressors (e.g. difficulty concentrating after family argument);no more than slight impairment in social, occupational or school functioning (e.g., temporarily falling behind in school work).
61 – 70	So mild symptoms (e.g. depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
51 – 60	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflict with peers or co-workers).
41 – 50	Serious symptoms (suicidal ideation, severe obsessional rituals, frequent shoplifting)

	OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).

American Psychiatric Association. Diagnostic and statistical manual of mental disorder, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association. 2000:739-41.

Appendix – Study 6

Supplementary Results

Statistical Analysis

We conducted two additional analysis to compare the results between the path-decomposition and counterfactual mediation approaches. Counterfactual mediation is based on the assumptions of conditional exchangeability (the exposed and the unexposed groups are exchangeable, conditional on the confounding variables). Two different causal mediation approaches were used in these analyses, namely, the stata program packages *meddeff* (Hicks & Tingley, 2011) and *paramed* (Emsley & Liu, 2013). The *meddeff* package was selected as it allows for data weighting and additional sensitivity analysis (*medsens*). Sensitivity analysis gives an estimate of unknown confounder bias required to remove the effect of the mediator (based on the error correlation between the mediator and the outcome, see table 1 and 2). However, the *medeff* output provides risk differences instead of odd ratios in the output, which may make a comparison with the KHB method difficult to interpret beyond the percentage mediation explained. Thus, we provide additional comparative analysis of the causal mediation we used *paramed* (see table 3 and 4). Paramed provides counter factual estimates for total, direct and indirect effects. However, *paramed* does not have an option for data weighting or sensitivity analysis.

Results

Results Comparison. The results in Table 1 and Table 2 demonstrate that there was very little difference in the percentage mediated between the traditional mediation approach and the counter factual mediation approach. The comparisons were equivalent for the important and unimportant mediators. Similarly, the odds ratios in Table 3 and Table 4 demonstrate that there was little difference in the total, direct and indirect effects between the traditional mediation approach and the counter factual mediation approach. Similar evidence can be observed for the homotypic relationships see Table 5 and 6.

Sensitivity analysis. Sensitivity analysis for confounding bias revealed that our results were relatively robust to confounder bias. Based on equal confounding estimates for the mediator and outcome, a confounding variable would have to explain 20% of the residual variance in both the mediator and outcome to eradicate the effects of self-concept and parent-child conflict on the relationship between early adolescent non-psychotic psychopathology and late adolescent PEs. Similarly, a confounding variable would have to explain between 20-40% of the residual variance in both the mediator and outcome to eradicate the effect of self-concept and parent child conflict on the relationship between early adolescent PEs and late adolescent non-psychotic psychopathology. This suggest that the results are relatively robust to confounding, however estimating whether such a percentage is large is subjective (Zhang et al., 2016). For comparison we provide the percentage of the variance explain by the observed confounding variables on the mediator and the outcome relationship (See Table 7). This is however with the important caveat that all of these major confounders have already simultaneously been taken into consideration in the calculation of the residual confounding that is required to remove the mediator effects. Thus, this comparison is unadjusted and likely over-emphasizes the importance of any one confounder. Additionally, unmeasured confounding is unlikely to reach the threshold of these major confounders.

Late Adolescent PEs

The residual variance required to prevent the effect of either self-concept and parent child conflict was estimated to be 10-20%. The results below suggest that a confounder as strong as childhood adversity would be required to remove the effect of parent-child on PEs. It is unlikely, but not impossible, that an unmeasured confounder would have this strength of effect.

Late Adolescent Internalizing Problems

The residual variance required to prevent the effect of either self-concept and parent child conflict was 30%. The results below suggest that a confounder with between three and four times the effect of childhood adversity would be required to remove the effect

of self-concept on Internalizing problems. It is unlikely that an unmeasured confounder would have this strength of effect.

Late Adolescent Externalizing Problems

The residual variance required to prevent the effect of either self-concept and parent child conflict ranged between 30-40%. The results below suggest that a confounder as twice as strong as family history of mental disorder and childhood adversity would be required to remove the effect of self-concept on Externalizing Problems. It is unlikely that an unmeasured confounder would have this strength of effect.

References

Hicks, R., & Tingley, D. (2011). Causal mediation analysis. The Stata Journal, 11(4), 605-619.

Emsley, R., & Liu, H. (2013). PARAMED: Stata module to perform causal mediation analysis using parametric regression models. Statistical Software Components S457581, Boston College Department of Economics, revised 26 Apr 2013.

Zhang, Z., Zheng, C., Kim, C., Van Poucke, S., Lin, S., & Lan, P. (2016). Causal mediation analysis in the context of clinical research. Annals of translational medicine, 4(21).

Table 1. Comparison between the weighted percentage mediation path decomposition and counterfactual mediation based on *meddeff,* for the relationship between early adolescent non-psychotic psychopathology and late adolescent psychotic experiences as well as sensitive bias estimates for the counter factual analyses.

Candidate Mediators	**Externalizing Problems and PEs**			**Internalizing Problems and PEs**		
	% Mediation		**Rho % Y_E/M_E**	**% Mediation**		**Rho % Y_E/M_E**
Parent Child Conflict						
Path-decomposition	33.6	-	-	24.7	-	-
Counter-Factual Mediation	33.6	.1	10	27.0	.2	20
Parent Child Positive						
Path-decomposition	9.7	-	-	6.1	-	-
Counter-Factual Mediation	10.3	-.1	10	7.0	-.1	10
Self-Concept						
Path-decomposition	18.6	-	-	27.6	-	-
Counter-Factual Mediation	20.3	-.2	20	31.1	-.2	20
Peer Trust						
Path-decomposition	-	-	-	4.6	-	-
Counter-Factual Mediation	-	-	-	4.9	-.1	10
Peer Alienation						
Path-decomposition	10.7	-	-	23.1	-	-
Counter-Factual Mediation	11.5	.1	10	24.8	.1	10

Note: Rho % Y_E/M_E: is the correlation represented as a percentage of the residual variance in both the mediator and the outcome that a confounder must explain for the average mediation effect to become zero (no effect).

Table 2. Comparison between the weighted percentage mediation path decomposition and counterfactual mediation based on *meddeff,* for the relationship between early adolescent psychotic experiences and late adolescent non-psychotic psychopathology as well as sensitive bias estimates for the counter factual analyses.

Candidate Mediators	**PEs and Externalizing Problems**			**PEs and Internalizing Problems**		
	% Mediation	**Rho**	**Rho % Y_E/M_E**	**% Mediation**	**Rho**	**Rho % Y_E/M_E**
Parent Child Conflict						
Path-decomposition	16.2	-	-	9.0	-	-
Counter-Factual Mediation	24.3	.4	40	13.4	.3	30
Parent Child Positive						
Path-decomposition	-	-	-	-	-	-
Counter-Factual Mediation	-	-	-	-	-	-
Self-Concept						
Path-decomposition	30.1	-	-	52.1	-	-
Counter-Factual Mediation	27.2	-.2	20	55.1	-.3	30
Peer Trust						
Path-decomposition	-	-	-	8.2	-	-
-Counter-Factual Mediation	-	-	-	9.5	-.1	10
Peer Alienation						
Path-decomposition	-	-	-	5.9	-	-
Counter-Factual Mediation	-	-	-	6.5	.1	10

Note: Rho % Y_E/M_E: is the correlation represented as a percentage of the residual variance in both the mediator and the outcome that a confounder must explain for the average mediation effect to become zero (no effect).

Table 3. Comparison between path decomposition and counterfactual mediation (*paramed*) total, direct and indirect effects for the relationship between early adolescent non-psychotic psychopathology and late adolescent psychotic experiences.

Candidate Mediators	**Externalizing Problems and PEs**			**Internalizing Problems and PEs**		
	Total	**Indirect**	**Direct**	**Total**	**Indirect**	**Direct**
	OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Parent Child Conflict						
Path-decomposition	**1.75** (1.26-2.42)	**1.26** (1.09-1.46)	**1.39** (0.97-1.98)	**1.53** (1.12-2.09)	**1.18** (1.08-1.30)	1.29 (0.93-1.79)
Counter-Factual Mediation	**1.77** (1.28-2.45)	**1.27** (1.10-1.48)	**1.39** (0.97-1.98)	**1.40** (1.02-1.92)	**1.09** (1.04-1.15)	1.28 (0.92-1.77)
Parent Child Positive						
Path-decomposition	**1.74** (1.26-2.42)	1.06 (0.98-1.14)	**1.65** (1.18-2.30)	**1.53** (1.12-2.09)	1.04 (0.99-1.08)	**1.47** (1.07-2.02)
Counter-Factual Mediation	**1.76** (1.27-2.44)	1.07 (0.98-1.15)	**1.65** (1.18-2.30)	**1.49** (1.09-2.03)	**1.02** (0.99-1.04)	**1.45** (1.06-1.99)
Self-Concept						
Path-decomposition	**1.78** (1.29-2.47)	**1.12** (1.06-1.17)	**1.59** (1.14-2.21)	**1.56** (1.14-2.14)	**1.17** (1.10-1.25)	**1.33** (0.97-1.84)
Counter-Factual Mediation	**1.82** (1.31-2.52)	**1.14** (1.08-1.20)	**1.60** (1.15-2.21)	**1.44** (1.05-1.98)	**1.09** (1.05-1.13)	**1.32** (0.96-1.81)
Peer Trust						
Path-decomposition	-	-	-	-	-	-
Counter-Factual Mediation	-	-	-	-	-	-
Peer Alienation						
Path-decomposition	**1.73** (1.24-2.41)	**1.04** (1.01-1.07)	**1.66** (1.19-2.32)	**1.47** (1.06-2.03)	**1.09** (1.03-1.14)	**1.35** (0.97-1.88)
Counter-Factual Mediation	**1.73** (1.24-2.41)	**1.04** (1.01-1.07)	**1.66** (1.19-2.31)	**1.39** (1.00-1.93)	**1.04** (1.02-1.07)	**1.34** (0.96-1.85)

Table 4. Comparison between path decomposition and counterfactual mediation (*paramed*) in the total, direct and indirect effects for the relationship between early adolescent psychotic experiences and late adolescent non-psychotic psychopathology.

Candidate Mediators	PEs and Externalizing Problems			PEs and Internalizing Problems		
	Total OR (95%CI)	Indirect OR (95%CI)	Direct OR (95%CI)	Total OR (95%CI)	Indirect OR (95%CI)	Direct OR (95%CI)
Parent Child Conflict						
Path-decomposition	1.49 (1.02-2.17)	1.07 (1.02-1.13)	1.39 (0.95-2.02)	1.98 (1.55-2.52)	1.05 (1.02-1.09)	1.88 (1.47-2.39)
Counter-Factual Mediation	1.49 (1.02-2.18)	1.09 (1.04-1.15)	1.37 (0.94-1.99)	2.04 (1.60-2.62)	1.08 (1.05-1.12)	1.88 (1.48-2.40)
Parent Child Positive						
Path-decomposition	-	-	-	-	-	-
Counter-Factual Mediation	-	-	-	-	-	-
Self-Concept						
Path-decomposition	1.46 (1.01-2.13)	1.20 (1.09-1.32)	1.22 (0.83-1.79)	1.86 (1.46-2.39)	1.35 (1.26-1.45)	1.38 (1.07-1.78)
Counter-Factual Mediation	1.46 (1.01-2.12)	1.20 (1.09-1.33)	1.21 (0.83-1.78)	1.91 (1.49-2.45)	1.38 (1.28-1.48)	1.39 (1.07-1.79)
Peer Trust						
Path-decomposition	-	-	-	1.99 (1.56-2.53)	1.04 (1.01-1.06)	1.91 (1.50-2.44)
Counter-Factual Mediation	-	-	-	2.00 (1.58-2.56)	1.05 (1.01-1.08)	1.92 (1.50-2.45)
Peer Alienation						
Path-decomposition	-	-	-	1.99 (1.56-2.54)	1.08 (1.03-1.13)	1.85 (1.44-2.36)
Counter-Factual Mediation	-	-	-	2.00 (1.57-2.56)	1.08 (1.03-1.14)	1.85 (1.45-2.37)

Table 5. Comparison between the weighted percentage mediation path decomposition and counterfactual mediation based on *meddeff,* for the homotypic relationship between early and late adolescent psychotic and non-psychotic psychopathology as well as sensitive bias estimates for the counter factual analyses.

Candidate Mediators	PEs		Internalizing Problems		Externalizing Problems	
	% Mediation	Rho % Y_E/M_E	% Mediation	Rho % Y_E/M_E	% Mediation	Rho % Y_E/M_E
Parent Child Conflict						
Path-decomposition	2.1	-	18.3	-	31.3	
Counter-Factual Mediation	2.2	20	18.2	30	33.1	40
Parent Child Positive						
Path-decomposition	-	-	3.4	-	-	-
Counter-Factual Mediation	-	-	3.3	20	-	-
Self-Concept						
Path-decomposition	14.1	-	12.6	-	2.9	
Counter-Factual Mediation	14.2	20	12.7	30	3.1	20
Peer Trust						
Path-decomposition	-	-	4.2	-	-	-
Counter-Factual Mediation	-	-	4.3	10	-	-
Peer Alienation						
Path-decomposition	8.3	-	2.9	-	-	-
Counter-Factual Mediation	8.2	20	2.8	20	-	-

Note: Rho % Y_E/M_E: is the correlation represented as a percentage of the residual variance in both the mediator and the outcome that a confounder must explain for the average mediation effect to become zero (no effect).

Table 6. Comparison between path decomposition and counterfactual mediation (*paramed*) in the direct and indirect effects for the homotypic relationship between early and late adolescent psychotic and non-psychotic psychopathology.

Candidate Mediators	PEs		Internalizing Problems		Externalizing Problems	
	Indirect	Direct	Indirect	Direct	Indirect	Direct
Parent Child Conflict						
Path-decomposition	1.03 (1.01-1.06)	4.70 (3.82-5.77)	1.46 (1.33-1.60)	6.25 (4.91-7.95)	2.63 (2.14-3.24)	7.33 (5.24-10.26)
Counter-Factual Mediation	1.04 (1.02-1.07)	4.66 (3.80-5.72)	1.24 (1.17-1.30)	6.25 (4.91-7.94)	2.73 (2.21-3.38)	7.22 (5.16-10.09)
Parent Child Positive						
Path-decomposition	-	-	1.09 (1.05-1.14)	8.12 (6.46-10.22)	-	-
Counter-Factual Mediation	-	-	1.05 (1.03-1.07)	8.10 (6.44-10.19)	-	-
Self-Concept						
Path-decomposition	1.21 (1.12-1.29)	4.04 (3.26-5.01)	1.39 (1.29-1.50)	6.52 (5.13-8.29)	1.16 (1.08-1.25)	14.99 (11.05-20.34)
Counter-Factual Mediation	1.21 (1.13-1.30)	4.01 (3.24-4.98)	1.21 (1.16-1.27)	6.51 (5.13-8.27)	1.20 (1.10-1.30)	14.96 (11.04-20.27)
Peer Trust						
Path-decomposition	-	-	1.08 (1.04-1.13)	7.81 (6.16-9.91)	-	-
Counter-Factual Mediation	-	-	1.04 (1.02-1.07)	7.80 (6.15-9.88)	-	-
Peer Alienation						
Path-decomposition	1.10 (1.04-1.16)	4.55 (3.68-5.62)	1.11 (1.05-1.17)	7.58 (5.97-9.64)	-	-
Counter-Factual Mediation	1.10 (1.04-1.16)	4.52 (3.66-5.58)	1.06 (1.03-1.09)	7.57 (5.96-9.61)	-	-

Note: Rho % Y_E/M_E: is the correlation represented as a percentage of the residual variance in both the mediator and the outcome that a confounder must explain for the average mediation effect to become zero (no effect).

Table 7. Percentage of the variance explain by the confounding variables on the mediator and the outcome relationship.

Mediators	**Adolescence Outcomes**		
Confounders	**Psychotic Experiences**	**Internalizing Problems**	**Externalizing Problems**
Self-Concept (%)			
Family History of Mental Disorder	9.37	3.08	14.16
Childhood Adversity	6.25	9.81	17.70
Socio Economic Status	8.59	2.5	8.85
Child-Parent Conflict (%)			
Family History of Mental Disorder	22.78	4.33	4.18
Childhood Adversity	11.39	8.30	3.93
Socio Economic Status	<0.001	0.87	1.21