Opening the black box: Environmental influences in the association between early biological risks and adult psychological development

By

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Table of Contents

List of Tables

List of Figures

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Abstract

Biological risks occurring during the prenatal and neonatal periods have been frequently associated with adult psychopathology. However, environmental influences are rarely examined along the same pathway, and outcomes in areas of psychosocial wellbeing have received little attention. It is important to examine environmental mechanisms in the association between biological risks and adult psychopathology, and to extend this pathway to psychosocial wellbeing, to identify potentially modifiable processes and whether the same mechanisms are implicated in both areas of adult psychological development.

This thesis examined the role of one environmental mechanism – childhood trauma – in the association between biological risks (prenatal stress, neurodevelopmental adversity) and adult psychopathology (depression, psychosis) as well as psychosocial wellbeing (self-concept). Four studies were designed: the first two investigated the effect of prenatal stress and neurodevelopmental adversity on depression and psychotic experiences in adulthood in the general population, and the role of caregiver- and peer-inflicted trauma. The last two studies used longitudinal data from the preterm population, which acted as a proxy measure indicating multiple exposures to neurodevelopmental adversity, and examined outcomes in psychotic experiences and self-concept in relation to peer-inflicted trauma (i.e peer bullying).

Findings from these studies consistently showed a mediating effect of childhood trauma, in particular peer bullying, even after accounting for important confounders and genetic risks. Despite biological risks having a small effect on the outcomes examined, a significant proportion was mediated via childhood trauma. A dose-response effect was also observed: increased exposure to childhood trauma was associated with increased risk for depression, psychotic experiences, and decreasing self-concept.

These findings suggest the importance in adopting a developmental cascade approach, where early biological risks may lead to increasing difficulties in childhood which cumulates in psychopathology or adverse wellbeing. Resources should focus on identifying high-risk groups who are more likely to be exposed to childhood trauma, as well as interventions to reduce childhood trauma in the general population. These findings further highlight the importance of routinely assessing childhood trauma and adopting a trauma-informed approach in clinical settings.

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
BLS	Bavarian Longitudinal Study
CI	Confidence Interval
DRFM	Developmental Risk Factor Model
ELBW	Extremely Low Birth Weight
EP	Extremely Preterm
EPDS	Edinburgh Postnatal Depression Scale
FAI	Family Adversity Index
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
IQ	Intelligent Quotient
LBW	Low Birth Weight
MDD	Major Depressive Disorder
NM	Neurodevelopmental Model
OR	Odds Ratio
PE	Psychotic Experiences
PT	Preterm
SE	Standardised Estimate
SES	Socio-Economic Status
SNP	Single-Nucleotide Polymorphism
TM	Trauma Model
VLBW	Very Low Birth weight
VP	Very Preterm
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Overview

There is a wealth of research in the literature linking early risks during the prenatal and neonatal periods with adult psychological development (e.g. O'Connor, 2015; Räikkönen & Pesonen, 2009; Van den Bergh et al., 2017). However, few studies have investigated environmental influences associated with these risks along the developmental pathway, and even fewer have investigated this in areas of positive wellbeing compared to areas of psychopathology. The aim of this chapter is to provide an overview on the importance of this early period, and to set the scene on how research into long-term adult psychological development after exposure to early risks can be better informed by the inclusion of other environmental factors across childhood. A new research approach is offered, focusing first on two outcomes of psychopathology – depression and psychosis, and one outcome in positive wellbeing – the development of self-concept.

1.2 The importance of studying early risks

Over the last few decades, there has been increasing interest in the study and follow-up of infants exposed to early risks, which may include premature birth, intrauterine growth restriction, exposure to prenatal stress, infections and other complications occurring during the prenatal or neonatal periods (Allen, 1993; Davies et al., 2020; Van den Bergh et al., 2017). The survival of some of these infants has increased drastically over the last few decades, from just 20% of extremely low birth weight (<1000 grams) infants surviving in the 1970s to 67% in the 1990s (O'Shea et al., 1997; Wilson-Costello et al., 2005). Survival rates for infants born between 22 and 25 weeks, considered as extremely preterm, have also increased from just 40% in the 1990s to 66% in 2014, and 91% of infants born below 32 weeks gestation are now surviving to discharge from initial hospital admission (Santhakumaran et al., 2018). However, despite their increased survival rates, up to 40% of those born

extremely preterm experience moderate or severe developmental impairments at 2.5 years of age (Johnson & Marlow, 2016; T. Moore et al., 2012). Despite improved survival, the proportion of those who experience significant disability has not changed, and these have been found to have major impact on their social, educational and psychological development even into adulthood (Johnson & Marlow, 2016; Marlow et al., 2021; Mendonca et al., 2019; Myrhaug et al., 2019; Wolke et al., 2019).

As more infants exposed to early risks are now surviving into adulthood, more may be faced with a number of challenges ranging from increased psychopathology to reduced functioning in domains of psychosocial wellbeing (Mendonca et al., 2019; Wolke et al., 2019). These also contribute to substantial economic cost, partly from the initial hospitalisation but also cost incurred throughout life from continued access to health, social and welfare services (Petrou et al., 2013, 2019). Thus, early risks occurring during the prenatal and neonatal periods can have lasting impact on adult development, so a new wave of research started to focus on the long-term outcomes of these infants, to better understand the effect of early risks and to mitigate their altered developmental trajectory.

1.3 Biological mechanisms associated with early risks

There is strong evidence in the literature for the involvement of biologically mediated mechanisms in the association between early risks and adult psychological development, in particular for adult psychopathology (D. R. Kim et al., 2015; Silveira et al., 2007; Van den Bergh et al., 2017). These early risks often occur during the prenatal and neonatal periods, and two risks in particular – prenatal stress and neurodevelopmental adversity – will be the focus of this thesis. Prenatal stress is commonly indicated by maternal psychopathology such as depression during pregnancy (Van den Bergh et al., 2017, 2018), but can also be a result of social and economic adversity in the family environment, which has been termed by some as family adversity in the literature (Lereya & Wolke, 2013; Najman et al., 2017).

Neurodevelopmental adversity in this thesis refers to both obstetric complications during the prenatal and neonatal periods, such as premature birth, as well as subsequent developmental impairments which normally manifest in childhood and may be attributed to brain alterations resulting from exposure to these obstetric complications (Kunugi et al., 2001). Both prenatal stress and neurodevelopmental adversity have been shown to have lasting impact on the development of the brain, endocrine and immune systems implicated in the onset of adult psychopathology (Costas-Carrera et al., 2020; Kunugi et al., 2001; Van den Bergh et al., 2017, 2018). These two indicators of early risks will be referred to as biological risks in this thesis, to differentiate them from environmental risks discussed in later chapters.

One of the most consistently implicated biological system is the hypothalamic-pituitary-adrenal (HPA)-axis, one of the core systems involved in stress regulation and response (Koss & Gunnar, 2018). Under typical activation, the stress hormone cortisol is released into the bloodstream which triggers the fight-or-flight response that is crucial for survival (Koss & Gunnar, 2018). However, under prolonged exposure to stress, the activation of the HPA-axis can be permanently altered (Koss & Gunnar, 2018). For example, prenatal stress such as maternal depression during pregnancy has been found to affect the transfer of stress hormones to the foetus via the placenta, which in turn alters the development of the HPA-axis in the foetus (D. R. Kim et al., 2015). This can predispose the offspring to a range of psychopathology in later life, including internalising problems such as depression and anxiety, and externalising problems such as conduct problems and substance misuse (Koss & Gunnar, 2018; Monk et al., 2019).

There is also some evidence implicating exposure to neurodevelopmental adversity, in particular obstetric complications, in abnormal brain development which may contribute to the development of adult psychopathology (Costas-Carrera et al., 2020). During normal development, the brain undergoes rapid structural and functional changes throughout the entire period of gestation (Andescavage et al., 2017; Davis et al., 2011).

Exposure to biological risks such as obstetric complications during the prenatal and neonatal periods can thus alter or damage the development of the brain, leading to permanent structural changes (Cordeiro et al., 2015; Nosarti, 2013; Volpe, 2009). Functional connectivity have also been found to be affected after exposure to obstetric complications, and have been implicated in specific developmental impairments such as cognitive and behavioural problems (Bäuml et al., 2015; Nosarti, 2013; Salzwedel et al., 2015). These brain alterations are also frequently associated with the onset of adult psychopathology such as psychosis (Costas-Carrera et al., 2020; De Peri et al., 2012).

Alterations to the function of the immune system have also been observed after disruption to typical foetal development (Monk et al., 2019). Specific indicators for obstetric complications such as maternal infection during pregnancy has been associated with increased placental inflammation and alterations to the development of the foetal immune system (D. R. Kim et al., 2015). Certain inflammatory markers have also been found in offspring of mothers who were depressed or experienced stressful events during pregnancy, and these have been implicated in adverse neurodevelopmental outcomes and adult psychopathology such as depression and psychosis (Allswede & Cannon, 2018; Marques et al., 2015; Plant et al., 2016). Although this is not a comprehensive overview of all the biological systems hypothesised to be involved, they offer some plausible explanations for how these biological risks – prenatal stress and neurodevelopmental adversity in particular – contribute to the onset of adult psychopathology.

1.4 Limitations of current understanding

There is vast amount of evidence from epidemiology and observational studies on the association between biological risks and adult psychopathology, and several biologically mediated mechanisms have been proposed (e.g. D. R. Kim et al., 2015; Van den Bergh et al., 2017). However, these biological risks are rarely sufficient in themselves to explain the

development of psychopathology (Costas-Carrera et al., 2020). The majority of follow-up studies in populations exposed to these biological risks have only examined one aspect of risk, such as premature birth, and the direct impact it has on an outcome (Aylward, 2002, 2010). These “main effect” models can only inform researchers on the likelihood of certain outcomes, rather than the mechanisms involved (Aylward, 2002, 2010), and does not allow the investigation of other risk factors occurring at different stages of development.

Additionally, while the majority of longitudinal research on biological risks and adult psychological development have focused on areas of psychopathology, the absence of psychopathology is not necessarily an indicator for positive psychological development (Bos et al., 2016; C. L. M. Keyes, 2007; Suldo & Shaffer, 2008). Positive psychological development has been previously proposed to be a dual model, composed of both the absence of psychopathology and the presence of positive wellbeing (Suldo & Shaffer, 2008; Westerhof & Keyes, 2010). There is thus an increasing interest in moving away from models of psychopathology and to focus more on positive wellbeing (Maddux, 2009), although few studies investigating long-term outcomes following exposure to these biological risks have focused on this aspect of development. This presents an opportunity to investigate whether the same mechanisms are associated with both areas of psychopathology as well as positive wellbeing, and to provide a holistic understanding on pathways from biological risks to both aspects of adult psychological development.

Furthermore, risks rarely occur in isolation, and other exposures along the developmental pathway may have additive or interactive effects that contribute to specific outcomes (Monk et al., 2019). However, the role of environmental influences in the association between biological risks and adult psychological development remains largely a “black box” – a term first used to describe the lack of understanding on mechanisms involved with diseases in traditional epidemiology studies (Savitz, 1994). Some theoretical models

have been proposed that acknowledge the joint influence of biological and environmental risks; one of the most well cited, the diathesis-stress model, proposes that not all individuals are equally affected by risks but that certain vulnerabilities may predispose individuals to adverse outcomes (Koss & Gunnar, 2018). For example, it has been shown that the effect of stressful life events on depression is much greater among those with genetic vulnerability for major depressive disorder (Colodro-Conde et al., 2018). There is also evidence of a cumulative effect of risks in schizophrenia, with those genetically vulnerable to schizophrenia being more likely to experience environmental risks, such as family conflict (Walder et al., 2014). These suggest that certain individuals may be more vulnerable to either the effects of subsequent risks or are simply exposed more frequently to further risks. It is therefore important to examine the joint influence of biological and environmental risk factors in predicting adult psychological development.

1.5 Towards a new aetiological understanding

To address these limitations, it is important to look beyond the initial postnatal years to identify environmental risks in childhood and adolescence. Understanding the way in which biological risks may increase vulnerability to subsequent environmental risks can also help identify potentially modifiable processes, which may be used to inform policy and practice (Slater & Quinn, 2012). Therefore, it is important to examine both the biological risks occurring early in life, and environmental influences occurring at different stages of development, to better understand how they relate to one another and their joint influence on adult psychological development, which includes both aspects of psychopathology and positive wellbeing.

One environmental risk which will be the focus of this thesis is childhood trauma, and the mechanism in which it may be associated with biological risks will be investigated in this thesis. This joint model of influence between biological and environmental risks will be primarily focused on outcomes in adult psychopathology, which is represented by depression and psychosis,

with a specific focus on psychosis. As a secondary outcome, this joint model will also be applied to one area of positive wellbeing – the development of self-concept – to examine whether the same mechanisms are involved as those associated with adult psychopathology.

The structure of the thesis is as follows: a comprehensive review of the role of biological risks in depression and psychosis is offered in chapter 2, focusing first on the association between prenatal stress and offspring depression, followed by the association between neurodevelopmental adversity and psychosis. Leading on from this, chapter 3 presents an opportunity of testing the role of neurodevelopmental adversity in special populations who are naturally exposed to multiple risks. The term naturalistic experiment is introduced and the possibility of using the special population as a proxy measure for neurodevelopmental adversity is also discussed in relation to psychosis. Chapter 4 offers a comprehensive review of the role of environmental risks, focusing particularly on childhood trauma, in the onset of depression and psychosis, followed by a discussion of the joint influence of biological and environmental risks in chapter 5. These are all discussed in relation to two adult outcomes in psychopathology – depression and psychosis.

In contrast to these models of psychopathology, chapter 6 will introduce the opportunity of examining a different type of outcome – positive wellbeing – in the form of self-concept. This will be examined using the special population first introduced in chapter 3, who are hypothesised to be a group exposed to multiple risks, to examine whether the same mechanisms associated with the development of psychosis are also implicated in the development of self-concept.

Chapter 7 outlines the overall aims and specific research questions proposed to address them, with a detailed description of the methodologies used presented in chapter 8. Chapters 9, 10 and 11 each examines one outcome – depression, psychosis, and self-concept – and the independent and joint

influence of biological and environmental risks. Lastly, chapter 12 offers a general discussion on the implications and quality of these findings, as well as future recommendations for longitudinal research in these areas.

Chapter 2: Biological risks and adult psychopathology

One of the most widely cited theoretical models on the association between biological risks and adult psychopathology is the programming model (D. J. Barker, 1998; D. R. Kim et al., 2015; A. Lewis et al., 2015). Although first applied to the field of physical health to explain the onset of cardiovascular diseases, it has also been used to explain the origin of psychopathology such as depression (Räikkönen & Pesonen, 2009). Another model – the Neurodevelopmental model of schizophrenia – also proposes the importance of the prenatal and neonatal periods, applied to the onset of psychosis and psychotic disorders such as schizophrenia (Murray & Lewis, 1987; Murray, 1994). Evidence supporting these two models are presented in this chapter, first focusing on the association between prenatal stress and offspring depression, and secondly on neurodevelopmental adversity and psychosis.

2.1 Prenatal programming model

2.1.1 Theoretical model

The prenatal programming model proposes that different environmental inputs during the prenatal period can lead to variations in the development of certain systems, which may programme the offspring to react differently to subsequent environment (D. R. Kim et al., 2015; O'Connor, 2015). One of the earliest evidences for a prenatal programming effect came from the association between foetal growth restriction and cardiovascular disease in adulthood (D. J. Barker, 1998; O'Connor, 2015). Since then, evidence has accumulated on the association between early foetal development and adverse health outcomes in adulthood, suggesting that factors occurring during the prenatal period can have long and lasting impact on brain and body functions (Fleming et al., 2015).

More recently the programming model has incorporated evolutionary perspectives and has been termed the experience-adaptive or predictive-adaptive response hypothesis in some literature (Bateson et al., 2014; O'Connor, 2015; Stenson et al., 2016). This assumes individuals to be active agents who are capable of adapting according to their environmental inputs, and individual differences may be viewed as adaptations to different environment rather than as normal or abnormal (Bateson et al., 2014; O'Connor, 2015). Problems may arise when the subsequent environment does not match early prenatal environment, and the adaptation strategies adopted by individuals are mismatched (Bateson et al., 2014; O'Connor, 2015).

This has been shown in the relationship between foetal growth restriction and cardiovascular disease, which has been hypothesised to be the result of a mismatch between a nutritionally restricted prenatal environment and nutritionally rich postnatal environment (Ellis et al., 2014; Stenson et al., 2016). Both animal and human studies have shown that a prenatal environment marked by nutritional deficit may programme the foetus to prepare for a similar environment after birth, therefore a different postnatal environment will result in a phenotype that's poorly adapted (Crespi & Denver, 2005; Ellis et al., 2014; O'Connor, 2015). Rapid catch-up growth in infants born with low birth weight has been associated with obesity in adulthood, suggesting that a nutritionally poor prenatal environment may programme systems governing food intake and storage (Crespi & Denver, 2005; Stenson et al., 2016). Adapting to this new postnatal environment, for example by delaying catch-up growth or restricting nutrition during the first two weeks after birth has been shown to reduce risk of obesity-related diseases in adulthood (Singhal et al., 2004).

Although the idea of prenatal programming has mainly been applied to areas of physical health, more recently there has been an interest in identifying prenatal risks for adult psychopathology such as depression (D. R. Kim et al., 2015; Räikkönen & Pesonen, 2009). Recent longitudinal studies have also investigated prenatal risks other than low birth weight – as an indicator for

foetal growth restriction – that may have a programming effect, such as prenatal stress (D. R. Kim et al., 2015; Monk et al., 2019; Van den Bergh, 2011). Prenatal stress has been hypothesised to have the same programming effect as foetal growth restriction, as a stressful prenatal environment may signal the offspring to prepare for a stressful postnatal environment by altering their stress response system to be more reactive to the environment (O'Connor, 2015). However, when these previously adaptive responses are carried over to the postnatal period and adulthood, which is marked by a very different environment compared to the prenatal period, it can result in a range of outcomes that may be judged as deviant or pathological (O'Connor, 2015).

Several areas of physiological changes have been proposed, with the strongest evidence implicating changes to the HPA-axis (O'Connor, 2015; Osborne et al., 2018; Van den Bergh et al., 2008, 2017). Exposure to prenatal stress has been found to activate the HPA-axis and increase levels of cortisol in the blood, which may be transferred to the foetus via the placenta, affecting the development of the foetus' HPA-axis and their subsequent response to stress (O'Connor, 2015). The prenatal period may also be a period where the development of the HPA-axis is more vulnerable to external input (O'Connor, 2015). As cortisol levels and the HPA-axis are involved in a number of biological systems, the effects of altered development therefore manifests across a range of adult psychopathology (O'Connor, 2015; Van den Bergh et al., 2017). Empirical evidence on the association between prenatal stress and one adult psychopathology in particular – depression – will be discussed in the following section.

2.1.2 Empirical evidence: Prenatal stress and offspring depression

A number of reviews have examined the association between prenatal stress and psychopathology in the offspring (D. R. Kim et al., 2015; Monk et al., 2019; O'Connor, 2015; Robinson et al., 2019; Van den Bergh et al., 2017). Prenatal stress is often indicated by psychological stress such as maternal psychopathology, although another type – social and economic stress – often

indicated by family adversity, can also be considered as a separate source of prenatal stress (Najman et al., 2017; Rutter, 1979; Van den Bergh et al., 2017; Winsper et al., 2012). The evidence is strongest for prenatal maternal psychopathology, with already four comprehensive reviews published on its association with offspring psychopathology in both childhood and adulthood (Kingston & Tough, 2014; Rees et al., 2019; Robinson et al., 2019; Tirumalaraju et al., 2020). A summary of findings on prenatal stress and offspring depression can be found in Table 1.

Focusing specifically on the association between prenatal maternal depression and offspring depression, a recent meta-analysis found that prenatal maternal depression was associated with a 1.78-times increased risk of depression in the adult offspring (Tirumalaraju et al., 2020) (Table 1). Although postnatal maternal depression was also associated with offspring depression in adulthood, the effect was slightly weaker (1.66-times increased risk) compared to prenatal maternal depression (Tirumalaraju et al., 2020). However, most of the studies included in the meta-analysis investigated prenatal and postnatal maternal depression separately, therefore it was not possible to determine how much of the association between prenatal maternal depression and offspring depression may be due to its continuity into the postnatal period, rather than a programming effect. Some studies found that it was maternal rather than paternal depression during pregnancy that had the strongest effect on offspring psychopathology, offering support for a programming effect that may be independent from genetic influences (Capron et al., 2015; Pearson et al., 2013) (Table 1). This is also consistent with evidence of a biologically mediated pathway from prenatal maternal depression to offspring depression, including alterations to the brain and HPA-axis, as well as changes to immune response and the nervous system implicated in depression (Robinson et al., 2019; Van den Bergh et al., 2017).

There is also evidence that family adversity – as a source of social and economic stress – is associated with offspring development independently from maternal depression (Lereya & Wolke, 2013; Najman et al., 2017)

(Table 1). Indicators of family adversity can include living conditions, education/employment status, substance misuse, criminal behaviours and relationship conflict, and has been frequently assessed in the literature using the Family Adversity Index (FAI) (Lereya & Wolke, 2013; Rutter, 1979; Steer et al., 2004; Winsper et al., 2012). Although family adversity is closely associated with prenatal maternal depression, it has been considered as a separate source of prenatal stress in previous studies with differential effects on offspring development (Lereya & Wolke, 2013; Najman et al., 2017). Trajectories of high family adversity or exposure to stressful life events have been shown to be independently associated with offspring depression in adulthood even after accounting for maternal depression (Kingsbury et al., 2016; Najman et al., 2017). These suggest that both sources of prenatal stress should be investigated to examine the potentially separate effects of psychological stress from maternal depression, and social and economic stress from family adversity. A summary of the major findings on the association between both sources of prenatal stress and offspring depression is shown in Table 1.

Table 1.

Summary of findings on the association between prenatal stress and offspring depression.

Study	Type	Exposure	Findings
Tirumalaraju et al. (2020)	Meta-analysis (6 longitudinal studies)	Maternal perinatal depression	Both prenatal and postnatal depression increased risk of offspring depression in adolescence and adulthood (>12 years) (OR: 1.70, 95%CI: 1.06 – 2.65). Prenatal depression associated with 78% increased risk (OR=1.78) and postnatal associated with 66% increased risk (OR=1.66).

Table 2. continued

Summary of findings on the association between prenatal stress and offspring depression.

Study	Type	Exposure	Findings
Plant et al. (2015)	Longitudinal cohort study (N=103)	Prenatal maternal depression (20 and 36 weeks)	Offspring of mothers with prenatal depression had 3.4 times (95%CI: 1.5 – 8.1) increased risk of depression in adulthood (18-25 years) than offspring of mothers who were not depressed during pregnancy.
Pearson et al. (2013)	Longitudinal cohort study (N=4566)	Prenatal and postnatal maternal depression	Prenatal maternal depression was independently associated with offspring depression at 18 years (OR: 1.29, 95%CI: 1.08 – 1.55), even after excluding mothers with postnatal depression.
Najman et al. (2017)	Longitudinal cohort study (N=2200)	Trajectory of maternal depression and family adversity from pregnancy to adulthood	Both trajectories of maternal depression and family adversity were associated with offspring depression at 30 years. After adjusting for each other, only family adversity trajectory was associated with offspring depression.
Kingsbury et al. (2016)	Longitudinal cohort study (N=10569)	Stressful life events during pregnancy (composite score of 42 items)	Every unit increase in stressful life events associated with 1.03 times increased risk of offspring depression at 17 to 18 years (95%CI: 1.01 – 1.06).

Both sources of prenatal stress also extend into the postnatal period (E. D. Barker et al., 2011; Lereya & Wolke, 2013), however there is relatively little research on the effect of prenatal maternal depression and family adversity on offspring depression independently from their continuity into the postnatal period. Research on outcomes other than offspring depression have shown

that prenatal maternal depression predicted childhood borderline personality disorder even after adjusting for postnatal family adversity and substance misuse during pregnancy (Winsper et al., 2015). It remains to be examined whether the effects of prenatal family adversity on offspring depression is separate from the effects of prenatal maternal depression, and how much of these effects remain when their continuity into the postnatal period is considered in one model.

2.2. Neurodevelopmental model of schizophrenia

2.2.1 Theoretical model

Similar to the idea of a prenatal programming effect, another model – the Neurodevelopmental model – emerged around the same period to explain the aetiology of schizophrenia (S. W. Lewis & Murray, 1987; Weinberger, 1987). This is one of the most influential and well cited models of schizophrenia (Bearden et al., 2015; Marenco & Weinberger, 2000). According to the model, the origin of schizophrenia and psychosis can be traced back to early impairments in the development of the nervous system, often due to obstetric complications such as maternal exposure to influenza, premature birth or foetal hypoxia (Bearden et al., 2015; Marenco & Weinberger, 2000; Murray, 1994). These complications can cause long lasting developmental impairments cumulating in psychosis in adolescence and adulthood (Clarke & Cannon, 2020). Evidence for this model primarily comes from brain imaging studies, which shows abnormal structural and functional connectivity in those with psychosis, suggesting disruptions to early brain development; as well as findings of neuropsychological deficits in childhood, which may be considered as early markers for the disorder (Bearden et al., 2015; Clarke & Cannon, 2020; Marenco & Weinberger, 2000).

Early evidence for abnormal brain development comes from post-partum studies, which repeatedly found reduced brain volumes and enlarged ventricles in deceased patients previously diagnosed with schizophrenia (S.

W. Lewis & Murray, 1987; Weinberger, 1987). These are consistent with brain lesions observed in those who are born with obstetric complications, such as those born preterm or with low birth weight (Miller et al., 2016; Volpe, 2009). Recent studies utilising brain imaging techniques have also observed similar brain abnormalities in patients diagnosed with schizophrenia, including reduced grey matter volume and neuronal synaptic density, which may be traced back to neuronal disturbances during the prenatal period (Adriano et al., 2012; Bearden et al., 2015; Vita et al., 2006). A meta-analysis also found enlarged ventricular volumes and reduced brain and hippocampus volumes in first-episode schizophrenia patients, suggesting that these brain abnormalities associated with schizophrenia are not due to the chronicity of the illness, but occur before the onset of the illness and may have origin in early brain development (Vita et al., 2006). The same reduction in hippocampal volume has been observed in the clinical, non-affected relatives and the healthy population after exposure to obstetric complications (Clarke & Cannon, 2020; Ebner et al., 2008). This suggests that the effect of obstetric complications on brain abnormalities may be independent of genetic risks and is an additional risk factor to brain alterations underlying the expression of psychosis (Clarke & Cannon, 2020; Ebner et al., 2008).

Further support for the theory comes from observations that there are often subtle signs of developmental impairments in childhood, long before the onset of illness (P. Jones et al., 1994; Pantelis et al., 2003). These impairments often include motor, cognitive and behavioural difficulties, which have been termed neurological soft signs of psychosis, as they may be a manifestation of neurodevelopmental lesions resulting from obstetric complications (Clarke & Cannon, 2020; P. Jones et al., 1994; Pantelis et al., 2003; Polanczyk et al., 2010). Studies have shown that prior to the onset of psychosis, those who later developed the disorder showed cognitive and motor impairments, minor physical abnormalities, and behavioural and emotional problems in childhood and adolescence (Clarke & Cannon, 2020; Dean et al., 2018; Polanczyk et al., 2010). They also showed marked deficits on almost all measures of neuropsychological functioning (Dickson et al., 2012), in particular for

working memory, attention, episodic learning and language (Bearden et al., 2015). These impairments are frequently associated with the onset of psychosis, and may be a result of adverse events during the prenatal and neonatal period (Bearden et al., 2015; McNeil et al., 2000; Mollon & Reichenberg, 2018).

2.2.2 Empirical evidence: Neurodevelopmental adversity and psychosis

There are two parts to the evidence supporting the Neurodevelopmental model of schizophrenia. First, there needs to be an association between obstetric complications and psychosis, and second, those who subsequently developed psychosis may also show developmental impairments in childhood resulting from these obstetric complications (Clarke & Cannon, 2020). Both obstetric complications and developmental impairments are referred to here as neurodevelopmental adversity, and evidence on both will be discussed here.

Although obstetric complications can include many adverse events during the prenatal and neonatal periods, they can be broadly categorised into three areas: disruptions during pregnancy (e.g. maternal infection), abnormal fetal growth and development (e.g. premature birth, low birth weight), and complications of delivery (e.g. hypoxia, resuscitation) (Cannon et al., 2002). The earliest evidence supporting the role of obstetric complications in psychosis comes from case-control studies, with higher prevalence of obstetric complications reported in those who were diagnosed with schizophrenia (Geddes et al., 1999; Geddes & Lawrie, 1995). However, case-control studies are subject to sampling bias, and obstetric complications were often reported by mothers retrospectively (Geddes & Lawrie, 1995). Better evidence emerged with longitudinal birth cohort studies where data could be collected prospectively and important confounders controlled for (Cannon et al., 2002). A summary table on the association between obstetric complications and psychosis can be found in Table 2.

Although there are some variations between studies on the effect sizes reported, obstetric complications in general are associated with around 1.5 to 2 times increased risk of psychosis in prospective studies (Clarke & Cannon, 2020). A recent meta-analysis which examined 98 different risk factors of psychosis also found between 1 to 2.5 times increased risk for most indicators of obstetric complications, such as low birth weight, premature birth, and maternal infection (Davies et al., 2020). Maternal infection, in particular influenza, has been widely investigated after it was first observed that there was an excess in the development of schizophrenia following the 1957 European influenza pandemic (Mednick et al., 1988; O'Callaghan et al., 1992). This became one of the earliest evidences supporting the role of obstetric complications in psychosis. There is also recent evidence that markers of maternal inflammation – as indicators of maternal infection – during the first two trimesters were associated with increased risk of psychosis in adulthood (Allswede & Cannon, 2018).

However, evidence on the influence of maternal influenza in particular has received little support in recent years (Davies et al., 2020; Selten et al., 2010). A small increased risk of 1.35 times has been reported following specific maternal infection such as herpes simplex in a previous meta-analysis of 5 studies, however no effect was found for maternal influenza (Davies et al., 2020). A Swedish registry study with almost 2 million participants also found no effect of maternal infection during pregnancy and offspring psychosis (Blomström et al., 2016). Maternal infection was associated with an increased risk of childhood infection, and an interaction effect was found between them on risk of non-affective psychosis (Blomström et al., 2016). There is thus mixed evidence on the direct effect of maternal infection on psychosis, and the association between them is likely to be moderated by other factors.

Other obstetric complications such as low birth weight and premature birth have received more support over the years, albeit the effect sizes are generally small (Davies et al., 2020). Birth cohorts and registry studies have reported around 2-times increased risk of psychosis in individuals born with birth

weight less than 2500 grams (Abel et al., 2010; Eide et al., 2013; Moilanen et al., 2010). A recent meta-analysis which included 23 studies on birth weight of less than 2500 grams also reported a pooled effect size of 1.53 times increased risk of psychosis (Davies et al., 2020). Similar effect sizes have been reported for premature birth, with a pooled effect of 1.35 times increased risk of psychosis for those born below 37 weeks gestation (Davies et al., 2020). There is some evidence for a dose-response effect, with those born even earlier (<32 weeks gestation) or with even lower birth weight (<2000 grams) at greater risk, with around 2.5 and 1.8 times increased risk of psychosis respectively (Davies et al., 2020; Nosarti et al., 2012) (Table 2). These effect sizes are small in magnitude but are comparable to the effects of prenatal stress on offspring depression.

There is also evidence that obstetric complications can lead to developmental impairments in childhood, such as cognitive and motor impairments (Allotey et al., 2018; Johnson et al., 2009; T. Moore et al., 2012). These are considered by the Neurodevelopmental model as neurological soft signs and are frequently associated with psychosis (Clarke & Cannon, 2020; Murray & Lewis, 1987; Pantelis et al., 2003) (see Table 2). On cognitive impairments, children with IQ scores 20 points below the mean (roughly 1.3 standard deviations below the norm) were 1.6 times more likely to develop psychotic experiences in childhood even after accounting for childhood demographic factors such as maternal education, social class and family history of psychiatric disorders (Horwood et al., 2008). Research into adulthood also found a 1.2 times increased risk of schizophrenia with every half standard deviation (7.5 points on a standardised IQ test) decrease in IQ score (Agnew-Blais et al., 2015). In terms of motor impairments, a recent meta-analysis found an association between delays in reaching motor milestones and risk of schizophrenia in adulthood, with a moderate effect size found in particular for delays in walking unsupported (Filatova et al., 2017). Another recent cohort study also found that children who showed developmental delays in motor abilities were almost twice as likely to develop schizophrenia compared to

regular developers, and 2.4 times as likely compared to early developers (Stochl et al., 2019) (Table 2).

Table 3.

Summary of findings on the association between neurodevelopmental adversity and psychosis.

Study	Type	Exposure	Findings
Davies et al. (2020)	Systematic review and meta-analysis (152 studies)	98 risk and protective factors examined	Selected findings: Prenatal influenza infection (OR=1.13); Obstetric complications (OR=1.52); Premature birth <37 weeks (OR=1.35); Low birth weight (<2500 grams, OR=1.53; <2000 grams, OR = 1.84); Small for gestational age (OR=1.40)
Blomström et al. (2016)	Swedish registry study (N=1 971 623)	Obstetric complications (Prenatal maternal infection)	Maternal infection during pregnancy was not associated with offspring psychosis, but there was an interaction effect between maternal infection and childhood infection to risk of non-affective psychosis.
Abel et al. (2010)	Swedish and Danish registry study (N=1.4 million)	Obstetric complications (Low birth weight)	Birth weight <3000 grams was associated with increased risk of schizophrenia, with the highest risk found in those with birth weight <2000 grams (OR=1.94). A dose-response effect is also found where lower birth weight is associated with higher risks.
Eide et al. (2013)	Norwegian registry study (N=873 612)	Obstetric complications (Foetal growth restriction)	Increased risk of schizophrenia with decreasing birth weight for gestational age, those who were 3 standard deviations below the birth weight according to gestational age had 2 times increased risk of schizophrenia.

Table 2. **continued**

Summary of findings on the association between neurodevelopmental adversity and psychosis.

Study	Type	Exposure	Findings
Moilanen et al. (2010)	Finish registry study (N=12 058)	Obstetric complications (Low birth weight)	Birth weight <2500 grams was associated with 2.5 times increased risk of schizophrenia, even after adjusting for family history.
Horwood et al. (2008)	UK (ALSPAC cohort) (N=6455)	Developmental impairments (IQ)	Those who scored ≤79 on IQ test (roughly 1.3 standard deviation below the average) had 1.55 times increased risk of psychotic experiences in childhood (12 years), even after adjusting for sociodemographic, family characteristics and childhood bullying and behavioural problems.
Agnew-Blais et al. (2015)	Longitudinal cohort study (N=9809)	Developmental impairments (IQ)	Lower childhood IQ (as indicated by half a standard deviation/7.5 scores below the mean) associated with 1.2 times increased risk of schizophrenia spectrum psychosis even after adjusting for sociodemographic and family characteristics.
Filatova et al. (2017)	Systematic review and meta-analysis (N=5 studies)	Developmental impairments (motor performance)	Those who reached motor milestones later were at increased risk of developing schizophrenia. A moderate effect size (g=0.46) was found for walking unsupported, and smaller effects found for sitting (g=0.18) and standing unsupported (g=0.29).
Stochl et al. (2019)	Finnish birth cohort (N=10,501)	Developmental impairments (motor performance)	Those classified as late developers in reaching developmental milestones (e.g. walking unsupported) had 1.92 hazard ratio of developing schizophrenia compared to regular developers, and 2.42 hazard ratio compared to early developers.

There is thus evidence that both obstetric complications and developmental impairments in childhood are implicated in the onset of psychosis. However, effect sizes are often small, and the term obstetric complications is used to describe a number of different risk factors, with large heterogeneity between studies (Clarke & Cannon, 2020). More recently it has also been proposed that rather than any individual complication per se, it was the cumulative effect of a number of risk factors across the prenatal and neonatal periods that subsequently increase risk of psychosis in adulthood (Cannon et al., 2020; Davies et al., 2020; Kotlicka-Antczak et al., 2018). Furthermore, the majority of research were conducted as observational studies in the general populations or in registry studies using linked medical records. These may have limitations as certain indicators for obstetric complications, such as preterm birth, are rare events (Chawanpaiboon et al., 2019) and requires large sample size to generate adequate power. Although registry studies using linked medical records have large sample sizes, these findings may be subject to bias as participants may be in contact more with healthcare services and may be diagnosed more often (Bohensky et al., 2010; Dalrymple et al., 1994).

One alternative approach is to investigate this in special populations who are naturally exposed to multiple risks, with a comparable sample of control subjects who are followed-up from birth to adulthood. This ensures that there is adequate sample size in both the risk group and control group. Furthermore, rather than examining any particular risk factor per se, the risk group may act as a proxy measure for exposure to multiple indicators of neurodevelopmental adversity, given that they are exposed to multiple risks. This new methodological approach will be discussed in detail in the following chapter, introducing the possibility of using a naturalistic experiment to examine the association between neurodevelopment adversity and psychosis.

2.3 Summary

Both the prenatal programming model and Neurodevelopmental model of schizophrenia emphasise the importance of the prenatal and neonatal periods

in the onset of adult psychopathology including depression and psychosis. These are supported by evidence of an association between prenatal stress, in the form of maternal prenatal depression or family adversity, and offspring depression. However, both sources of prenatal stress are rarely examined together and the effects of their continuity into the postnatal periods are often not tested in one model. There is also evidence for an association between neurodevelopmental adversity and psychosis, from both indicators of obstetric complications, such as preterm birth, as well as childhood developmental impairments, such as cognitive and motor impairments, which are proposed to be neurological soft signs of psychosis. However, the effect sizes of individual risk factors are often small, and large sample sizes are required when examining rare risks such as preterm birth. Thus, there may be an opportunity to use a special population who are naturally exposed to multiple risks, to investigate whether neurodevelopmental adversity – either directly measured in the general population or as a proxy measure in special population – is associated with psychosis.

Chapter 3: A proxy measure for neurodevelopmental adversity

Given the small effect sizes of specific indicators of neurodevelopmental adversity on psychosis, there may be an opportunity to study a population exposed to multiple neurodevelopmental adversities. This has been termed as a "naturalistic experiment" in the literature, which is a form of longitudinal study where a risk only occurs in a population at a specific time (Rutter et al., 2012). The exposure is therefore non-randomised, but it does allow causal inference to be drawn from any outcomes associated with that risk factor, although there may still be bias from selective attrition (Rutter et al., 2012). Adoption studies have often been used as an example of naturalistic experiment in determining the relative influence of genetic and environmental factors on child development (Haugaard & Hazan, 2003). One example is the English and Romanian adoptee study which has been used to study the effect of early environmental deprivation on developmental outcomes across multiple domains (Rutter et al., 2012; Sonuga-Barke et al., 2017). There may also be an opportunity to design a naturalistic experiment to study the effect of neurodevelopmental adversity on the risk of psychosis, using a special population who are disproportionally exposed to multiple neurodevelopmental adversities. This will be discussed in the following section in relation to one special population – the preterm population – and how they may act as a proxy measure for exposure to neurodevelopmental adversity when examining outcome in psychosis.

3.1 A naturalistic experiment

Preterm birth is defined by the World Health Organisation (WHO) as having a gestational age below 37 weeks (Chawanpaiboon et al., 2019). Roughly 11% of live births are born preterm worldwide, and it is one of the leading causes of neonatal morbidity in the first few years of life (Chawanpaiboon et al., 2019). Preterm birth is generally associated with a number of intrauterine

and extrauterine factors, including pre-eclampsia, maternal infection, maternal stress and low socio-economic status (SES) (Della Rosa et al., 2021; Williams & Drake, 2019). Up to 40% of those who survive the initial hospitalisation period experience significant developmental impairments in childhood, including cerebral palsy, cognitive and motor impairments, autism spectrum disorder (ASD), attention problems and psychiatric disorders, with higher risks found in those who are born extremely preterm, i.e. <28 weeks gestation (Johnson et al., 2009; Volpe, 2009; Williams & Drake, 2019; Wolke et al., 2019). Given the various obstetric complications and subsequent developmental impairments associated with preterm birth, the preterm population may be considered as a proxy measure for exposure to significant neurodevelopmental adversity. Thus, rather than examining the effect of specific indicators of neurodevelopmental adversity in a general population, which are often small in size, studies using the preterm population may provide a naturalistic experiment on the risk of psychosis in a group naturally at increased risk for neurodevelopmental adversity.

The following section will first introduce terms and definitions associated with preterm birth, as well as the preterm phenotype, which refers to characteristics and profiles associated with preterm birth (Johnson et al., 2018). This is followed by a discussion of current evidence on the long-term outcomes after preterm birth, specifically focusing on psychosis, and the use of this population as a proxy measure for neurodevelopmental adversity.

3.2 The preterm phenotype

The term preterm (PT) birth refers to all births with a gestational age below 37 weeks (World Health Organisation, 1977, 2017). Within this broad term, several other terms have been used by studies to represent varying degrees of prematurity and these can be found in Table 3. These include moderately preterm to late preterm (MP/LP), defined as having a gestational age between 32 and less than 37 weeks; very preterm (VP), defined as less than 32 weeks; and extremely preterm (EP), defined as less than 28 weeks (Williams &

Drake, 2019; World Health Organisation, 2017). The majority of those born PT are classified as MP/LP, and only 15% are classified as VP (Chawanpaiboon et al., 2019; Wolke et al., 2019).

Another term which has often been used interchangeably with PT is low birth weight (LBW). This is generally referred to birth weight of less than 2500 grams, and other terms representing varying degrees of LBW have also been used in the literature, including very low birth weight (VLBW; <1500g), and extremely low birth weight (ELBW; <1000g) (Hille et al., 2001; WHO, 1977; Williams & Drake, 2019; Wolke et al., 2019). Historically, studies rarely distinguished between PT birth and LBW as the majority of those born prematurely will also have lower birth weight (Williams & Drake, 2019). However, not all who are born with LBW are also PT; only 41% of those classified as being LBW were also born PT in a global survey from 138 countries (A. C. Lee et al., 2013). For those who are born VLBW though, the majority are also born VP, with a mean birth weight of around 1500 grams for those born at 30 weeks gestation (Robinson et al., 2020; Skjærven et al., 2000). Thus VP and VLBW are often used interchangeably in the literature and referred to as VP/VLBW (Robinson et al., 2020). A summary of the terms and definitions taken from the WHO (1977, 2017) can be found in Table 3.

Table 3.

Terms and definitions according to the WHO (1977, 2017).

Term	Abbreviations	Definition
Preterm birth	PT	<37 weeks gestation
Moderately preterm to late preterm	MP/LP	32 to 36 weeks
Very preterm	VP	<32 weeks gestation
Extremely preterm	EP	<28 weeks gestation
Low birth weight	LBW	<2500 grams
Very low birth weight	VLBW	<1500 grams
Extremely low birth weight	ELBW	<1000 grams

There is now strong evidence for the existence of a preterm phenotype – characteristics that are consistently associated with preterm birth (Johnson et

al., 2018). These include altered cognitive, motor, social, emotional and behavioural development from childhood into adulthood (Wolke et al., 2019). There is strong evidence for altered psychological phenotypes, in particular for neurodevelopmental disorders such as ASD, attention problems including attention deficit hyperactivity disorder (ADHD), as well as an increased risk for psychiatric disorders such as anxiety and depression (Fitzallen et al., 2021; Johnson et al., 2018; Williams & Drake, 2019; Wolke et al., 2019).

These altered phenotypes have been associated with widespread brain injuries that occur during the later stages of gestation, a period of rapid and active axonal migration and increase in brain volumes which are disrupted due to premature birth (Davis et al., 2011; Matthews et al., 2018; Volpe, 2009). Those born VP/VLBW are consistently shown to have structural and functional abnormalities in the brain from childhood into adulthood (Bäuml et al., 2015; de Kieviet et al., 2012; Meng et al., 2016). Up to 25% have enlarged lateral ventricle volumes, as well white matter lesions and reduced grey matter volumes across multiple brain regions (Hedderich et al., 2020; Meng et al., 2016). These brain alterations have also been found to underlie developmental impairments including motor and cognitive deficits, symptoms of ADHD and ASD, as well as the onset of serious psychiatric disorders including psychosis (Clarke & Cannon, 2020; J. H. Cole et al., 2015; C. E. Rogers et al., 2018).

Furthermore, those born VP/VLBW also show impairments in cognitive and motor functioning (Cheong et al., 2020; Johnson et al., 2009; Spittle et al., 2018). These have previously been proposed to be neurological soft signs of psychosis and are associated with both the onset and prognosis of psychosis in adulthood (Agnew-Blais et al., 2015; Dean et al., 2018). These developmental impairments, combined with findings on brain alterations from exposure to obstetric complications further support the use of the VP/VLBW population as a naturalistic experiment, with the VP/VLBW group acting as a proxy measure for significant exposure to neurodevelopmental adversity.

Evidence on the association between VP/VLBW birth and psychosis is discussed in the following section. To avoid repeating evidence already presented on gestational age and low birth weight in relation to psychosis in chapter 2, the focus here will just be on the VP/VLBW group. This is then followed by a discussion on the possibility of examining psychotic experiences rather than psychotic disorders in this population.

3.3 VP/VLBW birth and psychosis

The majority of research into VP/VLBW birth and psychosis come from registry studies, where there is evidence of increasing risk of psychosis with decreasing gestational age (D'Onofrio et al., 2013; Mathiasen et al., 2011; Nosarti et al., 2012) (Table 4). In particular, those born under 28 weeks (EP) are found to be at the highest risk of developing psychotic or bipolar disorders compared to those born after 32 weeks (D'Onofrio et al., 2013). Another study only found increased risk of schizophrenia among those born between 24 to 27 weeks (EP), and 31 to 32 weeks (VP), with larger effect size associated with increasing prematurity (odds ratio 2.4 for EP group vs 1.7 for VP group), and no increased risk was seen among those born after 32 weeks (Mathiasen et al., 2011). Those born below 32 weeks were also 2.5 times likely to be diagnosed with non-affective psychosis, compared to 1.6 times in those born moderate to late preterm (Nosarti et al., 2012).

Aside from these registry studies, a recent systematic review which included 4 longitudinal cohort studies (in two separate samples) found little evidence of increased risk of psychosis among those born VP/VLBW (Robinson et al., 2020). Of these studies, only one found increased reports of clinically significant delusional experiences among the VLBW group, although no differences were found between the groups when continuous scores were used instead of clinical cut-offs (Lærum et al., 2019; Robinson et al., 2020). A summary of findings on the association between VP/VLBW birth and psychosis can be found in Table 4.

Table 4.

Summary of findings on the association between VP/VLBW birth and psychosis.

Study	Type	Exposure	Findings
Robinson et al. (2020)	Systematic review (4 studies on psychosis)	VP/VLBW	Only one study (Lærum et al., 2019) found an association between VLBW and clinical delusion symptoms. No association when continuous measure used instead of clinical cut-off.
Nosarti et al. (2012)	Swedish registry study (N=1 301 522)	VP birth; birth weight for gestational age (<1 SD)	VP (<32 weeks gestation) associated with 2.5 times increased risk of nonaffective psychosis even after adjusting for family risk factors. Those born 32-36 weeks (compared to 37-41 weeks) had 1.6 times increased risk of nonaffective psychosis. No association between birth weight for gestational age and nonaffective psychosis.
Mathiasen (2010)	Denmark registry study (N=1,348,106)	EP, VP	EP (<28 weeks gestation) associated with 2.4 increased risk of schizophrenia. Those born 31-32 weeks had 1.68 times increased risk of schizophrenia. No associations were found between those born above 32 weeks. Comparison group was those born at-term (39-45 weeks gestation).
D'Onofrio (2013)	Swedish registry study (N=3,300,708)	EP	EP (<28 weeks gestation) was associated with 3.2 times increased hazard ratio of psychotic or bipolar disorders. This was reduced when genetic and environmental factors were accounted for. Risk of psychotic and bipolar disorders decreased as gestational age increased.

Most studies which found an association between VP/VLBW birth and psychosis come from registry studies, with clinical diagnoses, most often schizophrenia or non-affective psychotic disorders, as the outcome (Davies et

al., 2020; D'Onofrio et al., 2013; Mathiasen et al., 2011; Nosarti et al., 2012). However, psychotic disorders are rare in the general population (around 3% over the life time) (Perälä et al., 2007), and VP/VLBW birth also only make up 1-2% of all live births (Chawanpaiboon et al., 2019; Wolke et al., 2019), therefore only registry studies generate enough power to investigate the association between VP/VLBW birth and psychotic disorders. However, while birth registry studies have a large enough sample size, diagnoses may not always follow the same standard criteria between clinicians (Moilanen et al., 2003). Registry studies linked through medical records may also be biased as those born VP/VLBW are more frequently in contact with health services (Hummer et al., 2014; Petrou, 2005; Petrou et al., 2019), therefore they may also be diagnosed more often.

One possibility to overcome the need for large sample size is to assess psychotic experiences (PE), which are more prevalent in the general population compared to psychotic disorders (12.7% vs 2.8%), and are more amenable to large cohort studies (Sullivan et al., 2020). PE share some of the same symptoms as psychotic disorders such as hallucinations and delusions, and are often transient in most individuals, although a significant proportion may experience persistent PE (Sullivan et al., 2020; Van Os & Reininghaus, 2016). It has been proposed to be on the extended psychosis phenotype and is also a major risk factor for transitioning into psychotic disorders (Sullivan et al., 2020; Van Os & Reininghaus, 2016).

There has been some recent interest in examining PE in general population-based cohort studies. For example, in a sample of term-born participants, decreasing birth weight was associated with increased risk of PE at 12 years of age (Thomas et al., 2009). In a separate study with the same sample, no associations were found between gestational age and PE at 12 years (Zammit et al., 2009). This may be due the first study assessing foetal growth restriction (e.g. born at term but with lower birth weight) which may have a different risk profile compared to preterm birth without growth restriction (e.g. born preterm but with appropriate birth weight for gestational age).

Furthermore, PE was only examined in childhood, which may have a reduced power as the prevalence of PE has been shown to increase from adolescence to young adulthood (Sullivan et al., 2020). Gestational age and birth weight were also investigated in these studies as continuous variables, whereas findings from previous research suggest that only the extreme group i.e. VP/VLBW group, may show increased risk of psychosis (D'Onofrio et al., 2013; Mathiasen et al., 2011; Nosarti et al., 2012). Thus, there is an opportunity to examine risk of PE in the VP/VLBW population, using the VP/VLBW group as a proxy measure indicating multiple exposure to neurodevelopmental adversity, and compare this to findings from the general population using directly measured indicators of neurodevelopmental adversity.

3.4 Summary

Indicators of neurodevelopmental adversity, including both obstetric complications and developmental impairments, have often been used as support for the Neurodevelopmental model of schizophrenia. However, the effect of each specific risk is small, thus there may be an opportunity to use a special population who are exposed to multiple risks as a proxy measure for neurodevelopmental adversity. This chapter proposed the use of one such population – the VP/VLBW population – who are exposed to multiple obstetric complications and experience significant developmental impairments in childhood. This provides the opportunity to design a naturalistic experiment using a population of VP/VLBW born adults and their term-born controls, to examine risk of psychotic experiences in adulthood. Findings can be compared to those from the general population where neurodevelopmental adversity was directly measured, to examine whether the risk from neurodevelopmental adversity to psychosis is the same across both the general and VP/VLBW populations.

Chapter 4: Environmental risks and adult psychopathology

Previous chapters have focused on the association between two main biological risks – prenatal stress and neurodevelopmental adversity, and adult psychopathology in depression and psychosis. A case for using a proxy measure for neurodevelopmental adversity to examine psychosis was also presented. So far, little evidence has been offered on the role of environmental risks. Given the long temporal distance between biological risks occurring early in life and the onset of psychopathology in adulthood, it is expected that environmental factors occurring later in life may have a larger effect.

A number of environmental risk factors have been implicated in the onset of adult psychopathology, with childhood trauma being one of the most consistent predictors of depression and psychosis in the literature (e.g. Copeland et al., 2018; Croft et al., 2018; Varese, Smeets, et al., 2012). Although other environmental influences have been proposed as well, including more positive influence or protective factors such as maternal sensitivity, these are often in relation to educational or wellbeing outcomes (Jaekel et al., 2015; Paulus et al., 2018). Thus, the focus of this chapter will be on childhood trauma, given its consistent association with depression and psychosis.

Theoretical trauma models have mostly focused on the association between childhood trauma and psychosis (e.g. Read et al., 2001; Selten et al., 2013), thus evidence on psychosis will be presented first in line with these models. However, childhood trauma has also been implicated in depression and is hypothesised to have a non-specific effect across many areas of psychopathology (e.g. Copeland et al., 2018). Therefore, evidence on the effect of childhood trauma on depression is discussed as well, followed by the specificity of trauma and the differentiation between caregiver- and peer-inflicted trauma.

4.1 Theoretical models

4.1.1 Trauma model of psychosis

In traditional models of psychopathology, such as the diathesis-stress model, environmental influences were largely seen as exacerbating pre-existing genetic or biological risks, rather than having a direct effect in themselves (Read et al., 2001). Certain genetic predispositions may make individuals more vulnerable to the effects of stress in later life, and those with higher genetic vulnerability may have a much lower threshold of stress tolerance before developing psychopathologies (Read et al., 2001; Zubin & Spring, 1977). Environmental risks such as traumatic life events were thus only examined in the period leading up to the onset of adult psychopathology, without consideration of the direct effects they may have independently from genetic or biological influences (Read et al., 2001). This led to the development of a new model, to recognise the importance of childhood events and to include them as part of the longitudinal investigation of adult psychopathology.

This Trauma model of psychosis, otherwise known as the Traumagenic Neurodevelopmental model, proposes that adverse childhood experiences can have direct and lasting impact on emotional, behavioural, cognitive and physiological development (Read et al., 2001, 2014). There was already convincing evidence since the late 1990s that childhood trauma is associated with depression, anxiety, substance misuse and post-traumatic stress disorder (Figueroa et al., 1997; Kent & Waller, 2000; Kessler et al., 1997; Read et al., 2001). When this model was first proposed in the early 2000s for psychosis, the earliest available evidence came from retrospective studies which reported increased levels of childhood trauma in patients hospitalised with psychosis (Read et al., 2001). There was also the observation that brain and biological alterations found in individuals exposed to childhood trauma were similar to alterations found in those diagnosed with schizophrenia (Read et al., 2001, 2014). The origin of these brain alterations that are characteristic of

psychosis may thus not be specific to genetic or biological risks, but may also be due to environmental risks such as exposure to childhood trauma (Read et al., 2014).

Research over the last two decades proposed the involvement of biologically mediated mechanisms in the association between childhood trauma and psychosis, such as structural and functional alterations in the brain (Cancel et al., 2019; Read et al., 2014). For example, reduced brain volumes have been observed in individuals exposed to childhood trauma, which is also found in those diagnosed with psychosis (Misiak et al., 2017; Read et al., 2014; Ruby et al., 2017). Reduction in hippocampal and amygdala volumes have also been observed after exposure to childhood trauma in both clinical and general populations, and it has been proposed that the early stress associated with traumatic events can alter the trajectory of brain development (Aas et al., 2012; Calem et al., 2017; Hoy et al., 2012; Misiak et al., 2017; Paquola et al., 2016; Teicher et al., 2012). Functional connectivity in these areas may also be affected, which are involved in emotional processing and social cognition (Cancel et al., 2019). Furthermore, there is also consistent evidence of HPA-axis and dopamine dysregulation in those who experienced childhood trauma, which are implicated in psychotic experiences in adulthood (Egerton et al., 2016; Read et al., 2014). These biologically mediated mechanisms have also been implicated in the aetiology of other psychopathology such as depression (Heim et al., 2008), suggesting a common shared pathway from childhood trauma to adverse development in adulthood (Read et al., 2014).

4.1.2 Social defeat

Similar to the Trauma model, the social defeat model first emerged to explain the association between social factors such as migration, urbanicity and childhood trauma with psychosis, which was not adequately explained by genetic or biological risks (Selten et al., 2013; Selten & Cantor-Graae, 2005). Social defeat is defined as having persistent subordinate status, such as having certain characteristics that mark individuals as being different from their

environment (Selten & Cantor-Graae, 2005, 2007). The idea that social defeat can lead to psychopathologies was first observed in animal studies, most famously the resident/intruder paradigm, where introducing an intruder mouse to the cage of a resident mouse led to the intruder being severely attacked (Martinez et al., 1998; Toyoda, 2017). After repeated exposure to this social conflict, the intruder mouse showed increased activation of the HPA-axis and behavioural changes that may indicate depression-like symptoms (Martinez et al., 1998; Toyoda, 2017).

Early support for the model in the human population came from observations that characteristics such as being a migrant or living in urban environment is associated with increased risks of psychosis (Selten & Cantor-Graae, 2005, 2007). Both characteristics involve social competition, increased discrimination and deprivation (Selten & Cantor-Graae, 2005). Consistent with the idea of social defeat, epidemiological studies have consistently found increased risk of psychosis among marginalised groups, such as the African-Caribbean population in the UK (Selten & Cantor-Graae, 2007). Furthermore, it is the individual's interpretation, rather than the event itself, that is implicated in the feeling of social defeat (Selten et al., 2013). For example, studies have found that environmental deprivation only increased risk of psychosis if the majority of people were not from a deprived background (Selten et al., 2013; Zammit et al., 2010). Thus, social defeat arises from characteristics that separate individuals from others in their population.

Both biologically and psychologically mediated processes have been proposed. Social stress is hypothesised to induce physiological alterations in the dopamine system, as well as psychological alterations in the formation of cognitive schema, both of which are implicated on the pathway to psychosis (Selten et al., 2013). Animal models have shown dysregulation of the dopamine system as well as alterations in the HPA-axis after exposure to socially defeating events (Martinez et al., 1998; Selten & Cantor-Graae, 2005). Similar mechanisms are also thought to be implicated in humans, where repeated exposure to social stress can lead to increased response in the

dopamine system to external stimuli, which increases the salience of events and alter behavioural responses (Selten & Cantor-Graae, 2005).

Social stress can also lead to cognitive vulnerabilities including negative schemas about the self, others and the world (Selten et al., 2013; Stowkowy & Addington, 2012). Individuals may be biased to view the world as threatening, and hold more pessimistic views such as externalising the causes of negative events and seeing them as lasting and constant (Bentall et al., 2009; Howes & Murray, 2014). Holding negative schemas about the self and others has also been found to mediate the relationship between feelings of social defeat (characterised by feelings of failing and losing rank) and psychotic experiences (Stowkowy & Addington, 2012). There is also evidence that negative cognitive bias is implicated in depression as well as psychosis (Evans et al., 2005; Stowkowy & Addington, 2012), and feelings of social defeat may impact on a common pathway to other symptoms of psychopathology, including depression and anxiety (Jaya & Lincoln, 2016).

4.2 Empirical evidence

Although the social defeat theory includes many indicators for social stress, the focus of the empirical review will be on childhood trauma, which has been previously shown to be mediated by feelings of social defeat (Nierop et al., 2014). Many research on childhood trauma have focused on abuse (physical, emotional, sexual) and neglect by the primary caregiver (Carr et al., 2013; K. M. Keyes et al., 2012; Li et al., 2016), however, more recently studies have also included peer-inflicted trauma, i.e. peer bullying (Copeland et al., 2013; Croft et al., 2018; Lereya, Copeland, Costello, et al., 2015; Sahle et al., 2021; Varese, Smeets, et al., 2012). It is estimated that around 60% of children are exposed to some form of childhood trauma by the age of 16, and half of those would have experienced chronic trauma (Copeland et al., 2007). Given its high prevalence, a growing number of studies have examined the long-term effect of childhood trauma on adult psychopathology.

Although both theoretical models were primarily applied to the development of psychosis, there is evidence that childhood trauma has a non-specific effect on adult psychopathology in other areas such as depression (Copeland et al., 2018; McKay et al., 2021). It has been previously shown that the association between childhood trauma and psychopathology may be fully mediated through increased risk of internalising and externalising symptoms, suggesting that childhood trauma may have an effect on common symptoms shared across multiple domains of psychopathology (K. M. Keyes et al., 2012). Thus, evidence on both psychosis and depression in relation to childhood trauma will be discussed in this chapter, focusing first on psychosis.

4.2.1 Childhood trauma and psychosis

The association between childhood trauma and psychosis has received numerous support from empirical studies in recent years, and it has been estimated that roughly one third of psychosis cases can be attributed to exposure to childhood trauma (Croft et al., 2018; Varese, Smeets, et al., 2012). A summary of these main findings can be found in Table 5.

Both longitudinal cohort studies and meta-analysis have consistently shown the association between childhood trauma and psychosis (Croft et al., 2018; Kelleher et al., 2013; Varese, Smeets, et al., 2012). Exposure to any type of childhood trauma has been consistently associated with both psychotic disorders and psychotic experiences, with roughly three times increased risk of psychosis associated with exposure to any trauma (Croft et al., 2018; Varese, Smeets, et al., 2012). The effect is almost twice as large as the risk attributed to indicators of neurodevelopmental adversity, such as low birth weight and gestational age, which are around 1.2- to 1.8-times increased risk (Davies et al., 2020). The association between childhood trauma and psychosis remained even after taking important risk factors such as family history, genetic risks, and childhood psychological functioning into account (Croft et al., 2018). There is also evidence for a causal pathway, with

childhood trauma being predictive of new psychotic experiences among those who did not experience any symptoms at baseline (Kelleher et al., 2013).

A dose-response effect is also consistently reported in the literature, with higher risk of psychosis associated with increased number of traumas experienced, or the chronicity of the trauma experience (Croft et al., 2018; Kelleher et al., 2013; Varese, Smeets, et al., 2012). For example, those exposed to three or more types of trauma before 17 years had 4.7 times increased risk of psychotic experiences compared to the 1.9 times increased risk in those exposed to one type of trauma (Croft et al., 2018) (Table 5). A linear trend has been proposed with around 1.7 times increased risk for each additional type of trauma experienced in childhood and adolescence (Croft et al., 2018). The chronicity of exposure to trauma over time has also been shown to have a dose-response effect. Those who were exposed to trauma across three time periods in childhood and adolescence had a 3.5-times increased risk of psychotic experiences, compared to the 1.5-times increased risk of psychotic experiences among those exposed to trauma at one time period (Croft et al., 2018) (Table 5). These findings suggest the importance of examining not just the exposure to trauma, but also the degree of exposure, which can be measured by the number of traumas experienced as well as the chronicity of exposure during childhood and adolescence.

Table 5.

Summary of findings on the association between childhood trauma and psychosis

Study	Type	Exposure	Findings
Croft et al. (2018)	Longitudinal cohort study (N=4433)	Any childhood trauma (mixture of parent and child report)	Exposure to any childhood trauma up to 17 years associated with 2.9 times increased risk of PE in adulthood (95%CI: 2.15 – 3.93), even after adjusting for other individual and family risk factors. Dose-response effect: Exposed to one trauma (OR = 1.89) vs two trauma types (OR = 2.54) vs three or more trauma types (OR = 4.74). Exposed to trauma at one time point (OR = 1.53) vs two time points (OR = 2.29) vs three time points (OR = 3.45)
Kelleher et al. (2013)	Longitudinal cohort study (N=1112)	Childhood trauma (physical abuse and bullying)	Both forms of childhood trauma associated with 3-6 times increased risk of PE during follow-up (at 3 and 12 months when participants were between 13-16 years), even after adjusting for baseline PE.
Varese et al. (2012)	Meta-analysis (36 studies)	Any childhood adversity and trauma	Exposure to any childhood trauma associated with 2.8 times increased risk of psychosis (95%CI: 2.34 – 3.31). No differences in effect sizes across different types of studies (cross-sectional, longitudinal, case-control).

4.2.2 Childhood trauma and depression

There is also strong evidence on the role of childhood trauma in the development of depression, and a summary of key findings can be found in Table 6. A recent meta-analysis projected that over half of worldwide depression and anxiety cases are potentially modifiable by reducing childhood trauma (Li et al., 2016). Retrospective reports show that more than

two thirds of individuals diagnosed with chronic depression reported a history of childhood trauma (Negele et al., 2015). Another recent meta-analysis also found that having four or more adverse childhood experiences, which was indicated by both childhood trauma and family adversity (financial problems, family conflict, parental history of crime, separation/divorce), was associated with more than 4 times increased risk of depression in adulthood (Hughes et al., 2017). However, there was substantial heterogeneity between the studies and cross-sectional, case-control and prospective cohort studies were all analysed together (Hughes et al., 2017).

A recent umbrella review of 15 meta-analyses on the association between adverse childhood experiences and depression found a 2-times increased risk of depression after exposure to any adverse experiences (Sahle et al., 2021). However, adverse childhood experiences in this study were indicated by both childhood trauma (caregiver- and peer-inflicted trauma) and adverse life events, such as parental death (Sahle et al., 2021). Another meta-analysis with 8 prospective cohort studies that specifically examined the effects of childhood trauma (only caregiver-inflicted trauma) also found a 2-times increased risk of depression among those exposed to childhood trauma (Li et al., 2016) (Table 6). Although these studies did not rely on retrospective recall, most assessed childhood trauma using official child protection or court records, which may lead to an underestimation in the association between childhood trauma and depression as only the extreme cases of trauma are represented in court (Li et al., 2016). The prevalence of self-reported trauma has also been shown to be greater compared to informant report (22.6% for self-reported physical abuse compared to 0.3% for informant report) (Li et al., 2016; Stoltenborgh et al., 2015). Both have limitations, as self-reported trauma may be subject to retrospective recall bias, and has been shown to be more strongly associated with psychopathology compared with prospective reports (Newbury et al., 2018), whereas informant reports may lead to underestimation as only the most severe cases are reported (Li et al., 2016).

Prospectively collected data using both self- and informant-reported trauma may help address these limitations, especially as certain types of trauma, such as sexual abuse and bullying may not always be known to the informant, such as the parents (Holt et al., 2008; Li et al., 2016). A recent study which used both self- and parent-reported measures of childhood trauma found a dose-response effect, with a 1.2 times increased risk of being diagnosed with any depressive disorder for each additional exposure to trauma, even after adjusting for childhood psychiatric diagnoses and other adversities (Copeland et al., 2018) (Table 6). Furthermore, a recent genetically informed study added further support for the causal role of childhood trauma in both depression and psychosis (Warrier et al., 2021). These contribute to further evidence that childhood trauma is a risk factor for multiple domains of psychopathology (Copeland et al., 2018; K. M. Keyes et al., 2012; McKay et al., 2021).

Table 6.

Summary of findings on the association between childhood trauma and depression.

Study	Type	Exposure	Depression
Sahle et al. (2021)	Meta-analysis (15 studies with depression as outcome)	Childhood physical, emotional and sexual abuse, neglect, bullying, maladaptive parenting	Childhood maltreatment associated with 2.02 times increased risk of depression
Copeland et al. (2018)	Longitudinal cohort study (N=1420)	Childhood trauma	Increased exposure to childhood trauma associated with increased risk of depressive disorders in adulthood (OR = 1.2, with each additional exposure to trauma).

Table 6. continued

Summary of findings on the association between childhood trauma and depression.

Study	Type	Exposure	Depression
Li et al. (2016)	Meta-analysis (8 studies)	Childhood maltreatment (mixture of official records and retrospective self-report)	Those with a history of any maltreatment during childhood had 2.03 times increased risk of depression compared to those who were not exposed to maltreatment.
Negele et al. (2015)	Naturalistic and randomised-controlled trial (N=349 chronically depressed patients)	Retrospective self-report of childhood trauma	76% of chronically depressed patients reported a history of childhood trauma, and 37% reported multiple traumas. Those who reported a history of multiple childhood trauma also had higher depressive scores.

4.3 Specificity of trauma

Many studies investigating childhood trauma have used it as a composite measure, indicating the presence or absence of trauma experience. However, there is also some evidence to suggest that specific types of trauma may have stronger effects than others (Copeland et al., 2018; Croft et al., 2018; Li et al., 2016; McKay et al., 2021; Varese, Smeets, et al., 2012). Some evidence supporting the specificity of childhood trauma in depression and psychosis will be discussed in the following section, first on evidence from caregiver-inflicted trauma, followed by evidence on peer-inflicted trauma.

4.3.1 Caregiver-inflicted trauma

There is some evidence that specific types of caregiver-inflicted trauma may have differential effects on adult depression and psychosis. Childhood sexual abuse remains the most well researched childhood trauma in the literature, with 19 meta-analyses having been conducted covering 28 outcomes including psychopathology, psychosocial wellbeing and physical health

(Hailes et al., 2019). Childhood sexual abuse is associated with almost all outcomes studied, including a 2.7 times increased risk of depression and 2.4 times increased risk of psychosis (Hailes et al., 2019). There is also some evidence that childhood sexual abuse may be more strongly correlated with specific symptoms of psychosis such as hallucinations (Bentall et al., 2012, 2014). However, the most recent meta-analysis on the differential effects of specific trauma found no increased risk of psychopathology following exposure to childhood sexual abuse compared to exposures to emotional abuse, neglect, and peer bullying (McKay et al., 2021). This may be due to the inclusion of some studies which used court case reports of sexual abuse, which are known to underestimate the prevalence of sexual abuse compared to self-report (McKay et al., 2021).

Other trauma types have also been prospectively associated with psychosis and depression in recent years, but with different effect sizes (see Table 7). A meta-analysis on the association between childhood trauma and psychosis found the largest effect size for emotional abuse (3.4 odds ratio) (Varese, Smeets, et al., 2012), whereas another prospective longitudinal study found the highest risk was associated with sexual abuse (2.5 odds ratio) (Croft et al., 2018). Emotional abuse was also associated with the highest risk of depression in another study, followed by neglect and sexual abuse (Mandelli et al., 2015). It has been suggested that emotional abuse may underlie all forms of abuse and neglect by the caregiver, as they all involve a degree of emotional abuse which is characterised by making a child feel worthless, making verbal threats and being indifferent (Ackner et al., 2013; Mandelli et al., 2015). Emotional abuse is also one of the most frequently reported forms of childhood trauma in the literature, with a prevalence rate of 36.3% compared to sexual abuse (18.4% for girls only) up to 18 years (Stoltenborgh et al., 2015). This may explain the larger risk associated with emotional abuse. Similarly, when all types of trauma were adjusted for each other, the effect of emotional abuse was reduced in one study and no longer associated with psychosis, which further suggests that there may be significant overlap between emotional abuse and other types of trauma (Croft et al., 2018).

Physical abuse is the second most common form of childhood trauma, with a prevalence rate of 22.6% in the literature (Stoltenborgh et al., 2015). The effect of physical abuse has been found to be slightly larger for psychosis (2.95 times increased risk) compared to depression (around 2 times increased risk) (Li et al., 2016; Mandelli et al., 2015; Varese, Smeets, et al., 2012) (Table 7). Other types of childhood trauma such as neglect or vicarious abuse, i.e. observing domestic violence, have also been associated with increased risk of psychosis and depression, albeit with smaller effect sizes compared to other forms of trauma (between 1.7 to 1.9 times increased risk, see Table 7) (Croft et al., 2018; Li et al., 2016). These suggest that the association between childhood trauma and adult psychopathology may be strongest from directly experienced trauma rather than indirect trauma such as witnessing domestic violence. However, confidence intervals of each trauma type often overlapped in these studies, thus there may not be true differences in their effect. Furthermore, studies have shown that it is increased exposure to multiple types of trauma, rather than any particular trauma per se, that is associated with the highest risk of psychosis and depression (Copeland et al., 2018; Croft et al., 2018; McKay et al., 2021).

4.3.2 Peer-inflicted trauma

Although the majority of studies have focused on caregiver-inflicted trauma, there is increasing interest in the study of trauma inflicted by peers in schools, i.e. bullying. Bullying is commonly defined as the systematic abuse of power, where peers repeatedly engage in aggressive behaviour with the intention to harm, and often involves an imbalance of power between the bully and the victim (Olweus, 1993; Wolke & Lereya, 2015). Bullying can involve direct abuse, including physical and verbal aggression such as name calling and hitting, as well as indirect abuse, which includes social exclusion from activities and spreading rumours (Wolke et al., 2000; Wolke & Lereya, 2015).

From an evolutionary perspective, bullying may be seen as an adaptive strategy to enhance social status and secure survival through dominance over

others (Juvonen et al., 2003; Olthof et al., 2011; Volk et al., 2012). Thus bullies often embody characteristics such as being more popular and having good social skills (Guy et al., 2019; Woods et al., 2009), whereas victims are often more socially withdrawn, timid, emotionally reactive and have fewer friends (Cook et al., 2010). Although the prevalence rate differs across studies and cultures, on average, one third of children report to being bullied at some point in their lives, and around 10-14% reported chronic bullying (Wolke & Lereya, 2015; World Health Organization, 2012). Bullying was also the most frequently reported trauma experience up to 17 years of age compared to any other caregiver-inflicted trauma (Croft et al., 2018).

There is some evidence for a causal effect of peer bullying on adult psychopathology in the literature (Arseneault, 2018; S. E. Moore et al., 2017; Wolke & Lereya, 2015). Peer bullying has been frequently associated with internalising symptoms, depression and psychosis in childhood and adolescence (Catone et al., 2015; Lereya, Copeland, Costello, et al., 2015; Lereya, Copeland, Zammit, et al., 2015; Sigurdson et al., 2015; Wolke et al., 2015; Wolke & Lereya, 2015). In adulthood, peer bullying has been associated with a 2-times increased risk of developing psychotic experiences (Cunningham et al., 2016), and this remained even after adjusting for the effects of all other types of caregiver-inflicted trauma (Croft et al., 2018) (Table 7). There is also evidence of a specific effect of peer bullying on adult depression over and above the effects of caregiver-inflicted trauma, with those who were exposed to bullying in childhood 1.6 times more likely to develop depression compared to those who were exposed to caregiver-inflicted trauma only (Lereya, Copeland, Costello, et al., 2015) (Table 7). A dose-response effect has also been observed: those who experienced chronic peer bullying or reported more severe forms of bullying were at higher risk for experiencing emotional problems and psychotic experiences (Kelleher et al., 2013; Wolke et al., 2015). Effect sizes of peer bullying on depression and psychosis in comparison to caregiver-inflicted trauma are shown in Table 7.

Table 7.

Effect sizes of specific trauma on depression and psychosis.

			Effect on depression					
Study	Type	Assessment	Emotional abuse	Physical abuse	Sexual abuse	Neglect	Domestic violence	Peer bullying
Mandelli et al. (2015)	Meta-analysis (44 studies)	Retrospective, prospective self-report, clinical, semi-structured interview	OR=2.78	OR=1.98	OR= 2.42	OR=2.75	OR=2.05	N/A
Li et al. (2016)	Meta-analysis (8 studies)	Official records, retrospective self-report	N/A	OR=2.00	OR=2.66	OR=1.74	N/A	N/A
Sahle et al. (2021)	Umbrella meta-analysis (15 studies)	Self- and parent-report, health records	N/A	OR=1.55	OR=2.02	N/A	N/A	OR=2.07
Lereya, Copeland, Zammit et al. (2015)	Longitudinal cohort study (N=4101)	Self- and parent-report	N/A	N/A	N/A	N/A	N/A	Bullying at: 10 years (OR=1.55) 13 years (OR=1.91)
Lereya, Copeland, Costello et al. (2015)	2 longitudinal cohort studies (ALSPAC: N=3904; GSMS: N=1273)	Self- and parent-report	Any maltreatment (physical, emotional, sexual abuse or maladaptive parenting) vs none (ALSPAC: no significant differences; GSMS: OR=5.6). Peer bullying vs maltreatment: (ALSPAC: OR=1.6; GSMS: no significant differences)					ALSPAC (OR=3.0) GSMS (OR=6.9)

Table 7. **continued**

Effect sizes of specific trauma on depression and psychosis.

			Effect on psychosis					
Study	Type	Assessment	Emotional abuse	Physical abuse	Sexual abuse	Neglect	Domestic violence	Peer bullying
Varese et al. (2012)	Meta-analysis (36 studies)	Retrospective and prospective self-report	OR=3.40	OR=2.95	OR=2.38	OR=2.90	N/A	OR=2.39
Croft et al. (2019)	Longitudinal cohort study (N=4433)	Parent and self-report	OR=1.81 OR=1.25[a]	OR=1.69 OR=2.24 [a]	OR=2.50 OR=2.04 [a]	OR=1.89 OR=2.33 [a]	OR=1.79 OR=1.48 [a]	OR=2.05 OR=1.80 [a]
Lereya et al. (2015)	Longitudinal cohort study (N=4101)	Self- and parent-report	N/A	N/A	N/A	N/A	N/A	Bullying at: 10 years: OR=2.12 13 years: OR: 2.50

[a]Odds ratio after adjusting for other trauma

4.4 Summary

Childhood trauma is one of the most frequently assessed environmental risk factors in relation to adult psychopathology, and there is strong evidence on its association with depression and psychosis. Analysis of specific types of trauma suggest that it is directly experienced rather than indirect or witnessed trauma that is more strongly associated with depression and psychosis, and a dose-response effect has also been found, with the greatest risk from being exposed to multiple types of trauma or being exposed to trauma chronically in childhood and adolescence. Although most studies have focused on caregiver-inflicted trauma, there is also increasing evidence for the effects of peer bullying, which has been frequently associated with both depression and psychosis and may have a stronger effect compared to caregiver-inflicted trauma.

Chapter 5: The joint influence of biological and environmental risks on adult psychopathology

The previous chapters offered a comprehensive discussion on the effects of biological (prenatal stress and neurodevelopmental adversity) and environmental risks (childhood trauma) on two areas of adult psychopathology – depression and psychosis. However, the joint influence of these risks has rarely been examined. Some theoretical models on how biological and environmental risks may be associated with each other are discussed in this chapter, along with empirical evidence supporting their joint influence on depression and psychosis. First, the evidence will focus on the mediating role of childhood trauma in the association between prenatal stress and offspring depression, and second on the mediating vs moderating role of childhood trauma in the association between neurodevelopmental adversity and psychosis.

5.1 Cumulative effect model

5.1.1 Theoretical model

The cumulative effect model, otherwise known as the life course developmental model, acknowledges that early experiences are only significant in the context of later experiences, so rather than being directly linked to future outcomes, early risks may be mediated by further risks during childhood and adolescence (O'Connor, 2015). There are a number of important life transitions or milestones along the developmental pathway, and deviance from these may set individuals on a different trajectory, where they may face more challenges cumulating in psychopathology in adulthood (O'Connor, 2015). The onset of psychopathology is therefore the cumulation of a complex and dynamic relationship between different risk factors over time (O'Connor, 2015; Wickrama et al., 2008). The theory also assumes individuals to be highly malleable to experience, and hence environmental

influences may both exacerbate their risk of psychopathology or, in the right environment, protect them against psychopathology (O'Connor, 2015).

Using family adversity as an example, it has been proposed that individuals from disadvantaged backgrounds are at increased risk of psychopathology due to disruptions in successful transitions to adulthood (Wickrama et al., 2008). Early risk factors such as low SES and poor living conditions can create a stressful environment which prevents individuals from completing developmental transitions (Wickrama et al., 2008). For example, they may have poorer social skills and experience more problematic interpersonal relationships, as well as pursuing adult roles such as parenthood and cohabitation during their teenage years which may lead to the development of psychopathology (Wickrama et al., 2008). Early risks may thus lead to later risks by setting in motion a series of events that ultimately lead to psychopathology.

Childhood trauma may be another such key mechanism in the association between biological risks and adult psychopathology. The mediating role of childhood trauma will be discussed in the following section, focusing in particular on the association between prenatal stress and offspring depression. Traditional mediation model requires both the association between the risk and the mediator (path "a"), and between the mediator and the outcome (path "b") to be statistically significant (see Fig. 1) (Rucker et al., 2011). Path "c" represents the direct effect of the risk on the outcome, and the mediated or indirect effect is calculated as the product of path "a" and path "b" (Rucker et al., 2011). Evidence on path "c" and path "b" have already been presented in previous chapters. Evidence here will focus on path "a": the association between prenatal stress and childhood trauma, followed by a discussion of the mediated effect of childhood trauma (path "a" x path "b") .

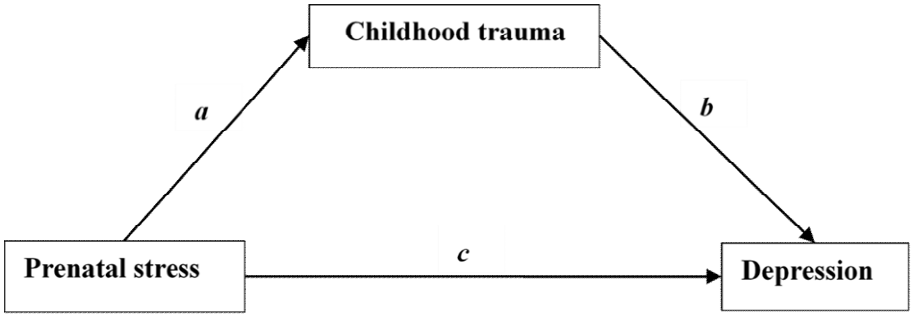

Figure 1.

Conceptual model showing the mediated effect of childhood trauma.

5.1.2 Empirical evidence

5.1.2.1 Prenatal stress and childhood trauma (path "a")

A recent meta-analysis and systematic review found that parental psychopathology during the perinatal period (from conception to 1 year after birth) was associated with a 3-times increased risk of childhood trauma, which was defined in this study as any caregiver-inflicted abuse or neglect (Ayers et al., 2019). However, parental psychopathology included both mothers and fathers, and the prenatal period was also not examined. Some longitudinal studies have investigated the association between prenatal stress and exposure to childhood trauma, and in one study a 2.4-times increased risk of being exposed to any caregiver-inflicted trauma was found in offspring of mothers who were depressed during pregnancy (Plant et al., 2015). Both biological and environmental mechanisms may be involved, such as a programming effect of maternal depression on infant temperament, which may lead to changes in parenting behaviours, as well as increasing partner conflict and maladaptive parenting (Bates & Pettit, 2015; Lereya & Wolke, 2013; Plant et al., 2015; Yehuda & Lehrner, 2018).

Examination of specific trauma also found higher risk for emotional abuse rather than physical abuse in mothers who were depressed, and is consistent with evidence that mothers with a history of depression show less emotional availability and sensitivity, but are not more physically aggressive (Conron et al., 2009; Kluczniok et al., 2016). However, this was examined in a sample

of mothers who were already under investigation for inflicting abuse or neglect, and maternal depression was not assessed during the prenatal period (Conron et al., 2009), thus further research is needed on the prospective association between prenatal maternal depression and risk for specific types of trauma.

There is also emerging evidence of an association between prenatal maternal depression and increased vulnerability to peer bullying, with offspring of mothers who experienced depressive symptoms during pregnancy 1.2 times more likely to be victimised even after adjusting for other family and school factors (Azeredo et al., 2017) (Table 8). However, prenatal maternal depression was only assessed retrospectively using one item during the first 24 hours after delivery (Azeredo et al., 2017). Prospectively assessed prenatal maternal depression was also found to be associated with increased risk of peer bullying, and this is regardless of whether reports of bullying came from the child, parent or teacher (Lereya & Wolke, 2013) (Table 8). Potential indirect pathways were found via maladaptive parenting and partner conflict, suggesting the involvement of environmental factors (Lereya & Wolke, 2013). Another explanation is that offspring of mothers with prenatal depression show altered stress regulation and report more emotional problems in childhood (O'Connor et al., 2013; Swales et al., 2018). This may indicate a programming effect of maternal depression on offspring emotional reactivity, which makes them more likely to be targeted by bullies who tend to pick on those with heightened emotional response (Lereya & Wolke, 2013; Wolke & Lereya, 2015).

Another source of prenatal stress – family adversity, as an indicator of social and economic stress – has also been associated with caregiver-inflicted trauma in childhood (Cicchetti & Valentino, 2015) (Table 8). Specific indicators of family adversity such as poverty and unemployment are consistent risk factors for physical and sexual abuse in childhood (Doidge et al., 2017). There is also some evidence to suggest that maternal depression may mediate the association between economic stress and caregiver-inflicted

trauma (Conrad-Hiebner & Byram, 2020). However, evidence on peer-inflicted trauma (i.e. peer bullying) suggest that these are two independent risk factors, as both prenatal maternal depression and family adversity were associated with peer bullying even after accounting for the effects of each other and their continuity into the postnatal period (Lereya & Wolke, 2013).

Family adversity in the study by Lereya and Wolke (2013) was assessed using the Family Adversity Index (FAI), a cumulative risk index consisting of 16 risk exposures (18 in a long version) (Rutter, 1979; Steer et al., 2004), which was grouped into no adversity, mild (1-2 adversities) and severe (more than 3 adversities), representing a dose-response effect (Lereya & Wolke, 2013). This has also been found across other studies, where it is increased exposure to, rather than any individual risk factor per se, that was associated with highest risk of peer bullying (Begle et al., 2010; Doidge et al., 2017). This suggests the importance of using a comprehensive cumulative index such as the FAI, and to investigate family adversity alongside maternal depression to examine two separate sources of prenatal stress and their potentially separate effects on childhood trauma.

Table 8.

Summary of findings on the association between prenatal stress and childhood trauma.

Study	Type	Exposure	Trauma type	Findings
Plant et al. (2015)	Longitudinal cohort study (N=103)	Prenatal maternal depression.	Caregiver-inflicted trauma	Increased risk of any caregiver-inflicted trauma up to 17 years (OR: 2.4, 95%CI: 1.0 – 5.7).
Conron et al. (2009)	Longitudinal cohort study (N=2386)	Changes in maternal depression from baseline to 36 months.	Caregiver-inflicted trauma	Changes in maternal depression associated with increased psychological aggression (β=2.28, 95%CI: 0.17 – 4.38), not physical abuse.

Table 8. **continued**

Summary of findings on the association between prenatal stress and childhood trauma.

Study	Type	Exposure	Trauma type	Findings
Azeredo et al. (2017)	Longitudinal cohort study (N=3441)	Prenatal maternal depression (retrospectively assessed)	Peer-inflicted trauma	Prenatal maternal depression increased risk of peer bullying at 11 years (OR:1.22, 95%CI: 1.05 – 1.41).
Lereya & Wolke (2013)	Longitudinal cohort study (N=8829)	Prenatal maternal psychopathology (depression and anxiety) and prenatal family adversity	Peer-inflicted trauma	Prenatal maternal psychopathology and family adversity both increased risk of peer bullying. Indirect pathways via partner conflict and maladaptive parenting.
Doidge et al. (2017)	Longitudinal cohort study (N=2443)	Childhood socio-economic adversity (poverty, parental education/occupation, housing, income).	Caregiver-inflicted trauma	Combined economic adversities associated with increased retrospective reports of physical and sexual abuse, and domestic violence, but not emotional abuse or neglect.

5.1.2.2 Mediated effect of childhood trauma on depression (path "a" x path "b")

There is thus some evidence that both indicators of prenatal stress may be associated with increased exposure to childhood trauma. Childhood trauma has also been shown previously to be associated with depression in adulthood (e.g. Copeland et al., 2018; Li et al., 2016). According to traditional mediation model (Rucker et al., 2011), there may also be an indirect pathway from

prenatal stress to offspring depression via increased exposure to childhood trauma.

Only one sample has been used so far to investigate the mediated effect of caregiver-inflicted trauma from prenatal maternal depression to adult offspring depression (Plant et al., 2015). An indirect pathway was found where prenatal maternal depression was associated with increased risk of being exposed to caregiver-inflicted trauma, which subsequently increased risk of depression in adulthood (Plant et al., 2015). Furthermore, the direct effect of prenatal maternal depression on offspring depression was also reduced when childhood trauma was added to the model, suggesting that a substantial amount of the risk associated with prenatal maternal depression can be attributed to exposure to childhood trauma (Plant et al., 2015). However, the evidence is still unclear on whether this mediated pathway is also found via peer-inflicted trauma, as only a composite measure of any caregiver-inflicted trauma was investigated in this study, thus it was not possible to differentiate between different types of trauma or whether a dose-response effect exists. Furthermore, prenatal family adversity was not examined, and there is some evidence that both prenatal maternal depression and family adversity may contribute independently to specific childhood trauma such as peer bullying (Lereya & Wolke, 2013). Future research should therefore investigate both forms of prenatal stress, as well as both caregiver- and peer-inflicted trauma, to examine whether maternal depression and family adversity have differential effects on different types of trauma, and their joint influence on offspring depression in adulthood.

5.2 Developmental Risk Factor model (DRFM)

5.2.1 Theoretical model

An increasingly popular model of schizophrenia has been termed the "Developmental Risk Factor model" (DRFM), which is an updated version of the Neurodevelopmental model of schizophrenia, and proposes an indirect

pathway from neurodevelopmental adversity to psychotic experiences or disorders via environmental risks in childhood (Murray et al., 2017; Murray & Fearon, 1999). Since the Neurodevelopmental model was first proposed, there has been emerging evidence to suggest the involvement of environmental and social risk factors in schizophrenia, especially for childhood trauma and substance misuse (Murray et al., 2017). The original model was thus extended to include these environmental influences and their joint influence with early neurodevelopmental adversity in the onset of psychosis.

Rather than assuming that psychosis is determined very early in life due to disruptions to the brain and associated networks, the alternative theory proposes that early obstetric complications may lead to certain characteristics and impairments that are deviant from typical development, such as impairments in cognitive and motor functioning (Murray et al., 2017; Murray & Fearon, 1999). These developmental impairments are viewed as cumulative risk factors rather than an early manifestation of psychosis, and may lead to a cascade of increasing difficulties in parent-child relationships, peer relationships and academic achievements, which in turn may lead to further difficulties with emotion regulation, event appraisal and negative cognitive bias (Murray et al., 2017; Murray & Fearon, 1999). These may then set in motion a vicious cycle where developmental impairments increase exposure to further risks, which can increase dopamine dysregulation and salience of negative experiences, and in turn these lead to more stress and further dysregulate dopamine release which ultimately cumulates in psychosis (Murray et al., 2017).

This model allows for the possibility of intervention and prevention at each stage of development, when deviance from typical development occurs (Murray & Fearon, 1999). Early exposure to neurodevelopmental adversity may thus increase vulnerability to further environmental risks, such as childhood trauma, and subsequently psychosis in adulthood. However, despite the relative plausibility of the model, few longitudinal studies have

tested the joint influence of neurodevelopmental adversity and childhood trauma, and the specific mechanism in how they may be associated with each other has not been examined. For example, there may be a mediated pathway (Fig. 2, path "a" x path "b") where early neurodevelopmental adversity increases subsequent exposure to childhood trauma, which increases risk of psychosis. Alternatively, there may be a moderated pathway where those exposed to neurodevelopmental adversity are more vulnerable to the effects of childhood trauma (interaction effect, Fig. 2, path "d"). It is important to test these alternate models to investigate the mechanism in which childhood trauma may be associated with neurodevelopmental adversity, and their joint influence on psychosis.

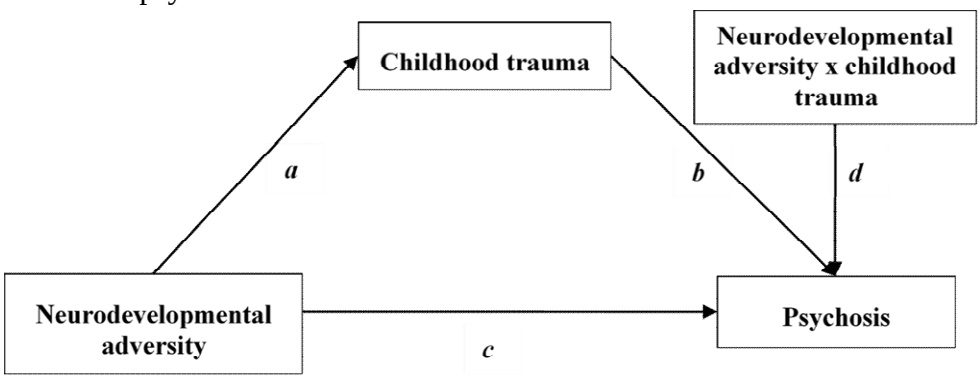

Figure 2.

Conceptual model showing the mediating vs moderating effect of childhood trauma.

5.2.2 Empirical evidence

5.2.2.1 Neurodevelopmental adversity and childhood trauma

Compared to prenatal stress, fewer studies have investigated the association between neurodevelopmental adversity and childhood trauma. The strongest evidence comes from studies in the VP/VLBW population – a proxy measure for a group exposed to significant neurodevelopmental adversity – and their increased exposure to peer bullying (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke et al., 2015, 2019) (see Table 9 for a summary of

findings). Risk factors for being victims of peer bullying are largely invariant across different stages of development; these include increased emotional reactivity, poor social competence, childhood emotional problems and being perceived as weaker, such as those with poorer physical health and experience more disabilities (Cook et al., 2010; Heuser et al., 2018; Juvonen et al., 2003; Sentenac et al., 2012; Wolke et al., 2019; Wolke & Lereya, 2015). Other developmental impairments such as poorer executive functioning and attention problems have also been associated with increased risk of being bullied by peers (Holmes et al., 2016; Ji et al., 2019).

All of these risk factors are more frequently found in the VP/VLBW population and are consistent with the preterm phenotype which has been previously described in chapter 3 (Johnson et al., 2018; Wolke et al., 2019). Those who are born VP/VLBW show increased prevalence of developmental impairments in cognitive and motor domains as well as increased risk for physical disabilities resulting from early damage to brain and organs (Allotey et al., 2018; Baumann et al., 2020; Johnson et al., 2009; Wolke et al., 2019). They also show increased emotional problems, shyness, and have an introverted personality which are all associated with increased peer problems and social difficulties (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Hertz et al., 2013; Heuser et al., 2018; Johnson & Marlow, 2011; Mathewson, 2017; Ritchie et al., 2018; Wolke et al., 2019). A systematic review of 7 studies in VLBW, ELBW and EP children found consistent evidence of increased exposure to peer bullying across all groups (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015). However, sample size in these studies are often small (N=60 to 287), and some used adult retrospective reports of bullying in childhood (Day, Van Lieshout, Vaillancourt, Saigal, et al., 2015; Day, Van Lieshout, Vaillancourt, & Schmidt, 2015). Prospectively assessed bullying experiences (assessing bullying experiences within the last 6 months during childhood) also showed increased risk of being bullied among children born VP/VLBW (Ritchie et al., 2018; Wolke et al., 2015). They are also at increased risk of being chronically bullied, which was defined in these studies as either being bullied more than twice a week, or being bullied consistently

across multiple time periods in childhood and adolescence (Ritchie et al., 2018; Wolke et al., 2015) (Table 9).

The association between neurodevelopmental adversity and childhood trauma in the general population have not received much attention in the literature, particularly on the association between obstetric complications and childhood trauma. It also remains unclear whether it is exposure to these obstetric complications per se, or the increased risk of developmental impairments resulting from these complications, that is associated with increased risk of childhood trauma. Previous research have shown that certain childhood characteristics, such as having a lower IQ and attention problems, were predictive of peer bullying in ELBW children (Yau et al., 2013) (Table 9). Thus, rather than being born VP/VLBW per se, it may be their subsequent increased risk of developmental impairments that is associated with being bullied. Further investigation is needed to examine whether the increased risk of peer bullying, or other types of trauma, is associated with exposure to obstetric complications such as preterm birth, or rather subsequent childhood developmental impairments such as cognitive and motor impairments.

Table 9.

Summary of findings on the association between neurodevelopmental adversity and childhood trauma.

Study	Type	Exposure	Trauma type	Findings
Day et al. (2015)	Systematic review of 7 studies	ELBW, VLBW or EP children vs controls	Peer-inflicted trauma	ELBW/VLBW/EP children reported more peer bullying than term born controls. Limitations include retrospective reports and small sample size.

Table 9. continued

Summary of findings on the association between neurodevelopmental adversity and childhood trauma.

Study	Type	Exposure	Trauma type	Findings
Wolke et al. (2015)	Longitudinal cohort study (BLS, N=580; EPICure, N=285)	VP/VLBW and EP children vs controls	Peer-inflicted trauma	In the BLS cohort, VP/VLBW children were twice as likely to be bullied chronically (bullied in both childhood and adolescence) compared to term-born controls, even after adjusting for childhood emotional problems and disability.
Ritchie et al. (2018)	Longitudinal cohort study (N=113)	EP/VP vs controls	Peer-inflicted trauma	Both EP and VP children were more likely to be chronically bullied (more than twice a week) compared to term-born controls. Predictors of peer problems included motor functioning, inattention and emotional problems.
Yau et al. (2013)	Longitudinal cohort study (N=287)	ELBW vs controls	Peer-inflicted trauma	ELBW boys reported more bullying compared to term-born boys, but no differences for girls. Predictors of bullying included lower IQ, functional difficulties, attention problems and childhood emotional problems.

5.2.2.2 Mediating vs moderating effect of childhood trauma on psychosis

Few studies have investigated the mediating role of childhood trauma in the association between neurodevelopmental adversity and psychosis in adulthood. Childhood IQ has been previously examined as a potential mediator in the association between obstetric complications and psychotic experiences in childhood, and although direct pathways were found from

specific obstetric complications such as maternal infection, no indirect pathways were found via childhood IQ (Zammit et al., 2009). Evidence from the VP/VLBW population suggest that once childhood trauma such as peer bullying is accounted for, the association between VP/VLBW birth and childhood emotional problems was reduced (Wolke et al., 2015). This suggest that part of the risk attributed to VP/VLBW birth can be explained by increased exposure to peer bullying. Given that VP/VLBW children are more likely to be bullied (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke et al., 2015, 2019), and bullying is associated with increased risk of psychosis (Croft et al., 2018; Varese, Smeets, et al., 2012), it is plausible that bullying may also mediate the association between VP/VLBW birth and psychosis. Further research is needed to examine this indirect pathway, via both peer bullying and other caregiver-inflicted trauma, and to investigate this both in the general population using directly measured indicators of neurodevelopmental adversity, as well as in the VP/VLBW population which is used as a proxy measure for multiple exposure to neurodevelopmental adversity.

Alternatively, childhood trauma may moderate the association between neurodevelopmental adversity and psychosis. One study investigated the effect of prenatal infection and peripubertal trauma on risk of schizophrenia, and found a moderated pathway where the risk of schizophrenia from being exposed to both risk factors was greater than if exposed to either risk factor alone (Debost et al., 2017). Peripubertal trauma assessed in this study did not include traditional measures of childhood trauma, but rather adverse life events such as family illness, foster care and parental occupational status (Debost et al., 2017). Furthermore, only one indicator of neurodevelopmental adversity – prenatal infection – was examined. The evidence is still unclear on the specific mechanism in which childhood trauma is associated with neurodevelopmental adversity and psychosis. Further investigation is thus needed to further examine the role of childhood trauma in the association between neurodevelopmental adversity and psychosis in adulthood, both in the general population and the VP/VLBW population.

5.3 Summary

Both the cumulative effect model and the Developmental Risk Factor model proposes a developmental cascade model of psychopathology, where failure to meet certain milestones or deviance from typical development can lead to further risks, cumulating in psychopathology in adulthood (Murray et al., 2017; Murray & Fearon, 1999; O'Connor, 2015). There is some evidence to suggest a mediating effect of childhood trauma from prenatal stress to offspring depression, although further research is needed on the potentially differential effects of different sources of prenatal stress via caregiver- vs peer-inflicted trauma. This developmental pathway has rarely been examined in longitudinal research on the association between neurodevelopmental adversity and psychosis. There may be a mediating or moderating effect of childhood trauma in the association between neurodevelopmental adversity and psychosis, which requires further investigation.

Chapter 6: Biological and environmental determinants of positive psychosocial wellbeing

The focus of discussion so far has been on the effect of biological and environmental risks on adult psychopathology, in particular depression and psychosis. Traditional models of psychopathology are primarily concerned with negative mental health, however, there is also increasing momentum in recent decades with a shift towards studying positive mental health or wellbeing (Gable & Haidt, 2005; Maddux, 2009). Mental health has been previously defined by the World Health Organisation (2005) as "a state of wellbeing", and health as "not merely the absence of disease or infirmity" (World Health Organisation, 1947). Thus, both the absence of psychopathology and the presence of positive wellbeing can be considered as necessary components to achieving optimal health.

Studies on negative mental health are often focused on symptoms of psychopathology, such as depression and psychosis, which are considered as deviant or maladaptive conditions (Maddux, 2009). On the other hand, studies on positive mental health primarily focus on three areas of wellbeing: hedonic or emotional wellbeing (feelings of happiness and satisfaction with life); eudaimonic or psychological wellbeing (self-actualisation, acceptance and optimal functioning); and social wellbeing (social acceptance and sense of belonging) (Westerhof & Keyes, 2010). According to the dual-model or the two continua model of mental health, psychopathology and wellbeing can be considered as related but distinct constructs, and the absence of psychopathology is not an indicator for positive emotional, psychological or social wellbeing (Westerhof & Keyes, 2010). For example, a significant proportion of individuals without psychopathology report low levels of self-evaluations in areas such as academic performance and social relationships, indicating reduced psychological and social wellbeing (Suldo & Shaffer, 2008). Similarly, promoting positive wellbeing has also been shown to facilitate resilience, where individuals report overall increase in subjective

wellbeing despite the presence of psychopathology (Bos et al., 2016). There is also evidence that psychopathology and positive wellbeing are only weakly related during childhood and adolescence, with largely distinct correlates, suggesting the importance of examining these concepts separately (Patalay & Fitzsimons, 2016).

Positive wellbeing has been proposed to be a multi-dimensional construct in the literature (Ruggeri et al., 2020), and the focus here will be on one aspect – self-concept – which reflects both psychological (e.g. self-acceptance) and social wellbeing (e.g. social acceptance) and is thus referred to as positive psychosocial wellbeing. Evidence will specifically focus on the association between VP/VLBW birth – a group previously proposed to be a proxy measure indicating multiple exposure to neurodevelopmental adversity – and self-concept, to examine whether neurodevelopmental adversity may be implicated in both psychosis and the development of self-concept. This is followed by a discussion on the role of childhood trauma, specifically peer bullying, and the mechanism in which it may relate to VP/VLBW birth in shaping the development of self-concept.

6.1 The role of self-concept in positive psychosocial wellbeing

Self-concept can be considered as one of the most fundamental components of psychosocial wellbeing (Craven & Marsh, 2008). Traditionally it has been used interchangeably with self-esteem, which is a global construct of how individuals feel about themselves as a whole (Craven & Marsh, 2008; Kernis, 2006; King, 1997). However, self-concept has been increasingly recognised as a separate construct with a multidimensional and hierarchical structure, which reflects evaluations and affective appraisals of specific areas of functioning, such as the academic, social, and physical aspects of the self (Craven & Marsh, 2008; Kernis, 2006; King, 1997). Positive self-concept has been theorised to be crucial to facilitating positive wellbeing, and specific constructs have also been implicated in certain behavioural outcomes, such

as academic performance, as well as hedonic wellbeing such as feelings of happiness (Garaigordobil, 2015; Rosenberg et al., 1995; Wentzel et al., 2021).

Rather than investigating the presence or absence of symptoms indicating psychopathology as the outcome, research on self-concept can investigate differences or change in levels of self-concept relative to a general pattern or norm. A general pattern in the development of self-concept has been identified in the literature, which shows an increasing trend across most self-concept domains from childhood to adulthood, similar to the development of global self-esteem (von Soest et al., 2016). This identification of a general trend allows the comparison and investigation of groups of people who do not follow this pattern of development, to allow further examination of factors that may influence trajectories of self-concept development.

This presents the opportunity to examine whether the same mechanisms involved in the onset of adult psychopathology are also found to affect the development of psychosocial wellbeing – indicated by self-concept. If so, this may suggest a common pathway from early biological risks to outcomes in both areas of psychopathology and psychosocial wellbeing. This will be investigated using the VP/VLBW population, which was previously proposed as a proxy measure for neurodevelopmental adversity in relation to psychosis. Evidence on the association between VP/VLBW birth and self-concept is discussed, followed by evidence on the association between childhood trauma and self-concept, and whether the same mechanisms associated with the onset of psychopathology may also be implicated in self-concept.

6.2 VP/VLBW and self-concept

Self-concept is not often examined when investigating adult outcomes in the VP/VLBW population, and most have focused on global self-esteem rather than self-concept in specific domains. Mixed findings have been reported in these studies, with some finding lower levels of global self-esteem among VP/VLBW children or adults (Islam et al., 2018; Rickards et al., 2001)

whereas others found no differences (Finnström et al., 2003; Roberts et al., 2013; Tideman et al., 2001; Vederhus et al., 2015) (see Table 10). Only one study investigated specific domains of self-concept in a VLBW population in adulthood, and found lower levels of athletic competence in VLBW adults compared to term-born controls (Lund et al., 2012). Those born small for gestational age (SGA) – an indicator for intrauterine growth restriction – also scored lower on social acceptance compared to term-born controls, but no differences emerged for the other domains of self-concept (Lund et al., 2012). However, these studies have only examined self-concept at one time point in either childhood/adolescence or adulthood, which does not take into account the developmental trajectory of self-concept, nor does it explain the mechanisms that may be associated with lower self-concept in the VLBW population.

Only one cohort with ELBW participants and term-born controls has examined the longitudinal trajectory of global self-esteem from adolescence to adulthood (see Table 10). Findings from this cohort showed that that ELBW individuals showed decreasing levels of global self-esteem from adolescence to adulthood, compared to term-born controls (Poole, Schmidt, Saigal, et al., 2018). One moderating factor may be motor impairments, with ELBW individuals who had better motor skills having higher levels of self-esteem compared to ELBW individuals with poorer motor skills (Poole, Schmidt, Ferro, et al., 2018). No study has examined the longitudinal development of self-concept across different domains in the VP/VLBW population, thus there is an opportunity to examine whether those born VP/VLBW also show altered trajectory in their self-concept development, and to investigate potential mechanisms that may be associated with this.

Table 10.

Summary of findings on the association between VP/VLBW birth and self-esteem or self-concept.

Study	Type	Exposure	Outcome	Findings
Lund et al. (2012)	Longitudinal cohort study (N=172)	VLBW, SGA vs term-born controls	Self-concept in adulthood	VLBW adults (20 years) scored lower on athletic competence self-concept than term-born controls. SGA participants also scored lower on social acceptance self-concept compared to controls.
Saigal et al. (2016)	Longitudinal cohort study (N=189)	ELBW vs term-born controls	Self-esteem in adulthood	ELBW adults (29-36 years) scored lower on global self-esteem (on average 8.4 points lower) compared to term-born controls.
Roberts et al. (2013)	Longitudinal cohort study (N=342)	EP/ELBW vs term-born controls	Self-esteem in adulthood	EP/ELBW adults (18 years) and term-born controls reported similar global self-esteem.
Vederhus et al. (2015)	Longitudinal cohort study (N=60)	EP vs term-born controls	Self-esteem in childhood and adulthood	EP children (10 years) scored lower on global self-esteem compared to term-born controls. In adulthood (18 years), only EP girls reported lower levels of self-esteem compared to term-born EP girls; EP boys reported higher self-esteem compared to term-born boys.

Table 10. continued

Summary of findings on the association between VP/VLBW birth and self-esteem or self-concept.

Study	Type	Exposure	Outcome	Findings
Finnström et al. (2003)	Longitudinal cohort study (N=139)	VLBW vs term-born controls	Self-esteem in childhood	VLBW children (12 years) reported similar levels of global self-esteem compared to term-born controls.
Rickards et al. (2001)	Longitudinal cohort study (N=172)	VLBW vs term-born controls	Self-esteem in childhood	VLBW children (14 years) scored lower on global self-esteem compared to term-born controls but no differences in other domains.
(Poole, Schmidt, Ferro, et al., 2018	Longitudinal cohort study (N=324)	ELBW vs normal birth weight controls	Self-esteem trajectory from childhood to adulthood	ELBW individuals show lower levels of global self-esteem from adolescence (14 years) to adulthood (32 years). Normal birth weight controls who show poorer motor skills also showed lower global self-esteem development.
Poole, Schmidt, Saigal, et al., 2018	Longitudinal cohort study (N=218)	ELBW vs normal birth weight controls	Self-esteem trajectory from childhood to adulthood	ELBW individuals showed persistently lower and decreasing levels of global self-esteem from adolescence (14 years) to adulthood (32 years).

6.3 Childhood trauma and self-concept

Childhood trauma has frequently been associated with outcomes in psychopathology, and there is also some evidence that childhood trauma may also affect the development of psychosocial wellbeing such as self-esteem and self-concept (Day et al., 2017; Leeuwis et al., 2015; Wolke & Lereya, 2015). Few have investigated the role of peer bullying in the development of self-concept, with some evidence that exposure to peer bullying is associated with lower self-concept relating to social acceptance and body satisfaction (Boulton et al., 2010) (Table 11). These may be areas of self-concept that rely most heavily on individuals' social context, and experiences of being rejected by peers can lead to evaluations of the self as someone who is undesirable, thus leading to lower self-concept in these areas (Duarte et al., 2017). The association is particularly strong between bullying and lower self-concept on body satisfaction, especially in girls, and bullying has also been shown to increase adolescents' desire for cosmetic surgery and eating disorder symptomology (Duarte et al., 2017; K. Lee et al., 2017) (Table 11).

However, there may be a reciprocal relationship between bullying and self-concept, and lower self-concept may also be a risk factor for being bullied (Boulton et al., 2010). For example, self-concept on social acceptance has been found to be both predictive of and predicted by bullying (Boulton et al., 2010). As bullies tend to pick on those who are unpopular or have fewer friends (Cook et al., 2010), those who already have low self-concept may be more likely to be bullied, which in turn can lead to lower levels of self-concept. It also remains unclear whether the effect of bullying on self-concept domains such as social acceptance and body satisfaction remain into adulthood. Further research on the prospective association between peer bullying in childhood and the development of self-concept from childhood into adulthood is needed to examine the long-term effects of bullying on the development of self-concept.

Table 11.

Summary of findings on the association between peer bullying and self-esteem or self-concept.

Study	Type	Exposure	Outcome	Findings
Duarte et al. (2017)	Prospective study (N=290)	Peer bullying	Body image	Peer bullying associated with body image shame: β= 0.42
K. Lee et al. (2017)	Prospective study (N=752)	Peer bullying	Body image	Victims of bullying had lower body esteem and increased desire for cosmetic surgery.
Boulton et al. (2010)	Prospective study (N=115)	Peer bullying	Self-concept in body satisfaction and social acceptance	Peer bullying associated with changes in social self-concept (β= -0.19), but not body self-concept.

6.4 Mechanisms associated with the development of self-concept

Previous studies examining either self-esteem or self-concept in the VP/VLBW population have mostly examined it as a direct outcome, without further investigation on mechanisms that may explain this association. VP/VLBW children have already been shown previously to be at increased risk of peer bullying in schools (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke et al., 2015), and peer bullying has also been associated with the development of lower self-concept in specific domains such as body satisfaction and social acceptance (Boulton et al., 2010; Duarte et al., 2017; K. Lee et al., 2017). Thus, peer bullying may be a plausible mediator in the association between VP/VLBW birth and altered development in self-concept. Another mechanism which may be involved is childhood developmental impairments, in particular motor impairments, which are more

prevalent in children born VP/VLBW (Allotey et al., 2018; Baumann et al., 2020; Johnson et al., 2009), and is also associated with decreased peer acceptance (Livesey et al., 2011).

Both peer bullying and motor impairments may be plausible mediators in the association between VP/VLBW birth and outcomes in self-concept development. The investigation of these mechanisms also offers the opportunity to identify potentially modifiable processes that may improve self-concept in an at-risk population. Furthermore, the indirect effect of VP/VLBW birth via peer bullying can be examined in relation to both outcomes in psychosis as well as self-concept, to better understand whether childhood trauma is a key environmental influence implicated in both the onset of psychopathology as well as reducing psychosocial wellbeing.

6.5 Summary

Although models of psychopathology remain a dominant area of research, there is increasing interest in examining positive wellbeing, and whether the same mechanisms are associated with both. One area of wellbeing – self-concept – is proposed to be affected by both VP/VLBW birth as well as childhood trauma (peer bullying), similar risks as those identified in relation to psychosis. This allows for the examination of whether VP/VLBW birth, as a proxy measure for neurodevelopmental adversity, is associated with increased risk in both psychosis and the development of self-concept, and the role of childhood trauma across these very different outcomes.

Chapter 7: Aim and Research questions

7.1 Aim of thesis

Previous chapters have shown that there is a wealth of research on the independent effects of biological and environmental risks on adult psychopathology, in particular for depression and psychosis, but much less research on their joint influence. Even fewer have investigated this in relation to outcomes in psychosocial wellbeing, such as self-concept. Childhood trauma may also be an important environmental risk factor associated with both biological risks and adult psychological development in both domains of psychopathology and psychosocial wellbeing.

The overall aim of this thesis is to investigate the role of childhood trauma in the association between two biological risks (prenatal stress and neurodevelopmental adversity) and adult psychological development, focusing primarily on two outcomes in psychopathology – depression and psychosis, followed by one indicator for psychosocial wellbeing – self-concept.

7.2 Summary of studies

Four studies were designed to address the overall aim of this thesis. The role of childhood trauma was examined in all studies, but differed regarding the type of biological risks and specific trauma examined. A summary of the exposures and outcomes examined can be found in Table 12. A brief description of each study and specific research questions can also be found below.

Table 12.

Summary of exposures and outcomes considered in each study.

Study	Biological risk	Population	Type of childhood trauma	Outcome
1	Prenatal stress (maternal depression; family adversity)	General population	Both caregiver- and peer-inflicted trauma	Depression
2	Neurodevelopmental adversity (obstetric complications; developmental impairments)	General population	Both caregiver- and peer-inflicted trauma	Psychotic experiences
3	Neurodevelopmental adversity (VP/VLBW as a proxy measure for multiple neurodevelopmental adversity)	VP/VLBW vs term-born controls	Peer-inflicted trauma (i.e. peer bullying)	Psychotic experiences
4	Neurodevelopmental adversity (VP/VLBW as a proxy measure for multiple neurodevelopmental adversity)	VP/VLBW vs term-born controls	Peer-inflicted trauma (i.e. peer bullying)	Self-concept

7.2.1 Study 1: Prenatal stress and offspring depression in adulthood: The mediating role of childhood trauma

Prenatal stress has been shown to have a programming effect on offspring depression (Tirumalaraju et al., 2020), but environmental influences beyond the initial postnatal years have rarely been examined along this pathway. There is some evidence that prenatal maternal depression may increase risk of childhood trauma (Plant et al., 2015), which has been consistently associated with depression in adulthood (Copeland et al., 2018; Li et al., 2016; Sahle et al., 2021). However, other sources of prenatal stress such as family adversity and the continuity of both sources of stress into the postnatal period have not been examined in conjunction with childhood trauma.

Research questions:

1. What are the direct effects of pre- and postnatal stress on offspring depression in adulthood?
2. Does increased exposure to childhood trauma mediate the association between pre- and postnatal stress and offspring depression?

7.2.2 Study 2: Testing the independent and joint contribution of exposure to neurodevelopmental adversity and childhood trauma to risk of psychotic experiences in adulthood

Both neurodevelopmental adversity (obstetric complications and developmental impairments) and childhood trauma are implicated in psychosis (Croft et al., 2018; Davies et al., 2020), but their joint effects have not been previously examined in detail. It has been proposed that early neurodevelopmental adversity may set the child on a trajectory that is increasingly deviant from typical development, which may increase exposure to traumatic events, and subsequently increase risk of psychosis via a common pathway (Murray et al., 2017; Murray & Fearon, 1999). However, it remains unclear whether children exposed to neurodevelopmental adversity are more likely to experience trauma (mediation effect), or more vulnerable to the effects of trauma (moderation effect).

Research questions:

1. What are the direct and independent effects of neurodevelopmental adversity and childhood trauma on psychotic experiences in adulthood?
2. Does increased exposure to childhood trauma mediate or moderate the association between neurodevelopmental adversity and psychotic experiences in adulthood?

7.2.3 Study 3: Testing the Neurodevelopmental, Trauma and Developmental Risk Factor models of psychosis using a naturalistic experiment

Those who are born VP/VLBW are often exposed to multiple neurodevelopmental adversity, including obstetric complications at birth and developmental impairments in childhood than those born at term (Wolke et al., 2019). Thus VP/VLBW may be used as a proxy indicating multiple neurodevelopmental adversity to investigate the relative contribution of biological and environmental risks for psychosis. Two special cohorts, one born EP and one born VP/VLBW are used to test which model of psychosis (the Neurodevelopmental model (NM), Trauma model (TM) or Developmental Risk Factor model (DRFM)) best explains the onset of psychotic experiences in adulthood. Childhood trauma is represented by childhood peer bullying.

Research questions:

1. Does being born VP/VLBW increase risk of psychotic experiences in adulthood (Is there support for the NM model of psychosis)?
2. Is peer bullying associated with increased risk of psychotic experiences in adulthood (Is there support for the TM model of psychosis)?
3. Are those born VP/VLBW birth exposed to more peer bullying (mediation effect) or more vulnerable to the effects of bullying (moderation effect), and does this explain their increased risk of psychotic experiences in adulthood (Is there support for the DRFM model of psychosis)?

7.2.4 Study 4: Very preterm birth and trajectories of domain-specific self-concept from childhood into adulthood

Given that those born VP/VLBW are disproportionally exposed to a number of neurodevelopmental adversities (Wolke et al., 2019), their self-concept

development may also be adversely affected. Previous research indicated persistently low levels of global self-esteem in this population (Poole, Schmidt, Ferro, et al., 2018; Poole, Schmidt, Saigal, et al., 2018). In contrast, the development of self-concepts in specific areas such as body satisfaction and social acceptance have not been examined previously in this population. Furthermore, rather than being born VP/VLBW per se, it may be other environmental risk factors, such as peer bullying, that best explain differences in the development of self-concept. A person-centred approach is used to identify different patterns of self-concept development in the whole population, before investigating what factors best explain differences in trajectories of self-concept development in this population.

Research questions:

1. Are there different trajectories in the development of self-concept from childhood to adulthood?
2. What factors best explain differences in these trajectories (is it VP/VLBW birth or other individual, social and family factors)?

Chapter 8: Methodology

Two types of cohorts are used to examine the research questions proposed in the previous chapter: a general population-based cohort and two cohorts of children born VP/VLBW or EP. These are described in detail in this chapter, followed by a description of exposures and outcomes included in each study, as well as statistical methodologies used to address each research question.

8.1 Design of the cohorts

8.1.1 General population: The ALSPAC cohort

The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort was established following recommendations by the WHO to conduct more cohort studies to investigate modifiable influences on child development (Boyd et al., 2013). All pregnant women who were resident in the county of Avon, South West England were eligible to participate if their estimated delivery date was between 1 April 1991 and 31 December 1992 (Boyd et al., 2013). This has also been referred to as “Children of the 90s” cohort (Boyd et al., 2013).

Recruitment was opportunistic and the total eligible sample included 20 248 pregnancies (Boyd et al., 2013). Of these, 14 541 pregnancies were successfully recruited antenatally between 1990 and 1992 (phase 1), and 14 676 children had known outcomes, which included 195 twins, 3 triplets and 1 quadruplet (Boyd et al., 2013). These resulted in 14 062 live born children, of which 13 988 were alive at 1 year (Boyd et al., 2013). Further phases of recruitment occurred: at 7 years (phase 2) an additional 456 children from 452 pregnancies were recruited; between 8 and 18 years (phase 3) 257 children from 254 pregnancies were recruited; and at roughly 24 years (phase 4) an additional 195 participants were enrolled (Boyd et al., 2013; Northstone et al., 2019).

The ALSPC cohort has been considered to be representative of the UK general population, although compared to the national average, children enrolled in ALSPAC had higher educational attainment at 16 years compared to non-participants and those who were lost to follow-up (Boyd et al., 2013). Those enrolled in ALSPAC were also more likely to be White girls and less likely to be eligible for free school meals, compared to those who were lost to attrition (Boyd et al., 2013). Attrition rates differed at each stage of assessment, with greatest attrition rates during infancy and transition to adulthood.

Data collection occurred in a number of phases: 4 questionnaires were sent to expecting mothers during pregnancy; 2 were sent at fixed period of 18 and 32 weeks gestation, one sent immediately after enrolment provided enrolment occurred before 14 weeks gestation, and the final questionnaire was only administered if mothers were enrolled before 30 weeks gestation (Boyd et al., 2013). The majority of women received at least three questionnaires (Fraser et al., 2013). For the index children, a total of 68 collection time points occurred between birth and 18 years of age, which included a mixture of child completed questionnaires, clinical assessments and mother/caregiver completed questionnaires about their child (Boyd et al., 2013). Since the age of 18, further clinical assessments were held when participants were approximately 24 years of age (Northstone et al., 2019).

Those who completed clinical assessments on depression and psychotic experiences at 24 years formed the target sample for the studies included in this thesis. Twins were removed from the dataset, along with those who were recruited in later phases (phases 2, 3 and 4), so only singletons and those recruited in phase 1 were part of the target sample. In total, 3506 participants who fulfilled these criteria had data on depression at 24 years, and 3514 had data on psychotic experience at 24 years.

8.1.2 VP/VLBW or EP population

Two special populations of those born VP/VLBW (BLS cohort) or EP (EPICure cohort) were used as proxy measures indicating multiple exposure to neurodevelopmental adversity. These two samples are described in detail below.

8.1.2.1 BLS cohort

The Bavarian Longitudinal Study (BLS) is a prospective population study of children born in South Bavaria between 1 February 1985 and 31 March 1986, who required admission to one of the 17 children's hospitals in the region within the first 10 days of birth (Wolke & Meyer, 1999). Parents were approached within 48 hours of infants' hospital admissions; in total, 70 600 births were registered in this region during this period, and 7505 met the inclusion criteria of the study (Wolke & Meyer, 1999). These ranged from very ill infants born prematurely to infants born at term but required brief in-patient observations (Wolke & Meyer, 1999). Term-born control children were recruited from obstetric units in the same hospital centres or adjacent to the children's hospital during the same period, and included 916 healthy infants who received standard care in postnatal wards (Wolke & Meyer, 1999).

Of the 7505 index children who met the inclusion criteria, 682 were born VP/VLBW and were alive at birth (Wolke, Baumann, et al., 2015; Wolke & Meyer, 1999). Of the 916 eligible healthy infants who served as the control group, 689 were born at term defined as 37 weeks or more in gestation weeks, and 350 were selected and matched to the VP/VLBW group based on sex, SES, marital status of parents and maternal age (Wolke et al., 2015; Wolke & Meyer, 1999). Thus, the initial sample size in the BLS consisted of 682 VP/VLBW and 350 term-born controls.

Apart from prenatal data which were obtained from medical histories in obstetric units, all other peri- and neonatal data were collected prospectively,

and prospective assessments were carried out at 5, 20, 56 months, 6, 8, 13, and 26 years (Wolke & Meyer, 1999). In total, 411 VP/VLBW and 308 term-born controls were eligible for participation in adulthood (26 years), where 186 had died (184 VP/VLBW and 2 term-born controls), 120 were not traceable (80 VP/VLBW and 40 term-born controls), and 7 VP/VLBW participants declined to participate at initial recruitment (Eryigit-Madzwamuse et al., 2015). A further 230 participants (151 VP/VLBW and 79 term-born controls) declined to participate or could not be contacted in adulthood, thus the total number of participants who were assessed in adulthood was 489 (260 VP/VLBW and 229 term-born controls) (Eryigit-Madzwamuse et al., 2015). The target sample consisted of 399 participants (202 VP/VLBW and 197 term-born controls) who completed assessment on psychotic experiences, and 460 (234 VP/VLBW and 226 term-born controls) who completed self-concept assessment in adulthood.

8.1.2.2 EPICure cohort

The EPICure study identified all EP infants born between 20 and 25 weeks gestation across 276 maternity units in the UK and Ireland, from March to December 1995 (Marlow et al., 2005; Wood et al., 2000). In total 4004 infants were identified, and 1185 were alive at birth, of which 843 survived and were admitted to neonatal intensive care units (Wood et al., 2000). Using a combination of early ultrasonography and the date of mother's last menstrual period, 811 infants were identified as having a gestational age between 20 weeks and 25 weeks and 6 days, and the remainder were identified as being born outside that range (Wood et al., 2000). Of the 811 infants eligible for inclusion, 497 died and 315 were discharged from hospital. A further 6 died before assessment at 6 years, and 3 more died between assessments at 6 and 19 years, thus the total eligible sample of EP infants was 306 in adulthood (19 years) (Linsell, 2017; Linsell et al., 2018).

When the EP children were 6 years old, 241 participated in follow-up assessments and of those, 204 were in mainstream schools (Marlow et al.,

2005). For each child in a mainstream school, teachers were asked to identify 3 classmates of the same sex and ethnic group as the EP child closest in birth date, and researchers randomly selected one of them to recruit to the control group, provided they were not born preterm (Marlow et al., 2005). Thus, the control group consisted of term-born children who were recruited at 6 years and matched with the EP group on basic characteristics. In total 160 children were selected to serve as controls at 6 years (Marlow et al., 2005). At 11 years, 110 of the original 160 control group identified at 6 years took part in further assessment, and an additional 43 controls were recruited at 11 years using the same procedure, i.e. a total of 153 term-born controls assessed at 11 years (Johnson et al., 2009). In adulthood (19 years), 65 controls who were previously assessed at 6 or 11 years remained in the study (Linsell, 2017; Linsell et al., 2018).

Drop-out analysis has been performed previously comparing characteristics of children who dropped out compared to those who remained in the study (Johnson et al., 2009). EP children who were not assessed were more likely to be from non-White ethnic group, had an operation for necrotizing enterocolitis, had parents who were unemployed, had lower cognitive scores and more cognitive impairments, defined as having an IQ score of 2 standard deviation or below compared to the norm (Johnson et al., 2009). Term-born controls who were not assessed at 11 years were also found to have lower cognitive scores (Johnson et al., 2009).

In total, 120 EPs and 64 term-born controls completed data on psychotic experiences at 19 years. A summary of cohort profiles and sample size included in the studies in this thesis can be found in Table 13.

Table 13.

Description of cohorts.

Cohort	Year of recruitment	Population	Sample size and outcome examined
ALSPAC	1991-1992	General population-based cohort	3506 (Depression) 3514 (Psychotic experiences)
BLS	1985-1986	VP/VLBW with term-born controls	399 (Psychotic experiences) 460 (Self-concept)
EPICure	1995	EP with term-born controls	184 (Psychotic experiences)

8.2 Measures

8.2.1 Outcomes of interest

Study 1: Depression

Clinical diagnosis of depression at 24 years is determined by Computerised Interview Schedule – Revised (CIS-R) in the ALSPAC cohort. Depression diagnosis is based on the International Classification of Diseases – 10th revision (ICD-10) criteria and categorised as mild, moderate or severe, based on depressive symptoms in the last 2 weeks (T. Bell et al., 2005; Dantchev et al., 2019; Patton et al., 1999). The CIS-R has received good validation in the literature and is one of the most widely used assessment tool for assessing psychopathology (T. Bell et al., 2005; Patton et al., 1999). A binary variable was used to represent no depression or any (mild, moderate or severe) depression. Further details can be found in chapter 9.

Study 2 and 3: Psychotic Experiences

Psychotic experiences (PE) represent symptoms of psychosis that are subclinical and are not considered severe or frequent enough to meet the clinical threshold for psychotic disorders (van Os et al., 2009). It is considered

to be on the psychosis continuum and include assessments on the same symptoms as those of psychotic disorders, including hallucinations, delusions and thought disorders (van Os et al., 2009). This was assessed in all three cohorts (ALSPAC, BLS and EPICure), using the Psychosis-Like Symptom Interview, a semi-structured interview (Horwood et al., 2008; Sullivan et al., 2020; Zammit et al., 2013). Coding of PE followed the definitions and rules for the SCAN (Schedules for Clinical Assessment in Neuropsychiatry), and grouped into those with suspected or definite PE, or no PE present (Horwood et al., 2008; Sullivan et al., 2020; Zammit et al., 2013). This has been shown to have very good inter-rater and test-retest reliability in both childhood and adulthood (Horwood et al., 2008; Sullivan et al., 2020; Zammit et al., 2013), and further details can be found in chapter 10.

Study 4: Self-concept

Self-concept refers to individuals' evaluations of themselves in particular areas or for specific attributes (King, 1997). Self-concept was only assessed in the BLS cohort, and include areas of body satisfaction, social acceptance, cognitive abilities, motor performance and maternal/family relationships (Harter & Pike, 1984). These were assessed at four time periods: 6, 8, 13 and 26 years, apart from body satisfaction which was not assessed at 6 years. Two different instruments were used: the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children (at 6 and 8 years) (Harter & Pike, 1984), and the German adaptation of Nicholls' self-concept of attainment (at 13 and 26 years) (Nicholls, 1978). Both assessed self-concept across the same five domains, although the number of items differed. Further detailed description can be found in chapter 11.

8.2.2 Exposures of interest

8.2.2.1 Biological risks

Two main indicators of biological risks are considered: prenatal maternal stress and neurodevelopmental adversity. Sources of prenatal maternal stress

include both prenatal maternal depression and family adversity, and neurodevelopmental adversity include a combination of obstetric complications and developmental impairments.

Study 1: Prenatal maternal stress: Maternal depression and family adversity

Both maternal depression and family adversity represent stressful events for the mother and are assessed in pregnancy and in the postnatal period (up to 2 years). Detailed descriptions of the instruments can be found in chapter 9. Maternal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS), a well validated measure of prenatal and postnatal depression in mothers (Cox et al., 1987; Hewitt et al., 2009). Family adversity was a composite measure consisting of living conditions, criminal behaviour, relationship problems and substance misuse (Steer et al., 2004), and computed as an ordered variable representing no adversity, few adversities (1-2 adversities) and many adversities (3 or more adversities).

Study 2, 3 and 4: Neurodevelopmental adversity

Neurodevelopmental adversity consisted of indicators of obstetric complications and developmental impairments in childhood. Detailed descriptions are given in study two and three and can be found in chapter 10. Obstetric complications represented birth-related adversities, including preterm birth (<37 weeks gestation), low birth weight (<2500 grams), exposure to maternal influenza during pregnancy, and whether baby was resuscitated at birth. Childhood developmental impairments represented cognitive and motor impairments in childhood (at 8 years). These were assessed using a standardised IQ test (Wechsler et al., 1992) and motor performance test (Movement Assessment Battery for Children; M-ABC) (Henderson & Sudgen, 1992). Those who scored either one standard deviation below the average IQ in the sample or scored below the 15th percentile of the sample on motor performance were grouped as having developmental impairments.

As the VP/VLBW population are naturally exposed to a number of obstetric complications and experience significant developmental impairments in childhood, they were used as a proxy measure for neurodevelopmental adversity and was the main biological risk examined in study 3 and 4.

8.2.2.2 Environmental risks

Childhood trauma is investigated across all studies in this thesis as the primary environmental risk and included both caregiver-inflicted and peer-inflicted trauma. Cohorts assessed childhood trauma at different periods but all up to 17 years of age (Croft et al., 2018; Wolke et al., 2015). Both the BLS and EPICure cohort assessed peer bullying only (Wolke et al., 2015), whilst the ALSPAC cohort assessed both caregiver and peer-inflicted trauma (Croft et al., 2018). Detailed description can be found in the methods section of each study in chapters 9, 10 and 11.

Coding of childhood trauma in the ALSPAC cohort reflected increased exposure to multiple traumas to examine the dose-response effect of childhood trauma (no exposure, exposure to one trauma, exposure to two or more traumas). Peer bullying in BLS and EPICure cohorts were coded as no exposure, exposure at one time period (childhood or adolescence), and exposure at both time periods (childhood and adolescence), which reflected the chronicity of exposure.

8.2.3 Other control variables

A number of control variables are included depending on the research question and outcome of interest. All studies controlled for sex of the participants and indicators of SES. Studies using ALSPAC cohort further controlled for genetic risks given the genetic heritability of depression and psychosis (Flint & Kendler, 2014; Sieradzka et al., 2015). Detailed descriptions of control variables can be found in each study in chapters 9, 10 and 11.

8.3 Statistical analysis

8.3.1 Statistical packages

IBM SPSS Statistics version 26 and 27 were used for all data cleaning and computation of variables. Statistical analyses were primarily conducted in R (versions 3.5.0, 3.6.0 and 3.6.3), and Mplus version 8 was also used in study 4 to model the growth trajectory of self-concept.

8.3.2 Statistical approaches

A combination of variable-centred and person-centred approaches are used to perform longitudinal data analyses. Variable-centred approach examines statistical associations between factors, such as the relationship between a risk factor and an outcome (Miller-Lewis et al., 2013). Person-centred approach on the other hand examines growth within a population and identify groups of people who develop in similar ways (Chow & Kennedy, 2014). A variable-centred approach can then be used to investigate what differentiates groups of people with different trajectories. The first three studies included in this thesis all used variable-centred approaches, while study four used both person-centred and variable-centred approach. The following statistical approaches were used in each study:

- Study 1: Logistic regression models; path analysis
- Study 2: Logistic regression models (including moderation), path analysis
- Study 3: Logistic regression models (including moderation), mediation analysis
- Study 4: Latent Class Growth Analysis, logistic regression models, mediation and path analysis

8.3.3 Missing data

Missing data is common in longitudinal research spanning several decades, and may affect the statistical power, although simulation of selective drop-out in longitudinal studies found that it does not reduce the validity of predicting outcomes (Wolke et al., 2009). To handle missing data, multiple imputation by chained equation (MICE) was carried out in R to impute all missing data on predictors, provided data is deemed likely to be missing at random. Multiple datasets are generated based on multiple predictions for each missing variable, and results are pooled together to account for uncertainties during the imputation process and to reduce bias (Azur et al., 2011; Buuren & Groothuis-oudshoorn, 2011). Missing data on outcome variables were not imputed, and the maximum sample size in each study was the total number of participants with complete data on the outcome of interest.

8.4 Summary

Three different longitudinal cohorts were used: one based on the general population (ALSPAC) and two on special populations (BLS: VP/VLBW; EPICure: EP) with term-born controls. Age of assessment in adulthood ranged from 19 years in EPICure, 24 years in ALSPAC, and 26 years in BLS. Four studies were designed for this thesis: the first two investigated outcomes in depression and psychotic experiences in the general population using data from ALSPAC. Biological risks included prenatal stress and exposure to neurodevelopmental adversity, and environmental risks included childhood trauma (both caregiver- and peer-inflicted trauma). The third study also examined psychotic experiences but using a special population (VP/VLBW, EP) from the BLS and EPICure cohorts, which acted as a proxy measure for neurodevelopmental adversity, and childhood trauma was represented by peer bullying. The final study examined self-concept development from childhood to adulthood in the BLS cohort, and the relative contribution of biological (VP/VLBW) and environmental factors (peer bullying) in the development of self-concept.

A number of different methodologies are used to address different research questions in each study. All studies used logistic regression analyses to first model the effect of biological and environmental risk on each outcome, and the mediating effect of childhood trauma was examined using either path analysis or mediation analysis (product of path coefficient method). Studies two and three further examined both the mediating and moderating influence of childhood trauma on psychotic experiences. A summary of study description can be found in Table 14.

Table 14.

Study descriptions.

Study	Cohort	Outcome	Biological risk	Environmental risk	Other variables	Statistical method
1	ALSPAC	Depression (24 years)	Prenatal stress (Maternal depression; family adversity)	Childhood trauma (caregiver- and peer-inflicted)	Sex, genetic risks	Logistic regression models; path analysis
2	ALSPAC	Psychotic experiences (24 years)	Neurodevelopmental adversity (obstetric complications; developmental impairments)	Childhood trauma (caregiver- and peer-inflicted)	Sex; family history of schizophrenia; maternal smoking; family adversity; maternal age; genetic risks	Logistic regression models with interaction; path analysis
3	BLS; EPICure	Psychotic experiences (19 and 26 years)	EP/VP/VLBW	Childhood trauma (Peer bullying)	Sex; SES	Logistic regression models with interaction; mediation analysis
4	BLS	Self-concept (6 to 26 years)	VP/VLBW	Childhood trauma (Peer bullying)	Sex; cognitive and motor impairments; maternal sensitivity; SES	Latent class growth analysis; logistic regression models, mediation/path analysis

Chapter 9: Prenatal stress, childhood trauma and offspring depression

9.1 Study 1: Prenatal stress and offspring depression in adulthood: the mediating role of childhood trauma

9.1.1 Abstract

Objective: There is repeated evidence for a prenatal programming effect for the development of offspring depression. However, examination of environmental influences along the pathway to offspring depression is sparse. The aim of the current study is to investigate the direct and indirect effects of pre- and postnatal stress on offspring depression in adulthood, via increased exposure to childhood trauma. **Methods**: A large longitudinal population-based cohort (N=3506) was followed up from birth and attended clinical assessment at 24 years. Diagnosis of depression was derived using the International Classification of Diseases – 10th revision (ICD-10). Two separate sources of pre- and postnatal stress were examined – maternal depression and family adversity, and childhood trauma was assessed prospectively across childhood until 17 years. **Results**: Both pre- and postnatal maternal depression and family adversity were associated with offspring depression at 24 years in simple logistic regression models. When all pathways were modelled simultaneously, only childhood trauma was directly associated with offspring depression, and mediated all pathways from both sources of pre- and postnatal stress to offspring depression (between 7-16% of the total effect mediated). Sensitivity analysis on specific trauma types found stronger evidence for a mediated pathway via physical, emotional abuse and peer bullying, compared to sexual abuse, emotional neglect and domestic violence. **Conclusions:** These findings indicate that reducing childhood trauma could be a target to decrease depression in the general population, and that the focus should also be on families at high risk of experiencing pre- or postnatal stress, to provide them with better support.

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9.1.2 Introduction

There is substantial evidence in the literature that adverse prenatal environment is associated with diseases and mortality in adulthood (A. Lewis et al., 2015). This has been formulated into the foetal programming hypothesis, which postulates that intrauterine adversity, for example growth restriction, can alter the biological systems of the developing child and increase their susceptibility to future diseases (D. J. Barker, 2007; O'Donnell & Meaney, 2016; Räikkönen & Pesonen, 2009; Van den Bergh et al., 2017). More recently the theory has been applied to the study of mental health disorders such as depression, and other sources of intrauterine adversity have also been investigated, in particular maternal stress in the prenatal period (O'Donnell & Meaney, 2016; Räikkönen & Pesonen, 2009).

Prenatal stress is often indicated by maternal mental health (e.g. depression) and family adversity (e.g. social and economic difficulties) in the literature (Lereya & Wolke, 2013). Although closely associated with each other, both have been independently associated with offspring outcomes (Lereya & Wolke, 2013) and can be considered as two separate sources of stress, one from psychological and one from social/economic stress. There is strong evidence that prenatal maternal depression is associated with offspring depression in adulthood (A. Rogers et al., 2020; Tirumalaraju et al., 2020). Prenatal family adversity such as financial or relationship difficulties have also been associated with offspring depression even after accounting for maternal mental health (Kingsbury et al., 2016; Najman et al., 2017). Both sources of prenatal stress have also been associated with alterations to the hypothalamic-pituitary-adrenal (HPA) axis (Osborne et al., 2018; Van den Bergh et al., 2008), increased inflammation (Plant et al., 2016), and

hyperresponsivity in the amygdala in the offspring (Knaap et al., 2018), offering support for a programming effect of prenatal stress on offspring depression through biologically mediated mechanisms (Hantsoo et al., 2019; D. R. Kim et al., 2015).

There is also evidence for the continuity of prenatal maternal depression into the postnatal period (E. D. Barker et al., 2011; Lereya & Wolke, 2013). Both pre- and postnatal maternal depression are also independently associated with emotional problems in childhood and psychopathology in adulthood, with postnatal depression proposed to act via environmental influences such as altered parenting behaviours or family environments (Munhoz et al., 2017; Pearson et al., 2013; Rees et al., 2019). Indicators of family adversity such as social and economic difficulties have also been shown to have a moderate persistence from the prenatal to postnatal period (Lereya & Wolke, 2013). Considering that both sources of stress continues into the postnatal period, it is important to account for these in order to examine the effect of prenatal stress independently from postnatal influences.

These early sources of stress may continue to exert influences throughout the developmental periods. However, periods beyond the early postnatal years are rarely examined when investigating the longitudinal association between prenatal stress and offspring depression. One of the most consistent childhood risk factors for depression is exposure to trauma (Copeland et al., 2018), which can lead to similar alterations to biological systems implicated in depression (Cattaneo et al., 2015). The evidence on childhood trauma is especially strong for caregiver-inflicted trauma, such as emotional, physical and sexual abuse, with lasting effect into adulthood (Lindert et al., 2014; Mandelli et al., 2015). Peer bullying has also been associated with increased risk of depression, even after controlling for childhood psychiatric disorders (Copeland et al., 2013) and genetic liability (Singham et al., 2017), consistent with a causal effect (S. E. Moore et al., 2017).

There is some evidence to suggest that childhood trauma may also mediate the effect of prenatal stress on offspring depression. Prenatal maternal depression has been associated with increased exposure to childhood trauma, possibly due to poorer attachment, maladaptive parenting and a programming effect of prenatal stress on offspring temperament (Azeredo et al., 2017; Lereya & Wolke, 2013; Pawlby et al., 2011). An indirect pathway has been found from maternal prenatal depression to offspring depression in adulthood via increased exposure to childhood trauma (Plant et al., 2015). However, sample size was small (N=103) and specific trauma types were not examined. Furthermore, given the moderate heritability of depression (Flint & Kendler, 2014), part of the association between prenatal maternal depression and offspring depression may be explained by genetic liability, which should be controlled for. Lastly, family adversity was not examined independently from maternal depression when testing the mediating effect of childhood trauma, thus it would be important to investigate whether the same pathways are found from social/economic stress as well as psychological stress.

The aim of this prospective longitudinal study was to the examine the direct effects of pre- and postnatal stress, as indicated by maternal depression and family adversity, and their indirect effects via childhood trauma on offspring depression in adulthood. In a large population-based sample followed up from pregnancy to 24 years, we first investigated the individual effects of pre- and postnatal stress and childhood trauma on offspring depression at 24 years. Secondly, we examined childhood trauma as a mediator in the pathway from pre- and postnatal stress to offspring depression.

9.1.3 Methods

9.1.3.1 Sample

The sample was drawn from the ALSPAC cohort, a prospective population study of 14 541 pregnant women who resided in the region of Avon, Southwest of England, with expected delivery dates between April 1, 1991 to December 31, 1992, and has been described previously (Boyd et al., 2013;

Fraser et al., 2013; Northstone et al., 2019). In total, 3506 participants who attended clinical assessment at 24 years were included. A fully searchable data dictionary and variable search tool can be found on the study website (http://www.bristol.ac.uk/alspac/researchers/our-data). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Bristol, a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants and parents following the recommendations of the ALSPAC Ethics and Law Committee at the time.

9.1.3.2 Measures

Depression at 24 years

Participants attended a study clinic at 24 years and the Computerised Interview Schedule – Revised (CIS-R) was used to derive diagnosis for depression based on the ICD-10 criteria (T. Bell et al., 2005; Patton et al., 1999). It is a self-administered computerised interview and is the standardised tool for assessing common mental health disorders (T. Bell et al., 2005; Patton et al., 1999). Severity of depression was categorised into mild, moderate and severe according to symptoms experienced in the past two weeks, using the ICD-10 criteria. The outcome of interest in the current study was a binary variable indicating no depression diagnosis or any depression diagnosis (mild, moderate or severe) (Dantchev et al., 2019).

Maternal depression

Maternal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-reported depression questionnaire that is well validated for use during pregnancy and in the post-partum period (Cox et al., 1987). Each item was scored from 0 to 3 and referred to feelings over the past

week. Traditionally a cut-off score of 13 or more has been used to indicate clinically significant symptoms (Hewitt et al., 2009; Matthey et al., 2006), however in the current study continuous scores are used to take into account subtle variations in symptoms. EPDS scores are averaged across two periods during pregnancy (at 18 and 32 weeks) and three periods postnatally (2, 8 and 21 months) to indicate prenatal and postnatal maternal depression.

Family adversity

Family adversity was measured during pregnancy and in the postnatal period using the long version of the Family Adversity Index (FAI), a cumulative index developed from the ALSPAC data based on Rutter's indicators of adversity (Steer et al., 2004). The original long index is comprised of 18 items including age of mother, housing situation, educational qualifications, financial situation, relationship with partner, family characteristics, social network, substance abuse, criminal behaviours and maternal psychopathology (Bowen et al., 2005). As maternal depression was investigated as a separate source of stress in the current study, the scale of maternal psychopathology was removed from the FAI to prevent over-controlling for the effect of maternal mental health. Thus, the FAI index comprised of 17 items and ranged from 0 to 17. Prenatal FAI indicates adversities experienced between 8- and 32-weeks' gestation, and postnatal FAI indicates adversities between 0-2 years of age. The distribution of the FAI within the ALSPAC cohort showed a non-normal, positively skewed distribution, and so was categorised into no adversity (score of 0), few adversities (score of 1-2), and many adversities (score of 3 or more).

Trauma

Childhood trauma experienced up to 17 years was derived in a previous study from 121 questions completed by either parents or participants on the frequency and severity of caregiver-inflicted trauma (types: physical abuse, emotional abuse, sexual abuse, emotional neglect, domestic violence) and peer bullying (Croft et al., 2018). A detailed description of the trauma

measure has been described previously (Croft et al., 2018). A composite measure of exposure to any trauma (caregiver or peer inflicted) was derived from these individual trauma exposures, and categorised into no exposure, exposure to one trauma, and exposure to two or more traumas. Specific trauma types were assessed in a sensitivity analysis.

Other control variables

Sex of the participant was coded as male or female at birth. Polygenic risk scores indexing the participants' cumulative genetic vulnerability for major depressive disorder (MDD) and neuroticism were derived from genome-wide association study (GWAS), which has been reported previously (H. J. Jones et al., 2018). Scores were standardised using a list of SNPs associated with these outcomes in the discovery samples at a p-threshold of 0.05 (H. J. Jones et al., 2018).

9.1.3.3 Statistical analysis

All analyses were conducted in R version 3.6.3. Simple logistic regression models were first used to examine the individual effect of each risk factor (prenatal and postnatal maternal depression, prenatal and postnatal FAI, childhood trauma) on offspring depression. Ordinal logistic regression models also examined the association between each pre- and postnatal risk and childhood trauma. Childhood trauma was coded as an ordered variable with linear terms, and proportional odds assumption was not violated.

Path analysis was used to estimate direct and indirect effects (product of coefficients method) from pre- and postnatal stress via childhood trauma to depression at 24 years, using the "semTools" package. Simple path models were first examined from each of the four indicators of pre- and postnatal stress to offspring depression via childhood trauma. These four pathways were then modelled simultaneously in one path model, controlling for the effects of covariates. Missing data on predictor variables were handled using multivariate imputation by chained equations ("mice" package) with 40

imputed datasets. Data were imputed up to the total sample with complete data on depression at 24 years (N=3506) using all predictors included in the analysis. Standardised path coefficients and 95% confidence intervals are reported.

Sensitivity analysis

We further examined the indirect effect of each specific trauma in separate path models. The same model was specified as above, with exposure to childhood trauma replaced by exposure to each specific trauma, and all paths from pre- and postnatal stress were modelled simultaneously.

9.1.4 Results

9.1.4.1 Sample characteristics

Characteristics of people lost to attrition have been reported previously in this cohort, with those dropping out more likely to be from households with financial difficulties, lower educational qualifications, poor housing and of mothers who were more likely to have experienced psychopathology during pregnancy (Wolke et al., 2009). The proportion of missing data in the current sample ranged from 0.2% to 27%.

The majority of participants were female (62.4%). More family adversities were reported during the postnatal period compared to prenatal period (19.5% vs 8.1% who experienced 3 or more adversities), and 29% reported multiple trauma exposure (exposed to two or more trauma) up to 17 years. The prevalence of depression was 10.8% at 24 years (Table 15), consistent with previous reports (Dantchev et al., 2019; Fernandes et al., 2020).

Table 15.

Study 1: Sample characteristics (N=3506).

	n	%
Sex (Female)	2186	62.4
Prenatal FAI (N=3390)		
1-2 adversities	1164	34.3
Three or more adversities	273	8.1
Postnatal FAI (N=3428)		
1-2 adversities	1539	44.9
Three or more adversities	667	19.5
Childhood trauma (N=3500)		
One trauma	1023	29.2
Two or more trauma	1016	29.0
Depression at 24	379	10.8
	M	SD
Prenatal maternal depression (N=3404)	6.45	4.26
Postnatal maternal depression (N=3427)	5.48	4.02
Standardised genetic risk score for MDD (N=2625)	-0.01	1.01
Standardised genetic risk score for Neuroticism (N=2625)	-0.04	1.00

9.1.4.2 Risk factors for offspring depression

Simple logistic regression models showed that all risk factors (prenatal and postnatal maternal depression, prenatal and postnatal FAI, childhood trauma) were associated with offspring depression at 24 years. Childhood trauma was associated with the highest odds of offspring depression (Table 16).

Table 16.

Study 1: Simple logistic regressions on the effect of pre- and postnatal maternal depression/FAI and childhood trauma on depression at 24 years (Multiple imputation, N=3506).

	Depression		
	OR	95% CI	p-value
Prenatal maternal depression[a]	1.05	1.02 – 1.08	<0.001
Postnatal maternal depression[a]	1.04	1.01 – 1.07	0.002
Prenatal FAI	1.53	1.19 – 1.97	0.001
Postnatal FAI	1.49	1.21 – 1.83	<0.001
Childhood trauma	1.73	1.46 – 2.07	<0.001

[a] Effect is associated with each increased score in the Edinburgh Postnatal Depression Scale.

9.1.4.3 Risk factors for childhood trauma

Maternal depression and family adversity during both the pre- and postnatal periods were all associated with increased exposure to childhood trauma, with similar effect sizes found between pre- and postnatal periods (Table 17).

Table 17.

Study 1: Simple ordinal logistic regressions on the effect of pre- and postnatal maternal depression/FAI on childhood trauma (Multiple imputation, N=3506).

	Childhood trauma		
	OR	95% CI	p-value
Prenatal maternal depression[a]	1.06	1.05 – 1.07	<0.001
Postnatal maternal depression[a]	1.07	1.05 – 1.08	<0.001
Prenatal FAI	1.75	1.58 – 1.94	<0.001
Postnatal FAI	1.78	1.65 – 1.92	<0.001

[a] Effect is associated with each increased score in the Edinburgh Postnatal Depression Scale.

9.1.4.4 Path analysis

Simple path analyses found direct and indirect effects of prenatal maternal depression and prenatal FAI on offspring depression via childhood trauma (see Appendices A – D). Indirect effects were also found from postnatal maternal depression and postnatal FAI via childhood trauma, but there was weaker evidence for their direct effects. When all pathways were modelled simultaneously and adjusted for control variables, no direct effects were

found from pre- and postnatal maternal depression and FAI. However, indirect pathways were found from all four indicators of pre- and postnatal stress to offspring depression via childhood trauma (Table 18, Fig. 3). The strongest indirect pathway was from postnatal FAI via childhood trauma, which mediated 16% of the total effect of pre- and postnatal stress on offspring depression. This was calculated by dividing the indirect effect by the total effect. Other indirect pathways (from pre- and postnatal maternal depression, prenatal FAI) via childhood trauma mediated between 7-10% of the total effect on offspring depression at 24 years.

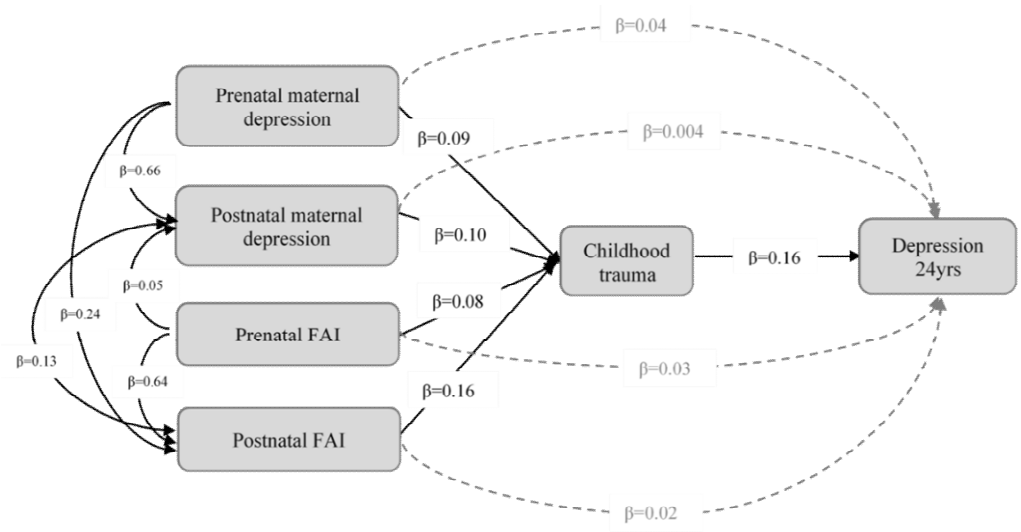

Figure 3.

Study 1: Indirect effects from pre- and postnatal maternal depression/FAI to depression at 24 years via childhood trauma.

Note. Standardised path estimates are shown, and all paths were modelled simultaneously, controlling for sex, genetic risk for MDD and neuroticism.

Table 18.

Study 1: Path analysis showing the direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via childhood trauma (Multiple imputation, N=3506).

	SE	95% CI	p-value
Depression[a] ~			
Prenatal maternal depression	0.04	-0.04 – 0.12	0.338
Postnatal maternal depression	0.004	-0.07 – 0.08	0.912
Prenatal FAI	0.03	-0.04 – 0.11	0.401
Postnatal FAI	0.02	-0.05 – 0.09	0.595
Childhood trauma	0.16	0.10 – 0.23	<0.001
Childhood trauma[a] ~			
Prenatal maternal depression	0.09	0.04 – 0.14	0.001
Postnatal maternal depression	0.10	0.05 – 0.16	<0.001
Prenatal FAI	0.08	0.03 – 0.13	0.002
Postnatal FAI	0.16	0.11 – 0.20	<0.001
Postnatal FAI~			
Prenatal FAI	0.64	0.59 – 0.68	<0.001
Prenatal maternal depression	0.24	0.20 – 0.29	<0.001
Postnatal maternal depression~			
Prenatal FAI	0.05	0.03 – 0.08	<0.001
Prenatal maternal depression	0.66	0.64 – 0.69	<0.001
Covariance			
Postnatal FAI ~~ Postnatal maternal depression	0.13	0.10 – 0.15	<0.001
Indirect effect[a]			
Prenatal maternal depression → Childhood trauma → Depression	0.015	0.004 – 0.025	0.008
Postnatal maternal depression → Childhood trauma → Depression	0.017	0.006 – 0.027	0.002
Prenatal FAI → Childhood trauma → Depression	0.012	0.003 – 0.022	0.012
Postnatal FAI → Childhood trauma → Depression	0.026	0.013 – 0.038	<0.001
Total effect	0.163	0.091 – 0.236	<0.001

[a]Pathways modelled simultaneously, and controlled for sex, genetic risk score for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression, and sex (male) and genetic risk for neuroticism on trauma.

9.1.4.5 Sensitivity analysis

Indirect pathways were found via physical abuse, emotional abuse and peer bullying when specific trauma types were examined (Appendices E – J). Physical abuse mediated the association between postnatal FAI and offspring depression and accounted for 14% of the total effect. Emotional abuse mediated the association between pre- and postnatal maternal depression as well as postnatal FAI on offspring depression, accounting for 9% to 17% of the total effect. Peer bullying further mediated the association between prenatal maternal depression and offspring depression and accounted for 6% of the total effect.

9.1.5 Discussion

The current study investigated the longitudinal association between pre- and postnatal stress (maternal depression and family adversity), childhood trauma and offspring depression in adulthood. Although both sources of pre- and postnatal stress were associated with offspring depression, when all pathways were simultaneously modelled, their direct effects were attenuated, and only indirect pathways were found from each of them to offspring depression via increased exposure to childhood trauma.

Maternal prenatal depression was initially associated with increased risk of depression in the offspring, consistent with previous research and the programming model (D. R. Kim et al., 2015; Plant et al., 2015; A. Rogers et al., 2020). Every increased score in mother's depressive symptoms was associated with a 5% increased risk of offspring depression at 24 years, and both direct and indirect effects were found from prenatal maternal depression to offspring depression via childhood trauma. However, this direct effect was reduced once other pathways from postnatal maternal depression and FAI were controlled for, and only childhood trauma was directly associated with offspring depression. This is consistent with previous findings (Plant et al., 2015) and suggest that part of the effect of prenatal maternal depression may be attributed to a continuity of depression in the postnatal period as well as

its association with family adversity, which has been shown previously (Najman et al., 2017).

Childhood trauma has also been consistently associated with risk of depression in adulthood in previous research (Copeland et al., 2018; Sahle et al., 2021) and has been found to have a non-specific risk on other mental health disorders as well (Croft et al., 2018; Sahle et al., 2021). With each additional trauma experienced, there was a 73% increased risk of depression at 24 years, and suggest a dose-response effect which has been reported previously (Copeland et al., 2018; Croft et al., 2018). Indirect pathways were found from all indicators of pre- and postnatal stress to offspring depression via increased exposure to childhood trauma. This is consistent with previous research on prenatal maternal depression (Plant et al., 2015) and extends this indirect pathway to family adversity as well, which has been shown previously to be associated with increased risk of childhood trauma (Conrad-Hiebner & Byram, 2020; Lereya & Wolke, 2013). These suggest potentially separate pathways from psychological stress and social/economic stress, involving both biological and environmental mechanisms. Furthermore, although the proportion of mediated effect varied, these findings consistently support the role of childhood trauma as an important environmental factor that should be routinely examined in longitudinal studies on the effects of prenatal stress on offspring depression.

Analysis of specific trauma revealed stronger evidence for indirect effects from postnatal FAI via physical abuse, and from postnatal maternal depression and FAI via emotional abuse. This suggests that environmental factors, such as increased harsh parenting and reduced emotional availability in mothers with depression and families with increased social and economic stress contributes to childhood trauma and offspring depression (Conrad-Hiebner & Byram, 2020; Conron et al., 2009; Kluczniok et al., 2016). Emotional abuse and peer bullying further mediated the association between prenatal maternal depression and offspring depression, even after accounting for postnatal influences. Biological mechanisms have been previously

proposed, such as a programming effect of prenatal maternal depression on infant temperament and emotional reactivity, which may lead to maladaptive parenting and increase vulnerability to peer bullying (Lereya & Wolke, 2013; O'Connor et al., 2003). Further investigation is needed to better understand biological and environmental mechanisms associated with different types of trauma.

9.1.5.1 Strengths and limitations

The longitudinal nature of the study and prospectively measured data allowed the testing of causal pathways from pre- and postnatal stress to offspring depression in adulthood. The large sample size allowed investigation on the specificity of trauma in a sensitivity analysis, which extends previous research (Plant et al., 2015). The finding of a mediated pathway from prenatal maternal depression to offspring depression via childhood trauma further suggest the involvement of biological mechanisms, such as a programming effect, as some of the indirect effect remained even after postnatal influences were modelled simultaneously in one model. Lastly, the inclusion of family adversity allowed examination of social/economic sources of stress separately to maternal depression and suggest that both may contribute independently to offspring depression via childhood trauma.

Some limitations include the high attrition rate over a period of 24 years which is unavoidable in longitudinal studies, with those dropping out more likely to be from households with lower SES and increased maternal psychopathology (Wolke et al., 2009). It has been previously shown in simulations that selective dropout does not affect predictive associations (Wolke et al., 2009), although the statistical power of maternal depression and family adversity on offspring depression may be affected. Secondly, the measure of trauma used in the current study included abuse or neglect from both the mother and partner (Croft et al., 2018). It is possible therefore that the association between maternal and offspring depression, and apparent mediation via childhood trauma, is confounded by partner-inflicted abuse

leading to depression in both the mother and offspring. Lastly, there may be other indirect pathways or confounding variables that are associated with increased exposure to childhood trauma, such as childhood psychiatric problems and genetic risks for other mental health vulnerabilities not considered in this study (Schoeler et al., 2019).

9.1.5.2 Conclusion

The current study investigated the direct and indirect effects of pre- and postnatal stress on offspring depression in adulthood via childhood trauma. When all pathways were modelled simultaneously, no direct paths were found from pre- and postnatal maternal depression or family adversity to offspring depression, but all four indirect pathways were found via childhood trauma. This suggests that the risk attributed to pre- and postnatal stress can be partly explained by increased exposure to childhood trauma, which is a potentially modifiable factor. These findings also highlight the importance of interventions to reduce childhood trauma, such as better access to interventions for pregnant mothers with depression, as well as increased family and social support for those at risk of economic and social adversity.

Chapter 10: Neurodevelopmental adversity, childhood trauma and psychosis

10.1 Study 2: Testing the independent and joint contribution of exposure to neurodevelopmental adversity and childhood trauma to risk of psychotic experiences in adulthood

10.1.1 Abstract

Exposure to neurodevelopmental adversity and childhood trauma are both independently associated with psychosis. However, there is little research on the mechanism underlying their relationship with each other. The current study investigated both the independent and joint effects of neurodevelopmental adversity and childhood trauma to better understand the aetiology of psychosis. A large population-based cohort (N=3514) followed from birth was assessed on psychotic experiences (PE) at 24 years. Neurodevelopmental adversity included obstetric complications (birth weight, gestational age, in-utero influenza exposure, resuscitation) and developmental impairment (cognitive and motor impairments). Trauma exposure included caregiver and peer inflicted trauma up to 17 years. Multiple regression models tested their independent and interactive effect on PE, and path analysis estimated the indirect effect of neurodevelopmental adversity on PE via trauma. Neurodevelopmental adversity (OR = 1.32, 95%CI: 1.08 – 1.62) and trauma (OR = 1.97, 95%CI: 1.65 – 2.36) independently increased the odds of PE. There was also an indirect relationship between neurodevelopmental adversity and PE via increased exposure to childhood trauma (β = 0.01, 95%CI: 0.004 – 0.024). In particular, peer bullying mediated the association between developmental impairment to PE (β = 0.02, 95%CI: 0.01 – 0.03). In conclusion, children with neurodevelopmental adversity, in particular those with developmental impairment, are more likely to be exposed to trauma. This new aetiological understanding of psychosis

suggest that PE may be partially modifiable through reducing exposure to peer bullying especially in children with developmental impairment.

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10.1.2 Introduction

A range of factors have been associated with the development of psychosis, including neurodevelopmental (e.g. obstetric complications, premature birth), trauma (e.g. bullying) and genetic risks (McCutcheon et al., 2020). Some of these factors have been grouped into meaningful frameworks based on theoretical models to explain the aetiology of psychosis. These models include the Neurodevelopmental model (NM) and the Trauma model (TM) (Murray & Lewis, 1987; Read, 1997), two of the most widely cited models of psychosis. However, more recently it has been recognised that these models are not mutually exclusive, and the Developmental Risk Factor model (DRFM) was proposed which emphasises the joint effects of neurodevelopmental and trauma related factors (Murray & Fearon, 1999). It remains unclear what the relative contribution of these factors are and how they may work together in their association with psychosis.

Both neurodevelopmental and trauma related factors have been implicated in the aetiology of psychosis. Brain insults that occur during early development from neurodevelopmental adversity can alter the formation and activity of neural circuits (Murray et al., 1992). Brain abnormalities have been identified in patients with schizophrenia (De Peri et al., 2012), and obstetric complications and birth related factors, such as perinatal infections, premature birth, and low birth weight have all been associated with increased risk of psychosis (Davies et al., 2020; Nosarti et al., 2012; Thomas et al.,

2009). Exposure to these early adversities may also lead to cognitive and motor impairments in childhood (Johnson et al., 2015). These are often considered as neurological soft signs of psychosis, and have been reported to precede the onset of psychosis (P. Jones et al., 1994).

Childhood trauma has also been consistently associated with psychosis (Dvir et al., 2013). One putative mechanism is the theory of social defeat, where prolonged exposure to victimisation may lead to hostile interpretations of social situations and the intention of others (Selten et al., 2013). Some recent meta-analyses have shown a two to four times increased risk of psychosis following exposure to any childhood trauma, whether from caregivers (e.g. abuse) or peers (e.g. bullying) (Dam et al., 2012; Varese, Smeets, et al., 2012). There is also evidence of a cumulative effect, with greater risk associated with increased level/dose of exposure to trauma that persists even when adjusted for genetic risk (Croft et al., 2018).

More recently authors have described how multiple risk factors could impact on a common biological pathway that could lead to psychosis (Murray et al., 2017; Murray & Fearon, 1999). As proposed by the DRFM, early neurodevelopmental adversity may increase children's likelihood of being exposed to trauma such as being bullied (Murray et al., 2017), which is associated with risk of psychosis. Bullies tend to pick on children with lower cognitive skills and poorer physical health, such as those born prematurely (Cook et al., 2010). However, the model has two different interpretations: children with neurodevelopmental adversity may be more vulnerable to the effects of trauma (moderation effect), or they may simply be more frequently exposed to trauma (mediation effect). It could also be a combination of both, and there has been little research examining the mechanism between these risk factors.

Other risk factors have also been associated with psychosis, including family adversity and genetic risk (McCutcheon et al., 2020). Both common and rare genetic variants have been associated with higher risk of schizophrenia

(Kelleher & Cannon, 2011), and there is some evidence that genetic risk is much greater in people who also had obstetric complications, suggesting that some risk factors act by increasing the likelihood of environmental risks in later life (Ursini et al., 2018). Family adversity can also be considered as a risk factor for neurodevelopmental adversity for the child, and maternal psychosocial stress has been associated with neurodevelopmental disorders such as attention deficit hyperactivity disorder (Okano et al., 2019). It is therefore important to account for the role of these risk factors when investigating pathways from neurodevelopmental adversity and trauma to psychosis.

The aim of this prospective longitudinal study from pregnancy to 24 years was to examine the relative contribution of exposure to neurodevelopmental adversity and childhood trauma to the aetiology of psychotic experiences (PE). PE are on the psychosis continuum (van Os et al., 2009), and are more prevalent in the population compared to psychotic disorders, which normally requires large sample size to investigate associations. Further research is necessary by using a larger population-based cohort to examine the mechanism underlying the pathway from neurodevelopmental adversity and trauma to PE. First, we examined the direct and independent effects of neurodevelopmental adversity and trauma on PE. Secondly, we investigated their joint effects and the indirect pathway from neurodevelopmental adversity to PE via trauma.

10.1.3 Methods

10.1.3.1 Sample

The ALSPAC cohort is a prospective population study of 14 062 children born to women who resided in the region of Avon, Southwest of UK with expected delivery dates between 1st April 1991 and 31st December 1992. The initial number of pregnancies enrolled is 14 541, combined with enrolment from later phases, the total sample consisted of 13 998 who were alive at 1 year of age. Detailed description of the sample has been reported previously

(Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Further phases of recruitment occurred at up to 7, 18 and 24 years, however only data from the core sample are used in this analysis. In total, 3514 participants completed assessment on PE at 24 years. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

10.1.3.2 Measures

Psychotic experiences

PE was assessed at 24 years using the semi-structured Psychosis-Like Symptom Interview, which included 12 core questions eliciting key psychotic experiences: hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, and other) and thought interference (broadcasting, insertion, and withdrawal) (Sullivan et al., 2020; Zammit et al., 2013). Each question started with a structured stem question asking if the participant had ever had that experience. Participants answering 'yes' or 'maybe' were cross-questioned to establish whether the experience was psychotic. Coding of PE followed glossary definitions and rating rules for the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). Interviewers rated psychotic experiences as not present, suspected, or definitely present. Unclear responses were rated down and only marked as definite when an example met SCAN rating rules. Data was collected and managed using REDCap electronic data capture tools (https://projectredcap.org/resources/citations/). Very good inter-rater and test-retest reliability (kappa = 0.81 and 0.90 respectively) were found similar to previous PE assessment at 12 and 18 years (Horwood et al., 2008; Sullivan

et al., 2020; Zammit et al., 2013). In this study PE were dichotomised into none experienced vs any suspected or definite experience present in the past 6 months.

Neurodevelopmental adversity

Neurodevelopmental adversity was derived from a combination of six variables, four indicating obstetric complications (birth weight, gestational age, influenza exposure during pregnancy, resuscitation at birth), and two indicating developmental impairment (IQ and motor impairments). Birth weight was coded as a categorical variable with those either below 2500 grams (low birth weight) or above (normal birth weight). Gestational age was also coded as a categorical variable with those either born below 37 weeks (preterm group) or above (term group). Influenza exposure at any point during pregnancy was obtained from self-reported questionnaires completed by mothers at 18 and 32 weeks of pregnancy and coded as either exposed or not exposed. Resuscitation at birth (via any method) was retrieved from computerised obstetric and neonatal records, coded as either received or not received.

IQ was assessed at age 8 using the short version of the Wechsler Intelligence Scale for Children 3rd UK edition (WISC-III; (Wechsler et al., 1992)). It was dichotomised so those who scored greater than 1 standard deviation below the mean were classified as having cognitive impairment. Motor skills was also assessed at 8 years using the Movement Assessment Battery for Children (M-ABC; (Henderson & Sudgen, 1992)), which measured motor performance across four different tasks. A final score averaging performances across these tasks was computed for participants who completed all four tasks. Those who scored below 15th percentile of the sample were classified as having motor impairment.

Severity of exposure to any neurodevelopmental adversity (any of the six variables indicating obstetric complications or developmental impairments) was derived using the following categories: (1) no exposure, (2) one

exposure, (3) two or more exposures. Further sensitivity analysis examined exposure to any indicators for obstetric complications (N=4) separately from developmental impairment (N=2); both were coded as either exposed or not exposed.

Trauma

Trauma variables were derived from 121 questions about the frequency and severity of traumatic events up to 17 years of age, and has been described previously in detail (Croft et al., 2018). All trauma measures up to 5 years were reported by parents, a mixture of parent and self-report were used from 5 to 11 years, and predominantly child report from 11 to 17 years. Briefly, five traumas were considered: physical abuse (physically hurt by caregivers), emotional abuse (saying hurtful things), sexual abuse (any adult or older child forcing or attempting to force participant into sexual activity), emotional neglect (how often caregivers take an interest in aspects of participants' lives) – all perpetrated by adults, and peer bullying (name-calling, blackmail, assault). Domestic violence was also assessed but not included as the focus is on directly experienced abuse rather than witnessing abuse.

Severity of exposure to trauma was derived using the following categories: (1) no exposure, (2) exposure to one trauma, (3) exposure to two or more trauma. Specific trauma exposure was also tested in a sensitivity analysis to investigate their independent and joint effect with neurodevelopmental exposure on PE.

Confounding variables

We examined a range of potential confounders. Sex of participants (male or female) was recorded at birth; family history of schizophrenia was assessed via questionnaires sent to both mothers and their partners during pregnancy (or 4 months post-delivery if mothers were enrolled after 30 weeks gestation), and coded as present if either the mother or partner reported a diagnosis. Polygenic risk scores for schizophrenia and bipolar disorder were derived

from genome-wide association study (GWAS) using SNPs associated with these outcomes in the discovery sample at p thresholds of 0.05 (Taylor et al., 2018). Family Adversity Index (short version) during pregnancy consisted of 15 items including maternal age, housing and financial difficulties, education and marital status, maternal psychopathology, substance use and crime (Bowen et al., 2005). It is a cumulative index developed in the ALSPAC based on Rutter's indicators of adversity (Steer et al., 2004). Scores ranged from 0 to 15 and was categorised into (1) no adversity (score 0), (2) few adversities (score 1 to 2) and (3) many adversities (score 3 or more). Maternal smoking was assessed via questionnaires during pregnancy and coded as either never smoked or smoked any cigarettes, and maternal age was recorded at delivery.

10.1.3.3 Statistical analysis

Primary analysis

Analyses were conducted using R version 3.6.3. The independent and direct effects of neurodevelopmental adversity and trauma on PE were assessed in multiple logistic regression models, controlling for all confounders and the addition of a multiplicative interaction term. Both variables were coded as an ordered variable with three levels (no exposure, one exposure, two or more exposures) with linear terms. Path analysis was used to examine the indirect effect of neurodevelopmental adversity on PE via increased exposure to trauma, adjusting for the same confounders as above. The 'lavaan' package was used in R and the package 'semTools' was used to handle missing data using multiple imputation.

Sensitivity analysis

A sensitivity analysis was carried out to first investigate obstetric complications separately from developmental impairment; path analysis was used to estimate their indirect effects on PE via any trauma exposure. In a further step, possible indirect pathways from obstetric complications and

developmental impairment via each type of trauma (physical abuse, emotional abuse, sexual abuse, emotional neglect, bullying) were also modelled using path analysis. The same packages “lavaan” and “semTools” were used.

Missing data

The amount of missing data in predictors and confounders ranged from 0.2% to 26.9%. We used multiple imputations by chained equations with 40 iterations in R, this was used for both multiple logistic regression models (‘mice’ library) as well as for path analysis (‘semTools’ library). Data were imputed for all exposure and confounding variables but not for outcome measure of PE (total N=3514). Complete case-analyses are shown in supplementary materials.

10.1.4 Results

10.1.4.1 Sample characteristics

Descriptive statistics for the sample are shown in Table 19. There were more females (62.2%) than males. Around half (54%) had no exposure to neurodevelopmental adversity, 13.3% had two or more exposures to neurodevelopmental adversity, and 23.2% were exposed to two or more trauma types up to 17 years. The most frequently reported traumas were bullying (29.2%), physical abuse (20.9%) and emotional abuse (20.5%). The prevalence of PE at 24 years was 12.6%.

Table 19.

Study 2: Sample characteristics.

		n	%
Exposure to any neurodevelopmental adversity (N=3514)	One exposure	1143	32.5
	2 or more	475	13.5
Obstetric complications	Exposed	*1173*	*33.4*
Birth weight (N=3470)	<2500g	*117*	*3.4*
Gestational age (N=3514)	<37 weeks	*139*	*4.0*
Influenza exposure during pregnancy (N=3409)	Exposed	*566*	*16.6*
Resuscitation (N=2139)[a]	Resuscitated	*622*	*29.1*
Developmental impairment	Exposed	*708*	*22.5*
IQ (N=2917)	<1 SD	*479*	*16.4*
Motor skills (N=2571)	<15th percentile	*315*	*12.3*
Any trauma exposure (N=3507)	One trauma	1067	30.4
	2 or more trauma	814	23.2
Physical abuse (N=3504)	Exposed	*731*	*20.9*
Emotional abuse (N=3504)	Exposed	*718*	*20.5*
Sexual abuse (N=3469)	Exposed	*354*	*10.2*
Bullying (N=3427)	Exposed	*999*	*29.2*
Emotional neglect (N=3386)	Exposed	*229*	*6.8*

Table 19. continued

Study 2: Sample characteristics.

		n	%
Psychotic experiences (N=3514)	Any suspected/definite	443	12.6
Confounders			
Sex (N=3514)	Female	2187	62.2
Family Adversity Index (N=3478)	1-2	1355	39.0
	More than 3	271	7.8
Maternal smoking during pregnancy (N=3232)	Yes	388	12.0
Family history of schizophrenia (N=2617)	Yes (either mother or father)	11	0.4
		M	SD
Maternal age at birth (N=3514)		29.45	4.58
Standardised genetic risk score (schizophrenia; N=2567)		-0.08	1.01
Standardised genetic risk score (bipolar; N=2631)		0.02	0.99

[a]Resuscitation includes any resuscitation methods used: bag & mask/oxygen, cardiac massage, facial oxygen, intubation, intermittent positive-pressure ventilation with intubation, mouth to mouth & nose, ventilation not otherwise specified, and any other methods.

10.1.4.2 Primary analysis

Direct and moderated effect

Pooled results from logistic regression model after multiple imputation are shown in Table 20. Both exposure to neurodevelopmental adversity and trauma were associated with increased risk of PE in adulthood, even after adjusting for each other and other confounders. Increased exposure to trauma was associated with the largest risk (1.97 odds) of experiencing PE at 24 years. We did not find evidence for an interaction between exposure to neurodevelopmental adversity and trauma in association with PE (see Table 20).

Table 20.

Study 2: Logistic regression models showing the effects of neurodevelopmental adversity and trauma on PE (N=3514).

	Suspected or definite PE					
	Unadjusted		Adjusted[a]		Adjusted with interaction[b]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Any neurodevelopmental adversity	1.41 (1.16 – 1.72)	*0.001*	1.32 (1.08 – 1.62)	*0.006*	1.32 (1.08 – 1.62)	*0.008*
Any trauma	2.07 (1.74 – 2.47)	*<0.001*	1.97 (1.65 – 2.36)	*<0.001*	2.02 (1.66 – 2.46)	*<0.001*
Any neurodevelopmental adversity x any trauma	-	-	-	-	1.11 (0.79 – 1.57)	0.544

[a]Adjusted for each other as well as confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounder: maternal smoking.

[b]Adjusted for each other as well as confounders, with interaction term added

Indirect effect

Path analysis found a significant indirect effect of neurodevelopmental adversity on PE via increased exposure to trauma, where trauma mediated the association between neurodevelopmental adversity and PE at 24 years (Table 21, Fig. 4). This indirect effect mediated 17.3% of the total effect of neurodevelopmental adversity on PE.

Table 21.

Study 2: Standardised path estimates showing the direct and indirect paths from neurodevelopmental adversity to PE via trauma (N=3514).

	SE	95% CI	p-value
PE at 24 years ~			
Neurodevelopmental adversity	0.065	0.009 – 0.121	*0.022*
Trauma	0.228	0.167 – 0.290	*<0.001*
Trauma (up to 17 years) ~			
Neurodevelopmental adversity	0.061	0.020 – 0.102	*0.003*
Indirect effect			
Neurodevelopmental adversity → Trauma → PE	0.014	0.004 – 0.024	*0.007*
Total effect	0.079	0.023 – 0.136	*0.006*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: maternal smoking; significant confounders on trauma up to 17 years: maternal smoking, FAI, and genetic risk score for schizophrenia.

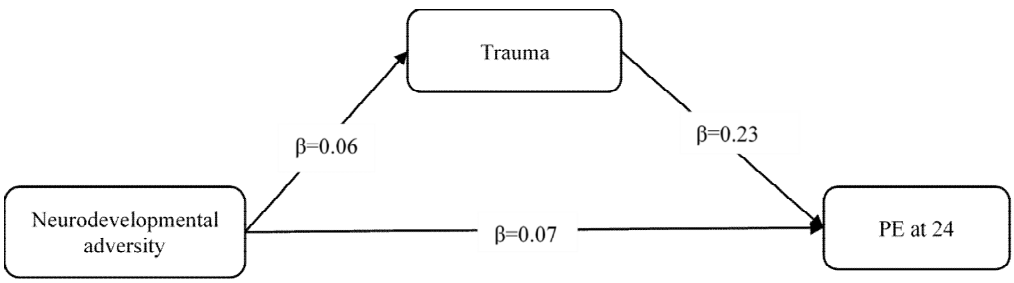

Figure 4.

Study 2: Indirect effect of neurodevelopmental adversity on PE via increased exposure to trauma.

10.1.4.3 Sensitivity analysis

When examining specific neurodevelopmental adversity, only developmental impairment, not obstetric complications, predicted PE at 24 years, both directly and indirectly via increased exposure to trauma (Appendix K). When specific trauma was examined and adjusted for each other, only peer bullying mediated the relationship between developmental impairment and PE (13.9% of the total effect mediated). Sexual abuse and emotional abuse both had direct effects on PE, but no indirect pathways were found (Appendix L, Fig. 5).

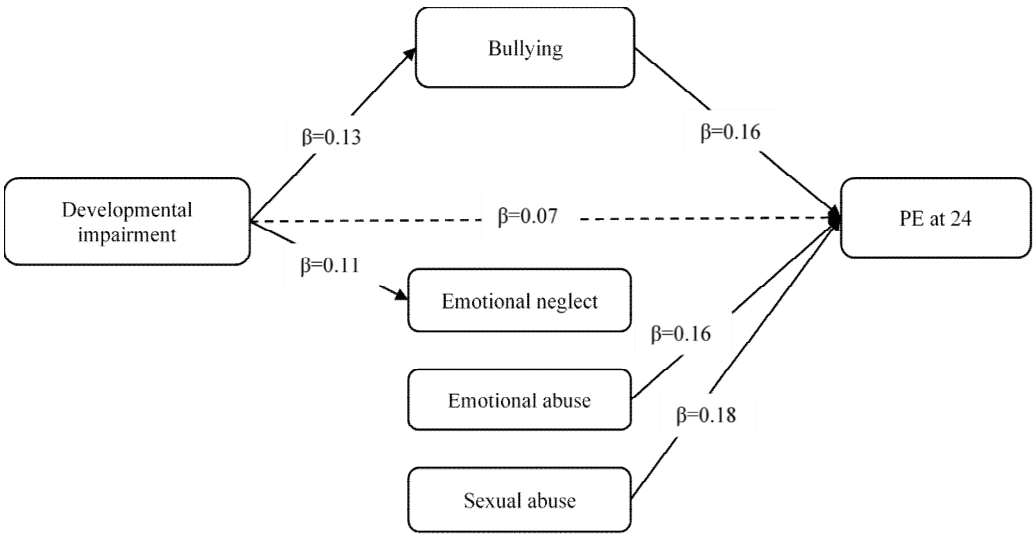

Figure 5.

Study 2: Direct and indirect pathways from developmental impairment and trauma to PE.

10.1.4.4 Complete case analyses

Both neurodevelopmental adversity and trauma were associated with increased risk of PE, however there was weaker evidence for an indirect pathway. When specific trauma was examined, an indirect pathway was

found from developmental impairment to PE via peer bullying, consistent with results after imputation (Appendices M – P).

10.1.5 Discussion

The current study examined the independent and joint effects of exposure to neurodevelopmental adversity and childhood trauma to risk of PE in adulthood. Both were independently associated with PE after adjusting for confounders, with trauma having a larger effect on PE than neurodevelopmental adversity. Children exposed to neurodevelopmental adversity were also more likely to experience trauma, which partly mediated the relationship between neurodevelopmental adversity and PE. Under a multiplicative model of risks, those with exposures to both neurodevelopmental adversity and trauma were not more vulnerable to risk of PE. Rather, those with neurodevelopmental adversity experienced trauma more often, which subsequently increased risk of PE in adulthood. Further sensitivity analysis found that it was peer bullying that mediated the relationship between developmental impairment and PE. No indirect pathways were found from obstetric complications or via caregiver-inflicted trauma.

Consistent with previous research, we have shown that exposure to any neurodevelopmental adversity was associated with increased risk of PE in adulthood (Nosarti et al., 2012; Thomas et al., 2009). These early neurodevelopmental factors may result in disruption to the formation of neural networks, as well as altered inflammatory responses which have been found in people with schizophrenia (Fatemi & Folsom, 2009). Furthermore, they may manifest in childhood as cognitive and motor impairments, which have been found to precede the onset of psychosis (P. Jones et al., 1994). However, in a sensitivity analysis only developmental impairment increased risk of PE when adjusted for all confounders, suggesting that those born with obstetric complications but not developmentally impaired were not at increased risk of PE. Although caution should be used when interpreting the

lack of findings for obstetric complications, as maternal influenza exposure was self-reported, while birth weight and gestational age have received mixed findings in the literature with small effect sizes reported (Davies et al., 2020).

The association between childhood trauma and PE is also consistent with previous research (Croft et al., 2018; Varese, Smeets, et al., 2012). Further investigation found that evidence of association with PE was strongest for emotional abuse, sexual abuse and peer bullying when adjusted for all other trauma types. Emotional and sexual abuse have been frequently reported in the literature as risk factors for psychotic symptoms and disorders (Gibson et al., 2016). No association was found for physical abuse after controlling for all other trauma types and confounders; similar findings have been reported previously (Gibson et al., 2016; Thompson et al., 2014). Emotional neglect showed no direct effect on PE over and above other indicators of trauma, consistent with the literature that neglect may be a risk factor for general psychopathology rather than psychosis (Gibson et al., 2016; Heins et al., 2011).

The association between peer bullying and PE also replicate findings from previous research (Dam et al., 2012). Bullying can lead to feelings of social defeat as well as negative evaluations of the self and others, which can increase hostile interpretations of ambiguous events (Selten et al., 2013). Furthermore, only peer bullying mediated the association between developmental impairment and PE. Bullying can be seen as a strategic way of asserting social dominance, and bullies tend to pick on those who are seen as vulnerable such as those with poorer cognitive and motor abilities (Cook et al., 2010), which may explain why those with developmental impairment were more likely to be bullied. This shows the importance of assessing bullying – an area often neglected in assessment of childhood trauma – especially among high-risk groups such as those with developmental impairment.

When testing the mechanism underlying the pathway from neurodevelopmental adversity and childhood trauma to PE, we found an indirect pathway from neurodevelopmental adversity to PE via increased exposure to childhood trauma. Further investigation revealed that the indirect pathway was from developmental impairment via peer rather than caregiver inflicted trauma, suggesting bullies may be more reactive in picking up behavioural impairments resulting from neurodevelopmental adversity. These findings suggest a cascade model of psychopathology where early developmental risk may lead to further adversity along the developmental pathway, cumulating in psychopathology.

10.1.5.1 Strengths and limitations

The current study tested the relative contribution of two main risk factors of psychosis and included comprehensive measures of neurodevelopmental adversity and childhood trauma to allow for rigorous testing of the relationship between them. The inclusion of a sensitivity analysis also allowed for detailed investigation on the specificity of the association between neurodevelopmental adversity and trauma on PE. Secondly, this study used a large, population-based birth cohort with 24 years of follow-up, with the inclusion of a number of important confounders including genetic risks. This allowed the demonstration of a temporal relationship between neurodevelopmental adversity, trauma and PE by using prospectively measured variables, consistent with findings from previous prospective studies (Croft et al., 2018).

There are also limitations; first, loss to follow-up is inevitable over a 24-year period, and the percentage of missing data in predictor and confounding variables ranged from 0.2% to 26.9%. However, previous research simulating the effects of selective dropout in longitudinal studies found that it may not reduce the validity of predicting outcomes (Wolke et al., 2009), and multiple imputation was also used to reduce bias. Results from complete case analysis showed weaker evidence for an indirect effect from neurodevelopmental

adversity to PE via any trauma. This could be due to a lack of statistical power as some covariates had large proportion of missing data, leading to a largely reduced sample size in the adjusted analysis. Despite this, an indirect effect was still found from developmental impairment to PE via peer bullying both before and after imputation, offering strong support for the role of peer bullying even in a much smaller sample size. Second, we tested for the moderated and mediated effects of neurodevelopmental adversity and trauma in two separate models, thus caution is needed when interpreting the lack of interaction found between these factors. Third, exposure to specific trauma types were coded as binary mediators, and misclassification of the dichotomous mediators may lead to downward bias and underestimation of the indirect effect (Blakely et al., 2013). This may lead to some estimation errors especially in terms of the proportion mediated by the mediator.

10.1.5.2 Conclusion

When testing the relative contribution of exposure to neurodevelopmental adversity and childhood trauma to PE, we found that both were independently associated with PE, even after adjusting for socio-demographic and genetic risks. We further found that children exposed to neurodevelopmental adversity were more frequently exposed to trauma, which mediated the relationship between neurodevelopmental adversity and PE. In particularly, this mediated pathway was found from developmental impairment and via peer bullying. Regardless of neurodevelopmental adversity, the risk of PE is partially modifiable through reducing childhood trauma. Furthermore, identifying children with developmental impairment may serve as early warning signs for increasing difficulties ahead (Cannon et al., 2020), such as being more frequently bullied by peers and subsequently experiencing PE. Interventions should be focused on assessing and reducing bullying in the general population, with a special focus on children at high-risk such as those with developmental impairment.

10.2 Study 3: Testing the Neurodevelopmental, Trauma and Developmental Risk Factor models of psychosis using a naturalistic experiment

10.2.1 Abstract

Background: The Neurodevelopmental and Trauma theories are two widely cited models of psychosis. A third – the Developmental Risk Factor model – recognises the combined role of neurodevelopmental adversity and trauma. Our objective was to test these theories using preterm populations as a natural experiment, given their increased exposure to neurodevelopmental adversity and trauma.

Methods: Two population-based preterm birth cohorts, the Bavarian Longitudinal Study (BLS; N=399) and EPICure Study (N=184) were included with term-born controls. Peer bullying in childhood was assessed by parent and child report and psychotic experiences (PE) were assessed in early adulthood. Different models of psychosis were tested using regression and mediation analyses.

Results: There was support for the Trauma and Developmental Risk Factor model in the BLS. Peer bulying increased the risk of PE for preterm and term-born participants equally (OR=4.87, 95% CI: 1.96 to 12.08). There was an indirect effect where preterm children were more likely to be bullied, which subsequently increased risk of PE. The results were replicated in EPICure.

Conclusions: Exposure to trauma which is experienced more often by neurodevelopmental risk children rather than neurodevelopmental risk per se increases the risk of psychotic experiences. The findings are consistent with the Trauma model and Developmental Risk Factor model. Interventions focused on reducing trauma may reduce the development of PE.

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Trauma and Developmental Risk Factor models of psychosis using a naturalistic experiment. *Psychological Medicine*, *51*(3), 460-469. https://doi.org/10.1017/S0033291719003349

10.2.2 Introduction

A range of theories have been proposed to explain the aetiology or development of psychosis but have been difficult to test as clinically diagnosed psychosis is rare (3% across the lifetime) (van Os et al., 2009). While in contrast, psychotic experiences (PE) are more frequently experienced in adolescence and adulthood (Zammit et al., 2013) and are characterised by the same cluster of symptoms as psychotic disorders, including hallucinations, delusions and thought disorders, but do not meet the threshold for a clinical diagnosis (van Os et al., 2009). They are considered to be on the same continuum and the risk of psychotic disorders in adulthood has been found to be greater in those with PE in adolescence, suggesting that PE may become persistent and subsequently develop into clinical impairment (van Os et al., 2009; Zammit et al., 2013). There is increasing evidence that factors found to be associated with psychosis are similarly associated with PE supporting their use in population studies (Johns & Os, 2001).

One of the most widely cited theory of psychosis is the Neurodevelopmental model (Marenco & Weinberger, 2000; Murray et al., 1992; Weinberger, 1987) (NM), which explains psychosis as a consequence of early disturbed events in the development of the nervous system, creating lesions and disrupting neuronal connections in the brain of the developing foetus (McNeil et al., 2000; Murray & Lewis, 1987; Robin M. Murray, 1994). The consequences of these early lesions could remain dormant until maturation of the prefrontal cortex in adolescence, leading to the use of neural networks that are not well developed and thus enabling the clinical expression of psychosis (Marenco & Weinberger, 2000; Murray, 1994). There is evidence from neuroimaging studies of brain abnormalities such as enlarged ventricular volumes in first-episode and chronic schizophrenia patients (Adriano et al.,

2012; De Peri et al., 2012), as well as studies showing increased prevalence of psychosis in people with a history of obstetric complications (Murray & Lewis, 1987). However, brain lesions are difficult to study in large population studies thus motor, cognitive and behavioural abnormalities in childhood prior to the onset of psychosis are often considered as intermediate phenotypes, with evidence of these abnormalities reported in previous studies (Dean et al., 2018; P. Jones et al., 1994; Pantelis et al., 2003). These developmental impairments are frequent after low birth weight and premature birth and have been found to increase the risk of psychosis in adulthood (Byrne et al., 2007; Nosarti et al., 2012). However, these developmental impairments have also been associated with exposure to early childhood deprivation and adversities (Sonuga-Barke et al., 2017); therefore, caution is needed to interpret these as support purely for the NM.

In contrast, another well-known theory of psychosis is the Trauma model (TM), which places emphasis on the role of childhood adversity (Read, 1997). Increased exposure to stressful events in childhood can bias cognitive processes and lead to hostile interpretations of anomalous experiences, as well as disrupt the chemical balance of the dopamine system which are found to be abnormal at psychosis onset (Guy et al., 2017; Read et al., 2014). Some studies have found that exposure to any trauma from caregivers (e.g. abuse) or peers (e.g. bullying) can increase the risk of psychotic disorders in later life (Croft et al., 2018; Varese et al., 2012), and others found increased risk of psychotic experiences with only certain types of trauma (C. J. Bell et al., 2019). The effects of childhood abuse may be partly due to gene-environment correlation, as abusive behaviour may originate from intergenerational transmission of violence (Hines & Saudino, 2002). Bullying does not have this gene-environment correlation and has similar effect sizes as other types of trauma on psychosis (Fisher et al., 2013; Wolke et al., 2014), even when controlling for genetic risks (Croft et al., 2018).

The third theory – the Developmental Risk Factor model (DRFM) – proposes an indirect or moderated pathway from neurodevelopmental adversity to

psychosis, through childhood trauma (Murray & Fearon, 1999). Early neurodevelopmental adversity can lead to social and behavioural problems, which in turn increase the likelihood of exposure to traumatic events (Murray et al., 2017). There are two mechanisms of how neurodevelopmental adversity and exposure to trauma may relate to psychosis. Firstly, children exposed to neurodevelopmental adversity may be disproportionally more affected when exposed to trauma (i.e. more vulnerable to the effects of trauma; moderation effect). The alternative model proposes that children exposed to neurodevelopmental adversity are simply more often exposed to trauma rather than being more vulnerable to its effects, i.e. mediation effect.

A test of these models requires the prospective study of children at risk of experiencing neurodevelopmental adversity, whose exposure to trauma in childhood and psychotic experiences in adulthood are assessed. Children born very preterm (VP; <32 weeks gestational age) or with very low birth weight (VLBW; <1500 gram) provide a natural experiment as they have widespread brain abnormalities persisting into adulthood (de Kieviet et al., 2012), making the whole population at risk for developmental difficulties (Volpe, 2009). Furthermore, they have more cognitive, motor, social and behavioural difficulties (Allotey et al., 2018), considered as intermediate phenotypes in the Neurodevelopmental model. Finally, VP/VLBW children are also more likely to be exposed to peer inflicted trauma such as being bullied (Wolke et al., 2015). Thus they represent an ideal naturalistic sample as a proxy to test the NM against the TM and DRFM of psychosis.

It is surprising that there are no studies examining the relationships between trauma and psychotic disorders in adulthood in VP/VLBW populations. One problem, as raised above, is that psychotic disorders are of low prevalence in the general population and VP/VLBW only make up 1-2% of all births, therefore large sample sizes are required in prospective studies. Psychotic experiences (PE) on the other hand are on the extended psychosis phenotype and more prevalent, and have been shown to be a significant risk factor for transitioning into psychotic disorders (Zammit et al., 2013). Only one study

(Thomas et al., 2009) found a significant effect of VP/VLBW on PE, although PE were only assessed at 12 years and childhood trauma was not examined.

The aim of this prospective longitudinal study from birth into adulthood was to simultaneously test which of the three models – the NM, the TM or the DRFM – best explains the development of PE. This was investigated in two prospective population-based cohort studies of preterm-born children: the German Bavarian Longitudinal Study (BLS), a regionally defined cohort study of VP/VLBW infants followed from birth until 26 years of age, and the EPICure study, a cohort of extremely preterm (EP; <26 weeks' gestation) children born in the United Kingdom (UK) and Ireland and followed up until 19 years of age. The BLS was the discovery sample, and the EPICure cohort the replication sample. The assessment of PE was identical in both samples.

10.2.3 Methods

10.2.3.1 Design and participants

BLS

The BLS is a prospective whole population study of children born in Southern Bavaria (Germany) between January 1985 and March 1986, who required admission from obstetric wards to neonatal special care within the first 10 days after birth (Wolke & Meyer 1999). The sample has been described in detail previously (Eryigit-Madzwamuse et al., 2015). In short, 202 (49%) VP/VLBW and 197 (64%) term-born adults matched on sex and SES who were also recruited at birth had completed PE assessment at 26 years (Fig. 6).

Ethical approval was obtained from the University of Munich Children's Hospital, the Bavarian Health Council and the Ethical Board of the University Hospital Bonn. Parents gave informed written consent and all participants gave informed written consent for the assessment in adulthood.

EPICure

The EPICure cohort included EP infants born before 26 weeks' gestation in the UK and Ireland from March through December 1995. The sample has been described in detail previously (Johnson et al., 2009). In summary, 120 (39%) EP and 64 (42%) term-born adults matched on sex and ethnic group completed PE assessment at 19 years (Fig. 6). EP participants were recruited at birth whereas term-born participants were recruited at 6 years. Ethical approval was given by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514). Parents gave informed written consent and all participants gave informed written consent for the assessment in adulthood.

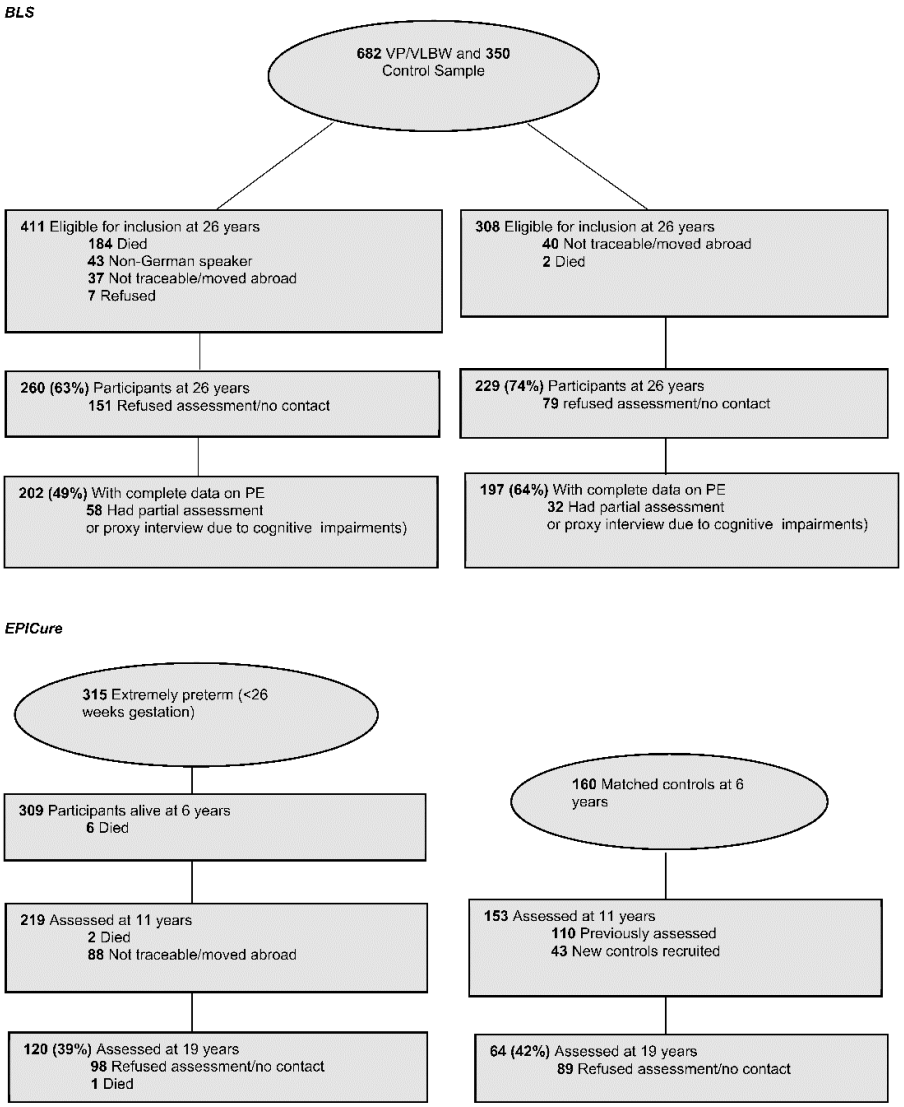

Figure 6.

Study 3: Participant flowchart in the BLS and EPICure cohort studies.

10.2.3.2 Measures

Peer bullying

BLS

Bullying experiences at age 6 and 8 were assessed prospectively via a structured parent interview which has been reported previously (Wolke et al., 2015). The child was considered a victim if they were bullied "1-3 days per month" to "everyday". Bullying at age 6 and 8 was combined so that being bullied at either age represented exposure to peer bullying in childhood.

Bullying at age 13 was self-assessed prospectively by children using one item of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001): "other children pick on or bully me". Responses were on a 3-point scale and children who answered "certainly true" or "somewhat true" were considered victims in adolescence. The following bulying variables were constructed: (1) not bullied; (2) bullied at one time period (childhood or adolescence) and (3) bullied at two time periods (childhood and adolescence).

EPICure

Bullying was reported by parents prospectively at age 6 and 11 using the same item of the SDQ as the BLS at age 13 (Wolke et al., 2015). The same coding procedure was used as the BLS to produce the following variables: (1) not bullied; (2) bullied at one time period (either 6 or 11 years) and (3) bullied at two time periods (both 6 and 11 years).

Cognition

Both BLS and EPICure used the same assessment of IQ (Kaufman Assessment Battery for Children; K-ABC) (Kaufman & Kaufman, 1983). The K-ABC is a standardised test with an average score of 100 and standard deviation of 15. IQ was taken at age 6, but substituted by IQ data at age 8 (in the BLS sample, N=1356, r=0.83) or age 11 (in the EPICure sample, N=306, r=0.89) if scores were missing at age 6. In total, 12 cases were substituted for BLS and 15 for EPICure.

Motor impairment

Children's motor impairment was assessed using the Test of Motor Impairment (TOMI) (Stott et al., 1968) at age 6 and 8 in BLS, and items from the Movement Assessment Battery for Children (M-ABC) (Henderson & Sudgen, 1992) at age 6 in EPICure, which is derived from the TOMI. Scores range from 0 to 16 in the TOMI and 0 to 5 in the M-ABC, with higher scores indicating more motor problems. For 33 participants in the BLS who did not have TOMI data at age 6, data were substituted by those taken at age 8 as there was a strong positive correlation between them (N=1204, r=0.63).

Psychotic experiences (PE)

Psychotic experiences were assessed by trained interviewers using a semi-structured psychotic-like symptoms interview (Zammit et al., 2013) in the BLS at age 26 and EPICure at age 19. The interview consists of 12 core questions covering hallucinations, delusions and thought disorders occurring in the past 6 months. Participants who answered "yes" or "maybe" were cross-questioned and probed to establish whether the experience was psychotic by the interviewer. Coding of PE followed definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; (World Health Organization, 1994)) and unclear responses were rated down and only marked as definite when an example met SCAN rating rules. Detailed description of the interview has been reported previously (Zammit et al., 2013). Interviewers rated each experience as not present, suspected or definitely present. In this study, PE was dichotomised into either no symptom or any suspected/definite psychotic symptoms if one or more symptoms were rated as suspected or definitely present. Previous studies reported good inter-rater and test-retest reliability (kappa = 0.83 and 0.86 respectively) in childhood and early adulthood (Horwood et al., 2008; Zammit et al., 2013).

Covariates

Potential covariates included in both cohorts were sex and SES at birth, grouped as low, middle and high, and computed as a weighted composite score of parents' education and occupation in the BLS (Wolke & Meyer, 1999). In EPICure it was classified based on parental occupation using Social Class based on Occupation (formerly Registrar General's Classification) (Office for National Statistics, 2005) . Male and upper social class served as reference groups.

10.2.3.3 Statistical analysis

Analysis was conducted using R version 3.5.0. Differences between VP/VLBW/EP and term-born controls were reported, with differences in IQ and motor impairment computed to determine whether the VP/VLBW/EP group are exposed to more neurodevelopmental adversity as per design as a naturalistic experiment.

Four different models were specified: first, VP/VLBW/EP was specified as a predictor of PE to test the NM (Fig. 7 path 1). Second, peer bullying, as an index of trauma, was specified as predictor of PE to test the TM (Fig. 7 path 2). Finally, two alternative models to test the DRFM were proposed. Peer bullying was specified as predictor, with VP/VLBW/EP as a risk factor for either (a) being more exposed to and disproportionally affected by bullying (interaction effect; Fig. 7 path 3), or (b) being exposed more often to peer bullying but not more vulnerable to the effects (mediation effect; Fig. 7 path 4).

Figure 7.

Study 3: Conceptual model showing the relationship between VP/VLBW/EP, trauma and PE.

Note. Pathway 1 tests the NM pathway; pathway 2 tests the TM pathway; pathway 3 tests the DRFM pathway (interaction effect); pathway 4 tests the DRFM pathway (mediation effect).

Simple and multiple logistic regression models (controlling for sex and SES) were computed to assess the first two models (NM and TM; Fig. 7, path 1 and path 2). Additionally, interaction effects between VP/VLBW/EP and bullying were also assessed to test the third model (DRFM; moderation effect, Fig. 7, path 3), with the Firth-type penalised likelihood approach used in EPICure due to small data sets (Heinze, 2009). Finally, RMediation package was used to test the mediation interpretation of the DRFM (Fig. 7, path 4).

10.2.3.4 Missing data

The prevalence of missing data was 9.8% in the BLS and 19% in EPICure. Multiple imputation was carried out in R using multivariate imputation by chained equations (MICE), with 40 iterations as recommended to improve power (Graham et al., 2007). Results from the imputed dataset are presented here and results from the complete case analysis are reported as a sensitivity analysis.

10.2.4 Results

10.2.4.1 Sample characteristics

Drop-out analyses have been described previously, with those dropping out more likely to be from lower SES, to have had more behavioural problems

and developmental impairment (Eryigit-Madzwamuse et al., 2015; Linsell, 2017).

Descriptive statistics for variables in both samples are shown in Table 22. Both BLS and EPICure cohorts had similar distribution of male and female participants. However, the BLS preterm-born children were more likely to be of lower SES (29.4%) than term born controls (22.8%). Both VP/VLBW children and EP children were more likely to be bullied in both childhood and adolescence (23.8%, 17.9%) compared to term born controls (14.3%, 9.3%). The rates of PE were 13.8% for BLS and 9.8% for EPICure, with no significant differences between VP/VLBW/EP and controls in either cohort.

Table 22.

Study 3: Sample characteristics of BLS and EPICure.

	BLS					EPICure				
	VP/VLBW		Control		p-value	EP		Control		p-value
	N	%	N	%		N	%	N	%	
Birth weight (M, SD), grams	1317.28 (320.35)		3370.81 (452.15)		<0.001	745.31 (122.72)		N/A[a]		
Gestational age (M, SD), weeks	30.41 (2.06)		39.67 (1.16)		<0.001	24.49 (0.72)		N/A[a]		
Sex										
Male	107	53.0%	94	47.7%	0.342	53	44.2%	25	39.1%	0.505
Female	95	47.0%	103	52.3%		67	55.8%	39	60.9%	
SES										
Upper class	46	22.9%	69	35.0%	0.025[+]	31	29.8%	9	17.6%	0.266
Middle class	96	47.8%	83	42.1%		30	28.8%	17	33.3%	
Lower class	59	29.4%	45	22.8%		43	41.3%	25	49.0%	
IQ (M, SD)	89.43 (14.04)		102.41 (11.22)		<0.001	88.80 (13.40)		108.22 (11.40)		<0.001
Normal	129	69.4%	187	94.9%	<0.001	74	63.2%	64	100%	<0.001
< -1 standard deviation	39	21.0%	10	5.1%		35	29.9%	0	0%	
< -2 standard deviation	18	9.7%	0	0%		8	6.8%	0	0%	

[a]N/A – not assessed - controls were only recruited at 6 years, therefore no perinatal data are available

Table 22. continued

Study 3: Sample characteristics of BLS and EPICure.

	BLS					EPICure				
	VP/VLBW		Control		p-value	EP		Control		p-value
	N	%	N	%		N	%	N	%	
Motor (M, SD)	3.11 (3.40)		1.12 (1.44)		<0.001	2.30 (1.47)		0.79 (0.77)		<0.001
Normal	83	49.1%	173	87.8%	<0.001	85	78.7%	53	100%	0.001
<15% normative sample	40	23.7%	17	8.6%		16	14.8%	0	0%	
<5% normative sample	46	27.2%	7	3.6%		7	6.5%	0	0%	
Peer bullying										
Not bullied	53	31.5%	80	40.8%	0.038	48	45.3%	38	70.4%	0.011
Bullied at one time period	75	44.6%	88	44.9%		39	36.8%	11	20.4%	
Bullied at both time periods	40	23.8%	28	14.3%		19	17.9%	5	9.3%	
Suspected or definite PE										
Absent	170	84.2%	174	88.3%	0.288	105	87.5%	61	95.3%	0.089
Present	32	15.8%	23	11.7%		15	12.5%	3	4.7%	

In both cohorts, VP/VLBW/EP children had more developmental impairments at age 6, as demonstrated by lower scores on IQ and motor tests than term-born controls (Table 22).

10.2.4.2 Model Testing

VP/VLBW/EP and PE (NM)

Pooled results from logistic regression models after imputation are shown in Table 23. VP/VLBW/EP was not a significant predictor of PE in either cohort.

Peer bullying and PE (TM)

Being bullied at both time periods was a significant predictor of PE in both BLS and EPICure cohorts and remained significant after adjustment for sex and SES. Being bullied at one time period also predicted PE but only in BLS, which showed an increased risk of PE with increased exposure (4.55 odds if bullied at both time periods vs 3.01 odds if bullied at one time period only) (Table 23).

VP/VLBW/EP, Peer bullying and PE (DRFM)

10.2.4.3 Interaction

No interaction effect between VP/VLBW/EP and peer bullying was found in predicting PE in either cohort (Table 23).

Table 23.

Study 3: Simple and multiple logistic regression models showing the effects of VP/VLBW/EP and peer bullying on psychotic experiences (PE) as well as showing the interaction between VP/VLBW/EP and peer bullying.

	Suspected or definite PE								
	Unadjusted			Adjusted for SES and sex			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
BLS (N=399)									
VP/VLBW	1.42	0.80 – 2.53	0.230	1.31	0.72 – 2.38	0.375	0.81	0.18 – 3.54	0.777
Peer bullying									
Not bullied	[Reference]			[Reference]			[Reference]		
Bullied at one time period	3.13	1.38 – 7.12	0.007	3.01	1.32 – 6.88	0.009	1.95	0.63 – 5.99	0.245
Bullied at both time periods	4.66	1.88 – 11.59	0.001	4.55	1.81 – 11.46	0.001	4.87	1.38 – 17.12	0.014
VP/VLBW x bullied at one period	-		-	-		-	2.39	0.43 – 13.17	0.317
VP/VLBW x bullied at both periods	-		-	-		-	1.03	0.16 – 6.64	0.978
EPICure (N=184)									
EP	2.90	0.81 – 10.44	0.104	1.78	0.44 – 7.25	0.420	0.95	0.16 – 5.64	0.952
Peer bulying									
Not bullied	[Reference]			[Reference]			[Reference]		
Bullied at one time period	2.90	0.78 – 10.79	0.115	2.23	0.55 – 9.00	0.262	2.20	0.24 – 20.37	0.489
Bullied at both time periods	7.34	1.90 – 28.43	0.004	6.85	1.58 – 29.68	0.011	1.63	0.05 – 57.55	0.788

Table 23. continued

Study 3: Simple and multiple logistic regression models showing the effects of VP/VLBW/EP and peer bullying on psychotic experiences (PE) as well as showing the interaction between VP/VLBW/EP and peer bullying.

	Suspected or definite PE								
	Unadjusted			Adjusted for SES and sex			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
EP x bullied at one period	-		-	-		-	1.11	0.07 – 16.77	0.941
EP x bullied at both periods	-		-	-		-	5.14	0.10 – 254.70	0.412

10.2.4.4 Mediation

In the BLS cohort, being born VP/VLBW increased risk of being bullied even after controlling for covariates in the ordinal logistic regression model (Table 24). Peer bullying was examined as an ordered mediator, and a significant mediation path was found between VP/VLBW and PE: β=0.29, 95%CI: 0.03 – 0.65, but no significant direct effect was found: β=0.27, 95%CI: -0.33 to 0.87. See Fig 8.

In the EPICure cohort, EP predicted being bullied in the adjusted ordinal logistic regression model. (Table 24). A significant mediation path was also found: β=0.77, 95%CI: 0.09 to 1.74. No significant direct effect was found: β=0.58, 95%CI: -0.82 to 1.98. See Fig 8.

Table 24.

Study 3: Simple and multiple ordinal logistic regression model showing the effects of VP/VLBW/EP on peer bullying.

	Peer bullying					
	Unadjusted			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value
BLS (N=399)						
VP/VLBW	1.33	1.05 – 1.67	0.016	1.31	1.04 – 1.65	0.023
EPICure (N=184)						
EP	1.81	1.21 – 2.71	0.004	1.76	1.17 – 2.65	0.008

10.2.4.3 Sensitivity analysis

The analyses were repeated using complete cases from both cohorts. There were no differences in the pattern or magnitude of effects reported above. Detailed outputs are presented in Appendices Q – S.

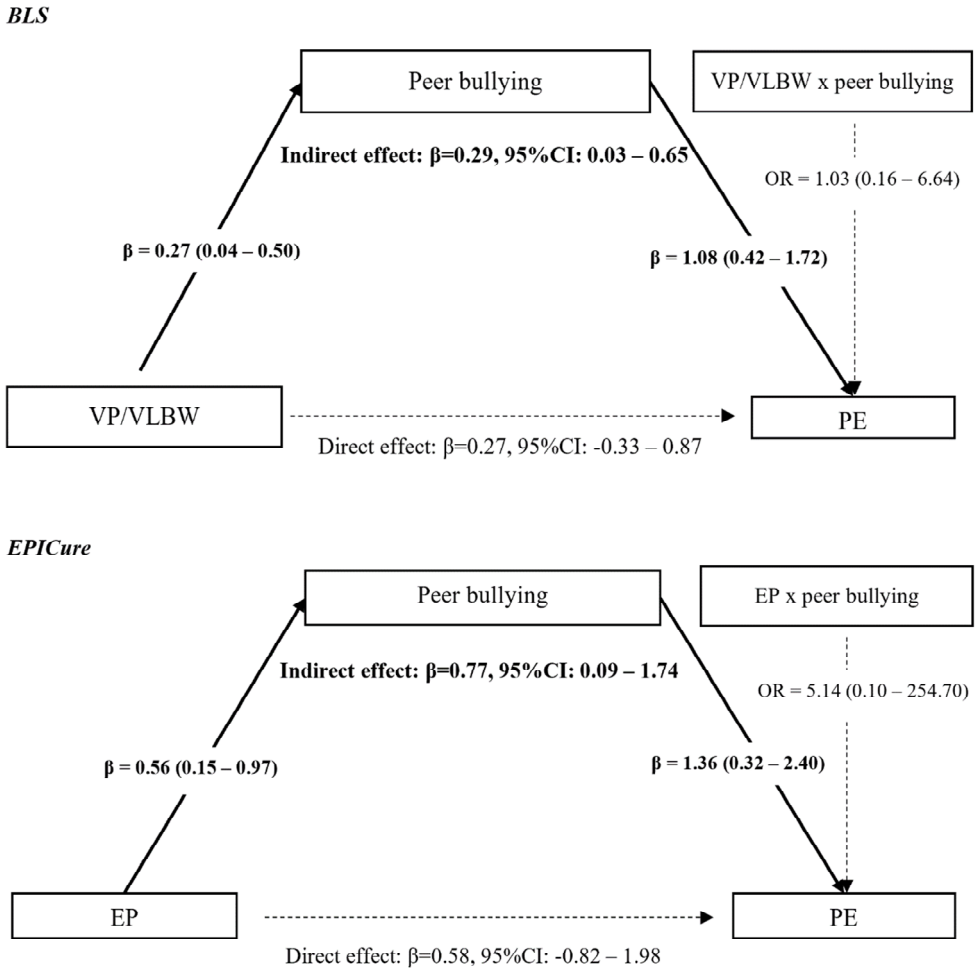

Figure 8.

Study 3: Mediation model showing association between VP/VLBW/EP, peer bullying and PE.

10.2.5 Discussion

This analysis of two birth cohorts found that peer bullying in middle childhood – regardless of birth weight or gestational age –increased the risk of psychotic experiences in adulthood, at both 19 years and 26 years. Preterm birth and associated neurodevelopmental risk did not have a direct effect on PE in either cohort. Test of mediation according to current statistical recommendations (Jaekel et al., 2018; Kenny & Judd, 2014; Rucker et al., 2011) did show an indirect effect of VP/VLBW/EP on PE through increasing children's risk of being bullied more often by peers. This was shown in both the BLS and EPICure sample. Preterm children were not more vulnerable to

the effects of bullying; rather, they were more likely to be bullied. In sum, these findings support both the Trauma and Developmental Risk Factor models, but no support was found for the Neurodevelopmental model.

The effect of peer bullying on PE is consistent with previous research (Croft et al., 2018; Fisher et al., 2013; Wolke et al., 2014) with bullying at two time periods, or chronic bullying, having almost twice as much impact as bullying at one time period only. Although chronic bullying increased risk of PE in both cohorts, only the BLS study showed a risk of PE with being bullied at one time only. One explanation could be that the prevalence of PE at 26 years was higher than in EPICure at 19 years, which combined with the smaller sample size and higher dropout rates, may have contributed to the sample not having enough power to detect the effect of being bullied at one time period.

It is surprising that no support was found for the Neurodevelopmental model, which proposes a direct effect of neurodevelopmental adversity on psychosis. The prevalence of PE was not significantly raised in the VP/VLBW/EP group – a population with a high prevalence of developmental deficits as shown previously (de Kieviet et al., 2012) and in this study (e.g. IQ and motor deficits in childhood). It contradicts a previous large registry study which found prematurity as a risk factor for psychosis (Nosarti et al., 2012). The prevalence of psychosis in the preterm population may be an overestimate in registry studies, as they are more often in contact with professionals due to pre-existing health conditions and may thus be diagnosed more often (Nosarti et al., 2012). Another explanation could be that previous studies examined psychotic disorders rather than PE, and the majority of people with PE do not go on to develop schizophrenia (Zammit et al., 2013). However, we still found support for the Trauma model, and we would have expected to find support for NM given the VP/VLBW/EP population represents an extreme group exposed to multiple neurodevelopmental adversities.

The finding that preterm-born children at high risk of being exposed to neurodevelopmental adversity were bullied more often is consistent with

previous longitudinal studies (Wolke et al., 2015) and supports the DRFM of psychosis, which proposes an indirect effect of neurodevelopmental adversity on psychosis (Murray & Fearon, 1999). However, these children were not more vulnerable to the effects of trauma, contradicting previous research that showed extremely low birth weight born adults to be more vulnerable to childhood adversities in the development of depression and anxiety (Van Lieshout et al., 2018). This study found that peer bullying increases the risk of PE equally for all children – however those exposed to neurodevelopmental adversity such as the preterm population are at increased risk of being exposed to peer bullying more often. Bullying is seen as a strategic way of achieving social dominance and those who are seen as vulnerable or are socially marginalised are likely targets of bullies (Juvonen et al., 2003). Preterm-born children have worse physical health, poorer cognitive and social skills, and have fewer friends to defend them (Allotey et al., 2018). Thus they are easy targets for bullies with low risk of retaliation.

10.2.5.1 Strengths and limitations

This is the first study to test three different theories of psychosis using four clearly defined models in two preterm cohorts from two countries (Germany and UK). Peer bullying was assessed repeatedly in both studies and the same measure for PE was used. Both studies also used the same measures of IQ and similar measures of motor impairment. Furthermore, the inclusion of VP/VLBW/EP children provided a naturalistic experiment to study the different models of psychosis as they are at high risk of being exposed to multiple neurodevelopmental adversities; thus this population acted as a proxy for testing the Neurodevelopmental model.

There are some limitations as well. First, it is inevitable in studies over 26 years that there is drop-out; those who dropped out were more likely to be socially disadvantaged and have developmental deficits (Eryigit-Madzwamuse et al., 2015; Linsell, 2017). However, there is some evidence from simulations of the effects of selective dropout that loss to follow up may

not reduce the validity of predicting outcomes in longitudinal studies (Wolke et al., 2009). Although there might still be a possibility of bias from reduced power due to a loss in follow-up, and there may be an association between social disadvantages and PE (Morgan et al., 2009). Attempts to mitigate bias was made by using multiple imputation, and a sensitivity analysis was carried out comparing results after imputation with complete case analyses. Nonetheless, the wide confidence interval in the EPICure cohort when testing interaction suggest the sample may have been underpowered to robustly test this pathway. Second, peer bullying was assessed by just one item from the SDQ in EPICure. Despite this, there was still a strong effect of bullying on PE in both samples, which adds to the generalisability of the finding that peer bullying is consistently associated with PE despite differences in measures (Day et al., 2016). Thirdly, we did not examine other childhood trauma apart from bullying. There is evidence that trauma from caregivers (physical and sexual abuse, neglect) are also associated with increased risk of psychosis (Croft et al., 2018; Varese, Smeets, et al., 2012), although findings from the previous study in the general population (study 2) suggest that bullying was the only trauma to have a mediating effect. Lastly, genetic factors were not examined. However, a previous study which controlled for genetic risks for schizophrenia found no change in the effects of peer bullying on psychosis (Croft et al., 2018). Furthermore, the VP/VLBW/EP population was used as a proxy for exposure to a range of neurodevelopmental adversity as a whole, as they are more likely to have had intrauterine infections (Kemp, 2014, p. 2014) as well as specific deficits in IQ, behavioural problems and brain abnormalities.

10.2.5.2 Conclusion

When testing the three developmental models against each other, the data consistently support the Trauma and the Developmental Risk Factor model in explaining the development of psychotic experiences. The study provides further evidence that peer bullying is a risk factor for PE in adulthood, and this risk is the same for children with or without exposure to

neurodevelopmental adversity. Those exposed to neurodevelopmental adversity are not more vulnerable to the impact of bullying, but they are more likely to be bullied (Øksendal et al., 2019), which increases their risk of PE. One plausible mechanism is that persistent bullying can lead to feelings of social defeat, which has been shown to disrupt cortisol levels, inflammatory response and the hypothalamic–pituitary–adrenal axis in both animal and human studies (Selten et al., 2013). Furthermore, prolonged social defeat from bullying can also lead to biased and hostile interpretation of social situations and the intention of others (Guy et al., 2017). We do not suggest there is a unified theory of psychosis, or that these models are mutually exclusive, as there are other theories of psychosis such as the stress-diathesis model which have received support. However, the study suggests that the risk of PE may be partially modifiable in childhood through effective anti-bullying strategies. Preterm-born children are more likely to be targets of bullying and this could be prevented. Furthermore, mental health services should routinely ask about histories of childhood trauma, particularly for people with psychosis, as it is a significant risk factor but is also one that is not frequently identified by health care professionals (Read et al., 2018a, 2018b).

Chapter 11: Biological and environmental determinants of self-concept

11.1 Study 4: Very preterm birth and trajectories of domain-specific self-concept from childhood into adulthood

11.1.1 Abstract

Self-concept refers to individuals' perceptions of themselves in specific domains and is closely related with their overall self-esteem. Lower self-esteem has been reported in those born preterm (<37 weeks gestation), but the development of self-concept has not been studied in this population. This study investigates whether differences in trajectories of domain-specific self-concepts are explained by premature birth or other risk factors, using the Bavarian Longitudinal Study (N=460), a population-based study of very preterm (VP; <32 weeks gestation)/very low birth weight (VLBW; <1500g) cohort and term born controls. Trajectories of body and social self-concept from 6 to 26 years were estimated using latent class growth analysis. Regression models examined the effects of VP/VLBW and other individual, social and family factors. Two trajectories, one stable and one decreasing were identified for both self-concepts. VP/VLBW birth was associated with decreasing self-concept in both domains, although the effect of VP/VLBW on social self-concept was weakened in the adjusted analysis. Furthermore, mediated pathways were found from VP/VLBW to decreasing social self-concept via chronic bullying (β=0.05, 95%CI: 0.002–0.12) and motor impairments (β=0.04, 95%CI: 0.01–0.07), suggesting that negative self-concept in the VP/VLBW population is partially modifiable through improving peer relationships and motor impairments in childhood.

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11.1.2 Introduction

There has been an increasing interest in examining whether exposure to significant biological adversity, such as preterm birth, and subsequent developmental impairment affects the development of global self-esteem (Poole, Schmidt, Saigal, et al., 2018). However, less attention has focused on the development of domain-specific self-concept in these at-risk populations. Domain-specific self-concept can be differentiated from global self-esteem, as the former reflects multidimensional perceptions individuals hold on specific domains such as body satisfaction, social acceptance and athletic competence, whereas the latter has been defined as the unidimensional evaluations of the self as a whole (Kernis, 2006; King, 1997). Both are associated with long-term outcomes in mental health, education and employability, although domain-specific self-concept has been found to be a better predictor of specific behavioural outcomes such as academic achievements (Kernis, 2006; von Soest et al., 2016). Although global self-esteem has been shown to be closely correlated with certain domain-specific self-concept such as body satisfaction (von Soest et al., 2016), other self-concept domains may show different development over time and are also influenced by different factors in the general population (Boulton et al., 2010; D. A. Cole et al., 2001; Schaffhuser et al., 2017). There is little research on the development of domain-specific self-concept over time in the preterm population, and the mechanism in which biological adversity may affect self-concept development remains to be investigated.

11.1.2.1 Self-concept development in the preterm population

Around 15 million infants, or 10.6% of all birth around the world, are preterm births (Chawanpaiboon et al., 2019). Of these, 15% are born very preterm (VP; <32 weeks gestation) or at very low birth weight (VLBW; <1500 grams) (Chawanpaiboon et al., 2019). The majority of research on the long-term

outcome following VP/VLBW birth has focused on mental health and neuro-cognitive outcomes, with consistent findings of increased psychiatric disorders, cognitive and motor impairments in both childhood and adulthood (Cheong et al., 2020; Johnson et al., 2009; Spittle et al., 2018; Wolke et al., 2019). In recent years there has also been a focus on examining social development in this population, such as global self-esteem in childhood (Finnström et al., 2003; Gire et al., 2019; Islam et al., 2018) or adulthood (Lund et al., 2012; Roberts et al., 2013; Saigal et al., 2016). Mixed findings have been reported, with some finding lower global self-esteem in VP/VLBW compared to term-born controls and others showing no differences. Only two publications have reported on the longitudinal development of global self-esteem and found consistently low self-esteem from childhood to adulthood (14-35 years) in extremely low birth weight individuals (<1000 gram) (Poole, Schmidt, Ferro, et al., 2018; Poole, Schmidt, Saigal, et al., 2018). However, no studies to our knowledge have investigated the long-term development of domain-specific self-concept in the VP/VLBW population. Furthermore, not all those born VP/VLBW will develop in the same way. Thus, rather than examining mean differences between groups over time, a person-centred approach can be used to examine growth in the whole population and group individuals together based on similar developmental trajectories (Chow & Kennedy, 2014). This then allows the investigation of whether it is being born VP/VLBW per se, or other risk factors in the population that are associated with or mediate the effect of VP/VLBW in the development of specific domains of self-concept.

One such risk factor to consider is peer bullying, which has been associated with negative self-concept in body satisfaction and social acceptance (Adams & Bukowski, 2008; Boulton et al., 2010). There is also strong evidence in the literature that VP/VLBW children are more likely to be bullied in school, as bullies tend to pick on those who are weaker, more emotionally reactive and have less friends, all of which are more likely to be found in VP/VLBW children (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke et al., 2015). Increased exposure to bullying may thus be associated with both

VP/VLBW birth and self-concept development and thus a potential mediator in particular for the domains of body satisfaction and social acceptance.

The association between VP/VLBW birth and domain-specific self-concept may also be explained by increased developmental impairments in childhood, such as cognitive and motor impairments which are more prevalent in VP/VLBW children (Johnson et al., 2009; Spittle et al., 2018). There is evidence that motor impairments may be associated with negative self-concept in domains of social acceptance and athletic competence, suggesting that motor impairments not only affect individuals' perceptions of their physical abilities, but may also increase risk of self-perceived peer rejection (Cocks et al., 2009; Shields et al., 2006). Childhood IQ has also been associated with reduced self-concept in cognitive competence (Paulus et al., 2018), and lower cognitive abilities may also affect the acquisition of prosocial skills, which in turn can affect social competence and peer acceptance (Bellanti & Bierman, 2000). Thus, both IQ and motor impairments may account for associations between VP/VLBW birth and differences in domain-specific self-concept development over time.

As well as these risk factors which are more prevalent in the VP/VLBW population, it is also important to account and control in analysis for risk factors previously reported in the general population. For example, one of the most consistent findings in the literature is that women have lower self-concept on physical appearance compared to men (Gentile et al., 2009). This gender gap appears largest during adolescence and has been found cross-culturally, suggesting the presence of universally shared social and cultural factors, such as increased exposure to unrealistic body standards portrayed in media (Perry & Pauletti, 2011; Wilgenbusch & Merrell, 1999). Longitudinal investigation of the trajectories of self-concept development further found that girls showed a steeper decline in their body self-concept compared to boys over a 2-year period in adolescence (Schaffhuser et al., 2017). Maternal sensitivity has also been associated with positive social self-concept, as positive parent-child interaction can provide the child with the first working

model of a person who is loved, and provide a template for all future social relationships (Harter, 2006; Paulus et al., 2018). Although sensitivity in interaction has not been shown to be overall lower in mothers of children born VP/VLBW (Bilgin & Wolke, 2015), it may still have an association with certain self-concept domains such as social acceptance. Additionally, SES will also be considered as a control variable as it has been shown to be associated with lower global self-esteem (Orth et al., 2010), but research is sparce on its association with domain-specific self-concept.

11.1.2.2 The present research

The overall aim of this prospective study was to examine patterns and predictors of domain-specific self-concept development in VP/VLBW and term born controls in the Bavarian Longitudinal Study (BLS), a regionally defined population-based cohort followed from birth until 26 years. The first aim was to identify distinct self-concept trajectories for each domain using a person-centered growth modelling approach, and secondly to examine whether VP/VLBW birth explained differences between these trajectories after accounting for other individual, social and family factors. Given that VP/VLBW birth has been associated with some of these risk factors, including peer bullying, IQ and motor impairments, further investigations were then carried out to examine whether these factors mediated any relationship between VP/VLBW and different self-concept trajectories.

11.1.3 Methods

11.1.3.1 Design and participants

The BLS is a prospective population-based study of children born in Southern Bavaria, Germany between January 1985 and March 1986, who required admission to hospitals within the first 10 days of birth (Wolke & Meyer, 1999). Detailed sample description has been reported previously (Eryigit-Madzwamuse et al., 2015). In total, 234 (57%) VP/VLBW and 226 (73%) term born controls (>36 weeks gestation) completed self-concept assessments

up to 26 years, see Fig 9. Ethical approval was obtained from the University of Munich Children's Hospital, the Bavarian Health Council and the Ethical Board of the University Hospital Bonn. Parents gave informed written consent in childhood and all participants gave informed written consent for the assessment in adulthood.

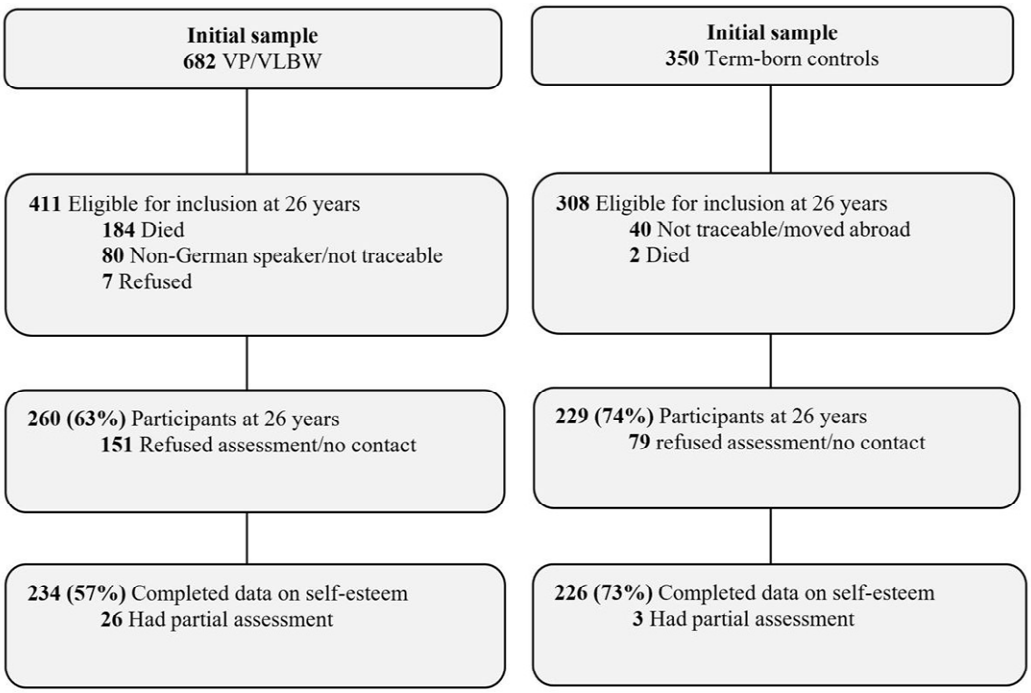

Figure 9.

Study 4: Participant flowchart.

11.1.3.2 Measures

Self-concept:

6 and 8 years

Self-concept at 6 years was assessed using the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children (Harter Scale (Harter & Pike, 1984)) on children's perception of their competence across four

domains: cognition (“know the alphabet”), motor (“can climb”), social acceptance (“has friends to play with”) and maternal relationships (“mother plays with them”). There are six items in each domain, each scored on a 4-point scale with ‘1’ indicating poor and ‘4’ good self-esteem. Pictures representing different items were used due to the young age of the participants, and participants were interviewed to rate their competence in each item. The same assessment was repeated at 8 years but included a fifth domain on body satisfaction (“happy with own looks”), which contained further six items.

13 and 26 years

Self-concept at 13 and 26 years was assessed with the German adaptation of Nicholls’ self-concept of attainment (Nicholls, 1978), which was designed to assess self-concept on the same five domains as the Harter Scale. Participants were presented with 25 faces in a vertical line, with a positive sentence (“happy with how I look”) at the top and a negative one (“not happy with how I look”) at the bottom. Participants were asked to tick the face that best represented how closely they identify with the sentence. Scores ranged from 1 to 25, with higher scores indicating higher perceived competence. There were 16 items at age 13 and 8 items at age 26, representing the same five domains as the Harter Scale. The domains of body satisfaction and social acceptance showed acceptable reliability across all age points of assessment (Cronbach’s alpha >0.70; see Appendix T), comparable to other studies which have also used the Harter Scale (Eapen et al., 2000; Gacek et al., 2014). The cognitive domain showed poor internal reliability across all ages (α=0.55-0.63), and motor and maternal relationships were only assessed using one item at 26 years, thus it was not possible to calculate internal reliability. Only domains with at least 3 assessment points into adulthood were included for analysis, and only if they were assessed by more than 2 items, thus motor and maternal relationships were excluded as they were only assessed by 1 item in adulthood, and the cognitive domain was also excluded due to the

questionable internal reliability. The domains of body satisfaction and social acceptance were examined in subsequent analysis.

Predictors of self-concept

Individual factors

Sex: Biological sex was coded as male or female, with male being the reference group.

Cognition: IQ at 6 years was assessed using the Kaufman Assessment Battery for Children Mental Processing Component (K-ABC; (Kaufman & Kaufman, 1983)), which is a standardized test with a mean score of 100 and standard deviation of 15.

Motor: Motor impairment was assessed at age 6 using the Test of Motor Impairment (TOMI; (Stott et al., 1968)). Scores ranged from 0 to 16 with higher scores indicating more motor problems.

Peer relationships

Peer bullying: Being bullied by peers at age 6 and 8 was assessed via a structured parent interview (Wolke et al., 2015), and being bullied at age 13 was reported by parents using one item from the Strengths and Difficulties Questionnaire (SDQ (Goodman, 2001)), both have been reported previously (Wolke et al., 2015). Any bullying at age 6 or 8 indicated being bullied in childhood, and at age 13 being bullied in adolescence. Three groups were constructed: 1) not bullied, 2) bullied at one time period (childhood or adolescence) and 3) bullied at both time periods (childhood and adolescence).

Parenting (Maternal Sensitivity)

Parent-child interaction was assessed using the Assessment of Mother-Child-Interactions with the Etch-a-Sketch (AMCIES) at age 6 (Wolke et al., 1995, 2013). Participants were observed and video-recorded during a collaborative

play situation and two independent psychologists who were blind to group and family characteristics evaluated the sessions. There were five subscales: maternal verbal control, maternal non-verbal control, maternal criticism, harmony and control of the session, with good inter-rater reliability (0.76-0.89) (Jaekel et al., 2012). Using principle component and reliability analyses, these scales were combined into an index scale of maternal sensitivity (α = 0.58).

Family context (SES)

SES at birth was computed as a weighted composite score of parents' education and occupation, grouped as low, middle and high (Wolke & Meyer, 1999), with upper social class as the reference group.

11.1.3.3 Statistical analysis

Primary analysis

Latent class growth analyses (LCGA) were conducted in MPlus version 8 to examine trajectories of self-concept from childhood to adulthood. Analyses were conducted separately for each self-concept domain. Body self-concept was assessed at 3 time periods (8, 13 and 26 years) and social self-concept was assessed at 4 time periods (6, 8, 13 and 26 years). Standardised mean scores for each self-concept were used in the analyses. Criteria assessing model fit included Bayesian Information Criteria (BIC), adjusted BIC (aBIC), Parametric Bootstrapped Likelihood Ratio Test (BLRT), Lo-Mendell-Rubins (LMR) test and Vuong-Lo-Mendell-Rubin Ratio (VLMR) test. To handle missing data, the full information maximum likelihood approach was used in MPlus. The estimated trajectory classes of participants were saved and exported to R 3.6.0 for further analyses. This method has been shown to create some bias as the trajectory of each participant is considered as an observed variable rather than a latent variable with proportional likelihood taken into account (Vermunt, 2010). However, missing data on predictor variables and

subsequent multiple imputation presents a complex problem within Mplus (Lanza, 2016), thus further analysis were conducted in R.

Simple logistic regression models first examined whether being born VP/VLBW explained differences between trajectories identified. Multiple logistic regression models were then used to examine whether other individual, social and family factors explained differences between the trajectories. The possible interaction between VP/VLBW birth and sex was further explored. A correlation table showing the relationship between all predictors can be found in Appendix U.

Mediation analysis

Peer bullying, IQ and motor impairments were examined as potential mediators if they were also significantly associated with differences in self-concept trajectories over time. Using the “lavaan” and “semTools” packages, path analysis was used to calculate standardised path estimates from VP/VLBW birth to peer bullying/IQ/motor impairments (path a), peer bullying/IQ/motor impairments to self-concept trajectories (path b), and VP/VLBW to self-concept trajectories (path c) (Fig. 10). If multiple mediators were associated with self-concept trajectories, they were examined in the same model and covariance between the mediators accounted for. The mediated effect is calculated as the product of path a and b, and estimated using the “RMediation” package which has been shown to generate reliable confidence intervals using the Monte Carlo method and is comparable to results from bootstrapping (Tofighi & MacKinnon, 2011, 2016).

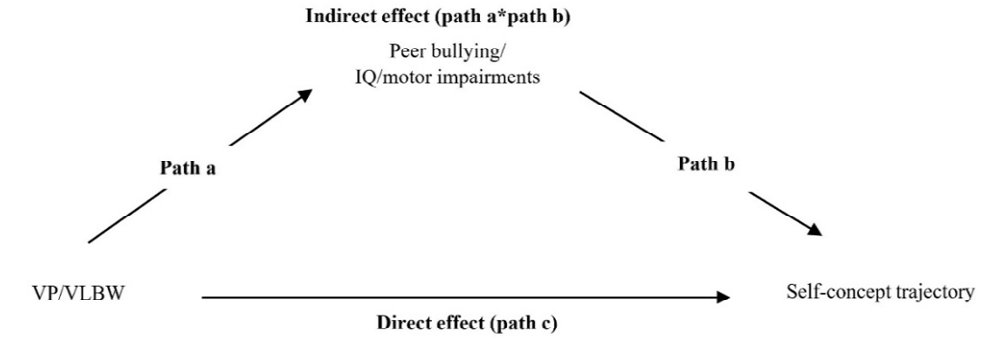

Figure 10.

Study 4: Conceptual model showing the direct and indirect effect of VP/VLBW on self-concept via peer bullying or neuro-cognitive impairments.

Sensitivity analysis

To avoid the problem of common method variance with self-reported self-concepts (Tehseen et al., 2017), only parent reported measures and observations of parenting behaviors were included as predictors. However, self-reported bullying has been found as more accurate as parents are not often aware of bullying in secondary school (Holt et al., 2008). As child-reported bullying was also available at 13 years in the BLS, and assessed using the same item from the SDQ, this was included in a sensitivity analysis to examine whether the effects of bullying varied with different data source. The prevalence of bullying when child-reported data was used at 13 years can be found in Appendix V.

Missing data

Both IQ and motor impairments were assessed at 6 and 8 years, thus data at 8 years was used to substitute missing data at 6 years as there is a strong correlation in the scores between the two ages. See Appendix W for details on numbers substituted as well as correlation between the two ages. The proportion of missing data ranged from 0.2% to 10.7%, and data was deemed likely to be missing at random. Missing data for all predictors were handled

using multivariate imputation by chained equations (“mice” package) in R with 40 imputed datasets.

11.1.4 Results

11.1.4.1 Sample characteristics

Drop-out analyses for BLS have been described previously, with those dropping out more likely to be from lower SES or to have more neurodevelopmental and behavior difficulties (Eryigit-Madzwamuse et al., 2015). The percentage of multiple births for the whole population was 9.3% (N=43), where 16.7% of VP/VLBW participants and 1.8% of term-born controls had a sibling who was included in the study (Table 25).

Detailed description of the sample is reported in Table 25 along with the average gestational age and birth weight of each group. The VP/VLBW group was more likely to be from lower SES, more frequently bullied in both childhood and adolescence, had on average less sensitive mothers, and had more cognitive and motor deficits compared to term controls. They also had a lower social self-concept score at 13 and 26 years.

Table 25.

Study 4: Sample characteristics.

	VP/VLBW		Control		p-value
	n	%	n	%	
Multiple births	39	16.7%	4	1.8%	<0.001
Sex					0.161
Male	124	53.0%	105	46.5%	
Female	110	47.0%	121	53.5%	
SES					0.018
Upper class	52	22.3%	76	33.6%	
Middle class	110	47.2%	98	43.4%	
Lower class	71	30.5%	52	23.0%	
Peer bullying					0.023
Not bullied	58	30.7%	93	41.9%	
Bullied at one time period	90	47.6%	108	48.6%	
Bullied at both time periods	41	21.7%	21	9.5%	
	M	SD	M	SD	p-value
Birth weight (grams)	1329.32	318.90	3362.26	446.75	<0.001
Gestational age (weeks)	30.59	2.17	39.65	1.18	<0.001
IQ	89.70	13.95	102.03	11.39	<0.001
Motor	3.08	3.37	1.24	1.74	<0.001
Maternal sensitivity	-0.05	0.72	0.18	0.56	0.001
Self-concept (z-score)					
Social 6 years	-0.10	1.06	0.09	0.94	0.051
Social 8 years	-0.80	1.01	0.07	0.99	0.117
Social 13 years	-0.14	1.15	0.13	0.82	0.005
Social 26 years	-0.14	1.11	0.14	0.85	0.002
Body 8 years	0.02	1.01	-0.01	1.00	0.755
Body 13 years	0.06	0.95	-0.06	1.04	0.198
Body 26 years	-0.03	1.11	0.03	0.87	0.559

11.1.4.2 Self-esteem trajectories

Model fit statistics for LCGA can be found in supplementary materials (Table 26) and trajectory plots can be found in Fig 11. Overall the classifications showed high entropy and average class probabilities were high for both body (0.85-0.98) and social self-concepts (0.75-0.97), indicating good model fit.

Table 26.

Study 4: Fit statistics for Latent Class Growth Analysis (LCGA) models estimated within body and social self-concept in the BLS.

	Body satisfaction			Social acceptance		
Indicator of model fit	1-trajectory LCGA model	2- trajectory LCGA model	3- trajectory LCGA model	1- trajectory LCGA model	2- trajectory LCGA model	3- trajectory LCGA model
BIC	3709.717	3651.973	3624.419	4853.333	4817.707	4809.124
aBIC	3676.668	3606.530	3566.582	4816.152	4768.133	4747.156
BLRT (k vs. k-1 class)	n/a	p < 0.001	p < 0.001	n/a	p < 0.001	p < 0.001
LMR (k vs. k-1 class)	n/a	p < 0.001	p = 0.075	n/a	p =0.010	p =0.075
VLMR (k vs. k-1 class)	n/a	p < 0.001	p = 0.066	n/a	p =0.008	p =0.067
Entropy	n/a	0.840	0.790	n/a	0.769	0.788
Participants per trajectory, %						
Trajectory 1	460	390 (84.8%)	351 (76.3%)	460	389 (84.6%)	284 (61.7%)
Trajectory 2	n/a	70 (15.2%)	62 (13.5%)	n/a	71 (15.4%)	150 (32.6%)
Trajectory 3	n/a	n/a	47 (10.2%)	n/a	n/a	26 (5.7%)

Note. BIC= Bayesian Information Criterion; aBIC= adjusted BIC; BLRT=Parametric Bootstrapped Likelihood Ratio Test; LMR=Lo-Mendell-Rubin Test; VLMR=Vuong-Lo-Mendell-Rubin Ratio Test

The 2-trajectory solution was found to be the best given the model fit criteria for both body and social self-concepts. Furthermore, they both showed similar trajectories from childhood to adulthood. Those who belonged to trajectory 1 for body (84.8%) and social self-concepts (84.6%) showed stable development over time (stable trajectory). Those who belonged to trajectory 2 for body (15.2%) and social self-concepts (15.4%) showed decreasing levels over time (decreasing trajectory).

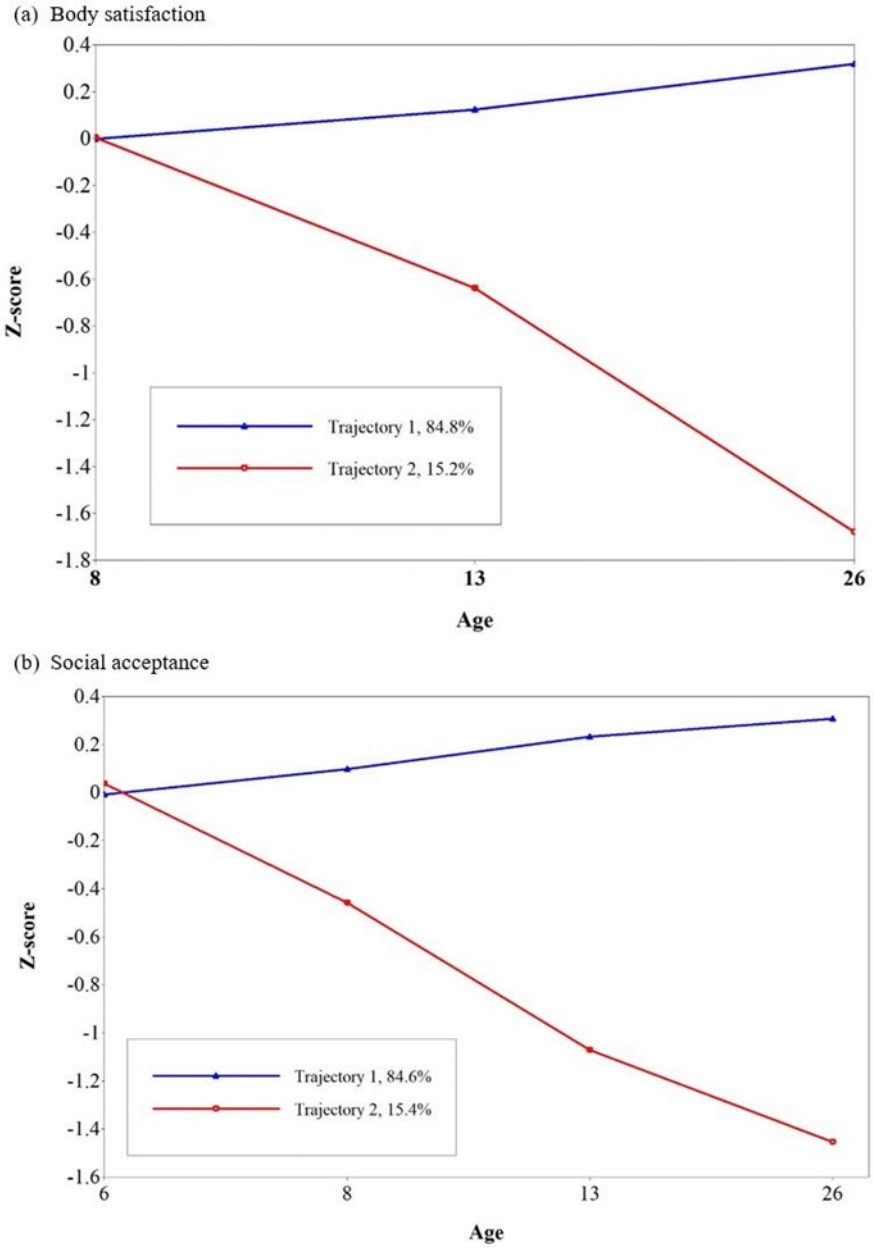

Figure 11.

Study 4: Trajectories for the development of (a) body self-concept from 8 years to 26 years and (b) social self-concept from 6 years to 26 years.

11.1.4.3 Primary analysis: Predictors of self-esteem trajectories

VP/VLBW

Being born VP/VLBW was a significant predictor for having decreasing body (OR=1.91, 95%CI: 1.13 – 3.25) and social self-concepts over time (OR=2.28, 95%CI: 1.33 – 3.89) (Table 27).

Individual, social and family contextual risk factors

When adjusted for all other predictors, there was still an effect of VP/VLBW on body self-concept (OR=2.00, 95%CI: 1.07 – 3.75), however the effect of VP/VLBW on social self-concept was reduced (OR=1.82, 95%CI: 0.96 – 3.45) (Table 27). Being female was predictive of having decreasing body (OR=3.03, 95%CI: 1.70 – 5.42) and social self-concept (OR=2.23, 95%CI: 1.28 – 3.91), however no interaction effect was found between VP/VLBW birth and sex. Motor impairment in childhood was further associated with decreasing social self-concept over time (OR=1.17, 95%CI; 1.06 – 1.29) (Table 27).

Table 27.

Study 4: Primary analysis: Simple and multiple logistic regression models on predictors of decreasing body and social self-concept trajectories (trajectory 2) (N=460).

		Body			Social		
		Trajectory 2			Trajectory 2		
		OR	95% CI	p-value	OR	95% CI	p-value
Biological risk	VP/VLBW (unadjusted)	1.91	1.13 – 3.25	0.016	2.28	1.33 – 3.89	0.003
Biological risk	VP/VLBW	2.00	1.07 – 3.75	0.031	1.82	0.96 – 3.45	0.066
Peer relations	Peer bullying						
	Bullied at one time period	0.86	0.45 – 1.64	0.643	0.91	0.47 – 1.75	0.778
	Bullied at both time periods	1.70	0.77 – 3.76	0.190	1.98	0.92 – 4.25	0.080
Individual differences	Sex [Reference: Male]	3.03	1.70 – 5.42	<0.001	2.23	1.28 – 3.91	0.005
	IQ	1.01	0.99 – 1.04	0.331	1.01	0.98 – 1.03	0.607
	Motor	1.02	0.92 – 1.14	0.694	1.17	1.06 – 1.29	0.003
Parenting	Maternal sensitivity	0.74	0.48 – 1.14	0.170	0.99	0.64 – 1.53	0.962
Family context	SES [Reference: Upper]						
	Middle class	0.56	0.27 – 1.14	0.108	0.68	0.36 – 1.29	0.236
	Lower class	1.86	0.94 – 3.65	0.073	0.65	0.31 – 1.33	0.238
Interaction term	VP/VLBW x sex	0.69	0.20 – 2.43	0.561	0.79	0.24 – 2.61	0.694

Mediation analysis

Only motor impairment was examined as a mediator, as no associations were found from peer bullying or IQ to self-concept trajectories (Table 28). An indirect pathway was found from VP/VLBW birth to decreasing social self-concept over time via increased motor impairments (β=0.03, 95%CI: 0.01 – 0.07), which accounted for 15.8% of the total effect of VP/VLBW birth on social self-concept trajectory (Table 28; Fig. 12).

Table 28.

Study 4: Standardised path estimates showing the direct and mediated effect of VP/VLBW on social self-concept via motor impairment (N=460).

	SE	95% CI
Motor impairment [a] ~		
VP/VLBW	0.13	0.03 – 0.24
Decreasing social trajectory [b] ~		
VP/VLBW	0.16	-0.01 – 0.33
Motor impairment	0.26	0.14 – 0.39
Mediated effect [c]		
VP/VLBW → motor impairment → decreasing social trajectory	0.03	0.01 – 0.07

[a]Adjusted for sex and SES

[b]Adjusted for each other, as well as sex, SES, bullying, IQ, and maternal sensitivity

[c]Estimate and 95% confidence interval calculated using Monte Carlo method in RMediation package

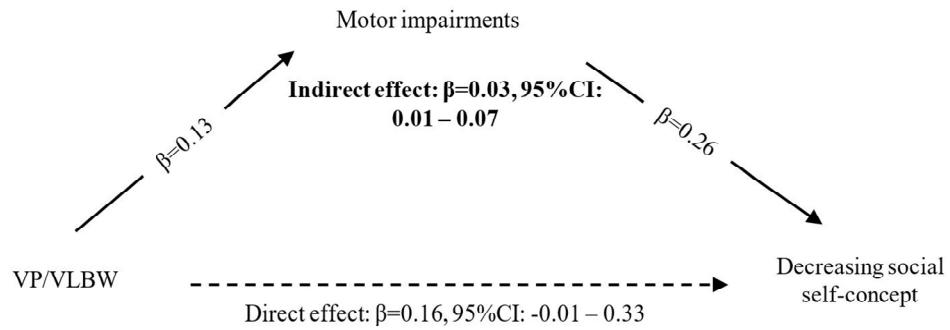

Figure 12.

Study 4: Indirect pathway from VP/VLBW to decreasing social self-concept via motor impairments.

11.1.4.4 Sensitivity analysis

When child reported bullying data was used at 13 years, a stronger effect of chronic bullying (being bullied at both time periods) emerged for both body (OR=2.21, 95%CI: 1.05 – 4.69) and social self-concept (OR=3.25, 95%CI: 1.52 – 6.99) trajectories (Table 29). As being bullied at one time period was not associated with increased risk of decreasing self-concept, only chronic bullying was examined in further analysis as a potential mediator (compared to not bullied or bullied at one time period only). Although VP/VLBW birth was associated with increased risk of chronic bullying, and chronic bullying was also associated with decreasing body self-concept, the mediated effect was not statistically significant (β=0.04, 95%CI: -0.001 – 0.11) (Fig. 13a).

As both chronic bullying and motor impairments were associated with decreasing social self-concept, both were examined as mediators in the same model. Both mediated pathways were significant: chronic bullying mediated 23.8% (β=0.05, 95%CI: 0.002 – 0.12) and motor impairments 19% (β=0.04, 95%CI: 0.01 – 0.07) of the total effect of VP/VLBW birth on social self-concept trajectory (Fig. 13b). No associations were found between motor impairments and chronic bullying.

Table 29.

Study 4: Sensitivity analysis using child reported bullying at 13 years: Simple and multiple logistic regression models on predictors of decreasing body and social self-concept trajectories (trajectory 2) (N=460).

		Body			Social		
		Trajectory 2			Trajectory 2		
		OR	95% CI	p-value	OR (95% CI)	95% CI	p-value
Biological risk	VP/VLBW (unadjusted)	1.91	1.13 – 3.25	0.016	2.28	1.33 – 3.89	0.003
Biological risk	VP/VLBW	2.01	1.07 – 3.79	0.031	1.76	0.92 – 3.34	0.086
Peer relations	Bullying						
	Bullied at one time period	0.89	0.45 – 1.75	0.735	1.37	0.68 – 2.76	0.382
	Bullied at both time periods	2.21	1.05 – 4.69	0.038	3.25	1.52 – 6.99	0.003
Individual differences	Sex [Reference: Male]	3.24	1.80 – 5.85	<0.001	2.44	1.37 – 4.33	0.003
	IQ	1.01	0.99 – 1.04	0.406	1.01	0.98 – 1.03	0.574
	Motor	1.02	0.92 – 1.14	0.683	1.19	1.07 – 1.32	0.001
Parenting	Maternal sensitivity	0.78	0.50 – 1.22	0.270	1.08	0.70 – 1.68	0.728
Family context	SES [Reference: Upper]						
	Middle class	0.52	0.26 – 1.07	0.077	0.63	0.33 – 1.21	0.166
	Lower class	1.75	0.89 – 3.43	0.106	0.61	0.30 – 1.27	0.186
Interaction term	VP/VLBW x sex	0.74	0.21 – 2.63	0.645	0.85	0.25 – 2.87	0.800

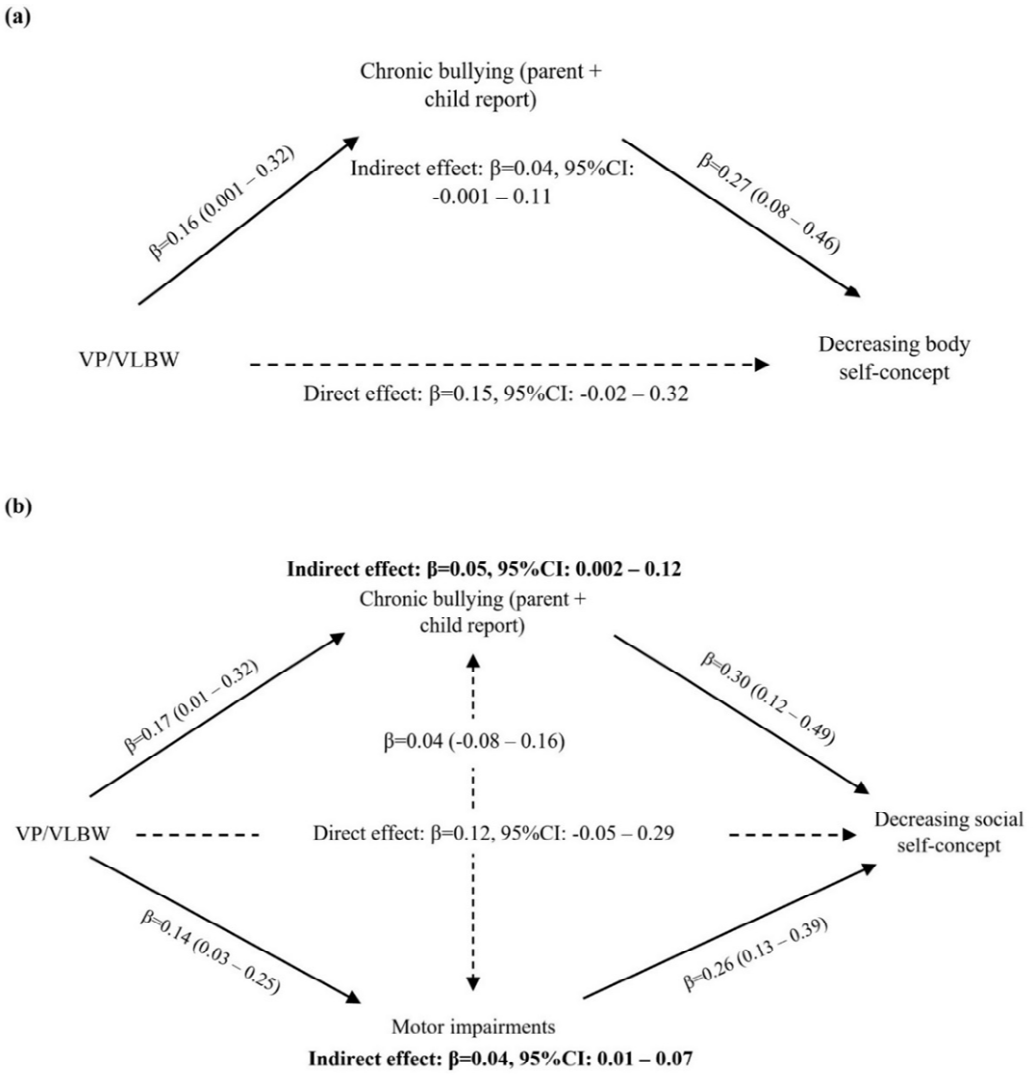

Figure 13.

Study 4: Indirect pathway from VP/VLBW to decreasing (a) body self-concept via chronic bullying (parent and child reported) and (b) social self-concept via both chronic bullying (parent and child reported) and motor impairments.

Note. Indirect estimate and 95% confidence interval calculated using Monte Carlo method in RMediation package.

11.1.5 Discussion

The current study aimed to identify trajectories and predictors of self-concept development in body satisfaction and social acceptance in the VP/VLBW population. Both self-concepts showed a stable trajectory and a decreasing trajectory from childhood to adulthood. VP/VLBW birth was associated with decreasing trajectories in both self-concept domains over time, although its association with decreasing social self-concept was weakened once other factors were taken into account. Being female was associated with the highest risk of having decreasing body and social self-concept from childhood to adulthood. Motor impairment was associated with decreasing social self-concept, and chronic bullying (being bullied at both time periods in childhood and adolescence) was further associated with decreasing body and social self-concept over time, but only when child-reported bullying was used at 13 years instead of parent-report.

Similar with findings on global self-esteem development from a previous extremely low birth weight cohort (Poole, Schmidt, Ferro, et al., 2018; Poole, Schmidt, Saigal, et al., 2018), this study found that VP/VLBW birth was associated with decreasing body and social self-concept from childhood to adulthood, although the association with decreasing social self-concept was weakened in the adjusted model. The effect of VP/VLBW birth on decreasing body self-concept remained even after adjusting for other factors, in contrast to a previous study which found no differences on body satisfaction between young adults born VLBW and controls (Lund et al., 2012). However, it has been shown previously that adults born VP (<32 weeks gestation) had three times increased risk of developing eating disorders and also show higher eating disorder symptoms including weight and shape concerns (Micali et al., 2015; Nosarti et al., 2012). This suggest that negative body self-concept may be specific to those born before 32 weeks gestation as no increased risk were observed for those born VLBW (Nosarti et al., 2012).

Chronic bullying was associated with both decreasing body and social self-concepts from childhood to adulthood, but only when child-reported data was used at 13 years. The risk of chronic bullying on body self-concept is consistent with previous findings which showed reduced body satisfaction and increased desire for cosmetic surgery in adolescents who were bullied (Carbone-Lopez et al., 2010; K. Lee et al., 2017). Chronic bullying was also the strongest predictor of having decreasing social self-concept from childhood to adulthood, consistent with findings that victims of bullying often have lower social status and are more isolated by peers who may be reluctant to associate with them for fear of losing their own social position (Guy et al., 2019). The effect of chronic bullying was not significant when parent-reported bullying was used at 13 years. One explanation is that self-reported bullying tends to be more accurate, especially during adolescence, as parents are often not aware of bullying behaviors in secondary schools (Holt et al., 2008). This is shown by the higher prevalence of chronic bullying when child-reported data was used (19.2% vs 15.1%). However, caution may be needed as there may be potential confounding due to systematic variance shared between self-reported bullying and self-reported self-concepts. Furthermore, there may be a bi-directional relationship where lower self-concept may have increased vulnerability to peer bullying, which has been shown previously (Boulton et al., 2010) and requires further investigation.

Although chronic bullying was associated with decreasing body self-concept, the mediated pathway from VP/VLBW birth was not statistically significant. However, a mediated pathway from VP/VLBW birth via chronic bullying was found for decreasing social self-concept from childhood to adulthood. This is consistent with evidence in the literature that VP/VLBW children are more likely to be exposed to bullying (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke et al., 2015), and this increased exposure to chronic bullying also accounted for almost a quarter of the effect of VP/VLBW birth on the development of social self-concept over time. This highlights the importance of preventing bullying in schools, especially for high-risk populations such as VP/VLBW children who are more likely to be bullied.

Motor impairment was another risk factor associated with decreasing levels of social self-concept, consistent with previous findings in those with physical impairments (Cocks et al., 2009; Shields et al., 2006; Vedul-Kjelsås et al., 2012). It further mediated the relationship between VP/VLBW birth and decreasing social self-concept, independently from the mediated effect of chronic bullying. This is consistent with the evidence that VP/VLBW children have more motor impairments in childhood (Cheong et al., 2020; Johnson et al., 2009; Spittle et al., 2018), and those with poorer motor skills have also been found to report more social rejection (Bejerot et al., 2013; Livesey et al., 2011; Øksendal et al., 2019). Being active and participating in sport activities are important for gaining popularity among peers (Livesey et al., 2011). VP/VLBW children who are unable to participate in these activities due to their functional limitations may thus perceive themselves more negatively on social acceptance.

Being female was also identified as a consistent risk factor for decreasing body and social self-concept from childhood to adulthood, replicating findings reported across cultures that females have more negative perceptions of their physical appearance (Gentile et al., 2009). It has been suggested that women in societies are valued more on body aesthetics and relational ties compared to men, and these thus become salient areas for self-evaluations (Bem, 1993; Walter et al., 2020). Furthermore, girls from a young age are exposed to unrealistic body imagery in the media, and the discrepancies that arise from comparing themselves to these images can lead to shame and anxiety around their bodies and decrease body satisfaction (Calogero, 2012; Fredrickson & Roberts, 1997). Interventions should thus focus more on reducing social comparisons and challenging unrealistic body images (Halliwell et al., 2011; Morton et al., 2012). Although no sex differences have been reported on social self-concept previously (Gentile et al., 2009), the current study showed that girls were more likely to report decreasing social acceptance. One explanation could be that girls report more jealousy in friendships than boys and expect more exclusivity in friendships, which has

been associated with increased loneliness and lower social acceptance (Parker et al., 2005).

Finally, maternal sensitivity and SES did not predict differences in the development of body and social self-concepts. Although SES has been associated with body dissatisfaction in previous research (Orth et al., 2010; Paxton et al., 2006), others found that SES was more strongly associated with global self-esteem and behavioural conduct (Muldoon & Trew, 2000). Maternal sensitivity in previous research was also associated with children's self-concept in childhood (Paulus et al., 2018), however they did not examine differences in self-concept trajectories into adulthood. Thus parenting behaviours may have a weaker role on the development of body and social self-concepts compared to other individual and social factors.

11.1.5.1 Strengths and limitations

This is the first study to our knowledge that has examined trajectories of body and social self-concepts from childhood to adulthood in a high-risk VP/VLBW population using a person-centered approach. This allowed the investigation of whether it is VP/VLBW birth per se, or other individual, social and family risk factors identified in the general population that affect the development of self-concepts. The inclusion of a secondary analysis to examine possible mediated pathways allowed further examination of the mechanisms underlying any associations found between VP/VLBW birth and self-concept development. The study further addressed the issue of common method variance by including observer or parent reported measures as predictors, as the outcome measure of self-concept was self-reported.

There are also some limitations: loss to follow-up is inevitable over a 26-year period. Those dropping out were more likely to be from lower SES and had more neurodevelopmental and social difficulties. Although previous simulations showed that selective drop-out may not reduce the validity of predicting outcomes in longitudinal studies (Wolke et al., 2009), it may have affected the number or types of trajectories identified. Second, only the

domains of body and social self-concepts were assessed in the current study, as the other domains showed either weaker internal reliability or were only assessed using one item in adulthood. Further longitudinal investigation is therefore needed with adequate items at all ages of assessment to examine the trajectories and predictors of self-concept in these domains. Thirdly, multiple births are more likely among those born preterm (Goldenberg et al., 2008). The prevalence of multiple births was 9.3% in the study population, and the majority of them were born VP/VLBW. This may violate the assumption that observations are independent of each other (Hibbs et al., 2010). Given the relatively small percentage of multiple births, analyses were repeated after excluding siblings, and there were no significant changes to the findings. Alternatively, other methods may be used to account for multiple births, such as multilevel modelling where clustering is taken into account (Marston et al., 2009). Lastly, there may be bias associated with using the most likely trajectory membership in further analysis, as it does not take into account classification error (Vermunt, 2010). Despite the relative high probability participants had of being in each trajectory, caution may be needed to interpret the subsequent findings.

11.1.5.2 Conclusion

When investigating the development of body and social self-concept in the VP/VLBW population, we found that although the effect of VP/VLBW birth on decreasing body self-concept remained, its effect on decreasing social self-concept was reduced when other risk factors were taken into account. This suggest that rather than VP/VLBW birth per se, it was other risk factors commonly identified in the general population, which the VP/VLBW population were more frequently exposed to, that explained differences in social self-concept trajectories. In particular, VP/VLBW were more frequently exposed to chronic peer bullying and reported more motor impairments in childhood, which in turn was associated with decreasing levels of social self-concept from childhood to adulthood. Thus, the risk is partially modifiable through preventing bullying in schools and increasing

support for children with motor difficulties, in particular for VP/VLBW children. Interventions should also focus on girls who are also more likely to have decreasing trajectories in both body and social self-concepts.

Chapter 12: General discussion

12.1 Summary of findings

The overall aim of this thesis was to examine the role of childhood trauma in the association between early biological risks and adult psychological development in two areas of psychopathology (depression, psychotic experiences) and one area of psychosocial wellbeing (self-concept). There was mixed evidence on the direct effect of early biological risks: although prenatal stress and neurodevelopmental adversity were initially associated with increased risk of depression and psychotic experiences in adulthood, part of their effect, especially prenatal stress, was attenuated after accounting for childhood trauma. VP/VLBW birth – as a proxy measure indicating multiple exposure to neurodevelopmental adversity – did not increase risk of psychotic experiences in adulthood, but was associated with lower body and social self-concept, with weaker effect on social self-concept after accounting for other factors.

There was consistent evidence for the effect of childhood trauma across all outcomes examined, both in the general and VP/VLBW populations. In particular, peer bullying emerged as a consistent risk factor for depression, psychotic experiences and lower body and social self-concept. Childhood sexual abuse was associated with the largest risk for depression and psychotic experiences, and along with emotional abuse and peer bullying, were independently associated with psychotic experiences over and above other types of trauma.

Finally, there was consistent evidence across all studies that childhood trauma, especially peer bullying, mediated the association between both indicators of biological risks (prenatal stress and neurodevelopmental adversity) and outcomes in depression, psychotic experiences, and self-concept. This was found in both the general population as well as the VP/VLBW population. Peer bullying mediated between 6-14% of the total

effect of early biological risks on adult depression and psychotic experiences, and between 24-57% of the total effect of VP/VLBW birth on psychotic experiences and decreasing social self-concept from childhood to adulthood. A summary of the key findings can also be found in Table 30.

Table 30.

Complete summary of findings.

Study	Biological risks	Childhood trauma	Outcome	Role of biological risks	Role of trauma	Indirect effect
1	Prenatal stress (maternal depression; family adversity)	Caregiver- and peer-inflicted trauma (as a composite measure, and specific trauma)	Depression	Prenatal stress initially associated with offspring depression, however, its effect was attenuated once all pathways from postnatal stress and childhood trauma were modelled simultaneously.	Increased exposure to trauma associated with increased risk of offspring depression. All trauma types significant, apart from domestic violence.	Childhood trauma mediated all pathways from pre- and postnatal stress to offspring depression (7-16% of total effect mediated), in particular for physical abuse, emotional abuse and peer bullying.
2	Neurodevelopmental adversity (obstetric complications and developmental impairments)	Caregiver- and peer-inflicted trauma (as a composite measure, and specific trauma)	Psychotic experiences	Neurodevelopmental adversity (in particular developmental impairments) had a direct effect on PE, but this was attenuated once specific trauma types were modelled simultaneously.	Increased exposure to trauma associated with increased risk of PE. Specific effects from: emotional, sexual abuse and bullying after adjusting for all trauma types.	Childhood trauma mediated the association between neurodevelopmental adversity and PE (17% of total effect accounted for). In particular, peer bullying mediated the association between developmental impairments and PE (14% of total effect accounted for).

Table 30. **continued**

Complete summary of findings.

Study	Biological risks	Childhood trauma	Outcome	Role of biological risks	Role of trauma	Indirect effect
3	VP/VLBW birth	Peer-inflicted trauma	Psychotic experiences	No evidence for direct effects of VP/VLBW or EP birth on PE in both cohorts.	Chronic bullying (being bullied in childhood and adolescence) associated with highest risk of PE.	Bullying mediated the association between VP/VLBW birth and PE (52% of total effect mediated) and between EP birth and PE (57% of total effect mediated).
4	VP/VLBW birth	Peer-inflicted trauma	Body and social self-concept	Direct effects from VP/VLBW birth to decreasing body and social self-concept, but the direct effect on social self-concept was attenuated after accounting for other factors.	Chronic bullying (being bullied in childhood and adolescence), assessed using both parent and child report, was associated with lower body and social self-concept.	Bullying accounted for 24% of the total effect of VP/VLBW birth on decreasing social self-concept from childhood to adulthood.

12.2 Integrated discussion

The direct effect of biological risks on adult psychopathology are often used to support the programming model (e.g. D. R. Kim et al., 2015), or the Neurodevelopmental model of schizophrenia (e.g. Marenco & Weinberger, 2000), and there is evidence in the literature that both prenatal stress and neurodevelopmental adversity are associated with risk of depression and psychosis in adulthood (Davies et al., 2020; Kingsbury et al., 2016; Najman et al., 2017; Tirumalaraju et al., 2020). These early risks are proposed to act by altering the development of the brain and bodily systems, and these alterations are thought to be implicated across different symptoms of psychopathology (D. R. Kim et al., 2015; Murray & Lewis, 1987; Weinberger, 1987). However, mixed findings have been reported across the studies in this thesis: although prenatal stress and neurodevelopmental adversity were associated with adult depression and psychotic experiences in the general population, part of this direct effect was weakened when the effect of childhood trauma was accounted for. Furthermore, those born VP/VLBW – a group at significant increased risk of experiencing multiple neurodevelopmental adversities – were not shown to be directly at increased risk of psychotic experiences. These offer mixed support for the programming model and the Neurodevelopmental model of schizophrenia, and the association between early biological risks and adult psychopathology is likely to be more complex.

There is more consistent support for the Trauma models across all four studies (i.e. Traumagenic Neurodevelopmental model, social defeat model) (Read et al., 2014; Selten et al., 2013), regardless of the risk exposure or outcome examined, in both the general and VP/VLBW populations. Rather than simply exacerbating a pre-existing vulnerability, childhood trauma is shown to be directly and independently associated with adult depression and psychotic experiences regardless of prior exposure to biological risks. Childhood trauma was further identified as a mediator across all outcomes examined. This is consistent with models adopting a developmental cascade approach –

such as the cumulative effect model or Developmental Risk Factor model – where early exposure to biological risks may set in motion a series of events and difficulties which cumulates in psychopathology (Murray et al., 2017; Murray & Fearon, 1999; O'Connor, 2015). Although other models apart from these exist in the literature, findings from the studies included in this thesis suggest that a comprehensive theory adopting a developmental cascade approach, which accounts for the mediating role of environmental adversity such as childhood trauma, appears most appropriate when modelling the longitudinal association between early biological risks and adult psychological development.

The consistent role of childhood trauma in the studies presented in this thesis suggests a common shared pathway and a widespread effect of childhood trauma across different areas of psychopathology. It has been theorised that childhood trauma may impact on the same biological and psychological processes, such as changes to the body's stress response system (HPA-axis), as well as biasing cognitive schemas about the self and the world, which can manifest in symptoms shared across different psychopathologies (Appiah-Kusi et al., 2017; Heim et al., 2008; K. M. Keyes et al., 2012; McKay et al., 2021). A dose-response effect of childhood trauma was also shown across all studies in this thesis, where those exposed to more trauma (exposed to multiple traumas or at multiple times) were at the highest risk of developing depression or psychotic experiences. This is also consistent with the social defeat theory: trauma can be considered as a form of social stress where individuals are persistently ostracised and discriminated against, and it is this repeated and prolonged exposure to social stress that can lead to neurobiological changes, as well as feelings of defeat or hostility towards the environment (Selten et al., 2013; Selten & Cantor-Graae, 2005).

Although the same neurobiological mechanisms may be involved in the onset of many psychopathologies (Nemeroff & Binder, 2014), there was also some evidence for the specificity of trauma in studies one and two of this thesis. Of all the types of trauma examined, childhood sexual abuse showed the largest

effect on depression and psychotic experiences. Sexual abuse has previously been shown to have the largest effect on depression (Li et al., 2016), with some possible mechanisms proposed including changes in the HPA-axis, neurotransmitters and inflammatory responses (Hailes et al., 2019; Nemeroff & Binder, 2014). However, these alterations are also implicated in other forms of childhood trauma, and childhood sexual abuse often co-occurs with other types of abuse like physical abuse, thus the effect of sexual abuse may be stronger due to its comorbidity with other types of trauma (Turner et al., 2010). Childhood sexual abuse has also been proposed to be more strongly associated with auditory hallucinations (Bentall et al., 2012), which can be considered as a source monitoring deficit, where individuals have difficulty differentiating between internal and external events (Ditman & Kuperberg, 2005). One possible mechanism is via dissociation, which is more likely among those with a history of sexual or physical abuse, and can lead to cognitive inhibition deficits and increased likelihood of misattributing internal events to external causes (Varese et al., 2012; Vonderlin et al., 2018). Furthermore, the finding that sexual abuse was associated with psychotic experiences even after controlling for the effects of other traumas may suggest a specific pathway that is independent from other types of trauma.

Childhood emotional abuse was another trauma exposure associated with adult depression in study one, and was independently associated with psychotic experiences over and above other trauma types in study two. While childhood sexual abuse may be more associated with hallucinations, emotional abuse has been proposed to be more strongly implicated in the formation of persecutory delusions (Ackner et al., 2013; Ashcroft et al., 2012). Emotional abuse has also been theorised to affect attachment, which can lead to the formation of maladaptive cognitive schemas and negative self-beliefs implicated in the onset of delusions (Ackner et al., 2013; Ashcroft et al., 2012; Riggs, 2010). Although specific symptoms were not examined in relation to psychotic experiences in study two, the finding that sexual abuse and emotional abuse both had direct effects on psychotic experiences over and above each other and other trauma types suggest they may be implicated

in different symptoms of psychosis. However, multiple symptoms often co-occur regardless of the type of trauma exposed to, suggesting that different types of childhood trauma may impact on the same mechanisms, or that those who are exposed to one trauma often experience other types of trauma as well (Bentall et al., 2012).

One of the most frequently reported forms of childhood trauma in studies one and two is peer bullying, which was consistently associated with all outcomes examined in this thesis, both in the general and VP/VLBW populations. Findings are also consistent with previous research which showed the enduring effect of peer bullying long after the experiences of being bullied (Arseneault, 2018). There is also some evidence in the literature that peer bullying may have a larger effect on adult psychopathology compared to caregiver-inflicted trauma (Lereya, Copeland, Costello, et al., 2015). However, those who are bullied are also more likely to have experienced caregiver-inflicted trauma at home, with around 40% of those who experienced any caregiver-inflicted trauma also experiencing peer bullying (Lereya, Copeland, Costello, et al., 2015). Part of this may be attributed to emotional dysregulation resulting from adverse home environments, which may increase children's vulnerability to being bullied (J. Kim & Cicchetti, 2010). There may be a vicious cycle where caregiver-inflicted abuse or neglect increases risk of peer bullying, which may be followed by further abuse that perpetuates over time (Bowes et al., 2013). Thus, rather than any individual trauma per se having a specific effect on adult psychopathology, there may be a complex pathway where caregiver-inflicted trauma has both a direct effect on adult psychopathology and an indirect effect via peer-inflicted trauma. Although analysis of specific trauma in studies one and two revealed stronger effects associated with certain types of childhood trauma, the most robust finding pertains to the dose-response effect of childhood trauma. This is also consistent with what has been reported in the literature (Copeland et al., 2018; Croft et al., 2018; McKay et al., 2021), and it is this cumulative exposure to multiple traumas that is associated with the highest risk of psychopathology.

Although there is some evidence for the direct effect of early biological risks on adult psychopathology in the studies presented in this thesis, a substantial part of its effect is mediated via increasing exposure to childhood trauma, in particular peer bullying. This suggests that the impact of early biological risks on childhood trauma may not be limited to caregiver-inflicted trauma occurring within the home environment, but it may also affect interaction with peers and the way in which peers respond to characteristics within the child. Different theories have been proposed to explain the way in which early biological risks may affect exposure to childhood trauma. According to the programming model, exposure to prenatal stress such as maternal depression during pregnancy may alter the stress response system of the offspring and lead to HPA-axis dysregulation which are implicated in depression (D. R. Kim et al., 2015). However, rather than a direct programming effect of prenatal maternal depression on offspring depression, findings from this thesis suggest an indirect effect via emotional abuse and peer bullying. Alterations in the HPA-axis and subsequent dysregulation in stress response in the offspring may programme the offspring to react more emotionally to their environment (O'Connor et al., 2013; Swales et al., 2018). A more reactive infant temperament may also increase risk of maladaptive parenting and parental conflict, which may contribute to risk of emotional abuse (Lereya & Wolke, 2013; Padilla et al., 2020). Furthermore, maladaptive parenting and parental conflict have also been found to mediate the association between prenatal maternal depression and peer bullying (Lereya & Wolke, 2013). Altogether, these suggest that prenatal maternal depression may have both a programming effect via infant temperament as well as an environmental effect via parenting behaviours, which can lead to certain emotional and behavioural changes in the child that elicit negative responses from both the caregiver and peers.

On the other hand, the association between neurodevelopmental adversity and childhood trauma may be more affected by individual characteristics. Neurodevelopmental adversity assessed in study two included both exposure to obstetric complications as well as childhood developmental impairments,

and only developmental impairments (cognitive and motor deficits) was associated with increased risk of peer bullying. Bullies often pick on those who are physically weaker and more vulnerable, and increased cognitive and motor difficulties have been previously associated with increased peer problems (Bowes et al., 2013; Ritchie et al., 2018). Similarly, VP/VLBW children who are disproportionally at risk of experiencing developmental impairments in childhood are also consistently shown to be at increased risk of peer bullying, both in the previous literature (Day, Van Lieshout, Vaillancourt, & Schmidt, 2015; Wolke, Baumann, et al., 2015) and in studies three and four of this thesis. Apart from developmental impairments, being born VP/VLBW is also associated with other characteristics that mark individuals as being potential victims, including being more socially withdrawn and experiencing more emotional problems in childhood (Cook et al., 2010; Juvonen et al., 2003; Wolke et al., 2019). Thus, while prenatal stress may be implicated in both trauma within the family and among peer groups via a programming effect and influencing the family environment, neurodevelopmental adversity may primarily affect the way in which peers react to individuals who embody certain characteristics that mark them as being easy targets for bullying.

Considering these findings against the Bradford-Hill criteria in assessing evidence for causality (Hill, 1965), there is some evidence to support the causal role of childhood trauma, in particular peer bullying in the onset of adult psychopathology. The effect of childhood trauma is similar in magnitude compared to what has been reported previously (around 2-4 times increased risk) (Croft et al., 2018; Kelleher et al., 2013; Li et al., 2016; Sahle et al., 2021; Varese et al., 2012), meeting the criterion for strengths and consistency. The use of longitudinal cohorts with prospectively collected data also suggest a temporal relationship between biological risks, childhood trauma and adult psychopathology in depression and psychotic experiences. A dose-response effect is also shown across all the studies, that the risk increases with either additional number of childhood traumas experienced or for those who are chronically exposed to the same trauma, and there is also

evidence in the literature on the plausibility of the effect of childhood trauma via both biological and psychological mechanisms (Read et al., 2014; Selten et al., 2013; Stowkowy & Addington, 2012). Together, these offer further support for a causal role of childhood trauma consistent with the literature (Copeland et al., 2018; Croft et al., 2018; Varese et al., 2012), and further extends this causal pathway to include biological risks in early life, which may act as early indicators for the challenges yet to come (Cannon et al., 2020).

Although there is now a growing body of evidence supporting the causal role of childhood trauma in adult psychopathology, part of this association may be confounded by genetic risks (Warrier et al., 2021). Childhood trauma has been previously shown to have a unidirectional effect on depression, but may have a bi-directional effect on schizophrenia, where genetic risks for schizophrenia was associated with increased exposure to childhood trauma, and childhood trauma was also associated with increased risk of psychosis (Warrier et al., 2021). In line with these findings, when polygenic risk scores for major depressive disorder and schizophrenia were controlled for in the general population in studies one and two, there was still an effect of childhood trauma on depression and psychotic experiences in adulthood, suggesting a causal effect independent from genetic influences. However, although genetic risk for major depressive disorder did not predict exposure to childhood trauma, genetic risk for schizophrenia was associated with increased risk of childhood trauma. This is consistent with the bi-directional effect found previously (Warrier et al., 2021) and suggest a gene-environment correlation, where offspring of parents with a history of schizophrenia may be more likely to experience childhood trauma, and also inherit more genetic risks which contribute to the onset of psychosis in adulthood (passive gene-environment effect) (Warrier et al., 2021). Alternatively, children with genetic risks for schizophrenia may also exhibit certain childhood characteristics which increase their likelihood of being exposed to trauma, and subsequently increase their risk of psychosis in adulthood (active and reactive gene-environment effect) (Warrier et al., 2021).

This passive gene-environment correlation is more likely for caregiver-inflicted trauma, as both the genetic and environmental risks are located within the family, thus parents who pass on genetic risks may also be more likely to inflict trauma (Warrier et al., 2021). Furthermore, there is some evidence to suggest the intergenerational transmission of trauma, where offspring of mothers with a history of childhood trauma are more likely to experience trauma themselves, possibly mediated via maternal depression (Plant et al., 2013, 2017). These all contribute to the difficulty of identifying causal pathways and separating the relative genetic and environmental effect of childhood trauma on adult psychopathology. However, findings from this thesis showed that the direct effect of childhood trauma on depression and psychotic experiences, as well as its mediated effect, remained even after controlling for the effects of genetic risks in the general population. This is consistent with other studies which showed a likely causal effect of childhood trauma over and above genetic influences (Croft et al., 2018), and extends this pathway to include early biological risks such as prenatal stress and neurodevelopmental adversity which may be implicated along the same developmental pathway.

Contrary to caregiver-inflicted trauma, peer bullying may not be subjected to the same genetic confounding effect, as the perpetrator of trauma is located outside the family. However, children with genetic risks may exhibit certain childhood characteristics which makes them more likely to be targeted by bullies. It has been shown previously that genetic risks for schizophrenia and bipolar disorders are associated with reduced cognitive functioning (Mistry et al., 2019; Riglin et al., 2017), which is a risk factor for being bullied (Bowes et al., 2013). This is also supported by an association between genetic risk for bipolar disorder and risk of peer bullying found in study two, suggesting that genetic vulnerabilities may manifest in certain childhood characteristics, such as cognitive impairments, which may increase susceptibility to being bullied by peers. Again, the consistent finding that peer bullying was associated with both depression and psychotic experiences in adulthood, even after

controlling for genetic risks, suggest a causal role of peer bullying that may be independent from the effect of genes (S. E. Moore et al., 2017).

Further confounding effect may come from the family environment, such as sibling bullying, which has been previously shown to increase the risk of peer bullying (Tippett & Wolke, 2015). Relationship with siblings is theorised to be crucial to the development of social skills, so those who are bullied by siblings may not develop adaptive social skills to interact with peers, which increases their vulnerability to being bullied (Wolke & Samara, 2004). Both sibling bullying and peer bullying are also predicted by negative parenting behaviours, such as abuse and neglect (Lereya et al., 2013), and those who experienced both sibling and peer bullying are also at the greatest risk of developing psychopathology (Dantchev et al., 2019). These suggest that different types of trauma may be considered as multiple mediators: early biological risks may increase exposure to caregiver-inflicted trauma via negative parenting behaviours, which increases risk to both sibling and peer bullying, and subsequently adult psychopathology. Peer bullying may thus be considered as both a cause for subsequent psychopathology as well as a consequence of early experiences (Lereya, Copeland, Costello, et al., 2015), including early biological risks, negative parenting behaviours, caregiver-inflicted trauma and sibling bullying, all of which may elicit certain behavioural and emotional changes in the child that increases their susceptibility to poor peer relationships (Bowes et al., 2013; Wolke, Tippett, et al., 2015).

A similar pattern of findings emerged when the same developmental cascade model was applied to domains of psychosocial wellbeing, i.e. self-concept. Traditional theoretical models such as the programming model or trauma models are often focused on outcomes in adult psychopathology (Räikkönen & Pesonen, 2009; Read et al., 2014; Van den Bergh et al., 2017). However, findings from study four in this thesis suggest that similar mechanisms are also implicated in the development of self-concept, in particular the direct and indirect effect of VP/VLBW birth on social self-concept via peer bullying.

Peer bullying has previously been proposed to affect a number of outcomes including mental health, physical health, psychosocial wellbeing and socio-economic attainment (Arseneault, 2018; Wolke, Copeland, et al., 2013). While peer bullying may be associated with both biological and psychological processes underlying the onset of adult psychopathology, its association with self-concept may involve more cognitively mediated processes such as negative appraisals of events, reduced sense of self-efficacy and perceived control (Arseneault, 2018; Catterson & Hunter, 2010; Guy et al., 2017; Singh & Bussey, 2011). These cognitive vulnerabilities may affect the way victims perceive themselves and their abilities or competence in certain domains, such as their body image or self-perceived social relationships, and the effect of bullying on social relationships has been found to last even into adulthood (Wolke, Copeland, et al., 2013).

It can therefore be argued that the same developmental cascade model is applicable to studying both the onset of psychopathology as well as altered development in psychosocial wellbeing, both among the general population and in special risk groups. The consistent mediating role of peer bullying across these outcomes suggest that early biological risks act to a considerable extent by increasing exposure to subsequent environmental risk (i.e. peer bullying), which in turn has a widespread effect on many areas of development. Psychopathology and psychosocial wellbeing have been previously proposed to be separate constructs with different antecedents in the literature, and are only weakly correlated with each other in childhood and adolescence (Patalay & Fitzsimons, 2016). However, findings from this thesis suggest that although different risks may be involved, they are mediated by the same factor – peer bullying. Given that both the absence of psychopathology and the presence of positive psychosocial wellbeing are necessary components for positive mental health (Westerhof & Keyes, 2010), the finding that similar mechanisms may be involved, despite different risk exposure or group status, suggest a common target for intervention.

12.3 Strengths and limitations

The studies included in this thesis has a number of strengths: first, all four studies included the use of longitudinal cohorts from three different countries (UK, Germany, Ireland) followed up from birth to adulthood. These included both a general population-based cohort in Avon, Southwest of England, as well as two special population cohorts (VP/VLBW or EP) with term-born controls in UK/Ireland and Germany. These prospective cohorts also had adequate sample sizes ranging from 184 to 399 in special populations and more than 3500 in the general population. The use of a large general population-based cohort generated enough statistical power to directly examine indicators of biological risks, while the special populations – the VP/VLBW and EP populations – were utilised as a naturalistic experiment using a proxy measure for biological risks. The replication of findings across both types of populations further increases the generalisability of the findings and adds support for the role of childhood trauma as both a predictor and a mediator.

Secondly, a number of control variables were included in all four studies, including demographic variables such as sex and indicators of SES, and studies using the general population-based cohort (study one and two) further controlled for genetic risks when modelling pathways to depression and psychotic experiences in adulthood. Both areas of psychopathology have a moderate amount of genetic heritability (Flint & Kendler, 2014; Sieradzka et al., 2015), and genetic risks may also confound some of the effect of childhood trauma on adult psychopathology (Warrier et al., 2021). Being female has also been shown in the previous literature (Gentile et al., 2009; Piccinelli & Wilkinson, 2000), and in study one and four in this thesis, to be associated with higher risk for depression and lower self-concept. Thus, the persistent effect of childhood trauma, even after accounting for these genetic risks and sex differences, provide further support for a likely causal effect of childhood trauma on adult psychological development independent from potential confounding influences.

Thirdly, psychotic experiences were examined as an outcome both in the general population as well as in the VP/VLBW and EP populations. The same measure of psychotic experiences was used across both groups, which has been well validated in the literature with very good inter-rater and test-retest reliability (Horwood et al., 2008; Sullivan et al., 2020; Zammit et al., 2013). Given the use of the same instrument, the finding of a consistent mediating effect of peer bullying across both studies further increases the validity of the result and reduces potential bias from the use of different instruments.

Finally, these studies used theoretically informed approaches and simultaneously tested different models of psychopathology that are widely cited in the literature, including the programming model, Neurodevelopmental model of schizophrenia, Trauma models and cumulative effect or Developmental Risk Factor model. This theoretically driven approach adds empirical support to some of these models which have received relatively little empirical testing, such as the Developmental Risk Factor model, and further extends the applicability of these theories to areas of psychosocial wellbeing as well as adult psychopathology.

There are also some limitations, firstly on the rates of drop-out which is inevitable in longitudinal studies spanning more than two decades. One of the ways in which selective drop-out may affect findings is by reducing statistical power, especially if those who dropped out were more likely to be exposed to biological risks such as prenatal stress and neurodevelopmental adversity (Eryigit-Madzwamuse et al., 2015; Johnson et al., 2009; Linsell, 2017; Wolke et al., 2009). Predictive associations between variables are not shown to be affected by drop-outs in previous simulation studies (Wolke et al., 2009), although there may be an underestimation in the effect sizes associated with biological risks. Furthermore, the proportion of missing data across variables used in the analyses ranged from 0.2% to 27%. Given that data is unlikely to be missing completely at random, multiple imputation by chained equations was used to impute missing data in all studies, which has been shown to reduce bias (Azur et al., 2011; Buuren & Groothuis-oudshoorn, 2011). The

inclusion of complete case analyses in two of the studies also showed similar findings to results after imputation, suggesting a reliable imputation process.

Another limitation is that the confounding effect of genetic risks was not examined in the VP/VLBW and EP cohorts, as these data were not available. Although genetic risks are often associated with adult psychopathology, there is recent evidence that genetic risks for ADHD, risk-taking, body-mass-index and intelligence are also associated with exposure to peer bullying (Schoeler et al., 2019). Only genetic risks for psychopathology (depression, neuroticism, schizophrenia, bipolar disorder) were controlled for in the general population in relation to childhood trauma, and genetic risks were not accounted for when modelling the effects of VP/VLBW birth on the development of self-concept. Future research controlling for multiple genetic risks can further differentiate the relative genetic and environmental contributions to peer bullying and other types of childhood trauma, and whether genetic risks may also be involved in the development of self-concept.

Further limitations come from the use of different measures across studies. For example, childhood trauma was a composite variable indicating both caregiver- and peer-inflicted trauma in the first two studies using data from the general population. However, only peer-inflicted trauma was investigated in the last two studies using data from the VP/VLBW and EP populations, as data on caregiver-inflicted trauma was not available in these cohorts. Although there is evidence that peer bullying was the only trauma that mediated the association between neurodevelopmental adversity and PE in adulthood over and above other trauma types, other types of trauma may have an impact on the development of self-concept. Parent-child relationships have been previously proposed to be important in the development of both global self-esteem and social self-concept (Deković & Meeus, 1997; Paulus et al., 2018), thus experiences of caregiver-inflicted trauma may also lead to changes in the development of self-concept. It would be important for future

studies to collect data on both types of trauma and to examine their differential effects on different areas of outcome.

Lastly, outcomes in adult psychopathology were primarily assessed as a binary variable, indicating either the presence or absence of a clinically significant depression diagnosis, or whether there were suspected/definite signs of psychotic experiences being present. Given that symptoms exist on a scale, with considerable overlap between different diagnostic disorders (Caspi & Moffitt, 2018), it may be important for future studies to adopt a dimensional approach to examine variations in self-reported symptoms as well as the odds of belonging to a clinical group. Furthermore, the presence of suspected/definite psychotic experiences was derived from questions on 12 core symptoms of psychosis, including areas of hallucination, delusions and thought disorder (Horwood et al., 2008; Sullivan et al., 2020; Zammit et al., 2013). There may be specificity in the association between specific trauma types and specific psychotic experiences (Bentall et al., 2012, 2014). Further research can also examine the mediating effect of specific trauma in the association between neurodevelopmental adversity and specific psychotic experiences.

12.4 Implications and future directions

The findings from the studies included in this thesis have two broad implications: first on methodological approaches to longitudinal research, and second on the design and implementation of interventions. It has been previously summarised that long-term follow-up studies in populations at-risk, such as the preterm population, contain several methodological flaws, one of which is the repeated use of main effect models to examine the direct association between an exposure and outcome (Aylward, 2002, 2010; Wolke et al., 2019). This direct effect model does not take into consideration other influences or causal mechanisms, which across all studies in this thesis was consistently identified as childhood trauma, that may be on the same pathway from biological risks to adult psychopathology and psychosocial wellbeing.

Consistent with a developmental cascade model such as the cumulative effect model or the Developmental Risk Factor model, early biological risks may be considered as early warning signs of difficulties that are more likely at each stage of development, which can increase exposure to further risk and deviance from typical development (Cannon et al., 2020; Murray et al., 2017; Murray & Fearon, 1999; O'Connor, 2015). Thus, future longitudinal studies should routinely adopt these developmental cascade models and test for the mediating effect of environmental factors when examining the long-term association between early biological risks and adult outcomes. This approach can also be applied to both areas of psychopathology and psychosocial wellbeing to achieve a holistic understanding on pathways to overall positive mental health.

Adopting this developmental cascade approach in research also allows the opportunity for interventions at different stages of development, and points to the importance of identifying mediating mechanisms that may be modifiable (O'Connor, 2015). Both prenatal stress and neurodevelopmental adversity were shown to be associated with increased risk of childhood trauma and subsequently adverse outcomes in areas of psychopathology and psychosocial wellbeing. These suggest the importance of early screening of pregnant mothers to identify who may be at risk, and provide them with appropriate support and interventions to reduce symptoms of depression (Daley et al., 2015; Dennis & Dowswell, 2013; Milgrom et al., 2015). The finding that family adversity was also a risk factor for childhood trauma, and indirectly to offspring depression indicates the importance of targeting not just psychological stress but also social and economic stress, such as poverty, living conditions and substance use. On the other hand, there may be more challenges in preventing or reducing exposure to neurodevelopmental adversity, such as preterm birth. Specific risk factors have been associated with preterm birth, including both intrauterine (e.g. placenta previa, cervix length) and extrauterine factors (e.g. antibiotics, anxiety) (Della Rosa et al., 2021). There is recent evidence that although rates of preterm birth have been decreasing in some countries, in others it may be rising due to multiple births

or induced delivery (Goldenberg et al., 2008; Zeitlin et al., 2013). Furthermore, despite improved medical care and survival rates, there has been little improvement in childhood developmental outcomes, and the benefits of early interventions are also not long-lasting (Cheong et al., 2020; Orton et al., 2009; Spittle et al., 2015).

Consistent with the idea of a developmental cascade, there is thus another opportunity to intervene in childhood (O'Connor, 2015), and children who were exposed to biological risks such as prenatal stress and neurodevelopmental adversity can be recognised as a group at increased risk of experiencing childhood trauma. Understanding certain mechanisms in which prenatal stress may be associated with exposure to childhood trauma, such as reduced emotional availability in mothers and maladaptive parenting (Kluczniok et al., 2016; Lereya & Wolke, 2013), can help tailor family interventions to improve parenting techniques, although further research is needed on whether this may also reduce risk of childhood trauma. Similarly, the identification that prenatal maternal depression, childhood developmental impairments and VP/VLBW birth were all associated with increased risk of peer bullying suggest that these are vulnerable groups who are more likely to be bullied. This means that early interventions can be offered, such as improving social skills and reducing social isolation, to mitigate their risk of being bullied and experiencing psychopathology in later life (Sommer et al., 2016). Although biological risks or family adversity may never be eliminated, part of their effect may be attenuated by focusing interventions on subsequent developmental challenges during childhood and adolescence.

As well as identifying vulnerable groups who are more likely to experience trauma, these findings also suggest the importance of reducing childhood trauma in the general population, regardless of prior exposure to biological risks. It has been previously hypothesised that around one third of cases of psychosis and almost half of depression cases may be prevented by reducing childhood trauma (Li et al., 2016; Varese et al., 2012). On top of this, findings from the studies in this thesis showed that a substantial amount of the total

effect of biological risks on adult depression and psychotic experiences, as well as decreasing levels of social self-concept, can be accounted for by childhood trauma. The proportion of effect mediated is even greater among the VP/VLBW group, where peer bullying may account for more than half of the risk of psychotic experiences associated with VP/VLBW birth. Thus, interventions aimed at reducing childhood trauma in general, as well as recognising those at high-risk and intervening earlier in this vulnerable group, may lead to further reduction in risks.

There has been some research into the effectiveness of early interventions aimed at preventing and reducing the effects of childhood trauma. For example, trauma-informed services have been piloted in schools, providing teachers with the relevant training and resources to recognise indicators for traumatic experiences, identifying vulnerable children, and creating linkage with relevant health and social services to provide comprehensive intervention plans (Tabone et al., 2020). There is some evidence for increased emotional support for children in classrooms assigned to the intervention (Tabone et al., 2020), although long-term research is still needed to examine the effectiveness of such programmes in reducing the rates and effects of childhood trauma. Anti-bullying interventions have also received some attention in the literature, and a recent meta-analysis found a small reduction in both bullying behaviours as well as symptoms of psychopathology following any anti-bullying programme (Fraguas et al., 2021). Similar reductions were seen regardless of the duration of intervention, suggesting that even short-term interventions may have long-lasting benefits (Fraguas et al., 2021). Virtual interventions have also been piloted previously with some success (Sapouna et al., 2010; Wolke & Sapouna, 2012), which may provide a cost-effective way of reducing bullying in schools.

Finally, there is also an opportunity for trauma to be incorporated as part of the intervention programme for people experiencing symptoms of depression and psychosis, as well as other areas of psychopathology. Although not all individuals presenting with symptoms of psychopathology have experienced

childhood trauma, clinicians may benefit from routinely screening for a history of trauma and to offer trauma-focused therapies for those whose onset of symptoms may be attributed to childhood trauma (Bloomfield et al., 2020; Gianfrancesco et al., 2019). Traditionally, treatment for specific psychopathology such as psychosis are often separate from treatment for trauma (Bloomfield et al., 2020), however, findings from this thesis suggest a need for further research on the potential benefit of integrating interventions for depression and psychosis with interventions for trauma. There has been increasing interest in the integration of trauma-informed care in health care services, although certain barriers have been proposed, including continued reliance on a biomedical model of psychopathology, controversy around blaming families for the onset of psychopathology, as well as a general reluctance of adopting a new approach which requires organisational training and support (Sweeney et al., 2016, 2018). However, clinicians should continue to be aware of the role of childhood trauma in the onset of adult psychopathology, and further research should investigate the feasibility and cost-effectiveness of integrating trauma-informed care into existing services, to help transition to a more holistic approach in targeting symptoms of psychopathology.

12.5 Conclusion

Investigation into long-term outcomes after exposure to early biological risks should routinely examine environmental influences which may mediate its effect on adult psychological development. The role of childhood trauma as a mediator in the association between biological risks and adult psychological development has been shown consistently across the four studies included in this thesis. Reducing childhood trauma may thus not only reduce risks of adult psychopathology and increase psychosocial wellbeing in the general population, but it may also mitigate some of the risks associated with being exposed to biological risks early in life. Understanding the ways in which biological risks increase exposure to childhood trauma, and subsequently influence adult development allow clinicians and researchers to identify early

warning signs and intervene at different stages. Lastly, as well as preventing and reducing incidences of childhood trauma, health care services should continue to recognise the role of childhood trauma and to further investigate the opportunity of adopting a trauma-informed approach to care.

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Appendices

Study 1: Supplementary materials

Appendix A.

Unadjusted pathway from prenatal maternal depression to depression at 24 years via trauma

	SE	95% CI	p-value
Depression ~			
Prenatal maternal depression	0.06	0.01 – 0.12	0.023
Trauma	0.17	0.11 – 0.23	<0.001
Trauma ~			
Prenatal maternal depression	0.25	0.21 – 0.29	<0.001
Indirect effect			
Prenatal maternal depression → Trauma → Depression	0.04	0.03 – 0.06	<0.001
Total effect	0.11	0.05 – 0.16	<0.001

Appendix B.

Unadjusted pathway from postnatal maternal depression to depression at 24 years via trauma

	SE	95% CI	p-value
Depression ~			
Postnatal maternal depression	0.04	-0.02 – 0.09	0.162
Trauma	0.18	0.12 – 0.24	<0.001
Trauma ~			
Postnatal maternal depression	0.25	0.21 – 0.29	<0.001
Indirect effect			
Postnatal maternal depression → Trauma → Depression	0.05	0.03 – 0.06	<0.001
Total effect	0.08	0.03 – 0.14	0.002

Appendix C.

Unadjusted pathway from prenatal FAI to depression at 24 years via trauma

	SE	95% CI	p-value
Depression ~			
Prenatal FAI	0.06	0.003 – 0.11	0.039
Trauma	0.18	0.12 – 0.23	<0.001
Trauma ~			
Prenatal FAI	0.24	0.20 – 0.28	<0.001
Indirect effect			
Prenatal FAI → Trauma → Depression	0.04	0.03 – 0.06	<0.001
Total effect	0.10	0.05 – 0.15	<0.001

Appendix D.

Unadjusted pathway from postnatal FAI to depression at 24 years via trauma

	SE	95% CI	p-value
Depression ~			
Postnatal FAI	0.06	0.002 – 0.12	0.043
Trauma	0.17	0.11 – 0.23	<0.001
Trauma ~			
Postnatal FAI	0.28	0.24 – 0.32	<0.001
Indirect effect			
Postnatal FAI → Trauma → Depression	0.05	0.03 – 0.07	<0.001
Total effect	0.11	0.05 – 0.16	<0.001

Appendix E.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via physical abuse.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.04	-0.04 – 0.12	0.291
Maternal depression (postnatal)	0.01	-0.06 – 0.09	0.757
FAI (prenatal)	0.04	-0.04 – 0.11	0.317
FAI (postnatal)	0.02	-0.05 – 0.09	0.572
Physical abuse	0.21	0.13 – 0.29	<0.001
Physical abuse [a] ~			
Maternal depression (prenatal)	0.05	-0.01 – 0.12	0.118
Maternal depression (postnatal)	0.05	-0.02 – 0.12	0.135
FAI (prenatal)	0.03	-0.03 – 0.09	0.306
FAI (postnatal)	0.11	0.05 – 0.17	<0.001
Indirect effect [a]			
Prenatal maternal depression → Physical abuse → Depression	0.011	-0.003 – 0.025	0.135
Postnatal maternal depression → Physical abuse → Depression	0.010	-0.004 – 0.025	0.145
Prenatal FAI → Physical abuse → Depression	0.007	-0.006 – 0.019	0.307
Postnatal FAI → Physical abuse → Depression	0.023	0.008 – 0.037	0.002
Total effect	0.164	0.091 – 0.237	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Appendix F.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via emotional abuse.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.04	-0.04 – 0.12	0.334
Maternal depression (postnatal)	0.00	-0.08 – 0.08	0.998
FAI (prenatal)	0.04	-0.04 – 0.11	0.307
FAI (postnatal)	0.02	-0.06 – 0.09	0.694
Emotional abuse	0.16	0.08 – 0.24	<0.001
Emotional abuse [a] ~			
Maternal depression (prenatal)	0.09	0.03 – 0.16	0.005
Maternal depression (postnatal)	0.15	0.08 – 0.21	<0.001
FAI (prenatal)	0.04	-0.02 – 0.10	0.203
FAI (postnatal)	0.18	0.13 – 0.24	<0.001
Indirect effect [a]			
Prenatal maternal depression → Emotional abuse → Depression	0.015	0.002 – 0.027	0.018
Postnatal maternal depression → Emotional abuse → Depression	0.023	0.007 – 0.038	0.004
Prenatal FAI → Emotional abuse → Depression	0.006	-0.003 – 0.016	0.207
Postnatal FAI → Emotional abuse → Depression	0.028	0.011 – 0.045	0.001
Total effect	0.164	0.091 – 0.237	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Appendix G.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via sexual abuse.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.04	-0.04 – 0.12	0.291
Maternal depression (postnatal)	0.02	-0.06 – 0.10	0.622
FAI (prenatal)	0.03	-0.05 – 0.11	0.423
FAI (postnatal)	0.03	-0.04 – 0.11	0.343
Sexual abuse	0.24	0.15 – 0.33	<0.001
Sexual abuse [a] ~			
Maternal depression (prenatal)	0.04	-0.04 – 0.13	0.280
Maternal depression (postnatal)	0.01	-0.07 – 0.09	0.726
FAI (prenatal)	0.06	-0.02 – 0.14	0.138
FAI (postnatal)	0.04	-0.03 – 0.11	0.303
Indirect effect [a]			
Prenatal maternal depression → Sexual abuse → Depression	0.011	-0.009 – 0.030	0.287
Postnatal maternal depression → Sexual abuse → Depression	0.003	-0.015 – 0.022	0.721
Prenatal FAI → Sexual abuse → Depression	0.014	-0.005 – 0.033	0.142
Postnatal FAI → Sexual abuse → Depression	0.009	-0.008 – 0.026	0.309
Total effect	0.164	0.091 – 0.236	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression, and sex (female) on childhood sexual abuse. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Appendix H.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via emotional neglect.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.05	-0.03 – 0.13	0.187
Maternal depression (postnatal)	0.03	-0.05 – 0.10	0.515
FAI (prenatal)	0.03	-0.04 – 0.11	0.387
FAI (postnatal)	0.04	-0.04 – 0.11	0.316
Emotional neglect	0.11	0.01 – 0.22	0.040
Emotional neglect [a] ~			
Maternal depression (prenatal)	0.003	-0.08 – 0.09	0.946
Maternal depression (postnatal)	-0.03	-0.11 – 0.06	0.580
FAI (prenatal)	0.11	0.02 – 0.19	0.012
FAI (postnatal)	0.06	-0.02 – 0.14	0.154
Indirect effect [a]			
Prenatal maternal depression → Emotional neglect → Depression	0.00	-0.009 – 0.010	0.941
Postnatal maternal depression → Emotional neglect → Depression	-0.003	-0.012 – 0.007	0.562
Prenatal FAI → Emotional neglect → Depression	0.012	-0.004 – 0.027	0.145
Postnatal FAI → Emotional neglect → Depression	0.007	-0.003 – 0.016	0.158
Total effect	0.164	0.091 – 0.237	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression, and sex (male) on emotional neglect. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Appendix I.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via domestic violence.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.05	-0.03 – 0.13	0.185
Maternal depression (postnatal)	0.02	-0.05 – 0.10	0.562
FAI (prenatal)	0.05	-0.03 – 0.12	0.236
FAI (postnatal)	0.04	-0.03 – 0.12	0.268
Domestic violence	-0.001	-0.09 – 0.09	0.988
Domestic violence [a] ~			
Maternal depression (prenatal)	0.12	0.05 – 0.18	0.001
Maternal depression (postnatal)	0.07	0.01 – 0.14	0.026
FAI (prenatal)	0.10	0.04 – 0.17	0.001
FAI (postnatal)	0.26	0.21 – 0.32	<0.001
Indirect effect [a]			
Prenatal maternal depression → Domestic violence → Depression	0.00	-0.010 – 0.010	0.988
Postnatal maternal depression → Domestic violence → Depression	0.00	-0.007 - 0.007	0.989
Prenatal FAI → Domestic violence → Depression	0.00	-0.009 – 0.009	0.986
Postnatal FAI → Domestic violence → Depression	0.00	-0.023 – 0.023	0.988
Total effect	0.164	0.091 – 0.237	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounder: sex (female) and genetic risk score for MDD on depression. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Appendix J.

Path analysis showing direct and indirect pathways from pre- and postnatal maternal depression/FAI to depression at 24 years via peer bullying.

	SE	95% CI	p-value
Depression [a] ~			
Maternal depression (prenatal)	0.04	-0.04 – 0.12	0.276
Maternal depression (postnatal)	0.02	-0.06 – 0.10	0.611
FAI (prenatal)	0.04	-0.03 – 0.12	0.247
FAI (postnatal)	0.04	-0.03 – 0.11	0.275
Peer bullying	0.11	0.03 – 0.18	0.007
Peer bullying [a] ~			
Maternal depression (prenatal)	0.09	0.03 – 0.15	0.005
Maternal depression (postnatal)	0.03	-0.04 – 0.09	0.430
FAI (prenatal)	0.01	-0.05 – 0.07	0.816
FAI (postnatal)	0.03	-0.02 – 0.09	0.232
Indirect effect [a]			
Prenatal maternal depression → Peer bullying → Depression	0.010	0.000 – 0.019	0.040
Postnatal maternal depression → Peer bullying → Depression	0.003	-0.004 – 0.009	0.432
Prenatal FAI → Peer bullying → Depression	0.001	-0.005 – 0.007	0.815
Postnatal FAI → Peer bullying → Depression	0.004	-0.003 – 0.010	0.260
Total effect	0.164	0.090 – 0.236	<0.001

[a] All paths adjusted for each other, as well as for sex and genetic risk for MDD and neuroticism. Significant confounders: sex (female) and genetic risk score for MDD on depression, and sex (male) on peer bullying. Additional pathways not shown here: from postnatal influences to prenatal influences, and covariance between postnatal maternal depression and postnatal FAI.

Study 2: Supplementary materials

Appendix K.

Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via trauma (N=3514).

	SE	95% CI	p-value
PE at 24 years ~			
Obstetric complications	0.046	-0.011 – 0.103	0.112
Developmental impairment	0.081	0.004 – 0.158	*0.040*
Trauma	0.224	0.162 – 0.286	*<0.001*
Trauma (up to 17 years) ~			
Obstetric complications	0.022	-0.019 – 0.064	0.286
Developmental impairment	0.074	0.017 – 0.130	*0.011*
Indirect effect			
Obstetric complications → Trauma → PE	0.005	-0.004 – 0.014	0.289
Developmental impairment → Trauma → PE	0.016	0.003 – 0.030	*0.016*
Total effect	0.148	0.055 – 0.242	*0.002*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: maternal smoking; significant confounders on trauma up to 17 years: maternal smoking, FAI, and genetic risk score for schizophrenia.

Appendix L.

Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via specific trauma (N=3514).

	SE	95% CI	p-value
PE at 24 years ~			
Obstetric complications	0.045	-0.012 – 0.102	0.122
Developmental impairment	0.072	-0.006 – 0.149	0.070
Physical abuse	-0.034	-0.168 – 0.100	0.619
Sexual abuse	0.179	0.066 – 0.293	*0.002*
Emotional abuse	0.163	0.052 – 0.273	*0.004*
Emotional neglect	0.041	-0.066 – 0.149	0.452
Peer bullying	0.156	0.079 – 0.233	*<0.001*
Physical abuse (up to 17 years) ~			
Obstetric complications	0.038	-0.013 – 0.089	0.140
Developmental impairment	0.029	-0.042 – 0.100	0.424
Sexual abuse (up to 17 years) ~			
Obstetric complications	0.035	-0.028 – 0.098	0.275
Developmental impairment	0.037	-0.050 – 0.124	0.402
Emotional abuse (up to 17 years) ~			
Obstetric complications	0.014	-0.038 – 0.066	0.593
Developmental impairment	-0.015	-0.087 – 0.057	0.689
Emotional neglect (up to 17 years) ~			
Obstetric complications	-0.072	-0.144 – 0.001	0.052
Developmental impairment	0.106	0.014 – 0.199	*0.024*
Peer bullying (up to 17 years) ~			
Obstetric complications	0.009	-0.039 – 0.056	0.713
Developmental impairment	0.133	0.069 – 0.198	*<0.001*
Developmental impairment ~			
Obstetric complications	0.052	0.003 – 0.102	*0.038*
Covariance			
Physical abuse ~~ Sexual abuse	0.475	0.407 – 0.543	*<0.001*
Physical abuse ~~ Emotional abuse	0.581	0.529 – 0.632	*<0.001*
Physical abuse ~~ Emotional neglect	0.076	-0.018 – 0.171	0.112
Physical abuse ~~ Peer bullying	0.145	0.08 – 0.210	*<0.001*
Sexual abuse ~~ Emotional abuse	0.252	0.173 – 0.332	*<0.001*

Appendix L continued.

Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via specific trauma (N=3514).

	SE	95% CI	p-value
Sexual abuse ~~ Emotional neglect	0.158	0.047 – 0.268	*0.005*
Sexual abuse ~~ Peer bullying	0.109	0.029 – 0.189	*0.007*
Emotional abuse ~~ Emotional neglect	0.118	0.026 – 0.211	*0.012*
Emotional abuse ~~ Peer bullying	0.104	0.038 – 0.171	*0.002*
Emotional neglect ~~ Peer bullying	0.189	0.104 – 0.273	*<0.001*
Indirect effect			
From obstetric complications via ~			
Physical abuse	-0.001	-0.007 – 0.004	0.645
Sexual abuse	0.006	-0.005 – 0.018	0.293
Emotional abuse	0.002	-0.006 – 0.011	0.591
Emotional neglect	-0.003	-0.011 – 0.005	0.463
Peer bullying	0.001	-0.005 – 0.008	0.692
From developmental impairment via ~			
Physical abuse	-0.001	-0.005 – 0.003	0.576
Sexual abuse	0.007	-0.009 – 0.022	0.394
Emotional abuse	-0.002	-0.014 – 0.009	0.691
Emotional neglect	0.004	-0.005 – 0.013	0.352
Peer bullying	0.021	0.008 – 0.034	*0.002*
Total effect	0.151	0.058 – 0.243	*0.001*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: maternal smoking. Significant confounders for each trauma: physical abuse – family history of schizophrenia, FAI; sexual abuse – sex (female), genetic risk score for schizophrenia; emotional abuse – maternal age, FAI and genetic risk score for schizophrenia; emotional neglect – sex (male), FAI; peer bullying – sex (male), FAI, genetic risk score for bipolar disorder.

Appendix M.

Complete case analysis: Logistic regression models showing the effects of neurodevelopmental adversity and trauma on PE (N=1871)

	Suspected or definite PE								
	Unadjusted			Adjusted [a]			Adjusted [b]		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Any neurodevelopmental adversity	1.42	1.06 – 1.89	*0.017*	1.37	1.02 – 1.83	*0.037*	1.37	1.02 – 1.83	*0.037*
Any trauma	2.13	1.65 – 2.75	*<0.001*	2.05	1.58 – 2.66	*<0.001*	2.06	1.54 – 2.75	*<0.001*
Any neurodevelopmental adversity x any trauma	-	-	-	-	-	-	1.06	0.63 – 1.79	0.821

[a] Adjusted for each other as well as confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounder: maternal smoking.

[b] Adjusted for each other as well as confounders, with interaction term added

Appendix N.

Complete case analysis: Standardised path estimates showing the direct and indirect paths from neurodevelopmental adversity to PE via trauma (N=1871).

	SE	95% CI	p-value
PE at 24 years ~			
Neurodevelopmental adversity	0.112	0.009 – 0.214	*0.032*
Trauma	0.238	0.158 – 0.318	*<0.001*
Trauma (up to 17 years) ~			
Neurodevelopmental adversity	0.054	-0.019 – 0.127	0.145
Indirect effect			
Neurodevelopmental adversity → Trauma → PE	0.013	-0.005 – 0.031	0.157
Total effect	0.124	0.021 – 0.227	*0.018*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: maternal smoking; significant confounders on trauma up to 17 years: maternal smoking, FAI, and genetic risk score for schizophrenia.

Appendix O.

Complete case analysis: Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via trauma (N=1784).

	SE	95% CI	p-value
PE at 24 years ~			
Obstetric complications	0.105	-0.054 – 0.264	0.196
Developmental impairment	0.115	0.010 – 0.219	*0.031*
Trauma	0.231	0.150 – 0.313	*<0.001*
Trauma (up to 17 years) ~			
Obstetric complications	0.044	-0.070 – 0.159	0.449
Developmental impairment	0.034	-0.043 – 0.110	0.393
Indirect effect			
Obstetric complications → Trauma → PE	0.010	-0.016 – 0.037	0.453
Developmental impairment → Trauma → PE	0.008	-0.010 – 0.026	0.393
Total effect	0.238	0.052 – 0.423	*0.012*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: maternal smoking; significant confounders on trauma up to 17 years: sex (male), maternal smoking, FAI, and genetic risk score for schizophrenia.

Appendix P.

Complete case analysis: Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via specific trauma (N=1773)

	SE	95% CI	p-value
PE at 24 years ~			
Obstetric complications	0.114	-0.046 – 0.275	0.163
Developmental impairment	0.099	-0.006 – 0.203	0.065
Physical abuse	-0.075	-0.263 – 0.113	0.435
Sexual abuse	0.227	0.073 – 0.381	*0.004*
Emotional abuse	0.140	-0.023 – 0.304	0.093
Emotional neglect	0.025	-0.122 – 0.171	0.741
Peer bullying	0.176	0.072 – 0.279	*0.001*
Physical abuse (up to 17 years) ~			
Obstetric complications	0.083	-0.056 – 0.221	0.241
Developmental impairment	-0.002	-0.095 – 0.091	0.968
Sexual abuse (up to 17 years) ~			
Obstetric complications	0.001	-0.168 – 0.169	0.994
Developmental impairment	0.033	-0.080 – 0.147	0.568
Emotional abuse (up to 17 years) ~			
Obstetric complications	0.023	-0.121 – 0.166	0.758
Developmental impairment	-0.439	-0.141 – 0.054	0.383
Emotional neglect (up to 17 years) ~			
Obstetric complications	-0.099	-0.294 – 0.097	0.322
Developmental impairment	0.079	-0.045 – 0.203	0.213
Peer bullying (up to 17 years) ~			
Obstetric complications	0.007	-0.125 – 0.140	0.914
Developmental impairment	0.121	0.035 – 0.208	*0.006*
Developmental impairment ~			
Obstetric complications	0.085	-0.056 – 0.225	0.236
Covariance			
Physical abuse ~~ Sexual abuse	0.476	0.388 – 0.564	*<0.001*
Physical abuse ~~ Emotional abuse	0.590	0.524 – 0.657	*<0.001*
Physical abuse ~~ Emotional neglect	0.026	-0.100 – 0.152	0.685
Physical abuse ~~ Peer bullying	0.152	0.068 – 0.236	*<0.001*

Appendix P continued.

Complete case analysis: Standardised path estimates showing the direct and indirect paths from obstetric complications and developmental impairment to PE via specific trauma (N=1773)

	SE	95% CI	p-value
Sexual abuse ~~ Emotional abuse	0.267	0.161 – 0.373	*<0.001*
Sexual abuse ~~ Emotional neglect	0.164	0.019 – 0.309	*0.027*
Sexual abuse ~~ Peer bullying	0.140	0.037 – 0.242	*0.008*
Emotional abuse ~~ Emotional neglect	0.145	0.020 – 0.270	*0.023*
Emotional abuse ~~ Peer bullying	0.115	0.027 – 0.203	*0.010*
Emotional neglect ~~ Peer bullying	0.187	0.076 – 0.298	*0.001*
Indirect effect			
From obstetric complications via ~			
Physical abuse	-0.006	-0.024 – 0.012	0.503
Sexual abuse	0.000	-0.038 – 0.038	0.994
Emotional abuse	0.003	-0.017 – 0.024	0.762
Emotional neglect	-0.002	-0.018 – 0.013	0.753
Peer bullying	0.001	-0.022 – 0.025	0.914
From developmental impairment via ~			
Physical abuse	0.000	-0.007 – 0.007	0.968
Sexual abuse	0.008	-0.019 – 0.034	0.573
Emotional abuse	-0.006	-0.022 – 0.010	0.444
Emotional neglect	0.002	-0.010 – 0.014	0.758
Peer bullying	0.021	0.002 – 0.040	*0.030*
Total effect	0.234	0.048 – 0.420	*0.014*

Note. All paths adjusted for confounders: sex, maternal age, maternal smoking, genetic risk score for schizophrenia and bipolar, family history of schizophrenia, and family adversity. Significant confounders on PE at 24 years: sex (male), maternal smoking. Significant confounders for each trauma: physical abuse – maternal smoking, FAI; sexual abuse – sex (female); emotional abuse – maternal age (older), FAI and genetic risk score for schizophrenia; emotional neglect – sex (male), family history of schizophrenia, FAI; peer bullying – sex (male), FAI.

Study 3: Supplementary materials

Appendix Q.

Complete case analysis: simple and multiple logistic regression models showing the effects of VP/VLBW/EP and peer bullying on PE, as well as showing the interaction between VP/VLBW/EP and peer bullying.

	Suspected or definite PE								
	Unadjusted			Adjusted for SES and sex			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
BLS (N=364)									
VP/VLBW	1.65	0.91 – 3.00	0.100	1.50	0.81 – 2.78	0.197	0.93	0.21 – 4.12	0.923
Peer bullying									
Not bullied	[Reference]			[Reference]			[Reference]		
Bullied at one time period	3.10	1.36 – 7.08	0.007	2.99	1.31 – 6.85	0.010	1.92	0.63 – 4.12	0.253
Bullied at both time periods	4.81	1.94 – 11.92	0.001	4.55	1.81 – 11.41	0.001	5.01	1.43 – 17.58	0.012
VP/VLBW x bullied at one period	-		-	-		-	2.47	0.44 – 13.72	0.302
VP/VLBW x bullied at both periods	-		-	-		-	0.97	0.15 – 6.30	0.976
EPICure (N=149)									
EP	2.81	0.60 – 13.21	0.191	1.65	0.30 – 9.05	0.564	0.78	0.13 – 4.65	0.786
Peer bullying									
Not bullied	[Reference]			[Reference]			[Reference]		
Bullied at one time period	2.00	0.48 – 8.42	0.344	1.48	0.31 – 7.00	0.620	1.10	0.04 – 29.79	0.956

Appendix Q. continued

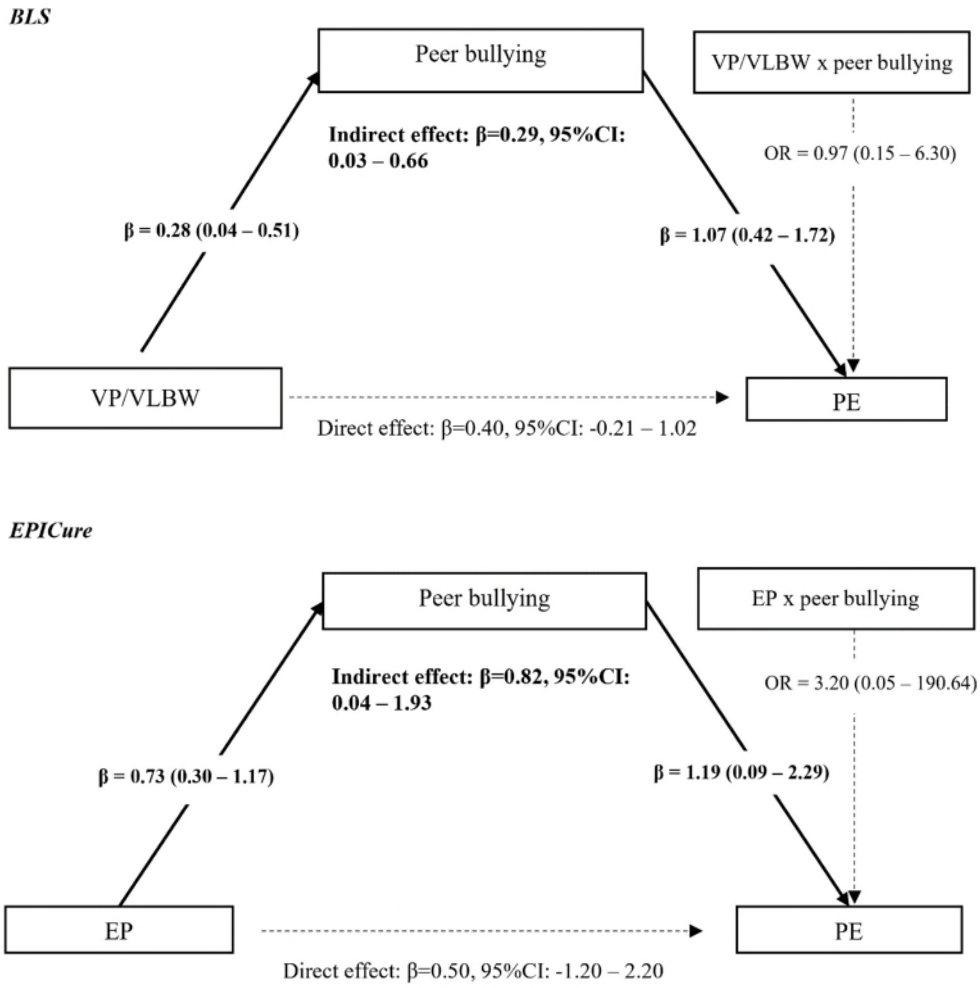
Complete case analysis: simple and multiple logistic regression models showing the effects of VP/VLBW/EP and peer bullying on PE, as well as showing the interaction between VP/VLBW/EP and peer bullying.

	Suspected or definite PE								
	Unadjusted			Adjusted for SES and sex			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Bullied at both time periods	6.25	1.51 – 25.86	0.011	5.40	1.14 – 25.66	0.034	2.10	0.05 – 90.68	0.698
EP x bullied at one period	-		-	-		-	1.83	0.05 – 72.13	0.748
EP x bullied at both periods	-		-	-		-	3.20	0.05 – 190.64	0.576

Appendix R.

Complete case analysis: simple and multiple ordinal logistic regression models showing the effects of VP/VLBW/EP on peer bullying

	Peer bullying					
	Unadjusted			Adjusted for SES and sex		
	OR	95% CI	p-value	OR	95% CI	p-value
BLS (N=364)						
VP/VLBW	1.34	1.06 – 1.69	0.014	1.32	1.04 – 1.66	0.021
EPICure (N=149)						
EP	2.07	1.34 – 3.23	0.001	1.99	1.28 – 3.13	0.002



Appendix S.

Mediation model showing association between VP/VLBW/EP, peer bullying and PE

Study 4: Supplementary materials

Appendix T.

Reliability (Cronbach's alpha) of each self-concept domain at 6, 8, 13 and 26 years.

	6 years	8 years	13 years	26 years
Body satisfaction	-	0.74	0.74	0.81
Social acceptance	0.75	0.75	0.88	0.73
Cognition	0.55	0.60	0.61	0.63
Maternal relationship[a]	0.67	0.73	0.80	-
Motor performance[a]	0.67	0.67	0.70	-

[a] Maternal relationship and motor performance were only assessed using one item at 26 years, thus no information available on the reliability of these two scales at 26 years.

Appendix U.

Correlations between predictors.

	1	2	3	4	5	6	7
1. VP/VLBW	-						
2. Sex	-.065	-					
3. Bullying	.170[a]	-.018	-				
4. Motor	.331[a]	-.019	.214[a]	-			
5. IQ	-.437[a]	.004	-.187[a]	-.470[a]	-		
6. SES	.127[a]	.009	.068	.057	-.159[a]	-	
7. Maternal sensitivity	-.178[a]	-.033	-.210[a]	-.216[a]	.258[a]	-.172[a]	-

[a] $p<0.01$

Appendix V.

Prevalence of bullying when child-reported data was used at 13 years

	VP/VLBW		Control		
	n	%	n	%	p-value
Bullying					*0.023*
Not bullied	59	31.2%	85	38.3%	
Bullied at one time period	83	43.9%	105	47.3%	
Bullied at both time periods	47	24.9%	32	14.4%	

Appendix W.

Correlation between assessment of IQ and motor impairments at 6 and 8 years and number of cases at 6 years substituted with 8 years data

Variable	Numbers substituted	Correlation with 8 years
IQ	18	0.83[a]
Motor	39	0.63[a]

[a] $p<0.01$