A Life-course Analysis of Gene-Environment Interplay in Schizophrenia and Major Depression

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Submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Biological Sciences

Statement of originality

I, Sandra Machlitt-Northen, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

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Publications relevant to this thesis

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Thesis Abstract

Background: Although genetic and environmental risk factors for schizophrenia (SCZ) and major depressive disorder (MDD) are well established, it is not clear whether the exposure to these environmental risks is genetically confounded through a mechanism known as gene-environment correlation (rGE). Identifying whether rGE is implicated in the aetiology of these two psychiatric disorders may help our understanding of how to treat or prevent psychopathologies.

Objective: This thesis aimed to investigate whether known environmental risk factors are correlated with the genetic susceptibilities to SCZ/MDD across three British community cohorts in childhood, adulthood and across the different developmental periods over time. We also wished to compare findings from a systematic literature review of empirical rGE studies for SCZ and depression to our own results.

Methods: Polygenic risk scores (PRS), which were derived from existing genome-wide associations studies (GWAS), were utilised to investigate the correlation between known environmental risk factors and the genetic liability to SCZ/MDD. For the systematic literature review we searched seven databases for publications reporting rGE for either psychopathology in participants of any age.

Results: We found associations between the genetic risk for SCZ and several psychosocial risk factors, such as marital status, whilst the genetic susceptibility to MDD was more strongly correlated with indicators of adverse socio-economic status across childhood and adulthood. Overall, the majority of rGE correlations remained stable across the investigated developmental periods. In contrast to our own results, rGE associations for SCZ and depression which were identified in the systematic literature review were largely the same across the included articles.

Conclusion: In summary, our findings propose that several known psychosocial and environmental risk factors for either SCZ or MDD are at least partially correlated with the genetic liability for these psychopathologies in childhood as well as adulthood.

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Chapter 1: Introduction

1.1 Overview

This chapter contains adapted content from the following publications as well as a manuscript which has been submitted for publication:

Assary, E., Vincent, J., **Machlitt-Northen, S**., Keers, R., & Pluess, M. (2020). The role of gene-environment interaction in mental health and susceptibility to the development of psychiatric disorders. In *Beyond Our Genes: Pathophysiology of Gene and Environment Interaction and Epigenetic Inheritance* (pp. 117-138). Springer International Publishing. https://doi.org/10.1007/978-3-030-35213-4_7

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This chapter will provide a detailed overview of existing studies pertinent to the topic of this thesis. Initially, the aetiology of schizophrenia (SCZ) as well as major depressive disorders (MDD) will be discussed in detail. Next, environmental as well as genetic factors involved in gene-environment interplay will be included. Moreover, a review of two types of gene-environment interplay, namely gene-environment interactions and gene-environment correlation will be provided, prior to discussing the different types of study designs, including

twin studies and their adaptations as well as molecular genetic studies. Finally, this chapter will outline the aims and hypotheses of this thesis.

1.2 Schizophrenia and Major Depressive Disorder

1.2.1 Schizophrenia

SCZ contributes approximately 7.4% (5.0–9.8) to the global burden of disease, with acute SCZ carrying the highest disability weight of all mental health disorders (0.756) based on evidence from to the 2010 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (Whiteford et al., 2013). SCZ is further linked to an average of 14.5 of potential years lost in life (95% Confidence Interval (CI) 11.2–17.8), with the number of years lost being higher for men than women (Hjorthøj et al., 2017).

It is a complex psychiatric disorder with the lifetime prevalence ranging between 0.4-0.87% in adults (McGrath et al., 2008; Perälä et al., 2007; Saha et al., 2005). Although few studies have estimated the SCZ prevalence in children, the limited number of epidemiological investigations are approximating the prevalence of childhood-onset SCZ to be between 1 in 30,000 - 40,000 children (Gochman et al., 2011; Mattai et al., 2010).

Family and twin studies highlighted that SCZ is highly heritable with a substantial estimate of 79% - 83% in adults (Cannon et al., 1998; Hilker et al., 2018; Sullivan et al., 2003).

Moreover, SCZ is characterised by positive symptoms, including hallucinations and delusions, cognitive impairment, such as processing speed or disorganised thinking, as well as negative symptoms, such as flat affect, social withdrawal or amotivation in adults (Gogtay et al., 2011; McCutcheon et al., 2020).

The diagnostic criteria for SCZ are defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Tandon et al., 2013). A SCZ diagnosis is based on the DSM framework whereby at least two of the five core symptoms (delusions, hallucinations,

disorganised speech, grossly disorganised or catatonic behaviour or negative symptoms, such as alogia, avolition or affective flattening) need to be present for at least month, with at least one of these two symptoms requiring to be either delusions, hallucinations or disorganised speech in DSM-5 (Tandon et al., 2013).

Importantly, the SCZ symptomology in children and adolescents can vary. For instance, SCZ can manifests itself as severe language deficits, motor dysfunction as well as infantile autism in children younger than six years of age, with symptoms ranging from negative symptoms to anxiety in adolescents (Jones et al., 2016; Watkins et al., 1988).

Childhood-onset SCZ is diagnosed using the same criteria as those used in adults, except that the deterioration in social or occupational function is modified to failure in educational attainment as well as interpersonal or occupational achievements (Driver et al., 2013; Tandon et al., 2013). However, the diagnosis of children with childhood-onset SCZ is difficult given that several developmental abnormalities regarding language, motor or social development are not diagnostic and positive symptoms are required for a SCZ diagnosis (Driver et al., 2013).

Although the primary onset for SCZ is in late adolescence or early adulthood (Gogtay et al., 2011; Wilson et al., 2015), this complex psychiatric disorder is further characterised by a prodromal phase in early adolescence with a steady but noticeable decline in academic and social functioning prior to psychotic symptoms setting in (Hollis, 2015; Kahn et al., 2015).

Further, neurochemical mechanisms emphasise the potential primary role that neurotransmitters, such as glutamate, dopamine, gamma aminobutyric acid (GABA) and acetylcholin play in the development of SCZ (Lisman et al., 2008; Weinberger, 1997). For instance, multiple brain tissue studies highlighted the impairment of the GABAergic system in individuals with SCZ, whereby cortical GABA concentrations as well as glutamatic acid decarboxylase$_{67}$ (GAD$_{67}$) activity, which synthesises GABA, were reduced (Perry et al., 1979;

Thompson et al., 2009). GABA dysfunction decreases the transcortical inhibition of motor circuitry resulting in failure to activate some cortical regions, whilst other areas are hyperfunctional in response to behavioural challenges (Daskalakis et al., 2002; Mattay et al., 1997). Moreover, in individuals with childhood-onset SCZ, similar patterns of cortical pathology were found compared to individuals with adulthood-onset SCZ, suggesting common physiopathology including neuronal damage as well as malfunction in the dorsolateral prefrontal cortex and hippocampal area (Bertolino et al., 1998).

Psychopharmacologic interventions for SCZ in children and adults, including antipsychotics are mainly focusing on alleviating symptoms, preventing relapses and reducing long-term morbidity, with antipsychotics in children highlighting differential treatment effects and significant adverse effects for some drugs, such as Clozapine (Shaw et al., 2006; Stępnicki et al., 2018). Although significant treatment progress has been achieved to date, understanding the complex underlying disease mechanisms will allow for a new generation of SCZ drugs and novel treatments approaches (Stępnicki et al., 2018).

1.2.2 Major Depressive Disorder

Depressive disorders contribute significantly to the global burden of disease, accounting for 4.46 % of the total Disability Adjusted Life Years (DALYs) and 12.1% of the total Years Lived with Disability (YLDs), according to the GBD 2000 study (Ustün et al., 2004). Moreover, it is associated with a 28.9-year quality-adjusted life expectancy loss at age 18, highlighting the significant weight on mortality and morbidity (Jia et al., 2015).

MDD is a chronic and debilitating psychiatric disorder with a prevalence estimate of 0.87% - 1.43% in pre-school children, 0.4% - 2.8% in children, 0.4% - 8.3% in adolescents and 16.2 - 19.5% in adults, (Cicchetti & Toth, 1998; Costello et al., 2006; Domènech-Llaberia et al., 2009; Kendler, Gatz, et al., 2006; Kessler et al., 2003; Kruijshaar et al., 2005).

Further, twin and family studies confirm that MDD has a moderate heritability of 37% - 39% in adults, with the genetic effects of depressive symptoms increasing from childhood to adolescence (Kendler & Prescott, 1999; Rice, 2010; Sullivan et al., 2000). This has been further confirmed by the Missouri Adolescent Female Twin Study (MOAFTS) which estimated that the heritability for MDD was approximately 40% in 12–19-year-old female adolescents, comparable to adults (Glowinski et al., 2003).

Whilst depressed mood as well as loss of interest or enjoyment are core symptoms of MDD, additional signs such as fatigue, anxiety, sleep disturbance and sexual or neurocognitive dysfunction are also common (Kennedy, 2008). Moreover, considerable evidence further suggests the link between MDD and suicidal ideation, with a lifetime suicide risk of 3.4%; 7% for men and 1% for women (Blair-West et al., 1999; Du et al., 2000). However, given the heterogenous symptomology of MDD, it is also important to point out that the presentation of the disease differs by gender in young adults, with key indicators, such as sadness and self-criticism, being more severe in women compared to men (Lopez Molina et al., 2014).

The diagnosis of MDD is based on the DSM-5 framework which proposes that an individual must exhibit at least five symptoms, such as feelings of guilt/worthlessness, diminished interest in pleasurable activities, appetite changes, poor concentration, lack of energy, sleep disturbances, psychomotor retardation/agitation, or suicidal thoughts over a two week period, of which one of these symptoms needs to be either anhedonia or depressed mood (Tolentino & Schmidt, 2018).

Besides, the presentation of the disease in children and adolescents can differ to that of adults, and thus is often left undiagnosed (Mullen, 2018). Specifically, younger children up to 8 years of age often present with irritability or anxiety and are less able to verbalise their feelings whilst adolescents over the age of 12 display more variations in weight and appetite, less hypersomnia and fewer delusions compared to adults (Dopheide, 2006; Mullen, 2018).

The diagnostic criteria are the same in children as in adults according to the DSM-5 framework for MDD, except that children and adolescents can present with irritable mood (Uher et al., 2014). However, given that irritability is common in children and adolescents and overlaps with several other psychiatric disorders, such as bipolar disorder (Stringaris, 2011), diagnosing children with MDD presents several clinical challenges.

The age of onset for MDD is generally earlier compared to SCZ, often before or during adolescence with recurrent MDD predicting psychosocial impairment in adulthood, regardless of age of onset (Costello et al., 2003; Kessler et al., 2005; Wilson et al., 2015).

Neuro-imaging studies highlight that individuals with MDD have reduced hippocampal volumes and exhibit loss of activity in the prefrontal cortex (Savitz & Drevets, 2009). The hippocampus is responsible for encoding emotions into memories and interacts with the amygdala which processes emotional stimuli (Savitz & Drevets, 2009), providing further evidence that the dysregulation of these neurobiological mechanisms may contribute to the development of MDD. Moreover, children with an increased risk for MDD also show greater activation in the nucleus accumbens, a key structure in the ventral striatum responsible for regulating emotions and motivations, as well as increased amygdala activation to fearful affective stimuli (Monk et al., 2008), suggesting a shared underlying neuropathology between children and adults with MDD.

Moreover, deficiencies in monoaminergic neurotransmission, including norepinephrine, serotonin and dopamine impacting brain circuits responsible for regulating mood and motivation are often directly targeted by antidepressants treatment (Hamon & Blier, 2013). Antidepressants are also used in moderate to severe cases of MDD in children (Mullen, 2018). However, these are often selective and only target one monoaminergic neurotransmitter (Hamon & Blier, 2013). Coupled with the fact that 10-30% of individuals with depression are treatment-resistant (Al-Harbi, 2012; Hamon & Blier, 2013), more research is needed to

understand the complex biological pathways and mechanisms involved in the aetiology of MDD, including the interplay between genetic and environmental factors.

1.2.3 Psychopathology through a developmental perspective

Conceptually, developmental psychology or psychological change over time focuses on the margins of normal and abnormal development (Cicchetti, 2016). Acknowledging this heterogeneity of development, and associated behavioural outcomes, as individuals move from one developmental stage to the next, is crucial in understanding the aetiology of psychiatric disorders (Gooding & Iacono, 1995).

In psychopathology, differences in behaviour which are present during the first months of life, may eventually become more prominent and complex in childhood (Prinzie et al., 2014). Specifically, a broad range of relevant individual differences in thinking and feeling, as well as in behavioural traits, may already be present in middle childhood (Prinzie et al., 2014). The transition from childhood to adolescence is another challenging developmental phase due to rapid psychological, social, as well as biological changes (Prinzie et al., 2014). As an example, children may display anger, fear or hyperactivity as toddlers, which then shift into being hot-tempered or argumentative in preschool with subsequent rule-breaking and aggressive behaviours being exhibited during the children's school years (Knafo & Jaffee, 2013).

Looking at these behavioural differences from a developmental perspective, it is important to consider two distinct paradigms. Firstly, that development tends to "cumulative" with past development affecting subsequent development; this does not solely apply to early adverse experiences but also to positive circumstances, such as increased social support aimed to reinforce adequate functioning and shifting away from problem behaviour (Sroufe, 2013). Secondly, that development is best described by probabilistic pathways as opposed to linear causality, whereby early maladaptation or adversity does not lead to psychopathology per se

but may induce processes which increase the likelihood if the pathway continues (Sroufe, 2013). However, even in the presence of pathology, adaptive coping mechanisms may still be at work (Cicchetti, 2016).

Taking this theory further, children can reach the same developmental outcome through many different conduits (i.e., equifinality) (Cicchetti & Rogosch, 1996), whereby children who have the same early risk factors may display vastly different outcomes and trajectories (i.e multifinality) (Cicchetti & Rogosch, 1996; Hyde et al., 2013). As an example, on the one hand, children with daring traits may have an increased risk for delinquency when they grow up in dangerous neighbourhoods or in families with low income, whilst similar children with a different upbringing may flourish to become proficient firefighters (Hyde et al., 2013). On the other hand, early exposure to either abusive parenting or alternatively warm parenting but with negative peer affiliation may equally contribute to symptoms of conduct disorder when the child reaches adolescence (Hyde et al., 2013).

One of the main principles of developmental psychopathology is that these differences in typical and atypical development are the joint consequence of both social and biological influences (Knafo & Jaffee, 2013). Moreover, it also acknowledges that environments which shape behaviours can also change across an individual's development (Knafo & Jaffee, 2013). In particular, home environments, including physical family home characteristics, sibling interactions and parenting styles, are critical constructs for developmental research, due to their constant influence from infancy up until late adolescence (Hannigan et al., 2017). Moreover, home environments are further influenced by genetic vulnerabilities which, to varying extents, are shared between family members (Hannigan et al., 2017). For example, when investigating the relationship between depressive symptoms and home environments when children moved from childhood into adolescence, developmental changes highlighted an increase in genetic influences and a decrease in the importance of shared environmental factors in twins (Hannigan

et al., 2017). These developmental progressions highlight the significance of investigating shifts in the aetiology of psychopathological associations through a developmental lens.

All in all, research needs to consider longitudinal studies which are conducted across childhood and adolescence to allow investigation of these developmental trajectories of evolving psychopathological outcomes, as well as helping to identify risk exposures and multilevel indicators of biological, clinical, behavioural and neurological functioning (Goodday & Duffy, 2019).

1.3 Gene-Environment Interplay

Complex behavioural traits are not just the result of genetic influences (Weiss & Terwilliger, 2000); there is also another factor to consider: the environment. Therefore, this next section of Chapter 1 presents an in-depth overview of the environmental as well as genetic factors which are known to be implicated in the development of SCZ and MDD and introduces the different types of gene-environment interplay.

1.3.1 Environmental Risk

A large range of psychosocial and environment risk factors across the life course are known to be implicated in the aetiology of SCZ and MDD. For the purpose of this thesis all environments, including psychosocial environments such as educational attainment as well as behaviours such as smoking, are referred to as 'environment risk factors'. Environmental risk factors in childhood and adulthood are discussed separately.

1.3.1.1 Environmental Risk Factors in Childhood

Childhood environment risk factors have been grouped into the following four categories: perinatal environments, parental substance abuse and associated risk factors, socioeconomic environments as well as psychosocial risk factors.

Perinatal Environments

Multiple studies suggest that early childhood environments and, specifically perinatal environments are implicated in the development of SCZ and MDD. These include risk factors such as very young but also older than average parental age at birth (Filatova et al., 2021; Fountoulakis et al., 2018; McGrath et al., 2014; Petersen et al., 2011), short gestational period (Chiu et al., 2019; Jones et al., 1998) and higher birth order (grand multiparity) (Easey, Mars, et al., 2019; Lahti et al., 2014).

Parental Substance Abuse and associated Risk Factors

The link between parental substance abuse and child mental health issues has long been established (Rognmo et al., 2012). For instance, research in 6,356 adolescents aged 12 highlighted the association between maternal smoking after birth, paternal smoking during pregnancy, and the development of psychotic experiences (adjusted Odds Ratio (AOR) = 1.20; 95% Confidence Interval (CI) [1.05– 1.37]; P-Value (p) = .007) due to the causal effects of tobacco exposure *in utero* (Zammit et al., 2009). Furthermore, Zhang et al (2022) argued that maternal moderate or heavy alcohol consumption in pregnancy was associated with depression in the offspring in a meta-analysis which included eight cohorts (Moderate: Odds Ratio (OR) = 1.74, 95% CI [1.22 -2.49]; p = .002/ heavy: OR = 2.41; 95% CI [1.55 - 3.73]; $p < .001$). Moreover, animal models have further confirmed that either 'active' pre-natal smoke exposure (actively smoking cigarettes) or 'passive' pre-natal smoke exposure (inhalation of side stream

smoke) is further associated with *in utero* growth retardation and low birth weight (Esposito et al., 2008).

Socioeconomic Environments in Childhood

Numerous studies have investigated the link between measures of social inequality at birth and a heightened risk of SCZ and MDD. Socio-economic status (SES) at birth or in early childhood (Gilman et al., 2002; Harrison et al., 2001) as well as financial difficulties (Hakulinen et al., 2020; Kendler et al., 1999) are some known environmental risk factors. For instance, individuals (n = 168) whose fathers belonged to a low social class or who were born into deprived areas had an increased risk of SCZ (OR = 2.1; 95% CI [0.8 - 5.5], with an even greater risk for those individuals who had both of these indicators (OR = 8.1; 95% CI [2.7 - 23.9]) (Harrison et al., 2001).

Psychosocial Risk Factors

Research proposes that poor performance in school is significantly associated with an increased risk of SCZ, (n = 907,011; HR= 3.90, 95% CI [2.8–5.3]) (MacCabe et al., 2008), whilst children with mothers who had lower grades in secondary school also had increased odds of major depressive episodes (n = 1,267; AOR=2.04; 95% CI [1.25–3.32)]) (Park et al., 2013).

1.3.1.2 Environmental Risk Factors in Adulthood

Adulthood environment risk factors have been grouped into the following three categories: substance abuse, socioeconomic environments and psychosocial risk factors.

Substance Abuse

Substance abuse studies in adults propose that most types of substance abuse heightens the overall risk of developing SCZ (n = 204,505 substance abuse cases and 21,305 SCZ cases; HR = 6.04; 95% CI [5.84 - 6.26]), with alcohol abuse having been identified as one of the strongest associations (HR = 3.38; 95% CI [3.24 - 3.53]) (Nielsen et al., 2017). Moreover, smoking has also been identified as an environmental risk factor which is known to be implicated in the aetiology of MDD. For instance, smoking increased the risk of developing MDD by 93% in woman (n= 165 MDD cases and 806 controls; HR = 1.93; 95% CI [1.02–3.69]) (Pasco et al., 2008).

Socioeconomic Environments

Several studies confirmed the link between SCZ or MDD and low socioeconomic status in adulthood. These environmental risk factors include financial difficulties (Kendler et al., 1999), low SES (Freeman et al., 2016) and unemployment (Brown & Harris, 1978; Evensen et al., 2016; Kendler et al., 1999; Marwaha et al., 2007). For example, individuals who received a SCZ diagnosis aged 15 to 25 years of age (n = 9,448) had increased odds of being unemployment at the age of 30 (OR = 39.4; 95% CI [36.5 – 42.6]), were lacking higher or secondary education (OR = 7.4; 95% CI [7.0 – 7.8]), and were more likely to live alone (OR = 7.6; 95% CI [7.2 – 8.1]) (Hakulinen et al., 2019).

Psychosocial Risk Factors

Further, educational achievement is a known risk factor for both psychopathologies (Cohen et al., 2020; Hakulinen et al., 2019; Keefe et al., 2005). For instance, individuals who graduate from college or high schools have a lower risk of depression (n = 827 cases and 3,590

controls; adjusted Risk Ratio (RR) = 0.73; 95% CI [0.56–0.96]) compared to individuals with lower educational attainment (adjusted RR, 0.75; 95% CI [0.62–0.91]) (Cohen et al., 2020).

Moreover, given that 12% of individuals with SCZ are never married with lonesome status having been estimated at 83% (Walid & Zaytseva, 2011), studies suggest that individuals with early onset SCZ further have the worst marital outcomes (n = 101 SCZ cases, T Value (t) = 2.96; Degrees of Freedom (df) = 68; p = .0021) (Deshmukh et al., 2016). Likewise, in individuals with MDD, separation/divorce also emerged as an environment risk factor with a bi-directional relationship (Bulloch et al., 2009). That means that individuals who are separated/divorced are more likely to experience MDD (n = 14,713; HR = 1.3; 95% CI [1.0–1.5]; p = .04), with individuals with MDD also having an increased risk of experiencing marital disruption (HR = 2.0; 95% CI [1.4–2.9]; p < .001) (Bulloch et al., 2009).

1.3.1.3 Developmental Perspective

From a developmental perspective, exposures to certain environments can be influenced by individual behaviours which consequently may change as individuals move between different developmental periods. For instance, Knafo & Jaffee (2013) explained that small differences in ability or temperament can lead to substantially larger differences in antisocial behaviour when individuals move from childhood to adulthood.

Besides, socio-cultural changes, for instance the decline of recreational use of tobacco and consequently changes in smoking behaviour, could further influence differential environment exposures over time (Rutter et al., 1997).

1.3.1.4 Heritability of Environments

Moreover, evidence from twin and family studies highlight that environments themselves are heritable (Jaffee & Price, 2007). For instance, Kendler & Karkowski-Shuman

(1997) showed in a sample of 2,164 female monozygotic and dizygotic twins from the Virginia Twin Registry that the probability of experiencing stressful life events was under genetic control in the development of MDD. Results from this study suggested that the genetic susceptibility to MDD, using a lifetime history of the illness, was correlated with a significantly heightened risk for divorce or breakup/assault/job loss/serious marital problems/serious illness or major financial problems, as well as the ability to get along with friends and family (Kendler & Karkowski-Shuman, 1997). This proposes that individuals may select themselves into adverse environments based on their genetic susceptibilities.

1.3.2 Genetic Risk

Genetic factors are known to play big role in the development of SCZ and MDD. This next section will examine candidate genes, genetic variation and polygenicity, heritability as well as the genetic overlap between SCZ and MDD. Additionally, an in-depth discussion of polygenic risk scores and the genetic tie between childhood and adulthood psychopathologies will be discussed in more detail.

1.3.2.1 Candidate Genes

Historically, psychiatric genetic research, which was often conducted in family studies (Weissman et al., 1984), had initially a focus on finding abnormal mutant genes which would interrupt a vital function and thus cause mental health disorders (Rutter et al., 2006; Weiss & Terwilliger, 2000). These candidate gene studies were popular until the early 2000s which included the discovery of the plexin A2 (*PLXNA2*) gene for SCZ which is situated on chromosome 1q32 (Mah et al., 2006). In this study, Mah et al (2006) utilised 320 SCZ cases and 325 matched controls from unrelated individuals as well as two family-based cohorts with 294 and 96 individuals, respectively, in order to test 14,000 genes for an association with the

disease. Association analysis identified the *PLXNA2* gene on chromosome 1 in region 1q32, which modulates regeneration, neuronal plasticity as well as the axonal guidance and is implicated in neuroinflammatory processes, as a likely candidate for SCZ susceptibility (Lee et al., 2019; Mah et al., 2006).

Unfortunately, many hypothesised candidate genes did not hold up in systematic studies because they did not possess enough statistical power or were confounded by population stratification (Dick et al., 2015; Duncan & Keller, 2011; Rietveld et al., 2014). Moreover, there is also an increased risk of false-positive findings due to often underpowered samples (Hayden et al., 2010). Hence, candidate gene studies have declined so much in popularity due to replication issues, that the Behavioural Genetics editor John Hewitt issued a policy on candidate gene association studies in 2012 stating: "(…) that many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge" (Hewitt, 2012).

More importantly, no single gene is responsible for complex psychopathological disorders. Rather, many genetic variants may contribute to the expression of some individual variation to the liability of a trait (Rutter et al., 2006). For instance, the 25 most-studied candidate genes for SCZ, including the Disrupted-in-Schizophrenia 1 gene *(DISC1)* were no more associated with SCZ than genetic variants in noncandidate genes from control datasets (Johnson et al., 2017).

1.3.2.2 Genetic Variation and Polygenicity

There are around three billion nucleotide base pairs in the human genome with two to three million base pairs which account for approximately 0.1% of DNA varying amongst individuals (Jorde & Wooding, 2004). About 85–90% of this genetic variation can be attributed

to differences within continental groups, whilst the remaining 10–15% of the genetic variation can be found between individuals from different continents (Jorde & Wooding, 2004).

The genetic variations provide an import insight into the phenotypic variability in human populations (Ionita-Laza et al., 2009). These include, amongst others, structural genetic variations, such as copy number variants which occur when genome sequences are repeated, but where the number of repeats differs between individuals (Pös et al., 2021). However, the focus of this thesis will be on the most common form of genetic variation referred to as single-nucleotide polymorphisms (SNPs) which account for approximately 90% of sequence differences in humans and have an overall frequency of roughly one SNP per 1000 bases (Wang & Moult, 2001).

Although research has moved from candidate genes to whole genome approaches in very large samples, risk alleles that survive correction for multiple testing only explain a very small proportion of the heritability (Gratten et al., 2014). For example, very early studies by the SCZ or MDD Working Group from the Psychiatric Genomics Consortium (PGC) detected only five SCZ-associated loci explaining 6% of the variance in liability to SCZ in a total of 9,394 SCZ cases from the discovery sample, whilst a mega-analysis in 9,240 MDD cases did not identify any significant genetic loci at all due to being underpowered (Ripke Wray, et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011).

These findings highlight that the genetic components of psychopathological outcomes are complex, likely highly polygenic and explained by hundreds, if not thousands, of genetic variants of very small effect (Culverhouse et al., 2018; Dudbridge & Newcombe, 2015; Gratten et al., 2014).

1.3.2.3 Heritability

It is also important to note that whilst the current SNP-based heritability estimates for SCZ and MDD are calculated to be approximately 24% and 8.9%, respectively, (Howard et al., 2019; Trubetskoy et al., 2022), there is still a significant difference between SNP-based and twin and family study heritability estimates.

This discrepancy is often referred to as the "missing heritability" issue (van der Sluis et al., 2010). Overinflation from twin or family studies due to shared environment, underinflation from genomic studies due to not taking non-additive effects into consideration as well as simply the fact that possible risk variants may not have been identified yet due to being rare or having a too small effect size, have all been proposed as possible reasons (Owen & Williams, 2021). However, recent modelling studies also suggest that careful phenotypic modelling may in fact enhance the genetic signal, and consequently statistical power (van der Sluis et al., 2010).

1.3.2.4 Genetic Overlap between SCZ and MDD

Furthermore, SCZ and MDD are distinctly separate psychiatric disorders with largely different pathologies and treatments. However, some of the symptomology overlaps between the two psychopathologies with depressive disorder being reported in up to 40% of SCZ cases (Upthegrove et al., 2017), proposing a shared genetic aetiology. This is supported by a British longitudinal twin study (n = 9,618 at age 16 and n = 2,873 nine months later) using the Longitudinal Experiences And Perceptions (LEAP) cohort (Zavos et al., 2016). This study identified moderate correlations between self-rated depressive symptoms with hallucinations, paranoia and cognitive disorganization as well as high genetic correlations between depression and psychotic experiences of 35%–53% in mid-adolescent twins (Zavos et al., 2016).

Additionally, whilst more recent GWAS findings from the SCZ and MDD PGC identified 108 SCZ-associated genetic loci and 44 independent loci for MDD, these empirical studies also propose that both share six genetic risk loci [Chromosome (Chr) 1: rs12129573, rs10789369; Chr2: rs11682175; Chr6: rs17693963, rs13194053; Chr14: rs12887734; Chr18: rs9636107, rs9960767, rs1261117; Chr22: rs9607782] (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018). Two shared risk variants for SCZ and MDD (Chr1: rs12129573 and Chr6: rs17693963) were also recently identified by Grotzinger et al (2022) which both match two of the risk variants identified by the PGC. Whilst the genetic overlap is not complete, some of the shared genetic loci are closely located on the Transcription Factor 4 gene which is situated on chromosome 18 in region 18q21.2, and is vital for normal brain development (Teixeira et al., 2021; Wray et al., 2018). Moreover, the MDD PGC further stated that the genetic risk score for SCZ explained .8% of the variance in susceptibility to MDD, with a substantial genetic correlation (r_g) between SCZ and MDD estimated to be r_g =0.34.

1.3.2.5 Polygenic Risk Scores

In order to quantify the genetic susceptibilities to these psychopathological disorders, researchers have recently used GWAS findings, such as from the PGC, whereby the identified markers from a training dataset are ranked by p-values based on evidence for their trait-association (Dudbridge & Newcombe, 2015). In a separate replication sample, which does not include the training dataset, individual additive scores called polygenic risk scores (PRS) are then calculated based on the aggregated weights for these risk-increasing alleles (Dudbridge, 2013; Dudbridge & Newcombe, 2015; Holland et al., 2016). Assuming that allelic counts have been standardised, PRS are calculated using the following formular: $PRS = \sum_i \beta_i x_i$, whereby β_i refers either to the regression coefficient or the log odds ratio (So & Sham, 2017).

The PRS can then either be created from some consistently associated genetic markers, all nominally significant genetic markers, or almost all genotyped genetic markers (Dudbridge & Newcombe, 2015) at different thresholds. However, clumping the genetic variants according to their linkage disequilibrium (LD) in order to find the most significant SNPs in the replication sample first, avoids duplication of information within the score (Dudbridge & Newcombe, 2015). Associated genetic markers are frequently in LD with other markers whereby all of them may demonstrate nominal associations (Dudbridge & Newcombe, 2015; So & Sham, 2017). If a single marker is responsible for all associations within a region then only that single causal variant needs to be included in the PRS; whereas if multiple causal markers are responsible then all of them should be included (Dudbridge & Newcombe, 2015).

PRS scores can then be applied in two different ways: 1) either to understand if associated markers are present in individuals who contributed to the PRS when testing trait associations in a replication sample, or 2) to predict risks of trait or disease (Dudbridge, 2013).

However, some important points regarding the application of PRS will also need to be pointed out. Firstly, the GWAS cohorts need to be well-powered because the effect size is utilised to weigh the allelic risk (Bogdan et al., 2018). Secondly, given that PRS typically account only for a small proportion of the variance, the target sample needs to be large enough to reject false positives or negatives (Bogdan et al., 2018). Lastly, utilising GWAS summary statistics of a particular ancestry group to calculate PRS may not be informative in other ancestral groups due to varying LD patterns which proposes the non-random association of genetic markers of different genetic loci (Bogdan et al., 2018; Dudbridge & Newcombe, 2015; Slatkin, 2008).

1.3.2.6 Genetic Tie between Childhood and Adulthood Psychopathologies

Finally, the evidence from molecular genetics studies further emphasises the genetic tie between childhood and adulthood psychopathologies suggesting shared genetic aetiology (Nivard et al., 2017).

For example, a recent genetic study in 8,230 adolescents from the Avon Longitudinal Study of Parents and Children suggested that the PRS for SCZ, calculated using GWAS data from the SCZ PGC from adult cohorts, is expressed as anxiety (OR per Standard Deviation (SD) increase in PRS, 1.17; 95% CI [1.06- 1.29]; Coefficient of Determination (R^2) = 0.005) or negative symptoms (OR per SD increase in PRS, 1.21; 95% CI [1.08-1.36]; R^2 = 0.007) in adolescence (Jones et al., 2016).

Conversely, the genetic risk for MDD, neuroticism and depression utilising GWAS summary statistics from adult cohorts, was associated with worse depressive symptoms in over 6,000 adolescence and young adults from the Avon Longitudinal Study (Kwong et al., 2021). This study highlighted that the PRS for MDD and depressive symptoms at age 24 (Beta Coefficient (β) = .146; 95% CI [0.107, 0.185]; $p < .001$) were stronger than at the age of 10.5 years of age (β = .075; 95% CI [0.044, 0.106]; $p < .001$), proposing that the genetic susceptibility may be involved in adolescence depression.

1.3.3 Types of Gene-Environment Interplay

Whilst differences amongst individuals can result from genetic or environmental influences, these do not work in isolation (Scarr & McCartney, 1983). Rather, the development of our behaviours depends on both, environmental exposures as well as our genetics (Scarr & McCartney, 1983). These factors work together in an intricate gene-environment interplay. These gene-environmental interdependences can influence behaviour and consequently psychopathological outcomes and can be grouped into four distinct mechanisms: variations in

heritability, epigenetic effects of specific environments on genes as well as gene-environment interaction (GxE) and gene-environment correlation (rGE) (Rutter, 2007).

Firstly, variations in heritability have been observed in relation to environmental changes (Rutter et al., 2006). Rutter et al (2006) argue that this mechanism may explain the greater heritability in a particular trait in the presence of environments which are advantageous as well as the effects on heritability in relation to major environmental hazards which are known to influence psychopathological outcomes. For instance, a study in 2,000 English and Welsh twins from the Twins Early Development Study aimed to assess the heritability of cognitive functioning in occurrence of very pre-mature birth and perinatal and obstetric complications which are associated with it (Koeppen-Schomerus et al., 2000). The authors proposed that extreme prematurity, defined as birth before 32 weeks of gestation, affected the children's verbal and non-verbal development at age 2 whereby shared environmental factors explain 84% of the variance (Koeppen-Schomerus et al., 2000).

Even if environments, including rearing experiences, diet or exposure to chemicals cannot change a gene sequence, they can and often will alter their genetic effects through a mechanism referred to as epigenetics (Rutter, 2007). One study which investigated 58 female monozygotic twins from the Maudsley Twin Study and the Dutch Twin Study highlighted that epigenetic factors may be implicated in the divergence of monozygotic twins (Rosa et al., 2008). Rosa et al (2008) suggested that discordant twins with bipolar disorder exhibited greater differences in the methylation of the maternal & paternal X chromosome (intra-pair difference for % of X inactivation: Mean ± Standard Error (SE) =17.3 ± 5.7) compared to a concordant twin pair with bipolar disorder (intra-pair difference for % of X inactivation: Mean ± SE = 5.1 ± 1.7), resulting in differences in X chromosome inactivation which in turn may influence the susceptibility to bipolar disorder.

Additionally, gene-environment interplay comes in two distinct forms, namely GxE and rGE. These two types of gene-environment interplay will be further assessed in section 1.4 below, with a particular emphasis on rGE which is central to this thesis.

1.4 Gene-Environment Interaction and Gene-Environment Correlation

1.4.1 Gene-Environment Interaction (GxE)

GxE occurs due to the nonlinear combination of environmental and genetic effects, whereby different genotypes react to the same environment differently (Karg & Sen, 2012; Plomin et al., 1977). In other words, the genetic risk moderates the effects of the environmental risk (Price & Jaffee, 2008).

This concept is supported by plenty of evidence from twin and family studies, such as Kendler et al. (1995), who conducted a GxE study in 2,164 female individuals from the Virginia Twin Registry in order to assess the interaction between stressful life events and the genetic liability to MDD. The study concluded that an individual with the lowest genetic vulnerability for MDD, such as having an unaffected monozygotic co-twin, had a probability of 6.2% or 0.5% per month, respectively, for developing MDD if being exposed or not exposed to stressful life events (Kendler et al., 1995). On the other hand, individuals with the highest genetic risk for MDD, such as having an affected monozygotic co-twin (Kendler et al., 1995), had probabilities of 1.1% if exposed and 14.6% if not exposed to stressful life events, highlighting that the genetic susceptibility to MDD is likely moderated by adverse environmental exposures.

However, the existence of GxE is further supported by molecular genetics studies. One of the first GxE studies by Caspi et al. (2003), which proposed interactions between the serotonin transporter gene 5-HTT polymorphism and stressful life events in individuals with

depressions, paved the way for hundreds of GxE candidate gene studies which followed (Caspi et al., 2003; Duncan & Keller, 2011).

For example, GxE studies in SCZ typically explored the role of the catechol-O-methyltransferase (COMT) protein coding gene, which is located on chromosome 22 and linked to the degradation of the catecholamine neurotransmitter, and the interaction with adverse environments, including cannabis use and stress (Caspi et al., 2005; Grossman et al., 1992; van Winkel et al., 2008). However, given the mounting concerns of candidate gene GxE studies relating to their methodological limitations (Duncan & Keller, 2011), as well as the increasing availability of GWAS, the interplay between genetic and environmental factors started to be explored across the whole genome.

For instance, one PRS GxE study assessed whether the genetic liability to SCZ moderates the association between self-reported psychotic experiences, including visual hallucinations, auditory hallucinations, delusions of reference as well as persecutory delusions and self- reported cannabis use in 109,308 participants from the UK Biobank (Wainberg et al., 2021). The GxE study found that cannabis use is a predictor for psychotic experiences in individuals with the highest genetic vulnerability to SCZ and was associated with a 68% increase in the AOR for delusions of reference (AOR = 1.68; [1.18, 2.38]), compared to individuals with a low genetic vulnerability with a 7% greater AOR (AOR = 1.07; [0.63, 1.82]) (Wainberg et al., 2021). Overall, this study highlighted that the PRS for SCZ modulates the association of self-reported psychotic experiences and cannabis use; in other words, individuals with the genetic liability to SCZ are especially vulnerable to psychotic experiences as a consequence of using cannabis (Wainberg et al., 2021).

Although it is crucial that we assess the interplay between genes and the environment in the aetiology of complex psychopathologies, it is also important to point out that much of the gene-environment interplay research focused disproportionately on GxE only, often

omitting rGE altogether. However, research proposes that complex psychopathologies may be shaped by both types of interplay (Eaves et al., 2003; Lau & Eley, 2008; Rutter et al., 2006).

Given the lack of studies investigating rGEs, this thesis therefore addresses this gap and explores correlations between SCZ and MDD and known environmental risk factors across different developmental periods over the life course.

1.4.2 Gene-Environment Correlation (rGE)

1.4.2.1 rGE Mechanisms

The second form of gene-environment interplay, which will be the main focus of this thesis, is a mechanism referred to as rGE, whereby the genotype influences the exposure of the individual to certain environments (Kendler & Eaves, 1986; Plomin et al., 1977; Scarr & McCartney, 1983). That means that rGE illustrates how an individual's genetic susceptibility can determine which environments they are experiencing and consequently the effects of these exposures on their own development (Plomin et al., 1977; Scarr & McCartney, 1983).

rGE can occur from causal influences of the genotype as well as non-causal mechanisms (Jaffee & Price, 2012). Non-causal effects, including evolutionary processes like natural selection or genetic drift, can contribute to allele frequencies in different populations (Jaffee & Price, 2007, 2012). For example, the sickle-cell haemoglobin (*HbS*) gene is associated with sickle cell anaemia but also provides significant protection against malaria in endemic regions (Aidoo et al., 2002). These specific genotypes will consequently correlate with environments which differ by ethnicity, even in homogenous ancestry groups (Abdellaoui et al., 2022; Jaffee & Price, 2007, 2012).

On the other hand, causal rGE associations come in three distinct forms: *passive*, *evocative* and *active* rGE (Knafo & Jaffee, 2013; Plomin et al., 1977).

Passive rGE happens when the biological parents pass on their genotypes to their offspring whilst also providing a home environment in which their offspring is growing up (Jaffee & Price, 2008; Plomin et al., 1977). The rearing environment is influenced by the parent's own behaviour, including personality features and intellectual qualities, which in turn is influenced by genetic factors (and the environment) (Rutter et al., 2006). For example, parental antisocial behaviour is more strongly associated with their offspring's disruptive behaviour in biological families, compared to adoptive family environments (Bornovalova et al., 2014). One important point to consider is that *passive* rGE can make studies of children with psychiatric parents difficult to interpret because parents do not just pass on the genetic risks but also often provide dysfunctional environments to the children (Rutter & Quinton, 1984).

Evocative rGE describes when a genetic susceptibility gives rise to a specific behaviour that provokes a response or reaction from the environment (Jaffee & Price, 2008; Plomin et al., 1977). For instance, a child's genetic predisposition towards interpersonal control explained the degree of maternal control they received (Klahr et al., 2013). Klahr et al. (2013) explained that children who expressed a low level of autonomy evoked more controlling behaviours from their mothers, whilst those with high level of autonomy were subjected to significantly lower maternal control.

Active rGE increases as individuals grow older (Jaffee & Price, 2008; Plomin et al., 1977). It describes how individuals actively shape or seek out specific environments which are based on their genetic liability (Jaffee & Price, 2008; Plomin et al., 1977). For instance, Loehlin (2010) suggests that there is an *active* rGE, albeit modest, between alcohol-drinking behaviour and sharing the same friends in female adolescents twins, with a stronger correlation in dizygotic than monozygotic twins, proposing that rGE may play a role in alcohol-related behaviour in adolescents.

1.4.2.2 rGE across Development

Research highlights that the interplay between genes and our environment can have time-dependent effects on the aetiology of psychopathological outcomes (Jaffee & Price, 2007). In other words, early exposure to certain events or environments, such as stress or adversity, can affect biological systems, resulting in lifelong effects depending on when the exposure occurred during the child's development (Halfon et al., 2014; Kendler & Baker, 2007).

From a developmental perspective, it has been proposed that there is change from *passive* rGE which occurs from birth onwards, to *evocative* and finally *active* rGE in adolescence, with *active* rGE being more common as children grow older (Jaffee & Price, 2007; Scarr & McCartney, 1983).

Taking this point further, correlations between child outcomes and parenting behaviours may not just be the result of parental genes influencing their own behaviour, but also the offspring's genes affecting their own behavioural traits as well as an overlap between the parental and their offspring's genes influencing each other's behaviours (Knafo & Jaffee, 2013). For example, parents will not just pass down the genetic risk for aggressiveness and provide an environment in which their offspring grows up in in line with their genetic susceptibilities, such as harsh parental punishments through *passive* rGE; but the child may then actively select environments which reinforces these aggressive traits through *active* rGE as they grow older, such as playing violent video games. Moreover, the child's aggressive behaviour, which is genetically influenced, may also affect how others treat them through *evocative* rGE. For example, the child's aggressiveness towards peers in school may evoke negative responses from others which consequently give rise to interpersonal conflicts as a result.

Furthermore, changes with regards to the extent of rGE, in relation to environmental factors and parental influences, have also been proposed as possible explanations why some traits or psychopathological outcomes, such as depression, are more heritable in adolescence compared to childhood (Hannigan et al., 2017; Rice, 2010). Whilst it is often theorised that *evocative* and *active* rGE may be responsible for these phenotypic variations when children grow older, it further highlights that different types of rGE are more prominent at different stages of development (Jaffee & Price, 2007).

In sum, these hypothesised shifts in rGE associations over time may help inform our understanding of how psychiatric disorders develop as individuals grow older and explain why intially small differences in temperament or personality may develop into much larger differences in these traits over time (Knafo & Jaffee, 2013).

This development shift in rGE has been confirmed by several molecular genetic studies. For example, Ensink et al (2020) utilised data from 1,154 children from the Dutch Amsterdam Born Children and their Development Study from ages 5 to 6 as well as 11 to 12 years to investigate whether the PRS for SCZ was correlated with the exposure to problem behaviour in the children and maternal risk factors, including alcohol consumption during pregnancy (OR = 0.811; SE = .066; p = .001) and low maternal education (OR = 0.759; SE = .068; p < .000). The PRS study proposed that the genetic risk for SCZ was associated with externalising problems in children aged 5 to 6 (β = 0.097, SE = 0.020, p = .001, R^2 = .011), possibly through *passive* rGE, but not in children 11 to 12 years of age (Ensink et al., 2020), highlighting that the strength of *passive* rGE decreased as individuals grew older.

Moreover, a recent longitudinal study followed 2,232 British twins from the Environmental Risk Longitudinal Twin Study until age 18 with the aim of investigating the associations between the PRS for several psychopathological outcomes, including SCZ and MDD and a range of socio-environment risk factors (Newbury et al., 2020). The authors stated

that there is some evidence to suggest that rGE increased over time, whereby the genetic susceptibility to SCZ was not associated with urbanicity at age 5 or 12, but was correlated at 18 years of age (OR = 1.14, 95% CI [1.02–1.27]), whilst the PRS for MDD was also only associated with deprivation when the individuals were older (Newbury et al., 2020). These findings could be explained by an increase in *active* rGE, whereby individuals actively seek environments based on their genetic susceptibility as they get older.

1.4.2.3 Co-existence of GxE and rGE

Although, it is commonly accepted that GxE and rGE shape much of modern psychological thinking, researchers often still struggle to disentangle the complex interplay between our genes and the environment given that these two distinct concepts often co-exist together (Silberg et al., 2001).

For example, recent research in 2,082 healthy individuals from the Australian Twin Registry Study highlighted that rGE is at least partially responsible for the correlation between SCZ and cannabis use (ever smoked cannabis versus never used cannabis: $R^2 = 0.47\%$, $p = 2.6\times10^{-4}$), possibly due to the shared genetic make-up across common genetic risk variants (Power et al., 2014). Conversely, another gene-environment interplay study has identified a bidirectional correlation between cannabis use and psychosis, which is one of the core symptoms of SCZ (Ferdinand et al., 2005). This study was conducted in a random sample of 1,580 four to 16-year-olds from the Zuid Holland Study who were followed for 14 years, whereby cannabis use predicted future psychotic symptoms in participants who did not experience psychotic symptoms prior to smoking cannabis (HR = 2.81; 95% CI [1.79–4.43]), but psychotic symptoms also predicted future cannabis use in individuals who did not smoke cannabis before suffering from psychotic symptoms (HR = 1.70; 95% CI [1.13–2.57]) (Ferdinand et al., 2005).

Identifying whether the genetic susceptibility for a psychiatric disorder is more common in a particular environment due to rGE or whether the genetic liability can modify the effects of a genotype through an environment will have an influence on how these psychopathological outcomes can be treated or prevented (Rutter & Silberg, 2002).

1.4.2.4 The Importance of rGE

The fact that about half of all lifetime cases for anxiety, impulse-control, mood or substance use disorders start emerging before age 14, and three fourths before 24 years of age, (Kessler et al., 2005), emphasises the need to better understand preventative or treatable environmental targets, specifically as individuals transition from childhood to adolescence and finally into adulthood. Identifying the biological pathways of how our genetic predispositions influence our behaviours and in turn our environment has important implications for the prevention and treatment of complex psychiatric diseases, including SCZ and MD (Jaffee & Price, 2007, 2012).

For instance, if the genetic liability to SCZ or MDD is correlated with a higher exposure to specific environmental factors, then these environments risk factors are partly under genetic control. From a clinical perspective, ignoring rGEs could lead to poorly targeted interventions (Wagner et al., 2013). In other words, any interventions which are intended to reduce a certain activity or behaviour would have little or no effect on the aetiology of the psychopathology. For example, if psychosis and cannabis use were only correlated with each other due to the direct influence of the high-activity catechol-O-methyltransferase loci, then preventing individuals from smoking cannabis would have no influence on psychosis rate (Jaffee & Price, 2007; Vandenbergh et al., 1997). Alternatively, it is also possible that the risk for psychopathology is determined by the exposure to an environmental risk, whereby the environmental risk consequently mediates the correlation associated between the

psychopathology and the genetic risk (Jaffee & Price, 2007). For instance, if the association between psychosis and the high-activity catechol-O-methyltransferase loci were entirely mediated by smoking cannabis, then reducing the use of cannabis in the whole population without any regard for the genotype would be an appropriate intervention (Jaffee & Price, 2007; Vandenbergh et al., 1997).

Lastly, research needs to assess not only the timing of exposures to adverse environments but also the impact of continuous adverse exposure and consequently its effect on the liability to psychopathological outcomes (Rutter & Quinton, 1984).

1.5 rGE Study Designs

Assessing which type of rGE influences psychopathological outcomes is absolutely critical in being able to target and prevent mental health disorders (Jaffee & Price, 2007). This next section provides a literature overview and describes the different rGE study designs in detail.

1.5.1 Twin Studies and their Adaptations

Twin studies and their adaptations have delivered plenty of evidence for rGE by highlighting that known environmental risk factors are heritable (Jaffee & Price, 2007; Rutter & Silberg, 2002). For instance, Lau & Eley (2008) investigated adolescent twins and siblings from 1,820 families from the G1219 longitudinal study, in order to assess rGE and GxE between the genetic susceptibility to depressive symptoms and negative life events and maternal punitive discipline through self-reported data. Findings suggested that the genetic liability for depressive phenotypes was correlated with increased social adversity through rGE (Lau & Eley, 2008).

Given that monozygotic (MZ) twins share 100% and dizygotic (DZ) twins share on average 50% of their genes, twin studies make use of the common genetic architecture; and when reared together, enable a better differentiation between shared and non-shared environments (Horwitz & Neiderhiser, 2011). However, one of the main drawbacks of the traditional twin design is that it either looks at children who are twins or parents who are twins, but generally does not take parent and child pairs who possess varying degrees of genetic relatedness into consideration (Narusyte et al., 2008). That means that *evocative* and *passive* rGE cannot be easily disentangled (Narusyte et al., 2008).

To overcome this limitation, some twin studies only utilise MZ twins, such as Lecei et al (2019) who explored whether rGE is involved in the association between psychosis and childhood trauma in 133 pairs of MZ twins from the TwinssCan study. The study found that rGE was not involved in the correlation between psychosis and childhood trauma, thus suggesting that this association may be causal.

Behavioural genetic studies have further extended the twin designs to Children-of-Twins (COT) and Extended Children-of-Twins (ECOT) (D'Onofrio et al., 2003; Narusyte et al., 2008). The COT design is often used for unexpressed genetic predispositions in some complex psychopathological outcomes, including SCZ, by comparing children of affected and unaffected twins to identify the processes involved through which the genetic risk is mediated (D'Onofrio et al., 2003). For instance, Silberg et al (2010) investigated 2,674 adult twins and their spouses as well as 2,940 of their children from the Virginia Twin Study of Adolescent Behavioral Development Study to better understand the environmental and genetic effects involved in the transmission of parental depression to offspring depression and conduct disturbance. The study proposed that *passive* rGE was, at least partially, responsible for the association between parental depression and children's conduct disorders whereby 4.28% of the total variance was explained by the best fit model (Silberg et al., 2010).

Although parenting COT studies allow for a better separation of *passive* rGE from direct environmental influences, they do not easily detect *evocative* rGEs as the methodology uses children of twins which therefore share between 12.5% to 25% of their genetic information (Narusyte et al., 2008).

In light of this, the COT model has been further adapted to the ECOT design by including the same measured constructs in a twin companion study: offspring influencing parents, and parents influencing offspring, allowing for an easier differentiation between *passive* and *evocative* rGE (Marceau et al., 2013; Narusyte et al., 2008). For instance, a recent ECOT study by Marceau et al (2013) investigated 909 twin parents and their adolescent children from the Twin and Offspring Study in Sweden (TOSS), as well as 405 adolescent children and their parents from the Nonshared Environment in Adolescence study from the United States of America (NEAD). The study explored the correlation between maternal negativity (Correlation (r) = .52 for TOSS , r = .58 for NEAD) and paternal negativity (r = .46 for TOSS, r = .49 for NEAD) with externalizing problems, suggesting that *evocative* rGE can be attributed to this association (Marceau et al., 2013).

The fact that twin studies and their adaptations rely on genetically related individuals is their greatest strength, but also their biggest weakness. Perhaps one of their most criticised limitations is the equal-environment assumption (EEA), which assumes that MZ twins and DZ twins share equivalent environmental exposures for a particular trait (Fosse et al., 2015), despite the fact that the MZ twins and DZ twins share a different amount of genetic information. To address this limitation, researchers suggested that the heritability for a particular trait could be estimated by doubling the difference between MZ and DZ concordance or correlation (Boomsma et al., 2002). However, parents or twins themselves may misclassify their own twin zygosity, which in turn questions the EEA assumptions in the classic twin design (Fosse et al., 2015).

Another assumption of the twin design is that random mating occurs among parents (Bezdjian et al., 2011). Bezdjian et al. (2011) argue that, whilst this may be low in magnitude, similarities between DZ twins would increase if assortative mating takes place, thus biasing shared environment and heritability estimates.

One additional final point that needs to be considered is whether twins are actually representative of the general population. Munn-Chernoff et al. (2013) found statistically significant differences in psychopathological means between twins and singletons, although it is important to mention that these may not bare any clinical significance. Whilst the study solely looked at internalization and disordered eating, it does raise the questions whether twin findings could be generalised to the rest of the population.

1.5.2 Adoption Studies

To surmount some of the challenges seen with the twin and extended twin designs, behavioural genetics research also conducts adoption studies to assess the interplay between child outcomes and family relationship variables (Harold et al., 2013). Adoption studies are designed to compare genetically-unrelated individuals in environments that are correlated, as well as genetically-related individuals in environments that are unrelated (Evans et al., 2002).

Different types of adoption designs exist, such as adoption-at-birth, where *passive* rGE is controlled for as well as adoption-at-conception studies, which is used to detect *evocative* rGE, with the most powerful designs gathering data from the adopted offspring and their biological parents, as well as from the adoptive parents or adoptive family offspring (Harold et al., 2013; Heath et al., 1985).

One study which used this adoption design to investigate rGE was O'Connor et al. (1998). The study assessed 38 adopted children with the genetic risk for antisocial behaviour and 40 adopted control children between the ages of 7 to 12 years from the Colorado Adoption

Project based on the biological mothers' self-report of antisocial behaviour prior to birth (O'Connor et al., 1998). In this longitudinal adoption study, adopted parents provided information on positive or inconsistent parenting, as well as negative control. Findings suggested that there was a correlation between adopted children with the genetic susceptibility to antisocial behaviour and negative parenting (analysis of variance (ANOVA) F (1 , 57) = 6.68, $p < .05$), indicative of *evocative* rGE (O'Connor et al., 1998).

At a first glance this may look like a much cleaner way to separate genetic from environmental factors compared to the traditional twin design. However, adoption studies do have to overcome multiple challenges too. The first one being the issue of the random placement (Bezdjian et al., 2011). Adoptive parents tend to have a higher socio-economic status compared to the general population and are generally of good health (Evans et al., 2002). Evans et al. (1993) further explain that random selection is not always possible as in some cases adoptive families are either related, such as aunts or uncles, or are often selected based on similarities to the biological parents. Secondly, that also means that the home environment of the adopted individual is restricted, as an adoption is essentially a 'between-family process' and there is a potential for shared environments to be underestimated and for genetic factors to be overestimated (Rhee & Waldman, 2002; Stoolmiller, 1999). On the other hand, developmental changes for some mental health outcomes, could cause different genes to be important in different development stages (Bezdjian et al., 2011). Bezdjian et al. (2011) therefore argue that, in some adoption studies, the genetic effect may in fact be underestimated.

Lastly, it is also important to consider whether the results from adopted individuals with a particular trait of interest are actually representative of the wider population (Evans et al., 2002). Some psychology studies, for instance on antisocial behaviour, argue that adopted individuals have a higher rate of antisocial behaviour than average (Rhee & Waldman, 2002).

That means that, depending on the psychopathological outcome, adoption studies may show stronger associations for a certain trait compared to the general population.

1.5.3 Molecular Genetics Studies

Despite the fact that twin and adoption studies are useful tools to assess rGE associations for some psychopathologies, molecular genetics studies have recently opened the door to explore the complex interplay between genes and the environment even further. Whilst the concept of rGE has been widely acknowledged for the last 40 years (Plomin et al., 1977), molecular genetics studies which would actually measure rGE at the level of measured genetic variation have only been conducted since the start of the century. For instance, one of the first substance dependency molecular genetics studies investigating rGE (as well as GxE) was conducted by Dick et al (2006) in 1,900 participants from the Collaborative Study of the Genetics of Alcoholism study. The study proposed that the *GABRA2* gene was associated with alcohol dependency (OR = 1.40; 95% CI [1.17-1.67]; $p = .0003$), with alcohol dependency also being significantly associated with being unmarried (OR = 2.16; 95% CI [1.83-2.56]; $p < .0001$) suggesting that rGE could, at least partially, be responsible for these correlations (Dick et al., 2006).

Molecular genetics studies not only confirm that rGE exist and reinforce findings from twin and adoption studies, but also support that correlations between the environment and our genes are mediated by personality or behavioural characteristics (Jaffee & Price, 2007). But not all molecular genetics studies follow the same methodology.

Given that a significant number of psychopathological outcomes are highly heritable, including SCZ (Sullivan et al., 2003), early molecular genetics studies often used a candidate gene approach to investigate specific genes for a particular biological process (Moore, 2017). For instance, Klauke et al (2011) investigated gene-environment interplay between a serotonin

transporter gene variant (5-HTTLPR/5-HTT rs25531) and the effects of childhood maltreatment on anxiety sensitivity in 350 healthy adults from Germany. Whilst the main aim of this candidate gene study was to investigate possible GxE, the study used bivariate correlation analysis to control for rGE and identified two significant rGE correlations between childhood maltreatment and two of the 5-HTT genotypes ($\beta = .12$, $p < .02$ and $\beta = .17$, $p < .01$) (Klauke et al., 2011).

Bearing in mind that most psychopathologies are polygenic, research has moved on to GWAS to identify genetic risk factors by considering millions of SNPs across the entire genome (Bush & Moore, 2012; Hyman, 2018). While molecular genetic studies, which directly measure the genotype, still only account for a small part of rGE research, these genetics studies further demonstrate the existence of rGE (Jaffee & Price, 2007).

One method which can be utilised is the Genome-wide Complex Trait Analysis (GCTA). GCTA estimates the genetic relationships between individuals for complex traits and was originally developed to address the missing heritability issue whereby detected genetic variants explain only a small proportion of the estimated heritability (Manolio et al., 2009; Yang et al., 2011). GCTA works on the assumption that each SNP randomly contributes to a specific phenotype and that these contributions are indeed correlated between individuals who have similar genotypes (Krishna Kumar et al., 2016). GCTA has been successfully used to assess rGE, such as by Trzaskowski et al (2014). The study investigated the genetic influence from approximately 3,000 unrelated children aged 7 to 12 years of age from the Twins Early Development Study on family socio-economic status (SES) and intelligence of the offspring (Trzaskowski et al., 2014). The study highlighted significant genetic influences on the family SES at ages 2 and 7 with a heritability estimate of 18% and 19% respectively, as well as on the offspring's IQ at age 7 (28%) and 12 (32%) years of age. However, one of the limitations of this GCTA method is that it requires large samples with more than 3,000 individuals for

genetic correlations given that even far related pairs of individuals are omitted from the analysis (Plomin, 2014).

One other promising molecular genetics approach, which we have applied in this research project, is the creation of PRS which has been described in section 1.3.2.5 *(Polygenic Risk Scores)*. This method has been successfully used for multiple psychopathological outcomes, including SCZ and MDD as well as to investigate rGE (Sørensen et al., 2018; Vassos et al., 2017; Wray et al., 2007).

For instance, one recent rGE PRS study by Pergola et al (2019) showed the correlation between the heightened genetic liability to SCZ and bullying victimisation in 650 adolescents aged 13-14 years of age from the Dutch Tracking Adolescents Individual Lives Survey explaining 1% of the variance. In other words, adolescents with an increased PRS for SCZ experienced more severe bullying compared to individuals with a lower PRS for SCZ and that bullying victimisation partially mediated the outcome of the genetic liability on the development of psychotic symptoms later on in life (Pergola et al., 2019). The authors concluded that one possible explanation for this finding could be *evocative* rGE whereby the genetic susceptibility to SCZ evokes reactions from other individuals, including bullying.

Moreover, another GWAS study that examined the co-variation between the offspring's genetic risk for multiple psychopathological outcomes and various environmental exposures in 6,710 unrelated individuals from the Twins Early Development Study. The study identified that the genetic susceptibility for SCZ in children was correlated with increased paternal age, even after adjusting for BMI and education ($R^2 = 0.002$; $\beta = 0.049$; $p = .0001$) (Krapohl et al., 2017). Whilst the study was unable to distinguish which type of rGE mechanism is present, the finding most likely reflects *passive* rGE, whereby the parental genotypes are passed down to the offspring which are also associated with environment-providing behaviours of the parents (Krapohl et al., 2017).

However, it is also important to highlight that although well-powered, longitudinal PRS studies investigating rGE are now emerging, very few are able to identify the type of rGE. This can only be achieved by including child as well as parental genotypes in order to discriminate between the different types of rGE (Krapohl et al., 2017) and has been utilised in our Paper 1 (Chapter 3) (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022).

1.6 Aims and Hypotheses

The aim of this research project was to make use of existing and emerging results from GWAS studies to estimate the genetic risk for SCZ and MDD in the general population using PRS across different developmental stages.

1.6.1 Chapter 3: Paper 1 (rGE for SCZ and MDD in Childhood)

1.6.1.1 Objective

The aim of Chapter 3 was to investigate rGE in SCZ and MDD in childhood by using two British community cohorts: the Millennium Cohort Study (MCS) (n = 7,280 children [6,874 mothers, 4,322 fathers]) and the 1958 National Child Development Study (NCDS) (N = 5,288) which were 42 years apart (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022).

Our first objective was to explore whether the genetic risk, measured as PRS, for either SCZ or MDD was correlated with established environmental or psychosocial risk factors in childhood.

Next, we wanted to assess whether any rGE differed between the two psychopathologies and between the two cohorts.

Finally, given that we had child as well as parental genotypes in MCS, we wanted to

identify whether rGE associations are due to passive or evocative rGE.

1.6.1.2 Hypotheses

Firstly, based on evidence from existing literature, we expected that known environmental or psychosocial risk factors for either psychopathology would be correlated with the genetic susceptibility to SCZ or MDD in children.

Secondly, given the partial genetic overlap between SCZ and MDD, we hypothesised that any rGE findings would differ between the two psychiatric disorders.

Thirdly, we expected that rGE correlations would also differ across the two British community cohorts, which were over 40 years apart, due to cultural and societal changes in environmental risk.

Finally, as we utilised the child as well as parental genotypes from one of the two selected community cohorts, we hypothesised that some of our identified rGE in children would be confounded by the parental genotypes, suggesting *passive* rGE.

1.6.2 Chapter 4: Paper 2 (rGE for SCZ and MDD in Adulthood)

1.6.2.1 Objective

The objective of our second paper was to examine rGE in SCZ and MDD in adulthood by using two cohorts from the general population: Understanding Society (USoc) (n = 7,384) and the NCDS (n = 5,288) which are both of different ages (Sandra Machlitt-Northen et al., 2022).

Firstly, we wanted to explore the presence rGE with regards to the genetic risk, measured as PRS, to either SCZ or MDD and known environmental or psychosocial risk factors in cohort participants aged 16 years or over.

Further, we aimed to assess if correlations between the genetic susceptibility to either psychopathology and environmental factors differed between SCZ and MDD.

Lastly, we wanted to compare any rGE association to identify if they matched across two different adult cohorts.

1.6.2.2 Hypotheses

Based on evidence from empirical studies, we hypothesised that we would detect significant correlations between established environmental or psychosocial risk factors and the PRS for SCZ or MDD.

Further, given the limited genetic overlap between the two psychopathologies and differences in heritability we expected that rGE associations would differ between SCZ and MDD.

Finally, we hypothesised that any detected rGE would vary between the two community cohorts because of different ages as well as cultural shifts in psychosocial and environmental risks.

1.6.3 Chapter 5: Paper 3 (rGE for SCZ and MDD over Time)

1.6.3.1 Objective

The aim of Chapter 5 was to investigate whether previously detected rGE findings from Study 1 and Study 2 (Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) change over time using MCS, USoc and the NCDS (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022).

Firstly, we wanted to assess whether rGE from Study 1 change across childhood from birth until age 16.

Secondly, we investigated whether any rGE from Study 2 change across adulthood in participants aged 16 years or over.

Thirdly, as we had phenotype data from participants from the NCDS from birth up to the age of 55, we further tested whether the strength of any rGE findings changed from childhood to adulthood.

Finally, we explored whether any changes in rGE findings over time for SCZ and MDD differed given the partial partial genetic overlap between SCZ and MDD.

1.6.3.2 Hypotheses

Given the evidence from other studies (Newbury et al., 2020), we expected that some of our previously identified rGE associations for either SCZ or MDD from Study 1 and Study 2 would increase over time due to active rGE as individuals shape and modify their own environments based on their genetic susceptibility (Plomin et al., 1977).

Moreover, we hypothesised that rGE associations would be stronger in adults for our rGE childhood vs adulthood comparison in NCDS.

Further, we expected that rGE changes over time would differ for both psychopathologies, based on their incomplete genetic overlap.

1.6.4 Chapter 6: Paper 4 (Systematic Review on rGE for SCZ and MDD)

1.6.4.1 Objective

The main aim of Paper 4 was to conduct a systematic review that describes and reviews empirical studies which investigated rGE for either SCZ or depressive phenotypes using PRS across all developmental stages, including our own rGE findings from Study 1, Study 2, and Study 3 (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022;

Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022).

Our second objective was to investigate whether rGE results for SCZ or depressive phenotypes differed due to the partial genetic overlap between the two psychiatric disorders.

1.6.4.2 Hypotheses

Based on evidence from our own three studies (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022; Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022), we hypothesised that we would identify rGE findings for both SCZ and depressive phenotypes .

Lastly, based on findings from Study 1, Study 2 and Study 3 as well as due to the fact that there is only an incomplete genetic overlap between SCZ and MDD, we expected that rGE findings would differ between the two psychopathologies.

Chapter 2: Methods

2.1 Overview

The methodology presented in this chapter has been published:

> **Machlitt-Northen S**, Keers R, Munroe PB, Howard DM, Trubetskoy V, Pluess M. Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene-environment correlation. J Child Psychol Psychiatry. 2022 Jul 4. doi: 10.1111/jcpp.13657.
>
> **Machlitt-Northen, S.,** Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. *Translational Psychiatry*, *12*(1), 477. https://doi.org/10.1038/s41398-022-02247-8
>
> **Machlitt-Northen, S**.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136

This thesis describes the findings of three empirical studies on rGE in childhood (Chapter 3), adulthood (Chapter 4) as well as across time (Chapter 5) regarding SCZ and MDD using genotypic and phenotypic data from three different British Community Cohorts. This chapter will provide an in-depth description of each of these cohorts: the Millennium Cohort study which includes 18,827 children who were born in a 12-month period after the year 2000, Understanding Society (USoc) which is comprised of 40,000 households of mixed ages as well as the 1958 National Child Development Study (NCDS) with 17,415 unrelated individuals who were born in a single week in 1958. Moreover, this chapter describes the selection of environmental measures used across the three empirical studies as well as detailed steps on the processing and analyses of genotype and phenotype data in depth. The methodology used in the systematic literature review (Paper 4 – Chapter 6) will not be described in this section and has been included in Chapter 6 instead.

2.2 Data

Participants from three British community cohorts, namely the MCS, USoc and NCDS were utilised across the three empirical studies and described in detail below.

2.2.1 Millennium Cohort Study (MCS)

The MCS cohort is a multi-disciplinary, observational cohort study and is comprised of 18,827 children from 18,552 families from different ethnic backgrounds (Connelly & Platt, 2014; Joshi & Fitzsimons, 2016; Nasir & Bloch, 2021). In contrast to other British cohort studies, MCS includes participants who were born over a 12-month period (Connelly & Platt, 2014). All participating cohort members from England or Wales were born between September 2000 and August 2001, with children from Scotland or Northern Ireland having been born between November 2000 and January 2002 (Connelly & Platt, 2014). At the age of 3, an additional 692 new families were added to the cohort, bringing the total number of cohort member to 19,517 (Staatz et al., 2021).

This British community study was designed to be representative of the total population which included that certain population groups, including children from disadvantaged areas, were intentionally over-recruited (Connelly & Platt, 2014).

Overall, about half of all children are male (n = 9,894), with just over 81% (n = 15,638) of cohort members self-identifying as white (Connelly & Platt, 2014; Staatz et al., 2021).

The first data sweep (MCS1) was completed by the parents when the cohort members were 9 months of age, with later data collections additionally including teacher reports (from MCS3 onwards), reports from older siblings (from MCS2 onwards) and child self-reports (from MCS4 onwards) (Connelly & Platt, 2014). During data sweep 6 (MCS6) when the cohort members reached 14 years of age, saliva samples were collected for DNA extraction from

9,259 children, 8,898 biological mothers and 5,179 biological fathers, forming 4,533 "mother-father-child-trios" (Fitzsimons et al., 2020; Gutman et al., 2015; Joshi & Fitzsimons, 2016).

We had access to phenotype data from cohort members as well as their biological parents from six data sweeps: aged 9 months (2001), 3 years (2004), 5 years (2006), 7 years (2008), 11 years (2012) and finally 14 years (2015). All data points were utilised in Chapter 3 and Chapter 5.

2.2.2 Understanding Society (USoc)

The USoc cohort is a household panel study and was first commissioned in 2007 (Platt et al., 2020). Is comprised of approximately 40,000 households with roughly 100,000 participants of mixed ages from across Britain (Buck & McFall, 2011; Platt et al., 2020). USoc builds on the British Household Panel Survey (BHPS) which originally started in 1991 and was comprised of 5,500 households from the United Kingdom, with 1,500 households from Wales and Scotland and 2,000 households from Northern Ireland having later been added in 1999 and 2001, respectively (Benzeval et al., 2014; Platt et al., 2020; Taylor et al., 2018). When the BHPS came to an end in 2009, BHPS households joined the USoc Main Survey (Benzeval et al., 2014). The main cohort was later further supplemented with an Immigrant and Ethnic Minority Boost Sample as well as an Ethnic Minority Boost Sample, (Buck & McFall, 2011; Lynn, 2009).

The USoc household panel design differs to that of longitudinal cohorts or birth cohort studies where a sample of participants with a specific age is followed (Buck & McFall, 2011). Rather, in USoc a nationally represented population sample is selected within their households covering all age groups, whereby individuals are longitudinally studied with regards to their changing household contexts (Buck & McFall, 2011; Platt et al., 2020).

Households are surveyed each year, either through online questionnaires or face-to-face interviews with participants aged 16 years or over completing the adult questionnaire (Buck & McFall, 2011). Further health assessments for all adults, including blood samples and a range of physical measures were conducted by a registered nurse in waves 2 and 3 (2010 - 2012) (Benzeval et al., 2014). Approximately 10,000 participants consented to donating blood DNA samples (Benzeval et al., 2014).

We utilised environmental phenotypes from nine data sweeps from data wave 1 (2009-2010) until data wave 9 (2017 - 2018) for Chapter 4 and Chapter 5.

2.2.3 1958 National Child Development Study (NCDS)

The NCDS is comprised of 17,415 unrelated individuals from either England, Scotland or Wales who were all born in a single reference week in March 1958 (Bann et al., 2018; Power & Elliott, 2006). Overall, the cohort largely consists of participants from a white ethnic background (98% of initial participants) with the cohort having been later augmented with immigrants who were born overseas in the same specific week in March 1958 and who had moved to Britain at age 7, 11 or 16 years (Bann et al., 2018; Power & Elliott, 2006).

NCDS originated from the Perinatal Mortality Survey which investigated infant mortality and still birth related obstetric and social factors from medical records as well as questionnaires completed by the midwife (Brown & Goodman, 2014). The first three data sweeps, at ages 7, 11 and 16, were performed by health visitors and consisted of parental interviews, questionnaires which were completed by teachers as well as child reports from the cohort members themselves (Brown & Goodman, 2014). The assessment of the NCDS participants continued throughout their lives with computer aided interviews replacing face-to-face interviews from the age of 30 onwards (Brown & Goodman, 2014). Between 2002 and 2004, nurses conducted a bio-medical survey on surviving cohort members aged 44 to 46 years

of age, including the collection of blood for DNA extraction from 9,293 individuals (Brown & Goodman, 2014; Centre for Longitudinal Studies, 2020).

We had access to phenotype data from ten data sweeps from 1958 (birth of participants), age 7, 11, 16, 23, 33, 42, 46, 50, up until 2013 (participants aged 55). For paper 1 (Chapter 3) we included phenotypic data from four data sweeps from birth (1958) up to 16 years of age (1974). For paper 2 (Chapter 4), we used data from six data sweep ranging age 23 (1981) until age 55 (2013). Lastly, for paper 3 (Chapter 5), we used all data points from birth (1958) up until 55 years of age (2013).

2.2.4 Ethics Approval and Informed Consent

Firstly, for MCS, the London Multicentre Research Ethics Committee (MREC) provided the ethics approval for the DNA collection as well each data sweep [MREC/01/6/19, MREC/03/2/022, 05/MRE02/46, 07/MRE03/32, 11/YH/0203, 13/LO/1786] (Fitzsimons et al., 2020; Shepherd & Gilbert, 2019).

Secondly, the University of Essex Ethics Committee approved ethics requests for the data collection on the main USoc study and the innovation panel data sweeps, including data linkage requests, except to health records (Institute for Social and Economic Research, 2021). The health record linkage request was accepted by the National Research Ethics Service (NRES) Oxfordshire REC A (08/H0604/124) at Wave 1, by the NRES Royal Free Hospital & Medical School (08/H0720/60) at BHPS Wave 18 as well as by NRES Southampton REC A (11/SC/0274) at Wave 4 (Institute for Social and Economic Research, 2021). Ethics approval for the collection of biosocial data, which was part of the USoc main survey in Wave 2 and 3, was granted by NRES (10/H0604/2) (Institute for Social and Economic Research, 2021).

Thirdly, the earlier NCDS data sweeps (1958 to 1965) were conducted prior to the establishment of the ethics committee system (Centre for Longitudinal Studies, 2014). Internal

ethical reviews were conducted between 1969 to 1991, with ethical approvals after the year 2000 having been provided by the South East and London MREC [01/1/44; 08/H0718/29; 12/LO/2010] (Centre for Longitudinal Studies, 2014).

For all three studies, informed consent was obtained from all cohort members.

2.3 Environmental Measures

Environmental risk factors which are known to be associated with either SCZ or MDD and were included in Studies 1, 2 and 3 are described in the next three sections.

2.3.1 Chapter 3 – Paper 1 (rGE for SCZ and MDD in Childhood)

Chapter 3 utilised the MCS and the NCDS cohorts. For MCS, we used six data sweeps, from age 9 months (2001) to 14 years (2015). Linked phenotypic data from NCDS was used from four data sweeps, from birth (1958) up to 16 years of age (1974).

Selected Environmental Measures for each Cohort

All coded environmental factors for Chapter 3 are presented in Appendix 1 for MCS and Appendix 2 for NCDS (childhood).

The following environmental risk factors in childhood were used for MCS for Chapter 3: A) Variables available at single timepoints included birthweight, gestational period, mother's employment status, mother's and father's interest in the child's education and father's involvement in childcare; B) Moreover, variables available at multiple timepoints were maternal/paternal alcohol consumption & smoking behaviour, parental marital status, whether mother or father reads to child or takes child for walks, finance issues, number of bedrooms, SES and tenure of accommodation.

The listed environmental risk factors for NCDS were as followed: A) Environments at single timepoints only were comprised of mother's and father's age at birth, birth weight, gestational period, parity, maternal smoking prior and during pregnancy, mother's marital status at birth, whether mother or father reads to child, housing issues, family alcohol issues and domestic tension; B) Environments which were recorded at multiple timepoints in NCDS were SES, finance issues, number of bedrooms, tenure of accommodation, free school meals, mother's and father's interest in the child's education, father's involvement in childcare, mother or father takes child for walks as well as father's employment status.

2.3.2 Chapter 4 – Paper 2 (rGE for SCZ and MDD in Adulthood)

Chapter 4 made use of environmental data from USoc and the NCDS cohorts. For USoc, we utilised nine annual data sweeps from 2009 to 2010 until 2017 to 2018, whilst phenotype data from NCDS came from six data sweep from when the individuals were 23 years of age (1981) until they reached 55 years (2013).

Selected Environmental Measures for each Cohort

In order to allow for a comparison between potential childhood and adulthood rGE findings in Chapter 5, we selected similar environmental risk factors which are known to be implicated in the aetiology of both psychopathologies.

All coded environmental factors for Chapter 4 are presented in Appendix 3 for USoc and Appendix 4 for NCDS (adulthood).

Following the review of environmental risk factors which are implicated in the aetiology of both psychopathologies in adulthood, the following variables were selected for USoc for Chapter 4: The only environmental variables which was available at single timepoints only was marital status. All other selected variables, namely alcohol consumption, education,

SES, number of bedrooms, income, employment status, finance issues and tenure of accommodation were recorded at multiple data sweeps.

Additionally, for NCDS, variables which were available at multiple timepoints and used in Chapter 4 were SES, employment status, number of bedrooms, tenure of accommodation, whether individual smoked and marital status.

2.3.3 Chapter 5 – Paper 3 (rGE for SCZ and MDD over Time)

Chapter 5 focused on environmental risk factors for SCZ or MDD that were significantly correlated with the PRS for either psychopathology from Chapter 3 or Chapter 4. Results from Studies 1 and 2 were screened before being included in Chapter 5. Any rGE correlations where at least one PRS p-value threshold had met the value of $p < .05$ prior to the application of correction for multiple testing were incorporated into Chapter 5. Any significant rGE correlations from Chapter 3 or Chapter 4 with environments which were only measured at a single timepoint were omitted from Chapter 5 as this study required longitudinal data in order to assess changes over time. Furthermore, for our childhood vs adulthood rGE-by-time analysis which utilised only the NCDS data, we only included significant environmental measures which were present in childhood *and* in adulthood.

Selected Environmental Measures for each Cohort

All coded environmental factors for Chapter 5 are presented in Appendix 5 for MCS, Appendix 6 for USoc and Appendix 7 for NCDS.

Chapter 5 made use of phenotypes from all three cohorts. Firstly, to investigate rGE changes over time in childhood, we utilised phenotype data from MCS (birth until 14 years of age) and childhood sweeps from NCDS (birth to 16 years of age). Secondly, to identify any rGE changes over time in adulthood we utilised nine data sweeps from USoc, and adulthood

sweeps from NCDS (23 years of age to 55 years old). Thirdly, in order to compare rGE childhood vs adulthood findings, we utilised the NCDS phenotype data from birth up to age 55.

To address our first objective which was to assess rGE over time in SCZ and MDD in childhood, we included the following environments which were significantly correlated with the genetic liability to either SCZ or MDD from Chapter 3: SES, finance issues, number of bedrooms, tenure of accommodation, maternal smoking, maternal and paternal alcohol consumption, parental marital status, mother or father takes child for a walk, mother or father reads to child, father's unemployment and maternal and paternal interest in the child's education.

Secondly, to identify any rGE changes over time in SCZ and MDD in adulthood, we made use of the following environments from Chapter 4 which were also significantly associated with the genetic susceptibility to either psychopathology: SES, number of bedrooms, tenure of accommodation, finance issues, marital status, employment status, income and whether adult smokes.

Finally, to compare rGE childhood vs adulthood findings in NCDS, we utilised the following environmental measures: Family SES in childhood vs SES of the individual in adulthood, father's employment status in childhood vs employment status of the individual in adulthood, family number of bedrooms in childhood vs number of bedrooms of the individual in adulthood, family tenure of accommodation in childhood vs tenure of accommodation of the individual in adulthood, marital status of mother at birth vs marital status of the individual in adulthood as well as mother's smoking behaviour prior and during pregnancy vs smoking behaviour of the individual during adulthood.

2.3.4 Coding of Environmental Factors

All environmental variables were coded in STATA v12.1 (StataCorp, 2011). Any responses which were not available ('N/A'), 'Don't know' or 'other' answers were excluded from the analyses. The full breakdown of coded environmental factors for each cohort is presented in Appendix 1 to 7.

2.4 Genetic Data

Genome-wide data was utilised from all three community cohorts.

Illumina's Infinium global screening array (GSA)-24 v1.0 from 21,324 cohort members, including 8,201 children and 13,123 biological parents was used for MCS (Fitzsimons et al., 2020).

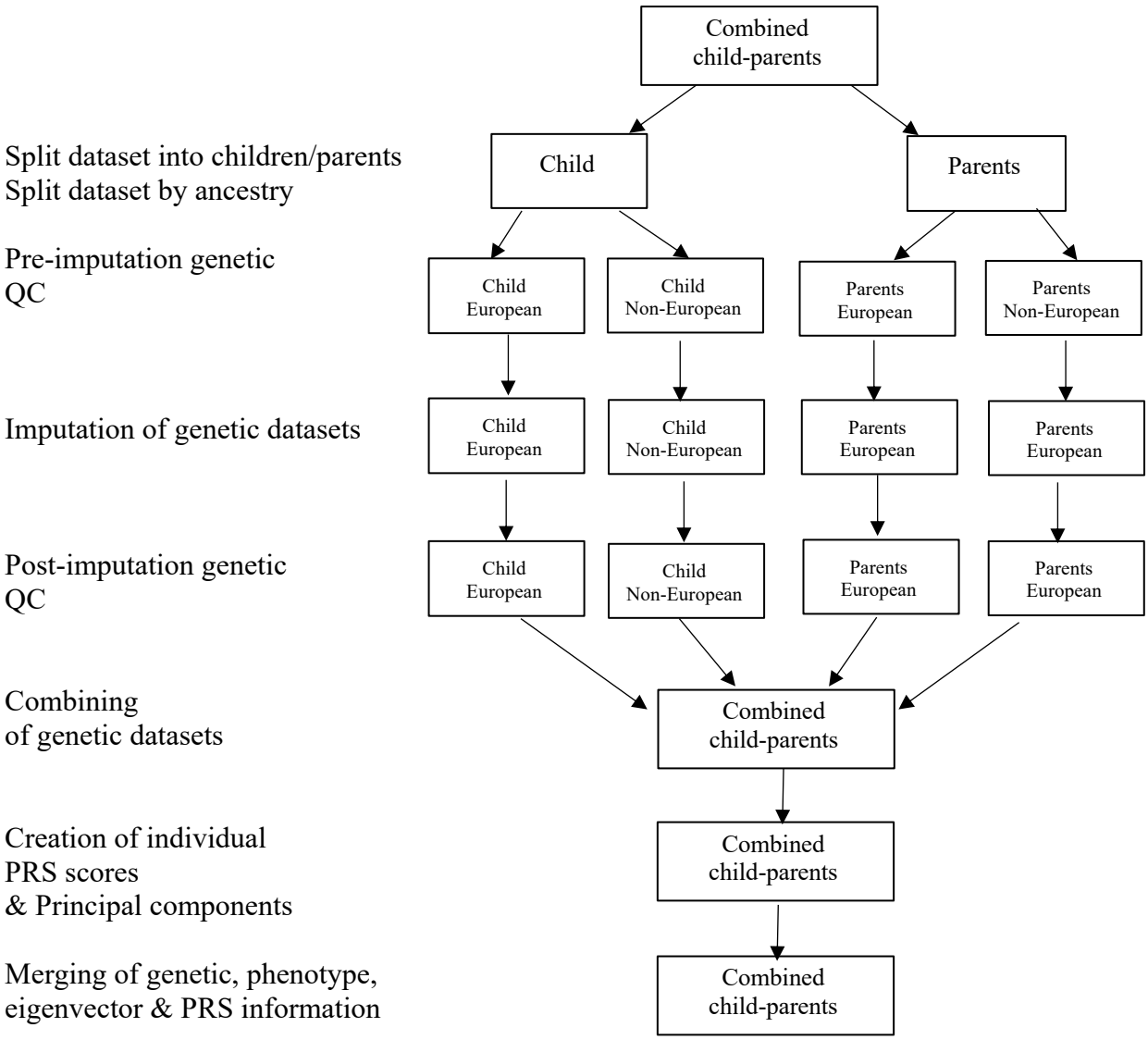
For USoc, we utilised genetic data from 9,961 individuals which was genotyped on the Illumina Infinium HumanCoreExome BeadChip array by the Wellcome Trust Sanger Institute as part of the participant's biomedical assessments during data sweep 2 and 3 (Benzeval et al., 2014). This genome-wide data in genome build 37 consists of more than 250,000 SNPs (Prins et al., 2017).

Finally, we utilised SNP data from three different arrays for NCDS. Firstly, 1,502 participants were genotyped on the Affymetix 500k 1.2M array for the Wellcome Trust Case Control Consortium 1 (WTCCC1) (Wellcome Trust Case Control Consortium, 2007), a further 2,922 cohort members were genotyped on the Illumina 1.2M chips for Wellcome Trust Case Control Consortium 2 (WTCCC2), with a total of 2,592 participants having been genotyped on the Infinium Humanhap 550k v3 arrays as part of the Type 1 Diabetes Genetics Consortium (T1DGC) (Barrett et al., 2009).

All genetic processing was performed on the Apocrita High Performance Computing Cluster platform from Queen Mary University of London (King et al., 2017).

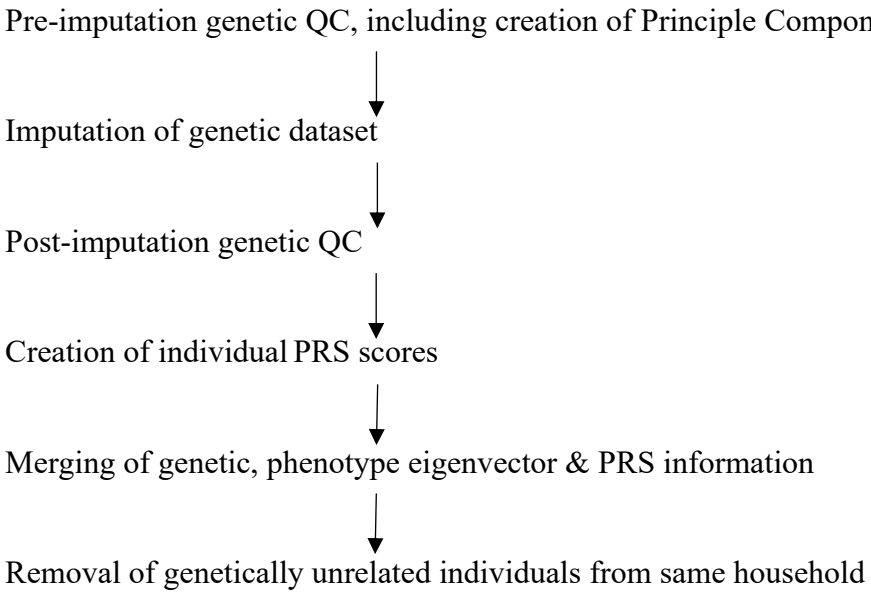
The dataset process flows for MCS, USoc and NCDS are described in *Figures* 1, 2 and 3.

Figure 1*: Dataset Process Flow for MCS*



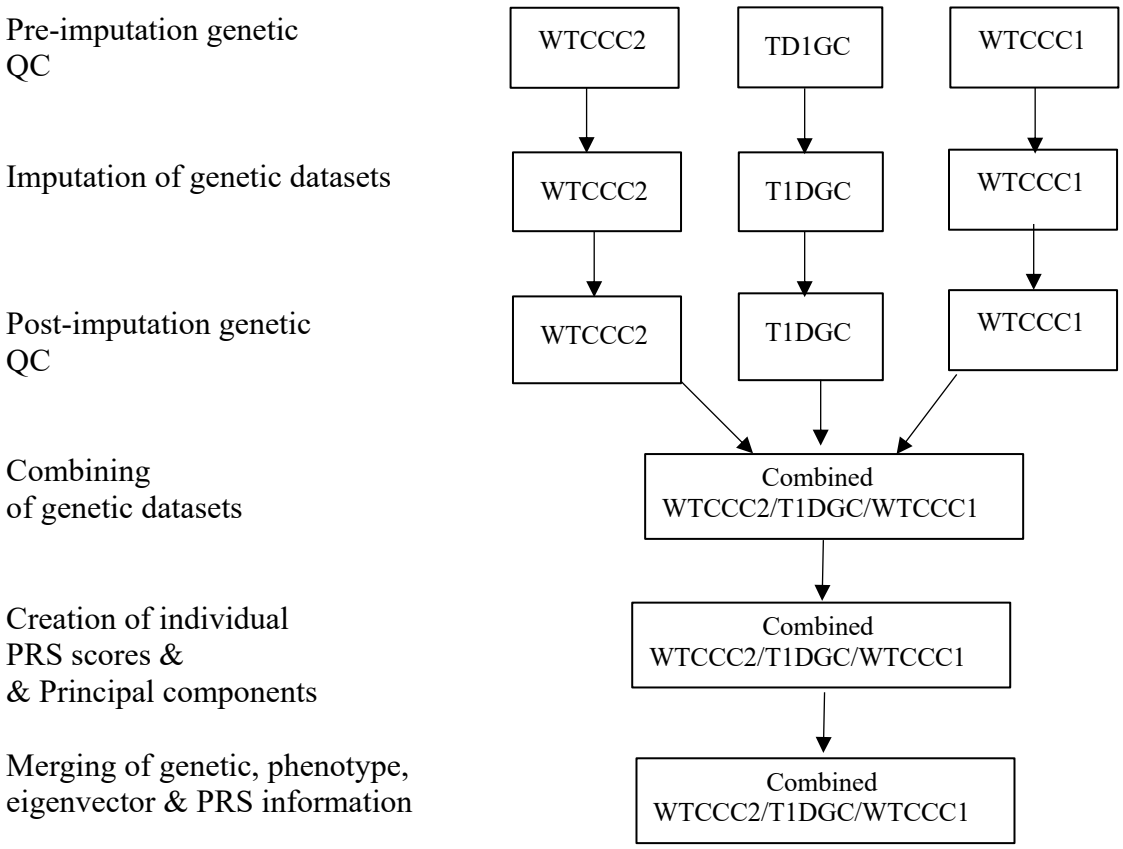
Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. MCS = Millennium Cohort Study. The initial combined child-parent genetic dataset included 21,324 samples which were genotyped on Infinium global screening arrays-24 v1.0 from Illumina (Fitzsimons et al., 2020), PRS = Polygenic Risk Scores

Figure 2*: Dataset Process Flow for USoc*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. USoc = Understanding Society – 9,921 individuals genotyped using Illumina Infinium HumanCoreExome BeadChip Kit by the Wellcome Trust Sanger Institute (Prins et al., 2017), PRS = Polygenic Risk Scores

Figure 3: *Dataset Process Flow for NCDS*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. NCDS = 1958 National Child Development Study. WTCCC2 = The Wellcome Trust Case Control Consortium 2 - 2,922 individuals (controls) genotyped using the Illumina 1.2M array (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=EGAS00000000028) , T1DGC = Type 1 Diabetes Genetics Consortium - 2,592 individuals (controls), genotyped on Infinium Humanhap 550k v3 chips (Barrett et al., 2009), WTCCC1 = The Wellcome Trust Case Control Consortium - 1,502 individuals (controls) genotyped using the Affymetix 500k 1.2M (Wellcome Trust Case Control Consortium, 2007), PRS = Polygenic Risk Scores

2.4.1 Pre-Quality Control Processing for MCS

Although, the main genotype file for MCS contained 21,446 samples, only the genotyped samples for whom phenotypic data existed were included in the analysis, reducing the total number to 21,324 samples.

Prior to Quality Control (QC), the combined MCS base dataset was divided into one child and one parent sub-sample. This was achieved by merging phenotypic family variable information (mother/father/child) with the base dataset and splitting the file into children and parents.

Furthermore, the MCS Illumina GSA array-24 SNP IDs were converted into rsIDs based on build GRCH37/hg19 (*Infinium Global Screening Array v1.0 Support files*). If multiple rsIDs matched against an Illumina ID, then the first rsID was assigned.

Each of these two MCS sub-sets was further split by ancestry into a European and non-European sub-set for the child and the parent sub-sample. Using PLINK 1.9 (Chang et al., 2015; Purcell et al., 2007), we created linkage-disequilibrium (LD)-pruned groups of SNP markers which were used to compute genome-wide identical-by-state (IBS) sharing before grouping individuals into homogeneous clusters (k=14). This was done through a multidimensional scaling analysis. Please note that no IBS could be calculated for two individuals which were subsequently removed from the sample. Next, the homogenous clusters were then overlaid with references from the 1,000 Genome Project (Auton et al., 2015). The largest cluster groups, which were closest to the European references, were used as the European subset, resulting in one child European sub-set with 7,025 individuals and one parent European subset with 11,269 individuals. All other cluster groups were then merged into non-European subsets, resulting in one child non-European sub-set with 1,176 individuals and one parents non-European subset with 1,852 individuals.

2.4.2 Quality Control (Pre-Imputation)

QC and imputation were conducted separately for all three community cohorts and their respective sub-samples: for MCS, we had 4 sub-samples (7,025 European children, 11,269 European parents, 1,176 non-European children and 1,852 non-European parents), for USoc we utilised 1 sub-sample (9,961 individuals) and for NCDS we used 3 sub-samples (WTCCC2 with 2,922 individuals, T1DGC with 2,592 individuals and WTCCC1 with 1,502 individuals).

All genetic QC processing steps were performed according to Coleman's GWAS codebook (Coleman et al., 2016) in PLINK 1.9 (Chang et al., 2015), unless otherwise stated. Firstly, duplicated individuals were removed and SNPs with minor allele frequencies (MAF) of < 1% were excluded. Then, all samples or variants with low quality or missing data were filtered for call rates iteratively in 1% intervals until a 99% threshold was reached (for MCS, 80 to 99% threshold (Fitzsimons et al., 2020), for USoc and NCDS 90 to 99%). Next, we assessed all SNPs for deviations from the Hardy-Weinberg-Equilibrium (HWE) with a p-value threshold of $< 1x10^{-5}$ before pruning the SNPs for LD with a r^2 cut-off of 0.2. Non-autosomal regions as well as high-LD regions were then excluded. Next, we compared the phenotypic and genotypic sex before removing discordant individuals. However, sex check for the NCDS WTCCC1 sub-sample was not performed due to the missing phenotype sex in the fam Plink file. Further, we tested individuals for relatedness using Identical-by-descent (IBD) checks with a pi-hat < 0.1875. Additionally, we assessed population stratification (> 6 SD from mean) using EIGENSOFT. We utilised this programme to compute the top 100 principal components (PCs) to describe model ancestry differences using EIGENSTRAT (Price et al., 2006) which contains a PERL wrapper smartpca.perl for running the smartpca program (Patterson et al., 2006). Any ancestry outliers were plotted in R v3.6.1 (R Core Team, 2018) against references from the 1,000 Genomes Project (Auton et al., 2015) before being excluded (see *Figure* 4 to 7 for MCS, *Figure* 9 for USoc and *Figure* 10 to 12 for NCDS). We also assessed unusual

genome-wide heterogeneity (> or < 3SD from mean) in the LD-pruned dataset. Next, using SNPFLIP v0.0.6 (Bakken Stovner, 2017), we discarded ambiguous SNPs and flipped reverse strand SNPs.

The three NCDS sub-samples required a genome build lift-over using liftOverPlink (Ritchie 2014). The WTCCC1 sub-sample was updated from B35 to B37, whereas both, the T1DGC and the WTCCC2 were updated from B36 to B37. The MCS and USoc datasets did not require a genome build lift-over.

For the MCS child sub-sets, 6,276 European individuals and 454,226 SNPs as well as 1,003 non-Europeans and 379,159 SNPs, respectively, passed genetic QC. Moreover, 9,854 European parents and 463,111 genetic variants as well as 1,350 non-European parents and 421,005 SNPs survived QC testing.

For USoc, we retained 9,039 individuals and 236,798 SNPs after QC testing.

For NCDS, the following number of individuals and number of genetic variants passed genetic QC; for WTCCC2: 2,631 individuals and 891,717 SNPs, for T1DGC: 2,485 individuals and 516,922 SNPs and WTCCC1: 1,432 individuals and 310,979 SNPs.

Finally, we created individual chromosome VCF files for each cohort and each sample subset in preparation for imputation.

All QC steps are displayed in Table 1 for MCS, Table 2 for USoc and Table 3 for NCDS.

Table 1: *Pre-Imputation QC for MCS*

	Child European		Child Non-European		Parents European		Parents Non-European	
	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals
Start	618,540 variants and 21,446 individuals							
Split into child & parent	618,540 variants for each: 8,201 children & 13,123 parents							
Convert into rsIDs	615,798 variants							
Add sex	615,798 variants							
Split dataset by ancestry	615,798	7,025	615,798	1,176	615,798	11,269	615,798	1,852
Duplicates	615,798	7,025	615,798	1,176	615,798	11,259	615,798	1,852
MAF	499,682	7,025	438,444	1,176	499,756	11,259	487,817	1,852
Missing data	468,278	6,822	408,416	1,136	478,399	10,731	466,498	1,723
HWE	466,731	6,822	391,009	1,136	476,457	10,731	434,895	1,723
Pruning	189,196	6,822	184,049	1,136	190,177	10,731	214,284	1,723
Adding Phenotype	189,196	6,822	184,049	1,136	190,177	10,731	214,284	1,723
Check gender	189,196	6,822	184,049	1,084	190,177	10,326	214,284	1,615
IBD check	189,196	6,561	184,049	1,068	190,177	10,261	214,284	1,572
Pop strat	189,196	6,353	184,049	1,003	190,177	9,961	214,284	1,411
Heterozygosity	189,196	6,276	184,049	1,003	190,177	9,854	214,284	1,350
Preparation for Imputation								
Start	466,731	6,276	391,009	1,003	476,457	9,854	434,895	1,350
SNPFlip (un-pruned)								
➢ SNPs flipped	226,875	6,276	189,453	1,003	231,282	9,854	210,573	1,350
➢ SNP ambiguous	12,505	6,276	11,850	1,003	13,346	9,854	13,890	1,350
Finish	454,226	6,276	379,159	1,003	463,111	9,854	421,005	1,350
VCF files								

Notes: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. MCS = Millennium Cohort Study, N = Number, MAF = Minor allele frequencies, HWE = Hardy-Weinberg Equilibrium, IBD = Identical-by-descent, Pop Strat = Population stratification, VCF files = creation of individual chromosome VCF files for imputation

Table 2: *Pre-Imputation QC for USoc*

	Number of Variants	Number of individuals
Start	248,606	9,921
Duplicates	248,606	9,921
MAF	248,606	9,908
Missing data	245,488	9,908
HWE	245,488	9,908
Pruning	58,856	9,908
Adding Phenotype	58,856	9,908
Check gender	58,856	9,880
IBD check	58,856	9,133
Pop strat	58,856	9,076
Heterozygosity	58,856	9,039
Preparation for Imputation		
Start	245,488	9,039
SNPFlip		
➢ SNPs flipped	315	9,039
➢ SNP ambiguous	8,375	9,039
Finish	236,798	9,039
VCF files		

Notes: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl.. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. USoc = Understanding Society, N = Number, MAF = Minor allele frequencies, HWE = Hardy-Weinberg Equilibrium, IBD = Identical-by-descent, Pop Strat = Population stratification, VCF files = creation of individual chromosome VCF files for imputation

Table 3: *Pre-Imputation QC for NCDS*

	WTCCC2		T1DGC		WTCCC1	
	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals
Start	1,157,986	2,922	561,303	2,592	490,032	1,502
Duplicates	1,157,986	2,916	561,303	2,592	490,032	1,496
MAF	964,060	2,916	536,881	2,592	420,099	1,496
Missing data	941,084	2,774	531,152	2,545	373,076	1,476
HWE	934,674	2,774	529,691	2,545	371,722	1,476
Pruning	121,437	2,774	98,911	2,545	80,684	1,476
Adding Phenotype	121,437	2,774	98,911	2,545	80,684	1,476
Check gender	121,437	2,771	98,911	2,540	--------	--------
IBD check	121,437	2,769	98,911	2,540	80,684	1,473
Pop strat	121,437	2,769	98,911	2,514	80,684	1,456
Heterozygosity	121,437	2,631	98,911	2,485	80,684	1,432
Preparation for Imputation						
Start	934,674	2,631	529,691	2,485	371,722	1,432
Liftover (un-pruned)	908,075	2,631	516,922	2,485	371,657	1,432
SNPFlip (un-pruned)						
➢ SNPs flipped	446,061	2,631	258,708	2,485	58	1,432
➢ SNP ambiguous	16,358	2,631	0	2,485	60,678	1,432
Finish	891,717	2,631	516,922	2,485	310,979	1,432
VCF files						

Notes: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. NCDS = 1958 National Child Development Study, N = Number, MAF = Minor allele frequencies, HWE = Hardy-Weinberg Equilibrium, IBD = Identical-by-descent, Pop Strat = Population stratification, VCF files = creation of individual chromosome VCF files for imputation, WTCCC2 = The Wellcome Trust Case Control Consortium 2, T1DGC = Type 1 Diabetes Genetics Consortium, WTCCC1 = The Wellcome Trust Case Control Consortium, SNP = Single nucleotide polymorphism

Figure 4: *Child Ancestry Grouping – European (MCS)*

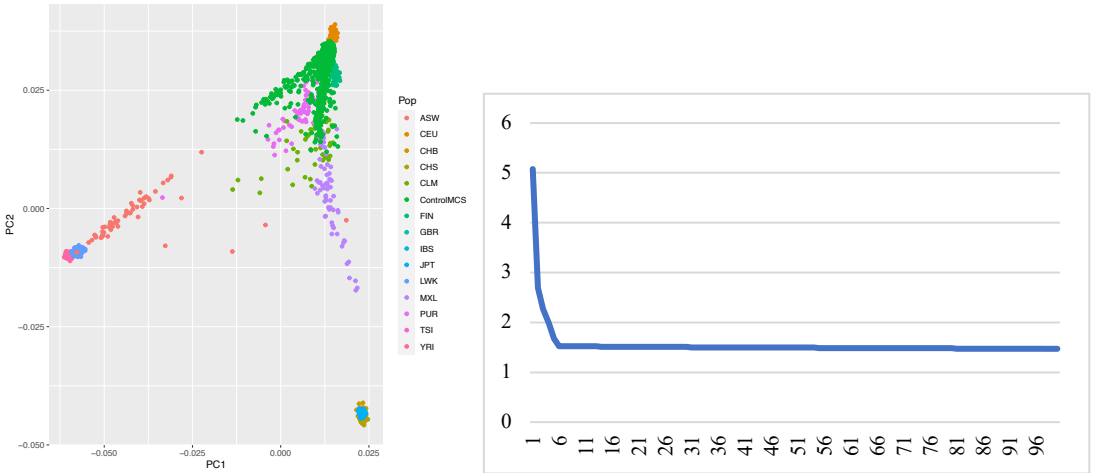
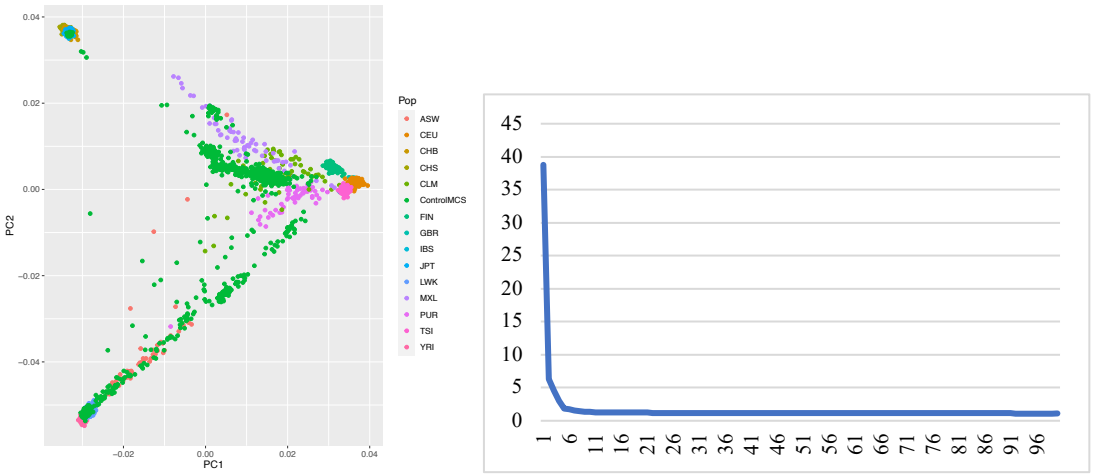


Figure 5*: Child Ancestry Grouping – Non-European (MCS)*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. MCS = Millennium Cohort Study. All ancestry groupings were plotted using R (R Core Team, 2018), ASW = Americans of African Ancestry in SW, CEU = Utah Residents (CEPH) with Northern and Western European Ancestry, CHB = Han Chinese in Beijing, China, CHS = Han Chinese South, CLM = Colombians from Medellin, Colombia, FIN = Finnish from Finland, GBR = British England and Scotland, IBS = Iberian Population in Spain, JPT = Japanese in Tokyo, Japan, LWK = Luhya in Webuye, Kenya, MXL = Mexican Ancestry from Los Angeles, PUR = Puerto Ricans from Puerto Rico, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria, CONTROLMCS refers to MCS sample; All line graphs were plotted in Microsoft Excel displaying the top 100 Principal Components

Figure 6: *Parent Ancestry Grouping – European (MCS)*

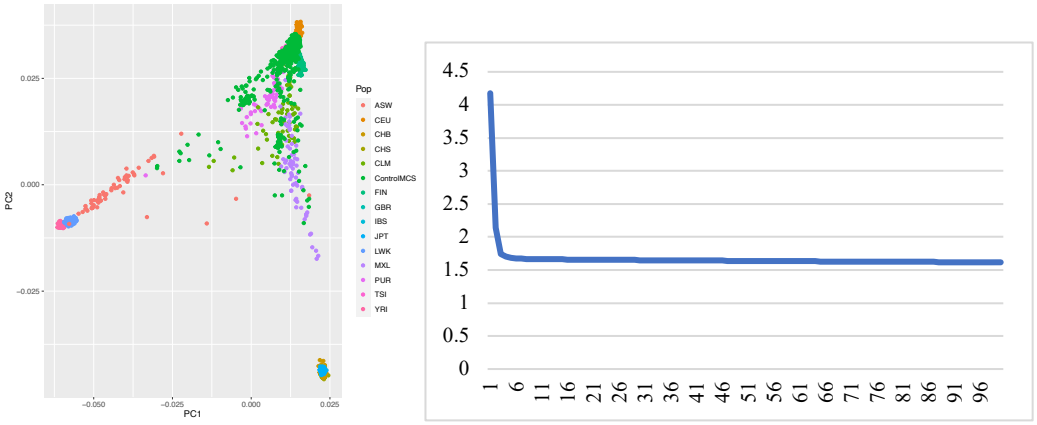
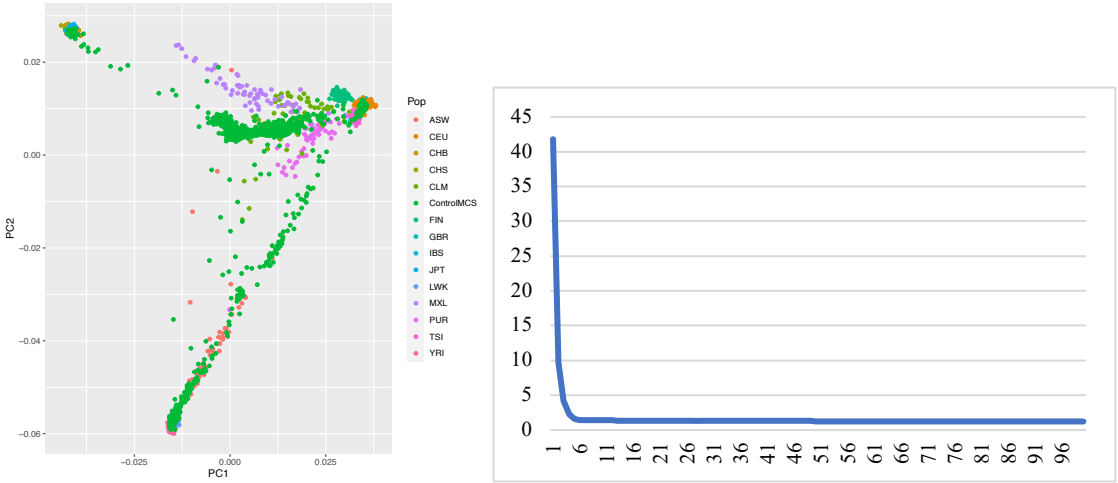
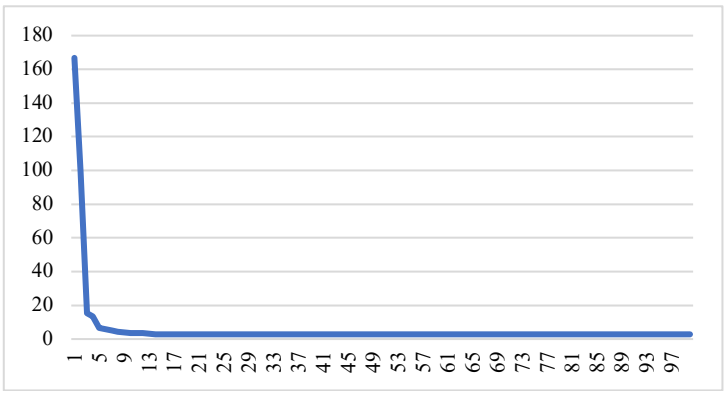


Figure 7: *Parent Ancestry Grouping – Non-European (MCS)*



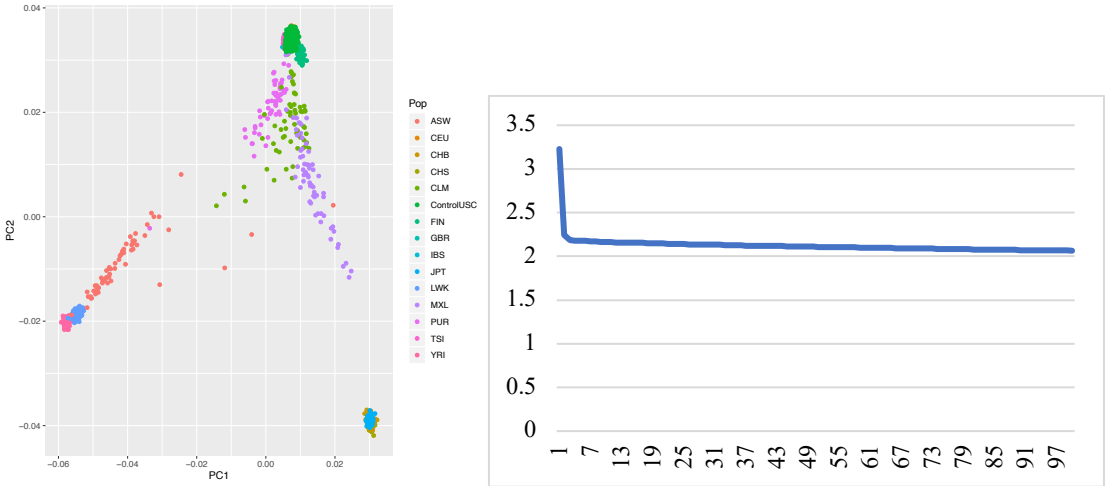
Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. MCS = Millennium Cohort Study. All ancestry groupings were plotted using R (R Core Team, 2018), ASW = Americans of African Ancestry in SW, CEU = Utah Residents (CEPH) with Northern and Western European Ancestry, CHB = Han Chinese in Beijing, China, CHS = Han Chinese South, CLM = Colombians from Medellin, Colombia, FIN = Finnish from Finland, GBR = British England and Scotland, IBS = Iberian Population in Spain, JPT = Japanese in Tokyo, Japan, LWK = Luhya in Webuye, Kenya, MXL = Mexican Ancestry from Los Angeles, PUR = Puerto Ricans from Puerto Rico, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria, CONTROLMCS refers to MCS sample; All line graphs were plotted in Microsoft Excel displaying the top 100 Principal Components

Figure 8: *Principal Components – Combined MCS*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. MCS = Millennium Cohort Study. All Principal Components were plotted using Microsoft Excel

Figure 9: *Ancestry Grouping - USoc*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. USoc = Understanding Society. All ancestry groupings were plotted using R (R Core Team, 2018), ASW = Americans of African Ancestry in SW, CEU = Utah Residents (CEPH) with Northern and Western European Ancestry, CHB = Han Chinese in Beijing, China, CLM = Colombians from Medellin, Colombia, FIN = Finnish from Finland, GBR = British England and Scotland, IBS = Iberian Population in Spain, JPT = Japanese in Tokyo, Japan, LWK = Luhya in Webuye, Kenya, MXL = Mexican Ancestry from Los Angeles, PUR = Puerto Ricans from Puerto Rico, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria, CONTROLUSC refers to Understanding Society sample. All Principal Components were plotted using Microsoft Excel

Figure 10: *WTCCC2 Ancestry Grouping - NCDS*

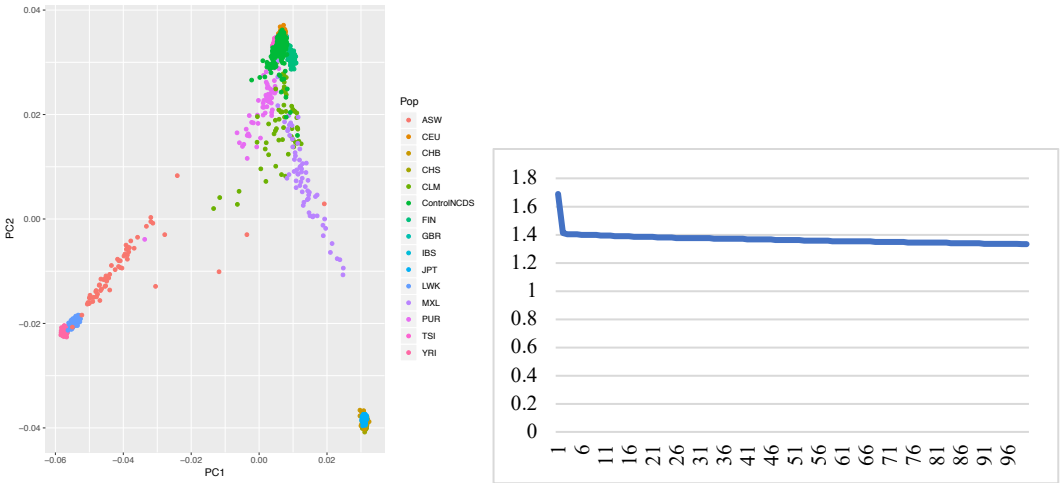


Figure 11: *T1DGC Ancestry Grouping - NCDS*

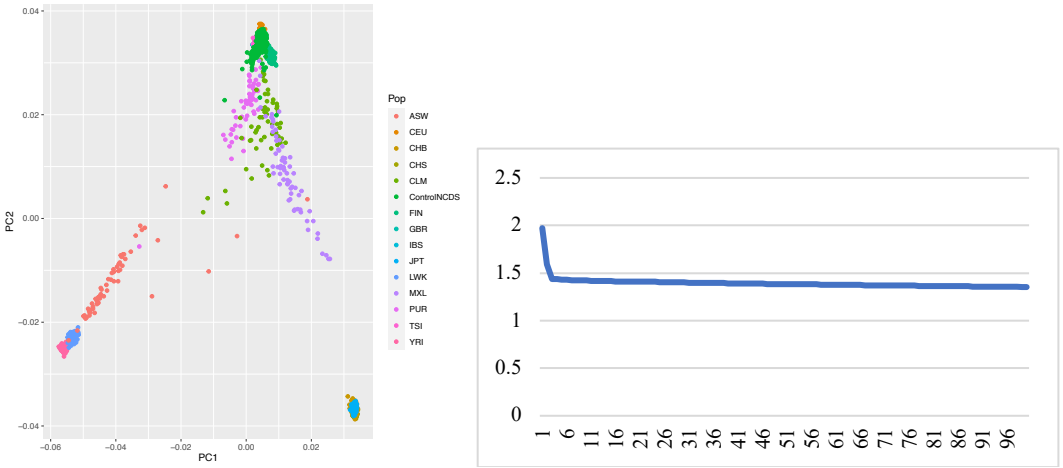
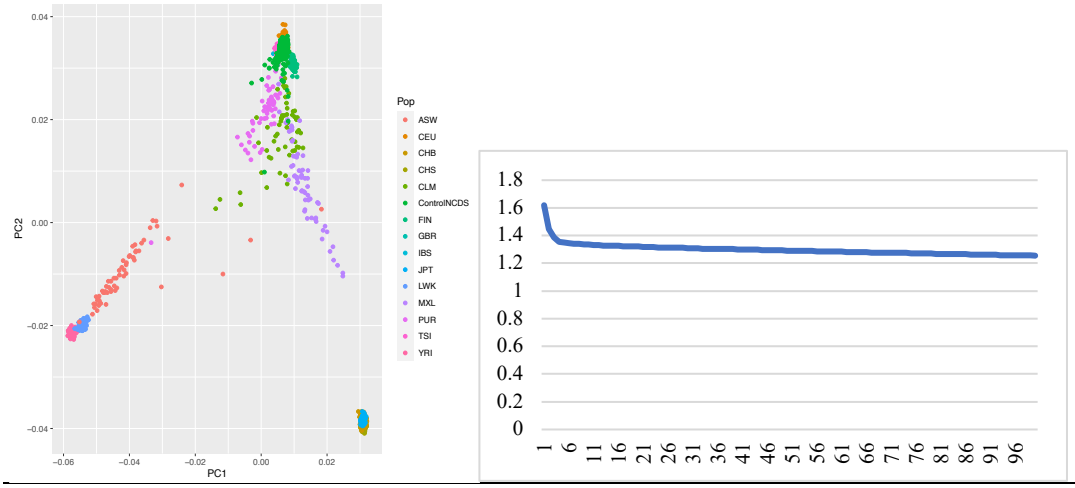


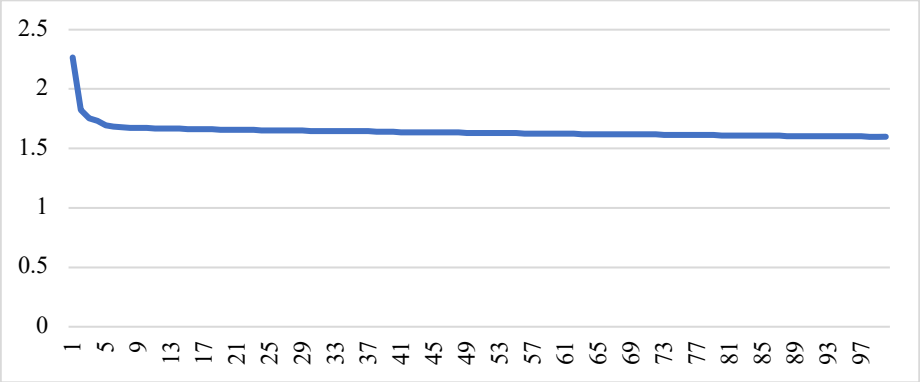
Figure 12: *WTCCC1 Ancestry Grouping - NCDS*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. NCDS = 1958 National Child Development Study. All ancestry groupings were plotted using R (R Core Team, 2018), ASW = Americans of African Ancestry in SW, CEU = Utah Residents (CEPH) with Northern and Western European Ancestry, CHB = Han Chinese in Beijing, China, CHS = Han Chinese South, CLM = Colombians from Medellin, Colombia, FIN = Finnish from Finland, GBR = British England and Scotland, IBS = Iberian Population in Spain, JPT = Japanese in Tokyo,

Japan, LWK = Luhya in Webuye, Kenya, MXL = Mexican Ancestry from Los Angeles, PUR = Puerto Ricans from Puerto Rico, TSI = Toscani in Italy, YRI = Yoruba in Ibadan, Nigeria, CONTROLNCDS refers to WTCCC2, T1DGC & WTCCC1 sample; All line graphs were plotted in Microsoft excel displaying the top 100 principal components

Figure 13: *Principal Components – Combined NCDS*



Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. All Principal Components were plotted using Microsoft Excel

2.4.3 Imputation

Imputation was performed separately for all cohorts and each individual sub-sample on the Michigan Imputation Server (Das et al., 2016). We made use of the Minimac4 v1.2.4 pipeline and the 1,000 Genomes Project Phase 3 v5 (Auton et al., 2015) as the reference panel. Moreover, all data was imputed using the array build GRCH37/hg19. Eagle v2.4 was selected as the phasing algorithm (Loh et al., 2016), whilst all cohort subsamples had the population filter set to European, except the two non-European MCS samples (child non-European and parents non-European) where the population was set to 'Other/Mixed'.

The reference overlap for MCS was more than 99.9% for all sub-samples, with USoc and all three NCDS sub-samples achieving a reference overlap of 99.48% and more than 99.6%, respectively.

Once imputation was completed, all remaining chunks for each chromosome were then merged into individual encrypted chromosome VCF.gz output files by the imputation server.

The imputation statistics per cohort are presented in Table 4.

Table 4: *Imputation Statistics per Cohort*

	MCS Child European	MCS Child Non-European	MCS Parents European	MCS Parents Non-European	USoc	NCDS WTCCC2	NCDS T1DGC	NCDS WTCC1
Start SNPs	454,226	379,159	463,111	421,005	236,798	891,717	516,922	310,979
Sample size	6,276	1,003	9,854	1,350	9,039	2,631	2,485	1,432
Chunks	154	154	154	154	153	154	153	153
Reference Overlap	99.99%	99.99%	99.99%	99.96%	99.48 %	99.62%	99.72%	99.72%
Matches	381,012	311,171	387,774	421,005	157,329	619,669	357,201	211,735
Allele switches	73,011	67,748	75,117	66,546	77,453	265,428	156,682	97,479
Allele mismatches	171	204	0	2,585	0	4	0	0
Imputation summary								
Sites excluded	171	204	187	2,806	775	3,213	1,617	909
Sites remaining	454,023	378,919	462,891	418,021	234,782	885,097	513,883	309,214
Typed only sites	32	36	33	178	1,241	3,407	1,422	856
Chunks excluded	0	1	0	0	1	1	0	1
Chunks remaining	0	153	0	154	152	153	153	152

Notes: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC and *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl.https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. MCS = Millennium Cohort Study, USoc = Understanding Society, NCDS = 958 National Child Development Study, WTCCC2 = The Wellcome Trust Case Control Consortium 2, T1DGC = Type 1 Diabetes Genetics Consortium, WTCCC1 = The Wellcome Trust Case Control Consortium, SNP = Single nucleotide polymorphism

2.4.4 Quality Control (Post-Imputation)

Post-imputation QC was performed separately for each cohort and each individual sub-sample. Firstly, using bcftools (Danecek et al., 2021), we filtered each chromosome file by imputation quality using R2 > 0.8 as a cut-off, before applying another filter for posterior genotype probability imputation confidence with a GP threshold of > 0.8. Then we removed any duplicated or failed SNPs. Next, all VCF chromosome files were merged and converted to PLINK format. Using PLINK 1.9 (Chang et al., 2015), we first updated the variant IDs with the rsIDs using the 1,000 Genomes Project Phase 3 reference panel (Auton et al., 2015). Any SNPs with MAF with less than 5% were discarded. Moreover, missing SNPs, including those set as missing (> 0.01) as well as individuals with less than 99% genotype completeness were removed. Further, the sex for all individuals was added back into each of the individual datasets for each cohort.

Following post-imputation QC, the total number of remaining individuals and SNPs for MCS were: 6,276 individuals and 5,483,692 for the European child sub-set, 1,003 individuals and 5,030,227 SNPs for the non-European sub-set, 9,854 individuals and 5,556,113 SNPs for the European parents and 1,350 individuals and 4,903,732 SNPs for the non-European parent sub-set.

For USoc, a total of 9,039 individuals and 5,218,682 passed post-imputation QC.

For NCDS the following number of individuals and SNPs remained: 2,631 individuals and 6,329,018 SNPs for WTCCC2, 2,485 individuals and 6,067,828 SNPs for T1DGC as well as 1,432 individuals and 4,653,890 SNPs for WTCC1.

Moreover, the individual subsets within MCS and NCDS were combined into a single dataset for each of the cohorts before removing any tri-allelic sites. The final combined MCS and NCDS datasets were comprised of 6,634,361 and 6,398,736 SNPs as well as 18,476 individuals (7,280 children, 6,874 mothers, 4,322 fathers,) and 5,288 individuals, respectively.

This step was not performed for USoc as only a single genotype dataset was used for all genetic QC processing.

Finally, using smart.pca, we re-ran the principal component analysis on the final combined cohort dataset which was first LD-pruned for MCS and NCDS only (see *Figure* 8 for MCS and *Figure* 13 for NCDS). We then selected the top PCs out of the computed first 100 PCs which explained most of the variance. For MCS, used the top 8, namely 166.783, 98.866, 15.149, 13.293, 6.624, 5.758 as well as 4.939, whereas for USoc we selected the top 4 PCs, 3.228, 2.247, 2.184 and 2.181. Further, for NCDS the following 5 top PCs explained the majority of the variance: 2.266, 1.822, 1.756, 1.732 and 1.695.

The post-imputation QC results per cohort are presented in Table 5.

Table 5: *Post-imputation QC Results per Cohort*

	MCS Child European		MCS Child Non-European		MCS Parents European		MCS Parents Non-European	
	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals
Imputation quality & Posterior genotype probability confidence filter: Total across all chromosomes	8,756,148	6,276	10,873,270	1,003	8,860,035	9,854	10,657,688	1,350
Exclude failed SNPs: Total across all chromosomes	8,756,139	6,276	10,873,254	1,003	8,860,011	9,854	10,657,659	1,350
Exclude duplicate SNPs: Total across all chromosomes	8,755,977	6,276	10,873,032	1,003	8,859,863	9,854	10,657,447	1,350
Merging of chromosomes & QC								
Merging chromosomes	8,755,975	6,276	10,873,032	1,003	8,859,847	9,854	10,657,447	1,350
Update varID with rsID	8,572,264	6,276	10,658,889	1,003	8,673,530	9,854	10,448,840	1,350
MAF	5,483,692	6,276	5,030,227	1,003	5,556,113	9,854	4,903,732	1,350
Removing missing SNPs	5,483,692	6,276	5,030,227	1,003	5,556,113	9,854	4,903,732	1,350
Check completeness	5,483,692	6,276	5,030,227	1,003	5,556,113	9,854	4,903,732	1,350
Update sex	5,483,692	6,276	5,030,227	1,003	5,556,113	9,854	4,903,732	1,350

	USoc		NCDS WTCCC2		NCDS T1DGC		NCDS WTCCC1	
	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals	N of Variants	N of individuals
Imputation quality & Posterior genotype probability confidence filter: Total across all chromosomes	7,415,075	9,039	11,305,682	2,631	9,973,010	2,485	6,697,116	1,432
Exclude failed SNPs: Total across all chromosomes	7,415,043	9,039	11,305,666	2,631	9,972,993	2,485	6,697,114	1,432
Exclude duplicate SNPs: Total across all chromosomes	7,414,933	9,039	11,305,406	2,631	9,972,801	2,485	6,697,014	1,432
Merging of chromosomes & QC								
Merging chromosomes	7,414,923	9,039	11,305,406	2,631	9,972,791	2,485	6,697,012	1,432
Update varID with rsID	7,257,111	9,039	11,062,080	2,631	9,757,707	2,485	6,556,279	1,432
MAF	5,218,682	9,039	6,329018	2,631	6,067,828	2,485	4,653,890	1,432
Removing missing SNPs	5,218,682	9,039	6,329,018	2,631	6,067,828	2,485	4,653,890	1,432
Check completeness	5,218,682	9,039	6,329,018	2,631	6,067,828	2,485	4,653,890	1,432
Update sex	5,218,682	9,039	6,329,018	2,631	6,067,828	2,485	----------	----------

Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC and *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. MCS = MCS =

Millennium Cohort Study, USoc = Understanding Society, NCDS = 958 National Child Development Study, WTCCC2 = The Wellcome Trust Case Control Consortium 2, T1DGC = Type 1 Diabetes Genetics Consortium, WTCCC1 = The Wellcome Trust Case Control Consortium, MAF = Minor allele frequency, SNP = Single nucleotide polymorphism, varID = Variant ID, rsID = Reference SNP Cluster ID, N = Number

2.4.5 Polygenic Risk Scoring (PRS)

Using PRSice (Euesden et al., 2015), we calculated individual Polygenic Risk Scores (PRS) at seven p-value thresholds (0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 1) for all three cohorts. This was based on the 2014 and 2018 GWAS summary statistics from the SCZ Working Group of the Psychiatric Genomics Consortium (PGC) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and the MDD PCG (Wray et al., 2018), respectively. The SCZ GWAS summary statistics were derived from 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). On the other hand, the MDD summary statistics made use of 135,458 cases and 344,901 control (Wray et al., 2018). The PRS base files from the SCZ and MDD Working group (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018) identified 108 and 44 risk loci, respectively.

However, due to NCDS having been used as a control sample by the SCZ and MDD PGC, we utilised revised GWAS results for this cohort. The updated SCZ GWAS summary statistics excluded studies from the United Kingdom such as NCDS (but included Irish cohort), whereas for MDD, individuals from the *GEN*etic and clinical *P*redictors *O*f treatment response in *D*epression (GenPod) randomised clinical trial together with 23andme were omitted. Therefore, the re-calculated SCZ and MDD GWAS results, which were created in 2021, were derived from 49,881 cases and 69,697 controls as well as 59,369 cases and 110,318 controls, respectively.

Next, PRSice discarded ambiguous or mismatched SNPs as well as any SNPs with an info score of less than 0.9. The LD threshold for clumping was set to $r^2 < 0.1$.

For MCS, the final PRS target file contained 5,719,587 SNPs after removing any ambiguous variants. The MCS base file contained 4,557,199 SNPs (135,078 after clumping) for SCZ and 4,358,953 SNPs (111,957 after clumping) for MDD.

Additionally, once ambiguous SNPs were removed, the USoc target file was comprised of 4,487,120 variants in total, whereby 3,807,785 variants (79,234 after clumping) were included in the SCZ base file and 3,752,443 variants (75,527 after clumping) for MDD.

For NCDS, the final PRS target file was comprised of 5,510,316 SNPs once ambiguous variants had been removed, with the base file being comprised of 4,057,385 SNPs (89,331 after clumping) for SCZ and 4,361,112 SNPs (101,553 after clumping) for MDD.

2.5 Merging of Phenotype and Genetic Data

Phenotype data and PRS scores for each individual were combined into a single data file for all three cohorts separately using STATA v12.1 (StataCorp, 2011).

2.5.1 Post-QC Processing for MCS

For MCS, 137 individuals which were duplicated in the raw phenotype file were subsequently removed from the combined dataset. A total of 18,476 individuals, comprised of 7,280 children, 6,874 mothers and 4,322 fathers were used for the final analysis.

2.5.2 Post-QC Processing for USoc

For USoc only, after applying a randomised selection process, we obtained a single dataset of genetically unrelated individuals who lived in different households using STATA v12.1 (StataCorp, 2011). This randomised selection was done for several reasons. Firstly, genetically unrelated individuals from the same household are assigned the same household panel data in USoc. In other words, these family members with different genetic data but the same shared environment would not increase variance in the environmental data and thus lead to bias. Secondly, in order to be able to compare rGE findings between the British community

cohorts, we needed to ensure consistency in our selected methodology. Applying a different approach in USoc would make these samples less comparable. In addition, given that the USoc sample is focusing on adults aged 16 years and over only, we omitted any responses from cohort members who were less than 16 years of age and who were born in either 1995 (18 individuals) or 1994 (43 individuals) from wave 1 (2009-2010) using STATA v12.1 (StataCorp, 2011). Further, responses from individuals who were born in 1995 (16 individuals) were removed from wave 2 (2010-2011).

A total of 7,384 individuals remained after the post-QC processing steps as displayed in detail in Table 6.

Table 6: *Random USoc Sample*

	N removed	N remaining
Start	-	9,921
Keep genotyped individuals with Principal components scores only	845	9,076
Wave 1	1,124	7,952
Wave 2	512	7,440
Wave 3	21	7,419
Wave 4	1	7,418
Wave 5	0	7,418
Wave 6	0	7,418
Wave 7	2	7,416
Wave 8	0	7,416
Wave 9	0	7,416
Keep genotyped individuals with PRS scores only	31	7,384

Notes: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. USoc = Understanding Society, N = Number of individuals, PCA were created for all genotyped individuals which passed QC before outliers were removed and merged with the total phenotype dataset.

2.5.3 Post-QC Processing for NCDS

No additional post-QC processing was necessary for NCDS.

2.6 Power Calculation

The power calculations for all three cohorts were computed in G*Power v3.1.9.6 using a fixed linear regression F-test (Faul et al., 2009). Comparable studies, such as Krapohl et al (2017), yielded statistically significant rGE results which explained between 0.2% ($R^2 = 0.002$) and 6.5% ($R^2 = 0.065$) of the variance. Based on these results, we decided to take a conservative approach, aiming to detect significant rGE correlations for SCZ and MDD accounting for a minimum of 0.5% of the variance, thus using an expected effect size (f^2) of 0.005. Minimum sample sizes were calculated using 80% power and an error rate of 5% ($\alpha = 0.05$ divided by the number of environments tested). Thus, Chapter 3 used an $\alpha = .00132$ for MCS and $\alpha = .00104$ for NCDS, whilst Chapter 4 utilised an $\alpha = .002778$ for USoc, $\alpha = .0042$ for NCDS with Chapter 5 making use of an $\alpha = .0021$ for MCS, $\alpha = .0042$ for USoc and $\alpha = .00111$ for NCDS.

Overall, the final minimum sample size requirements for Chapter 3 were 3,291 individuals for MCS and 3,403 individuals for NCDS. For Chapter 4 we required at least 2,943 individuals from USoc and 2,749 individuals from NCDS. Finally, for Chapter 5 the minimum sample size was estimated to be 3,074 individuals for MCS, 2,760 individuals for USoc and 3,376 individuals for NCDS.

2.7 Data Analysis

This section describes the data analyses in detail that were performed in STATA v12.1 (StataCorp, 2011) for all three empirical studies.

2.7.1 Descriptive Statistics and Pairwise Correlation Coefficients

All descriptive statistics and all pairwise correlation coefficients for all three community studies were computed in STATA v12.1 (StataCorp, 2011).

Descriptive statistics were calculated for the whole cohort as well as the genotyped sub-sample for each environment at each timepoint for all three cohorts separately. Descriptive statistics included the mean and standard deviation (SD) for continuous or polytomous variables and number of participants (n) and percentage of participants (%) for binary variables.

For MCS, the whole cohort sample refers to all cohort members with genotype data (aged 14 years of age) for which we had phenotype data for. Additionally, as some MCS phenotype data was only available as household panel data, we matched the mother's responses (or father's responses if mother's responses were unavailable) by assigning the same value to all members in the same family for the following environments: tenure of accommodation, number of bedrooms, SES, financial difficulties, and marital status. For NCDS the whole cohort denotes to all participants who completed the biomedical survey at the age of 44 and for whom we had phenotype data for.

To identify differences between the whole cohort samples and the genotyped sub-samples for all three cohorts, we used independent t-tests for continuous or polytomous variables and chi-square tests for binary environmental measures.

Moreover, correlation matrices using pairwise correlation coefficients were calculated for all three community studies in order to assess multicollinearity across all markers of SES, i.e. for all three cohorts this included tenure of accommodation, SES, number of bedrooms, employment, finance issues and employment. For USoc we further included income in the correlation matrices. Any polytomous or continuous variables were z-scored.

All descriptive statistics are provided in Appendix 8 for MCS, Appendix 9 for USoc and Appendix 10 for NCDS. All correlation matrices are described in Appendix 11 for MCS, Appendix 12 for USoc and Appendix 13 for NCDS.

2.7.2 Chapter 3 – Paper 1 (rGE for SCZ and MDD in Childhood)

Chapter 3 utilised the childhood MCS and the childhood NCDS data sweeps.

Regression Models

Firstly, environments which were only recorded at a single time point were used in logistic or linear regression models, whilst environmental variables which were available at different timepoints were combined into longitudinal models in the form of logistic or linear mixed effects models or random effects models.

For MCS, all regressions used the child PRSs from 7,280 children.

Covariates were included in all regression models for both cohorts, i.e., sex (both cohorts), year of data collection (MCS) or current age (NCDS) as well as the top 8 and 5 PCs for MCS and NCDS, respectively.

We applied Bonferroni correction in order to correct for multiple testing with a corrected $p = 5.81 \times 10^{-4} = 0.05/86$ (α divided by the number of environments). Any associations between the environmental variable and the child PRS were considered statistically significant if one PRS thresholds at a minimum fell below the corrected p-value.

Sensitivity Analysis

Sensitivity analyses were executed for all significant rGE findings for both cohorts. For MCS, in order to differentiate between passive or evocative rGE, we made use of the maternal and/or paternal PRSs which were added as covariates into the regression or longitudinal

models. Given that we did not have the parental genotypes for NCDS, we tested whether any significant results could be confounded by clinical cases. Hence, we re-run all regression models or longitudinal models by removing individuals who either self-reported a diagnosis of SCZ (n = 877) or one of the main SCZ symptoms, namely psychosis (n = 2) or hallucinations (n = 16) during the adulthood data sweep 9 at the age of 55. For MDD, we omitted individuals who self-reported depression (n = 1,397). These individuals responded with 'yes' to the question from data sweep 9 (age 55) whether they had experienced depression since the previous interview (University of London et al., 2020).

Regression Coefficient Comparison

Further, to evaluate whether the regression coefficients between the original regression analysis and the sensitivity analysis were statistically different, we performed interaction analysis between 1) the independent variables and the maternal/paternal PRS in MCS as well as 2) the independent variables and the SCZ or depression diagnosis/symptoms in NCDS. Next, we evaluated the Wald Chi-squared test statistics which resulted from the PRS interaction terms to evaluate any statistically significant differences between the regression coefficients.

In addition, we replicated the interaction analysis for any corresponding findings between the two psychopathologies by interacting the child PRS for SCZ or MDD with every independent variable in MCS. This analysis was not performed in NCDS as we did not obtain any matching rGE findings between the two investigated psychopathologies.

2.7.3 Chapter 4 – Paper 2 (rGE for SCZ and MDD in Adulthood)

Chapter 4 made use of the USoc as well as NCDS adulthood environment.

Regression Models

Similar to Chapter 3, we computed linear or logistic regression models for environmental measures which were available at a single data sweep only, whilst linear and logistic longitudinal mixed effects or random effects regression models were utilised for environmental variables with repeated measurements.

The following covariates were included for both cohorts in all regression models: the top 4 and 5 PCs for USoc and NCDS, respectively, age (USoc) or year of data collection (NCDS) as well as the participant sex.

For Chapter 4, we also took a conservative approach and applied the Bonferroni correction for multiple testing for both psychopathologies across both cohorts. In order to reject the null hypothesis, at least one PRS threshold had to meet the corrected p of $\leq 1.67 \times 10^{-3}$ (p = .05 divided by the number of dependent variables [n = 30]).

Sensitivity Analysis

Moreover, we conducted sensitivity analyses for both cohorts to evaluate if significant results could have been implicated by the presence of clinical cases.

Firstly, in USoc, no information on diagnosis or symptoms for SCZ were recorded, and thus, sensitivity analyses were only performed for MDD. For MDD, this was done by re-running all regressions models for any statistically significant findings which survived multiple testing correction by omitting individuals who were clinically diagnosed with depression (n = 448) as well as those with psychiatric issues who received treatment (n = 111).

Secondly, as we did not obtain significant SCZ findings in NCDS after multiple testing, we only conducted our sensitivity analysis for MDD by re-running all regression models after excluding individuals with self-reported depression (n = 1,397) at age 55 (data sweep 9).

Regression Coefficient Comparison

Lastly, we performed multiple interaction analyses, between the independent variables and the MDD symptoms, with the aim to assess whether there are significant differences between the original MDD regression findings and the MDD sensitivity analyses in both cohorts. We then used the test statistics which were a result of applying a Wald Chi-squared test to calculate whether the interaction coefficients are statistically significant.

Given that we did not have any SCZ diagnosis for USoc to perform sensitivity analyses as well as the fact that we did not obtain any significant findings for SCZ in NCDS, we only conducted interaction analyses for MDD for each of the two cohorts. Also, this interaction analysis was not performed to assess matching results between the two disorders as we did not obtain any matching rGE findings in either USoc or NCDS.

2.7.4 Chapter 5 – Paper 3 (rGE changes for SCZ and MDD over Time)

Chapter 5 utilised childhood and adulthood data sweeps from all three cohorts (MCS, USoc as well as NCDS).

Interaction Analysis

We ran separate interaction analyses for each of the three cohorts for all significant childhood or adulthood environments identified in Chapter 3 and Chapter 4 in order to assess whether rGEs differed over time for all seven PRS thresholds. At the start, we combined environmental variables with repeated measures at multiple timepoints into logistic or linear longitudinal models, either mixed effects or random effects models. Then, we fitted these longitudinal models with full factorial two-way interactions between the time variable and the PRS, which were both defined as continuous variables.

The MCS interaction analysis used the child's PRS only.

All interaction analysis used sex as well as the top 8, 4, or 5 PCs for MCS, USoc and NCDS as covariates, respectively. Additionally, as individuals from USoc are of mixed ages, we added the birth year as an additional covariate.

The regression beta coefficient (β) was used to identify a change in the strength of rGE findings, whereby a positive β suggests an increase and a negative β indicates a decrease in rGE strength across either the childhood or adulthood rGE-across-time analysis.

Childhood vs Adulthood Comparison

Next, given that we had environmental measures from birth up to age 55 from NCDS only, we tested whether significant rGE findings differed between childhood and adulthood in one cohort only. First, the childhood and adulthood environmental variables were coded as binary values (0 = childhood, 1 = adulthood). We then fitted the PRS and the binary environmental measures as two-way interactions into the longitudinal regression models, which were either mixed effects models or random effect models. All interaction comparison were calculated for all seven PRS thresholds.

All interaction comparison models included the top 5 PCs as well as sex as covariates.

The β was again used to interpret a change in rGE strength between any environments which were available in childhood and adulthood in NCDS.

Correction for Multiple Testing

In sum, all childhood rGE by time interactions, adulthood rGE by time calculations as well as all child vs adult rGE comparison from all three cohorts were corrected for multiple testing with the Benjamini-Hochberg correction. Overall, we obtained 560 outputs based on 80 calculations with seven PRS thresholds each across the three cohorts. The adjusted α was obtained by first ranking each p-value, which was then divided by the number of tests for each

PRS threshold before the output was multiplied by .05 (adjusted α = (rank divided by 560) times .05).

At least one PRS threshold had to meet the Benjamini-Hochberg correction in order to be considered statistically significant.

Sensitivity Analysis

Moreover, we also conducted sensitivity analysis for any significant findings after the Benjamini-Hochberg correction.

For MCS, we included the maternal and paternal PRS into the childhood interaction analysis as covariates with the aim to better understand whether passive rGE may have, at least partially, contributed to this childhood rGE change over time.

Although we did not have parental genotypes available for the other two cohort, we wanted to assess if clinical cases could have confounded our results. Thus, for USoc, we omitted individuals who received treatment for psychiatric problems (n = 111) or had been diagnosed with clinical depression (n = 448). As already discussed in the Chapter 4 data analysis section, unfortunately, we did not have any information on SCZ diagnosis or symptoms in USoc and therefore could not perform any sensitivity analysis for any significant SCZ findings.

Equally, for NCDS, we also omitted any individuals who self-reported a SCZ diagnosis (n = 877), hallucinations (n = 16) or psychosis (n = 2) as well as depression (n = 1,397) aged 55 in order to re-run all significant SCZ or MDD rGE by time interaction models again, respectively.

Regression Coefficient Comparison

Finally, to investigate whether the beta coefficients differ between the original interaction analyses and our sensitivity analyses, we added interactions between a) every independent variable and the maternal/paternal PRS in MCS and b) independent variable and SCZ/MDD diagnosis or symptoms for either USoc or NCDS. We then conducted Wald Chi-squared tests to assess whether the regression coefficients for the added interactions differed.

Chapter 3: Paper 1 - rGE for SCZ and MDD in Childhood

3.1 Overview

The research presented in this chapter has been published:

Machlitt-Northen S, Keers R, Munroe PB, Howard DM, Trubetskoy V, Pluess M. Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene-environment correlation. J Child Psychol Psychiatry. 2022 Jul 4. doi: 10.1111/jcpp.13657.

This chapter presents the above publication.

3.2 Abstract

Although established environmental and genetic influence contribute to the aetiology of SCZ and MDD, it is unclear if the exposure to some of these environmental risks is genetically confounded through rGE.

The aim of Chapter 3 was, firstly, to investigate if the genetic risk for SCZ in MDD is associated with known psychosocial or environmental risk factors in childhood by utilising two British community cohorts: MCS and NCDS. Secondly, we wanted to explore if these correlations differ between SCZ and MDD, and thirdly, between MCS and NCDS which are 42 years apart.

We applied PRS from large, existing GWAS to test the correlation between the child's genetic susceptibility for either psychopathology and established environmental risk factors. Moreover, given that we had the parental genotype from MCS, we were able to test if any rGE findings were due to passive or evocative rGE.

Overall, the child PRS for SCZ and MDD was associated with known environmental and psychosocial risk factors in both cohorts. We observed more rGE findings for MDD compared to SCZ, largely for indicators of low SES and parental behaviours.

When controlling for the parental genotype in MCS we identified that more than half of the significant associations reflected passive rGE.

Our results highlight that known psychosocial and environmental risk factors for either psychopathology are at least partially correlated with the genetic susceptibility to SCZ or MDD in children.

3.3 Introduction

Substantial evidence from family, twin and adoption studies imply that environments are heritable by inferring genetic contributions from familial associations (Jaffee & Price, 2007). Whilst molecular genetic studies are able to quantify the genotype directly, and thus provide further evidence for the presence of rGE in the development of complex psychopathologies (Jaffee & Price, 2007), research is starting to investigate the impact of gene-environment interplay across critical developmental periods, including childhood.

Firstly, one vital research goal is to be able to differentiate between developmental outcomes or environments which are causally associated with psychopathologies or whether early manifestations of genetic susceptibility can reflect pleiotropy in childhood (Riglin et al., 2017; Thapar & Riglin, 2020). Pleiotropy represents the concept that a genetic variant can influence multiple seemingly unrelated phenotypes (Avinun, 2020; He & Zhang, 2006). Given that genetic correlations between diseases and traits are widespread, three processes have been suggested: a) *biological pleiotropy* whereby a genetic variant can directly influence more than one phenotype, b) *spurious pleiotropy* which defines when the association between a genetic variant and multiple phenotypes is the result of bias, such as recruitment bias or phenotypic misclassification and c) *mediated pleiotropy* whereby the influence of a genetic variant on a specific phenotype is mediated by the influence of another phenotype, including

environmentally mediated pleiotropy which arises from the fact that environments and behaviours are heritable through rGE (Avinun, 2020).

One study which was conducted by Schellhas et al (2021) investigated the impact of the PRS for caffeine consumption and maternal smoking on the child mental health outcomes in 7,964 children and 7,921 mothers from the Avon Longitudinal Study of Parents and Children (Schellhas et al., 2021). The authors highlighted associations between the child and maternal PRS for smoking initiation and sensation-seeking behaviour traits across childhood, suggesting that these associations could be explained by pleiotropic effects (Schellhas et al., 2021).

Secondly, differential PRS correlations for the same psychopathological outcome, depending on age-at-onset, highlight potential aetiological differences across the different developmental stages (Thapar & Riglin, 2020). In other words, the expression of environmental or genetic effects may change across development, resulting in either the same genes being expressed differently depending on the age or different genes affecting the same psychopathological outcome at different ages (Eaves et al., 2003). Despite the fact that GWAS summary statistics from adult samples have been utilised in order to identify the impact of genetic variants on the aetiology of psychiatric disorders, it is still not fully understood what the effects of these genetic variants are on child outcomes (Jansen et al., 2018).

Thirdly, studying gene-environment interplay is further complicated by the divide between childhood/adolescent research and adulthood research (Thapar & Riglin, 2020). The authors suggest that taking a developmental approach is vital but challenging, given that longitudinal datasets with appropriate measurement approaches, such as parent or teacher informants, are required (Thapar & Riglin, 2020).

Fourthly, whilst several studies have now started to investigate rGE in childhood or adolescence (Ensink et al., 2020; Fearon et al., 2015; Jansen et al., 2018; Krapohl et al., 2017; Riglin et al., 2017; Trotta et al., 2016), many are unable to distinguish between *passive* or

evocative rGE, which would require offspring as well as parental genotypes (Krapohl et al., 2017). However, understanding whether the child's genetic liabilities are related to their home rearing environment through *passive* rGE or whether the offspring's genetic susceptibility evokes the type of parenting or responses that they receive through *evocative* rGE is crucial (Elam et al., 2017; Plomin et al., 1977). Having a clear understanding of the biological pathways of genes and how they are implicated in our behaviours which are consequently correlated with environments, is vital for the prevention and treatment of these complex psychopathologies (Jaffee & Price, 2007, 2012).

Chapter 3 has addressed all of these research gaps by drawing on established environmental risk factors in childhood and genetic measures from biological parents and their offspring in order to assess and differentiate between *passive* and e*vocative* rGE in children with the genetic liability to either SCZ or MDD.

3.3.1 Objectives

Chapter 3 had four main aims. Given that GWAS results were obtained from adult samples, we wanted to initially test whether rGEs are present in children using two community studies from the general population, MCS and NCDS, specifically.

Additionally, we aimed to identify the type of rGE (*passive* or *evocative*) by including the parental genotype from MCS.

Moreover, we wanted to investigate whether any of our significant rGE correlations were similar between the two psychopathologies, bearing in mind that there is only a partial overlap between the genetic risk variants for SCZ and MDD.

Lastly, we aimed to assess whether rGE findings were similar between the two different populations whereby children were born after the year 2000 from MCS and in 1958 from NCDS.

3.3.2 Hypotheses

We expected that known environmental risk factors for SCZ and MDD would be correlated with the genetic susceptibility for either psychiatric disorder in children, despite the fact that GWAS results for PRSs are based on adult samples.

We also hypothesised that a proportion of the observed rGE associations would reflect *passive* rGE.

In addition, we predicted that rGE findings would differ between the two psychopathologies and between the two British community cohorts: MCS and NCDS.

3.4 Methods

3.4.1 Environmental Factors

We included the following perinatal factors in Chapter 3: gestational period, parity, birth weight as well as mother's and father's age at birth.

Additionally, parental substance abuse associated factors including mother's and father's alcohol consumption, maternal and paternal smoking behaviour as well as maternal smoking prior and during pregnancy were added.

Besides, socio-economic indicators such as SES, financial difficulties, unemployment, tenure of the house (owned or rented), housing issues, number of bedrooms in the family home and whether or not the child received free school meals were also included.

Finally, the following psychosocial environments were added: parental marital status, domestic tension, maternal and paternal interest in the child's education, whether the mother or father reads to the child or is taking their offspring to the park or for walks and paternal involvement in childcare.

The environment factors used for each cohort are displayed in Table 7. The detailed breakdown of how each environmental factor was coded is displayed in Appendix 1 (MCS) and 2 (NCDS).

Table 7: *Environments by Cohort*

Environmental risk factor	Available in MCS	Available in NCDS
Perinatal environments		
Gestational period	X	X
Parity		X
Birth weight	X	X
Mother's age at birth		X
Father's age at birth		X
Parental substance abuse		
Maternal smoking prior to pregnancy		X
Maternal smoking during pregnancy		X
Maternal smoking	X	
Paternal smoking	X	
Family alcohol issues		X
Maternal alcohol consumption	X	
Paternal alcohol consumption	X	
Socio-economic risk factors		
SES	X	X
Finance issues	X	X
Number of bedrooms in the family home	X	X
Tenure of accommodation	X	X
Housing issues	X	
Maternal employment	X	
Paternal employment		X
Child receives free school meals		X
Psychosocial environments		
Maternal interest in the child's education	X	X
Paternal interest in the child's education	X	X
Paternal involvement in childcare	X	X
Mother takes child for walks/park	X	X
Father takes child for walks/park	X	X
Marital status	X	X
Mother reads to child	X	X
Father reads to child	X	X
Domestic tension		X

Note: MCS = Millennium Cohort Study, NCDS = 1958 National Child Development Study, SES = Socio-economic status

3.4.2 Genetic Processing

Genome-wide data was utilised from 8,201 children and 13,123 biological parents from MCS (Fitzsimons et al., 2020) as well as 1,502 participants from the WTCCC1 (Wellcome Trust Case Control Consortium, 2007), 2,922 cohort members from WTCCC2 and 2,592 individuals from T1DGC (Barrett et al., 2009) for NCDS.

The genetic processing, including genetic QC, imputation as well as post-imputation QC for both cohorts are described in detail in the Methods chapter in section 2.4 titled 'Genetic data'.

A total of 7,280 children as well as 6,874 and 4,322 biological mothers and fathers, respectively, survived genetic processing for MCS, whilst 5,288 cohort members remained for NCDS.

3.4.3 PRS Creation

For MCS and NCDS, we calculated the PRS for each individual at seven p-value thresholds using PRSice (Euesden et al., 2015) based on the GWAS summary statistics from the SCZ and MDD PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018) as outlined in section 2.4.5 in the Methods chapter.

3.4.4 Data Analysis

Power analysis for both cohorts were run in G*Power v3.1.9.6 (Faul et al., 2009), whilst all other data analyses were carried out in Stata v12.1 (StataCorp, 2011).

Descriptive statistics and correlation matrices for indicators of SES were calculated for both cohorts.

Additionally, logistic or linear regressions were run for environment factors at a single time point, with longitudinal variables combined into linear and logistic mixed effects or random effects models using age/year, the top principal components and sex as covariates.

All calculations were corrected for multiple testing using the Bonferroni correction with $p = 5.81 \times 10^{-4}$, whereby at least one PRS threshold needed to have meet the corrected p in order for this finding to be considered significant.

Sensitivity analyses were executed for all significant association, with the maternal and/or paternal PRS having been added as a covariate for MCS, whilst individuals with a self-reported diagnoses of either SCZ/psychosis/hallucinations or depressions were removed prior to re-running the regression models.

Regression coefficients between the regression findings and sensitivity analysis were compared in an interaction model.

Detailed descriptions of all calculations can be found in section 2.7 in the Methods chapter.

3.5 Results

3.5.1 Descriptive Statistics and Power Calculation

Based on our analyses, both cohorts were sufficiently powered apart from one environmental measure: paternal interest in the child's education at data sweep 4 for MCS as well as at data sweep 7, 11, and 16 for NCDS.

When comparing descriptive statistics between the total cohort and the genotyped sample several differences emerged. Firstly, the MCS genotyped sampled had less parents who were married at all data waves, an increased number of cohort members who identified as SES class 1 category at data sweeps 1 as well as 3 to 4, parents who lived in rented accommodation in data sweep 6 and an increased proportion of mother's smoked at data sweep 1. Secondly,

for NCDS, the genotyped sample had an increased proportion of parents with rented accommodation at age 7.

3.5.2 rGE Results for MCS

Firstly, for MCS we detected one signification correlation between the child's genetic susceptibility for SCZ and parental marital status, whereby offspring whose parents were divorced, separated, or widowed had an increased PRS. Whilst the correlations between the genetic liability for SCZ in the children and increased birth weight as well as mother's who smoked were both significant, neither survived after multiple testing correction.

Secondly, we identified multiple correlations between the child's genetic susceptibility to MDD and markers of material disadvantage, namely rented accommodation, finance issues, lower SES, unemployment and decreased number of bedrooms in the family room. However, only the associations between the genetic risk for MDD and rented accommodation as well as low SES survived after Bonferroni correction.

Further, we identified several significant associations between the offspring's genetic liability to MDD and psychosocial risk factors, such as lack of father's involvement in childcare, mothers and fathers who did not read to their children and parents being divorced, separated or widowed, of which only the latter survived correction for multiple testing.

Finally, environmental risk factors relating to substance consumptions, including mothers who smoked, but decreased maternal and paternal alcohol consumption were association with the child's PRS for MDD. The decreased paternal alcohol consumption and the genetic liability to MDD did not remain significant after applying Bonferroni correction. Both remaining rGE correlations depict maternal consumption behaviours at multiple timepoints during childhood.

All MCS results are displayed in Table 8 for three PRS thresholds (0.01, 0.5 and 1).

Our sensitivity analyses which were conducted for all significant findings after multiple testing showed that the correlations between the genetic liability to SCZ and MDD and the parents' marital status of being divorce, single or widowed were confounded by the parental genotype. In addition, the associations between the genetic risk for MDD and rented accommodation were further confounded by the parental PRS, suggesting passive rGE.

The comparison of regression coefficients between any similar findings across both psychopathologies, which was only applicable to marital status, suggested that there was no significant difference. In other words, the strength of rGE for marital status was similar for both psychiatric disorders.

The sensitivity and interaction analyses results for MCS are displayed in Table 9 for three PRS thresholds (0.01, 0.5 and 1).

The full MCS results are provided in Appendix 14.

Table 8: *Regression Results of rGE in the MCS Sample*

Environment	SCZ				MDD		
	PRS Threshold z-scored	Beta	95%CI	P-Value	Beta	95%CI	P-Value
SES *(5 Professional/ managerial 4 Intermediate 3 Small employer/self-employed 2 Lower supervisory/technical 1 Semi-routine/routine)*	0.01	-0.01	-0.06-0.03	5.32E-01	-0.07	-0.10--0.03	**1.04E-04****
	0.5	-0.02	-0.09-0.05	5.44E-01	-0.1	-0.19--0.01	2.54E-02*
	1	-0.02	-0.09-0.05	5.79E-01	-0.09	-0.17--0.00	4.34E-02*
Finance Issues *(0=no, 1=yes)*	0.01	0.01	-0.14-0.16	8.59E-01	0.19	0.08-0.30	8.35E-04*
	0.5	0.11	-0.12-0.34	3.43E-01	0.29	0.01-0.56	3.88E-02*
	1	0.09	-0.14-0.32	4.36E-01	0.21	-0.05-0.46	1.10E-01
Number of Rooms *(continuous)*	0.01	0	-0.04-0.04	9.51E-01	-0.05	-0.08--0.02	2.85E-03*
	0.5	0	-0.06-0.07	9.29E-01	-0.07	-0.15-0.01	7.61E-02
	1	0	-0.06-0.07	8.80E-01	-0.05	-0.13-0.03	1.88E-01
Tenure *(0=owns,1=rents)*	0.01	0.22	-0.04-0.47	9.91E-02	0.43	0.24-0.63	**1.14E-05****
	0.5	0.28	-0.11-0.68	1.55E-01	0.62	0.14-1.10	1.20E-02*
	1	0.27	-0.13-0.66	1.87E-01	0.51	0.06-0.96	2.76E-02*
Mother's interest in child's education *(0=interested, 1=uninterested)*	0.01	0.16	-0.10-0.41	2.41E-01	0.1	-0.10-0.30	3.16E-01
	0.5	0.08	-0.31-0.48	6.81E-01	0.09	-0.43-0.61	7.33E-01
	1	0.07	-0.33-0.47	7.28E-01	0.09	-0.40-0.58	7.10E-01
Father's involvement in upbringing *(0=yes, 1=no)*	0.01	0.26	0.01-0.50	4.05E-02	0.26	0.07-0.46	8.15E-03*
	0.5	0.3	-0.08-0.67	1.22E-01	0.36	-0.20-0.92	2.03E-01
	1	0.29	-0.09-0.67	1.29E-01	0.32	-0.23-0.86	2.53E-01
Father's interest in child's education *(0=interested, 1=uninterested)*	0.01	0.12	-0.15-0.38	3.99E-01	0.12	-0.08-0.32	2.54E-01
	0.5	0.08	-0.33-0.48	7.09E-01	0.39	-0.17-0.94	1.73E-01
	1	0.09	-0.32-0.50	6.67E-01	0.41	-0.12-0.95	1.31E-01
Mother walks *(0=weekly, 1=monthly or less)*	0.01	-0.03	-0.20-0.14	7.51E-01	-0.1	-0.22-0.03	1.32E-01
	0.5	-0.17	-0.43-0.09	2.00E-01	-0.1	-0.42-0.23	5.61E-01
	1	-0.18	-0.44-0.09	1.90E-01	-0.15	-0.46-0.15	3.23E-01
Father walks *(0=weekly, 1=monthly or less)*	0.01	-0.06	-0.25-0.13	5.42E-01	-0.1	-0.25-0.05	1.82E-01
	0.5	-0.13	-0.43-0.16	3.85E-01	-0.21	-0.63-0.22	3.41E-01
	1	-0.15	-0.45-0.15	3.39E-01	-0.17	-0.57-0.23	4.10E-01
Smoking Mother *(0=no, 1=yes)*	0.01	0.08	0.02-0.15	1.67E-02*	0.2	0.15-0.26	**0.00E+00****
	0.5	0.11	0.01-0.22	3.86E-02*	0.45	0.30-0.60	**7.10E-09****
	1	0.11	0.00-0.22	4.77E-02*	0.39	0.24-0.54	**1.61E-07****
Smoking Father *(0=no, 1=yes)*	0.01	0.19	-0.16-0.54	2.92E-01	0.17	-0.09-0.43	1.94E-01
	0.5	0.12	-0.41-0.66	6.57E-01	0.37	-0.38-1.12	3.37E-01
	1	0.12	-0.42-0.66	6.64E-01	0.27	-0.44-0.98	4.64E-01
Gestational period *(continuous)*	0.01	0.02	-0.03-0.06	4.82E-01	0.01	-0.02-0.04	5.60E-01
	0.5	0.03	-0.04-0.09	3.97E-01	-0.07	-0.15-0.02	1.16E-01
	1	0.03	-0.04-0.10	4.13E-01	-0.04	-0.12-0.03	2.65E-01
birth weight *(continuous)*	0.01	0.02	-0.03-0.08	3.90E-01	0.01	-0.03-0.05	7.80E-01
	0.5	0.08	0.00-0.16	4.22E-02*	-0.07	-0.18-0.04	2.05E-01
	1	0.08	0.00-0.16	4.91E-02*	-0.05	-0.16-0.05	2.95E-01
Marital status *(0=married/civil partner, 1=divorced/separated)*	0.01	0.1	0.06-0.15	**1.07E-05****	0.09	0.06-0.13	**2.17E-07****
	0.5	0.18	0.11-0.25	**8.36E-07****	0.2	0.10-0.29	**3.61E-05****
	1	0.17	0.10-0.24	**2.25E-06****	0.18	0.09-0.27	**4.96E-05****

Alcohol Mother *(0=less than 1-2 weekly, 1=more than 1-2 weekly)*	0.01	-0.04	-0.09-0.01	8.00E-02	-0.09	-0.13--0.05	**3.08E-06****
	0.5	0.02	-0.05-0.09	6.06E-01	-0.26	-0.36--0.15	**2.91E-06****
	1	0.02	-0.06-0.09	6.81E-01	-0.25	-0.35--0.14	**3.67E-06****
Alcohol Father *(0=less than 1-2 weekly, 1=more than 1-2 weekly)*	0.01	-0.12	-0.38-0.13	3.32E-01	-0.17	-0.36-0.02	8.50E-02
	0.5	-0.17	-0.56-0.22	3.92E-01	-0.65	-1.22--0.09	2.32E-02*
	1	-0.19	-0.58-0.20	3.42E-01	-0.54	-1.07--0.00	4.83E-02*
Employment Mother *(0=employed, 1=unemployed)*	0.01	0	-0.10-0.10	9.67E-01	0.11	0.03-0.19	6.38E-03*
	0.5	0.05	-0.11-0.21	5.42E-01	0.19	-0.01-0.40	6.37E-02
	1	0.04	-0.12-0.20	5.97E-01	0.19	-0.01-0.38	6.17E-02
Father Reads *(0=daily/weekly, 1=never/monthly)*	0.01	0.09	-0.15-0.32	4.61E-01	0.08	-0.10-0.25	3.77E-01
	0.5	-0.11	-0.47-0.24	5.36E-01	0.59	0.08-1.09	2.27E-02*
	1	-0.11	-0.47-0.26	5.62E-01	0.61	0.13-1.08	1.18E-02*
Mother Reads *(0=daily/weekly, 1=never/monthly)*	0.01	-0.03	-0.24-0.18	7.64E-01	0.15	0.00-0.31	4.94E-02*
	0.5	0.07	-0.24-0.39	6.49E-01	0.6	0.20-1.01	3.42E-03*
	1	0.06	-0.26-0.38	7.21E-01	0.63	0.24-1.01	1.31E-03*

Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), rGE = gene-environment correlation, MCS = Millennium Cohort Study, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

Table 9: *Sensitivity and Interaction Analysis in the MCS Sample*

Environment	Threshold z-scored	Sensitivity				Interaction terms		Compare SCZ/MDD	
		Beta	95%CI	P-Value	Corrected with	Wald chi-squared	P-Value	Wald chi-squared	P-Value
SCZ									
Marital status	0.01	-0.3	-0.43--0.17	8.45E-06	Mother & father PRS	0.89	3.58E-01	0.06	0.801
	0.5	-0.21	-0.42-0	5.27E-02		3.89	4.87E-02	1.57	0.21
	1	-0.2	-0.41-0.01	6.38E-02		1.8	1.80E-01	2.15	0.143
MDD									
SES	0.01	0.02	-0.05-0.08	5.82E-01	Mother & father PRS	2.29	1.30E-01		
	0.5	-0.1	-0.27-0.07	2.41E-01		0.05	8.25E-01		
	1	-0.08	-0.23-0.08	3.37E-01		0.03	8.67E-01		
Tenure	0.01	-0.04	-0.23-0.15	6.94E-01	Mother & father PRS	24.97	<0.0001		
	0.5	0.33	-0.12-0.78	1.52E-01		1.48	2.24E-01		
	1	0.23	-0.18-0.65	2.71E-01		2.99	8.40E-02		
Smoking Mother	0.01	0.15	0.09-0.22	7.86E-07	Mother PRS only	51.72	1.00E-05		
	0.5	0.39	0.22-0.55	3.78E-06		83.65	1.00E-05		
	1	0.31	0.16-0.47	9.25E-05		87.49	1.00E-05		
Marital status	0.01	0.01	-0.09-0.12	8.18E-01	Mother & Father PRS	0.85	3.58E-01	0.06	0.801
	0.5	0	-0.31-0.31	1.00E+00		3.89	4.87E-02	1.57	0.21
	1	0.01	-0.29-0.31	9.55E-01		1.8	1.80E-01	2.15	0.143
Alcohol Mother	0.01	-0.06	-0.11--0.02	3.11E-03	Mother PRS only	0.07	7.85E-01		
	0.5	-0.22	-0.34--0.10	2.30E-04		1.85	1.73E-01		
	1	-0.22	-0.33--0.10	1.98E-04		0.82	3.67E-01		

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), MCS = Millennium Cohort Study, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

3.5.3 rGE for NCDS

In NCDS, we detected two correlations between psychosocial risk factors, including lack of father's involvement in childcare as well as father's who do not read to their offspring and the genetic liability to SCZ in children. However, once we corrected for multiple testing, only the association between the genetic risk for SCZ and lack of father's involvement in childcare remained.

In addition, whilst domestic tension as well as housing issues and the correlation with the PRS for SCZ emerged, neither survived Bonferroni correction.

Similar to MCS, we further identified associations between socioeconomic environments, specifically finance issues, decreased number of bedrooms in the family home,

rented accommodation, lower SES itself, as well as unemployment and the genetic risk for MDD, of which only the associations with rented accommodation, lower SES, and decreased number of bedrooms in the family home remained after applying Bonferroni correction.

Besides, psychosocial risk factors such as younger mothers, maternal and paternal lack of interest in their offspring's education, in addition to mothers and fathers not taking their child for walks were further correlated with the genetic liability to MDD. However, only the association between the PRS for MDD and mother's and father's lack of interest in the child's education survived correction for multiple testing.

All NCDS results are displayed in Table 10 for three PRS thresholds (0.01, 0.5 and 1).

All significant rGE correlations after multiple testing were re-run in our sensitivity analyses by removing individuals with self-reported diagnosis of either SCZ/psychosis/hallucinations for SCZ or depression for MDD. The comparison of regression coefficients between the original regressions and our sensitivity analysis highlighted that our results were not confounded by the presence of clinical cases.

Additionally, none of the rGE findings for NCDS were similar between SCZ and MDD.

The sensitivity and interaction analyses results for NCDS are displayed in Table 11 for three PRS thresholds (0.01, 0.5 and 1).

The full NCDS results are provided in Appendix 15.

Table 10: *Regression Results of rGE in the NCDS Sample*

Environment	SCZ				MDD		
	PRS Threshold z-scored	Beta	95%CI	P-Value	Beta	95%CI	P-Value
SES *(5 Professional 4 Managerial/ Technical 3 Skilled 2 Partly-skilled 1 Unskilled)*	0.01	0.01	-0.02-0.03	6.33E-01	-0.06	-0.08--0.03	**3.56E-06****
	0.5	0	-0.02-0.03	8.34E-01	-0.05	-0.07--0.03	**2.53E-05****
	1	0	-0.02-0.03	8.24E-01	-0.05	-0.07--0.03	**4.66E-05****
Finance Issues *(0=no, 1=yes)*	0.01	0.04	-0.07-0.16	4.57E-01	0.17	0.06-0.28	1.83E-03*
	0.5	0.05	-0.06-0.16	3.97E-01	0.15	0.05-0.26	4.69E-03*
	1	0.04	-0.07-0.15	4.78E-01	0.15	0.05-0.26	4.40E-03*
Number of Rooms *(continuous)*	0.01	0	-0.02-0.03	8.47E-01	-0.05	-0.07--0.02	**2.08E-04****
	0.5	0	-0.03-0.02	7.79E-01	-0.04	-0.07--0.02	**4.44E-04****
	1	0	-0.03-0.02	7.41E-01	-0.04	-0.07--0.02	7.68E-04*
Tenure *(0=owns, 1=rents)*	0.01	-0.07	-0.29-0.16	5.56E-01	0.47	0.26-0.68	**9.88E-06****
	0.5	0	-0.21-0.21	9.88E-01	0.31	0.11-0.52	2.76E-03*
	1	-0.01	-0.22-0.20	9.42E-01	0.29	0.08-0.49	6.02E-03*
Mother's interest in child's education *(0=interested, 1=uninterested)*	0.01	0.05	-0.05-0.15	3.13E-01	0.17	0.08-0.26	**1.81E-04****
	0.5	0.05	-0.05-0.14	3.32E-01	0.13	0.04-0.22	4.61E-03*
	1	0.05	-0.05-0.14	3.40E-01	0.12	0.03-0.21	7.13E-03*
Father's involvement in childcare *(0=involved, 1=uninvolved)*	0.01	0.19	0.07-0.31	1.51E-03*	0.05	-0.05-0.16	3.34E-01
	0.5	0.21	0.10-0.32	**2.50E-04****	0.06	-0.05-0.16	2.95E-01
	1	0.2	0.09-0.32	**3.00E-04****	0.06	-0.05-0.16	2.90E-01
Father's interest in child's education *(0=interested, 1=uninterested)*	0.01	0.02	-0.09-0.14	6.65E-01	0.2	0.10-0.30	**1.21E-04****
	0.5	0.03	-0.08-0.13	5.98E-01	0.19	0.09-0.29	**2.04E-04****
	1	0.02	-0.09-0.12	7.14E-01	0.18	0.08-0.28	**4.73E-04****
Mother walks *(0 = Most weeks/occasionally 1 = Hardly ever)*	0.01	0.04	-0.12-0.20	6.20E-01	0.14	-0.01-0.29	5.93E-02
	0.5	0.07	-0.08-0.22	3.68E-01	0.2	0.06-0.35	7.23E-03*
	1	0.07	-0.09-0.22	3.92E-01	0.21	0.06-0.36	5.07E-03*
Father walks *(0 = Most weeks/occasionally 1 = Hardly ever)*	0.01	0.02	-0.11-0.15	7.56E-01	0.15	0.02-0.27	1.96E-02*
	0.5	0.07	-0.06-0.19	3.13E-01	0.1	-0.02-0.22	1.10E-01
	1	0.06	-0.07-0.19	3.47E-01	0.1	-0.02-0.22	9.69E-02
Maternal smoking prior pregnancy *(0 = no, 1 = yes)*	0.01	0.03	-0.03-0.09	3.44E-01	0.02	-0.04-0.08	4.46E-01
	0.5	0.03	-0.03-0.08	4.05E-01	0.03	-0.02-0.09	2.54E-01
	1	0.02	-0.04-0.08	4.26E-01	0.03	-0.02-0.09	2.69E-01
Maternal smoking during pregnancy *(0 = no, 1 = yes)*	0.01	0.03	-0.04-0.09	4.25E-01	0.04	-0.02-0.10	1.87E-01
	0.5	0.01	-0.06-0.07	8.27E-01	0.03	-0.03-0.09	2.62E-01
	1	0.01	-0.06-0.07	8.24E-01	0.03	-0.03-0.09	2.66E-01
Parity *(continuous)*	0.01	0	-0.03-0.03	9.73E-01	0	-0.02-0.03	7.59E-01
	0.5	-0.01	-0.04-0.02	4.89E-01	0.01	-0.02-0.03	6.24E-01
	1	-0.01	-0.04-0.02	4.15E-01	0.01	-0.02-0.03	6.70E-01
Mother's age *(continuous)*	0.01	0	-0.03-0.03	7.84E-01	-0.04	-0.06--0.01	1.05E-02*
	0.5	0	-0.03-0.02	7.45E-01	-0.02	-0.05-0.01	1.74E-01
	1	-0.01	-0.03-0.02	6.97E-01	-0.02	-0.05-0.01	2.02E-01
Father's age *(continuous)*	0.01	0	-0.03-0.03	9.83E-01	0	-0.03-0.03	9.72E-01
	0.5	-0.01	-0.03-0.02	7.27E-01	0	-0.02-0.03	8.21E-01
	1	-0.01	-0.03-0.02	7.22E-01	0	-0.03-0.03	8.48E-01

Gestational period *(continuous)*	0.01	-0.01	-0.05-0.02	3.79E-01	-0.02	-0.05-0.01	2.65E-01
	0.5	0	-0.04-0.03	7.61E-01	-0.01	-0.04-0.02	5.77E-01
	1	0	-0.03-0.03	8.40E-01	-0.01	-0.04-0.02	4.95E-01
birth weight *(continuous)*	0.01	0	-0.03-0.03	8.97E-01	-0.03	-0.06--0.00	3.09E-02
	0.5	0	-0.03-0.03	9.49E-01	-0.02	-0.05-0.01	1.96E-01
	1	0	-0.03-0.03	9.68E-01	-0.02	-0.05-0.01	1.89E-01
Marital status *(0=married, stable union, 1=divorced, separated)*	0.01	0.06	-0.12-0.24	4.97E-01	0.08	-0.09-0.25	3.39E-01
	0.5	-0.06	-0.23-0.11	4.84E-01	0.05	-0.12-0.21	5.59E-01
	1	-0.07	-0.24-0.10	4.26E-01	0.04	-0.12-0.21	6.19E-01
Housing Issues *(0 = no, 1 = yes)*	0.01	0.13	-0.01-0.27	6.87E-02	0.15	0.02-0.28	1.89E-02
	0.5	0.16	0.03-0.29	1.45E-02*	0.09	-0.04-0.21	1.65E-01
	1	0.17	0.04-0.30	1.04E-02*	0.08	-0.05-0.20	2.15E-01
Family Alcohol issues *(0 = no, 1 = yes)*	0.01	0.23	-0.14-0.60	2.17E-01	0.13	-0.21-0.48	4.39E-01
	0.5	0.06	-0.29-0.42	7.30E-01	0.22	-0.12-0.57	1.98E-01
	1	0.03	-0.32-0.38	8.63E-01	0.23	-0.11-0.58	1.78E-01
Domestic tension *(0 = no, 1 = yes)*	0.01	0.21	0.05-0.37	8.71E-03*	0.13	-0.01-0.28	7.03E-02
	0.5	0.18	0.03-0.33	2.04E-02*	0.12	-0.02-0.27	8.76E-02
	1	0.17	0.02-0.32	2.61E-02*	0.13	-0.02-0.27	8.26E-02
Employment father *(0 = employed 1 = unemployed)*	0.01	0.01	-0.24-0.25	9.64E-01	-0.02	-0.24-0.21	8.77E-01
	0.5	0.07	-0.16-0.30	5.78E-01	0.16	-0.06-0.38	1.61E-01
	1	0.06	-0.17-0.29	5.91E-01	0.17	-0.06-0.39	1.45E-01
Father Reads *(0 = weekly/occasionally 1 = Hardly ever)*	0.01	0.08	0.00-0.15	3.89E-02*	0.01	-0.06-0.08	7.68E-01
	0.5	0.08	0.01-0.15	2.17E-02*	0.01	-0.06-0.07	8.44E-01
	1	0.09	0.02-0.16	1.67E-02*	0	-0.06-0.07	8.98E-01
Mother Reads *(0 = weekly/occasionally 1 = Hardly ever)*	0.01	-0.02	-0.11-0.08	7.48E-01	0.01	-0.08-0.09	8.75E-01
	0.5	0.07	-0.01-0.16	9.37E-02	0.03	-0.06-0.11	5.53E-01
	1	0.08	-0.01-0.16	8.01E-02	0.02	-0.06-0.10	6.17E-01
Free School Meals *(0 = no, 1 = yes)*	0.01	0.07	-0.11-0.26	4.42E-01	0.09	-0.09-0.26	3.31E-01
	0.5	0.09	-0.09-0.26	3.34E-01	0.12	-0.05-0.29	1.80E-01
	1	0.08	-0.09-0.26	3.51E-01	0.12	-0.05-0.29	1.69E-01

Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152. https://doi.org/10.1111/jcpp.13657. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), rGE = gene-environment correlation, NCDS = 1958 National Child Development Study, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

Table 11: *Sensitivity and Interaction Analysis in the MCS Sample*

Environment	Threshold z-scored	Sensitivity			Interaction terms	
		Beta	95%CI	P-Value	Wald chi-squared	P-Value
SCZ						
Father's involvement in childcare	0.01	0.21	0.08-0.34	1.17E-03	1.57	2.11E-01
	0.5	0.2	0.08-0.32	1.35E-03	2.03	1.54E-01
	1	0.19	0.07-0.32	1.57E-03	1.04	3.07E-01
MDD						
SES	0.01	-0.1	-0.09--0.03	1.49E-05	0.22	6.42E-01
	0.5	-0.1	-0.08--0.03	3.85E-05	1.74	1.87E-01
	1	-0.1	-0.08--0.03	4.97E-05	2	1.58E-01
Number of Rooms	0.01	-0.1	-0.08--0.03	2.01E-04	1.4	2.36E-01
	0.5	-0.1	-0.08--0.02	5.76E-04	2.92	8.75E-02
	1	-0.1	-0.08--0.02	7.77E-04	3.32	6.83E-02
Tenure	0.01	0.53	0.29-0.78	2.21E-05	0.03	8.56E-01
	0.5	0.36	0.12-0.60	3.22E-03	1.08	2.99E-01
	1	0.35	0.11-0.59	4.57E-03	1.41	2.35E-01
Mother's interest in child's education	0.01	0.18	0.07-0.29	1.02E-03	<0.001	9.90E-01
	0.5	0.12	0.01-0.23	2.71E-02	0.04	8.37E-01
	1	0.11	0.00-0.22	4.44E-02	0.02	8.79E-01
Father's interest in child's education	0.01	0.19	0.07-0.31	1.71E-03	0.12	7.31E-01
	0.5	0.17	0.06-0.29	4.07E-03	0.1	7.53E-01
	1	0.16	0.04-0.28	8.00E-03	0.05	8.21E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), rGE = gene-environment correlation, NCDS = 1958 National Child Development Study, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

3.6 Discussion

The aim of Chapter 3 was to investigate whether known psychosocial and environmental risk factors in childhood are correlated with the genetic susceptibility, using PRS, to either SCZ or MDD in children.

In addition, we wanted to further assess whether any significant rGE correlations were either due to *passive* or *evocative* rGE in MCS or if these could have been confounded by the presence of clinical cases in NCDS.

Finally, we wanted to explore whether rGE associations differed between the two psychopathologies as well as between the two cohorts from two different generations.

3.6.1 rGE for SCZ

In MCS, we found statistically significant correlations for SCZ concerning a heightened risk for parents being either divorced, separated or widowed. Perhaps it is not surprising that this association likely reflects *passive* rGE given that it was partially confounded by the parents PRS, highlighting that the parents do not just pass on their genotype to their offspring, but also provide the home environment in which the child grows up in.

In NCDS, we detected a correlation between the genetic liability to SCZ and father's not playing a role in childcare. As we did not have the parental genotypes in NCDS, we were unable to distinguish between *passive* or *evocative* rGE.

Overall, we expected more rGEs to emerge for SCZ given that this complex psychopathology is highly heritable. Whilst this finding could be explained by the low prevalence in the general population (Jaffee & Price, 2007), we would also like to point out that this limitation should have been, at least partially, overcome using PRS methodology.

3.6.2 rGE for MDD

Our study delivered evidence for statistically significant correlations between established environmental risk factors in childhood and the genetic susceptibility to MDD.

To begin with, multiple rGE associations involved indicators of low SES in MCS as well as in NCDS. Given that we had the parental genotype in MCS, our sensitivity analyses highlighted that only rented accommodation (tenure) was confounded by the genotype of the parents, thus suggesting *passive* rGE. Given that the association between low SES and the genetic risk for MDD in children in MCS cannot be explained by *passive* rGE, it is possible that this correlation does not reflect rGE and could be a consequence of the MDD symptomology itself.

Further, it is also important to highlight that several detected rGEs reflect parental behaviours. For example, in MCS only, the sensitivity analyses emphasised that the association between the PRS for MDD and maternal smoking can be explained by *passive* rGE, whilst the PRS for MDD and maternal alcohol consumption can be, at least partially, attributed to *evocative* rGE. Although other studies confirmed an association between the PRS for MDD and alcohol dependency due to their shared genetic susceptibility (Andersen et al., 2017), our study highlighted that the child PRS for MDD was protective in regard to the maternal alcohol consumption. In other words, our study proposed that the genetic liability to MDD in the offspring provokes a response from the mothers, resulting in decreased drinking through *evocative* rGE.

Moreover, we further detected correlations between psychosocial risk factors, including mothers and fathers who were not interested in their offspring's education, and the genetic liability to MDD. Although we cannot control for parental genotypes in NCDS and therefore cannot distinguish which form of rGE was present, it is plausible that *passive* rGE plays at least partially a role in these psychosocial behaviours. This has been further confirmed by another recent PRS study in 702 cohort members of the Dunedin birth cohort Study whereby the parent's PRS for educational attainment was mediating self-control and cognitive abilities in parents (Wertz et al., 2019).

3.6.3 Comparison between SCZ and MDD

The third objective of this study was to discover whether any of our rGE findings were similar between SCZ and MDD.

Overall, we detected eight significant rGE associations between psychosocial and environmental risk factors and the genetic susceptibility for MDD, but only two emerged for the PRS for SCZ. Several points warrant further review.

Firstly, whilst the association between the child's PRS for SCZ and MDD were both correlated with parental marital status in MCS, the strength of rGE associations for both psychopathologies were comparable based on the regression coefficient comparison, suggesting that this finding could be, at least partially, attributed to the partial genetic overlap between SCZ and MDD.

Secondly, our findings highlight that, overall, the number of significant rGEs differed between SCZ and MDD, whereby environmental risk factors in childhood were more strongly correlated with the PRS for MDD, and not SCZ.

Given that SCZ is highly heritable but less prevalent, with MDD being less heritable but more prevalent, it is possible that rGEs play less of a role in childhood for individuals with the genetic risk for SCZ. Moreover, it is also plausible that rGEs are more strongly associated with adverse environments in childhood due to this lower heritability as evidenced by findings from family and twin studies. That means, that greater non-shared environments in childhood may contribute to *passive* or *evocative* rGE associations, with the genetic share of the variance being less influential, thus rGEs being more evident in MDD in childhood.

3.6.4 Comparison between the Two Cohorts: MCS and NCDS

The last aim of Chapter 3 was to identify whether our rGE correlations were similar between MCS and NCDS with cohort members from different generations which are over 40 years apart.

Our results suggested that there is only a small overlap of findings between the two community studies.

First, single parenthood was associated with the genetic susceptibility to either psychopathology in participants from MCS only, and not in NCDS. Given that more than 97% of mothers were married in NCDS, but only 70% in MCS, this discrepancy could be attributed

to a cohort effect, whereby the totality of environmental, social and cultural influences for individuals being born into a certain generation creates a uniqueness specific to these individuals only (Keyes et al., 2010).

Secondly, we also identified that two markers of low SES, namely tenure of accommodation and SES itself, which were correlated with the PRS for MDD matched across MCS and NCDS, suggesting that these environmental measures are stabile across generations.

Thirdly, the genetic susceptibility to SCZ was correlated with father's not being involved in childcare in NCDS only, and not in MCS. This finding could be explained by generational differences in gender responsibilities (Davis & King, 2018) whereby participants from the NCDS who were born in 1958 may have had father's who's were less involved in their children's upbringing.

Fourthly, another rGE associations which was only detected in NCDS was the correlation between the genetic liability to MDD and mothers and fathers who were not interest in their offspring's education. Given that schools are increasingly carrying out more educational monitoring as part of the educational reform acts (Davies & Brember, 2001), one interpretation of this finding is that parental educational support may be less relevant for children now compared to the offspring who were born in 1958.

Lastly, in MCS only, we also identified an association between lower alcohol consumption, but increased maternal smoking and the genetic liability to MDD which could explained by cultural changes in environmental risk. These findings are not unique to our analyses in Chapter 3. For example, Sellers et al (2020) investigated the role of maternal smoking in pregnancy in relation to child mental health outcomes in the same community cohorts, specifically MCS and NCDS. The study re-emphasised that there is a stronger correlation between social disadvantage and maternal smoking during pregnancy in MCS when compared to NCDS. However, it is also important to point out that whilst we had maternal

smoking variables available in MCS and NCDS, we were unable to test associations between the PRS for either SCZ or MDD and parental alcohol consumption behaviours in NCDS.

3.7 Limitations

Chapter 3 has many strengths, including the utilisation of genome-wide data from thousands of unrelated individuals across two British longitudinal community cohorts. However, several limitations also need to be pointed out.

We utilised the GWAS summary statistics from the SCZ and MDD PGC in order to create the PRS scores used in our regression models. However, given that NCDS was used as a control sample by both working parties, we applied revised GWAS results which omitted multiple UK studies and thus may have impacted our chances to identify significant rGE associations in the NCDS cohort.

Moreover, several environmental measures, namely paternal interest in the offspring's education were underpowered for several data sweeps across both cohorts.

Additionally, we also detected multiple statistical differences between the full MCS and NCDS cohort as well as the genotyped sub-sample.

Further, although a large number of psychosocial and environmental measures were similar across MCS and NCDS, some variables were only available in one of the cohorts, such as maternal and paternal alcohol consumption which was only available in MCS.

Besides, Chapter 3 utilised British cohorts only, thus our findings should be considered in context and may not be applicable to populations from other countries.

Lastly, we only had the parental genotypes available in MCS, and were therefore unable to distinguish whether any rGE associations could be attributed to *passive* or *evocative* rGE in NCDS.

3.8 Implications

Foremost, Chapter 3 emphasised that several known environmental risks in childhood are indeed associated with the genetic susceptibility to SCZ and MDD through rGE, although more findings have been observed for MDD. Whilst these results may propose that treatments or interventions which target these environments could be ineffective in individuals who carry a genetic susceptibility (Wagner et al., 2013), it is necessary to highlight that PRSs for complex psychiatric disorders only explain a small fraction of the overall variance, for instance 2% for MDD (Lewis & Vassos, 2020). Besides, it is not feasible to provide interventions on an individual level by utilising PRS results from genetic studies which are better used to guide interventions strategies (Horwitz & Neiderhiser, 2011).

Putting our results from Chapter 3 into perspective, most children from the general population who have an increased genetic liability to MDD will continue to develop into healthy adults. Therefore, our findings do not propose that targeted interventions will be unsuccessful in children with a higher genetic liability to psychopathological outcome. In spite of this, it is vital that systematic approaches focusing on parents and their offspring together are prioritised given our rGE findings for multiple known environmental outcomes (such as maternal smoking). For example, guiding parents to respond to their offspring differently may be a viable intervention aimed at changing the offspring's behavioural outcomes for *evocative* rGE associations, whilst strategies which focus less on parenting behaviours and more on changing the child's behaviour may be more effective for *passive* rGE findings (Horwitz & Neiderhiser, 2011; Neiderhiser et al., 2007).

However, the significance of rGEs in childhood is likely further dependent on other factors, including personality traits of the parents which can moderate rGE correlations between parenting behaviours and the child's genotype (Oppenheimer et al., 2013). Understanding these moderating variables in rGE studies would help further advance our

understanding about who would derive benefit from interventions aimed to improve parenting behaviours.

3.9 Conclusion

Chapter 3 highlighted that the genetic liability to SCZ and MDD in children is correlated with several established psychosocial and environmental risk factors in childhood through rGE. rGE correlations were less pronounced for SCZ, but more for MDD. More than half of rGEs in MCS represent *passive* rGE and are confounded by the genotypes of the mother and/or father, suggesting that parents not only pass on their genes but also provide the home environment in which the child grows up in. Overall, our rGE findings for SCZ and MDD did not overlap, proposing that the complex interplay between genes and environment is disorder specific. Additionally, we found that various markers of low SES were stable across the two generations which are represented by cohort members from the MCS who were born after the turn of the century and participants from NCDS born in 1958. However, several psychosocial risk factors and parental behaviours, including single parenthood or increased maternal smoking likely changed over time, possible due to cultural or societal changes.

All in all, results highlight that the relationship between the genetic liability to SCZ and MDD in children and established environmental risk factors in childhood is complex and stresses the need to consider rGE in the aetiology of complex psychopathologies.

Chapter 4: Paper 2 – rGE for SCZ and MDD in Adulthood

4.1 Overview

The research presented in this chapter has been published:

Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. *Translational Psychiatry*, *12*(1), 477. https://doi.org/10.1038/s41398-022-02247-8

This chapter presents the above publication.

Whilst evidence from twin and family studies as well as molecular genetics studies associate many putative individual traits and vulnerabilities with the genetic liabilities to SCZ or MDD through rGE, it is still unknown whether these psychosocial and environmental risk factors differ between children or adults.

We wanted to explore associations between the PRS for either SCZ or MDD and established environmental risk factors in adulthood across two community cohorts: USoc and NCDS.

Our results propose that rGE findings only partially overlap between the two psychopathologies and between the two British cohorts.

Specifically, in USoc, correlations were identified between the genetic risk SCZ and single marital status, whilst adverse socioeconomic environmental factors were associated with the genetic liability to MDD.

Conversely, in NCDS, we replicated significant associations between indicators of low SES and the genetic vulnerability to MDD.

Overall, our findings suggest that rGE correlations may play a bigger role in MDD compared to SCZ which is in line with our findings from Chapter 3, possibly through *active*

rGE whereby individuals select themselves into adverse environments based on their own genetic liability.

4.2 Introduction

Modifications to behavioural or lifestyle choices have the potential to diminish the risk of pathological outcomes prior to the disorder being initiated (Socrates et al., 2021). However, given that some environments are heritable, it is important to investigate whether the genetic vulnerability to complex psychiatric disorders may be correlated with the exposure to these environmental risk factors through rGE (Jaffee & Price, 2008; Plomin et al., 1977).

For example, Socrates et al (2021) investigated associations between 529 lifestyle choices as well as nutritional and personality traits and the PRS for SCZ in 307,823 unaffected individuals from the UK biobank. The study highlighted not just that an increased PRS for SCZ was associated with self-reported risk-taking behaviour ($p = 3 \times 10^{-38}$) but also that self-reported risk-taking in undiagnosed participants was also positively correlated with lifetime distance moved ($p = 3\times 10^{-123}$; $r^2 = 0.001$) and self-reported substance abuse ($p = 8 \times 10^{-74}$; $r^2 = 0.008$) (Socrates et al., 2021). An additional comparison of PRS–trait associations in 599 medicated and non-medicated participants with SCZ proposed that medicated individuals had lower levels of self-reported risk-taking suggesting that the genetics for risk-taking may be a component of the genetic vulnerability to SCZ due to the mediation by drug-taking and/or migration ($p = 3 \times 10^{-3}$) (Socrates et al., 2021).

In addition, another rGE study explored the association between environmental factors, such as urbanicity, and genetic risk, expressed as PRS, for five mental health disorders, including depression in 41,198 cohort members aged 19 years or older who participated in wave three of the Norwegian Nord-Trøndelag Health study (HUNT3) (Sund et al., 2021). The authors proposed that the genetic susceptibility to depression was higher for individuals in

urban areas compared to rural areas in individuals with most severe symptoms according to the Hospital Anxiety and Depression Scale Score (OR = 1.33; 95% CI [1.14 to 1.56]; $p < .05$) suggesting rGE (Sund et al., 2021).

Another point to consider is that, although *passive* and *evocative* rGEs are present from birth and across childhood, *evocative* and *active* rGE are increasing across development as individuals get older and become more independent (Knafo & Jaffee, 2013; Scarr & McCartney, 1983). For example, individuals who are more aggressive in their social interactions may be more likely exposed to hostility and rejection from others, which consequently reinforces negative social behaviour through *evocative* rGE (Deater-Deckard & Mayr, 2005; Plomin et al., 1977). On the other hand, adults with a genetic predisposition that positively influences cognitive skills may find solving problems inherently rewarding and thus are more likely to pursue cognitive challenges (Deater-Deckard & Mayr, 2005; Plomin et al., 1977).

Given this evidence, many putative individual traits and vulnerabilities are associated with the genetic liabilities to SCZ or MDD through rGE. Based on our results from Chapter 3 which highlighted more rGE associations for MDD compared to SCZ and stronger associations between the PRS for MDD and socio-economic environments, partially through *passive* rGE, it is not clear whether these rGE are the same in adulthood. It is imperative to better understand whether environmental targets which are aimed to treat or even prevent these psychopathologies change between different developmental stages windows or whether these stay the same from childhood all the way into adulthood.

Likewise, given that both psychopathologies share six genetic risk loci between them (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018), have high heritability estimates in adulthood (Cannon et al., 1998; Hilker et al., 2018; Kendler & Prescott, 1999; Rice, 2010; Sullivan et al., 2003; Sullivan et al., 2000), and cover

different symptomology in adults compared to children, it is further critical to assess if these rGE associations are similar between the disorders in adulthood.

4.2.1 Objectives

The first objective of Chapter 4 was to assess whether known environmental risks and the PRS for SCZ and MDD are associated with each other in participants aged 16 years or older from two British community cohorts from the general population, namely USoc which started in 2009 and the NCDS which started in 1958.

Secondly, given differences in heritability and the partial genetic overlap between the two psychopathologies, we wanted to explore whether correlations between environmental factors and genetic susceptibility differ between SCZ and MDD in adulthood.

Thirdly, we wanted to compare rGE findings across the two adult cohorts to investigate if these findings could have been driven by cohort effects, since specific psychosocial or environmental risk factors for SCZ or MDD may have changed over time due to cultural or society factors.

4.2.2 Hypotheses

Given findings from empirical studies and theory (Hunjan et al., 2021; Jaffee & Price, 2008; Socrates et al., 2021; Sund et al., 2021), we hypothesised that 1) we would detect significant associations between established psychosocial and environmental risk factors and the genetic susceptibility for either SCZ or MDD. Further, we expected that any detected rGE findings would differ between the SCZ and MDD. Finally, we hypothesised that rGE associations would be different between the two community cohorts of different ages given cultural shifts in psychosocial or environmental risks.

4.3 Methods

4.3.1 Environmental Factors

The following environmental risk factors which are known to be implicated in the development of SCZ or MDD were selected for Chapter 4 across three categories:

Firstly, for *economic environmental factors* we selected SES (Harrison et al., 2001), unemployment (Evensen et al., 2016; Kendler et al., 1999; Marwaha et al., 2007) as well as financial difficulties (Kendler et al., 1999). We expanded our selection to additional markers of SES, including number of bedrooms in the house, tenure or accommodation (owned vs rented) and income. Secondly, for our *substance abuse* category, we included smoking (de Leon & Diaz, 2005; Pasco et al., 2008) and alcohol consumption (Grant et al., 2004) (Nielsen et al., 2017). Lastly, the following *psychosocial factors* were selected: marital status (Bulloch et al., 2009; Deshmukh et al., 2016; Walid & Zaytseva, 2011) and educational attainment (Cohen et al., 2020).

The environmental factors used for USoc and NCDS are displayed in Table 12. The detailed breakdown of how each environmental factor was coded is displayed in Appendix 3 (USoc) and 2 (NCDS).

Table 12: *Environments by Cohort*

Environmental risk factor	Available in USoc	Available in NCDS
Socio-economic risk factors		
SES	X	X
Finance issues	X	
Number of bedrooms in the family home	X	X
Tenure of accommodation	X	X
Employment	X	X
Income	X	
Substance abuse		
Alcohol consumption	X	
Smoking		X
Psychosocial risk factors		
Educational attainment	X	
Marital status	X	X

Note: USoc = Understanding Society, NCDS = 1958 National Child Development Study, SES = Socio-economic status

4.3.2 Genetic Processing

We utilised genome-wide SNP data from 9,961 participants from USoc, who were genotyped on the Illumina Infinium HumanCoreExome BeadChip array (Benzeval et al., 2014; Prins et al., 2017) as well as 1,502; 2,92 and 2,592 individuals from NCDS from the WTCCC1, WTCCC2 and T1DGC, respectively (Barrett et al., 2009; Wellcome Trust Case Control Consortium, 2007). The genetic QC, imputation, post-imputation QC for USoc as well as NCDS are described in section 2.4 ('Genetic data') in the Methods chapter (Chapter 2). In sum, 9,039 cohort members from USoc and 5,288 individuals from NCDS passed genetic processing.

4.3.3 PRS Creation

Existing GWAS summary statistics were utilised from the SCZ and MDD working groups of the PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018) in order to compute individual-level PRS at seven p-value thresholds in PRSice (Euesden et al., 2015). This is described in detailed in section 2.4.5 (*'Polygenic Risk Scoring (PRS)'*) in the Methods chapter (Chapter 2). For USoc only, following the PRS

creation, we selected a randomised sample of genetically unrelated individuals from different households in STATA v12.1 (StataCorp, 2011), of which a total of 7,384 individuals remained for final analysis.

4.3.4 Data Analysis

First, using G*Power v3.1.9.6 (Faul et al., 2009), we calculated the minimum sample size for both cohorts. All other data analyses were performed in STATA v12.1 (StataCorp, 2011). Next, descriptive statistics as well as correlation matrices for markers of SES were run for USoc and NCDS. Further, linear or logistic regressions were computed for any phenotypic measures at a single data sweep, whilst longitudinal linear or logistic mixed-effects or random effects models were computed for longitudinal variables. Age/year of data collection, sex and the top principal components were included as covariates in all regressions. Moreover, the Bonferroni correction for multiple testing was applied across all calculations with a corrected $p \leq 1.67 \times 10^{-3}$. Findings were considered significant if at least one p-value PRS threshold met the corrected Bonferroni p-value.

Sensitivity analyses were performed to assess any confounding by clinical cases whereby participants who received psychiatric treatment and participants with a clinical diagnosis were removed for USoc. No information on SCZ diagnosis or symptoms was available in USoc. For NCDS, individuals who reported depression were omitted.

Lastly, interaction analyses were computed to compare the regression beta coefficients between the original regression models and the sensitivity analyses.

Section 2.7.3 (Chapter 4 – Paper 2 (rGE in adulthood in SCZ and MDD) in the Methods chapter (Chapter 2) describes the data analysis in more detail.

4.4 Results

4.4.1 Descriptive Statistics and Power Calculation

According to our power analysis, USoc and NCDS were sufficiently powered for our analysis apart from SES at data sweep 8 and 9 in USoc as well as employment at age 23 and tenure at age 23 and 55 in NCDS.

For USoc, our comparison between the whole cohort and the genotype sub-sample suggested that some statistically significant differences emerged. Specifically, participants from the genotyped sample had a lower number of bedrooms in the family home at all data waves and were less likely to be married at wave 1.

We did not identify any statistically significant differences when comparing the whole NCDS sample and the genotyped sub-sample for any of the selected environmental measures.

4.4.2 rGE Results for USoc

Our analyses in USoc highlighted that the genetic liability to SCZ was correlated with unemployment, financial difficulties, as well as being single or divorced. However, only the association between the PRS for SCZ and marital status survived the Bonferroni correction.

Besides, the genetic susceptibility for MDD was correlated with unemployment, low income, finance issues, decreased number of bedrooms in the family home, being single or divorced, as well as low SES. After correcting for multiple testing, all associations except the correlation between the PRS for MDD and SES or marital status remained.

All USoc results are displayed in Table 13 for three PRS thresholds (0.01, 0.5 and 1).

Unfortunately, as we did not have any information on SZC diagnosis or symptoms available in USoc, a sensitivity analysis could not be run for the surviving SCZ finding.

On the other hand, we were able to compute sensitivity analyses for the significant MDD findings suggesting that none of the correlations were confounded by participants who were treated for psychiatric problems or who reported depression.

The sensitivity and interaction analyses results for USoc are displayed in Table 14 for three PRS thresholds (0.01, 0.5 and 1).

The full USoc results are provided in Appendix 16.

Table 13: *Regression Results of rGE in the USoc Sample*

Environment	SCZ				MDD		
	Threshold	**Beta**	**95%CI**	**P-Value**	**Beta**	**95%CI**	**P-Value**
SES *(5 Professional 4 Managerial 3 Skilled 2 Partly-skilled 1 Unskilled)*	0.01	-0.02	-0.05-0.01	1.45E-01	-0.03	-0.06--0.00	2.62E-02*
	0.5	-0.02	-0.05-0.01	2.25E-01	-0.01	-0.04-0.02	4.94E-01
	1	-0.02	-0.05-0.01	2.70E-01	-0.01	-0.04-0.02	4.17E-01
Number of Rooms *(continuous)*	0.01	-0.02	-0.04-0.01	1.72E-01	-0.04	-0.07--0.02	**4.36E-04****
	0.5	-0.02	-0.04-0.00	8.94E-02	-0.03	-0.05--0.00	3.46E-02*
	1	-0.02	-0.04-0.00	9.69E-02	-0.03	-0.05--0.00	2.74E-02*
Marital status *(0=married, 1=single/divorced)*	0.01	0.08	0.02-0.13	5.42E-03*	0.08	0.03-0.14	2.38E-03*
	0.5	0.09	0.04-0.15	**1.13E-03****	0.01	-0.04-0.07	6.00E-01
	1	0.09	0.03-0.15	**1.63E-03****	0.02	-0.04-0.07	5.18E-01
Income *(Grouped into 50 sub-groups)*	0.01	-0.02	-0.04-0.00	1.08E-01	-0.03	-0.05--0.01	**6.72E-04****
	0.5	-0.02	-0.04-0.00	7.76E-02	-0.02	-0.04--0.00	4.75E-02*
	1	-0.02	-0.04-0.00	6.57E-02	-0.02	-0.04--0.00	4.31E-02*
Alcohol consumption *(0=not drinking, 1-7=drinking days per week)*	0.01	0	-0.02-0.03	9.56E-01	0.01	-0.01-0.04	3.29E-01
	0.5	-0.01	-0.03-0.02	5.80E-01	0	-0.03-0.02	7.07E-01
	1	-0.01	-0.03-0.02	6.42E-01	-0.01	-0.03-0.02	6.25E-01
Employment *(0=employed, 1=unemployed)*	0.01	0.16	0.04-0.27	7.81E-03*	0.2	0.09-0.32	**5.50E-04****
	0.5	0.15	0.03-0.26	1.18E-02*	0.21	0.09-0.32	**3.98E-04****
	1	0.15	0.04-0.27	8.50E-03*	0.2	0.09-0.31	**5.61E-04****
Tenure *(0=owns, 1=rents)*	0.01	0.05	-0.17-0.28	6.48E-01	0.13	-0.10-0.37	2.51E-01
	0.5	0.02	-0.22-0.25	8.86E-01	0.1	-0.14-0.33	4.15E-01
	1	0.01	-0.22-0.25	9.01E-01	0.09	-0.14-0.32	4.29E-01
Finance Issues *(0=no issues, 1=issues)*	0.01	0.12	0.03-0.20	7.99E-03*	0.24	0.16-0.33	**2.91E-08****
	0.5	0.14	0.05-0.22	2.29E-03*	0.23	0.14-0.32	**1.52E-07****
	1	0.14	0.05-0.22	1.90E-03*	0.23	0.15-0.32	**1.36E-07****
Education *(0=A-level or above, 1=GCSE or below)*	0.01	0	-0.36-0.37	9.94E-01	0.2	-0.17-0.57	2.96E-01
	0.5	-0.05	-0.42-0.32	7.88E-01	0.09	-0.27-0.46	6.18E-01
	1	-0.05	-0.42-0.32	7.90E-01	0.1	-0.27-0.46	6.03E-01

Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), rGE = gene-environment correlation, USoc = Understanding Society, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

Table 14: *Sensitivity and Interaction Analysis in the USoc Sample*

Environment	Threshold z-scored	Sensitivity			Interaction	
		Beta	95%CI	P-Value	Wald chi-square	p-value
MDD						
Number of Rooms	0.01	-0.04	-0.07--0.02	4.78E-04	1.98	1.60E-01
	0.5	-0.02	-0.05-0.00	8.45E-02	0.01	9.35E-01
	1	-0.02	-0.05-0.00	6.81E-02	0.01	9.43E-01
Income	0.01	-0.04	-0.06--0.02	2.98E-04	2.86	9.08E-02
	0.5	-0.02	-0.04--0.00	3.79E-02	0.36	5.48E-01
	1	-0.02	-0.04--0.00	2.89E-02	0.61	4.34E-01
Employment	0.01	0.18	0.07-0.30	1.68E-03	3.33	6.79E-02
	0.5	0.16	0.05-0.28	5.18E-03	0.17	6.80E-01
	1	0.16	0.05-0.28	5.07E-03	0.4	5.30E-01
Finance Issues	0.01	0.23	0.14-0.32	9.91E-07	2.33	1.27E-01
	0.5	0.19	0.10-0.28	6.60E-05	0.02	8.99E-01
	1	0.19	0.10-0.28	5.42E-05	0.02	8.80E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), USoc = Understanding Society, Beta = Beta Coefficient, CI = Confidence Interval

4.4.3 rGE for NCDS

In NCDS, we did not obtain any statistically significant correlations between the genetic susceptibility to SCZ and any of our selected environments after correcting for Bonferroni.

Conversely, the PRS for MDD was associated with lower number of bedrooms in the home, low SES, rented accommodation as well as smoking. After correcting for multiple testing, only the correlations with rented accommodation and low number of bedrooms remained.

All NCDS results are displayed in Table 15 for three PRS thresholds (0.01, 0.5 and 1).

Our findings were not confounded by the presence of clinical cases based on our sensitivity analyses after omitting participants with depression.

The sensitivity and interaction analyses results for NCDS are displayed in Table 16 for three PRS thresholds (0.01, 0.5 and 1).

The full NCDS results are provided in Appendix 15.

Table 15: *Regression Results of rGE in the NCDS Sample*

Environment	SCZ				MDD		
	Threshold	**Beta**	**95%CI**	**P-Value**	**Beta**	**95%CI**	**P-Value**
SES *(5 Professional 4 Managerial 3 Skilled 2 Partly-skilled 1 Unskilled)*	0.01	0	-0.03-0.02	9.04E-01	-0.02	-0.04-0.00	6.29E-02
	0.5	0.02	-0.01-0.04	1.89E-01	-0.02	-0.04-0.00	8.95E-02
	1	0.02	-0.01-0.04	1.77E-01	-0.02	-0.04-0.00	1.11E-01
Number of Rooms *(continuous)*	0.01	0	-0.03-0.02	6.99E-01	-0.03	-0.04--0.01	8.93E-03*
	0.5	-0.01	-0.03-0.01	3.66E-01	-0.03	-0.05--0.01	**1.51E-03****
	1	-0.01	-0.03-0.01	3.92E-01	-0.03	-0.05--0.01	1.84E-03*
Marital status *(0=in relationship, 1=not in relationship)*	0.01	0.06	-0.01-0.13	8.36E-02	-0.01	-0.08-0.05	6.89E-01
	0.5	0.02	-0.04-0.09	4.70E-01	-0.02	-0.09-0.04	4.29E-01
	1	0.02	-0.04-0.09	4.91E-01	-0.02	-0.08-0.04	4.77E-01
Smoking *(0=no, 1=yes)*	0.01	0.06	-0.14-0.27	5.52E-01	0.21	0.02-0.40	3.06E-02*
	0.5	0.12	-0.07-0.32	2.11E-01	0.24	0.05-0.42	1.20E-02*
	1	0.12	-0.07-0.32	2.07E-01	0.23	0.05-0.42	1.45E-02*
Employment *(0=Employed, 1=Unemployed)*	0.01	0.08	-0.02-0.18	1.22E-01	0.08	-0.01-0.18	8.92E-02
	0.5	0.08	-0.01-0.18	8.86E-02	0.05	-0.04-0.15	2.78E-01
	1	0.07	-0.02-0.17	1.33E-01	0.04	-0.05-0.14	3.59E-01
Tenure *(0=owns, 1=rents)*	0.01	0.01	-0.11-0.13	8.39E-01	0.1	-0.01-0.20	8.24E-02
	0.5	0	-0.11-0.11	9.62E-01	0.16	0.05-0.27	3.33E-03*
	1	0.01	-0.10-0.12	9.07E-01	0.15	0.04-0.26	6.04E-03*

Note: *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), rGE = gene-environment correlation, NCDS = 1958 National Child Development Study, PRS = Polygenic Risk Score, Beta = Beta Coefficient, CI = Confidence Interval

Table 16: *Sensitivity and Interaction analysis in the NCDS Sample*

Environment		Sensitivity			Interaction	
	Threshold z-scored	Beta	95%CI	P-Value	Wald chi-square	p-value
MDD						
Number of Rooms	0.01	-0.02	-0.05--0.00	5.00E-02	0.11	7.38E-01
	0.5	-0.02	-0.05--0.00	3.22E-02	0.34	5.58E-01
	1	-0.02	-0.05--0.00	3.32E-02	0.32	5.72E-01
Tenure	0.01	0.05	-0.07-0.18	4.10E-01	0.56	4.54E-01
	0.5	0.09	-0.03-0.21	1.39E-01	2.27	1.32E-01
	1	0.08	-0.04-0.21	1.79E-01	2.35	1.25E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), NCDS = 1958 National Child Development Study, Beta = Beta Coefficient, CI = Confidence Interval

4.5 Discussion

The objectives of Chapter 4 were firstly to assess whether the PRS to either SCZ or MDD, was associated with known psychosocial or environmental risk factors in individuals over the age of 16 from two large British cohorts, USoc and NCDS, as well as establish if these rGE associations differ between the two psychopathologies and the two community cohorts.

4.5.1 rGE for SCZ

Overall, our results propose that the genetic vulnerability to SCZ is correlated with a higher likelihood of being single or divorced. It is possible that this association may reflect *evocative* rGE which proposes that the genetic liability for SCZ evokes behaviours or negative reactions in others which in turn can then lead to relationship problems (Jaffee & Price, 2007; Plomin et al., 1977).

But it is also important to point out that all significant associations for SCZ only emerged in USoc. Given that we did not have any information on SCZ diagnosis or symptoms, no sensitivity analysis could be run. Consequently, we are unable to reject the alternative

hypothesis that any detected correlations reflect indirect effects of SCZ itself, such as hallucinations, psychotic episodes or cognitive disabilities which in turn may have detrimental consequences in everyday life.

4.5.2 rGE for MDD

Chapter 4 highlighted significant correlations between the genetic susceptibility to MDD and several markers of low socio-economic status, such as unemployment, financial difficulties, low income, low number of bedrooms and rented accommodation. However, we would also like to highlight that the finding for SES itself did not survive Bonferroni correction. Moreover, it is also important to bring to light that several markers of low SES are correlated with each other as per our environmental correlation matrices analyses in USoc as well as in NCDS.

Overall, these correlations between the PRS for MDD and indicators of adverse socio-economic environments are in line with previous empirical studies which propose that a wide range of mental health outcomes are indeed associated with low SES (Muntaner et al., 1998; Stansfeld et al., 1998). For instance, some markers of SES including unemployment and low income were predictive of antidepressant treatment responses in over 2,500 individuals with MDD who took part in the *S*equenced *T*reatment *A*lternatives to *R*elieve *D*epression (STAR*D) clinical trial (Wertz et al., 2019). It is therefore plausible that cohort members with the genetic vulnerability to MDD could experience subclinical symptoms of the disease itself which in turn could prevent these individuals from progressing in their careers or even securing work. Consequently, this lack of work may contribute to difficulties in purchasing accommodation as identified in NCDS.

Whilst at least some of these correlations as identified in this chapter may in fact indicate intermediate subclinical phenotypes of MDD itself as opposed to causal pathways to

depression, it is possible that these associations are comprised of a combination of both. Although we are unable to confirm the causality of our results, our sensitivity analysis suggested that none of these correlations between the genetic risk for MDD and adverse socio-economic environmental risk factors could be explained by the presence of clinical cases in USoc or NCDS. Therefore, our environmental risk associations may be, at least partially, attributed to the genetic liability to MDD through *active* rGE whereby the individuals select and shape their own environments due to their genetic predisposition (Jaffee & Price, 2007; Plomin et al., 1977). That means that the genetic susceptibility to MDD may mediate through adverse socio-economic environments based on the individual's own selection in these environments.

4.5.3 Comparison between SCZ and MDD

A further aim of this chapter was to explore whether any rGE associations were similar between SCZ and MDD. The regression analyses showed that none of the significant correlations for either psychopathology matched between them. If any of our findings could indeed be explained by genetic confounding than these mismatches may be due to the partial genetic overlap between SCZ and MDD.

4.5.4 Comparison between the Two Cohorts: USoc and NCDS

The third aim of Chapter 4 was to explore if any correlations between the genetic risk for SCZ or MDD and our selected environmental risk factors different between the two community cohorts. Surprisingly, we identified significant differences in rGE findings between USoc and NCDS. First, only one rGE finding emerged for SCZ across both cohorts. It is possible that psychiatric disorders with a low base rate, such as SCZ, may affect PRS predictions in non-clinical cohorts from the general population (Anderson et al., 2019). This

means that, replicating the similar findings across different cohort studies with different numbers of participants could be more challenging.

Furthermore, results for USoc and NCDS did not match completely for the environmental measures that were available in both community cohorts. For example, employment status was an available phenotype in USoc and NCDS, however, we only found an association between the genetic risk for MDD and unemployment in USoc. In contrast, the genetic liability for MDD was correlated with tenure of accommodation, specifically owning a home, in NCDS only. These differences between both cohorts could be explained by a cohort effect or age effect, which proposes that differential environmental exposures are unique to participants from that cohort and depend on what age individuals enter the study (Keyes et al., 2014; Sutin et al., 2013). It is plausible that this phenomenon could be attributed to Chapter 4 where participants from USoc, which started in 2009, were of mixed ages, whilst participants from NCDS were all born in a single week in 1958.

In sum, future studies need to assess, not just whether there are fundamental differences between rGE results across different cohorts, but also between critical developmental stages, including childhood, adolescence, and adulthood.

4.6 Limitations

Chapter 4 has many strengths, including the utilisation of two well characterised and established community cohort studies. Nevertheless, several limitations should also be noted.

Given that no data on either SCZ diagnoses or associated symptoms were available in USoc, we were unable to assess whether our finding could have been confounded by the presence of clinical cases.

Further, our power analysis highlighted that some of the tested correlations were under-powered for some environments in both cohorts. Besides that, we identified some differences

between the genotype subsample and the whole USoc cohort with reference to the number of bedrooms at data sweep 1 and marital status at all timepoints. Thus, our results may not be generalisable to the whole USoc cohort.

Chapter 4 utilised genotype and phenotype data from two British community cohorts as well as GWAS summary statistics from individuals of mostly European ancestry who in addition originate from high income countries (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018). In turn, PRS will be more predictive in individuals from these ancestries and thus cannot be applied to other populations (Palk et al., 2019). In addition, we would like to emphasise that these GWAS summary statistics which were used to calculate individual-level PRS originated from associations in cohorts which did not account for environmental influences. That means that it is unclear to what extent any of our applied PRS reflect environmental influences. Consequently, this may have affected the specificity of our SCZ and MDD findings and results need to be considered with this in mind.

Lastly, not all of our selected environmental risk factors were present in USoc and NCDS. As a result, the community cohort comparison should be regarded as exploratory.

4.7 Implications

It is possible that rGE reflects pleiotropy of our genes on specific environmental contexts, which proposes that a genetic variant can influence several phenotypes (He & Zhang, 2006) and consequently the aetiology of complex psychopathologies, suggesting that any environmental interventions would be rendered ineffective (Jaffee & Price, 2007). However, we would like to put our findings into perspective.

Whilst an increased PRS for SCZ or MDD would suggest that these individuals are at an increased risk for either psychopathology, these individual PRS scores should not be taken

as deterministic given that these only account for a small proportion of the phenotypic variance and thus are currently unsuitable for implementation in clinical settings (Lewis & Vassos, 2017).

Although our analyses propose that the associations between established psychosocial and environmental risk factors and the genetic susceptibility to either SCZ and MDD in adults over the age of 16 may be confounded, at least partially, by genes, it does not exclude the alternative explanations that adverse environment can contribute to the aetiology of these complex psychiatric outcomes (Knafo & Jaffee, 2013).

We would also like to point out that Chapter 4 does not aim to fully explain the complicated gene-environment interplay in SCZ and MDD, neither do our results propose that any preventative or targeted environmental treatments will be deemed unsuccessful. In particular, socio-economic environments are conceptually complex, are difficult to measures (Oakes & Rossi, 2003) and often the consequence of numerous non-genetic and genetic influences.

Further, whilst preventative interventions may still be useful in targeting specific environments which are correlated with genetic susceptibilities and thus mediating any adverse outcomes, research should also focus on boosting an individual's strengths in order to promote resiliency to adverse environmental exposures (Leve et al., 2010).

Finally, it is imperative that studies use cohorts with genotype data from several generations in order to better understand and disentangle which rGE mechanism is involved in the development of SCZ and MDD in adulthood with the aim to further help our understanding of the aetiology of these complex psychiatric disorders.

4.8 Conclusion

In sum, our analyses in Chapter 4 emphasise that several indicators of social adversity and low socio-economic status are associated with the genetic susceptibility for MDD in adult participants from two British community cohorts from the general population. Our findings propose that rGE plays a role in the development of MDD in adulthood whereby individuals may actively select and shape their own adverse environments which are associated with their genetic vulnerability. Besides, our results highlight that the correlation between the genetic PRS for psychopathological outcomes and established environmental risks are mostly disorder specific. On the one hand, the genetic risk for MDD was more strongly associated with markers of adverse socio-economic status, whilst the genetic vulnerability to SCZ was only correlated with one psychosocial risk factors, namely being single, divorced or separated. Lastly, the detected rGE associations differed between the two community cohorts, proposing that environmental influences may change as a result of societal or cultural changes.

Overall, Chapter 4 presents additional evidence that psychosocial and environmental risk factors for SCZ and MDD are confounded by the genetic liability for these psychiatric disorders. It is therefore possible that established risk factors for either psychopathology may mediate a genetic risk for SCZ or MDD but may not necessarily be causal. Future studies need to assess the true causality between the genetic susceptibility to complex psychopathologies and associated environmental risk factors. This can be achieved by utilising cohorts with intergenerational genotypes, including genetic data from children and parents, in order to allow for the differentiation of which type of rGE is present in the development of psychopathological outcomes.

Chapter 5: Paper 3 – rGE in SCZ and MDD over Time

5.1 Overview

The research presented in this chapter has been published:

Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136

This chapter presents the above publication.

Research suggests that rGE associations become stronger over time as individuals actively modify and select themselves into environments which are correlated with their genetic susceptibilities.

Whilst some studies suggest that this shift from *passive* to *evocative* or *active* rGE happens when children transition into adolescence and early adulthood, few studies have investigated exactly when and which rGE associations change across the different developmental stages.

Chapter 5 utilised longitudinal data from three British community cohorts (MCS, USoc and NCDS) with the aim to assess whether the strength of previously identified rGE correlations from Chapters 3 and 4 change across childhood, adulthood, from birth up to age 55 as well as whether findings differ between the two psychopathologies.

Overall, findings highlight that the majority of rGEs do not change across the different developmental stages.

Additionally, few changes in rGE differed between SCZ and MDD whereby the majority of findings could not be explained by the presence of clinical cases. It is therefore

possible that our results reflect changes in cultural or environmental risk, whereby the genetic risk factors likely having less of an impact on rGE changes over time.

5.2 Introduction

In view of the complex development of SCZ and MDD from childhood to adulthood as well as the changing environmental exposures across different developmental stages (Halfon et al., 2014; Kendler & Baker, 2007; Price & Jaffee, 2008), it is imperative to assess changes in gene-environment interplay over time.

However, several important points will need to be considered. Firstly, given that SCZ is characterised by a prodromal phase in early adolescence, with childhood-onset SCZ presenting before the before the age of 13, there are clear age-dependent variations in the phenomenology of this disorder (Fernandez et al., 2019; Hollis, 2015; Kahn et al., 2015).

For instance, a study into lateral biases in participants with early onset SCZ (n = 21), and late onset SCZ (n = 19), as well as their respective control groups suggested that reduced perceptual bias was displayed in the early-onset SCZ group ($t = 2.43$; $p < .05$), but not in individuals with late-onset SCZ ($t = 0.19$; $p > .05$), suggestive of an increased loss of hemispheric differentiation and reduced functional asymmetries in participants with early onset SCZ (Bellgrove et al., 2004).

Further, whilst there is limited research which focuses specifically on the symptom profiles and phenomenology between child and adolescent depression as well as depression in adulthood, research proposes that there is heterogeneity between these different developmental stages, with evidence largely coming from studies examining familial aggregation rates as well as epidemiology studies (Rice, 2010).

One of these studies was Jaffee et al (2002) who investigated the aetiology of MDD in 998 participants from the Dunedin Multidisciplinary Health and Development cohort from

birth up to age 26 divided into four defined groups: 1) Participants with childhood-onset MDD, but no MDD in adulthood, 2) Participants with adult-onset MDD, 3) Participants with child-onset MDD, continuing into adulthood and 4) Non-cases. The study proposed that participants with adulthood-onset MDD and non-cases had a similar risk profile, whilst participants with childhood or adolescent-onset MDD displayed increased rates of childhood risk factors, such as parental psychopathology as well as motor deficits, suggesting that there is likely an aetiological heterogeneity between child, adolescent and adult MDD.

Moreover, research suggests that rGE associations become stronger over time as individuals actively modify and select themselves into environments which are correlated with their genetic susceptibilities (Jaffee & Price, 2007). For instance, Nivard et al (2017) explored the association between the PRS for SCZ and psychopathological outcomes in 6,127 children from the Avon Longitudinal Study of Parents And Children as well as 2,588 children from the Netherlands Twin Register at 7, 10, 12 or 13 and 15 years. The study not only highlighted a significant genetic overlap between the PRS for SCZ and psychopathology (estimate = 0.0182; SE = 0.005; Z-Score (Z) = 3.66, p = .0002), but also that these associations became stronger as children got older, such as stronger association for SCZ and depression over time (Z = 2.93; p < .003) (Nivard et al., 2017).

Whilst psychology studies imply that a shift from *passive* to *evocative* or *active* rGE happens when children transition into adolescence and early adulthood (Scarr & McCartney, 1983), few studies have explored the exact timing of this shift, with even fewer studies having investigated rGE correlations featuring a range of psychosocial and environmental risk factors across the different developmental stages.

In sum, investigating developmental psychopathology across critical development periods such as late adolescence and early adulthood plays a vital role (Beam & Turkheimer, 2013). Although there is an abundance of longitudinal studies which are conducted in children

and adolescents, as well as adults to a lesser extent, longitudinal studies which are spanning across the different developmental stages are hard to find (Beam & Turkheimer, 2013).

Chapter 5 addresses these gaps by exploring rGE changes over time for SCZ and MDD across different developmental periods involving a range of established environmental risk factors in childhood as well as adulthood.

5.2.1 Objectives

The aim of Chapter 5 was to investigate whether previously identified rGE associations in SCZ and MDD from Chapter 3 (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) and Chapter 4 (Sandra Machlitt-Northen et al., 2022) change a) across childhood in MCS and NCDS, b) across adulthood in USoc and NCDS and c) across the life course from birth up to 55 years of age in NCDS.

The final objective of Chapter 5 was to explore whether rGE changes over time differ between the two psychopathologies given the genetic overlap between them is only partial.

5.2.2 Hypotheses

In view of the results from similar studies (Newbury et al., 2020), we expected that rGE associations identified in Chapter 3 and Chapter 4 would increase across childhood as well as adulthood due to *active* rGE whereby individuals actively select or modify environments based on their underlying genetic vulnerabilities (Plomin et al., 1977).

Moreover, we hypothesised that when comparing childhood vs adulthood rGEs in NCDS that any associations would be stronger in adults as rGE mechanisms shift from *passive* & *evocative* rGE to *active* rGE as individuals get older.

Lastly, we expected that rGE changes over time would not be identical between SCZ and MDD due to their incomplete genetic overlap.

5.3 Methods

5.3.1 Environmental Factors

Chapter 5 concentrated on a range of psychosocial and environmental risk factors from Chapter 3 and Chapter 4 for either SCZ or MDD which were significantly associated with the genetic vulnerability to these psychopathologies. At least one p-value threshold must have met a of $p \leq .05$ before Bonferroni correction was applied.

In order to assess rGE changes over time, only environmental factors from Chapter 3 and Chapter 4 which were available at multiple timepoints were included.

All selected psychosocial and environmental and psychosocial risk factors for the rGE changes across childhood, adulthood as well as the childhood vs adulthood analysis are described in Table 17.

Table 18 describes which environmental risk factors were used for each cohort. The detailed breakdown of how each environmental factor was coded is displayed in Appendix 5 for MCS, Appendix 6 for USoc and Appendix 7 for NCDS.

Table 17: *Selected Environmental Risk Factors*

Analysis	Economic situation	Substance abuse	Psychosocial outcomes
Childhood rGE by time analysis	- SES, - tenure, - financial issues, - number of bedrooms, - employment	- maternal smoking, - maternal alcohol consumption, - paternal alcohol consumption	- parental marital status, - father's involvement in the child's upbringing, - maternal interest in the child's education, - paternal interest in the child's education, - mother takes child for walks, - father takes child for walks, - mother reads to child - father reads to child
Adulthood rGE by time analysis	- SES, - tenure, - financial issues, - number of bedrooms, - employment, - income	- Smoking	- Marital status
childhood vs adulthood rGE by time analysis	- Family SES in childhood vs SES of individual in adulthood, - Family tenure in childhood vs tenure of individual in adulthood, - Family number of bedrooms in childhood vs number of bedrooms of individual in adulthood, - Father's employment in childhood vs employment of individual in adulthood	- Mother's smoking behaviour prior and during pregnancy vs smoking behaviour of individual during adulthood	- Marital status of mother at birth vs marital status of individual in adulthood

Note: *Adapted from* Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC. Any significant findings from Chapter 3 and Chapter 4 which were not available at multiple timepoints were excluded from our rGE across time analysis.

Table 18: *Selected Environmental Risk Factors by Cohort*

Analysis	Significant Environmental risk factor	Used in MCS	Used in NCDS	Used in USoc
Childhood rGE by time analysis	SES[2]	Yes	Yes	N/A
	Finance Issues[1]	Yes	Yes	
	Number of Rooms[2]	Yes	Yes	
	Tenure[2]	Yes	Yes	
	Smoking Mother[2]	Yes	Variable unavailable	
	Alcohol consumption Mother[2]	Yes	Variable unavailable	
	Alcohol consumption Father[1]	Yes	Variable unavailable	
	Marital status[2]	Yes	No longitudinal data	
	Mother takes child for walks[1]	Yes	Yes	
	Father takes child for walks[1]	Yes	Yes	
	Alcohol Mother[1]	Yes	Variable unavailable	
	Employment[1]	No longitudinal data	Yes	
	Mother's interest in child's education[2]	No longitudinal data	Yes	
	Father's involvement in childcare[2]	No longitudinal data	Yes	
	Father's interest in child's education[2]	No longitudinal data	Yes	
	Mother reads to child[1]	Yes	No longitudinal data	
	Father reads to child[1]	Yes	No longitudinal data	
	birthweight[1]	No longitudinal data	No longitudinal data	
	Mother's age[1]	No longitudinal data	No longitudinal data	

	Housing Issues[1]	No longitudinal data	No longitudinal data	
	Domestic tension[1]	No longitudinal data	No longitudinal data	
Adulthood rGE by time analysis	SES[1]	N/A	Yes	Yes
	Number of Rooms[2]		Yes	Yes
	Tenure[2]		Yes	Yes
	Finance Issues[2]		Variable unavailable	Yes
	Marital status[2]		Yes	Yes
	Employment[2]		Yes	Yes
	Income[2]		Variable unavailable	Yes
	Smoking[1]		Yes	Variable unavailable
Childhood vs adulthood rGE by time analysis	Family SES in childhood vs SES of individual in adulthood	N/A	Yes	N/A
	Father's employment in childhood vs employment of individual in adulthood		Yes	
	Family number of bedrooms in childhood vs number of bedrooms of individual in adulthood		Yes	
	Family tenure in childhood vs tenure of individual in adulthood		Yes	
	Marital status of mother at birth vs marital status of individual in adulthood		Yes	
	Mother's smoking behaviour prior and during pregnancy vs smoking behaviour of individual during adulthood		Yes	

Note: *Adapted from* Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC. [1] identified as significant environmental risk factor in Chapter 3 or 4, [2] identified as significant environmental risk factor after multiple testing in Chapter 3 or 4. Any significant environmental risk factors which correlated with the genetic risk for SCZ or MDD from Chapter 3 or 4 which were available as childhood and adulthood measures in NCDS were selected for the childhood vs adulthood rGE by time comparison.

5.3.2 Genetic Processing and PRS creation

All genetic processing steps, including QC, imputation and post-imputation QC as well as the PRS creation for all three cohorts (MCS, USoc and NCDS) are described in detail in section 2.4 ('Genetic data') in Chapter 2.

In the end, a total of 7,280 children (including 6,874 mothers and 4,322 fathers) from MCS, 7,384 individuals from USoc as well as 5,288 participants from NCDS remained.

5.3.3 Data Analysis

5.3.3.1 Data Sweeps

Firstly, we utilised phenotype data from the MCS from 9 months up until age 14 as well as childhood data from birth to age 16 from NCDS for our rGE across childhood analysis. Secondly, for our rGE across adulthood analysis we used nine data sweeps from USoc from individuals aged 16 years or over as and adulthood data from NCDS from age 23 up until age 55. Thirdly, in order to compute our comparison of rGE in childhood versus adulthood we utilised data from birth up until age 55 from NCDS.

5.3.3.2 Interaction Models

Minimum sample sizes for all three cohorts were generated using G*Power v3.1.9.6 (Faul et al., 2009). All data analyses were performed in Stata v12.1 (StataCorp, 2011). We used correlation matrices for SES and full descriptive statistics which were originally run as part of Chapters 3 and 4 to assess whether any environments were underpowered. For the rGE across childhood and adulthood analyses, environmental factors at multiple timepoints were combined into logistic and linear longitudinal models (with either mixed or random effects) before being fitted with full factorial two-way interactions between time and the PRS which

were both fitted as continuous variables. Only the child PRS was used for MCS. Childhood and adulthood environmental factors were coded binary (0 = childhood, 1 = adulthood) and added to the interaction models instead of the time variable for our childhood vs adulthood comparison in NCDS. All interactions used sex, the top PCs and birth year for USoc as covariates. The regression beta coefficient (β) was used to assess changes in rGE strength, whereby a positive β suggested an increase and a negative β a decrease in strength of rGE associations across time.

All interaction results across all three cohorts (80 calculations at PRS 7 thresholds) were corrected for multiple testing with the Benjamini-Hochberg correction with an adjusted α = (p-value rank divided by the total number of outputs) * 0.05. Results were deemed statistically significant if at least one p-value threshold had met the multiple testing correction. The ranking of all results with the Benjamini-Hochberg correction is displayed in Appendix 22.

Sensitivity analyses were calculated for any significant findings which survived the Benjamini-Hochberg correction by adding the maternal and/or paternal PRS as covariates for MCS, excluding participants with clinical depression or psychiatric problems for USoc as well as individuals with self-reported depression in NCDS. No sensitivity analysis was performed for any SCZ USoc results due to a lack of SCZ diagnosis or symptoms in the dataset. To assess whether sensitivity results were statistically different from the original interaction models, we interacted all independent variables with the parental PRS for MCS or the SCZ/MDD symptoms for either USoc or NCDS to calculate the Wald Chi-squared test statistics.

A detailed description of all data analyses which were performed can be found in section 2.7.4 (Chapter 5 – Paper 3 (rGE in childhood)) in Chapter 2.

5.4 Results

5.4.1 Descriptive Statistics and Power Calculation

All three community cohorts were sufficiently powered in line with our power calculation, with the exception of SES at data sweep 8-9 in USoc and for NCDS, employment at age 23, father's interest in the child's education at 7, 11 and 16 years of age as well as tenure of accommodation at age 23 and 55.

Moreover, we identified some differences between the whole cohorts and the genotype samples as outlined in Chapters 3 and 4. Specifically, the genotyped MCS sample had more individuals in SES class 1 at data sweeps 1, 3 and 4, parents living in rented accommodation at data sweep 6, higher number of mothers who smoked at data sweep 1 and lower proportion of unmarried parents at all data sweeps. Additionally, individuals from the genotyped sub-sample had higher odds of being unmarried at data sweep 1 and had a decreased number of bedrooms at all data sweeps in USoc. Besides, a higher number of parents rented accommodation in the genotyped sample at age 7 in NCDS.

5.4.2 rGE Results across Childhood

The first objective of Chapter 5 was to assess changes in rGE strength over time for each longitudinal environmental exposure and each p-value threshold across childhood in MCS and NCDS.

Firstly, for MCS we identified that the association between the genetic liability to SCZ and rented accommodation got weaker across childhood. In other words, tenure of accommodation is less correlated with the PRS for SCZ as children get older. Additionally, the strength of rGE between low SES and the genetic vulnerability to SCZ and MDD increased across childhood. That means that low SES was more strongly associated with an increased genetic risk to either psychopathology as children became older. However, only the change in

rGE between the PRS for SCZ and rented accommodation survived the Benjamini-Hochberg correction. Moreover, according to our sensitivity analysis, this change in rGE was not confounded by the parental PRSs. See *Figure* 14.

Secondly, for NCDS, the strength of rGE between low number of bedrooms and the genetic risk for SCZ increased across childhood, meaning that as children grow up low number of bedrooms is more strongly correlated with the genetic liability to SCZ. However, this finding did not survive multiple testing correction. See *Figure* 15.

All other rGEs for either MCS or NCDS did not change and remained stable across childhood.

The full MCS results are provided in Appendix 18 and the full NCDS childhood results are provided in Appendix 20.

The sensitivity and interaction analyses results for MCS are displayed in Table 19 for three PRS thresholds (0.01, 0.5 and 1).

Table 19: *Sensitivity and Interaction Analysis in the MCS Sample*

Environment	Threshold z-scored	Sensitivity			Interaction	
		Beta	95%CI	P-Value	Wald chi-square	p-value
SCZ						
Child Tenure-by-time	0.01	-0.07	-0.12--0.02	5.58E-03	0.95	3.31E-01
	0.5	-0.08	-0.13--0.02	7.47E-03	1.95	1.63E-01
	1	-0.08	-0.13--0.02	8.34E-03	1.47	2.26E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), MCS = Millennium Cohort Study, Beta = Beta Coefficient, CI = Confidence Interval

Figure 14: *rGE Changes across Childhood (Interaction Terms PRS*Time) - MCS*

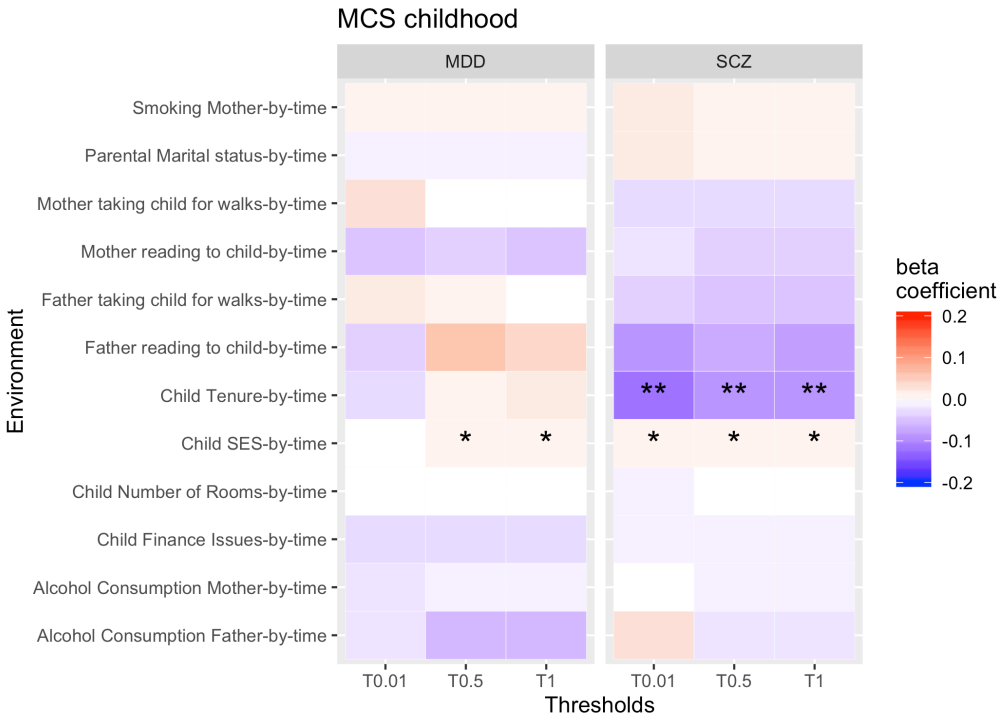
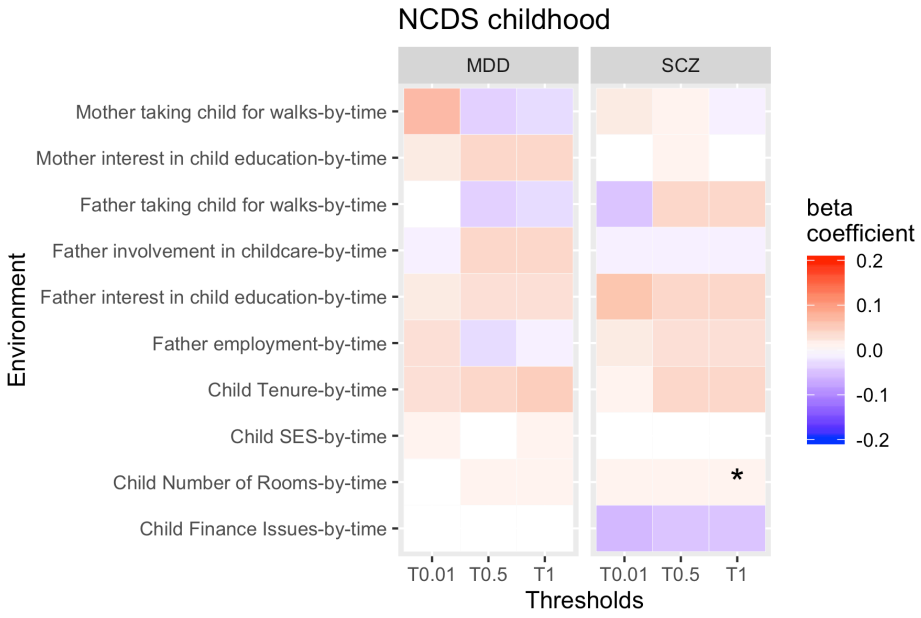


Figure 15: *rGE Changes across Childhood (Interaction Terms PRS*Time) - NCDS*



Note: *Adapted from* Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing. Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted). Heatmaps were created in R v3.5.0 (R Core Team, 2018)

5.4.3 rGE Results across Adulthood

The second goal of Chapter 5 was to explore rGE changes over time for each p-value threshold and longitudinal environmental exposure in adulthood in USoc and NCDS.

Firstly, in USoc, we identified that the association between low number of bedrooms and the genetic liability to SCZ as well as MDD increased across adulthood. That means that as adults grow older, the association between low number of bedrooms and the genetic risk for either psychopathology got stronger. Although, we would like to point out that the effect sizes were very small and only the rGE changes for SCZ remained statistically significant after applying the Benjamini-Hochberg correction. Further, we identified that the rGE between the genetic risk for MDD and low SES decreased, whilst the correlation with rented accommodation increased across adulthood. That means that tenure of accommodation is more strongly correlated, whilst SES is less strongly associated with the genetic liability to MDD as adults get older. Both of our findings survived correction for multiple testing.

Overall, our sensitivity analyses in USoc highlighted that the change in strength of rGE between tenure of accommodation and the PRS for MDD is confounded by the presence of clinical cases. That means, that this result was largely driven by individuals with depression. See *Figure* 16.

Secondly, for NCDS, we established that the rGE between the genetic liability to SCZ and higher SES increased over time, whilst the association with rented accommodation decreased in adulthood. That means that an increased PRS for SCZ is less associated with tenure of accommodation, but more strongly correlated with higher SES as adults get older. Additionally, we found that the association between being single and the genetic liability for SCZ increased across adulthood. On the other hand, the correlation between being married/or in a relationship and the PRS for MDD also increased across adulthood. In other words, the strength of rGE between the genetic susceptibility to either psychopathology and marital status

gets stronger as individuals age. Unfortunately, none of our NCDS findings remained after applying the Benjamini-Hochberg correction. See *Figure* 17.

The strength of rGEs for all other associations did not change and remained stable across adulthood for USoc and NCDS.

The full USoc results are provided in Appendix 19 and the full NCDS adulthood results are provided in Appendix 20.

The sensitivity and interaction analyses results for USoc are displayed in Table 20 for three PRS thresholds (0.01, 0.5 and 1).

Table 20: *Sensitivity and Interaction Analysis in the USoc Sample*

Environment	Threshold z-scored	Sensitivity			Interaction	
		Beta	95%CI	P-Value	Wald chi-square	p-value
MDD						
Adult SES-by-time	0.01	0	-0.01-0	8.24E-02	1.75	1.86E-01
	0.5	-0.01	-0.01-0	2.36E-02	0.08	7.71E-01
	1	-0.01	-0.01-0	1.98E-02	0.06	8.08E-01
Adult Tenure-by-time	0.01	0.14	0.07-0.22	3.14E-04	8.46	3.60E-03
	0.5	0.16	0.09-0.24	2.04E-05	7.64	5.70E-03
	1	0.16	0.09-0.23	2.49E-05	1.15	2.84E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), USoc = Understanding Society, Beta = Beta Coefficient, CI = Confidence Interval

Figure 16: *rGE Changes across Adulthood (Interaction Terms PRS*Time) - USoc*

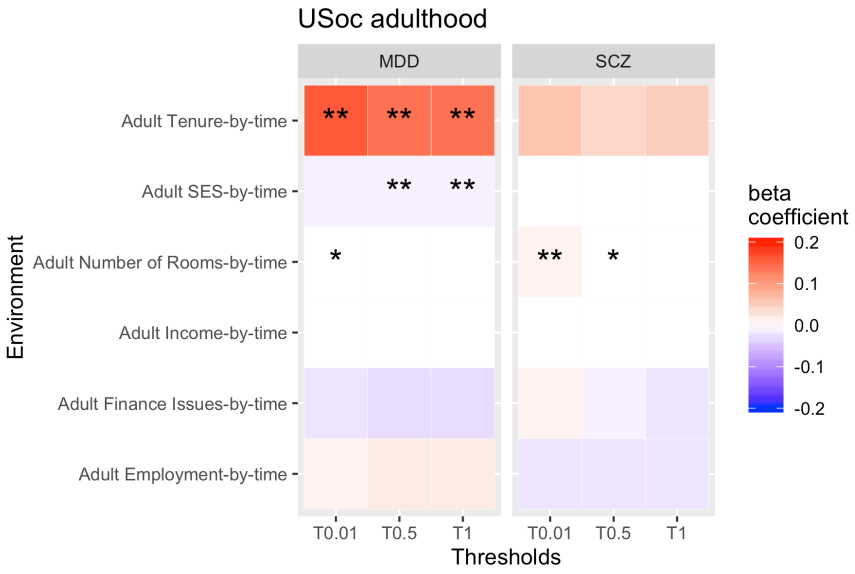
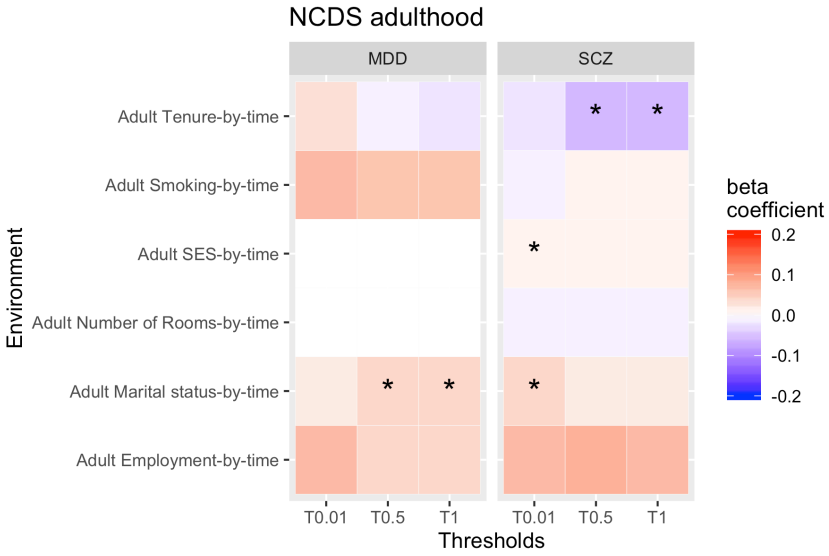


Figure 17*: rGE Changes across Adulthood (Interaction Terms PRS*Time) - NCDS*



Note: *Adapted from* Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC. * * = significant, ** = significant after correcting for multiple testing. Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted). Heatmap were created in R v3.5.0 (R Core Team, 2018)

5.4.4 Comparison between Childhood and Adulthood

The third aim of Chapter 5 was to explore whether there are significant differences in the strength of rGEs between childhood and adulthood in participants from NCDS.

The results for the childhood versus adulthood comparison highlighted that the strength of rGE associations between a higher SES and the genetic risk for SCZ was stronger in adulthood compared to childhood. On the other hand, the strength of rGE between low family SES in childhood versus adulthood and the genetic susceptibility to MDD increased over time and was stronger in adulthood compared to childhood. Additionally, the rGE between the genetic susceptibility for MDD and unemployment decreased over time. In other words, the correlation between father's unemployment status and the PRS for MDD was stronger, compared to the adult individual's unemployment status. Lastly, the strength of rGE associations between rented accommodation in the family home versus the adult home and the genetic liability to MDD got weaker over time. That means that this rGE was stronger in childhood.

Overall, all of our NCDS findings, except the rGE between unemployment and the PRS for MDD, remained after applying the multiple testing correction. See *Figure* 18.

According to our sensitivity analyses none of our findings were confounded by clinical cases.

In line with our findings for our rGE across childhood and adulthood analyses, we found that the majority of rGEs remained stable between childhood and adulthood and did not change in NCDS.

The full NCDS childhood vs adulthood results are provided in Appendix 20.

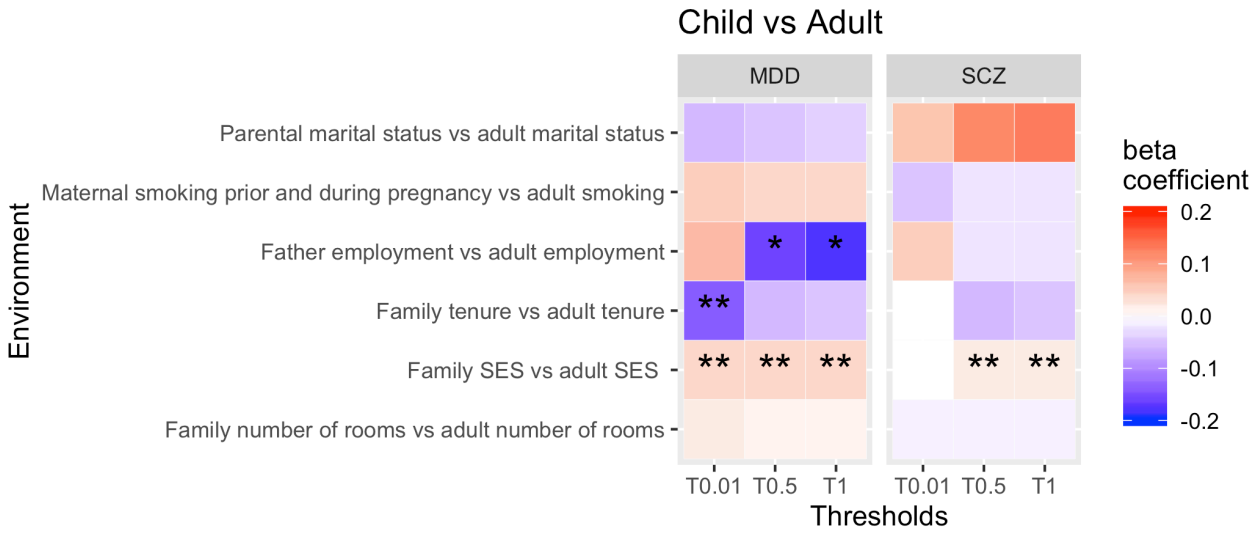
The sensitivity and interaction analyses results for NCDS are displayed in Table 21 for three PRS thresholds (0.01, 0.5 and 1).

Table 21: *Sensitivity and Interaction Analysis in the NCDS Sample*

Environment	Threshold z-scored	Sensitivity			Interaction	
		Beta	95%CI	P-Value	Wald chi-square	p-value
SCZ						
Family SES vs adult SES (0=child, 1=adult)	0.01	0	-0.04	8.82E-01	0.15	7.00E-01
	0.5	0.03	0.01-0.05	8.77E-04	1.17	2.80E-01
	1	0.03	0.01-0.05	7.05E-04	1.19	2.76E-01
MDD						
Family SES vs adult SES (0=child, 1=adult)	0.01	0.04	0.02-0.06	2.31E-06	0.16	6.90E-01
	0.5	0.05	0.03-0.07	5.22E-08	2.69	1.01E-01
	1	0.05	0.03-0.07	5.94E-08	3.06	8.01E-02
Family tenure vs adult tenure (0=child, 1=adult)	0.01	-0.2	-0.28--0.11	3.76E-06	0.25	6.15E-01
	0.5	-0.1	-0.22--0.05	1.55E-03	1.08	2.98E-01
	1	-0.1	-0.21--0.05	1.71E-03	1.43	2.31E-01

Note: * = significant, ** = significant after correcting for multiple testing, Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted), NCDS = 1958 National Child Development Study, Beta = Beta Coefficient, CI = Confidence Interval

Figure 18: *Childhood vs Adulthood Comparison in NCDS*



Note: *Adapted from* Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC. * = significant, ** = significant after correcting for multiple testing. Not all thresholds have been included (0.1, 0.2, 0.4, 0.4 have been omitted). Heatmap was created in R v3.5.0 (R Core Team, 2018)

5.5 Discussion

The objective of Chapter 5 was to explore whether the strength of rGE associations changes across childhood and adulthood featuring established psychosocial and environmental risk factors as well as the PRS SCZ and MDD from MCS, USoc and NCDS. This chapter builds on Chapters 3 and 4 utilising the same data (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022).

5.5.1 rGE across Childhood

Results highlighted that rGE associations for SCZ as well as MDD appear relatively stable over time across childhood, with the exception of the change in strength of rGE between the PRS for SCZ and tenure of accommodation. That means that, overall, the strength of rGE did not change between birth (NCDS)/9months (MCS) up until 14 (MCS) or 16 (NCDS) years of age for most of the rGE correlations.

Whilst studies propose that rGE associations may increase over time and become stronger as children start to actively modify and select their own environments based on their genetic susceptibilities (Jaffee & Price, 2007; Plomin et al., 1977), such as Newbury et al. (2020) who discovered rGE changes for indicators of SES which were associated with the genetic susceptibility to SCZ and MDD in childhood and adolescence, out findings propose that the rGE shift from *passive* to either *evocative* or *active* rGE does not yet take place in children.

Specifically, we only detected one statistically significant result whereby the strength of rGE between rented accommodation and the PRS for SCZ became weaker across childhood. Given that our sensitivity analysis proposed that this change in rGE strength cannot be attributed to *passive* rGE, it is therefore possible, that our finding reflects changes in

sociocultural environments, for instances homeownership due to the changes in financial support and expansion of mortgage markets (Aalbers, 2008). Another possible reason for our lack of findings could be explained by the fact that our MCS and NCDS samples only included phenotype data of participants up to the age of 14 (MCS) or 16 (NCDS). However, it is also conceivable that these environmental factors did, in fact, not change for adolescents in Britain during this period.

Overall, it is important to highlight that children and adolescents undergo rapid changes as they move from one developmental stage to another, and thus detailed and specific environmental and phenotypic measures are required in order reliably identify these changes. (Knafo & Jaffee, 2013). Therefore, available phenotypic data from MCS and NCDS may have lacked specificity in order to identify these changes in rGE across childhood and adolescence.

Finally, it is also possible that the psychosocial and environmental factors are cohort specific (Atingdui, 2011) which consequently may not highlight universal changes in rGE strength in early developmental periods.

5.5.2 rGE across Adulthood

First of all, we found that the rGE strength between low number of bedrooms in the family home and the genetic risk for SCZ got stronger across adulthood in USoc. It is possible, that this finding signifies the increasing urbanisation which is known to be implicated in the aetiology of SCZ (Pedersen & Mortensen, 2001). Nevertheless, it is also important to point out that the effect sizes for this finding were very small and thus caution should be taken when interpreting these results.

Although research proposes that time-dependent effects on our genes and environments can have an impact on the development of complex psychiatric disorders (Jaffee & Price, 2007), it is also plausible that these changes in strength of rGE could be attributed to

generational changes in environmental risk through a 'cohort effect', given that this finding was only detected in USoc but not in NCDS.

Moreover, our results highlighted that the impact of the genetic liability to MDD on known environmental risks only resulted in a change of rGE strength for tenure of accommodation and SES across adulthood and was only detected in USoc. Specifically, the correlations between low SES and the PRS for MDD got weaker over time as adults select themselves into environments through *active* rGE. Nevertheless, it is also important to point out that whilst the strength of rGE between rented accommodation and the genetic vulnerability to MDD increased as adults got older, our sensitivity analysis suggested that this result may have been confounded by the presences of clinical cases with depression. In other words, it is possible that this change in rGE strength may in fact be a spurious finding which was is largely driven by individuals with depression and thus should be interpreted as such.

Overall, we identified no other changes in rGE strength for the remaining associations in participants from USoc who were of mixed ages, nor in cohort members from the NCDS who were followed from the age of 23 up until the age 55. But then again, studies may require larger sample sizes in order to detect rGE changes (Thapar & Riglin, 2020).

In sum, the strength of rGE associations remained stable for the majority of selected psychosocial and environmental risk factors for both psychopathologies.

5.5.3 Comparison of Childhood vs Adulthood in NCDS

Our findings proposed that changes in rGE strengths between the genetic risk for SCZ as well as MDD and family SES in childhood versus individual's SES in adulthood was stronger in adulthood compared to childhood. Contrarywise, the association between family tenure in childhood versus individual's tenure in adulthood and the genetic susceptibility to MDD was stronger in childhood. One possible explanation for this finding is that

transgenerational transmission could play a confounding part in rGE associations being stronger in children (Branje et al., 2020).

Further, shared genetic inheritance between offspring and their biological parents as well as parents providing a home environment which is consistent with their own genetic make-up could consequently give rise to similarities in transgenerational behaviours.

Nevertheless, conversely to our own results, one Dutch study which investigated the correlation between wellbeing and depressive symptoms in 43,427 twins between the ages of 7 and 99 years from the Netherlands Twin Registry identified that, genetic influence got stronger from adolescence onwards (Baselmans et al., 2018). Specifically, the study highlighted that environmental factors play an important part in explaining the association between depressive symptoms wellbeing in childhood only, whereas from adolescence onward, genetic effects account for substantial proportion in the correlation.

Bearing in mind that the NCDS cohort members were born in 1958 and entered into early adulthood in the 1980's, it is plausible that societal changes, such as the UK Housing Act which was introduced under the Thatcher legislation in order to increase homeownership (Tunstall, 2003) could also have contributed to our finding. However, we would also like to highlight, that the development of MDD from one developmental stage to the next is complex and influenced by genetic and environmental influences.

Further, whilst our childhood versus adulthood comparison in NCDS was specifically focused on changes in the strength of rGE from birth up until the individuals reached 55 years of age, it is important to point out that no phenotypic data was available between age 16 and age 23 which consequently did not allow us to differentiate between every developmental period.

On a final note, the child's environmental risk refers predominately to parental or family environments, whereas the environmental risk in adulthood is referring to the cohort

members themselves and thus, these may not be adequately comparable. Therefore, it is important to highlight that results from the childhood versus adulthood comparison in NCDS should be considered exploratory and should aim to inspire future research to assess rGE correlations across all development windows.

5.5.4 Comparison of SCZ and MDD

The last aim of Chapter 5 was to identify whether any changes in strength of rGE differed between the two psychopathologies. In fact, we identified that our findings for SCZ and MDD did not match between children and adults.

Firstly, we discovered one statistically significant change in the strength of rGE association for SCZ in childhood (tenure of accommodation), however, we did not identify any findings for MDD.

Further, Chapter 5 highlighted only one change in rGE strength over time in adulthood for SCZ (number of bedrooms), yet two changes of rGEs over time emerged for MDD (tenure of accommodation and SES).

Additionally, our NCDS comparison of childhood versus adulthood rGEs detected only one rGE change over time for SES which was similar between the two psychopathologies. On the other hand, the change of rGE strength for tenure of accommodation only changed for MDD and not for SCZ in our childhood versus adulthood comparison.

All in all, although it is possible that the mismatched findings between the two psychopathologies in childhood and adulthood could be explained by the fact that there is only a partial genetic overlap between SCZ and MDD, it is further conceivable that our findings reflect generational changes in environmental risk.

5.6 Limitations

Chapter 5 has many strengths, including the investigation of changes in rGE strength across childhood and adulthood as well as utilising three well-powered British community cohorts. However, we would like to point out several limitations.

The three community cohorts included individuals of different ages and generations. Specifically, MCS included children up to 14 years of age who were born within a 12-month period at the turn of the century, the USoc cohort included participants of mixed ages (aged 16 to 97 at data sweep 1) whereas cohort members from NCDS were all born in 1958 and were followed up until 55 years of age. Additionally, we only utilised environmental risk factors which were correlated with the genetic vulnerability to SCZ or MDD in Chapters 3 and 4. Consequently, environmental data did not match completely across the three samples (MCS, USoc and NCDS). Moreover, the longitudinal environmental data which was utilised from the cohorts was collected at different ages as well as different intervals. Besides, the comparison of childhood versus adulthood rGEs which was only performed in one cohort (NCDS) was unable to differentiate between late childhood and adolescence due to the lack of timepoints between the data collection at age 16 and the data collection at age 23. Moreover, descriptive statistics indicated that we were underpowered for several environmental risk factors in USoc and NCDS. We also identified some statistically significant differences between the whole cohort and the genotyped subsample for all three cohorts as outlined in section 5.4.1 (Descriptive statistics and power calculation). Lastly, we did not investigate whether gender differences play an active part in the stability of rGE.

5.7 Implications

Whilst research emphasises that the genetic liability to complex psychiatric disorders does not change throughout life, individual behaviours which consequently influence the

exposure to certain environments can change as individuals move from childhood, to adolescence and adulthood, with the effect of these exposures being further contingent on whether these take place in critical development periods (Halfon et al., 2014; Knafo & Jaffee, 2013). Consequently, rGE studies need to be longitudinal in nature in order to understand how environmental changes can influence psychiatric outcomes across time (Leve et al., 2010).

Regardless, we would like to highlight that the presence of rGE associations does not reject the probability that environmental exposure could have reciprocal or causal consequences on these complex psychiatric disorders (Knafo & Jaffee, 2013). If so, then the field of psychology has to further assess to which extent these environmental influences can form targeted interventions or even treatments for the psychopathological outcomes (Knafo & Jaffee, 2013).

However, overall, we detected few changes in the strength of rGE associations over time, with small effect sizes. To put this into perspective, the impact of our findings across the general population would be very small. In addition, using PRS for polygenic psychiatric disorders in a clinically meaningful way is still challenging due to the insufficient predictive power (Palk et al., 2019).

Lastly, findings further proposed that some of the changes in rGE may be the result of changes in cultural or environmental risk across several generations, which consequently highlights that the genetic risk for either psychopathology would overall have little impact on the general population.

5.8 Conclusion

Chapter 5 utilised genotypic and longitudinal phenotypic data from three well-powered generational cohorts (MCS, USoc and NCDS) in order to assess whether known rGE associations which were identified in Chapters 3 and 4 change across childhood and adulthood

for either SCZ or MDD. Firstly, our results emphasised that the strength of rGE for either psychopathology did largely not change in childhood, with the exception of one indicator for low SES for the PRS for SCZ. Secondly, rGE associations only changed across adulthood for one marker of urbanisation for SCZ as well as two indicators of low SES for MDD. Thirdly, when comparing rGE in childhood versus adulthood in NCDS, we detected that the association between SES and the genetic liability to both psychopathologies got stronger as individuals got older, whilst the correlation between rented accommodation and the PRS for MDD was stronger in childhood compared to adulthood. Fourthly, our findings emphasise that changes in the strength of rGE across the different developmental stages are likely disorder specific. Finally, the effect sizes for rGE changes across time were very small and thus results should be considered exploratory and interpreted with caution.

Chapter 6: Paper 4 – Systematic Review of rGE in SCZ and Depression

6.1 Overview

The research presented in this chapter has been submitted for publication and is currently under review:

Machlitt-Northen, S., Begum, S., Pluess, M. (2023). Gene-Environment Correlation in Schizophrenia and Depressive Disorders: A Systematic Review [Under Review]

This chapter presents the above manuscript.

Behavioural and molecular genetics studies as well as results from Chapters 3, 4, and 5 provide evidence for rGE associations between the genetic susceptibility for SCZ or depressive phenotypes and environmental risk factors.

The main objective of Chapter 6 was to conduct a systematic literature review including our own publications from Chapters 3, 4 and 5, in order to investigate empirical research which aimed to explore rGE associations for either SCZ or depressive phenotypes, with a special focus on studies measuring the genetic susceptibility as PRS. Secondly, we wanted to assess whether any identified rGE for either psychopathology differed between the two disorders given the incomplete genetic overlap.

We searched Pubmed, Scopus, APA PsycInfo, APA PsycArticles, Ovid Medline(r), Embase and Web of Science on 30th May 2022 for any empirical studies in humans which reported psychosocial or environmental risk factors and the PRS for either SCZ or depression.

A total of 641 non-duplicate records were retrieved, whereby 18 studies, including Chapters 3, 4 and 5 met the inclusion criteria with a final sample size of 361,475 unique participants.

We followed the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (PRISMA) guidelines throughout.

Our findings suggest that rGE results for SCZ and depressive phenotypes are similar between the two psychopathologies. Specifically, participants with an increased PRS for either disorder were more likely to have parents who were single, live in urban areas and had increased odds of being adopted.

Nevertheless, Chapter 5 also highlighted some contradicting results between the genetic risk for SCZ and depression and associations with adversity, whereby some included articles identified correlations whilst other studies did not identify any associations.

Overall, our systematic review suggested that the genetic vulnerability to psychopathological outcomes is correlated with a wide range of known psychosocial as well as environment risk factors, further highlighting that rGE plays an important part in the aetiology of mental disorders.

6.2 Introduction

6.2.1 Rationale

Results from behavioural and molecular genetics studies as well as our findings from Chapters 3, 4 and 5 provide evidence for rGE associations between the genetic susceptibility for SCZ or depressive phenotypes and environmental risk factors.

The identification of either a causal environmental cascade or a true rGE association would clearly determine the type of medical intervention required and thus has important implications for the treatment of psychological conditions.

In light of our own rGE findings, we wanted to better understand whether results from Chapters 3, 4, and 5 are in line with other rGE research, featuring PRS for SCZ or depression, by conducting a systematic review of the current literature.

6.2.2 Objectives

The main aim of Chapter 5 was to conduct a systematic literature review which describes current empirical studies investigating rGE in either SCZ or depression using PRS in individuals of all ages and across all developmental stages, including our own rGE findings. We have included all forms of depressive phenotypes in the systematic review, such as major depressive disorder and depressive symptoms, which are being referred to as just 'depression' throughout this systematic review.

Secondly, given that molecular genetics studies stress that some psychopathological outcomes share some risk loci between them (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018), we wanted to further explore whether there were any distinct differences in rGE results between SCZ and depression.

Based on findings from our previous studies we hypothesised that we would identify other rGE studies which identified correlations between known environmental risk factors and the PRS for either SCZ or depression, but that these would differ for the two psychopathologies given the small genetic overlap.

6.3 Methods

6.3.1 Registration and Protocol

Out study was pre-registered in PROSPERO, an international prospective register of systematic reviews and conducted according to our outlined protocol (ID: CRD42022332793). Moreover, we followed the 2020 PRISMA guidelines throughout (Page et al., 2021).

6.3.2 Eligibility Criteria

Our systematic review only included empirical research, including pre-prints such as our own pre-prints from Chapters 3, 4, and 5 at the time which have been published since, which reported environmental risk factors as well as the PRS for either SCZ or depression or one of their common symptoms, including psychosis and hallucinations. We considered studies from any county as well as all human participants without any age or publications year restrictions.

The following were excluded, published abstracts, conference abstracts, conference papers, review papers and meta-analysis, non-English studies as well as any publications where outcome measures were not relating to either SCZ or depression.

6.3.3 Information Sources

On 30th May 2022, we searched Scopus Pubmed, Scopus, APA PsycInfo, APA PsycArticles, Ovid Medline(r), Embase and Web of Science for articles using keyword the following search advanced search keywords (any field): 'gene-environment correlation' OR 'rGE' OR "gene-environment covariation' AND 'schizophrenia' OR 'schizophrenic' OR 'hallucination' OR 'psychosis' OR 'psychotic' OR 'depression' OR 'depressive' AND 'polygenic risk score' OR 'polygenic score' OR 'PRS' OR 'genome-wide association study' OR 'genome-wide association studies' OR 'GWAS' OR 'PGS' OR 'PGSs' OR 'genetic risk score' OR 'polygenic index'.

6.3.4 Searching Strategy

In order to confirm the number of records, each information sources as described in section 6.3.3 (Information Sources) were searched first by one independent reviewer (S.M.N)

and followed by a second independent reviewer (S.B). The total number of records for each of the data sources is described in Table 22.

Table 22: *Records by Data Source*

Data source	Reviewer 1 (S.M.N)	Reviewer 2 (S.B)
Pubmed	43	43
Scopus	598	598
APA PsycInfo	39	39
APA PsycArticles	52	52
Web of Science	53	53
Embase	62	62
Ovid Medliner (excluding Ovidbooks/journals)	25	25
Combined		872
Pre-prints		3
Duplicates removed		231
Total		**641**

Notes: Number of records retrieved by data source – accessed 30th May 2022

6.3.5 Selection Process

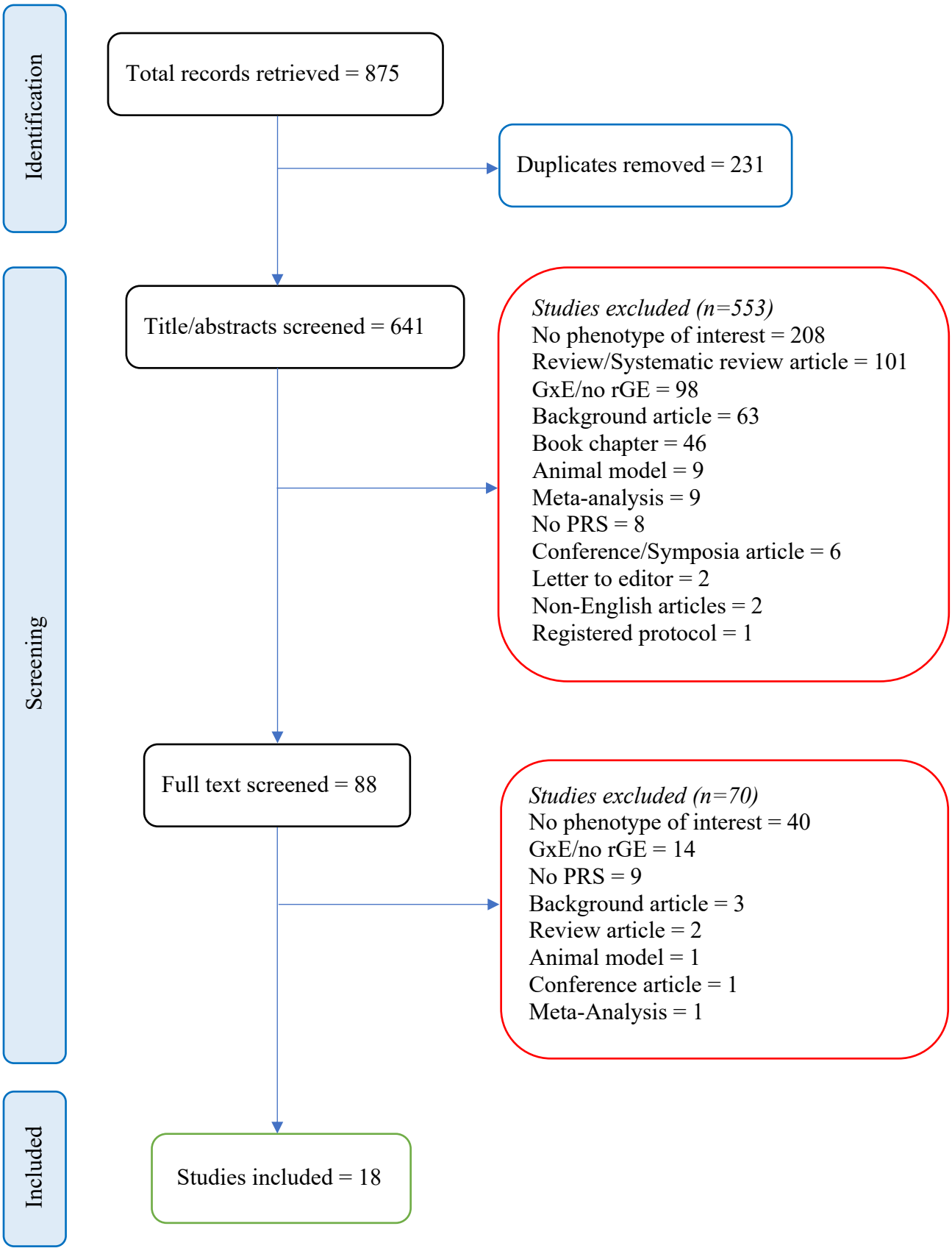
The retrieved titles and abstracts, as well as the full texts if required were independently screened against the inclusion/exclusion criteria by the two independent reviewers (S.M.N and S.B.). All ratings were blinded. Once all individual records were screened, all reviewers' ratings were unblinded. Any opposing ratings were resolved through discussion.

6.3.6 Data Collection

Both reviewers (S.M.N and S.B.) performed the data extraction of the included articles. One reviewer performed the data extraction, with the second reviewer checking the extraction and vice versa. Any articles which were deemed as not fulfilling the inclusion criteria by both

reviewers during the data extraction process were further excluded. Disagreements were additionally resolved through discussions with a third reviewer (M.P.) (see Figure 19).

Figure 19: *Study Selection Flow Chart*



6.3.7 Data Items

Out of the included 18 articles, we extracted important study features, including basic cohort characteristics, any statistical analyses which were performed as well as whether a correction for multiple testing was applied. Findings were presented in tables corresponding to our data extraction. For the purpose of this systematic literature review, only rGE results for SCZ or depression were extracted, even if additional psychopathological outcomes were investigated in any of the included articles.

The following data was extracted from each included publication: Author(s), year of publication, whether rGE was investigated in SCZ or depression, cohorts used, the sample population (including ethnicity, gender distribution, age), how PRS were generation, the GWAS summary statistics used, environmental measures, which statistics model was applied, information about the multiple testing correction and the main results, such as odds ratios, hazard ratio, standardised or non-standardised regression coefficients, correlation coefficients, or other effect measures.

6.3.8 Quality Risk of Bias Assessment Tool

Each included article was independently assessed for quality by either reviewer 1 (S.M.N) or reviewer 2 (S.B.) by utilising the National Institutes of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Any disagreements were resolved through discussion (See Table 24).

6.3.9 Effect Measures

The main effect measure identified was the strength of the correlation between the PRS for either SCZ or depression and environmental risk factors, expressed as either the regression/correlation coefficients or odd ratios. Further, we also extracted information on cohort characteristics as well as GWAS summary statistics which were used.

6.3.10 Synthesis Methods

For all included studies we summarised the cohort characteristics and associated basic summary statistics in a tabular format. All included articles were divided into two separate groups, namely a) studies investigation rGE associations in SCZ and b) studies investigating rGE associations in depression. rGE findings were summarised in a narrative synthesis format and presented for each psychopathology separately. We did not conduct a meta-analysis given the low number of included articles, the inconsistent statistical reporting as the due to the heterogeneity across the included studies.

6.3.11 Reporting Bias Assessment and Certainty Assessment

We referred to cited references in the included articles in case of any unclear or missing information. Certainty assessment for the included articles entailed the assessment and evaluation of the limitations in the studies.

6.4 Results

6.4.1 Study Selection

We retrieved 875 records which included three of our own studies (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022; Sandra Machlitt-Northen et al.,

2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022). In order to remove duplicates, all records were imported into Endnote (Endnote team, 2019). A total of 641 non-duplicates were further imported into a systematic review software, called Rayyan (Ouzzani et al., 2016). The two independent reviewers (S.M.N. and S.B.) then screened the final 641 unique titles and abstracts individually in Rayyan, in line with the inclusion & exclusion criteria as described in section 6.3.2 (Eligibility criteria). Overall, 553 articles were omitted. Full texts were screened for the remaining 88 studies, of which a total of 70 articles were excluded based on our eligibility criteria. Finally, we downloaded the full texts for the included 18 articles. Figure 19 describes the full screening workflow.

6.4.2 Study Characteristics

Overall, out systematic review included a total of 361,575 unique participants across 18 studies which reported rGE associations for SCZ and depression, featuring PRS. Table 23 describes the basic study characteristics. A total of six articles explored rGE in SCZ, whilst four studies investigated rGE in depression, with eight articles describing rGE across both psychopathologies. All of our 18 included articles were published in the last decade, ranging from 2016 (Trotta et al., 2016) and all the way to 2022 (Feurer et al., 2022; Peel et al., 2022). Sixteen European cohorts were utilised across the 18 empirical studies, including the 1958 National Child Development Study (NCDS) (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022; Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022), the UK Biobank (Coleman et al., 2020; Lehto et al., 2020) and the Twins Early Development Study (TEDS) (Krapohl et al., 2017; Peel et al., 2022). The majority of articles made use of cohorts with mainly European ancestry. The total cohort sizes varied significantly, spanning from a total sample size (n) of n = 180 (Feurer et al., 2022) to n = 243,480 (Lehto et al., 2020). Overall, the ratio of males to

females different widely between the included articles. For example, one study utilised a sample which was made up of 38.5% females (Aas et al., 2021) whilst another study included 69% females (Coleman et al., 2020). Besides, the final articles included participants across all age groups, whereby we identified seven articles exploring rGE across childhood (Bolhuis et al., 2021; Ensink et al., 2020; Feurer et al., 2022; Krapohl et al., 2017; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022; Peel et al., 2022; Sallis et al., 2021), one study was conducted in adolescence (Su et al., 2018) with another assessing rGE in adolescents and young adults (Pries et al., 2020), a total of nine studies were conducted in adults (Aas et al., 2021; Coleman et al., 2020; Das, 2019; Lehto et al., 2020; Sandra Machlitt-Northen et al., 2022; Paksarian et al., 2018; Sund et al., 2021; Trotta et al., 2016) with one studies spanning across all development windows (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022).

Table 23: *Included Articles - Study Characteristics*

Author(s)	Year of publication	SCZ or Depression	Cohorts used	Sample size	Gender distribution	Age (in years)	Ethnicity
Aas et al	2021	SCZ	European Network of National Schizophrenia Networks Studying Gene–Environment Interaction	1,074 (384 first-episode psychosis cases, 690 controls)	Cases: females 38.5% Controls: females 53.1%	Cases: mean=31.8 Controls: mean=38.2	European
Bolhuis et al	2021	SCZ Depression	Discovery: Generation R Study Control: Avon Longitudinal Study of Parents and Children (ALSPAC)	Generation R: 1,901 ALSPAC: 3,641	Generation R: females 50.3%	Generation R: mean (SD)=9.69 (0.26)	European
Coleman et al	2020	SCZ Depression	UK Biobank	92,957 (29,475 cases, 63,482 controls)	Cases: females 69% Controls: females 48.6%	Cases: mean (SD)=62.3 (7.5) Controls: mean SD=64.9 (7.6)	European
Das	2019	Depression	Health and Retirement Study	4,644	females 57.3%	Over 50	European
Ensink et al	2020	SCZ Depression	Amsterdam Born Children and their Development study (ABCD)	1,154 children	Not available	mean (SD) at timepoint 1= 5.11 (0.2) mean (SD) at timepoint 2= 11.55 (0.3)	European
Feurer et al	2022	Depression	community cohort for a 2-year longitudinal study on the intergenerational transmission of depression risk	180 youth + biological mothers	females 52.2%	8 - 14	European
Krapohl et al	2017	SCZ	Twins Early Development Study (TEDS)	6,710 unrelated individuals	Not available	birth to adolescence	European
Lehto et al	2020	SCZ Depression	UK Biobank	240,329 Not adopted, 3,151 Adopted in childhood	Not Adopted: females 54.45% Adopted: females 51.98%	Not Adopted mean (SD)=56.89 (8.01) Adopted 56.83 (8.45)	European

Machlitt-Northen et al [Chapter 3]	2022	SCZ Depression	1. 1958 National Child Development Study (NCDS) 2. Millennium Cohort Study (MCS)	NCDS: 5,288 MCS: 7,280 children (4,322 Fathers and 6,874 Mothers)	NCDS: females 50.45% MCS: females 51.02%	NCDS: birth - 16 MCS: 9 months - 14	NCDS: European MCS: largely European
Machlitt-Northen et al [Chapter 4]	2022	SCZ Depression	1. 1958 National Child Development Study (NCDS) 2. Understanding Society (USoc)	NCDS: 5,288 USoc: 7,384	NCDS: females 50.45% USoc: females 57.98%	NCDS: 23-55 USoc: over 16	NCDS: European USoc: European
Machlitt-Northen et al [Chapter 5]	2022	SCZ Depression	1. 1958 National Child Development Study (NCDS) 2. Millennium Cohort Study 3. Understanding Society	NCDS: 5,288 MCS: 7,280 children (4,322 Fathers and 6,874 Mothers) USoc: 7,384	NCDS: females 50.45% MCS: females 51.02% USoc: females 57.98%	NCDS: birth - 55 MCS: 9 months - 14 USoc: over 16	NCDS: European MCS: largely European USoc: European
Paksarian et al	2018	SCZ	Danish population registry data (consisting off the Danish Civil Registration System, the Danish Neonatal Screening Biobank, the Danish Psychiatric Central Research Register)	1,692 cases and 1,724 controls forming 1,549 complete matched pairs	Controls: females 44.54% Cases: females 44.54%	Controls: median (IQR)=20 (3.9) Cases: median (IQR)=20 (3.9)	European
Pries et al	2020	SCZ	TwinssCan	593 young adult twins and siblings	females: 61% males: 39%	Mean (SD)=17.60 (3.81)	European
Peel et al	2022	SCZ Depression	Twins Early Development Study (TEDS)	3,963 unrelated individuals	females 62%	1 - 16	European
Sallis et al	2021	SCZ	1. Avon Longitudinal Study of Parents and Children (ALSPAC) 2. Replication sample: Norwegian Mother, Father and Child Cohort Study (MoBa)	ALSPAC: 7,977 children (+ 8,196 mothers and 1,481 fathers) MoBa: 7,244	Not available	ALSPAC: 0-17 MoBa: trauma measured at age 8	ALSPAC: European MoBa: European

Su et al	2018	Depression	Collaborative Studies on Genetics of Alcoholism (COGA) Prospective Study	709 adolescents from 336 COGA extended families	females 49.4%	Mean (SD)=13.01 (1.14)	European American
Sund et al	2021	Depression	Nord-Trøndelag Health study (HUNT3)	41,198	females 56.2%	mean (SD)=54.4 (15.7)	European
Trotta et al	2016	SCZ	Genes and Psychosis (GAP) study	80 cases 110 controls	Cases: females 45% controls: females 47.3%	Cases: mean (SD)=28.8 (9.5) Controls: mean (SD)=30 (10.4)	European

Note: SCZ = Schizophrenia, SD = Standard Deviation, ALSPAC = Avon Longitudinal Study of Parents and Children, ABCD = Amsterdam Born Children and their Development study, TEDS = Twins Early Development Study, NCDS = 1958 National Child Development Study, MCS = Millennium Cohort Study, USoc = Understanding Society, MoBa = Norwegian Mother, Father and Child Cohort Study, HUNT3 = Nord-Trøndelag Health study, GAP = Genes and Psychosis study

6.4.3 Risk of Bias in Studies

All of our included empirical studies were assessed as 'good' according to our selected risk of bias assessment tool; the National Institutes of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies. Additionally, all included articles clearly described the research question as well as the cohort population. We did not identify any studies which reported follow-up dropout rates. Power, variance or effect measures as well as sample size were reported in nine studies. Lastly, only three of our included empirical studies stated participation rates of at least 50% of eligible participants. Table 24 described the full results for each study.

Table 24: *Quality Assessment: National Institutes of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies.*

Reference	Aas et al., 2021			Bolhuis et al., 2021			Coleman et al., 2020			Das, 2019			Ensink et al., 2020			Feurer et al., 2022		
Criteria	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**
1. Was the research question or objective in this paper clearly stated?	Y			Y			Y			Y			Y			Y		
2. Was the study population clearly specified and defined?	Y			Y			Y			Y			Y			Y		
3. Was the participation rate of eligible persons at least 50%?			NR			NR			NR	Y				N				NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y			Y			Y			Y			Y			Y		
5. Was a sample size justification, power description, or variance and effect estimates provided?			NR	Y			Y			Y				N			N	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y			Y			Y			Y			Y			Y		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y			Y			Y			Y			Y			Y		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y			Y			Y			Y			Y			Y		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and	Y			Y			Y			Y			Y			Y		

implemented consistently across all study participants?																		
10. Was the exposure(s) assessed more than once over time?		N			N			N			N			N			N	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y			Y			Y			Y			Y			Y		
12. Were the outcome assessors blinded to the exposure status of participants?			NR			NR			NR			NR			NR			NR
13. Was loss to follow-up after baseline 20% or less?			NR			NR			NR			NR			NR			NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y			Y			Y			Y			Y			Y		
Quality rating	Good			Good			Good			Good			Good			Good		

Reference	Krapohl et al., 2017			Lehto et al., 2020			Machlitt-Northen et al., 2022 (Chapter 3)			Machlitt-Northen et al., 2022 (Chapter 4)			Machlitt-Northen et al., 2022 (Chapter 5)			Paksarian et al., 2018		
Criteria	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**	**Yes**	**No**	**Other**
1. Was the research question or objective in this paper clearly stated?	Y			Y			Y			Y			Y			Y		
2. Was the study population clearly specified and defined?	Y			Y			Y			Y			Y			Y		
3. Was the participation rate of eligible persons at least 50%?		N			N			N			N			N				NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y			Y			Y			Y			Y			Y		
5. Was a sample size justification, power description, or variance and effect estimates provided?		N			N		Y			Y			Y				N	

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y			Y			Y			Y			Y			Y		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y			Y			Y			Y			Y			Y		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y			Y			Y			Y			Y			Y		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y			Y			Y			Y			Y			Y		
10. Was the exposure(s) assessed more than once over time?		N			N			N			N			N			N	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y			Y			Y			Y			Y			Y		
12. Were the outcome assessors blinded to the exposure status of participants?			NR			NR			NR			NR			NR			NR
13. Was loss to follow-up after baseline 20% or less?			NR			NR			NR			NR			NR			NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y			Y			Y			Y			Y			Y		
Quality rating	Good			Good			Good			Good			Good			Good		

Notes: *CD, cannot determine; NA, not applicable; NR, not reported

6.4.4 Results of Individual Studies

6.4.4.1 Overview of PRS Generation and Environmental Exposures

The selected environmental risk factors included parental risk factors, such as maternal and paternal age at birth (Ensink et al., 2020; Krapohl et al., 2018), adversity and childhood trauma (Bolhuis et al., 2021; Pries et al., 2020), socioeconomic indicators, such as tenure of accommodation (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) and urbanicity (Paksarian et al., 2018) as well as psychosocial risk factors, including single parenthood (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) or paternal involvement in childcare (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022). A total of 12 empirical studies utilised the GWAS summary statistics from the SCZ Psychiatric Genomics Consortium (PGC) (2014), whereas two articles used GWAS findings from Pardiñas et al (2018). On the other hand, GWAS summary statistics from the PGC for major depression disorder (MDD) from Wray et al (2018) where used by six of the included articles, with two studies utilising the 2019 GWAS results from Howard et al (2019). Conversely, five studies made use of the depression GWAS summary statistics from the Social Science Genetic Association Consortium (SSGAC) from Okbay et al (2016). Only eight of the included empirical studies corrected for multiple testing, with the Bonferroni correction having been used four time, the Benjamini–Hochberg correction and the Matrix Spectral Decomposition were both applied twice as well as one study which made use of the Sidák correction.

Table 25 describes the environmental measures, PRS creation and multiple testing correction for each of the included articles.

Table 25: *PRS Creation and Environmental Measures*

Author(s)	GWAS summary statistics for PRS	Environmental measures	Statistics model applied (including covariates)	Multiple testing correction
Aas et al (2021)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC	Psychotic disorders Childhood Adversity	Linear regression covariates: 10 PCs, sex, age and education level	Not specified
Bolhuis et al (2021)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC, MDD GWAS (Wray et al 2018) from PGC	Emotional and behavioural problems Childhood adversities	Poisson regression models/Linear regression models covariates: child, age, sex, 4 ancestry PCs	Not specified
Coleman et al (2020)	SCZ GWAS (Schizophrenia Working Group (2014) from PGC, MDD GWAS (Wray et al 2018) from PGC	Childhood Trauma	Logistic regression covariates: 6 ancestry PCs, initial assessment centre and genotyping batch	Bonferroni correction
Das (2019)	Depressive symptoms GWAS (Okbay et al. 2016) from SSGAC	Childhood Trauma Depressive symptoms	Logit and Multinomial Logit Models covariates: age, ethnicity, gender, years of education, self-rated physical health, and number of health conditions diagnosed over lifetime	Not specified
Ensink et al (2020)	SCZ GWAS (Schizophrenia Working Group (2014) from PGC, Depressive symptoms GWAS (Okbay et al. 2016) from SSGAC	Maternal environmental risk factors Children's internalizing and externalizing problems	1. Univariable linear regression 2. Univariable logistic regression 3. Hierarchical regression analysis covariates: age, and gender in Model 1, environmental risk factors in Model 2, and PRS in Model 3	Matrix Spectral Decomposition
Feurer et al (2022)	MDD GWAS (Howard et al., 2019) from PGC	Youth experiences of dependent and independent stress	Linear mixed model covariates (used in different models): current symptoms & diagnoses, demographic variables (i.e., youth age, sex, family income), 10 ancestral PCs	Not specified
Krapohl et al (2017)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC	paternal age at birth	Single-Score and Multiscore Genomic-Relatedness Matrix Restricted Maximum-Likelihood Models covariates: 30 PCs, genotyping array, and plate	Sidák correction

Lehto et al (2020)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC, Depressive symptoms GWAS (Okbay et al. 2016) from SSGAC	childhood adoption	Multivariate linear/logistic regression models covariates: sex, age, and 15 PCs	Not specified
Machlitt-Northen et al (2022) [Chapter 3]	SCZ GWAS (Schizophrenia Working Group 2014) from PGC, MDD GWAS (Wray et al 2018) from PGC	low birth weight, parity, short gestational period, maternal/paternal age at birth, maternal smoking prior and during pregnancy, parental smoking, alcohol consumption, SES, unemployment, financial difficulties, housing issues, tenure, number of bedrooms in family home, free school meals, maternal and paternal interest in child's education, paternal involvement in childcare, taking the child for walks or to the park, reading to child, parental marital status, domestic tension	Logistic and linear regressions logistic or linear mixed effects longitudinal models or random effects longitudinal models covariates: Year of data collection (MCS), current age (NCDS), sex and the top 8 and 5 principal components for NCDS and MCS, respectively	Bonferroni correction
Machlitt-Northen et al (2022) [Chapter 4]	SCZ GWAS (Schizophrenia Working Group 2014) from PGC, MDD GWAS (Wray et al 2018) from PGC	unemployment, financial difficulties, SES, income, number of bedrooms, tenure, alcohol consumption, smoking, educational attainment, marital status	1.Linear or logistic regressions for variables at a single data point 2. Linear and logistic mixed-effects regressions or random effects longitudinal models for repeated measurements covariates: PCs, age/year of data collection and sex as covariates	Bonferroni correction

Machlitt-Northen (2022) [Chapter 5]	SCZ GWAS (Schizophrenia Working Group 2014) from PGC, MDD GWAS (Wray et al 2018) from PGC	1) Childhood rGE by time analysis: SES, tenure, financial issues, number of bedrooms, employment, maternal smoking, maternal & paternal alcohol consumption, parental marital status, father's involvement in child's upbringing, maternal & parental interest in child's education, mother/father takes child for walks, mother/father reads to child, 2(Adulthood rGE by time analysis: SES, tenure, financial issues, number of bedrooms, employment, income, smoking, marital status 3) Childhood vs. adulthood rGE by time analysis: SES in childhood vs. SES in adulthood, tenure in childhood vs. tenure in adulthood, number of bedrooms in childhood vs. number of bedrooms of in adulthood, father's employment in childhood vs. employment in adulthood, mother's smoking behaviour prior and during pregnancy vs. smoking behaviour in adulthood, marital status of mother at birth vs. marital status in adulthood	Logistic or linear mixed effects or random effects longitudinal models fitted with full factorial two-way interactions between the PRS and time covariates: birth year (USoc), sex and the top 5, 4 and 8 principal components for MCS, USoc and NCDS,	Benjamini–Hochberg correction
Paksarian et al (2018)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC	urbanicity at birth residence in the capital at age 15	Generalized Estimating Equations covariates: first 10 PCs, age, sex, and year of birth	Not specified
Peel et al (2022)	SCZ GWAS from Pardiñas et al. 2018, Depressive symptoms GWAS (Okbay et al. 2016) from SSGAC, MDD GWAS (Wray et al 2018) from PGC	Self-reported childhood trauma	Univariable linear regression models Multivariable linear regression models covariates: birth year, gender, genotyping batch and first 10 PCs	Benjamini–Hochberg correction

Pries et al (2020)	SCZ GWAS from Pardiñas et al. 2018	childhood adversity daily-life stressors	multilevel linear regression covariates: age, sex, top 2 PCs	Bonferroni correction
Sallis et al (2021)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC	Trauma exposure: Bullying, Domestic violence, Sexual abuse, Emotional neglect, Emotional cruelty, Physical cruelty	ALSPAC: 1. Unadjusted logistic regression 2. Sensitivity analysis to control for a) age, b) only data from children with mother/father genotypes which were also used as covariates, c) adjusted for additional psychiatric phenotypes MoBa: logistic regression covariates: chip, batch and 10 PCs	Not specified
Su et al (2018)	Depressive symptoms GWAS (Okbay et al. 2016) from SSGAC	Parental knowledge Personality domains	Multivariate path analysis covariates: age, sex, 3 ancestry PCs and mothers' depressive symptoms PRS	Not specified
Sund et al (2021)	MDD GWAS from PGC (Howard et al., 2019)	Residential area urbanicity using five symptoms of poor mental health as outcomes	Mixed effect logistic regression models covariates: age, sex and 5 ancestry PCs	Not specified
Trotta et al (2016)	SCZ GWAS (Schizophrenia Working Group 2014) from PGC	Childhood adversity	Logistic regression covariates: 1) 10 PCs, 2) 10 PCs, sex, age and education level	Not specified

Note: SCZ = Schizophrenia, MDD = Major Depressive Disorder, PGC = Psychiatric Genetics Consortium, GWAS = Genome-wide Association Study, SSGAC = Social Science Genetic Association Consortium, PCs = Principal Components, PRS = Polygenic Risk Score, SES = Socio-economic status, ALSPAC = Avon Longitudinal Study of Parents and Children, MoBa = Norwegian Mother, Father and Child Cohort Study, NCDS = 1958 National Child Development Study, MCS = Millennium Cohort Study, USoc = Understanding Society

6.4.4.2 SCZ rGE Findings

Overall, 14 of the empirical studies explored rGE in SCZ which are each described in detail in Table 26 in a narrative approach and have been categorised into four groups: adversity, maternal and paternal factors, socioeconomic factors, and psychosocial factors. Some publications may appear in multiple categories. Although four articles highlighted correlations between the genetic susceptibility to SCZ and childhood adversity/trauma exposure (Aas et al., 2021; Bolhuis et al., 2021; Coleman et al., 2020; Sallis et al., 2021), three studies confirmed that no association was present between childhood adversity (Pries et al., 2020; Trotta et al., 2016) or interpreting childhood events as traumatic (Peel et al., 2022) and the PRS for SCZ.

A total of three article explored rGE associations concerning maternal and paternal risk factors. For example, the PRS for SCZ was associated with decreased maternal age at birth (Ensink et al., 2020) as well as increased paternal age (Krapohl et al., 2017). On the other hand, the genetic vulnerability to SCZ was further correlated with fathers being less likely to be involved in childcare (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) as well as lower maternal education (Ensink et al., 2020). The correlation between socioeconomic indicators and the genetic liability to SCZ was explored by two studies, including urbanisation at age 15 (Paksarian et al., 2018) and changes in the strength of rGE for rented accommodation which decreased in childhood, whilst the strength of rGE for low number of bedrooms increased in adulthood (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022). Lastly, rGEs for SCZ also involved psychosocial risk factors based on results from two studies which included single parenthood (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) and higher odds of being adopted (Lehto et al., 2020).

Table 26: *rGE findings for SCZ*

Author(s)	Main results
Adversity	
Aas et al (2021)	No association between adult SCZ PRS and childhood adversity assessed as a binary measure in either cases or controls (β case = 0.02; 95% CI [−0.14-0.22]; p = .65; β control = 0.03; 95% CI [−0.09-0.25]; p = .34, respectively), but small positive correlation between SCZ PRS and childhood adversity as a continuous score in the controls, but not in cases (β control = 0.09; 95% CI [0.02–0.16]; p = .02; β case = 0.02; 95% CI [−0.08-0.11], p = .74)
Bolhuis et al (2021)	Child SCZ PRS was associated with the total burden of childhood adversity (Pt < 0.5: OR = 1.08, 95% CI [1.02–1.15], p = .01), and adversity before age 5 years (Pt < 0.5: OR = 1.05, 95% CI [0.98–1.13], p = .13). Childhood adversity occurring before age five and age ten years explained part of the associations between SCZ PRS and internalizing problems, anxious depressed problems, somatic complaints, thought problems, and attention problems. The proportion of these mediations were 22% (95% CI -1; 65%), 23% (95% CI 0; 77%), 19% (95% CI -2; 83%), 14% (95% CI 0; 34%) and 19% (95% CI 1; 54%), respectively.
Coleman et al (2020)	Significant correlations between adult PRS for SCZ and trauma exposure (OR = 1.146, 95% CI [1.13-1.162]; strongest p = 9.70 x 10^{-83}).
Trotta et al (2016)	Adult PRS for SCZ did not increase exposure to, or reporting of, childhood adversity in first-presentation psychosis cases and controls.
Peel et al (2022)	No association between increased child PRS for SCZ and experiencing or interpreting events as traumatic.
Pries et al (2020)	No association between increased PRS for SCZ and childhood adversity or daily-life stressors.
Sallis et al (2021)	ALSPAC: Positive association between PRS for SCZ and exposure to trauma across childhood and adolescence. Effect sizes were consistent for both child or maternal PRS [0–17 years: odds ratio (OR Child) 1.14, 95% CI [1.08–1.20], p = 8.4 × 10−6; OR Mother 1.13, 95% CI [1.06–1.20], p = 8.5 × 10−5] MoBa: Some evidence of association between the PRS for SCZ and trauma exposures at age 8 years, consistent with those estimated in discovery cohort at a similar age (5–10.9 years).
Maternal and paternal childhood environments	
Ensink et al (2020)	Child SCZ PRS was negatively associated with maternal education (lower education) (OR = 0.759, R2 = .021, p < .0001), use of alcohol during pregnancy (decreased alcohol use during pregnancy) (OR = 0.811, R2 = .013, p < .001) and age of the mother at gestation (younger mother) (β = -0.160, R2 = 0.26, p = <.0001). SCZ PRS was associated with externalizing behaviour problems in children at age 5–6 (β = 0.097, R2 = .011, p = .001).
Krapohl et al (2017)	Child SCZ PRS was positively associated with paternal age (higher paternal age), even when adjusting for education and BMI-associated polygenic variation even when adjusting for education and BMI-associated polygenic variation (R2 = 0.002, β = 0.049; p = 1 x 10^{-04})
Machlitt-Northen et al (2022) [Chapter 3]	For NCDS: Lack of father's involvement in childcare was associated with the PRS for SCZ (β = 0.21, 95% CI [0.10–0.32]; strongest p = 2.50 x 10^{-04}).
Socioeconomic environments	

Machlitt-Northen et al (2022) [Chapter 5]	rGEs for SCZ appear to be relatively stable across childhood, except for tenure of accommodation for individuals with higher PRS for SCZ (β = -0.01, 95% CI [-0.15--0.05]; strongest p = 1.29 x 10^{-04}) for MCS only. Strength of rGE between PRS for SCZ and low number of bedrooms got stronger in adulthood (β = 0.01, 95% CI [0.00-0.01]; strongest p = 5.21 x 10^{-04}) for USoc. Strength of rGE between the PRS for SCZ and higher SES was stronger in adulthood compared to childhood (β = 0.03, 95% CI [0.01-0.04]; strongest p = 1.11 x 10^{-03}) in NCDS.
Paksarian et al (2018)	Those with higher adult PRS for SCZ were more likely reside in the capital compared to rural areas at age 15 (OR=1.19, 95% CI [1.01–1.40]), but not at birth (OR=1.09, 95% CI [0.95–1.26]).
Psychosocial environments	
Lehto et al (2020)	Each standard deviation increase in the PRS for SCZ, was associated with 5% (OR, 1.05; 95% CI [1.01–1.09]; p = .01) increase in the odds of being adopted
Machlitt-Northen et al (2022) [Chapter 3]	For MCS: Child PRS for SCZ was correlated with single parenthood (β = 0.18, 95% CI [0.11–0.25]; strongest p = 8.36 x 10^{-07}) and was partially confounded by the parental genotype, most likely reflecting passive rGE.
Machlitt-Northen et al (2022) [Chapter 4]	For USoc: Associations between the adult PRS for SCZ and being single or divorced (β = 0.05, 95% CI [0.04-0.15]; strongest p = 1.13 x 10^{-03}). For NCDS: No significant rGE associations.

Note: Some articles may appear in more than one category. SCZ = Schizophrenia, PRS = Polygenic Risk Score, rGE = Gene-Environment Correlation, SES = Socioeconomic Status, OR = Odds Ratio, β = beta coefficient, CI = Confidence Interval, p = p-value, NCDS = 1958 National Child Development Study, MCS = Millennium Cohort Study, USoc = Understanding Society, ALSPAC = Avon Longitudinal Study of Parents and Children, MoBa = Norwegian Mother, Father and Child Cohort Study, OR = Odds Ratio, β = beta coefficient, CI = Confidence Interval, p = p-value, R2 = effect size

6.4.4.3 Depression rGE Findings

rGE results for all depression phenotypes are described in Table 27 in a narrative approach and have been categorised into the same four groups as the rGE SCZ findings, namely adversity, maternal and paternal factors, socioeconomic factors, and psychosocial factors. Some publications may appear in multiple categories.

In line with our rGE SCZ findings, we also obtained some conflicting results across multiple publications with regards to the correlation between adversity and the genetic liability for depression. Specifically, the genetic risk for either MDD or depression symptoms was associated with trauma exposure (Coleman et al., 2020; Das, 2019). In addition, the genetic liability for depression was correlated with increased levels of self-generated dependent stress as well as independent stress in children and adolescents (Feurer et al., 2022), whilst Das (2019) proposed that the PRS for depressive symptoms was only positively associated with childhood physical abuse in woman. On the other hand, no associations were found between the PRS for depression and self-reported childhood trauma experiences or interpretation (Peel et al., 2022) or childhood adversity (Bolhuis et al., 2021). Three further studies explored the associations between maternal or paternal risk factors and the genetic liability to either MDD or depressive symptoms, including lower parental knowledge (Su et al., 2018), mothers and fathers not being interested in the child's education as well as increased maternal smoking (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) and heightened maternal prenatal anxiety (Ensink et al., 2020). Finally, correlations between socioeconomic markers and the genetic vulnerability to depression were reported in four publications. These rGE findings included correlations between an PRS for depression and heightened proportion of urban residents (Sund et al., 2021) and low SES in childhood and rented accommodation in adulthood (Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022).

Table 27: *rGE findings for depression*

Author(s)	Main results
Adversity	
Bolhuis et al (2021)	No association between PRS for depression and childhood adversity.
Coleman et al (2020)	Significant correlations between adult PRS for MDD and trauma exposure (OR = 1.198, 95% CI [1.182-1.214]; strongest p = 5.32 x 10^{-157}).
Das (2019)	PRS for depressive symptoms predicted both stable and unstable trauma reports. Among women, depressive symptoms PRS was positively associated with stable reports of childhood physical abuse (coefficient = 0.31, p < .05). No rGE pattern was found for stable substance abuse reports.
Feurer et al (2022)	Higher levels of PRS for depression in youth was associated with higher levels of dependent (β = 0.19, r = .23, p = .02) and independent stress (β = 0.12, r = .32, p < .001), even after controlling for maternal history of MDD. Youth PRS for depression was associated with exposure to both minor (β = 0.09, r = .30, p = <.001) and major dependent life events (β = 0.06, r = .27, p = < .001) and exposure to minor (β = 0.09, r = .32, p = < .001), but not major, independent life events.
Peel et al (2022)	No association between increased PRS for MDD and experiencing or interpreting events as traumatic.
Maternal and paternal environment	
Ensink et al (2020)	Child PRS for depression was positively associated with maternal prenatal anxiety (higher maternal prenatal anxiety score) (β = 0.110, R2 = .012; p < 0.0001), and current rates of distress in the mother at children's aged 5–6 (higher maternal distress score) (β = 0.108, R2 = .012; p = .002).
Machlitt-Northen et al (2022) [Chapter 3]	For MCS: Child PRS for MDD was correlated with more maternal smoking (β = 0.20, 95% CI [0.15–0.2]; strongest p = 0.00 x 10^{-00}) and less maternal alcohol consumption during childhood (β = -0.26, 95% CI [-0.036—0.15]; strongest p = 2.91 x 10^{-06}). Maternal smoking for but not maternal alcohol consumption was confounded by parental genotypes. For NCDS: PRS for MDD was associated with paternal & maternal lack of interest in the child's education (β = 0.20, 95% CI [0.10 to 0.3]; strongest p = 1.21 x 10^{-04}), (β = 0.17, 95% CI [0.08 to 0.26]; strongest p = 1.81 x 10^{-04}) respectively.
Su et al (2018)	Adolescents' depressive symptoms PRS predicted lower parental knowledge which in turn was associated with more subsequent MDD (β = -0.15, 95% CI [0.002-0.018]; p < 0.01). Adolescents' depressive symptoms PRS also had indirect effects on these outcomes via agreeableness β = -0.19, 95% CI [0.002-0.022]; p < 0.01). These genetic effects are apparent after controlling for mothers' genetic risk for depressive symptoms (which accounted for passive rGE), thus indicative of evocative rGE.
Socioeconomic environments	
Machlitt-Northen et al (2022) [Chapter 3]	For MCS: Child PRS for MDD was correlated with low SES (β = -0.07, 95% CI [-0.10--0.03]; strongest p = 1.04 x 10^{-04}) and rented accommodation (tenure) (β = 0.43, 95% CI [0.24–0.63]; strongest p = 1.14 x 10^{-05}). Only tenure was confounded by the parental genetic risk, most likely through passive rGE.

	For NCDS: PRS for MDD was associated with low SES (β = -0.05, 95% CI [-0.07--0.03]; strongest p = 2.53 x 10^{-05}), rented accommodation (β = 0.47, 95% CI [0.26 to 0.68]; strongest p = 9.88 x 10^{-06}) and low number of bedrooms (β = -0.05, 95% CI [-0.07—0.02]; strongest p = 2.08 x 10^{-04}).
Machlitt-Northen et al (2022) [Chapter 5]	rGEs for MDD appear to be relatively stable across childhood. PRS for MDD on established environmental risk factors only changed for SES (β = 0.01, 95% CI [-0.02--0.01]; strongest p = 4.27 x 10^{-05}) and tenure of accommodation (β = 0.16, 95% CI [0.08-0.23]; strongest p = 6.77 x 10^{-05}) in adulthood in USoc. Association between PRS for MDD and low SES got weaker in adulthood (β = 0.04, 95% CI [0.02-0.05]; strongest p = 1.04 x 10^{-06}), strength of rGE between PRS for MDD and rented accommodation was stronger in childhood compared to adulthood (β = -0.14, 95% CI [-0.21--0.07]; strongest p = 1.11 x 10^{-04}).
Machlitt-Northen et al (2022) [Chapter 4]	For USoc: Significant correlation between the adult PRS for MDD and decreased number of bedrooms (β = 0.04, 95% CI [-0.07--0.02]; strongest p = 4.36 x 10^{-04}), low income (β = -0.03, 95% CI [-0.05--0.01]; strongest p = 6.72 x 10^{-04}), finance issues (β = 0.24, 95% CI [0.16-0.33]; strongest p = 2.91 x 10^{-08}) and unemployment (β = 0.21, 95% CI [0.09-0.32]; strongest p = 3.98 x 10^{-04}). For NCDS: Significant correlation between the adult PRS for MDD and decreased number of bedrooms (β = -0.03, 95% CI [-0.05--0.01]; strongest p = 1.51 x 10^{-03})
Sund et al (2021)	Adult PRS for depression was higher for residents of urban than rural areas. The Hospital Anxiety and Depression Scale Score (HADS-D) (≥8) (OR: 1.18, 95% CI [1.08-1.29]) significant at p<0.05. HADS-D (≥11) (OR: 1.33, 95% CI [1.14-1.56]) significant at p<0.05.
Psychosocial environments	
Lehto et al (2020)	Each standard deviation increase in the PRS for depressive symptoms was associated with 6% (OR, 1.06; 95% CI [1.03–1.10]; p = .01) increase the odds of being adopted.
Machlitt-Northen et al (2022) [Chapter 3]	For MCS: Child PRS for MDD was correlated with single parenthood (β = 0.09, 95% CI [0.06–0.13]; strongest p = 2.17 x 10^{-07}), which was not confounded by the parental genetic risk.

Note: Some articles may appear in more than one category. MDD = Major Depressive Disorder, PRS = Polygenic Risk Score, rGE = Gene-Environment Correlation, SES = Socioeconomic Status, HADS-D = The Hospital Anxiety and Depression Scale Score, NCDS = 1958 National Child Development Study, MCS = Millennium Cohort Study, USoc = Understanding Society, OR = Odds Ratio, β = beta coefficient, CI = Confidence Interval, p = p-value, r = effect size

6.4.4.4 Comparison of SCZ and Depression rGE Findings

This systematic review resulted in a similar number of articles which reported rGE findings across the two psychopathologies. The comparison of SCZ and depression rGE results highlighted that, overall, there are more similarities than differences between the two psychiatric disorders.

6.4.4.5 Similarities between SCZ and Depression

Firstly, our systematic review identified similar discrepancies for both psychopathologies between the genetic risk and childhood adversity. Secondly, individuals with an increased PRS for either psychiatric disorder had increased odds of being adopted (Lehto et al., 2020), were more likely to live in urban areas (Paksarian et al., 2018; Sund et al., 2021) and had single parents (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022). Thirdly, surprisingly the genetic liability for either psychopathology was protective and correlated with lower maternal alcohol consumption either in pregnancy or in childhood (Ensink et al., 2020; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022). Finally, the genetic risk for SCZ as well as depression was associated with educational phenotypes, such as lower maternal education for SCZ and maternal & paternal lack of interest in the offspring's education for MDD (Ensink et al., 2020; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022; Su et al., 2018).

6.4.4.6 Differences between SCZ and Depression

Whilst we identified more similarities between the rGE findings for SCZ and depression, we would also like to highlight some differences which emerged between the two psychopathologies. For example, several early environmental risk factors relating to fathers,

including increased paternal age at birth (Krapohl et al., 2017) and lack of involvement in childcare (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) were only identified for the PRS for SCZ, but did not emerge for depression. And the genetic susceptibility to depression was more strongly correlated with markers of disadvantaged socioeconomic status, such as unemployment, low income or financial difficulties (Sandra Machlitt-Northen et al., 2022) compared to SCZ.

6.5 Discussion

The main objective of this study was to explore rGE findings for SCZ and depression in studies featuring genome-wide-based PRS across all periods of human development through a systematic review. Secondly, we wanted to investigate whether any identified rGEs matched between the two psychiatric disorders.

Results from 18 empirical studies which met our inclusion criteria suggest that the PRS for either psychopathology was correlated with a wide range of established environmental risk factors, such as maternal and paternal factors, adversity, psychosocial factors as well as socioeconomic factors. Overall, rGE findings for SCZ and depression were similar between the two psychiatric disorders.

6.5.1 rGE Findings for SCZ

The genetic liability to SCZ, measured as PRS, was significantly correlated with several psychosocial and environmental risk factors across different periods of development. According to research which proposes that the offspring of younger mothers but older father have a heightened risk of psychopathology (McGrath et al., 2014), our results support this finding by highlighting correlations between the PRS for SCZ and lower maternal age, but increase paternal age at birth most likely through *passive* rGE (Ensink et al., 2020; Krapohl et

al., 2017). Although it is not inconceivable that women with the PRS for either SCZ or psychiatric disorders have a heightened risk of early pregnancy, it is also important to state that age-related paternal de novo mutations are not likely to be a causal factor in the development of SCZ in the children, with reduced male fertility, delayed parenthood or problems finding a partner all being plausible rationales (Grattan et al., 2015; Gratten et al., 2016; Howard, 2005; Myhrman et al., 1996; Petersen et al., 2011).

Moreover, whilst population-based studies provide plenty of evidence for correlations between the PRS for SCZ and childhood adversity, it was unexpected that Chapter 6 identified inconsistent rGE results across several publications. Although it is possible that an age or cohort effect is responsible for these discrepancies, which explain that environmental exposures or even cohort characteristics are specific to individuals within that study (Keyes et al., 2014), our systematic review shows that rGE associations between the genetic liability to SCZ and childhood adversity are, in fact, identified across a range of different cohorts, such as Generation R (Bolhuis et al., 2021) and ALSPAC (Sallis et al., 2021). Further, no SCZ rGE correlations were identified in the Genes and Psychosis (GAP) study (Trotta et al., 2016), TwinssCan (Pries et al., 2020) nor in TEDS (Peel et al., 2022). Taking this into account, it is therefore also likely that these discrepancies in rGE findings could be attributed to disparities in reported adverse events types, retrospective reports of trauma or how individuals interpret traumatic childhood events (Aas et al., 2021; Das, 2019).

Besides, whilst the correlation between urbanisation at birth and the genetic vulnerability to SCZ is well established (Pedersen & Mortensen, 2001), our review did not support this finding, but highlighted possible rGE associations between the PRS for SCZ and urbanisation at age 15 (Paksarian et al., 2018). Although this result could be explained by *active* rGE correlations amongst the parents, who may have selected themselves into more urban environments based on their genetic make-up, it is also important to point out that parents pass

on their genetic susceptibilities to their children whilst also providing the home environment which reflects passive rGE (Jaffee & Price, 2007; Paksarian et al., 2018). Unfortunately, the authors were unable to disentangle which rGE mechanism could have driven this association but proposed that it is possible that the correlation between urbanisation at age 15 and the PRS for SCZ may not be entirely genetically confounded (Paksarian et al., 2018).

On the whole, we would like to stress that the effect sizes for most of the SCZ rGE findings, which were measured as odds ratios or beta coefficients, were small and thus rGE alone cannot fully explain the associations between the genetic susceptibility to SCZ and the environmental risk factors identified in this systematic review. Given that the predictive abilities of PRS are still extremely low for complex psychopathologies (Lewis & Vassos, 2017), findings from Chapter 6 cannot fully exclude the possibility that rGE associations as well as the genetic liability and known environment risk factors may all be implicated in the aetiology of SCZ.

6.5.2 rGE Findings for Depression

In line with our SCZ rGE results, we also identified inconsistent results between childhood adversity and the genetic susceptibility to depression across our included studies. One study by Das (2019) proposed that it is possible that retrospective self-reports of trauma are less robust than expected, specifically seeing that the agreement between later reports and actual trauma experiences is often unclear. This finding highlights that possible childhood adversity rGE findings may need to be interpreted with caution and future studies require objective, robust as well as prospective measures (Das, 2019). Moreover, we would also like to point out that our 12 included empirical depression studies utilised different GWAS summary statistics for the different depressive phenotypes in order to calculate individual-based PRS scores. Therefore, we cannot exclude the alternative possibility that the associations

between the genetic risk for depression and adversity may not be entirely genetically confounded, seeing that the PRS for depression has an area under the ROC curve (AUC) of 0.57 and only accounts for 2% of the variance in depression risk, thus highlighting that most of the depression disease risk is still not accounted for by PRS (Lewis & Vassos, 2020).

Additionally, we found evidence for correlations between the genetic susceptibility to depression in children and adolescents and early parental behaviours, such as lower parental knowledge (Su et al., 2018) and higher maternal prenatal anxiety (Ensink et al., 2020). Only, two empirical studies were able to detect that *evocative* rGE was likely the underlying type of rGE present in these correlations (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022; Su et al., 2018), highlighting that the offspring's PRS for depression can evoke specific behaviours from their biological parents which consequently can lead to poor quality relationships between them, resulting in negative child outcomes (Su et al., 2018). However, not all studies were able to distinguish rGE mechanism, which consequently does not exclude the possibility that at least some correlations between parental behaviours and the genetic susceptibility to depression may also be characterised by *passive* rGE in which the parents do not just pass on their genetic make-up but also provide the environment in which the child grows up in (Plomin et al., 1977).

Further, multiple studies identified associations between indicators of low SES as well as urbanisation and the PRS for depression. It is not inconceivable that some of the rGE correlations with low number of bedrooms or rented accommodation (Sandra Machlitt-Northen et al., 2022) are in fact driven by urbanisation itself. One longitudinal study investigating rGE changes across time, which proposed that correlations between rented accommodation get stronger as individuals got older, supports this hypothesis (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022). Subsequently, is it plausible that these rGE

associations are driven by *active* rGE, which proposes that individuals actively select their own environments based on their genetic propensities (Jaffee & Price, 2007; Plomin et al., 1977).

Finally, in line with the SCZ rGE findings, effect sizes for the depression rGE were small to moderate for the majority of empirical studies. Therefore, it is plausible that the depression rGE associations do not fully explain the complex interplay between the environment and our genes and thus, a combination rGE as well as causal correlations may be both implicated in the aetiology of depressive phenotypes.

6.5.3 Comparison of SCZ and Depression rGE Findings

Firstly, whilst different summary statistics were utilised by different depression studies to calculate the PRS for depression, correlations between a range of environmental risk factors and the genetic liability for SCZ or depression were similar for the most part between the two psychiatric disorders. However, this result is in contrast to our recently published studies (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, & M. Pluess, 2022; Sandra Machlitt-Northen et al., 2022; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022) which proposed that the PRS for MDD was more strongly correlated with known environmental risk factors compared to SCZ. Although both psychopathologies are heritable, there is only limited genetic overlap between the two (Ripke O'Dushlaine, et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Schulze et al., 2014; Wray et al., 2018), indicating that it is likely that at least some of the identified rGE associations could be attributed to societal or environmental changes. Specifically, some rGE results may not be genetically confounded but may in fact be the results of cultural or intergenerational shifts.

Secondly, we also identified that the PRS for either psychopathology was associated with protective maternal risk factors in pregnancy or childhood, namely decreased maternal

alcohol consumption (Ensink et al., 2020; S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022). Given that these surprising results are not in line with other research outcomes (Easey, Dyer, et al., 2019; Easey et al., 2021), it is possible that our findings may be cohort specific.

6.6 Strength and Limitations

Our systematic review has many strengths, such as investigating all rGE associations relating to SCZ or depression in studies featuring PRS across all periods of human development. However, in light of this we would also like to highlight some limitations.

Most empirical studies made use of cohorts which were comprised of participants of largely European ancestry, whereby one study (Su et al., 2018) utilised participants of European Americans ancestry. That means that our rGE findings can only be generalised to that particular European population. Sadly, this limitation has been identified by other genetic studies who conducted systematic reviews and is not unique to studies investigating rGE (Dixon et al., 2022; Johnson et al., 2022). It is therefore imperative that GWAS findings can be diversified to other populations in order to assess the genetic confounding in the development of psychopathological outcomes better. Further, we identified a prominent heterogeneity with regards to the utilisation of GWAS summary statistics, specifically for the depressive phenotypes, which consequently may have had an impact on the number of risk SNPs which were included in the final analysis and thus may have contributed to some of the conflicting rGE correlations. Given that the 'depression symptoms vs disorder' debate is well known (Kendell, 1976) and the fact that there is a high overlap of these common depression genetic variants (Wray et al., 2018), there are some still some genetic variations in these different depressive phenotypes. Therefore, it is imperative that studies clearly and consistently state which depressive phenotype was investigated. Besides, a large number of studies were

unable to disentangle between the different rGE mechanisms. The accessibility of transgenerational genotypes in genetic studies is vital in order to identify whether *passive*, *active* or *evocative* rGE is at work (Krapohl et al., 2017) which in turn will affect whether environments can be targeted for interventions or treatments. Additionally, we identified significant sample size differences between the 18 empirical studies which were included, with only a few studies highlighting power calculations. It is imperative that well-powered studies which do not overlap with the discovery or target sample are utilised (Dudbridge, 2013). Moreover, our systematic review identified several significant differences in the way the statistical and sensitivity analyses were conducted in addition to the lack of multiple testing for a large proportion of included studies. Finally, whilst the importance of rGE is gaining acceptance in the field of psychology the overall number of included studies which focused on rGE in SCZ, or depression is still small. Thus, our systematic review should be considered exploratory.

6.7 Limitations of the Review Process

In light of the study limitations section, we would also like to point out a few limitations with regard to our review process.

As the number of included studies was small and given the heterogeneity of environmental risk factors, we applied a narrative approach. Further, although our systematic review was conducted in line with the PRISMA guidelines and made use of a well-accepted risk of quality assessment tool, we would like to acknowledge that there is currently no standard quality bias tool which is consistently used for systematic reviews investigating rGE in PRS studies. Lastly, the 18 included empirical studies concentrated on rGE associations in either SCZ or depression. Chapter 6 did not include all symptoms of these two psychopathologies given that these symptoms could also overlap with other psychiatric disorders.

6.8 Implications for Future Research

Firstly, given the presence of rGE associations does not propose that targeting specific environments will be ineffective for individuals who possess an heightened genetic vulnerability to either SCZ or to depression (S. Machlitt-Northen, R. Keers, P. B. Munroe, D. M. Howard, V. Trubetskoy, et al., 2022), treatments or interventions should aim to provide cross-generational support for children as well as their biological parents depending on the type of rGE which is present. Moreover, given that the rGE mechanism may change over time and the fact that the impact of genes and their corresponding environments can have time-dependent effects on the aetiology of psychopathological outcomes, longitudinal treatments and intervention approaches may need to take into account that rGE correlations will manifest differently depending on the developmental period (Jaffee & Price, 2007; Scarr & McCartney, 1983). Therefore, targeted environments may need to shift over time. Further, based on the fact that most included studies utilised participants of European ancestry, it is important to point out that the predictive abilities of the resulting PRS scores will consequently be more accurate in these populations (Palk et al., 2019). Therefore, future research must concentrate on carrying out GWAS studies in underrepresented populations with the aim to be able to test rGE association across diverse populations. As Chapter 6 also identified contradicting rGE results for either psychopathology implicating childhood adversity or trauma, robust phenotypic measures which involve objective exposures need to be utilised to avoid recall bias. Lastly, given the heterogeneity of methodological approaches identified in our systematic review, future research should aim for robust power analyses, clear statistical models as well as consider multiple testing corrections in order to increase the confidence in individual PRS estimations.

6.9 Conclusion

One key aims in the field of psychology is understanding the effect of genetic and environmental factors on the developmental of complex psychiatric outcomes (Assary et al., 2020). Although rGE associations are often regarded as confounding factors, it is imperative that this phenomenon is investigated in more detail on its own (Sund et al., 2021). Based on the findings of our systematic review, we found that those individuals with an increased genetic susceptibility to either SCZ or depression, measured as PRS, had higher odds of being adopted, were more likely to have single parents as children and lived in urban areas. Although, our review also highlighted inconsistent evidence for correlations between childhood adversity and the genetic risk to either psychopathology, rGE results between SCZ and depression largely matched between the two psychiatric disorders. Overall, based on the evidence from empirical studies featuring genome-wide data included in Chapter 6, a wide range of known environmental factors are associated with the PRS for SCZ or depression, further emphasising the significance of recognising the complex gene-environment interplay in the aetiology of complex psychopathologies.

Chapter 7: General Discussion & Future Direction

7.1 Overview

The aim of this thesis was to investigate rGE associations featuring PRS from published GWAS studies for two complex psychopathologies (specifically SCZ and MDD) and established environmental and psychosocial risk factors, as well as to evaluate rGE changes over time between the different developmental periods. This thesis utilised individuals from three British community cohorts, namely MCS, USoc and NCDS, across childhood and adulthood.

Chapter 7 will, firstly, provide a short summary of the key findings from Chapter 3 (rGE in childhood), Chapter 4 (rGE in adulthood), Chapter 5 (rGE changes over time) as well as Chapter 6 (rGE Systematic Review in SCZ and depression). Next, the results of Chapters 3, 4, 5 and 6 will be compared and discussed in detail. Finally, this section will provide in-depth discussion on limitations as well as the implications and future direction of rGE research in psychiatry and clinical psychology.

7.2 Summary of Results

This section will provide a short overview of key findings from Chapters 3, 4, 5 and 6.

7.2.1 Summary of Key Findings from Chapter 3 (rGE for SCZ and MDD in Childhood)

Our results have highlighted that the PRS for either psychopathology was correlated with a range of established psychosocial and environmental risk factors in childhood in the two cohorts which are 42 years apart: MCS and NCDS.

Specifically, we found that rGE was more pronounced in MDD compared to rGE in SCZ. Only father's lack of involvement in childcare and single parenthood were associated

with the PRS for SCZ in childhood. On the other hand, an increased genetic susceptibility for MDD was associated with parental behaviours, including maternal smoking and parental lack of interest in their offspring's education, as well as several indicators of low SES, such as rented accommodation and decreased number of bedrooms.

More than half of rGE associations could be attributed to *passive* rGE.

7.2.2 Summary of Key Findings from Chapter 4 (rGE for SCZ and MDD in Adulthood)

Our results emphasised that rGE in adulthood was more pronounced for MDD compared to SCZ, as observed in individuals over the age of 16 in USoc and NCDS.

Precisely, the adult PRS for SCZ was only correlated with being single, divorced or widowed whilst the genetic vulnerability to MDD was correlated with several markers of SES, including low income, finance issues, unemployment and decreased number of bedrooms.

Findings were not confounded by the presence of clinical cases according to a series of sensitivity analyses.

7.2.3 Summary of Key Findings from Chapter 5 (rGE Changes for SCZ and MDD over Time)

We observed that, overall, rGE does not significantly change across different developmental periods from childhood to adulthood in MCS, USoc and NCDS.

We only considered those environmental risk factors which were significantly associated with the genetic vulnerability for either SCZ and MDD prior to multiple testing in Chapter 3 and Chapter 4. Overall, we identified few rGE changes over time. Specifically, the correlation between higher PRS for SCZ and rented accommodation increased in childhood. rGE changes over time in adulthood highlighted that the associations between the PRS for SCZ and decreased number of bedrooms increased. Further, the genetic risk for MDD and rented

accommodation got stronger over time, whilst the correlation with low SES got weaker as adults got older. Moreover, Chapter 5 proposed that the strength of rGE between the PRS for SCZ and high SES as well as the genetic liability for MDD and low SES both increased from childhood to adulthood, whilst the strength of rGE between the PRS for MDD and rented accommodation decreased from childhood into adulthood. However, the majority of detected rGE remained relatively stable over time.

Our sensitivity analysis proposed that most of our results were not confounded by the presence of clinical cases.

7.2.4 Summary of Key Findings from Chapter 6 (Systematic Review of rGE in SCZ and Depression)

Our results from the systematic review provided further evidence that the PRS for SCZ or depression is correlated with a wide range of psychosocial and environmental risk factors. However, in contrast to our results from Chapters 3, 4 and 5, these rGE associations are largely similar between the two psychiatric disorders which is in contrast to our own results from Chapter 6.

Precisely, individuals with a heightened genetic susceptibility to either psychopathology had increased odds of being adopted, were more likely to live in urban areas and have single parents.

However, Chapter 6 also revealed inconsistent findings between childhood adversity and trauma and the PRS for either SCZ or depression, with some empirical studies proposing rGE associations whilst other studies detected no rGE.

A summary of all environmental measures which were significantly correlated with the PRS for SCZ and MDD across all chapters has been provided in Table 27.

Table 28: *Overview of rGE Findings for SCZ and Depression from Chapters 3, 4, 5 and 6*

Environmental risk factors significantly correlated with the PRS for SCZ or MDD	**Chapter 3: rGE in childhood**		**Chapter 4: rGE in adulthood**		**Chapter 5: rGE changes over time**		**Chapter 6: Systematic Review**	
	PRS for SCZ	**PRS for MDD**	**PRS for SCZ**	**PRS for MDD**	**PRS for SCZ**	**PRS for MDD**	**PRS for SCZ**	**PRS for depression**
Socio-economic indicators and urbanisation								
Low SES		X				X		
High SES					X			
Rented accommodation (tenure)		X			X	X		
Decreased number of bedrooms		X		X	X			
Low income				X		X		
Financial issues				X				
Unemployment				X				
Urbanisation*							X	X
Parental behaviours								
Maternal smoking		X						
Decreased maternal alcohol consumption during pregnancy or during childhood		X					X	
Lack of parental interest in child's education/ low parental knowledge or education		X					X	X
Lack of father's involvement in childcare	X							
Higher maternal prenatal anxiety and distress*								X
Psychosocial risk factors								
Marital status: single/divorced/separated	X	X	X					
Young age of the mother at gestation							X	
Older fathers at gestation							X	
Increased odds of being adopted*							X	X
Childhood adversity or trauma*								
Childhood adversity							X	X

Note: For Chapters 3, 4 and 5 - only environmental measures which were significantly correlated with the PRS for SCZ or MDD for any of the utilised cohorts were listed. For Chapter 6 - PRS for depression is referring to either the PRS for MDD or the PRS for depressive symptoms. *Environmental measures were not tested as part of the analysis in Chapters 3, 4 or 5.

7.3 Discussion

This next section will integrate and discuss findings from all four studies in more detail whilst specifically focusing on comparing rGE for SCZ and MDD between childhood and adulthood, assessing how these rGE associations change across the different development periods, investigating how our results compare to findings from other empirical studies as identified through the systematic review, and finally highlighting rGE differences between SCZ and MDD.

7.3.1 Comparison of Findings from Chapter 3 (rGE for SCZ and MDD in Childhood) and Chapter 4 (rGE for SCZ and MDD in Adulthood)

Given that GWAS summary statistics, which are used to calculate PRS, are obtained from adult datasets, one of the objectives of Chapter 3 was to test whether adult-based PRS for either SCZ or MDD are applicable to children from the UK population. In line with our hypothesis, results highlighted several associations between the PRS for SCZ and MDD and known environmental risk factors in childhood.

Overall, the rGE results for SCZ and MDD in childhood confirm that about half of the rGE correlations can be attributed to *passive* rGE, further reinforcing that parents do not just pass on their genetic liabilities to psychopathology to their offspring but also bestow the family environment in which their children grow up in. On the other hand, our analysis of rGE associations in SCZ and MDD in adulthood highlighted several possible *active* rGE associations which mainly involved indicators of low SES and urbanisation, proposing that adults actively seek out environments in line with their genetic vulnerabilities.

Similarities

Firstly, whilst both rGE analyses in childhood and adulthood identified associations

between the genetic susceptibility to SCZ and MDD and established adverse environments, rGE appeared to be more common in MDD compared to SCZ rGE in both sets of analyses. Given this consistent finding across both developmental periods, it is possible that the limited genetic overlap between the two psychopathologies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray et al., 2018) could explain the difference in rGE associations between SCZ and MDD.

Secondly, we also identified one psychosocial risk factor which was associated with the PRS for SCZ across both developmental periods. Specifically, rGE correlations between single parenthood status in childhood and the single marital status of individuals in adulthood were both associated with the genetic risk for SCZ. This rGE correlation likely reflects *passive* rGE in childhood as confirmed by our sensitivity analysis which we conducted in Chapter 3, whereby parents pass on their genes and provide the family environment in which the offspring is growing up. In adulthood, on the other hand, this correlation more likely reflects *evocative* rGE, suggesting that individuals with the genetic vulnerability to SCZ may evoke negative behaviours from their spouses or partners which, in turn, could lead to a lack of establishing or maintaining relationships. These findings show that SCZ rGE associations remain stable over time, with a developmental shift of the underlying mechanisms changing from *passive* to *evocative* rGE as individuals grow older and move from childhood to adulthood, in line with theory (Jaffee & Price, 2007).

Lastly, whilst we identified several rGE associations between MDD and indicators of adverse socio-economic status in childhood (low SES, rented accommodation) and adulthood (finance issues, unemployment, low income), we only detected one match for one marker of low socio-economic status across the two developmental periods. Decreased number of bedrooms in the family home in childhood and decreased number of bedrooms in the adult home were both significantly associated with the PRS for MDD across both developmental

periods. Although we were unable to disentangle which form of rGE is present in childhood or adulthood, it is likely that *passive* rGE could be, at least partially, responsible for this association in the offspring, with *active* rGE being the most likely explanation in adults. It is important to consider, that the environment risk of decreased number of bedrooms may in fact reflect adverse socio-economic situations. Given that low SES is not just associated with a wide range of health conditions but also MDD (Dohrenwend, 1990; Freeman et al., 2016; Johnson et al., 1999), our findings propose that this association may in fact be genetically confounded across both developmental periods as rGE mechanisms shift from *passive* to *active* rGE over time.

Differences

The majority of rGE findings for MDD differed between childhood and adulthood. Whilst the genetic risk for MDD in childhood was associated with psychosocial environments or parental behaviours as well as indicators of low SES, conversely, the adulthood rGE results for MDD were only associated with markers of low SES. It also has to be pointed out that, unsurprisingly, parental behaviours such as maternal smoking will be less relevant in adulthood compared to childhood. However, we have tested the equivalent adulthood behaviours, such as smoking and alcohol consumption in Chapter 4.

Given the results from our studies in childhood and adulthood, our findings propose that, overall, rGE associations differ between them for MDD, suggesting that possible environmental targets for treatment or interventions may need to change depending on the developmental period of the individual.

7.3.2 Comparison of Findings from Chapter 3 (rGE for SCZ and MDD in Childhood), 4 (rGE for SCZ and MDD in Adulthood) with Findings from Chapter 5 (rGE Changes for SCZ and MDD over Time)

Similarities

Whilst we only identified two significant SCZ rGE associations in childhood and one in adulthood, after correcting for multiple testing, these SCZ rGE were stable and did not change across time.

Similarly, the majority of rGE correlations for MDD in childhood and adulthood also remained stable in our rGE across time analysis after correction for multiple testing.

Further, our rGE changes across time analyses proposed that, in general, rGE associations stayed relatively stable throughout childhood and adulthood with only few changes in strength of rGE over time. However, these findings did not support our hypothesis. This was based on theory and previous research findings, proposing that rGE associations get stronger as individuals select themselves into their own environments in line with their genetic make-up through *active* rGE (Jaffee & Price, 2007; Newbury et al., 2020; Plomin et al., 1977).

Whilst larger sample sizes (Thapar & Riglin, 2020) and more frequent data points during critical stages of development may be required to detect subtle changes in rGE over time, we cannot reject the alternative explanation that actual changes in environmental, cultural or societal risk could also play a part in rGE changes over time.

Differences

Interestingly, the few changes in strength of rGE which we discovered in our rGE changes across time analysis were all related to indicators of low SES for both psychopathologies, and none related to behaviours, such as smoking behaviours of parents versus the smoking behaviour of the individual as an adult. In other words, the strength of rGE

associations featuring behaviours or psychosocial environments remain the same for each developmental period, whilst rGE correlations relating to adverse socio-economic status may change over time.

Moreover, when comparing if any rGEs for MDD which we found in childhood or adulthood changed over time, we only detected that the strength of rGE for low SES and rented accommodation changed in childhood, but none of our adulthood MDD rGE findings changed over time. This observation highlights that rGEs for MDD relating to indicators of low SES not only differ between childhood and adulthood, but also change in strength during these two investigated developmental periods.

7.3.3 Comparison of Findings from the Systematic Review with Results from our own Studies

Similarities

Overall, findings from the empirical studies included in the systematic review confirmed that the PRS for SCZ and MDD are associated with adverse psychosocial and environmental risk factors, in line with results reported in our own studies which were also included in the systematic review.

We identified only one rGE match between our own findings reported in childhood and the empirical studies included in our systematic review; specifically, the association between PRS for MDD and lack of parental interest in child's education or low parental knowledge/ education in childhood. Given that parenting and parent behaviours play a vital role in the development of children and adolescents, it is surprising that we did not identify more matches between our own findings and the empirical studies included in systematic review.

Differences

However, several important differences between our own findings compared to the systematic review need to be noted. Firstly, our own rGE findings for SCZ and MDD in childhood did not highlight any correlations with early childhood risk factors, including low maternal/high paternal age at gestation, but this was identified in other empirical rGE studies (Ensink et al., 2020; Krapohl et al., 2017). Also, whilst several of our included studies in the systematic review investigated the link between urbanisation and the PRS for SCZ or MDD (Paksarian et al., 2018; Sund et al., 2021), few studies assessed the associations between the genetic susceptibility to either psychopathology and indicators or low SES, such as finance issues.

Overall, comparing our own findings with the systematic review is challenging. We did not test for correlations between the PRS for either psychopathology and childhood adversity, urbanisation, adoption status as well as maternal prenatal anxiety or distress, given that these environments were not the focus of our thesis but were all correlated with the genetic vulnerability to either SCZ or MDD in the systematic review. In light of these discrepancies, the comparison of results reported with findings from the systematic review should be considered exploratory.

7.3.4 Comparison of SCZ versus MDD Findings from our own Studies in Childhood, Adulthood, across Time and the Systematic Review

Similarities

On the whole, analyses of rGE associations for SCZ and MDD in childhood, adulthood and over time highlighted that rGE was more evident for MDD compared to SCZ. Whilst we anticipated that rGE would differ between the psychiatric disorders given that the genetic overlap between them is only partial (Schizophrenia Working Group of the Psychiatric

Genomics Consortium, 2014; Wray et al., 2018), we expected rGEs for SCZ to be more prominent due to the higher heritability. It is possible that the discrepancy in rGE findings between SCZ and MDD could be accredited to a lower base rate for SCZ in the general population (Jaffee & Price, 2007). Although, as we utilised PRS in our analysis, this methodology should have, at least partially, addressed this issue. Whilst SCZ is highly heritable, it is also not inconceivable that rGE is more pronounced for MDD, specifically in childhood, due to having a lower heritability which consequently could be explained by the greater non-shared environments as highlighted by numerous twin studies.

Differences

The systematic review for SCZ and MDD showed that, in general, rGE findings are similar between the two disorders. Although, this finding is in contrast with our findings from childhood, adulthood and across time, it is also possible that some rGE results, as proposed by some of the empirical studies, may have been the result of environmental changes, and thus are not confounded by the genetic risk for these psychopathologies.

However, some points warrant further discussion. Firstly, we would like to point out that we retrieved a similar number of studies investigating SCZ and MDD. But a large proportion of included studies only focused on rGE associations in one of the two disorders and did not directly compare SCZ and MDD results.

Secondly, it is also important to acknowledge that, overall, there are significant genetic correlations between different psychopathological traits and psychiatric disorders (Martin et al., 2018; Peel et al., 2022). In particular, the genetic vulnerability for psychopathological traits and diagnosed psychiatric disorders in the population is shared either across different diagnoses (such as for bipolar disorder and SCZ) or for certain psychiatric disorders (such as attention-deficit-hyperactivity disorder) (Martin et al., 2018). Research also highlights substantial

comorbidities among psychopathological disorders in childhood as well as in adulthood, with these comorbidities being predominantly of genetic origin (Plomin, 2022). This genetic overlap between psychopathological outcomes is not the exception, but the rule. However, despite these genetic correlations between psychiatric disorders, they are consider distinct and unique according to existing nosology (Plomin, 2022). That means that currently nosology does not actually reflect the underlying genetic architecture of psychiatric disorders (Plomin, 2022).

Given the known shared genetic overlap between SCZ and MDD (Wray et al., 2018), it is therefore possible that this similarity in genetic foundations may have impacted findings of the systematic review and thus resulted in similar results between the two psychopathologies across the empirical studies which were included in the review. Therefore, the comparison of SCZ and MDD rGE findings in childhood, adulthood, across time, and within the rGE systematic review results should be considered exploratory.

7.4 Limitations

In spite of the many strengths of this thesis, such as the utilisation of three well-powered longitudinal cohorts from different generations, some limitations should also be noted.

Firstly, we only made use of psychosocial and environmental risk factors which were known to be implicated in the development of either SCZ or MDD. Also, not all selected environmental measures were available across all three selected community cohorts, and some were not measured during critical development periods, such as between ages 16 and 23 for NCDS. It is therefore possible, that some rGE correlations may not have been detected due to the lack of data points during these stages of rapid human development.

In addition, our study utilised three British community cohorts of different ages and from different generations. Whilst this allowed for a direct comparison of rGE changes across

different decades, it is also not inconceivable that cultural or societal changes in environmental risk could have contributed to cohort-specific findings as described in Chapters 3, 4 and 5 (Atingdui, 2011). For instance, the strength of the correlation between the PRS for SCZ and rented accommodation decreased over time in childhood. Given that our sensitivity analysis emphasised that this change in rGE over time cannot be attributed to *passive* rGE, it is likely that sociocultural changes play a part in this association.

Additionally, we lacked information on SCZ diagnosis or symptomology in USoc, which did not allow us to assess whether the presence of clinical cases could have contributed to any significant SCZ rGE findings.

Our descriptive statistics highlighted that we were also underpowered for some environmental risk factors for all three cohorts (See Appendices 8 to 10). We also identified some significant differences between the whole community cohorts and the genotype sub-samples for all three samples (See Appendix 8 to 10).

Further, in order to create PRS for NCDS, we utilised revised GWAS summary statistics from the PGC which excluded UK, but not Irish cohorts, for the updated SCZ GWAS, as well as 23andme and GenPod for the MDD GWAS summary statistics. It is therefore possible that some rGE associations for either psychopathology were not detected in NCDS.

It also needs to be highlighted that the PRS which were applied in our analyses in Chapters 3, 4 and 5 resulted from associations in GWAS datasets which did not take environmental influences into consideration. That means that we cannot rule out that any applied PRS also reflected environmental risk.

Lastly, our analyses from Chapters 3, 4 and 5 utilised UK cohorts only and thus any rGE findings cannot be generalised to populations from other countries or ethnicities.

7.5 Implications

7.5.1 Theoretical Implication

Findings from Chapters 3, 4, 5 and 6, as well as results from empirical twin, family and molecular genetic studies, propose that the genetic risk for SCZ and MDD is not independent of the environmental risk in the development of these two psychopathologies. In other words, many known adverse environmental risk factors for SCZ and MDD appear to mediate the genetic risk.

Moreover, our rGE results highlight that many childhood environments which are, at least partially, under genetic control are in fact parental behaviours, such as lack of interest in the child's education. However, research has shown that the significance of rGE correlations between the offspring's genotype and the parenting behaviour can also vary depending on the personality traits of the parents (Oppenheimer et al., 2013). That means that the variability of exposure to certain parental rearing environments can impact rGE associations and subsequently influence how successful early interventions would be.

Further, rGE associations largely differed across developmental periods as highlighted in Chapter 3, 4 and 5, with half of the identified rGE correlations in childhood being attributed to *passive* rGE whilst possible *active* rGE correlations were identified in adulthood. These findings help our understanding of how psychopathological outcome may develop over time and how environments which are often shaped by behaviours change across the different developmental periods.

Still, our rGE findings do not preclude the possibility that environmental risk factors are reciprocal or even causal in the development of psychopathological outcomes. For instance, genetically influenced behaviours may not just evoke responses from others but may also reinforce those specific behaviours in a causal manner (Knafo & Jaffee, 2013). In turn, if environments play a causal role in the aetiology of complex psychiatric disorders, then

reducing these environmental exposures through preventative interventions or treatments may consequently reduce the likelihood of developing psychopathological outcomes.

However, it is also important to highlight that our reported rGE findings do not explain how much of the genetic susceptibility to SCZ and MDD independently contributes to the aetiology of these psychiatric disorders. From an intervention and treatment perspective, it is imperative that we don't just understand whether exposures have causal or noncausal effects but also how large these effects are (Knafo & Jaffee, 2013). Future studies will need to further disentangle how much of the environmental risk factors can be attributed to the mediation of the genetic risk for SCZ and MDD versus how much of the environmental exposures are independent of the genetic risk. This can only be achieved with the use of transgenerational genotypes in well-powered cohorts.

7.5.2 Practical Implication

This thesis has established several important rGE associations for SCZ and MDD which contribute towards a deeper understanding of the aetiology of these complex psychopathologies with several potential practical implications.

Firstly, given that PRS generally account for only a small percentage in heritability in complex psychopathological outcomes, a heightened PRS for SCZ or MDD should not be interpreted as deterministic and should not be considered more than a possible indicator of an individual's lifetime risk for these psychiatric disorders (Lewis & Vassos, 2017, 2020). Whilst genetic predictions will make further advances in the future, the use of PRS in a clinical setting is perhaps best suited in diseases with a higher accuracy of risk prediction (Lewis & Vassos, 2017, 2020). This has recently been supported by a psychiatric study in 8,541 adults with SCZ and psychosis from the Bio*Me* cohort (Landi et al., 2021). The study highlighted that the PRS for SCZ did not improve the outcomes prediction in relation to clinical features in psychosis

cases compared with information gathered from a routine psychiatric assessment in a clinical care setting (Landi et al., 2021). In addition to not having a high predictive power, this finding further underlined that PRS need to be able to encode information which are otherwise not easily obtainable in order to achieve clinical utility for psychiatric disorders (Landi et al., 2021). However, some preventative interventions may benefit from the inclusion of PRS. For example, combining the offspring's biological risk for psychiatric disorders with information on social circumstances may identify vulnerable child-caregiver dyads which in turn would help social services and clinicians provide adequate training and support to the parents on how to care for these children (Jaffee & Price, 2012).

Moreover, findings from Chapters 3, 4, 5 and 6 do not propose that targeting some of the established environmental risk factors for SCZ or MDD will be ineffective in individuals with an increased genetic susceptibility for these two psychopathologies. Reducing some of the adverse environments may still reduce the likelihood of developing complex psychiatric disorders to some degree even though it may not fully eliminate the possibility of developing SCZ or MDD.

In addition, given that effect sizes for the majority of our rGE findings for SCZ and MDD across the three empirical studies described in Chapter 3, 4 and 5 were small in magnitude, our findings will need to be interpreted with that in mind. As a result, many of these correlations will likely only have a small impact on individuals from the general population.

Further, given that rGE findings for SCZ and MDD differed somewhat between the two psychiatric disorders as highlighted in Chapters 3, 4 and 5, any environments which are targeted for preventative or treatment purposes would need to be specific to the underlying psychopathology.

Lastly, as highlighted in the discussion section, rGE associations for SCZ and MDD are largely different in childhood and adulthood. Thus, environmental risk factors which are

targeted for treatment will need to be specific to the developmental period within which they are most likely relevant. Consequently, interventions will need to vary depending on which developmental period the individual with the underlying psychopathological outcome is in.

7.5.3 Developmental Implications

There is strong evidence for associations between the genetic susceptibilities for psychiatric outcomes and environmental exposures in childhood which are associated with an increased risk of psychopathology later in life.

Several hypothesised mechanisms warrant further discussion. Firstly, the conventional understanding in social and clinical science is that at least some day-to-day environments in childhood may be causal in amplifying the risk for psychopathology later in life (Knafo & Jaffee, 2013). For example, this may include negative parenting behaviours, such as harsh discipline or adverse home environments including poverty (Knafo & Jaffee, 2013), which may directly contribute to the development of psychiatric disorders over time.

Further, it is plausible that psychiatric symptoms themselves can increase the risk of negative life events which, in turn, may lead to psychopathology as individuals grow older (Kendler, Gardner, et al., 2006). For instance, youths or individuals in early adulthood who display a lot of anger towards others, such as in the workplace, may struggle holding down a job, which could subsequently lead to financial hardship, driving psychopathological outcome later on in life.

Thirdly, It is also possible that above average pre-adolescence psychiatric symptoms may mark a gradual upward trajectory of these symptoms and consequently result in psychiatric disorders later on in life (Goodyer et al., 2000). For instance, elevated depressive symptoms in pre-adolescence have been found to predict depressive symptoms in adolescence (Goodyer et al., 2000).

However, a fourth proposed mechanism suggests that behaviours associated with psychiatric symptoms may not be causal themselves but simply indicate a genetic susceptibility to psychopathology which seems to influence exposure to environmental risk factors through rGE, which is in line with findings from our own studies presented in this thesis. For example, research proposes that the offspring's genetic susceptibility likely influences family chaos and parenting styles at age 9 through rGE, with these shared environmental factors also influencing depressive symptoms at age 12 (Wilkinson et al., 2013). However, the same genetic factors which are associated with family chaos and parenting at age 9 may also subsequently influence depressive symptoms of the adolescent at age 12 (Wilkinson et al., 2013).

Depending on whether the associations between genetic risk and developmental outcomes are causal, non-causal, or a sign of a more complex reciprocal relationship over time, has important implications across the different developmental stages (Knafo & Jaffee, 2013). Specifically, if rGE associations are indeed contributing causally to the development of SCZ and MDD, then it may be necessary, depending on the underlying type of rGE that is present, to concentrate on systemic approaches for mental health treatment on both offspring and their parents. Taking this point further, preventative interventions need to adopt a developmental approach which is contingent on whether rGE is *passive*, such as in infancy or early childhood, or shifting to *evocative/active* associations as individuals grow older. For instance, mothers carrying a genetic susceptibility for increased alcohol consumption, which will likely be passed on to their offspring, may drink more during pregnancy which could consequently result in foetal alcohol disorders. This *passive* rGE could be prevented by providing interventions to reduce alcohol consumption in expecting mothers with a risk for such behaviours (Jaffee & Price, 2012).

Secondly, as children grow older, *evocative* rGE could be circumvented in situations when challenging children elicit insensitive or even harsh care from their parents, by screening

for such children and providing parent training before child behaviour problems emerge (Jaffee & Price, 2012). This training could involve teaching parents to respond differently to their offspring, subsequently changing behavioural outcomes in these children (Horwitz & Neiderhiser, 2011). These preventative actions could be further extended to teachers, social workers or carers who are in frequent contact with such children.

Thirdly, behavioural interventions, such as behavioural activation therapy, may be able to target specific behavioural processes which are involved in selecting and moulding an individual's environments based on their own genetic predispositions in *active* rGE, including system-level interventions via early school and education programs (Perlstein & Waller, 2022).

In sum, it is important to identify children at genetic risk for psychiatric disorders who grow up in potential negative or adverse environments, as well as any parents who care for challenging offspring, early on in order to provide adequate family support and thus reduce the risk of psychopathological outcomes in these children.

7.6 Future Direction

In light of our rGE findings, this next section is going to provide suggestions for future studies which have been grouped into three categories: 1) GWAS considerations, 2) the need to understand the psychopathological outcome of interest as well as 3) methodological considerations.

GWAS considerations

Evolutionary processes like natural selection or genetic drift can contribute to different allele frequencies in different populations (Jaffee & Price, 2007, 2012) and can introduce spurious associations which in turn can lead to bias in GWAS studies (Abdellaoui et al., 2022; Jaffee & Price, 2007, 2012). Whilst population stratification is commonly controlled for by

using principal components that reflect the strongest genetic variations as covariates, caution should be taken when applying geographic clustering of DNA by region which can further affect GWAS results and reduce SNP-based heritability estimates especially for SES-related outcomes as highlighted by a recent study by Abdellaoui et al (2022).

Further, findings from Chapter 6 have highlighted the disproportional use of European cohorts in psychiatric rGE research. More specifically, despite Europeans only accounting for 16% of the total population, they make up about 79% of all GWAS participants (Martin et al., 2019). As GWAS favours common risk variants in the population under study as well as the fact that LD differentiates even marginal effect-size estimates for complex, polygenic traits (Martin et al., 2019), the predictive power of PRS, which utilises these GWAS summary statistics, will consequently be more powerful in these European subpopulations (Palk et al., 2019). Therefore, GWAS studies need to diversify and include other ethnic groups to ensure that psychiatric genetic research can adequately test associations across all populations.

Understanding the Psychopathological Outcome of Interest

Another important consideration in rGE research is the presence of *behavioural contamination.* Factors specific to an individual can influence their perception and, thus the individual's retrospective report of the environment which, in turn, can bias sample selection and falsely give rise to rGE (Jaffee & Price, 2007). Also, given that environmental exposures change as individuals move through the different developmental stages and the fact that effects of these exposures may vary depending on when they occur during critical developmental periods (Halfon et al., 2014; Knafo & Jaffee, 2013), it is imperative that cohorts apply frequent and objective phenotypic and environmental measures (Das, 2019; Jaffee & Price, 2007). This is of particular relevance for studies conducted in children who undergo rapid changes between childhood and adolescence, requiring detailed environmental measurements at appropriate

timepoints (Knafo & Jaffee, 2013).

Moreover, the heritability for some complex psychological traits, such as intelligence, increases as we age despite genetic stability (Plomin & Deary, 2015). This phenomenon, which researchers refer to as *genetic amplification* or *Wilson effect* (Bouchard, 2013; Plomin & Deary, 2015) could be explained by the presence of rGE as slight genetic differences are amplified when children create, modify and select themselves into environments which are correlated with their genetic make-up (Plomin & Deary, 2015). It is therefore crucial that future research considers longitudinal and developmental approaches where possible, in order to appropriately assess rGE associations for psychopathological outcomes.

Methodological Considerations

rGE studies also face several additional methodological challenges, specifically given that gene-environment research is often focused on GxE studies and rGE findings repeatedly failed replication (Jaffee & Price, 2008). Studies require large sample sizes in order to detect small rGE effect sizes, robust environmental measures as well as a clear understanding of the biological pathways of how gene variants can influence our behaviours to be able to interpret any rGE findings (Jaffee & Price, 2007).

Whilst the rGE analyses for SCZ and MDD from Chapters 3, 4 and 5 utilised male and female participants across three selected British community cohorts, meta-analyses propose that the male to female ratio of individuals being diagnosed with SCZ is 1.4 and an OR of 0.63 for MDD (Abate, 2013; Aleman et al., 2003). Therefore, future studies should aim to investigate whether rGE correlations for complex psychopathological outcomes will also consequently differ between males and females across the different developmental periods.

In order to disentangle the complex gene-environment interplay in psychopathological outcome, studies will need to adopt transgenerational designs to distinguish which form of rGE

mechanism is present. This study design, as utilised in MCS described in Chapter 3 of this thesis, would be able to assess whether the child genotype is confounded by the maternal or paternal genotypes (Krapohl et al., 2017) and thus enable a distinction to be made between *passive* or *evocative* rGE.

Lastly, although research needs to take careful precautions to prevent any possible confounding between rGE and GxE (Jaffee & Price, 2007), studies should consider rGE and GxE as a whole through joint analysis in multi-disciplinary approaches (Lau & Eley, 2008). For instance, the genetic risk for depressive symptoms may influence the exposure to negative life events through rGE, whilst these life events may also interact with the genetic susceptibilities on symptoms through GxE (Lau & Eley, 2008). This would allow for better differentiation of the type of gene-environment interplay and thus help identify more targeted medical interventions and prevention treatments.

7.7 Conclusions

To conclude, this thesis provides further evidence for rGE correlations in SCZ and MDD across different developmental periods, using three well-powered British community cohorts, to support our understanding of the aetiology of these complex psychopathological disorders.

Chapter 3 suggests that about half of the identified rGE correlations in childhood can be attributed to *passive* rGE, whereby parents pass on their genetic susceptibilities to their offspring and provide the child's family environment.

Conversely, our analysis of rGE correlations in SCZ and MDD in adulthood in Chapter 4 proposes possible *active* rGE correlations implicating indicators of low SES.

However, whilst evidence from empirical studies and theorical frameworks propose that rGE gets stronger over time as individuals actively select and modify their own

environments according to their genetic make-up, Chapter 6, which investigated rGE changes over time in SCZ and MDD, did not support this view and highlighted that the majority of rGE associations were actually stable across childhood and adulthood.

All three analyses showed that rGE associations in MDD were more strongly pronounced across the different developmental stages compared to SCZ, which could be explained by the lower heritability and possible non-shared environments in individuals with a heightened PRS for MDD.

Overall, the reported rGE findings are in line with other rGE studies which were supported by the systematic literature review, showing that adverse early maternal or paternal behaviours as well as psychosocial and environmental risk factors are correlated with the PRS for SCZ and MDD.

Whilst findings from our three own studies support the hypothesis that there are clear differences in rGE findings between SCZ and MDD, which could be attributed to the fact that there is only a partial genetic overlap between the two psychiatric disorders, this finding was not confirmed by the systematic review.

Although this thesis provides a solid and comprehensive overview of rGE correlations in SCZ and MDD in childhood and adulthood as well as across different generations, future studies need to focus on replicating and extending rGE research across these complex psychopathological outcomes, as outlined in the future direction section. This will further help disentangle the complicated interplay between our genes and the environment, with the aim to help support, prevent or even treat individuals with chronic and debilitating mental health conditions.

Appendix

All appendices are *Adapted from* Machlitt-Northen, S., Keers, R., Munroe, P.B., Howard, D.M., Trubetskoy, V. and Pluess, M. (2022), Polygenic scores for schizophrenia and major depression are associated with psychosocial risk factors in children: evidence of gene–environment correlation. J Child Psychol Psychiatr, 63: 1140-1152., Suppl. https://doi.org/10.1111/jcpp.13657. CC-BY-NC; Machlitt-Northen, S., Keers, R., Munroe, P. B., Howard, D. M., & Pluess, M. (2022). Polygenic risk scores for schizophrenia and major depression are associated with socio-economic indicators of adversity in two British community samples. Translational Psychiatry, 12(1), 477, Suppl. https://doi.org/10.1038/s41398-022-02247-8. CC-BY-NC and Machlitt-Northen, S.; Keers, R.; Munroe, P.B.; Howard, D.M.; Pluess, M. Gene–Environment Correlation over Time: A Longitudinal Analysis of Polygenic Risk Scores for Schizophrenia and Major Depression in Three British Cohorts Studies. Genes 2022, 13, 1136. https://doi.org/10.3390/genes13071136. CC-BY-NC.

Appendix 1: *Coded Variables for MCS (Chapter 3)*

Environment Name	Variable		Coded as	Wave						Mixed-effect regression		Random effects model
	Code	Name		1	2	3	4	5	6	Random slope	Random slope + intercept	
Alcohol mother	APALDR00	Frequency of alcohol consumption per week	0 = 1-2 times per month, Less than once a month, Never 1 = 5-6 times per week, 3-4 times per week, 1-2 times per week Only coded mother's responses	X								X
	CPALDR00	Frequency of alcohol consumption per week				X						
	DPALDR00	Frequency of alcohol consumption per week					X					
	EPALDR00	Frequency of alcohol consumption per week						X				
	FPALDR00	Frequency of alcohol consumption per week							X			
Alcohol father	APALDR00	Frequency of alcohol consumption per week	0 = 1-2 times per month, Less than once a month, Never 1 = 5-6 times per week, 3-4 times per week, 1-2 times per week	X						X		
	CPALDR00	Frequency of alcohol consumption per week				X						
	DPALDR00	Frequency of alcohol consumption per week					X					

	EPALDR00	Frequency of alcohol consumption per week	Only coded father's responses					X				
	FPALDR00	Frequency of alcohol consumption per week							X			
Finance Issues	APMAFI00	How well respondent manages financially (self-rated)	0 = Living comfortably, doing alright, just about getting by 1 = finding it quite difficult, finding it very difficult Coded mother's responses, if unavailable, used father's responses	X						X		
	BPMAFI00	How well respondent manages financially (self-rated)			X							
	FPMAFI00	How well respondent manages financially (self-rated)							X			
Parent's marital status	APFCIN00	Current legal marital status	0 = Married, 1st and only marriage, Remarried, 2nd or later marriage, Civil Partner (legally recognised) 1 = Legally separated, Divorced, Widowed, former Civil Partner, Surviving Civil Partner Coded mother's responses, if unavailable, used father's responses	X								X
	CPFCIN00	Current legal marital status				X						
	DPFCIN00	Current legal marital status					X					
	EPFCIN00	Current legal marital status						X				
	FPFCIN00	Current legal marital status							X			
Mother reads to child	CPREOF0	How often do you read to CM	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded mother's responses only			X				X		
	DPREOF00	How often do you read to CM					X					

Father reads to child	CPREOF0	How often do you read to CM	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded father's responses only			X				X		
	DPREOF00	How often do you read to CM					X					
Rooms	APROMA00	Number of rooms - grouped	Continuous variable Coded mother's responses, if unavailable, used father's responses	X							X	
	BPROMA00	Number of rooms - grouped			X							
	CPROMA00	Number of rooms - grouped				X						
	DPROMA00	Number of rooms - grouped					X					
	FPROMA00	Number of rooms (excl bath/toilets/halls)							X			
SES	ADD05C00	DV NS-SEC 5 classes (last known job)	1 = Semi-routine and routine 2 = Lower supervisory and technical 3 = Small employers and self-employed 4 = Intermediate 5 = Managerial and professional Coded mother's responses, if unavailable, used father's responses	X							X	
	BDD05S00	Respondent NS-SEC 5 classes			X							
	CDD05C00	DV NS-SEC 5 classes (last known job)				X						
	DDD05C00	DV NS-SEC 5 classes (last known job)					X					
Smoking Mother	APSMUS0A	Current smoking MC1	0 = No, does not smoke 1 = Yes, cigarettes, Yes, roll-ups, Yes, cigars,	X								X
	EPSMUS0A	Current use of tobacco products						X				

	FPSMUS0A	Current use of tobacco products	Yes, a pipe, Yes, other tobacco product Coded mother's responses only						X			
Smoking Father	APSMUS0A	Current smoking MC1	0 = No, does not smoke 1 = Yes, cigarettes, Yes, roll-ups, Yes, cigars, Yes, a pipe, Yes, other tobacco product Coded father's responses only	X						X		
	EPSMUS0A	Current use of tobacco products						X				
	FPSMUS0A	Current use of tobacco products							X			
Tenure	ADROOW00	Tenure of current home (owns/rents)	0 = Own outright, Own - mortgage/loan, Part rent/part mortgage (shared equity) 1 = Rent from local authority, Rent from Housing Association, Rent privately, Living with parents, Live rent free, Other Coded mother's responses, if unavailable, used father's responses	X						X		X (for sensitivity analysis)
	BDROOW00	Tenure of current home (owns/rents)			X							
	CDROOW00	Tenure of current home (owns/rents)				X						
	DPROOW00	Tenure of current home (owns/rents)					X					
	EPROOW00	DV Housing Tenure						X				
	FDROOW00	S6 DV Housing Tenure							X			
Mother walks child	CPWALK00	Frequency take child to park or playground	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded mother's responses only			X				X		
	DPWALK00	Frequency take child to park or playground					X					

Father walks child	CPWALK00	Frequency take child to park or playground	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded father's responses only			X				X		
	DPWALK00	Frequency take child to park or playground										
Birth weight	APWTLB00	Birth weight (pound)	Continuous variable	X						Only available at single timepoint		
Employment mother	APMACT00	Main activity	0 = In a job and currently working, On paternity/parental leave, self-employed 1 = Full-time student, Looking after the home and family Coded mother's responses only	X						Only available at single timepoint		
Father's interest in child's education	EQ20B	S5 TS How interested CM's father appears to be in their education	0 = Very interested, Fairly interested, Neither interested or uninterested 1 = Fairly uninterested, Very uninterested					X		Only available at single timepoint		
Mother's interest in child's education	EQ20A	S5 TS How interested CM's mother appears to be in their education	0 = Very interested, Fairly interested, Neither interested or uninterested 1 = Fairly uninterested, Very uninterested					X		Only available at single timepoint		
Father's role in upbringing	APCHFA00	Fathers' involvement in upbringing	0 = Strongly agree, Agree, Neither agree nor disagree 1 = Disagree, Strongly disagree	X						Only available at single timepoint		

			Coded mother's responses, if unavailable, used father's responses							
Gestation	ADGEST00	DV Cohort Member Gestation time in days	Continuous variable	X						Only available at single timepoint

Note: MCS = Millennium Cohort Study. Any 'N/A', 'Don't know', 'Blanks', 'Refusals', 'Can't say' or 'other' answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 2: *Coded Variables for NCDS – Childhood (Chapter 3)*

Environment Name	Variable		Coded as	Variable timeline (Age of participant)				Mixed-effect regression	
	Code	Name		0	7	11	16	Random slope	Random slope + intercept
SES	N492	0 Social class mother's husband (GRO 1951)	5 Professional 4 Managerial/ Technical 3 Skilled 2 Partly skilled 1 Unskilled	X					X
	N190	1P Social class of father, male head (GRO 1960)			X				
	N1687	2PD Social class of father or male head (GRO 1966)				X			
	N1687	2PD Social class of father or male head (GRO 1966)					X		
Finance Issues	N315	1P Family difficulties - Financial	0 = No 1 = Yes		X			X	
	N1230	2P Serious financial hardship last yr				X			
	N2441	3P Serious financial trouble last yr					X		
Number of Rooms	N201	1P Number of rooms in household	Continuous variable		X				X
	N1156	2P Number of rooms in accommodation				X			

	N1156	2P Number of rooms in accommodation					X		
Tenure	N200	1P Tenure of accommodation	0 = owns 1 = rents (including social housing)		X			X	
	N1152	2P Tenure of accommodation				X			
	N2471	3P Type of accommodation					X		
Mother's interest in child's education	N43	1S Mother's interest in childs education	0 = Interested (including some interest) 1 = Not interested		X			X	
	N852	2S Mothers' interest in childs education				X			
	N2325	3S Mother's interest in chlds education					X		
Father's interest in child's education	N44	1S Father's interest in childs education	0 = Interested (including some interest) 1 = Not interested		X			X	
	N851	2S Fathers' interest in childs education				X			
	N2324	3S Father's interest in chlds education					X		
Father's involvement in childcare	N183	1P Dads role in management of child	0 = Involved (including some involvement) 1 = Not involved		X			X	
	N1147	2P Dads role in management of child				X			
Mother walks child	N181	1P Outings with mother	0 = Most weeks/occasionally 1 = Hardly ever		X			X	
	N1145	2P Does mum take child for walks,visits				X			

Father walks child	N182	1P Outings with father	0 = Most weeks/occasionally 1 = Hardly ever		X			X	
	N1146	2P Does dad take child for walks, visits				X			
Employment father	N188	1P Unemployed, sick and retired (GRO 1960)	0 = Employed (including retired) 1 = Unemployed/sick		X			X	
	N1172	2P Father, male head's occupation				X			
	N2383	3P Father or father figure's occupation (GRO 1970)					X		
Free school meals	N1229	2P Does any child get free school meals	0 = No 1 = Yes			X		X	
	N2440	3P Does any child get free school meals					X		
Maternal Smoking prior pregnancy	N502	0 Smoking prior to pregnancy	0 = Non-Smoker 1 = Smoker	X					
Maternal Smoking during pregnancy	N503	0 Smoking during pregnancy	0 = Non-Smoker 1 = Smoker	X					
Parity	N504	0 Parity	Continuous variable where 0 = no previous pregnancy	X					
Mother's age at birth	N553	0 Mother's age last birthday, in years	Continuous variable	X					
Father's age at birth	N494	0 Husband's age in years,1958	Continuous variable	X					
Gestational period	N497	0 Gestation period in days	Continuous variable	X					
Birth weight	N574	0 Weight of baby in ounces	Continuous variable	X					
Mother marital status at birth	N545	0 Mother's present marital status	0 = Married/ Twice married/Stable Union 1 = Unmarried/Separated/Divorced/Widowed	X					

Housing Issues	N314	1P Family difficulties-Housing	0 = No 1 = Yes		X				
Family Alcohol issues	N325	1P Family difficulties-Alcoholism	0 = No 1 = Yes		X				
Domestic Tension	N322	1P Family difficulties-Domestic tension	0 = No 1 = Yes		X				
Father reads to child	N180	1P Father reads to child	0 = Weekly/ occasionally 1 = Hardly ever		X				
Mother reads to child	N179	1P Mother reads to child	0 = Weekly/ occasionally 1 = Hardly ever		X				
Schizophrenia	N9EMOP05	Type of Emotional Problem - Schizophrenia	0 = No 1 = Yes	Used for sensitivity analysis only					
Hallucinations	N9EMOP04	Type of Emotional Problem - Hallucinations	0 = No 1 = Yes	Used for sensitivity analysis only					
Psychosis	N9EMOP07	Type of Emotional Problem - Psychosis	0 = No 1 = Yes	Used for sensitivity analysis only					
Depression	N9EMOP01	Type of Emotional Problem - Depression	0 = No 1 = Yes	Used for sensitivity analysis only					

Note: NCDS = 1958 National Child Development Study. Any ‘N/A’, ‘Don’t know’ or ‘other’ answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 3: *Coded Variables for USoc (Chapter 4)*

Environment	Variable		Coded as	Wave									Mixed-effect regression		Random effects model
	Code	Name		1	2	3	4	5	6	7	8	9	Random slope	Random slope + intercept	
Alcohol intake	b_scnalcl7d	On how many days did you have an alcoholic drink?	Coded as number of days per week on which alcohol is consumed		X								X		
	e_scnalcl7d	number of days had alcoholic drink in last 7						X							
Education	a_hiqual_dv	Highest qualification ever reported	0 = Educated to A-level or above 1 = Educated to GSCE level or below	X									X		
	b_hiqual_dv	Highest qualification			X										
	c_hiqual_dv	Highest qualification				X									
	d_hiqual_dv	Highest qualification					X								
	e_hiqual_dv	Highest qualification						X							
	f_hiqual_dv	Highest qualification							X						
	g_hiqual_dv	Highest qualification								X					
	h_hiqual_dv	Highest qualification									X				
	i_hiqual_dv	Highest qualification										X			
Number of Rooms	a_hsbeds	number of bedrooms (top-coded)	Continuous variable	X										X	
	b_hsbeds	number of bedrooms (top-coded)			X										
	c_hsbeds	number of bedrooms (top-coded)				X									

	d_hsbeds	number of bedrooms (top-coded)					X									
	e_hsbeds	number of bedrooms (top-coded)						X								
	f_hsbeds	number of bedrooms (top-coded)							X							
	g_hsbeds	number of bedrooms (top-coded)								X						
	h_hsbeds	number of bedrooms (top-coded)									X					
	i_hsbeds	number of bedrooms (top-coded)										X				
SES	a_jbrgsc_dv	Current job: Registrar General's Social Class	5 = Professional 4 = Managerial-technical 3 = Skilled non-manual and manual 2 = Partly skilled 1 = Unskilled	X											X	
	b_jbrgsc_dv	Current job: Registrar General's Social Class			X											
	c_jbrgsc_dv	Current job: Registrar General's Social Class				X										
	d_jbrgsc_dv	Current job: Registrar General's Social Class					X									
	e_jbrgsc_dv	Current job: Registrar General's Social Class						X								
	f_jbrgsc_dv	Current job: Registrar General's Social Class							X							
	g_jbrgsc_dv	Current job: Registrar General's Social Class								X						
	h_jbrgsc_dv	Current job: Registrar General's Social Class									X					
	i_jbrgsc_dv	Current job: Registrar General's Social Class										X				
Income	a_fimngrs_dv	total monthly personal income gross - 50-iles	Grouped into 50 sub-groups – 2% per group (total 100%)	X											X	
	b_fimngrs_dv	total monthly personal income gross - 50-iles			X											
	c_fimngrs_dv	total monthly personal income gross - 50-iles				X										
	d_fimngrs_dv	total monthly personal income gross - 50-iles					X									

	e_fimngrs_dv	total monthly personal income gross - 50-iles							X							
	f_fimngrs_dv	total monthly personal income gross - 50-iles								X						
	g_fimngrs_dv	total monthly personal income gross - 50-iles									X					
	h_fimngrs_dv	total monthly personal income gross - 50-iles										X				
	i_fimngrs_dv	total monthly personal income gross - 50-iles											X			
Employment	a_jbstat	Current economic activity	0 = employed/retired/ maternity leave/ apprenticeship 1 = unemployed/education/ sick/in care/unpaid/gov training	X												X
	b_jbstat	Current economic activity			X											
	c_jbstat	Current economic activity				X										
	d_jbstat	Current economic activity					X									
	e_jbstat	Current economic activity						X								
	f_jbstat	Current economic activity							X							
	g_jbstat	Current economic activity								X						
	h_jbstat	Current economic activity									X					
	i_jbstat	Current economic activity										X				
Financial situation	a_finnow	Subjective financial situation - current	0 = Comfortable financially and just getting by financially 1 = Experiencing financial difficulties	X											X	
	b_finnow	Subjective financial situation - current			X											
	c_finnow	Subjective financial situation - current				X										
	d_finnow	Subjective financial situation - current					X									
	e_finnow	Subjective financial situation - current						X								

	f_finnow	Subjective financial situation - current							X							
	g_finnow	Subjective financial situation - current								X						
	h_finnow	Subjective financial situation - current									X					
	i_finnow	Subjective financial situation - current										X				
Tenure	a_hsownd	house owned or rented	0 = owner/shared ownership /mortgaged 1 = rented/ rent-free	X												X
	b_hsownd	house owned or rented			X											
	c_hsownd	own accommodation				X										
	d_hsownd	house owned or rented					X									
	e_hsownd	own accommodation						X								
	f_hsownd	house owned or rented							X							
	g_hsownd	house owned or rented								X						
	h_hsownd	house owned or rented									X					
	i_hsownd	house owned or rented										X				
Marital Status	a_mlstat	Present legal marital status	0 = Married/in civil partnership 1 = single/separated/ divorced/ widowed	X									Only available at single timepoint			
Depression	a_hcond17	Clinical depression	0 = no 1 = yes	X									Only used for sensitivity analysis			
	c_hcond17	Clinical depression				X										
	e_hcond17	Clinical depression						X								
	f_hcond17	Clinical depression							X							
	g_hcond17	Clinical depression								X						

	h_hcond17	Clinical depression									X		
	i_hcond17	Clinical depression										X	
Psychiatric problems	bk_hlprxi	Received treatment for psychiatric problems	0 = no 1 = yes	Individuals who previously participated in the British Household Panel study (now USoc) and received treatment for psychiatric problems during that time									Only used for sensitivity analysis
	bp_hlprxi	Received treatment for psychiatric problems											

Note: USoc = Understanding Society. Any 'N/A', 'Don't know' or 'other' answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 4: *Coded Variables for NCDS – Adulthood (Chapter 4)*

Environment	Variable		Coded as	Variable timeline (Age of participant)						Mixed-effect regression	
	Code	Name		23	33	42	46	50	55	Random slope	Random Slope + intercept
SES	N6149	4I Current or last job 1980 social class	5 Professional 4 Managerial/ occupations 3 Skilled 2 Partly-skilled 1 Unskilled	X							X
	N540056	CASOC2:2 A4a/b) CURRENT/LAST JOB: RGs Social Class 1981			X						
	SC	(Current Job) Social Class				X					
	N7SC	(Derived) Social Class (RGSC SC based on Occ 1990)					X				
	N8SC	[SC2] Curr Job: Social Class (RGSC SC based on Occ 1990)						X			
	N9CSC	Social class 1990 based on soc2010 (CM current job)							X		
Employment	N4755	4I Whether currently unemployed	0 = Employed or Self-employed (full or part-time) 1 = Unemployed, sick, disabled Removed retired	X						X	
	ECONACT	CMs current main activity				X					
	N8ECON02	[ECONACT2] (Recoded) CM's current economic activity						X			
	ND9ECACT	(Derived) Current economic activity status							X		
Number of Rooms	N5323	4I Number of bedrooms	Continuous variable	X						X	
	N502947	CMI:57 D9 No. rooms (apart from the bathroom & kitchen)			X						
	BEDROOMS	Number of bedrooms in current acco				X					
	N7NUMRMS	Number of rooms in the house					X				
	ND8NUMRM	(Derived) Number of rooms in the house (n8numrms)						X			
	N9NUMRMS	Number of rooms in home							X		

Tenure	N5333	4I Whether owner or renter	0 = owns/part-owns 1 = rents (including social housing)	X						X	
	TENURE91	DV:Housing tenure in 1991			X						
	TENURE2	Is current accom owned or rented				X					
	N7TEN	Home ownership / tenure status					X				
	N8TEN	[TENURE] Home ownership / tenure status						X			
	N9TEN	Whether CM owns or rents home or some other arrangement							X		
Marital status	PARTSTAT	4D Current partnership status	0 = married/ co-habiting/ in relationship 1 = not in relationship	X						X	
	N502549	CMI:51 C52 CM is cohabiting/married other			X						
	DMSPPART	Whether CM had current partner in hhld in NCDS V (FF)				X					
	N7MS12	Person's marital status - 02					X				
	ND8SPPHH	(Derived) Cohort member lives with a spouse or partner						X			
	ND9COHAB	(Derived) Whether CM cohabiting as a couple							X		
Smoking	CURRENTN	4D Smoking patterns	0 = Never smoked 1 = Smoker/ Ex-smoker	X						X	
	SMOKING	CM current smoking status				X					
	N8SMOKIG	[SMOKING] Smoking frequency						X			
Depression	N9EMOP01	Type of Emotional Problem - Depression	0 = No 1 = Yes						X	Used for sensitivity analysis only	

Note: NCDS = 1958 National Child Development Study. Any ‘N/A’, ‘Don’t know’ or ‘other’ answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 5: *Coded Variables for MCS (Chapter 5)*

Environment Name	Variable		Coded as	Wave						Interaction Model	
	Code	Name		1	2	3	4	5	6	Mixed effect	Random effect
Alcohol mother	APALDR00	Frequency of alcohol consumption per week	0 = 1-2 times per month, Less than once a month, Never 1 = 5-6 times per week, 3-4 times per week, 1-2 times per week Only coded mother's responses	X							X
	CPALDR00	Frequency of alcohol consumption per week				X					
	DPALDR00	Frequency of alcohol consumption per week					X				
	EPALDR00	Frequency of alcohol consumption per week						X			
	FPALDR00	Frequency of alcohol consumption per week							X		
Alcohol father	APALDR00	Frequency of alcohol consumption per week	0 = 1-2 times per month, Less than once a month, Never 1 = 5-6 times per week, 3-4 times per week, 1-2 times per week Only coded father's responses	X						X	
	CPALDR00	Frequency of alcohol consumption per week				X					
	DPALDR00	Frequency of alcohol consumption per week					X				
	EPALDR00	Frequency of alcohol consumption per week						X			
	FPALDR00	Frequency of alcohol consumption per week							X		
Finance Issues	APMAFI00	How well respondent manages financially (self-rated)	0 = Living comfortably, doing alright, just about getting by 1 = finding it quite difficult, finding it very difficult Coded mother's responses, if	X						X	
	BPMAFI00	How well respondent manages financially (self-rated)			X						
	FPMAFI00	How well respondent manages financially (self-rated)							X		

			unavailable, used father's responses								
Parent's marital status	APFCIN00	Current legal marital status	0 = Married, 1st and only marriage, Remarried, 2nd or later marriage, Civil Partner (legally recognised) 1 = Legally separated, Divorced, Widowed, former Civil Partner, Surviving Civil Partner Coded mother's responses, if unavailable, used father's responses	X							X
	CPFCIN00	Current legal marital status				X					
	DPFCIN00	Current legal marital status					X				
	EPFCIN00	Current legal marital status						X			
	FPFCIN00	Current legal marital status							X		
Mother reads to child	CPREOF0	How often do you read to CM	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded mother's responses only			X				X	
	DPREOF00	How often do you read to CM					X				
Father reads to child	CPREOF0	How often do you read to CM	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded father's responses only			X				X	
	DPREOF00	How often do you read to CM					X				
Rooms	APROMA00	Number of rooms - grouped	Continuous variable Coded mother's responses, if	X						X	
	BPROMA00	Number of rooms - grouped			X						

	CPROMA00	Number of rooms - grouped	unavailable, used father's responses			X					
	DPROMA00	Number of rooms - grouped					X				
	FPROMA00	Number of rooms (excl bath/toilets/halls)							X		
SES	ADD05C00	DV NS-SEC 5 classes (last known job)	1 = Semi-routine and routine 2 = Lower supervisory and technical 3 = Small employers and self-employed 4 = Intermediate 5 = Managerial and professional Coded mother's responses, if unavailable, used father's responses	X						X	
	BDD05S00	Respondent NS-SEC 5 classes			X						
	CDD05C00	DV NS-SEC 5 classes (last known job)				X					
	DDD05C00	DV NS-SEC 5 classes (last known job)					X				
Smoking Mother	APSMUS0A	Current smoking MC1	0 = No, does not smoke 1 = Yes, cigarettes, Yes, roll-ups, Yes, cigars, Yes, a pipe, Yes, other tobacco product Coded mother's responses only	X							X
	EPSMUS0A	Current use of tobacco products						X			
	FPSMUS0A	Current use of tobacco products							X		
Tenure	ADROOW00	Tenure of current home (owns/rents)	0 = Own outright, Own - mortgage/loan, Part rent/part mortgage (shared equity) 1 = Rent from local authority, Rent from Housing Association, Rent privately, Living	X						X	(X for Sensitivity analysis)
	BDROOW00	Tenure of current home (owns/rents)			X						
	CDROOW00	Tenure of current home (owns/rents)				X					
	DPROOW00	Tenure of current home (owns/rents)					X				
	EPROOW00	DV Housing Tenure						X			

	FDROOW00	S6 DV Housing Tenure	with parents, Live rent free, Other Coded mother's responses, if unavailable, used father's responses						X		
Mother walks child	CPWALK00	Frequency take child to park or playground	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded mother's responses only			X				X	
	DPWALK00	Frequency take child to park or playground					X				
Father walks child	CPWALK00	Frequency take child to park or playground	0 = Every day, Several times a week, Once or twice a week 1 = Once or twice a month, Less often, Not at all Coded father's responses only			X				X	
	DPWALK00	Frequency take child to park or playground					X				

Note: MCS = Millennium Cohort Study. Any 'N/A', 'Don't know', 'Blanks', 'Refusals', 'Can't say' or 'other' answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 6: *Coded Variables for USoc (Chapter 5)*

Environment	Variable		Coded as	Wave									Interaction Model	
	Code	Name		1	2	3	4	5	6	7	8	9	Mixed Effect	Random Effect
Number of Rooms	a_hsbeds	number of bedrooms (top-coded)	Continuous variable	X									X	
	b_hsbeds	number of bedrooms (top-coded)			X									
	c_hsbeds	number of bedrooms (top-coded)				X								
	d_hsbeds	number of bedrooms (top-coded)					X							
	e_hsbeds	number of bedrooms (top-coded)						X						
	f_hsbeds	number of bedrooms (top-coded)							X					
	g_hsbeds	number of bedrooms (top-coded)								X				
	h_hsbeds	number of bedrooms (top-coded)									X			
	i_hsbeds	number of bedrooms (top-coded)										X		
SES	a_jbrgsc_dv	Current job: Registrar General's Social Class	5 = Professional 4 = Managerial-technical 3 = Skilled non-manual and manual 2 = Partly skilled 1 = Unskilled	X									X	
	b_jbrgsc_dv	Current job: Registrar General's Social Class			X									
	c_jbrgsc_dv	Current job: Registrar General's Social Class				X								
	d_jbrgsc_dv	Current job: Registrar General's Social Class					X							
	e_jbrgsc_dv	Current job: Registrar General's Social Class						X						
	f_jbrgsc_dv	Current job: Registrar General's Social Class							X					

	g_jbrgsc_dv	Current job: Registrar General's Social Class								X				
	h_jbrgsc_dv	Current job: Registrar General's Social Class									X			
	i_jbrgsc_dv	Current job: Registrar General's Social Class										X		
Income	a_fimngrs_dv	total monthly personal income gross - 50-iles	Grouped into 50 sub-groups – 2% per group (total 100%)	X									X	
	b_fimngrs_dv	total monthly personal income gross - 50-iles			X									
	c_fimngrs_dv	total monthly personal income gross - 50-iles				X								
	d_fimngrs_dv	total monthly personal income gross - 50-iles					X							
	e_fimngrs_dv	total monthly personal income gross - 50-iles						X						
	f_fimngrs_dv	total monthly personal income gross - 50-iles							X					
	g_fimngrs_dv	total monthly personal income gross - 50-iles								X				
	h_fimngrs_dv	total monthly personal income gross - 50-iles									X			
	i_fimngrs_dv	total monthly personal income gross - 50-iles										X		
Employment	a_jbstat	Current economic activity	0 = employed/retired/ maternity leave/ apprenticeship 1 = unemployed/education/ sick/in care/unpaid/gov training	X									X	
	b_jbstat	Current economic activity			X									
	c_jbstat	Current economic activity				X								
	d_jbstat	Current economic activity					X							X
	e_jbstat	Current economic activity						X						
	f_jbstat	Current economic activity							X					
	g_jbstat	Current economic activity								X				

	h_jbstat	Current economic activity									X			
	i_jbstat	Current economic activity										X		
Financial situation	a_finnow	Subjective financial situation - current	0 = Comfortable financially and just getting by financially 1 = Experiencing financial difficulties	X										X
	b_finnow	Subjective financial situation - current			X									
	c_finnow	Subjective financial situation - current				X								
	d_finnow	Subjective financial situation - current					X							
	e_finnow	Subjective financial situation - current						X						
	f_finnow	Subjective financial situation - current							X					
	g_finnow	Subjective financial situation - current								X				
	h_finnow	Subjective financial situation - current									X			
	i_finnow	Subjective financial situation - current										X		
Tenure	a_hsownd	house owned or rented	0 = owner/shared ownership /mortgaged 1 = rented/ rent-free	X										X
	b_hsownd	house owned or rented			X									
	c_hsownd	own accommodation				X								
	d_hsownd	house owned or rented					X							
	e_hsownd	own accommodation						X						
	f_hsownd	house owned or rented							X					
	g_hsownd	house owned or rented								X				
	h_hsownd	house owned or rented									X			

	i_hsownd	house owned or rented										X		
Depression	a_hcond17	Clinical depression	0 = no 1 = yes	X									Used for Sensitivity Analysis	
	c_hcond17	Clinical depression				X								
	e_hcond17	Clinical depression						X						
	f_hcond17	Clinical depression							X					
	g_hcond17	Clinical depression								X				
	h_hcond17	Clinical depression									X			
	i_hcond17	Clinical depression										X		
Psychiatric problems	bk_hlprxi	Received treatment for psychiatric problems	0 = no 1 = yes	Individuals who previously participated in the British Household Panel study (now USoc) and received treatment for psychiatric problems during that time									Used for Sensitivity Analysis	
	bp_hlprxi	Received treatment for psychiatric problems												

Note: USoc = Understanding Society Any 'N/A', 'Don't know' or 'other' answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 7: *Coded Variables for NCDS (Chapter 5)*

Childhood

Environment Name	Variable		Coded as	Age of participant				Interaction model	
	Code	Name		0	7	11	16	Mixed effect	Random effect
SES	N492	0 Social class mother's husband (GRO 1951)	5 Professional 4 Managerial/ Technical 3 Skilled 2 Partly-skilled 1 Unskilled	X				X	
	N190	1P Social class of father, male head (GRO 1960)			X				
	N1687	2PD Social class of father or male head (GRO 1966)				X			
	N1687	2PD Social class of father or male head (GRO 1966)					X		
Finance Issues	N315	1P Family difficulties -Financial	0 = No 1 = Yes		X			X	
	N1230	2P Serious financial hardship last yr				X			
	N2441	3P Serious financial trouble last yr					X		
Number of Rooms	N201	1P Number of rooms in household	Continuous variable		X			X	
	N1156	2P Number of rooms in accommodation				X			
	N1156	2P Number of rooms in accommodation					X		
Tenure	N200	1P Tenure of accommodation	0 = owns 1 = rents (including social housing)		X			X	
	N1152	2P Tenure of accommodation				X			
	N2471	3P Type of accommodation					X		
Mother's interest in child's education	N43	1S Mother's interest in childs education	0 = Interested (including some interest) 1 = Not interested		X			X	
	N852	2S Mothers' interest in childs education				X			

	N2325	3S Mother's interest in chlds education					X		
Father's interest in child's education	N44	1S Father's interest in childs education	0 = Interested (including some interest) 1 = Not interested		X			X	
	N851	2S Fathers' interest in childs education				X			
	N2324	3S Father's interest in chlds education					X		
Father's involvement in childcare	N183	1P Dads role in management of child	0 = Involved (including some involvement) 1 = Not involved		X			X	
	N1147	2P Dads role in management of child				X			
Mother walks child	N181	1P Outings with mother	0 = Most weeks/occasionally 1 = Hardly ever		X			X	
	N1145	2P Does mum take child for walks,visits				X			
Father walks child	N182	1P Outings with father	0 = Most weeks/occasionally 1 = Hardly ever		X			X	
	N1146	2P Does dad take child for walks,visits				X			
Employment father	N188	1P Unemployed,sick and retired (GRO 1960)	0 = Employed (including retired) 1 = Unemployed/sick		X				X
	N1172	2P Father,male head's occupation				X			
	N2383	3P Father or father figure's occupation (GRO 1970)					X		
Maternal Smoking prior pregnancy	N502	0 Smoking prior to pregnancy	0 = Non-Smoker 1 = Smoker	X				Used for childhood vs adulthood comparison	
Maternal Smoking during pregnancy	N503	0 Smoking during pregnancy	0 = Non-Smoker 1 = Smoker	X					
Schizophrenia	N9EMOP05	Type of Emotional Problem - Schizophrenia	0 = No 1 = Yes					Used for sensitivity analysis	
Hallucinations	N9EMOP04	Type of Emotional Problem - Hallucinations	0 = No 1 = Yes						
Psychosis	N9EMOP07	Type of Emotional Problem - Psychosis	0 = No 1 = Yes						
Depression	N9EMOP01	Type of Emotional Problem - Depression	0 = No 1 = Yes						

Note: NCDS = 1958 National Child Development Study. Any ‘N/A’, ‘Don’t know’ or ‘other’ answers have been excluded from the analysis. SES = Socio-Economic Status

Adulthood

Environment	Variable		Coded as	Variable timeline (Age of participant)						Interaction Model	
	Code	Name		23	33	42	46	50	55	Mixed Effect	Random Effect
SES	N6149	4I Current or last job 1980 social class	5 Professional 4 Managerial/ occupations 3 Skilled 2 Partly-skilled 1 Unskilled	X						X	
	N540056	CASOC2:2 A4a/b) CURRENT/LAST JOB: RGs Social Class 1981			X						
	SC	(Current Job) Social Class				X					
	N7SC	(Derived) Social Class (RGSC SC based on Occ 1990)					X				
	N8SC	[SC2] Curr Job: Social Class (RGSC SC based on Occ 1990)						X			
	N9CSC	Social class 1990 based on soc2010 (CM current job)							X		
Employment	N4755	4I Whether currently unemployed	0 = Employed or Self-employed (full or part-time) 1 = Unemployed, sick, disabled Removed retired	X						X	
	ECONACT	CMs current main activity				X					
	N8ECON02	[ECONACT2] (Recoded) CM's current economic activity						X			
	ND9ECACT	(Derived) Current economic activity status							X		
Number of Rooms	N5323	4I Number of bedrooms	Continuous variable	X						X	
	N502947	CMI:57 D9 No. rooms (apart from the bathroom & kitchen)			X						
	BEDROOMS	Number of bedrooms in current acco				X					
	N7NUMRMS	Number of rooms in the house					X				
	ND8NUMRM	(Derived) Number of rooms in the house (n8numrms)						X			
	N9NUMRMS	Number of rooms in home							X		
Tenure	N5333	4I Whether owner or renter	0 = owns/part-owns	X						X	
	TENURE91	DV:Housing tenure in 1991			X						

	TENURE2	Is current accom owned or rented	1 = rents (including social housing)			X					
	N7TEN	Home ownership / tenure status					X				
	N8TEN	[TENURE] Home ownership / tenure status						X			
	N9TEN	Whether CM owns or rents home or some other arrangement							X		
Marital status	PARTSTAT	4D Current partnership status	0 = married/ co-habiting/ in relationship 1 = not in relationship	X						X	
	N502549	CMI:51 C52 CM is cohabiting/married other			X						
	DMSPPART	Whether CM had current partner in hhld in NCDS V (FF)				X					
	N7MS12	Person's marital status - 02					X				
	ND8SPPHH	(Derived) Cohort member lives with a spouse or partner						X			
	ND9COHAB	(Derived) Whether CM cohabiting as a couple							X		
Smoking	CURRENTN	4D Smoking patterns	0 = Never smoked 1 = Smoker/ Ex-smoker	X						X	
	SMOKING	CM current smoking status				X					
	N8SMOKIG	[SMOKING] Smoking frequency						X			

Note: NCDS = 1958 National Child Development Study. Any ‘N/A’, ‘Don’t know’ or ‘other’ answers have been excluded from the analysis. SES = Socio-Economic Status

Appendix 8: *Descriptive Statistics for MCS*

Environment	Wave	Total Millennium Cohort Study				Genotyped target group				Unpaired t-test/ chi-squared (95%CI)
		Number of participants	% Participants	Mean	(SD)	Number of participants	% Participants	Mean	(SD)	
Mother takes child for walks/park		7,628	100			6,384	100.00			
Yes	3	6,735	88.29	N/A	N/A	5,650	88.50	N/A	N/A	
No		893	11.71			734	11.50			χ^2=.149 p =.700
Mother takes child for walks/park		7,459	100			6,257	100.00			
Yes	4	6,107	81.87	N/A	N/A	5,120	81.83	N/A	N/A	
No		1,352	18.13			1,137	18.17			χ^2=.005 p =.945
Father takes child for walks/park		4,262	100			3,852	100.00			
Yes	3	3,614	84.80	N/A	N/A	3,259	84.61	N/A	N/A	
No		648	15.20			593	15.39			χ^2=.057 p=.812
Father takes child for walks/park		4,139	100			3,735	100.00			
Yes	4	3,332	80.50	N/A	N/A	2,999	80.29	N/A	N/A	
No		807	19.50			736	19.71			χ^2=.054 p =.816
Tenure		8,046	100			6,726	100.00			
Owner, mortgaged, shared owner	1	5,320	66.12	N/A	N/A	4,487	66.71	N/A	N/A	
Rent, rent-free		2,726	33.88			2,239	33.29			χ^2=.574 p =.449
Tenure		7,694	100			6,408	100.00			
Owner, mortgaged, shared owner	2	5,376	69.87	N/A	N/A	4,501	70.24	N/A	N/A	
Rent, rent-free		2,318	30.13			1,907	29.76			χ^2=.225 p =.635
Tenure		7,909	100	N/A	N/A	6,493	100.00	N/A	N/A	χ^2=.245

Owner, mortgaged, shared owner	3	5,566	70.38			4,594	70.75			p =.621
Rent, rent-free		2,343	29.62			1,899	29.25			
Tenure	4	7,757	100	N/A	N/A	6,353	100.00	N/A	N/A	χ^2=.262 p =.609
Owner, mortgaged, shared owner		5,535	71.35			4,558	71.75			
Rent, rent-free		2,222	28.65			1,795	28.25			
Tenure	5	1,991	100	N/A	N/A	1,610	100.00	N/A	N/A	χ^2=.070 p =.792
Owner, mortgaged, shared owner		888	44.60			711	44.16			
Rent, rent-free		1,103	55.40			899	55.84			
Tenure	6	21,136	100	N/A	N/A	6,885	100.00	N/A	N/A	χ^2=19.414 p =<0.0001
Owner, mortgaged, shared owner		15,117	71.52			4,733	68.74			
Rent, rent-free		6,019	28.48			2,152	31.26			
Smoking Mother	1	8,045	100	N/A	N/A	6,728	100.00	N/A	N/A	χ^2=81.152 p =<0.0001
Not Smoking		5,970	74.21			4,948	73.54			
Smoking		2,075	25.79			1,780	26.46			
Smoking Mother	5	7,924	100	N/A	N/A	6,636	100.00	N/A	N/A	χ^2=.352 p =.553
Not Smoking		6,271	79.14			5,225	78.74			
Smoking		1,653	20.86			1,411	21.26			
Smoking Mother	6	8,294	100	N/A	N/A	6,936	100.00	N/A	N/A	χ^2=.157 p =.692
Not Smoking		6,702	80.81			5,587	80.55			
Smoking		1,592	19.19			1,349	19.45			
Smoking Father	1	4,286	100	N/A	N/A	3,857	100.00	N/A	N/A	χ^2=.012 p=.913
Not Smoking		3,099	72.31			2,793	72.41			
Smoking		1,187	27.69			1,064	27.59			
Smoking Father	5	4,492	100	N/A	N/A	4,047	100.00	N/A	N/A	χ^2=.014

Not Smoking		3,654	81.34			3,296	81.44			p =.907
Smoking		838	18.66			751	18.56			
Smoking Father		4,841	100			4,352	100.00			
Not Smoking	6	4,012	82.88	N/A	N/A	3,620	83.18	N/A	N/A	χ^2=.151
Smoking		829	17.12			732	16.82			p =.698
Rooms	1	8,047	100	5.49	1.47	6,727	100	5.50	1.46	p=.882
Rooms	2	7,694	100	5.87	1.56	6,408	100	5.88	1.55	p=.739
Rooms	3	7,911	100	6.05	1.61	6,495	100	6.06	1.60	p=.681
Rooms	4	7,753	100	6.19	1.65	6,349	100	6.20	1.64	p=.650
Rooms	6	8,548	100	6.33	1.67	6,789	100	6.34	1.64	p=.533
SES		11,582	100			6,210	100.00			
Class I		3,506	30.27			2,184	35.17			
Class II		1,049	9.06	3.23	1.72	367	5.91	3.14	1.75	
Class III		819	7.07			258	4.15			
Class IV		1,651	14.25			1,206	19.42			
Class V	1	4,557	39.35			2,195	35.35			p=.0005
SES		7,957	100			3,671	3,671 100.00			
Class I		1,708	21.47			906	24.68			
Class II		604	7.59	3.55	1.61	131	3.57	3.54	1.63	
Class III		828	10.41			248	6.76			
Class IV		1,216	15.28			836	22.77			
Class V	2	3,601	45.26			1,550	42.22			p=0.761
SES		11,586	100			6,065	100			
Class I		3,374	29.12	3.27	1.70	2,080	34.30	3.16	1.73	
Class II	3	906	7.82			290	4.78			p=.0001

Class III		1,023	8.83			334	5.51			
Class IV		1,778	15.35			1,275	21.02			
Class V		4,505	38.88			2,086	34.39			
SES		11,539	100			6,032	100			
Class I		3,279	28.42			2,022	33.52			
Class II		858	7.44	3.30	1.69	265	4.39	3.20	1.72	
Class III		1,128	9.78			384	6.37			
Class IV		1,669	14.46			1,222	20.26			
Class V	4	4,605	39.91			2,139	35.46			p=.0001
Mother Reads to child		7,867	100			6,583	100			
Yes	3	7,459	94.81	N/A	N/A	6,251	94.96	N/A	N/A	χ^2=.151
No		408	5.19			332	5.04			p=.698
Mother Reads to child		7,699	100			6,449	100			
Yes	4	6,938	90.12	N/A	N/A	5,830	90.40	N/A	N/A	χ^2=.326
No		761	9.88			619	9.60			p=.568
Father Reads to child		4,323	100			3,907	100			
Yes	3	3,592	83.09	N/A	N/A	3,246	83.08	N/A	N/A	χ^2=.0001
No		731	16.91			661	16.92			p=.992
Father Reads to child		4,203	100			3,795	100.00			
Yes	4	3,189	75.87	N/A	N/A	2,884	75.99	N/A	N/A	χ^2=.016
No		1,014	24.13			911	24.01			p=.900
Marital Status		12,334	100			6,730	100			
Married, in relationship		8,589	69.64	N/A	N/A	4,288	63.71	N/A	N/A	
Single, divorced, separated, widowed	1	3,745	30.36			2,442	36.29			χ^2=96.66 p<.0001
Marital Status	3	12,190	100	N/A	N/A	6,582	100.00	N/A	N/A	χ^2=99.66

Married, in relationship		9,154	75.09			4,495	68.29			p<.0001
Single, divorced, separated, widowed		3,036	24.91			2,087	31.71			
Marital Status	4	11,907	100	N/A	N/A	6,454	100	N/A	N/A	
Married, in relationship		9,021	75.76			4,421	68.50			
Single, divorced, separated, widowed		2,886	24.24			2,033	31.50			χ^2=162.98 p<.0001
Marital Status	5	12,420	100	N/A	N/A	6,637	100	N/A	N/A	
Married, in relationship		9,564	77.00			4,546	68.49			
Single, divorced, separated, widowed		2,856	23.00			2,091	31.51			χ^2=173.80 p<.0001
Marital Status	6	13,131	100	N/A	N/A	6,933	100	N/A	N/A	
Married, in relationship		9,922	75.56			4,625	66.71			
Single, divorced, separated, widowed		3,209	24.44			2,308	33.29			χ^2=178.33 p<.0001
Finance Issues	1	8,043	100	N/A	N/A	6,723	100	N/A	N/A	
Financially comfortable		7,264	90.31			6,086	90.53			
Financial issues		779	9.69			637	9.47			χ^2=.187 p =.665
Finance Issues	2	7,694	100	N/A	N/A	6,408	100	N/A	N/A	
Financially comfortable		6,997	90.94			5,835	91.06			
Financial issues		697	9.06			573	8.94			χ^2=.056 p =.809
Finance Issues	6	8,553	100	N/A	N/A	6,793	100	N/A	N/A	
Financially comfortable		7,706	90.10			6,159	90.67			
Financial issues		847	9.90			634	9.33			χ^2=1.410 p =.235
Alcohol Consumption Mother	1	8,045	100	N/A	N/A	6,728	100	N/A	N/A	
Monthly or less; Never		4,844	60.21			3,994	59.36			
Weekly or daily		39.79	39.79			2,734	40.64			χ^2=1.095 p=.295
Alcohol Consumption Mother	3	7,865	100	N/A	N/A	6,581	100	N/A	N/A	χ^2=.676

Monthly or less; Never		4,411	56.08			3,646	55.40			p=.411
Weekly or daily		3,454	43.92			2,935	44.60			
Alcohol Consumption Mother		7,698	100			6,448	100			
Monthly or less; Never	4	4,120	53.52	N/A	N/A	3,389	52.56	N/A	N/A	χ^2=1.302
Weekly or daily		3,578	46.48			3,059	47.44			p=.254
Alcohol Consumption Mother		7,719	100			6,492	100			
Monthly or less; Never	5	5,326	69.00	N/A	N/A	4,438	68.36	N/A	N/A	χ^2=.667
Weekly or daily		2,393	31.00			2,054	31.64			p=.414
Alcohol Consumption Mother		7,903	100			6,654	100			
Monthly or less; Never	6	5,417	68.54	N/A	N/A	4,523	67.97	N/A	N/A	χ^2=.541
Weekly or daily		2,486	31.46			2,131	32.03			p=.462
Alcohol Consumption Father		4,286	100			3,857	100			
Monthly or less; Never		1,468	34.25	N/A	N/A	1,281	33.21	N/A	N/A	χ^2=.980
Weekly or daily	1	2,818	65.75			2,576	66.79			p=.322
Alcohol Consumption Father		4,322	100			3,906	100			
Monthly or less; Never	3	1,501	34.73	N/A	N/A	1,323	33.87	N/A	N/A	χ^2=.671
Weekly or daily		2,821	65.27			2,583	66.13			p=.413
Alcohol Consumption Father		4,200	100			3,792	100			
Monthly or less; Never	4	1,454	34.62	N/A	N/A	1,278	33.70	N/A	N/A	χ^2=.618
Weekly or daily		2,746	65.38			2,514	66.30			p=.432
Alcohol Consumption Father		4,387	100			3,965	100			
Monthly or less; Never		2,405	54.82	N/A	N/A	2,142	54.02	N/A	N/A	χ^2=.535
Weekly or daily	5	1,982	45.18			1,823	45.98			p=.464
Alcohol Consumption Father		4,609	100	N/A	N/A	4,164	100	N/A	N/A	χ^2=.334
Monthly or less; Never	6	2,468	53.55			2,204	52.93			p=.563

Weekly or daily		2,141	46.45			1,960	47.07			
Birth weight	1	7,041	100	6.96	1.35	5,985	100	6.97	1.33	p=.618
Gestation period	1	7851	100	275.96	13.82	6,971	100	276.14	13.52	p=.431
Employment	1	8,005	100	N/A	N/A	6,701	100	N/A	N/A	
		4,089	51.08			3,501	52.25			χ^2=1.984
		3,916	48.92			3,200	47.75			p=.159
Father role	1	7,766	100	N/A	N/A	6,532	100	N/A	N/A	
		7,448	95.91			6,263	95.88			χ^2=.005
		318	4.09			269	4.12			p=.944
Father's Interest in Child's Education	4	3,204	100	N/A	N/A	2,863	100	N/A	N/A	
		2,995	93.48			2,673	93.36			χ^2=.032
		209	6.52			190	6.64			p=.859
Mother's Interest in Child's Education	4	4,294	100	N/A	N/A	3,828	100	N/A	N/A	
		4,066	94.69			3,630	94.83			χ^2=.077
		228	5.31			198	5.17			p=.782

Note: MCS = Millennium Cohort Study. MCS phenotype data is available as household panel data. The mother's responses (or father's responses if unavailable) for tenure, rooms, SES, financial difficulties and marital status had been matched to the whole family by assigning the same value to all family members in the same household. Therefore, when calculating descriptive statistics, only the mother's responses had been used for the genotyped target sample for tenure, rooms, SES, financial difficulties and marital status. Total Millennium Cohort Study = refers to all individuals who provided DNA data (cohort member aged 14 years of age and their biological parents) for which we have phenotype data for. SES = Socio-economic status

Appendix 9: *Descriptive Statistics for USoc*

Environment	Wave	Total Understanding Society				Genotyped				t-test/ chi-squared 95%CI
		Number of participants	% participants	Mean	(SD)	Number of participants	% participants	Mean	(SD)	
Marital Status	1	6,844	100	N/A	N/A	5,272	100	N/A	N/A	χ^2= 25.70 p = <0.0001
Married, in relationship		3,943	57.61			2,794	53.00			
Single, divorced, separated, widowed		2,901	42.39			2,478	47.00			
Alcohol consumption	2	6,271	100	3.10	1.93	4,606	100	3.12	1.96	p=.448
Alcohol consumption	5	5,182	100	3.17	1.90	3,790	100	3.17	1.92	p=.864
Income	1	6,939	100	24.75	14.85	5,335	100	24.95	14.67	p=.461
Income	2	9,768	100	24.93	14.76	7,279	100	25.04	14.53	p=.617
Income	3	9,508	100	25.02	14.70	7,066	100	25.13	14.50	p=.631
Income	4	9,080	100	25.05	14.69	6,732	100	25.13	14.50	p=.734
Income	5	8,709	100	25.04	14.69	6,448	100	25.15	14.54	p=.633
Income	6	8,033	100	25.15	14.64	5,938	100	25.27	14.48	p=.615
Income	7	7,650	100	25.12	14.65	5,666	100	25.26	14.46	p=.594
Income	8	7,292	100	25.16	14.62	5,387	100	25.28	14.42	p=.665
Income	9	6,829	100	25.05	14.69	5,038	100	25.09	14.47	p=.899
Rooms	1	6,986	100	2.99	.98	5,359	100	2.93	0.99	p=.0006
Rooms	2	9,809	100	2.30	.98	7,307	100	2.94	0.99	p=.0001
Rooms	3	9,548	100	3.01	.98	7.088	100	2.95	.98	p=.0001
Rooms	4	9,061	100	3.02	.98	6,722	100	2.96	.98	p=.0001
Rooms	5	8,710	100	3.03	.97	6,442	100	2.97	.98	p=.0002
Rooms	6	8,072	100	3.04	.98	5,960	100	2.98	0.99	p=.0001
Rooms	7	7,727	100	3.05	.99	5,719	100	3.00	0.99	p=.0002

Rooms	8	7,377	100	3.05	.99	5,435	100	2.99	.99	p=.0007
Rooms	9	6,889	100	3.08	.99	5,055	100	3.01	1.00	p=.001
SES		3,938	100			2,963	100			
Class I		151	3.83			100	3.37			
Class II		480	12.19			363	12.25			
Class III	1	1,614	40.99	3.29	.90	1,198	40.43	3.31	.89	
Class IV		1,452	36.87			1,116	37.66			
Class V		241	6.12			186	6.28			p=.365
SES		5,547	100			4,019	100			
Class I		183	3.3			118	2.94			
Class II		717	12.93			525	13.06			
Class III	2	2,283	41.16	3.29	.88	1,636	40.71	3.30	.87	
Class IV		2,058	37.1			1,517	37.75			
Class V		306	5.52			223	5.55			p=.474
SES		5,331	100			3,842	100			
Class I		168	3.15			110	2.86			
Class II		685	12.85			497	12.94			
Class III	3	2,223	41.7	3.29	.87	1,592	41.44	3.30	.87	
Class IV		1,967	36.9			1,429	37.19			
Class V		288	5.4			214	5.57			p=.542
SES		5,063	100			3,640	100			
Class I		150	2.96			106	2.91			
Class II	4	662	13.08	3.29	.87	481	13.21	3.30	.87	
Class III		2,082	41.12			1,485	40.80			
Class IV		1,886	37.25			1,356	37.25			p=.819

Class V		283	5.59			212	5.82			
SES	5	4,862	100	3.30	.87	3,477	100	3.31	.88	
Class I		140	2.88			98	2.82			
Class II		648	13.33			460	13.23			
Class III		1,967	40.46			1,401	40.29			
Class IV		1,831	37.66			1,308	37.62			
Class V		276	5.68			210	6.04			p=.641
SES	6	4,404	100	3.33	.86	3,150	100	3.33	.86	
Class I		111	2.52			79	2.51			
Class II		555	12.6			401	12.73			
Class III		1,758	39.92			1,249	39.65			
Class IV		1,736	39.42			1,245	39.52			
Class V		244	5.54			176	5.59			p=.962
SES	7	4,135	100	3.34	.86	2,975	100	3.34	.86	
Class I		107	2.59			73	2.45			
Class II		513	12.41			376 12.64	376 12.64			
Class III		1,640	39.66			1,177 39.56	1,177 39.56			
Class IV		1,634	39.52			1,171 39.36	1,171 39.36			
Class V		241	5.83			178 5.98	178 5.98			p=.927
SES	8	3,818	100	3.34	.87	2,754	100	3.35	.86	
Class I		100	2.62			64	2.32			
Class II		470	12.31			344	12.49			
Class III		1,507	39.47			1,090	39.58			
Class IV		1,505	39.42			1,084	39.36			p=.824

Class V		236	6.18			172	6.25			
SES	9	3,449	100	3.35	.87	2,485	100	3.35	.87	p=.886
Class I		87	2.52			59	2.37			
Class II		427	12.38			314	12.64			
Class III		1,331	38.59			968	38.95			
Class IV		1,391	40.33			988	39.76			
Class V		213	6.18			156	6.28			
Financial Issues	1	6,839	100	N/A	N/A	5,268	100	N/A	N/A	χ^2= 0.060 p =.807
Financially comfortable		6,183	90.41			4,753	90.22			
Financial issues		656	9.59			515	9.78			
Financial Issues	2	9,740	100	N/A	N/A	7,258	100	N/A	N/A	χ^2=.989 p =.320
Financially comfortable		8,893	91.3			6,595	90.87			
Financial issues		847	8.7			663	9.13			
Financial Issues	3	9,429	100	N/A	N/A	7,014	0	N/A	N/A	χ^2=.291 p =.442
Financially comfortable		8,625	91			6,392	91.13			
Financial issues		804	8.53			622	8.87			
Financial Issues	4	8,960	100	N/A	N/A	6,658	100	N/A	N/A	χ^2=.796 p =.372
Financially comfortable		8,255	92.13			6,108	91.74			
Financial issues		705	7.87			550	8.26			
Financial Issues	5	8,610	100	N/A	N/A	6,387	100	N/A	N/A	χ^2=.296 p =.587
Financially comfortable		8,019	93			5,934	92.91			
Financial issues		591	6.86			453	7.09			
Financial Issues	6	7,921	100	N/A	N/A	5,861	100	N/A	N/A	χ^2=1.02 p =.317
Financially comfortable		7,562	95.47			5,574	95.10			
Financial issues		359	4.53			287	4.90			

Financial Issues	7	7,549	100	N/A	N/A	5,602	100	N/A	N/A	χ^2=.210 p =.647
Financially comfortable		7,210	95.51			5,341	95.34			
Financial issues		339	4.49			261	4.66			
Financial Issues	8	7,232	100	N/A	N/A	5,346	100	N/A	N/A	χ^2=.646 p =.421
Financially comfortable		6,867	94.95			5,059	94.63			
Financial issues		365	5.05			287	5.37			
Financial Issues	9	6,803	100	N/A	N/A	5,016	100	N/A	N/A	χ^2=1.19 p =.275
Financially comfortable		6,466	95.05			4,745	94.60			
Financial issues		337	4.95			271	5.40			
Tenure	1	6,953	100	N/A	N/A	5,331	100	N/A	N/A	χ^2=2.66 p =.103
Owner, mortgaged, shared owner		5,358	77.06			4,041	75.80			
Rent, rent-free		1,595	23			1,290	24.20			
Tenure	2	9,786	100	N/A	N/A	7,287	100	N/A	N/A	χ^2=3.172 p =.075
Owner, mortgaged, shared owner		7,608	77.74			5,581	76.59			
Rent, rent-free		2,178	22.26			1,706	23.41			
Tenure	3	9,532	100	N/A	N/A	7,075	100	N/A	N/A	χ^2=2.730 p =.098
Owner, mortgaged, shared owner		7,439	78.04			5,445	76.96			
Rent, rent-free		2,093	22			1,630	23.04			
Tenure	4	9,040	100	N/A	N/A	6,703	100	N/A	N/A	χ^2=2.649 p =.104
Owner, mortgaged, shared owner		7,095	78.48			5,188	77.40			
Rent, rent-free		1,945	21.52			1,515	22.60			
Tenure	5	8,696	100	N/A	N/A	6,431	100	N/A	N/A	χ^2=2.861 p =.091
Owner, mortgaged, shared owner		6,834	79			4,980	77.44			
Rent, rent-free		1,862	21.41			1,451	22.56			

Tenure	6	8,056	100	N/A	N/A	5,949	100	N/A	N/A	χ^2=3.149 p =.076
Owner, mortgaged, shared owner		6,398	79.42			4,651	78.18			
Rent, rent-free		1,658	20.58			1,298	21.82			
Tenure	7	7,706	100	N/A	N/A	5,703	100	N/A	N/A	χ^2=2.744 p =.098
Owner, mortgaged, shared owner		6,132	80			4,471	78.40			
Rent, rent-free		1,574	20			1,232	21.60			
Tenure	8	7,329	100	N/A	N/A	5,397	100	N/A	N/A	χ^2=2.072 p =.150
Owner, mortgaged, shared owner		5,860	80			4,259	78.91			
Rent, rent-free		1,469	20			1,138	21.09			
Tenure	9	6,850	100	N/A	N/A	5,028	100	N/A	N/A	χ^2=1.763 p =.184
Owner, mortgaged, shared owner		5,561	81			4,033	80.21			
Rent, rent-free		1,289	18.82			995	19.79			
Employment	1	6,903	100	N/A	N/A	5,306	100	N/A	N/A	χ^2=.062 p =.803
employed/retired/maternity leave/apprenticeship		5,854	85			4,491	84.64			
unemployed/education/sick/in care/unpaid/gov training		1,049	15			815	15.36			
Employment	2	9,737	100	N/A	N/A	7,253	100	N/A	N/A	χ^2=<.0.0001 p =.978
employed/retired/maternity leave/apprenticeship		8,302	85			6,183	85.25			
unemployed/education/sick/in care/unpaid/gov training		1,435	15			1,070	14.75			
Employment	3	9,477	100	N/A	N/A	7,040	100	N/A	N/A	χ^2=.004 p =.950
employed/retired/maternity leave/apprenticeship		8,199	87			6,093	86.55			
unemployed/education/sick/in care/unpaid/gov training		1,278	13.49			947	13.45			
Employment	4	9,037	100	N/A	N/A	6,700	100	N/A	N/A	χ^2=.086

employed/retired/maternity leave/apprenticeship		7,978	88.28			5,925	88.43			p =.770
unemployed/education/sick/in care/unpaid/gov training		1,059	11.72			775	11.57			
Employment	5	8,672	100	N/A	N/A	6,419	100	N/A	N/A	
employed/retired/maternity leave/apprenticeship		7,735	89			5,713	89.00			
unemployed/education/sick/in care/unpaid/gov training		937	11			706	11.00			χ^2=.046 p =.830
Employment	6	7,996	100	N/A	N/A	5,913	100	N/A	N/A	
employed/retired/maternity leave/apprenticeship		7,276	91			5,379	90.97			
unemployed/education/sick/in care/unpaid/gov training		720	9			534	9.03			χ^2=.003 p =.957
Employment	7	7,627	100	N/A	N/A	5,650	100	N/A	N/A	
employed/retired/maternity leave/apprenticeship		6,996	91.73			5,171	91.52			
unemployed/education/sick/in care/unpaid/gov training		631	8.27			479	8.48			χ^2=.177 p =.674
Employment	8	7,252	100	N/A	N/A	5,366	100	N/A	N/A	
employed/retired/maternity leave/apprenticeship		6,676	92.06			4,930	91.87			
unemployed/education/sick/in care/unpaid/gov training		576	7.94			436	8.13			χ^2=.139 p =.709
Employment	9	6,791	100	N/A	N/A	5,015	100	N/A	N/A	
employed/retired/maternity leave/apprenticeship		6,276	92			4,623	92.18			
unemployed/education/sick/in care/unpaid/gov training		515	7.58			392	7.82			χ^2=.221 p =.638
Education	1	6,112	100	N/A	N/A	4,691	100	N/A	N/A	
A-Level and above		3,637	59.51			2,801	59.71			
GCSE and below		2,475	40.49			1,890	40.29			χ^2=.046 p =.830
Education	2	8,609	100	N/A	N/A	6,404	100	N/A	N/A	χ^2=<.0001

A-Level and above		5,178	60.15			3,852	60.15			p =.996
GCSE and below		3,431	39.85			2,552	39.85			
Education	3	8,401	100	N/A	N/A	6,221	100	N/A	N/A	
A-Level and above		5,102	60.73			3,774	60.67			χ^2=.006
GCSE and below		3,299	39.27			2,447	39.33			p =.936
Education	4	8,076	100	N/A	N/A	5,960	100	N/A	N/A	
A-Level and above		5,032	62.31			3,702	62.11			χ^2=.055
GCSE and below		3,044	37.69			2,258	37.89			p =.815
Education	5	7,749	100	N/A	N/A	5,710	100	N/A	N/A	
A-Level and above		4,880	62.98			3,590	62.87			χ^2=.688
GCSE and below		2,869	37.02			2,120	37.13			p =.407
Education	6	7,172	100	N/A	N/A	5,273	100	N/A	N/A	
A-Level and above		4,584	63.92			3,354	63.61			χ^2=.125
GCSE and below		2,588	36.08			1,919	36.39			p =.724
Education	7	6,854	100	N/A	N/A	5,052	100	N/A	N/A	
A-Level and above		4,415	64.41			3,245	64.23			χ^2=.042
GCSE and below		2,439	36			1,807	35.77			p =.837
Education	8	6,538	100	N/A	N/A	4,812	100	N/A	N/A	
A-Level and above		4,250	65			3,114	64.71			χ^2=.103
GCSE and below		2,288	35			1,698	35.29			p =.748
Education	9	6,133	100	N/A	N/A	4,506	100	N/A	N/A	
A-Level and above		4,022	65.58			2,945	65.36			χ^2=.057
GCSE and below		2,111	34.42			1,561	34.64			p =.812

Notes: USoc = Understanding Society. SES = Socio-economic status

Appendix 10: *Descriptive Statistics for NCDS*

Childhood

Environment	Year	Total NCDS				Genotyped (Combined)				t-test/ chi-squared 95%CI
		Number of participants	% Participants	Mean	(SD)	Number of participants	% Participants	Mean	(SD)	
Maternal Smoking prior pregnancy	0	8,850	100	N/A	N/A	5,089	100.00	N/A	N/A	
Non-Smoker		5,329	60.21			3,040	59.74			χ^2=.308
Smoker		3,521	39.79			2,049	40.26			p=.579
Maternal Smoking during pregnancy	0	8,771	100	N/A	N/A	5,042	100.00	N/A	N/A	
Non-Smoker		5,943	67.76			3,373	66.90			χ^2=1.077
Smoker		2,828	32.24			1,669	33.10			p=.299
Parity	0	8,881	100	1.24	1.46	5,101	100	1.25	1.46	p=.578
Mother's age at birth	0	8,877	100	27.51	6.60	5,098	100	27.46	5.57	p=.597
Father's age at birth	0	8,606	100	30.59	6.31	4,950	100	30.53	6.26	p=.613
Gestational period (in days)	0	8,033	100	281.13	11.93	4,630	100	281.04	11.90	p=.685
Birth weight (in ounces)	0	8,592	100	117.81	18.15	4953	100	117.90	18.28	p=.767
Mother marital status at birth	0	8,879	100	N/A	N/A	5,101	100	N/A	N/A	
Married		8,609	96.96			4,951	97.06			χ^2=.112
Unmarried		270	3.04			150	2.94			p=.738
Housing Issues	7	7,786	100	N/A	N/A	4,486	0	N/A	N/A	
No		7,275	93.44			4,218	94.03			χ^2=1.661
Yes		511	6.56			268	5.97			p=.198
Family Alcohol issues	7	7,152	100	N/A	N/A	4,123	100.00	N/A	N/A	χ^2=.002
No		7,094	99.19			4,089	99.18			p=.968

Yes		58	0.81			34	0.82			
Divorce/Separation/Desertion	7	7,852	100	N/A	N/A	4,508	100	N/A	N/A	χ^2=<.001 p=.996
No		7,586	96.61			4,350	96.50			
Yes		266	3.39			158	3.50			
Domestic Tension	7	7,156	100	N/A	N/A	4,128	100	N/A	N/A	χ^2=.121 p=.728
No		6,797	94.98			3,927	95.13			
Yes		359	5.02			201	4.87			
Father reads to child	7	7,909	100	N/A	N/A	4,551	100.00	N/A	N/A	χ^2=1.874 p=.171
Yes		5,727	72.41			3,347	73.54			
No		2,182	27.59			1,204	26.46			
Mother reads to child	7	8,148	100	N/A	N/A	4,688	100.00	N/A	N/A	χ^2=2.276 p=.131
Yes		6,926	85.00			4,031	85.99			
No		1,222	15.00			657	14.01			
Financial difficulties	7	7,388	100	N/A	N/A	4,266	100.00	N/A	N/A	χ^2=.207 p=.649
No		6,912	93.56			4,004	93.86			
Yes		476	6.44			262	6.14			
Financial difficulties	11	7,817	100	N/A	N/A	4,481	100.00	N/A	N/A	χ^2=1.891 p=.169
No		7,055	90.25			4,078	91.01			
Yes		762	9.75			403	8.99			
Financial difficulties	16	6,924	100	N/A	N/A	3,987	100.00	N/A	N/A	χ^2=.493 p=.483
No		6,316	91.22			3,654	91.65			
Yes		608	8.78			333	8.35			
Father's involvement in childcare	7	7,979	100	N/A	N/A	4,594	100.00	N/A	N/A	χ^2=2.29 p=.130
Yes		7,178	89.96			4,171	90.79			
No		801	10.04			423	9.21			

Father's involvement in childcare	11	7,610	100	N/A	N/A	4,379	100.00	N/A	N/A	χ^2=.391 p=.532
Yes		6,872	90.30			3,970	90.66			
No		738	9.70			409	9.34			
Father's interest in child's education	7	5,373	100	N/A	N/A	3,114	100	N/A	N/A	χ^2=.017 p=.991
Yes		4,245	79.01			2,464	79.13			
No		1,128	20.99			650	20.87			
Father's interest in child's education	11	5,836	100	N/A	N/A	3,328	100.00	N/A	N/A	χ^2=.062 p=.803
Yes		4,673	80.07			2,672	80.29			
No		1,163	19.93			656 19.7	19.71			
Father's interest in child's education	16	5,475	100	N/A	N/A	3,109	100.00	N/A	N/A	χ^2=.169 p=.681
Yes		4,433	80.97			2,506	80.60			
No		1,042	19.03			603	19.40			
Father takes child on walks/outings	7	7,961	100	N/A	N/A	4,585	100.00	N/A	N/A	χ^2=.306 p=.580
Yes		7,556	94.91			4,362	95.14			
No		405	5.09			223	4.86			
Father takes child on walks/outings	11	7,687	100	N/A	N/A	4,412	100.00	N/A	N/A	χ^2=1.539 p=.215
Yes		7,031	91.47			4,064	92.11			
No		656	8.53			348	7.89			
Mother's interest in child's education	7	7,802	100	N/A	N/A	4,496	100.00	N/A	N/A	χ^2=.037 p=.848
Yes		6,760	86.64			3,901	86.77			
No		1,042	13.36			595	13.23			
Mother's interest in child's education	11	7,106	100	N/A	N/A	4,061	100.00	N/A	N/A	χ^2=.033 p=.855
Yes		6,168	86.80			3,520	86.68			

No		938	13.20			541	13.32			
Mother's interest in child's education	16	6,061	100	N/A	N/A	3,448	100.00	N/A	N/A	
Yes		5,078	83.78			2,882	83.58			χ^2=.062
No		983	16.22			566	16.42			p=.803
Mother takes child on walks/outings	7	8,185	100	N/A	N/A	4,707	100.00	N/A	N/A	
Yes		8,083	98.75			4,658	98.96			χ^2=1.087
No		102	1.25			49	1.04			p=.297
Father takes child on walks/outings	11	7,951	100	N/A	N/A	4,561	100.00	N/A	N/A	
Yes		7,528	94.68			4,335	95.04			χ^2=.058
No		423	5.32			226	4.96			p=.811
Number of rooms child	7	8,195	100	4.83	1.34	4,715	100	4.82	1.30	p=.489
Number of rooms child	11	8,049	100	5.02	1.36	4,608	100	5.00	1.30	p=.535
Number of rooms child	16	7,032	100	4.97	1.49	4,051	100	4.96	1.48	p=.635
SES child	0	8,485	100	2.96	.89	4,881	4,881 100.00	2.96	.87	
Class I		694	8.18			375	7.68			
Class II		1,013	11.94			602	12.33			
Class III		5,153	60.73			2,981	61.07			
Class IV		1,200	14.14			687	14.07			
Class V		425	5.01			236	4.84			p=.908
SES child	7	7,981	100	3.00	.89	4,601	100.00	3.01	.88	
Class I		466	5.84			233	5.06			
Class II		1,382	17.32			793	17.24			
Class III		4,399	55.12			2,579	56.05			
Class IV		1,264	15.84			709	15.41			p=.586

Class V		490	6.14			287	6.24			
SES child	11	7,579	100	3.05	.90	4,349	100.00	3.07	.89	
Class I		378	4.99			200	4.60			
Class II		1,274	16.81			711	16.35			
Class III		3,959	52.24			2,311	53.14			
Class IV		1,492	19.69			858	19.73			
Class V		476	6.28			269	6.19			p=.522
SES child	16	6,453	100	3.11	.87	3,722	100.00	3.11	.87	
Class I		287	4.45			160	4.30			
Class II		914	14.16			512	13.76			
Class III		3,467	53.73			2,024	54.38			
Class IV		1,398	21.66			799	21.47			
Class V		387	6.00			227	6.10			p=.692
Tenure child	7	7,927	100	N/A	N/A	4,561	100.00	N/A	N/A	
Owns/part-owns		3,651	46.06			2,008	44.03			χ^2=4.826
rents		4,276	53.94			2,553	55.97			p=.028
Tenure child	11	8,022	100	N/A	N/A	4,599	100.00	N/A	N/A	
Owns/part-owns		3,884	48.42			2,166	47.10			χ^2=2.040
rents		4,138	51.58			2,433	52.90			p=.153
Tenure child	16	7,053	100	N/A	N/A	4,056	100.00	N/A	N/A	
Owns/part-owns		3,716	52.69			2,077	51.21			χ^2=2.257
rents		3,337	47.31			1,979	48.79			p=.133
Free school meals	11	7,954	100	N/A	N/A	4,553	100.00	N/A	N/A	
No		7,262	91.3			4,164	91.46			χ^2= .089
Yes		692	8.70			389	8.54			p=.765
Free school meals	16	6,991	100	N/A	N/A	4,021	100.00	N/A	N/A	χ^2= 1.878

No		6,420	91.83			3,722	92.56			p=.171
Yes		571	8.17			299	7.44			
Employment father	7	8,594	100	N/A	N/A	4,934	100.00	N/A	N/A	χ^2=.082 p=.775
Employed		8,455	98.38			4,851	98.32			
Unemployed		139	1.62			83	1.68			
Employment father	11	8,387	100	N/A	N/A	4,800	100.00	N/A	N/A	χ^2=.019 p=.889
Employed		8,165	97.35			4,671	97.31			
Unemployed		222	2.65			129	2.69			
Employment father	16	6,578	100	N/A	N/A	3,790	100.00	N/A	N/A	χ^2=.039 p=.844
Employed		6,330	96.23			3,650	96.31			
Unemployed		248	3.77			140	3.69			

Adulthood

Marital status as an adult	23	8,084	100	N/A	N/A	4,605	100	N/A	N/A	χ^2=2.046 p=.153
Married/Co-habiting/In relationship		4,117	50.93			2,406	52.25			
Not in relationship		3,967	49.07			2,199	47.75			
Marital status as an adult	33	7,800	100	N/A	N/A	4,442	100	N/A	N/A	χ^2=.956 p=.328
Married/Co-habiting/In relationship		6,781	86.94			3,889	87.55			
Not in relationship		1,019	13.06			553	12.45			
Marital status as an adult	42	9,087	100	N/A	N/A	5,129	100	N/A	N/A	χ^2= 1.980 p=.159
Married/Co-habiting/In relationship		7,443	81.91			4,260	83.06			
Not in relationship		1,644	18.09			869	16.94			
Marital status as an adult	46	7,480	100	N/A	N/A	4,280	100	N/A	N/A	χ^2=.329 p=.566
Married/Co-habiting/In relationship		6,309	84.34			3,627 84.74	3,627 84.74			
Not in relationship		1,171	15.66			653 15.26	653 15.26			

Marital status as an adult	50	8,181	100	N/A	N/A	4,661	100	N/A	N/A	χ^2=.979 p=.322
Married/Co-habiting/In relationship		6,592	80.58			3,789	81.29			
Not in relationship		1,589	19.42			872	18.71			
Marital status as an adult	55	7,664	100	N/A	N/A	4,422	100	N/A	N/A	χ^2=.339 p=.561
Married/Co-habiting/In relationship		6,126	79.93			3,554	80.37			
Not in relationship		1,538	20.07			868	19.63			
Number of rooms adult	23	7,884	100	2.70	0.92	4,483	100	2.69	.91	p=.622
Number of rooms adult	33	8,341	100	4.62	2.13	4,730	100	4.60	1.55	p=.604
Number of rooms adult	42	9,053	100	3.05	0.92	5,113	100	3.07	.90	p=.407
Number of rooms adult	46	8,514	100	5.46	1.73	4,853	100	5.48	1.70	p=.592
Number of rooms adult	50	8,161	100	5.51	1.83	4,651	100	5.40	1.80	p=.671
Number of rooms adult	55	1,350	100	4.79	1.98	774	100	4.73	1.90	p=.545
SES adult	23	6,364	100	3.01	0.77	3,627	100	3.00	.76	p=.500
Class I		207	3.25			121	3.34			
Class II		1,036	16.28			586	16.16			
Class III		3,815	59.95			2,201	60.68			
Class IV		1,113	17.49			621	17.12			
Class V		193	3.03			98	2.70			
SES adult	33	7,808	100	3.26	0.88	4,414	100	3.21	.88	p=.458
Class I		255	3.27			149	3.38			
Class II		1,130	14.47			637	14.43			
Class III		3,455	44.25			1,988	45.04			
Class IV		2,534	32.45			1,403	31.79			
Class V		434	5.56			237	5.37			
SES adult	42	7,810	100	3.32	0.87	4,437	100	3.32	.86	p=.929

Class I		239	3.06			139	3.13			
Class II		922	11.81			503	11.34			
Class III		3,196	40.92			1,838	41.42			
Class IV		3,004	38.46			1,718	38.72			
Class V		449	5.75			239	5.39			
SES adult	46	7,465	100	3.38	0.84	4,280	100	3.37	.83	
Class I		164	2.20			87	2.03			
Class II		818	10.96			475	11.10			
Class III		2,912	39.01			1,729	40.40			
Class IV		3,121	41.81			1,750	40.89			
Class V		450	6.03			239	5.58			p=.313
SES adult	50	7,069	100	3.39	0.85	4,075	100	3.39	.84	
Class I		159	2.25			90	2.21			
Class II		780	11.03			438	10.75			
Class III		2,698	38.17			1,581	38.80			
Class IV		2,983	42.20			1,732	42.50			
Class V		449	6.35			234	5.74			p=.742
SES adult	55	6,056	100	3.39	0.86	3,518	100	3.39	.85	
Class I		134	2.21			75	2.13			
Class II		706	11.66			394	11.20			
Class III		2,264	37.38			1,355	38.52			
Class IV		2,547	42.06			1,472	41.84			
Class V		405	6.69			222	6.31			p=.847
Tenure adult	23	4,615	100	N/A	N/A	2,679	100	N/A	N/A	χ^2=.0009
Owns/part-owns		2,522	54.65			1,465	54.68			p=.976

rents		2,093	45.35			1,214	45.32			
Tenure adult	33	7,606	100	N/A	N/A	4,338	100	N/A	N/A	χ^2=.481 p=.488
Owns/part-owns		6,290	82.70			3,609	83.20			
rents		1,316	17.30			729	16.80			
Tenure adult	42	8,806	100	N/A	N/A	4,986	100	N/A	N/A	χ^2=.018 p=.892
Owns/part-owns		7,534	85.56			4,270	85.64			
rents		1,272	14.44			716	14.36			
Tenure adult	46	8,460	100	N/A	N/A	4,826	100	N/A	N/A	χ^2=.498 p=.480
Owns/part-owns		7,399	87.46			4,241	87.88			
rents		1,061	12.54			585	12.12			
Tenure adult	50	8,114	100	N/A	N/A	4,623	100	N/A	N/A	χ^2=1.142 p=.285
Owns/part-owns		7,028	86.62			4,035	87.28			
rents		1,086	13.38			588	12.72			
Tenure adult	55	4,507	100	N/A	N/A	2,533	100	N/A	N/A	χ^2=.012 p=.915
Owns/part-owns		3,609	80.08			2,031	80.18			
rents		898	19.92			502	19.82			
Smoking adult	23	8,085	100	N/A	N/A	4,606	100	N/A	N/A	χ^2=.841 p=.359
Non-smoker		2,526	31.24			1,403 30.46	1,403 30.46			
Smoker		5,559	68.76			3,203 69.54	3,203 69.54			
Smoking adult	42	9,079	100	N/A	N/A	5,127	100	N/A	N/A	χ^2=.579 p=.447
Non-smoker		4,156	45.78			2,313	45.11			
Smoker		4,923	54.22			2,814	54.89			
Smoking adult	50	8,189	100	N/A	N/A	4,667	100	N/A	N/A	χ^2=.343 p=.558
Non-smoker		3,855	47.08			2,172	46.54			
Smoker		4,334	52.92			2,495	53.46			

Employment adult	23	3,403	100	N/A	N/A	1,898	100	N/A	N/A	χ^2=.125 p=.724
Employed		2,800	82.28			1,569	82.67			
Unemployed/disabled/in education		603	17.72			329	17.33			
Employment adult	42	9,011	100	N/A	N/A	5,091	100	N/A	N/A	χ^2=.828 p=.363
Employed		7,839	86.99			4,456	87.53			
Unemployed/disabled/in education		1,172	13.01			635	12.47			
Employment adult	50	8,047	100	N/A	N/A	4,599	100	N/A	N/A	χ^2=1.593 p=.207
Employed		7,091	88.12			4,087	88.87			
Unemployed/disabled/in education		956	11.88			512	11.13			
Employment adult	55	7,258	100	N/A	N/A	4,198	100	N/A	N/A	χ^2=.743 p=.389
Employed		6,234	85.89			3,630	86.47			
Unemployed/disabled/in education		1,024	14.11			568	13.53			

Notes: NCDS = 1958 National Child Development Study. NCDS Total = refers to all individuals who submitted the biomedical survey at the age of 44 and for whom we have phenotype data for. SES = Socio-economic status

Appendix 11: *Correlation Matrices for MCS*

Environment		z_SES_1	z_SES_2	z_SES_3	z_SES_4
z_Rooms_1	*r*	0.2781	0.25	0.2697	0.2463
	p	0	0	0	0
z_Rooms_2	*r*	0.3243	0.2942	0.3115	0.2843
	p	0	0	0	0
z_Rooms_3	*r*	0.3206	0.293	0.315	0.2886
	p	0	0	0	0
z_Rooms_4	*r*	0.3348	0.2858	0.3188	0.305
	p	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, SES= socio-economic status, polytomous/continuous variables were z-scored

Environment		z_SES_1	z_SES_2	z_SES_3	z_SES_4
tenure_1	*r*	-0.3858	-0.2964	-0.3662	-0.3408
	p	0	0	0	0
tenure_2	*r*	-0.3595	-0.2787	-0.3502	-0.3193
	p	0	0	0	0
tenure_3	*r*	-0.3739	-0.2743	-0.3592	-0.332
	p	0	0	0	0
tenure_4	*r*	-0.3694	-0.2688	-0.3518	-0.3322
	p	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES= socio-economic status, polytomous/continuous variables were z-scored

Environment		tenure_1	tenure_2	tenure_3	tenure_4	tenure_6
z_Rooms_1	*r*	-0.3203	-0.2896	-0.2787	-0.2657	-0.2633
	p	0	0	0	0	0
z_Rooms_2	*r*	-0.3797	-0.3776	-0.3568	-0.3421	-0.3409
	p	0	0	0	0	0
z_Rooms_3	*r*	-0.3784	-0.3673	-0.3822	-0.359	-0.3408
	p	0	0	0	0	0
z_Rooms_4	*r*	-0.383	-0.3786	-0.3855	-0.3927	-0.3755
	p	0	0	0	0	0
z_Rooms_6	*r*	-0.3588	-0.3426	-0.3518	-0.3491	-0.3754
	p	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		z_SES_1
Employment_1	*r*	-0.3302
	p	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		tenure_1
Employment_1	*r*	0.3351
	p	0

Note: *r* = correlation coefficient, p= p-value

Environment		z_Rooms_1
Employment_1	*r*	-0.1054
	p	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		Finance_1	Finance_2	Finance_6
z_Rooms_1	*r*	-0.1284	-0.1183	-0.0737
	p	0	0	0
z_Rooms_2	*r*	-0.1435	-0.1416	-0.0957
	p	0	0	0
z_Rooms_6	*r*	-0.1313	-0.1457	-0.1198
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, finance = financial difficulties, polytomous/continuous variables were z-scored

Environment		Finance_1	Finance_2
tenure_1	*r*	0.1736	0.1744
	p	0	0
tenure_2	*r*	0.1813	0.2033
	p	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties

Environment		Finance_1
Employment_1	*r*	0.1217
	p	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties

Environment		Finance_1	Finance_2
z_SES_1	*r*	-0.1184	-0.1214
	p	0	0
z_SES_2	*r*	-0.0952	-0.1247
	p	0	0

Note: *r* = correlation coefficient, p= p-value, SES= socio-economic status, finance = financial difficulties, polytomous/continuous variables were z-score

Appendix 12: *Correlation Matrices for USoc*

Environment		z_Rooms_1	z_Rooms_2	z_Rooms_3	z_Rooms_4	z_Rooms_5	z_Rooms_6	z_Rooms_7	z_Rooms_8	z_Rooms_9
z_Income_1	*r*	0.1186	0.121	0.1274	0.1424	0.1571	0.1724	0.175	0.1726	0.1766
	p	0	0	0	0	0	0	0	0	0
z_Income_2	*r*	0.1332	0.1302	0.1393	0.155	0.1671	0.1821	0.1841	0.1934	0.2057
	p	0	0	0	0	0	0	0	0	0
z_Income_3	*r*	0.1163	0.1131	0.1185	0.1404	0.1455	0.1598	0.1621	0.1749	0.1829
	p	0	0	0	0	0	0	0	0	0
z_Income_4	*r*	0.1288	0.1257	0.1353	0.1464	0.1531	0.1644	0.1714	0.1835	0.19
	p	0	0	0	0	0	0	0	0	0
z_Income_5	*r*	0.118	0.1187	0.1248	0.1362	0.1481	0.1681	0.1705	0.1751	0.1857
	p	0	0	0	0	0	0	0	0	0
z_Income_6	*r*	0.1507	0.1399	0.1497	0.1601	0.1721	0.1841	0.1971	0.1909	0.1982
	p	0	0	0	0	0	0	0	0	0
z_Income_7	p	0.1429	0.132	0.1412	0.1467	0.1586	0.1759	0.1723	0.1813	0.1847
	r	0	0	0	0	0	0	0	0	0
z_Income_8	p	0.1484	0.146	0.1606	0.1615	0.1725	0.1791	0.1792	0.1839	0.1913
	p	0	0	0	0	0	0	0	0	0
z_Income_9	*r*	0.1281	0.1288	0.147	0.1509	0.1536	0.1705	0.1723	0.1808	0.1881
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		z_SES_1	z_SES_2	z_SES_3	z_SES_4	z_SES_5	z_SES_6	z_SES_7	z_SES_8	z_SES_9
z_Income_1	*r*	0.4277	0.4034	0.4015	0.3968	0.3852	0.3655	0.3555	0.349	0.3581
	p	0	0	0	0	0	0	0	0	0
z_Income_2	*r*	0.3958	0.4313	0.4251	0.4272	0.4035	0.3786	0.3617	0.3603	0.3456
	p	0	0	0	0	0	0	0	0	0
z_Income_3	*r*	0.3818	0.4078	0.4241	0.4097	0.3939	0.3734	0.3424	0.3498	0.3286
	p	0	0	0	0	0	0	0	0	0
z_Income_4	*r*	0.365	0.3894	0.4025	0.4272	0.4131	0.3853	0.3625	0.3651	0.3548
	p	0	0	0	0	0	0	0	0	0
z_Income_5	*r*	0.3954	0.3927	0.3972	0.4105	0.4347	0.41	0.3881	0.3731	0.3719
	p	0	0	0	0	0	0	0	0	0
z_Income_6	*r*	0.3608	0.3753	0.3817	0.3878	0.3992	0.4066	0.3834	0.3764	0.3807
	p	0	0	0	0	0	0	0	0	0
z_Income_7	p	0.3582	0.3714	0.3752	0.3748	0.3791	0.372	0.3882	0.3758	0.3749
	r	0	0	0	0	0	0	0	0	0
z_Income_8	p	0.347	0.3421	0.3556	0.3404	0.3492	0.3397	0.3435	0.3845	0.3789

	p	0	0	0	0	0	0	0	0	0
z_Income_9	*r*	0.3014	0.3223	0.3397	0.3337	0.3443	0.3409	0.3407	0.3609	0.4064
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES= socio-economic status, polytomous/continuous variables were z-scored

Environment		z_SES_1	z_SES_2	z_SES_3	z_SES_4	z_SES_5	z_SES_6	z_SES_7	z_SES_8	z_SES_9
z_Rooms_1	*r*	0.1396	0.1478	0.1284	0.133	0.1408	0.1303	0.1391	0.1405	0.1405
	p	0	0	0	0	0	0	0	0	
z_Rooms_2	*r*	0.142	0.1653	0.1464	0.1412	0.147	0.1428	0.1514	0.1557	0.1507
	p	0	0	0	0	0	0	0	0	0
z_Rooms_3	*r*	0.1539	0.1734	0.1565	0.1544	0.1559	0.1441	0.1506	0.1523	0.154
	p	0	0	0	0	0	0	0	0	0
z_Rooms_4	*r*	0.1588	0.1808	0.1716	0.1597	0.1695	0.1589	0.1631	0.1639	0.1566
	p	0	0	0	0	0	0	0	0	0
z_Rooms_5	*r*	0.1783	0.1865	0.1831	0.1737	0.1803	0.1691	0.1757	0.1792	0.1777
	p	0	0	0	0	0	0	0	0	0
z_Rooms_6	*r*	0.1949	0.2001	0.194	0.1944	0.1945	0.1773	0.1851	0.1842	0.1924
	p	0	0	0	0	0	0	0	0	0
z_Rooms_7	p	0.2021	0.2076	0.1956	0.2018	0.1901	0.1833	0.1826	0.1761	0.1809
	r	0	0	0	0	0	0	0	0	0
z_Rooms_8	p	0.2144	0.2133	0.2065	0.2117	0.1926	0.1801	0.1815	0.174	0.1795
	p	0	0	0	0	0	0	0	0	0
z_Rooms_9	*r*	0.2161	0.2136	0.2081	0.2093	0.2008	0.1881	0.1912	0.1947	0.1992
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, SES= socio-economic status, polytomous/continuous variables were z-scored

Environment		Finance_1	Finance_2	Finance_3	Finance_4	Finance_5	Finance_6	Finance_7	Finance_8	Finance_9
Employment_1	*r*	0.2159	0.1948	0.1763	0.1719	0.1737	0.1638	0.165	0.1518	0.149
	p	0	0	0	0	0	0	0	0	0
Employment_2	*r*	0.1874	0.2359	0.1803	0.1649	0.1687	0.1443	0.1327	0.1472	0.1338
	p	0	0	0	0	0	0	0	0	0
Employment_3	*r*	0.1935	0.1919	0.2162	0.1935	0.1722	0.1454	0.1648	0.1639	0.1301
	p	0	0	0	0	0	0	0	0	0
Employment_4	*r*	0.1617	0.1766	0.2092	0.2199	0.1878	0.1477	0.177	0.1413	0.1527
	p	0	0	0	0	0	0	0	0	0
Employment_5	*r*	0.1671	0.1637	0.1983	0.1942	0.2025	0.1482	0.1702	0.1465	0.1343
	p	0	0	0	0	0	0	0	0	0
Employment_6	*r*	0.1424	0.1801	0.2131	0.1902	0.1752	0.1967	0.1889	0.1605	0.1506
	p	0	0	0	0	0	0	0	0	0

Employment_7	p	0.1431	0.1851	0.1964	0.1762	0.1726	0.1665	0.2156	0.1727	0.1369
	r	0	0	0	0	0	0	0	0	0
Employment_8	p	0.144	0.1735	0.1805	0.1819	0.1829	0.1854	0.2043	0.1893	0.1572
	p	0	0	0	0	0	0	0	0	0
Employment_9	*r*	0.1372	0.1554	0.1954	0.1866	0.1853	0.1694	0.2192	0.1804	0.1822
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties

Environment		Finance_1	Finance_2	Finance_3	Finance_4	Finance_5	Finance_6	Finance_7	Finance_8	Finance_9
tenure_1	*r*	0.218	0.1868	0.1998	0.2163	0.1759	0.1561	0.1811	0.1732	0.1566
	p	0	0	0	0	0	0	0	0	0
tenure_2	*r*	0.2117	0.181	0.1821	0.1948	0.1704	0.1495	0.1654	0.1635	0.1392
	p	0	0	0	0	0	0	0	0	0
tenure_3	*r*	0.2066	0.1792	0.1869	0.1965	0.1703	0.1474	0.165	0.1709	0.1443
	p	0	0	0	0	0	0	0	0	0
tenure_4	*r*	0.2102	0.1827	0.1908	0.2056	0.1759	0.152	0.1684	0.163	0.1467
	p	0	0	0	0	0	0	0	0	0
tenure_5	*r*	0.2139	0.1887	0.1939	0.2075	0.1778	0.1563	0.1704	0.1686	0.1399
	p	0	0	0	0	0	0	0	0	0
tenure_6	*r*	0.2263	0.1908	0.1827	0.2092	0.1808	0.157	0.1683	0.1694	0.1502
	p	0	0	0	0	0	0	0	0	0
tenure_7	p	0.2216	0.1924	0.1767	0.2198	0.1819	0.1559	0.1814	0.1681	0.1406
	r	0	0	0	0	0	0	0	0	0
tenure_8	p	0.2171	0.185	0.1843	0.2237	0.1881	0.1597	0.1881	0.1775	0.1456
	p	0	0	0	0	0	0	0	0	0
tenure_9	*r*	0.2137	0.1838	0.1931	0.2164	0.1977	0.175	0.1884	0.1839	0.1531
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties

Environment		tenure_1	tenure_2	tenure_3	tenure_4	tenure_5	tenure_6	tenure_7	tenure_8	tenure_9
Employment_1	*r*	0.2904	0.2895	0.2959	0.3017	0.2994	0.3055	0.3012	0.2992	0.2952
	p	0	0	0	0	0	0	0	0	0
Employment_2	*r*	0.2816	0.2798	0.2836	0.2833	0.2901	0.2892	0.2759	0.2763	0.2784
	p	0	0	0	0	0	0	0	0	0
Employment_3	*r*	0.2764	0.2709	0.268	0.2698	0.2655	0.2714	0.2693	0.2703	0.2708
	p	0	0	0	0	0	0	0	0	0
Employment_4	*r*	0.2731	0.2667	0.2693	0.2756	0.268	0.2778	0.2706	0.2693	0.2716
	p	0	0	0	0	0	0	0	0	0
Employment_5	*r*	0.249	0.2446	0.2483	0.2516	0.2572	0.2634	0.2564	0.2571	0.256

	p	0	0	0	0	0	0	0	0	0
Employment_6	*r*	0.2498	0.2408	0.2381	0.2469	0.2441	0.2507	0.2548	0.2469	0.2451
	p	0	0	0	0	0	0	0	0	0
Employment_7	p	0.2735	0.2565	0.2562	0.2578	0.2513	0.2647	0.261	0.2661	0.2718
	r	0	0	0	0	0	0	0	0	0
Employment_8	p	0.2542	0.2562	0.2566	0.2548	0.2494	0.2554	0.256	0.2546	0.2648
	p	0	0	0	0	0	0	0	0	0
Employment_9	*r*	0.2371	0.2399	0.2505	0.253	0.2388	0.2444	0.2384	0.2502	0.2505
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value

Environment		z_Income_1	z_Income_2	z_Income_3	z_Income_4	z_Income_5	z_Income_6	z_Income_7	z_Income_8	z_Income_9
Finance_1	*r*	-0.105	-0.0783	-0.0739	-0.0814	-0.0762	-0.0806	-0.0706	-0.0511	-0.0489
	p	0	0	0	0	0	0	0	0.0017	0.0037
Finance_2	*r*	-0.0569	-0.0929	-0.0661	-0.0752	-0.0667	-0.0609	-0.069	-0.0503	-0.0385
	p	0	0	0	0	0	0	0	0.0002	0.0066
Finance_3	*r*	-0.062	-0.072	-0.0994	-0.0977	-0.0873	-0.0885	-0.0794	-0.0692	-0.0684
	p	0	0	0	0	0	0	0	0	0
Finance_4	*r*	-0.0606	-0.0703	-0.0783	-0.111	-0.0865	-0.0825	-0.0758	-0.0795	-0.0756
	p	0	0	0	0	0	0	0	0	0
Finance_5	*r*	-0.0756	-0.0692	-0.0779	-0.0927	-0.1067	-0.0782	-0.0819	-0.0798	-0.0729
	p	0	0	0	0	0	0	0	0	0
Finance_6	*r*	-0.0525	-0.0523	-0.0635	-0.0736	-0.0801	-0.1077	-0.0834	-0.0797	-0.0689
	p	0.0007	0.0001	0	0	0	0	0	0	0
Finance_7	p	-0.0492	-0.0597	-0.0675	-0.0818	-0.0755	-0.0775	-0.1104	-0.0914	-0.0855
	r	0.0019	0	0	0	0	0	0	0	0
Finance_8	p	-0.0484	-0.0462	-0.0527	-0.0544	-0.0506	-0.0526	-0.0679	-0.0864	-0.0671
	p	0.0029	0.0008	0.0001	0.0001	0.0003	0.0002	0	0	0
Finance_9	*r*	-0.0518	-0.0449	-0.0552	-0.0705	-0.0593	-0.0706	-0.0711	-0.0664	-0.0872
	p	0.0021	0.0016	0.0001	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties, polytomous/continuous variables were z-scor

Environment		z_Income_1	z_Income_2	z_Income_3	z_Income_4	z_Income_5	z_Income_6	z_Income_7	z_Income_8	z_Income_9
Employment_1	*r*	-0.379	-0.3122	-0.2901	-0.2607	-0.2399	-0.222	-0.2037	-0.1879	-0.1629
	p	0	0	0	0	0	0	0	0	0
Employment_2	*r*	-0.303	-0.374	-0.3074	-0.277	-0.2564	-0.2382	-0.2199	-0.1955	-0.1794
	p	0	0	0	0	0	0	0	0	0
Employment_3	*r*	-0.2685	-0.2864	-0.3604	-0.2888	-0.2706	-0.2473	-0.2196	-0.2005	-0.1935
	p	0	0	0	0	0	0	0	0	0

Employment_4	*r*	-0.247	-0.2574	-0.2933	-0.3355	-0.2778	-0.2561	-0.2344	-0.2079	-0.1985
	p	0	0	0	0	0	0	0	0	0
Employment_5	*r*	-0.2302	-0.2283	-0.2651	-0.262	-0.3288	-0.2693	-0.2362	-0.2055	-0.1935
	p	0	0	0	0	0	0	0	0	0
Employment_6	*r*	-0.1962	-0.2065	-0.2373	-0.2256	-0.244	-0.2839	-0.2319	-0.1981	-0.1871
	p	0	0	0	0	0	0	0	0	0
Employment_7	p	-0.174	-0.1773	-0.1944	-0.205	-0.2036	-0.2176	-0.2597	-0.2028	-0.1937
	r	0	0	0	0	0	0	0	0	0
Employment_8	p	-0.1678	-0.1681	-0.1926	-0.1979	-0.1998	-0.2211	-0.2095	-0.2524	-0.2164
	p	0	0	0	0	0	0	0	0	0
Employment_9	*r*	-0.1517	-0.1472	-0.1754	-0.1842	-0.1791	-0.1872	-0.18	-0.196	-0.2421
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, polytomous/continuous variables were z-scored

Environment		tenure_1	tenure_2	tenure_3	tenure_4	tenure_5	tenure_6	tenure_7	tenure_8	tenure_9
z_Rooms_1	*r*	-0.3543	-0.3473	-0.3443	-0.3395	-0.3331	-0.3407	-0.3239	-0.3133	-0.3019
	p	0	0	0	0	0	0	0	0	0
z_Rooms_2	*r*	-0.3502	-0.3413	-0.3293	-0.3281	-0.3183	-0.3256	-0.3103	-0.3062	-0.2949
	p	0	0	0	0	0	0	0	0	0
z_Rooms_3	*r*	-0.351	-0.3382	-0.3493	-0.3394	-0.3269	-0.3372	-0.3214	-0.3206	-0.3124
	p	0	0	0	0	0	0	0	0	0
z_Rooms_4	*r*	-0.3534	-0.3379	-0.3442	-0.3559	-0.3429	-0.3532	-0.3413	-0.3364	-0.326
	p	0	0	0	0	0	0	0	0	0
z_Rooms_5	*r*	-0.3494	-0.3269	-0.3318	-0.3395	-0.3452	-0.3554	-0.3417	-0.3371	-0.321
	p	0	0	0	0	0	0	0	0	0
z_Rooms_6	*r*	-0.3495	-0.3294	-0.3367	-0.3489	-0.3512	-0.3679	-0.3601	-0.3559	-0.3425
	p	0	0	0	0	0	0	0	0	0
z_Rooms_7	p	-0.3406	-0.3297	-0.33	-0.3411	-0.3437	-0.3601	-0.3685	-0.3613	-0.3495
	r	0	0	0	0	0	0	0	0	0
z_Rooms_8	p	-0.3471	-0.3346	-0.3356	-0.3455	-0.3458	-0.3576	-0.3642	-0.3759	-0.3604
	p	0	0	0	0	0	0	0	0	0
z_Rooms_9	*r*	-0.3308	-0.3229	-0.3242	-0.3311	-0.329	-0.3384	-0.3463	-0.3565	-0.3672
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		tenure_1	tenure_2	tenure_3	tenure_4	tenure_5	tenure_6	tenure_7	tenure_8	tenure_9
z_SES_1	*r*	-0.1445	-0.1479	-0.1629	-0.1541	-0.1679	-0.1545	-0.1658	-0.1691	-0.1679
	p	0	0	0	0	0	0	0	0	0
z_SES_2	*r*	-0.1612	-0.1724	-0.1789	-0.1712	-0.185	-0.1882	-0.1803	-0.1699	-0.1753

	p	0	0	0	0	0	0	0	0	0
z_SES_3	*r*	-0.1666	-0.1747	-0.1829	-0.1798	-0.1921	-0.1909	-0.1839	-0.1793	-0.187
	p	0	0	0	0	0	0	0	0	0
z_SES_4	*r*	-0.1609	-0.1635	-0.1724	-0.1686	-0.1771	-0.1852	-0.1852	-0.186	-0.1948
	p	0	0	0	0	0	0	0	0	0
z_SES_5	*r*	-0.168	-0.164	-0.1805	-0.1785	-0.1876	-0.1906	-0.1894	-0.1826	-0.189
	p	0	0	0	0	0	0	0	0	0
z_SES_6	*r*	-0.1339	-0.1443	-0.1611	-0.1531	-0.1576	-0.1661	-0.1664	-0.1585	-0.1677
	p	0	0	0	0	0	0	0	0	0
z_SES_7	p	-0.1355	-0.1399	-0.1476	-0.1511	-0.1536	-0.1594	-0.158	-0.1584	-0.1672
	r	0	0	0	0	0	0	0	0	0
z_SES_8	p	-0.139	-0.1256	-0.144	-0.1419	-0.1469	-0.1525	-0.1439	-0.1466	-0.1627
	p	0	0	0	0	0	0	0	0	0
z_SES_9	*r*	-0.1162	-0.0957	-0.1156	-0.1121	-0.1168	-0.1282	-0.1288	-0.1222	-0.1465
	p	0	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		z_SES_1	z_SES_2	z_SES_3	z_SES_4	z_SES_5	z_SES_6	z_SES_7	z_SES_8	z_SES_9
Employment_1	*r*	-0.0563	-0.1421	-0.16	-0.1823	-0.1732	-0.1631	-0.1946	-0.1796	-0.1608
	p	0.0022	0	0	0	0	0	0	0	0
Employment_2	*r*	-0.1001	-0.0784	-0.1478	-0.1805	-0.1593	-0.1551	-0.1622	-0.1508	-0.1077
	p	0	0	0	0	0	0	0	0	0
Employment_3	*r*	-0.0769	-0.1007	-0.0728	-0.1262	-0.1325	-0.1272	-0.1066	-0.0988	-0.0662
	p	0	0	0	0	0	0	0	0	0.0011
Employment_4	*r*	-0.1	-0.1201	-0.1069	-0.0972	-0.1454	-0.1158	-0.1072	-0.1197	-0.0909
	p	0	0	0	0	0	0	0	0	0
Employment_5	*r*	-0.1162	-0.1082	-0.0811	-0.1014	-0.0703	-0.1118	-0.0998	-0.0727	-0.0648
	p	0	0	0	0	0	0	0	0.0002	0.0014
Employment_6	*r*	-0.0878	-0.1147	-0.0748	-0.0773	-0.1027	-0.0759	-0.065	-0.0127	-0.0499
	p	0	0	0	0	0	0	0.0005	0.516	0.015
Employment_7	p	-0.1077	-0.0958	-0.0761	-0.0825	-0.0633	-0.0481	-0.0157	-0.0407	-0.0612
	r	0	0	0	0	0.0005	0.0095	0.3927	0.0366	0.0028
Employment_8	p	-0.0935	-0.0841	-0.065	-0.0754	-0.0714	-0.0508	-0.0441	-0.0289	-0.0757
	p	0	0	0.0004	0	0.0001	0.0072	0.0211	0.1301	0.0002
Employment_9	*r*	-0.0601	-0.0662	-0.041	-0.0585	-0.0708	-0.0359	-0.0283	-0.0407	-0.0156
	p	0.0055	0.0003	0.0285	0.002	0.0002	0.0654	0.1494	0.0424	0.4369

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		z_Rooms_1	z_Rooms_2	z_Rooms_3	z_Rooms_4	z_Rooms_5	z_Rooms_6	z_Rooms_7	z_Rooms_8	z_Rooms_9
Finance_1	*r*	-0.0871	-0.0963	-0.0938	-0.1033	-0.109	-0.1074	-0.1113	-0.1002	-0.0993
	p	0	0	0	0	0	0	0	0	0
Finance_2	*r*	-0.057	-0.0634	-0.0675	-0.086	-0.0865	-0.0905	-0.0913	-0.0953	-0.0986
	p	0	0	0	0	0	0		0	0
Finance_3	*r*	-0.0695	-0.0634	-0.0705	-0.072	-0.0703	-0.0829	-0.0825	-0.0866	-0.096
	p	0	0	0	0	0	0		0	0
Finance_4	*r*	-0.0709	-0.0607	-0.0639	-0.0723	-0.0754	-0.0885	-0.0947	-0.0948	-0.0883
	p	0	0	0	0	0	0		0	0
Finance_5	*r*	-0.0412	-0.0474	-0.0434	-0.0497	-0.0561	-0.0623	-0.0652	-0.0707	-0.0781
	p	0.0055	0.0002	0.0006	0.0001	0	0	0	0	0
Finance_6	*r*	-0.0501	-0.0542	-0.0527	-0.0596	-0.0678	-0.0707	-0.0711	-0.0755	-0.0855
	p	0.0012	0	0.0001	0	0	0	0	0	0
Finance_7	p	-0.0573	-0.0652	-0.0623	-0.0683	-0.0705	-0.0744	-0.0744	-0.0918	-0.1083
	r	0.0003	0	0	0	0	0	0	0	0
Finance_8	p	-0.0788	-0.0651	-0.0656	-0.0663	-0.0738	-0.0697	-0.071	-0.0771	-0.0896
	p	0	0	0	0	0	0	0	0	0
Finance_9	*r*	-0.0649	-0.0652	-0.0604	-0.0684	-0.0655	-0.0688	-0.0667	-0.0687	-0.0666
	p	0.0001	0	0	0	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial difficulties, rooms = number of bedrooms, polytomous/continuous variables were z-scored

		z_Room~1	z_Room~2	z_Room~3	z_Room~4	z_Room~5	z_Room~6	z_Room~7	z_Room~8	z_Room~9
Employment_1	*r*	-0.0282	-0.0327	-0.0332	-0.0461	-0.0489	-0.0656	-0.069	-0.0643	-0.0645
	p	0.0402	0.0173	0.0186	0.0014	0.001	0	0	0.0001	0.0001
Employment_2	*r*	-0.0438	-0.0279	-0.0355	-0.0409	-0.0512	-0.0534	-0.0482	-0.0524	-0.0634
	p	0.0014	0.0175	0.0031	0.0009	0	0	0.0003	0.0001	0
Employment_3	*r*	-0.0351	-0.0138	-0.0158	-0.0221	-0.0224	-0.0174	-0.0226	-0.0205	-0.0291
	p	0.0131	0.2516	0.1841	0.0722	0.0743	0.1837	0.091	0.1347	0.0402
Employment_4	*r*	-0.0286	-0.0207	-0.0189	-0.031	-0.0226	-0.0254	-0.0288	-0.03	-0.0375
	p	0.0482	0.0918	0.1252	0.0114	0.0727	0.0524	0.0312	0.0289	0.0084
Employment_5	*r*	-0.0353	-0.024	-0.0204	-0.0305	-0.0202	-0.0293	-0.0228	-0.0261	-0.0357
	p	0.0169	0.0557	0.1037	0.0157	0.1075	0.0253	0.0894	0.0578	0.0123
Employment_6	*r*	-0.0419	-0.0318	-0.0335	-0.0345	-0.0255	-0.0328	-0.0323	-0.0295	-0.0363
	p	0.0065	0.0149	0.0105	0.0086	0.0528	0.0121	0.0169	0.0335	0.0115
Employment_7	p	-0.0527	-0.036	-0.0377	-0.0423	-0.0369	-0.0367	-0.0363	-0.0392	-0.0448
	r	0.0009	0.0071	0.0048	0.0017	0.0062	0.0069	0.0065	0.0047	0.0018
Employment_8	p	-0.0659	-0.0675	-0.0725	-0.0706	-0.0675	-0.065	-0.0706	-0.0712	-0.0762
	p	0	0	0	0	0	0	0	0	0
Employment_9	*r*	-0.0438	-0.0386	-0.0453	-0.0497	-0.0489	-0.0511	-0.0444	-0.0508	-0.0464
	p	0.0093	0.0065	0.0014	0.0005	0.0006	0.0004	0.0019	0.0004	0.0012

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Appendix 13: *Correlation Matrices for NCDS*

Childhood

Environment		z_Rooms_7	z_Rooms_11	z_Rooms_16
z_SES_7	*r*	0.2887	0.311	0.3025
	p	0	0	0
z_SES_11	*r*	0.2472	0.3007	0.2812
	p	0	0	0
z_SES_16	*r*	0.2911	0.3117	0.3137
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		tenure_7	tenure_11	tenure_16
Finance_7	*r*	0.1458	0.1418	0.1428
	p	0	0	0
Finance_11	*r*	0.1468	0.1639	0.1669
	p	0	0	0
Finance_16	*r*	0.1325	0.155	0.158
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial issues

Environment		tenure_7	tenure_11	tenure_16
z_SES_7	*r*	-0.3485	-0.3493	-0.3447
	p	0	0	
z_SES_11	*r*	-0.3609	-0.3742	-0.3734
	p	0	0	0
z_SES_16	*r*	-0.3577	-0.366	-0.3721
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		z_SES_7	z_SES_11	z_SES_16
Finance_7	*r*	-0.1642	-0.1763	-0.1615
	p	0	0	0
Finance_11	*r*	-0.1217	-0.1343	-0.1436
	p	0	0	0
Finance_16	*r*	-0.1419	-0.1566	-0.1611
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, finance = financial issues, polytomous/continuous variables were z-scored

Environment		z_Rooms_7	z_Rooms_11	z_Rooms_16
tenure_7	*r*	-0.3055	-0.3271	-0.2911
	p	0	0	
tenure_11	*r*	-0.2953	-0.3312	-0.2835
	p	0	0	0
tenure_16	*r*	-0.2887	-0.3078	-0.3011
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		z_Rooms_7	z_Rooms_11	z_Rooms_16
Finance_7	*r*	-0.0642	-0.059	-0.0456
	p	0	0.0003	0.0084
Finance_11	*r*	-0.055	-0.0516	-0.0575
	p	0.0004	0.0006	0.0006
Finance_16	*r*	-0.0629	-0.0363	-0.0555
	p	0.0002	0.0296	0.0005

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, finance = financial issues, polytomous/continuous variables were z-scored

Environment		z_Rooms_7	z_Rooms_11	z_Rooms_16
Employment_7	*r*	-0.0276	-0.0332	-0.0291
	p	0.0584	0.028	0.0724
Employment_11	*r*	-0.0382	-0.0369	0.0096
	p	0.0118	0.0142	0.5553
Employment_16	*r*	-0.0497	-0.0327	-0.0449
	p	0.0036	0.0562	0.0059

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		Finance_7	Finance_11	Finance_16
Employment_7	*r*	0.2744	0.0853	0.1419
	p	0	0	0
Employment_11	*r*	0.19	0.2632	0.2185
	p	0	0	0
Employment_16	*r*	0.1941	0.1872	0.3347
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, finance = financial issues

Environment		z_SES_7	z_SES_11	z_SES_16
Employment_7	*r*	-0.1026	-0.0846	-0.1083
	p	0	0	0
Employment_11	*r*	-0.1141	-0.1124	-0.1009
	p	0	0	0
Employment_16	*r*	-0.1273	-0.1312	-0.1031
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		tenure_7	tenure_11	tenure_16
Employment_7	*r*	0.0647	0.0676	0.1027
	p	0	0	0
Employment_11	*r*	0.107	0.1283	0.1201
	p	0	0	0
Employment_16	*r*	0.1177	0.1039	0.1316
	p	0	0	0

Note: *r* = correlation coefficient, p= p-value

Adulthood

Environment		z_Rooms_23	z_Rooms_33	z_Rooms_42	z_Rooms_46	z_Rooms_50	z_Rooms_55
z_SES_23	*r*	0.0264	0.1421	0.1408	0.2558	0.2628	0.2994
	p	0.1153	0	0	0	0	0
z_SES_33	*r*	0.0364	0.0996	0.1341	0.2488	0.2552	0.2036
	p	0.0243	0	0	0	0	0
z_SES_42	*r*	0.0511	0.1169	0.15	0.276	0.2652	0.2698
	p	0.0016	0	0	0	0	0

z_SES_46	*r*	0.0607	0.1287	0.155	0.2725	0.2704	0.304
	p	0.0002	0	0	0	0	0
z_SES_50	*r*	0.0374	0.1192	0.1591	0.2735	0.2822	0.296
	p	0.0269	0	0	0	0	0
z_SES_55	*r*	0.0588	0.1066	0.1355	0.2662	0.2761	0.2936
	p	0.0012	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		z_Rooms_23	z_Rooms_42	z_Rooms_50	z_Rooms_55
Unemployment_23	*r*	0.0292	-0.0679	-0.0979	-0.0876
	p	0.21	0.0038	0.0001	0.1526
Unemployment_42	*r*	-0.0115	-0.0165	-0.0549	-0.1056
	p	0.452	0.2385	0.0002	0.004
Unemployment_50	*r*	0.0024	-0.0381	-0.0586	-0.0732
	p	0.8827	0.0108	0.0001	0.0578
Unemployment_55	*r*	-0.0063	-0.0563	-0.0771	-0.1098
	p	0.7048	0.0003	0	0.0032

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Environment		tenure_23	tenure_42	tenure_50	tenure_55
Unemployment_23	*r*	0.1423	0.1196	0.1004	0.1218
	p	0	0	0	0.0002
Unemployment_42	*r*	0.0956	0.257	0.2059	0.1986
	p	0	0	0	0
Unemployment_50	*r*	0.1005	0.2179	0.2289	0.2226
	p	0	0	0	0
Unemployment_55	*r*	0.0817	0.1837	0.1922	0.2129
	p	0.0001	0	0	0

Note: *r* = correlation coefficient, p= p-value

Environment		z_SES_23	z_SES_42	z_SES_50	z_SES_55
Unemployment_23	*r*	-0.1567	-0.0784	-0.0898	-0.0514
	p	0	0.0022	0.0008	0.0753
Unemployment_42	*r*	-0.0846	.	-0.1173	-0.1075
	p	0	.	0	0
Unemployment_50	*r*	-0.091	-0.0885	.	-0.0651
	p	0	0	.	0.0002
Unemployment_55	*r*	-0.095	-0.0753	-0.0857	.
	p	0	0	0	.

Note: *r* = correlation coefficient, p= p-value. SES = socio-economic status, some missing values due to insufficient responses, polytomous/continuous variables were z-scored

Environment		tenure_23	tenure_33	tenure_42	tenure_46	tenure_50	tenure_55
z_SES_23	*r*	-0.1391	-0.219	-0.1978	-0.1762	-0.1684	-0.1899
	p	0	0	0	0	0	0
z_SES_33	*r*	-0.0556	-0.2291	-0.233	-0.1917	-0.1938	-0.1981
	p	0.0081	0	0	0	0	0
z_SES_42	*r*	-0.0487	-0.17	-0.2061	-0.1593	-0.1711	-0.1658
	p	0.0202	0	0	0	0	0
z_SES_46	*r*	-0.0469	-0.1691	-0.1661	-0.1435	-0.1424	-0.1449
	p	0.0285	0	0	0	0	0
z_SES_50	*r*	-0.0343	-0.1771	-0.187	-0.1655	-0.1788	-0.1867
	p	0.1179	0	0	0	0	0
z_SES_55	*r*	-0.0219	-0.1661	-0.1564	-0.1136	-0.136	-0.1958
	p	0.3518	0	0	0	0	0

Note: *r* = correlation coefficient, p= p-value, SES = socio-economic status, polytomous/continuous variables were z-scored

Environment		tenure_23	tenure_33	tenure_42	tenure_46	tenure_50	tenure_55
z_Rooms_23	*r*	-0.1674	-0.0509	-0.0221	-0.0111	-0.0022	-0.0433
	p	-0.1692	-0.0511	-0.0225	-0.0114	-0.0029	-0.0448
z_Rooms_33	*r*	0	0.0017	0.143	0.4655	0.8565	0.0373
	p	-0.1886	-0.228	-0.115	-0.115	-0.1145	-0.1368
z_Rooms_42	*r*	0	0	0	0	0	0
	p	-0.1317	-0.1633	-0.1878	-0.1413	-0.1484	-0.1381
z_Rooms_46	*r*	0	0	0	0	0	0
	p	-0.1823	-0.2496	-0.2614	-0.2673	-0.2374	-0.2616
z_Rooms_50	*r*	0	0	0	0	0	0
	p	-0.1907	-0.2553	-0.2472	-0.2515	-0.2842	-0.2765
z_Rooms_55	*r*	0	0	0	0	0	0
	p	-0.1334	-0.1801	-0.2249	-0.2704	-0.2145	-0.3374

Note: *r* = correlation coefficient, p= p-value, rooms = number of bedrooms, polytomous/continuous variables were z-scored

Appendix 14: *PRS Results for MCS (Chapter 3)*

SCZ														
Environment	**SCZ**				**Bonferroni Correction**		**Sensitivity**				**Interaction terms**		**Compare SCZ & MDD**	
	Threshold z-scored	**Beta**	**95%CI**	**P-Value**	**0.05/86**	**statistically significant?**	**Beta**	**95%CI**	**P-Value**	**Corrected with**	**Wald chi-squared**	**P-Value**	**Wald chi-squared**	**P-Value**
SES	0.01	-0.01	-0.06-0.03	5.32E-01	0.000581395	FALSE								
	0.1	-0.02	-0.08-0.04	5.14E-01	0.000581395	FALSE								
	0.2	-0.02	-0.09-0.04	4.64E-01	0.000581395	FALSE								
	0.3	-0.02	-0.09-0.05	5.47E-01	0.000581395	FALSE								
	0.4	-0.02	-0.09-0.04	4.96E-01	0.000581395	FALSE								
	0.5	-0.02	-0.09-0.05	5.44E-01	0.000581395	FALSE								
	1	-0.02	-0.09-0.05	5.79E-01	0.000581395	FALSE								
Finance Issues	0.01	0.01	-0.14-0.16	8.59E-01	0.000581395	FALSE								
	0.1	0.14	-0.06-0.34	1.78E-01	0.000581395	FALSE								
	0.2	0.12	-0.09-0.34	2.63E-01	0.000581395	FALSE								
	0.3	0.11	-0.11-0.33	3.23E-01	0.000581395	FALSE								
	0.4	0.12	-0.10-0.35	2.89E-01	0.000581395	FALSE								
	0.5	0.11	-0.12-0.34	3.43E-01	0.000581395	FALSE								
	1	0.09	-0.14-0.32	4.36E-01	0.000581395	FALSE								
Number of Rooms	0.01	0	-0.04-0.04	9.51E-01	0.000581395	FALSE								
	0.1	0	-0.06-0.05	8.81E-01	0.000581395	FALSE								
	0.2	0	-0.06-0.06	8.92E-01	0.000581395	FALSE								
	0.3	0	-0.06-0.06	9.62E-01	0.000581395	FALSE								
	0.4	0	-0.06-0.06	9.52E-01	0.000581395	FALSE								
	0.5	0	-0.06-0.07	9.29E-01	0.000581395	FALSE								
	1	0	-0.06-0.07	8.80E-01	0.000581395	FALSE								
Tenure	0.01	0.22	-0.04-0.47	9.91E-02	0.000581395	FALSE								
	0.1	0.29	-0.05-0.63	9.95E-02	0.000581395	FALSE								
	0.2	0.22	-0.14-0.59	2.31E-01	0.000581395	FALSE								
	0.3	0.26	-0.11-0.64	1.70E-01	0.000581395	FALSE								
	0.4	0.29	-0.09-0.68	1.37E-01	0.000581395	FALSE								
	0.5	0.28	-0.11-0.68	1.55E-01	0.000581395	FALSE								
	1	0.27	-0.13-0.66	1.87E-01	0.000581395	FALSE								
	0.01	0.16	-0.10-0.41	2.41E-01	0.000581395	FALSE								

Mother's interest in child's education	0.1	0.15	-0.19-0.49	3.92E-01	0.000581395	FALSE				
	0.2	0.06	-0.30-0.43	7.31E-01	0.000581395	FALSE				
	0.3	0.05	-0.33-0.43	7.97E-01	0.000581395	FALSE				
	0.4	0.07	-0.31-0.46	7.07E-01	0.000581395	FALSE				
	0.5	0.08	-0.31-0.48	6.81E-01	0.000581395	FALSE				
	1	0.07	-0.33-0.47	7.28E-01	0.000581395	FALSE				
Father's involvement in childcare	0.01	0.26	0.01-0.50	4.05E-02	0.000581395	FALSE				
	0.1	0.19	-0.14-0.52	2.66E-01	0.000581395	FALSE				
	0.2	0.19	-0.16-0.54	2.88E-01	0.000581395	FALSE				
	0.3	0.27	-0.10-0.63	1.48E-01	0.000581395	FALSE				
	0.4	0.28	-0.09-0.65	1.34E-01	0.000581395	FALSE				
	0.5	0.3	-0.08-0.67	1.22E-01	0.000581395	FALSE				
	1	0.29	-0.09-0.67	1.29E-01	0.000581395	FALSE				
Father's interest in child's education	0.01	0.12	-0.15-0.38	3.99E-01	0.000581395	FALSE				
	0.1	0.14	-0.21-0.49	4.34E-01	0.000581395	FALSE				
	0.2	0.09	-0.29-0.46	6.45E-01	0.000581395	FALSE				
	0.3	0.09	-0.30-0.48	6.41E-01	0.000581395	FALSE				
	0.4	0.08	-0.31-0.48	6.87E-01	0.000581395	FALSE				
	0.5	0.08	-0.33-0.48	7.09E-01	0.000581395	FALSE				
	1	0.09	-0.32-0.50	6.67E-01	0.000581395	FALSE				
Mother walks	0.01	-0.03	-0.20-0.14	7.51E-01	0.000581395	FALSE				
	0.1	-0.14	-0.37-0.09	2.20E-01	0.000581395	FALSE				
	0.2	-0.13	-0.38-0.11	2.80E-01	0.000581395	FALSE				
	0.3	-0.15	-0.40-0.10	2.46E-01	0.000581395	FALSE				
	0.4	-0.16	-0.41-0.10	2.30E-01	0.000581395	FALSE				
	0.5	-0.17	-0.43-0.09	2.00E-01	0.000581395	FALSE				
	1	-0.18	-0.44-0.09	1.90E-01	0.000581395	FALSE				
Father walks	0.01	-0.06	-0.25-0.13	5.42E-01	0.000581395	FALSE				
	0.1	-0.11	-0.37-0.14	3.89E-01	0.000581395	FALSE				
	0.2	-0.1	-0.38-0.18	4.81E-01	0.000581395	FALSE				
	0.3	-0.11	-0.40-0.17	4.36E-01	0.000581395	FALSE				
	0.4	-0.14	-0.43-0.15	3.45E-01	0.000581395	FALSE				
	0.5	-0.13	-0.43-0.16	3.85E-01	0.000581395	FALSE				
	1	-0.15	-0.45-0.15	3.39E-01	0.000581395	FALSE				
Smoking Mother	0.01	0.08	0.02-0.15	1.67E-02	0.000581395	FALSE				
	0.1	0.1	0.00-0.19	4.05E-02	0.000581395	FALSE				
	0.2	0.08	-0.02-0.18	9.72E-02	0.000581395	FALSE				
	0.3	0.11	0.01-0.22	3.20E-02	0.000581395	FALSE				

	0.4	0.11	0.01-0.22	3.55E-02	0.000581395	FALSE								
	0.5	0.11	0.01-0.22	3.86E-02	0.000581395	FALSE								
	1	0.11	0.00-0.22	4.77E-02	0.000581395	FALSE								
Smoking Father	0.01	0.19	-0.16-0.54	2.92E-01	0.000581395	FALSE								
	0.1	0.22	-0.25-0.69	3.54E-01	0.000581395	FALSE								
	0.2	0.22	-0.28-0.72	3.86E-01	0.000581395	FALSE								
	0.3	0.13	-0.39-0.64	6.28E-01	0.000581395	FALSE								
	0.4	0.13	-0.40-0.65	6.32E-01	0.000581395	FALSE								
	0.5	0.12	-0.41-0.66	6.57E-01	0.000581395	FALSE								
	1	0.12	-0.42-0.66	6.64E-01	0.000581395	FALSE								
Gestational period	0.01	0.02	-0.03-0.06	4.82E-01	0.000581395	FALSE								
	0.1	0.01	-0.05-0.07	6.68E-01	0.000581395	FALSE								
	0.2	0.02	-0.04-0.09	4.43E-01	0.000581395	FALSE								
	0.3	0.03	-0.04-0.09	4.39E-01	0.000581395	FALSE								
	0.4	0.03	-0.04-0.09	4.24E-01	0.000581395	FALSE								
	0.5	0.03	-0.04-0.09	3.97E-01	0.000581395	FALSE								
	1	0.03	-0.04-0.10	4.13E-01	0.000581395	FALSE								
birth weight	0.01	0.02	-0.03-0.08	3.90E-01	0.000581395	FALSE								
	0.1	0.08	0.01-0.15	3.48E-02	0.000581395	FALSE								
	0.2	0.08	0.00-0.16	3.67E-02	0.000581395	FALSE								
	0.3	0.08	0.00-0.16	4.58E-02	0.000581395	FALSE								
	0.4	0.08	0.00-0.16	3.97E-02	0.000581395	FALSE								
	0.5	0.08	0.00-0.16	4.22E-02	0.000581395	FALSE								
	1	0.08	0.00-0.16	4.91E-02	0.000581395	FALSE								
Marital status	0.01	0.1	0.06-0.15	1.07E-05	0.000581395	TRUE	-0.3	-0.43--0.17	8.45E-06	Mother & father	0.89	3.58E-01	0.06	8.01E-01
	0.1	0.17	0.10-0.23	1.20E-07	0.000581395	TRUE	-0.19	-0.38--0.01	3.86E-02		4.45	3.50E-02	2.35	1.12E-01
	0.2	0.16	0.09-0.22	2.80E-06	0.000581395	TRUE	-0.25	-0.44--0.05	1.42E-02		6.68	9.70E-03	2.12	1.45E-01
	0.3	0.17	0.10-0.23	1.61E-06	0.000581395	TRUE	-0.2	-0.41-0.00	5.17E-02		8.35	3.90E-03	2.85	9.14E-02
	0.4	0.18	0.11-0.25	4.41E-07	0.000581395	TRUE	-0.19	-0.40-0.01	6.69E-02		3.9	4.82E-02	1.95	1.63E-01
	0.5	0.18	0.11-0.25	8.36E-07	0.000581395	TRUE	-0.21	-0.42-0.00	5.27E-02		3.89	4.87E-02	1.57	2.10E-01
	1	0.17	0.10-0.24	2.25E-06	0.000581395	TRUE	-0.2	-0.41-0.01	6.38E-02		1.8	1.80E-01	2.15	1.43E-01
Alcohol Mother	0.01	-0.04	-0.09-0.01	8.00E-02	0.000581395	FALSE								
	0.1	0	-0.07-0.06	9.47E-01	0.000581395	FALSE								
	0.2	0.01	-0.06-0.08	8.49E-01	0.000581395	FALSE								
	0.3	0.02	-0.05-0.09	5.81E-01	0.000581395	FALSE								
	0.4	0.02	-0.05-0.09	5.54E-01	0.000581395	FALSE								
	0.5	0.02	-0.05-0.09	6.06E-01	0.000581395	FALSE								
	1	0.02	-0.06-0.09	6.81E-01	0.000581395	FALSE								

Alcohol Father	0.01	-0.12	-0.38-0.13	3.32E-01	0.000581395	FALSE						
	0.1	-0.1	-0.44-0.24	5.63E-01	0.000581395	FALSE						
	0.2	-0.13	-0.49-0.23	4.88E-01	0.000581395	FALSE						
	0.3	-0.13	-0.51-0.24	4.84E-01	0.000581395	FALSE						
	0.4	-0.16	-0.54-0.22	4.09E-01	0.000581395	FALSE						
	0.5	-0.17	-0.56-0.22	3.92E-01	0.000581395	FALSE						
	1	-0.19	-0.58-0.20	3.42E-01	0.000581395	FALSE						
Employment Mother	0.01	0	-0.10-0.10	9.67E-01	0.000581395	FALSE						
	0.1	0.06	-0.08-0.20	3.76E-01	0.000581395	FALSE						
	0.2	0.05	-0.10-0.20	5.14E-01	0.000581395	FALSE						
	0.3	0.05	-0.10-0.20	5.24E-01	0.000581395	FALSE						
	0.4	0.05	-0.10-0.21	5.06E-01	0.000581395	FALSE						
	0.5	0.05	-0.11-0.21	5.42E-01	0.000581395	FALSE						
	1	0.04	-0.12-0.20	5.97E-01	0.000581395	FALSE						
Father Reads	0.01	0.09	-0.15-0.32	4.61E-01	0.000581395	FALSE						
	0.1	0.02	-0.29-0.33	9.01E-01	0.000581395	FALSE						
	0.2	-0.04	-0.37-0.30	8.25E-01	0.000581395	FALSE						
	0.3	-0.08	-0.42-0.27	6.64E-01	0.000581395	FALSE						
	0.4	-0.11	-0.46-0.25	5.57E-01	0.000581395	FALSE						
	0.5	-0.11	-0.47-0.24	5.36E-01	0.000581395	FALSE						
	1	-0.11	-0.47-0.26	5.62E-01	0.000581395	FALSE						
Mother Reads	0.01	-0.03	-0.24-0.18	7.64E-01	0.000581395	FALSE						
	0.1	0.09	-0.19-0.37	5.27E-01	0.000581395	FALSE						
	0.2	0.07	-0.23-0.37	6.27E-01	0.000581395	FALSE						
	0.3	0.08	-0.23-0.39	6.23E-01	0.000581395	FALSE						
	0.4	0.07	-0.25-0.38	6.79E-01	0.000581395	FALSE						
	0.5	0.07	-0.24-0.39	6.49E-01	0.000581395	FALSE						
	1	0.06	-0.26-0.38	7.21E-01	0.000581395	FALSE						
MDD												
SES	0.01	-0.07	-0.10--0.03	1.04E-04	0.000581395	TRUE	0.02	-0.05-0.08	5.82E-01	Mother & father	2.29	1.30E-01
	0.1	-0.06	-0.12-0.00	6.41E-02	0.000581395	FALSE	-0.02	-0.14-0.09	6.95E-01		1.00	3.18E-01
	0.2	-0.09	-0.18--0.00	3.86E-02	0.000581395	FALSE	-0.08	-0.25-0.09	3.70E-01		0.22	6.41E-01
	0.3	-0.08	-0.17-0.02	1.07E-01	0.000581395	FALSE	-0.1	-0.28-0.07	2.57E-01		0.07	7.93E-01
	0.4	-0.09	-0.18--0.00	4.53E-02	0.000581395	FALSE	-0.13	-0.30-0.04	1.41E-01		0.02	8.89E-01
	0.5	-0.1	-0.19--0.01	2.54E-02	0.000581395	FALSE	-0.1	-0.27-0.07	2.41E-01		0.05	8.25E-01
	1	-0.09	-0.17--0.00	4.34E-02	0.000581395	FALSE	-0.08	-0.23-0.08	3.37E-01		0.03	8.67E-01
Finance Issues	0.01	0.19	0.08-0.30	8.35E-04	0.000581395	FALSE						
	0.1	0.08	-0.11-0.27	4.04E-01	0.000581395	FALSE						

	0.2	0.24	-0.04-0.52	9.72E-02	0.000581395	FALSE							
	0.3	0.23	-0.05-0.51	1.14E-01	0.000581395	FALSE							
	0.4	0.23	-0.04-0.51	9.76E-02	0.000581395	FALSE							
	0.5	0.29	0.01-0.56	3.88E-02	0.000581395	FALSE							
	1	0.21	-0.05-0.46	1.10E-01	0.000581395	FALSE							
Number of Rooms	0.01	-0.05	-0.08--0.02	2.85E-03	0.000581395	FALSE							
	0.1	-0.07	-0.12--0.01	1.95E-02	0.000581395	FALSE							
	0.2	-0.11	-0.19--0.03	1.07E-02	0.000581395	FALSE							
	0.3	-0.09	-0.18--0.01	3.36E-02	0.000581395	FALSE							
	0.4	-0.08	-0.16-0.01	7.18E-02	0.000581395	FALSE							
	0.5	-0.07	-0.15-0.01	7.61E-02	0.000581395	FALSE							
	1	-0.05	-0.13-0.03	1.88E-01	0.000581395	FALSE							
Tenure	0.01	0.43	0.24-0.63	1.14E-05	0.000581395	TRUE	-0.04	-0.23-0.15	6.94E-01	Mother & father	24.97	<0.0001	
	0.1	0.39	0.06-0.73	2.13E-02	0.000581395	FALSE	0.06	-0.25-0.38	7.01E-01		13.97	2.00E-04	
	0.2	0.52	0.02-1.01	4.13E-02	0.000581395	FALSE	0.17	-0.29-0.64	4.64E-01		17.01	<0.0001	
	0.3	0.45	-0.06-0.95	8.57E-02	0.000581395	FALSE	0.33	-0.15-0.81	1.75E-01		10.65	1.10E-03	
	0.4	0.49	0.00-0.98	4.94E-02	0.000581395	FALSE	0.35	-0.12-0.81	1.42E-01		6.22	1.27E-02	
	0.5	0.62	0.14-1.10	1.20E-02	0.000581395	FALSE	0.33	-0.12-0.78	1.52E-01		1.48	2.24E-01	
	1	0.51	0.06-0.96	2.76E-02	0.000581395	FALSE	0.23	-0.18-0.65	2.71E-01		2.99	8.40E-02	
Mother's interest in child's education	0.01	0.1	-0.10-0.30	3.16E-01	0.000581395	FALSE							
	0.1	0.1	-0.26-0.46	5.81E-01	0.000581395	FALSE							
	0.2	0.26	-0.27-0.78	3.40E-01	0.000581395	FALSE							
	0.3	0.13	-0.41-0.68	6.30E-01	0.000581395	FALSE							
	0.4	0.03	-0.49-0.55	9.15E-01	0.000581395	FALSE							
	0.5	0.09	-0.43-0.61	7.33E-01	0.000581395	FALSE							
	1	0.09	-0.40-0.58	7.10E-01	0.000581395	FALSE							
Father's involvement in childcare	0.01	0.26	0.07-0.46	8.15E-03	0.000581395	FALSE							
	0.1	0.38	0.01-0.74	4.46E-02	0.000581395	FALSE							
	0.2	0.42	-0.14-0.97	1.39E-01	0.000581395	FALSE							
	0.3	0.38	-0.19-0.96	1.90E-01	0.000581395	FALSE							
	0.4	0.37	-0.19-0.94	1.94E-01	0.000581395	FALSE							
	0.5	0.36	-0.20-0.92	2.03E-01	0.000581395	FALSE							
	1	0.32	-0.23-0.86	2.53E-01	0.000581395	FALSE							
Father's interest in child's education	0.01	0.12	-0.08-0.32	2.54E-01	0.000581395	FALSE							
	0.1	0.16	-0.22-0.54	4.19E-01	0.000581395	FALSE							
	0.2	0.37	-0.20-0.94	2.01E-01	0.000581395	FALSE							
	0.3	0.45	-0.14-1.04	1.33E-01	0.000581395	FALSE							
	0.4	0.38	-0.18-0.94	1.89E-01	0.000581395	FALSE							

	0.5	0.39	-0.17-0.94	1.73E-01	0.000581395	FALSE							
	1	0.41	-0.12-0.95	1.31E-01	0.000581395	FALSE							
Mother walks	0.01	-0.1	-0.22-0.03	1.32E-01	0.000581395	FALSE							
	0.1	-0.17	-0.40-0.05	1.28E-01	0.000581395	FALSE							
	0.2	-0.2	-0.54-0.13	2.33E-01	0.000581395	FALSE							
	0.3	-0.18	-0.52-0.17	3.11E-01	0.000581395	FALSE							
	0.4	-0.09	-0.42-0.25	6.06E-01	0.000581395	FALSE							
	0.5	-0.1	-0.42-0.23	5.61E-01	0.000581395	FALSE							
	1	-0.15	-0.46-0.15	3.23E-01	0.000581395	FALSE							
Father walks	0.01	-0.1	-0.25-0.05	1.82E-01	0.000581395	FALSE							
	0.1	-0.16	-0.44-0.12	2.60E-01	0.000581395	FALSE							
	0.2	-0.28	-0.69-0.14	1.98E-01	0.000581395	FALSE							
	0.3	-0.25	-0.69-0.19	2.66E-01	0.000581395	FALSE							
	0.4	-0.24	-0.67-0.19	2.74E-01	0.000581395	FALSE							
	0.5	-0.21	-0.63-0.22	3.41E-01	0.000581395	FALSE							
	1	-0.17	-0.57-0.23	4.10E-01	0.000581395	FALSE							
Smoking Mother	0.01	0.2	0.15-0.26	0.00E+00	0.000581395	TRUE	0.15	0.09-0.22	7.86E-07	Mother only	51.72	1.00E-05	
	0.1	0.28	0.18-0.38	3.12E-08	0.000581395	TRUE	0.18	0.07-0.29	1.50E-03		63.83	1.00E-05	
	0.2	0.45	0.30-0.60	7.70E-09	0.000581395	TRUE	0.36	0.19-0.52	1.93E-05		84.88	1.00E-05	
	0.3	0.46	0.31-0.62	8.30E-09	0.000581395	TRUE	0.38	0.22-0.55	8.73E-06		86.07	1.00E-05	
	0.4	0.43	0.28-0.58	4.41E-08	0.000581395	TRUE	0.36	0.19-0.52	2.39E-05		82.44	1.00E-05	
	0.5	0.45	0.30-0.60	7.10E-09	0.000581395	TRUE	0.39	0.22-0.55	3.78E-06		83.65	1.00E-05	
	1	0.39	0.24-0.54	1.61E-07	0.000581395	TRUE	0.31	0.16-0.47	9.25E-05		87.49	1.00E-05	
Smoking Father	0.01	0.17	-0.09-0.43	1.94E-01	0.000581395	FALSE							
	0.1	0.09	-0.40-0.58	7.25E-01	0.000581395	FALSE							
	0.2	0.01	-0.73-0.76	9.71E-01	0.000581395	FALSE							
	0.3	0.21	-0.57-0.99	6.01E-01	0.000581395	FALSE							
	0.4	0.13	-0.63-0.89	7.39E-01	0.000581395	FALSE							
	0.5	0.37	-0.38-1.12	3.37E-01	0.000581395	FALSE							
	1	0.27	-0.44-0.98	4.64E-01	0.000581395	FALSE							
Gestational period	0.01	0.01	-0.02-0.04	5.60E-01	0.000581395	FALSE							
	0.1	-0.03	-0.08-0.03	3.61E-01	0.000581395	FALSE							
	0.2	-0.03	-0.12-0.05	4.59E-01	0.000581395	FALSE							
	0.3	-0.05	-0.14-0.04	2.57E-01	0.000581395	FALSE							
	0.4	-0.06	-0.14-0.02	1.68E-01	0.000581395	FALSE							
	0.5	-0.07	-0.15-0.02	1.16E-01	0.000581395	FALSE							
	1	-0.04	-0.12-0.03	2.65E-01	0.000581395	FALSE							
birth weight	0.01	0.01	-0.03-0.05	7.80E-01	0.000581395	FALSE							

	0.1	-0.01	-0.08-0.06	8.02E-01	0.000581395	FALSE								
	0.2	-0.03	-0.14-0.08	6.18E-01	0.000581395	FALSE								
	0.3	-0.02	-0.14-0.09	6.74E-01	0.000581395	FALSE								
	0.4	-0.05	-0.16-0.06	3.58E-01	0.000581395	FALSE								
	0.5	-0.07	-0.18-0.04	2.05E-01	0.000581395	FALSE								
	1	-0.05	-0.16-0.05	2.95E-01	0.000581395	FALSE								
Marital status	0.01	0.09	0.06-0.13	2.17E-07	0.000581395	TRUE	0.01	-0.09-0.12	8.18E-01	Mother & Father	0.85	3.58E-01	0.06	8.01E-01
	0.1	0.1	0.03-0.16	2.50E-03	0.000581395	FALSE	-0.16	-0.36-0.04	1.24E-01		4.45	3.50E-02	2.35	1.12E-01
	0.2	0.14	0.05-0.24	2.79E-03	0.000581395	FALSE	-0.15	-0.46-0.15	3.33E-01		6.68	9.70E-03	2.12	1.45E-01
	0.3	0.14	0.04-0.24	4.30E-03	0.000581395	FALSE	-0.11	-0.43-0.21	5.13E-01		8.35	3.90E-03	2.85	9.14E-02
	0.4	0.15	0.06-0.25	1.93E-03	0.000581395	FALSE	-0.06	-0.37-0.26	7.29E-01		3.90	4.82E-02	1.95	1.63E-01
	0.5	0.2	0.10-0.29	3.61E-05	0.000581395	TRUE	0	-0.31-0.31	1.00E+00		3.89	4.87E-02	1.57	2.10E-01
	1	0.18	0.09-0.27	4.96E-05	0.000581395	TRUE	0.01	-0.29-0.31	9.55E-01		1.8	1.80E-01	2.15	1.43E-01
Alcohol Mother	0.01	-0.09	-0.13--0.05	3.08E-06	0.000581395	TRUE	-0.06	-0.11--0.02	3.11E-03	Mother's only	0.07	7.85E-01		
	0.1	-0.2	-0.27--0.12	6.89E-08	0.000581395	TRUE	-0.19	-0.26--0.11	4.54E-06		2.43	1.19E-01		
	0.2	-0.25	-0.36--0.14	4.26E-06	0.000581395	TRUE	-0.22	-0.34--0.10	2.91E-04		3.73	5.33E-02		
	0.3	-0.27	-0.38--0.15	3.61E-06	0.000581395	TRUE	-0.22	-0.34--0.09	5.38E-04		2.37	1.24E-01		
	0.4	-0.26	-0.36--0.15	4.52E-06	0.000581395	TRUE	-0.21	-0.33--0.09	4.99E-04		1.9	1.68E-01		
	0.5	-0.26	-0.36--0.15	2.91E-06	0.000581395	TRUE	-0.22	-0.34--0.10	2.30E-04		1.85	1.73E-01		
	1	-0.25	-0.35--0.14	3.67E-06	0.000581395	TRUE	-0.22	-0.33--0.10	1.98E-04		0.82	3.67E-01		
Alcohol Father	0.01	-0.17	-0.36-0.02	8.50E-02	0.000581395	FALSE								
	0.1	-0.4	-0.76--0.03	3.31E-02	0.000581395	FALSE								
	0.2	-0.59	-1.14--0.04	3.50E-02	0.000581395	FALSE								
	0.3	-0.62	-1.20--0.03	3.82E-02	0.000581395	FALSE								
	0.4	-0.67	-1.23--0.10	2.14E-02	0.000581395	FALSE								
	0.5	-0.65	-1.22--0.09	2.32E-02	0.000581395	FALSE								
	1	-0.54	-1.07--0.00	4.83E-02	0.000581395	FALSE								
Employment Mother	0.01	0.11	0.03-0.19	6.38E-03	0.000581395	FALSE								
	0.1	0.13	-0.01-0.26	7.36E-02	0.000581395	FALSE								
	0.2	0.11	-0.10-0.32	2.90E-01	0.000581395	FALSE								
	0.3	0.11	-0.10-0.33	2.99E-01	0.000581395	FALSE								
	0.4	0.15	-0.06-0.35	1.71E-01	0.000581395	FALSE								
	0.5	0.19	-0.01-0.40	6.37E-02	0.000581395	FALSE								
	1	0.19	-0.01-0.38	6.17E-02	0.000581395	FALSE								
Father Reads	0.01	0.08	-0.10-0.25	3.77E-01	0.000581395	FALSE								
	0.1	0.27	-0.06-0.60	1.06E-01	0.000581395	FALSE								
	0.2	0.45	-0.05-0.94	7.67E-02	0.000581395	FALSE								
	0.3	0.46	-0.06-0.98	8.58E-02	0.000581395	FALSE								

	0.4	0.48	-0.03-0.99	6.27E-02	0.000581395	FALSE				
	0.5	0.59	0.08-1.09	2.27E-02	0.000581395	FALSE				
	1	0.61	0.13-1.08	1.18E-02	0.000581395	FALSE				
Mother Reads	0.01	0.15	0.00-0.31	4.94E-02	0.000581395	FALSE				
	0.1	0.26	-0.01-0.53	6.35E-02	0.000581395	FALSE				
	0.2	0.43	0.02-0.84	3.98E-02	0.000581395	FALSE				
	0.3	0.47	0.05-0.89	3.00E-02	0.000581395	FALSE				
	0.4	0.62	0.21-1.03	3.26E-03	0.000581395	FALSE				
	0.5	0.6	0.20-1.01	3.42E-03	0.000581395	FALSE				
	1	0.63	0.24-1.01	1.31E-03	0.000581395	FALSE				

Note: All results were corrected for multiple testing using the Bonferroni correction (corrected $p=\alpha/n$ total environments; resulting in $5.81 \times 10^{-4} = 0.05/86$). Sensitivity analysis was performed for all statistically significant results after multiple testing only. Corrected with = refers to whether the maternal or paternal genotype were included as covariates in the sensitivity analysis. Interaction statistics refer to the interaction analysis which compared the beta coefficients from the regression analyses and the sensitivity analyses. For maternal smoking & maternal alcohol consumption, the interaction analysis included interaction terms between the child PRS and the maternal PRSs as well as principal components from the population stratification, sex and year as covariates, but not other interaction terms due to multicollinearity. Compare SZD & MDD = refers to the interaction analysis to compare beta coefficients between any significant findings matching between both cohorts. All regressions were calculated using STATA v12.1 (StataCorp, 2011).

Appendix 15: *PRS Results for NCDS (Chapter 3)*

SCZ											
Environment	**SCZ**				**Bonferroni Correction**		**Sensitivity**			**Interaction terms**	
	Threshold z-scored	**Beta**	**95%CI**	**P-Value**	**0.05/86**	**statistically significant?**	**Beta**	**95%CI**	**P-Value**	**Wald chi-squared**	**P-Value**
SES	0.01	0.01	-0.02-0.03	6.33E-01	0.000581395	FALSE					
	0.1	0	-0.02-0.03	8.06E-01	0.000581395	FALSE					
	0.2	0	-0.02-0.03	7.29E-01	0.000581395	FALSE					
	0.3	0	-0.02-0.03	9.07E-01	0.000581395	FALSE					
	0.4	0	-0.02-0.03	9.28E-01	0.000581395	FALSE					
	0.5	0	-0.02-0.03	8.34E-01	0.000581395	FALSE					
	1	0	-0.02-0.03	8.24E-01	0.000581395	FALSE					
Finance Issues	0.01	0.04	-0.07-0.16	4.57E-01	0.000581395	FALSE					
	0.1	0.06	-0.05-0.17	3.22E-01	0.000581395	FALSE					
	0.2	0.05	-0.06-0.16	3.46E-01	0.000581395	FALSE					
	0.3	0.06	-0.05-0.17	3.11E-01	0.000581395	FALSE					
	0.4	0.05	-0.06-0.15	4.15E-01	0.000581395	FALSE					
	0.5	0.05	-0.06-0.16	3.97E-01	0.000581395	FALSE					
	1	0.04	-0.07-0.15	4.78E-01	0.000581395	FALSE					
Number of Rooms	0.01	0	-0.02-0.03	8.47E-01	0.000581395	FALSE					
	0.1	-0.01	-0.04-0.02	4.22E-01	0.000581395	FALSE					
	0.2	-0.01	-0.03-0.02	5.81E-01	0.000581395	FALSE					
	0.3	0	-0.03-0.02	7.87E-01	0.000581395	FALSE					
	0.4	0	-0.03-0.02	7.85E-01	0.000581395	FALSE					
	0.5	0	-0.03-0.02	7.79E-01	0.000581395	FALSE					
	1	0	-0.03-0.02	7.41E-01	0.000581395	FALSE					
Tenure	0.01	-0.07	-0.29-0.16	5.56E-01	0.000581395	FALSE					
	0.1	-0.01	-0.22-0.21	9.48E-01	0.000581395	FALSE					
	0.2	-0.02	-0.23-0.20	8.78E-01	0.000581395	FALSE					
	0.3	0.02	-0.20-0.23	8.69E-01	0.000581395	FALSE					
	0.4	0	-0.21-0.22	9.65E-01	0.000581395	FALSE					
	0.5	0	-0.21-0.21	9.88E-01	0.000581395	FALSE					
	1	-0.01	-0.22-0.20	9.42E-01	0.000581395	FALSE					
Mother's interest in child's eduction	0.01	0.05	-0.05-0.15	3.13E-01	0.000581395	FALSE					
	0.1	0.03	-0.06-0.13	4.79E-01	0.000581395	FALSE					

	0.2	0.03	-0.06-0.12	5.19E-01	0.000581395	FALSE					
	0.3	0.06	-0.04-0.15	2.29E-01	0.000581395	FALSE					
	0.4	0.05	-0.04-0.15	2.61E-01	0.000581395	FALSE					
	0.5	0.05	-0.05-0.14	3.32E-01	0.000581395	FALSE					
	1	0.05	-0.05-0.14	3.40E-01	0.000581395	FALSE					
Father's involvement in childcare	0.01	0.19	0.07-0.31	1.51E-03	0.000581395	FALSE	0.21	0.08-0.34	1.17E-03	1.57	2.11E-01
	0.1	0.21	0.09-0.32	2.90E-04	0.000581395	TRUE	0.22	0.10-0.34	4.26E-04	0.55	4.60E-01
	0.2	0.23	0.11-0.34	7.09E-05	0.000581395	TRUE	0.23	0.11-0.35	2.11E-04	1.33	2.49E-01
	0.3	0.22	0.11-0.34	8.06E-05	0.000581395	TRUE	0.22	0.10-0.34	3.64E-04	1.33	2.49E-01
	0.4	0.21	0.10-0.32	1.83E-04	0.000581395	TRUE	0.2	0.08-0.32	1.02E-03	1.8	1.80E-01
	0.5	0.21	0.10-0.32	2.50E-04	0.000581395	TRUE	0.2	0.08-0.32	1.35E-03	2.03	1.54E-01
	1	0.2	0.09-0.32	3.00E-04	0.000581395	TRUE	0.19	0.07-0.32	1.57E-03	1.04	3.07E-01
Father's interest in child's education	0.01	0.02	-0.09-0.14	6.65E-01	0.000581395	FALSE					
	0.1	0.01	-0.10-0.11	9.21E-01	0.000581395	FALSE					
	0.2	0.02	-0.09-0.12	7.79E-01	0.000581395	FALSE					
	0.3	0.04	-0.06-0.15	4.51E-01	0.000581395	FALSE					
	0.4	0.03	-0.07-0.14	5.29E-01	0.000581395	FALSE					
	0.5	0.03	-0.08-0.13	5.98E-01	0.000581395	FALSE					
	1	0.02	-0.09-0.12	7.14E-01	0.000581395	FALSE					
Mother walks	0.01	0.04	-0.12-0.20	6.20E-01	0.000581395	FALSE					
	0.1	0.1	-0.06-0.25	2.27E-01	0.000581395	FALSE					
	0.2	0.11	-0.05-0.26	1.75E-01	0.000581395	FALSE					
	0.3	0.09	-0.06-0.25	2.37E-01	0.000581395	FALSE					
	0.4	0.08	-0.07-0.24	2.87E-01	0.000581395	FALSE					
	0.5	0.07	-0.08-0.22	3.68E-01	0.000581395	FALSE					
	1	0.07	-0.09-0.22	3.92E-01	0.000581395	FALSE					
Father walks	0.01	0.02	-0.11-0.15	7.56E-01	0.000581395	FALSE					
	0.1	0.07	-0.06-0.19	3.15E-01	0.000581395	FALSE					
	0.2	0.09	-0.03-0.22	1.53E-01	0.000581395	FALSE					
	0.3	0.08	-0.05-0.20	2.30E-01	0.000581395	FALSE					
	0.4	0.07	-0.05-0.20	2.53E-01	0.000581395	FALSE					
	0.5	0.07	-0.06-0.19	3.13E-01	0.000581395	FALSE					
	1	0.06	-0.07-0.19	3.47E-01	0.000581395	FALSE					
Maternal smoking prior pregnancy	0.01	0.03	-0.03-0.09	3.44E-01	0.000581395	FALSE					
	0.1	0.04	-0.02-0.10	1.96E-01	0.000581395	FALSE					
	0.2	0.03	-0.03-0.09	3.73E-01	0.000581395	FALSE					
	0.3	0.03	-0.03-0.09	2.98E-01	0.000581395	FALSE					
	0.4	0.03	-0.03-0.09	3.86E-01	0.000581395	FALSE					

	0.5	0.03	-0.03-0.08	4.05E-01	0.000581395	FALSE		
	1	0.02	-0.04-0.08	4.26E-01	0.000581395	FALSE		
Maternal smoking during pregnancy	0.01	0.03	-0.04-0.09	4.25E-01	0.000581395	FALSE		
	0.1	0.03	-0.04-0.09	4.05E-01	0.000581395	FALSE		
	0.2	0.01	-0.05-0.07	7.60E-01	0.000581395	FALSE		
	0.3	0.02	-0.05-0.08	6.30E-01	0.000581395	FALSE		
	0.4	0.01	-0.05-0.07	7.94E-01	0.000581395	FALSE		
	0.5	0.01	-0.06-0.07	8.27E-01	0.000581395	FALSE		
	1	0.01	-0.06-0.07	8.24E-01	0.000581395	FALSE		
Parity	0.01	0	-0.03-0.03	9.73E-01	0.000581395	FALSE		
	0.1	0	-0.03-0.02	7.73E-01	0.000581395	FALSE		
	0.2	-0.01	-0.04-0.02	4.67E-01	0.000581395	FALSE		
	0.3	-0.01	-0.04-0.02	5.23E-01	0.000581395	FALSE		
	0.4	-0.01	-0.04-0.02	4.06E-01	0.000581395	FALSE		
	0.5	-0.01	-0.04-0.02	4.89E-01	0.000581395	FALSE		
	1	-0.01	-0.04-0.02	4.15E-01	0.000581395	FALSE		
Mother's age	0.01	0	-0.03-0.03	7.84E-01	0.000581395	FALSE		
	0.1	0	-0.03-0.03	8.99E-01	0.000581395	FALSE		
	0.2	0	-0.03-0.03	8.39E-01	0.000581395	FALSE		
	0.3	0	-0.03-0.02	7.49E-01	0.000581395	FALSE		
	0.4	0	-0.03-0.02	7.81E-01	0.000581395	FALSE		
	0.5	0	-0.03-0.02	7.45E-01	0.000581395	FALSE		
	1	-0.01	-0.03-0.02	6.97E-01	0.000581395	FALSE		
Father's age	0.01	0	-0.03-0.03	9.83E-01	0.000581395	FALSE		
	0.1	0	-0.03-0.03	9.35E-01	0.000581395	FALSE		
	0.2	0	-0.03-0.03	8.94E-01	0.000581395	FALSE		
	0.3	0	-0.03-0.03	8.24E-01	0.000581395	FALSE		
	0.4	-0.01	-0.03-0.02	7.27E-01	0.000581395	FALSE		
	0.5	-0.01	-0.03-0.02	7.27E-01	0.000581395	FALSE		
	1	-0.01	-0.03-0.02	7.22E-01	0.000581395	FALSE		
Gestational period	0.01	-0.01	-0.05-0.02	3.79E-01	0.000581395	FALSE		
	0.1	-0.01	-0.04-0.03	7.33E-01	0.000581395	FALSE		
	0.2	0	-0.03-0.03	8.26E-01	0.000581395	FALSE		
	0.3	-0.01	-0.04-0.02	6.98E-01	0.000581395	FALSE		
	0.4	-0.01	-0.04-0.02	6.91E-01	0.000581395	FALSE		
	0.5	0	-0.04-0.03	7.61E-01	0.000581395	FALSE		
	1	0	-0.03-0.03	8.40E-01	0.000581395	FALSE		
birth weight	0.01	0	-0.03-0.03	8.97E-01	0.000581395	FALSE		

	0.1	0	-0.03-0.03	8.25E-01	0.000581395	FALSE		
	0.2	0	-0.03-0.03	9.57E-01	0.000581395	FALSE		
	0.3	0	-0.03-0.03	9.09E-01	0.000581395	FALSE		
	0.4	0	-0.03-0.03	9.13E-01	0.000581395	FALSE		
	0.5	0	-0.03-0.03	9.49E-01	0.000581395	FALSE		
	1	0	-0.03-0.03	9.68E-01	0.000581395	FALSE		
Marital status	0.01	0.06	-0.12-0.24	4.97E-01	0.000581395	FALSE		
	0.1	-0.03	-0.20-0.14	7.29E-01	0.000581395	FALSE		
	0.2	-0.02	-0.19-0.15	8.09E-01	0.000581395	FALSE		
	0.3	-0.04	-0.21-0.13	6.69E-01	0.000581395	FALSE		
	0.4	-0.05	-0.22-0.12	5.29E-01	0.000581395	FALSE		
	0.5	-0.06	-0.23-0.11	4.84E-01	0.000581395	FALSE		
	1	-0.07	-0.24-0.10	4.26E-01	0.000581395	FALSE		
Housing Issues	0.01	0.13	-0.01-0.27	6.87E-02	0.000581395	FALSE		
	0.1	0.16	0.03-0.29	1.50E-02	0.000581395	FALSE		
	0.2	0.17	0.04-0.31	8.83E-03	0.000581395	FALSE		
	0.3	0.17	0.04-0.30	9.19E-03	0.000581395	FALSE		
	0.4	0.16	0.03-0.30	1.38E-02	0.000581395	FALSE		
	0.5	0.16	0.03-0.29	1.45E-02	0.000581395	FALSE		
	1	0.17	0.04-0.30	1.04E-02	0.000581395	FALSE		
Family Acohol issues	0.01	0.23	-0.14-0.60	2.17E-01	0.000581395	FALSE		
	0.1	0.17	-0.18-0.53	3.36E-01	0.000581395	FALSE		
	0.2	0.13	-0.23-0.48	4.81E-01	0.000581395	FALSE		
	0.3	0.1	-0.25-0.45	5.82E-01	0.000581395	FALSE		
	0.4	0.07	-0.28-0.42	6.97E-01	0.000581395	FALSE		
	0.5	0.06	-0.29-0.42	7.30E-01	0.000581395	FALSE		
	1	0.03	-0.32-0.38	8.63E-01	0.000581395	FALSE		
Domestic tension	0.01	0.21	0.05-0.37	8.71E-03	0.000581395	FALSE		
	0.1	0.17	0.02-0.32	2.83E-02	0.000581395	FALSE		
	0.2	0.17	0.02-0.32	3.03E-02	0.000581395	FALSE		
	0.3	0.17	0.02-0.32	2.44E-02	0.000581395	FALSE		
	0.4	0.17	0.02-0.32	2.54E-02	0.000581395	FALSE		
	0.5	0.18	0.03-0.33	2.04E-02	0.000581395	FALSE		
	1	0.17	0.02-0.32	2.61E-02	0.000581395	FALSE		
Employment father	0.01	0.01	-0.24-0.25	9.64E-01	0.000581395	FALSE		
	0.1	0.07	-0.16-0.30	5.56E-01	0.000581395	FALSE		
	0.2	0.07	-0.16-0.30	5.62E-01	0.000581395	FALSE		
	0.3	0.08	-0.15-0.31	5.20E-01	0.000581395	FALSE		

	0.4	0.06	-0.17-0.29	5.91E-01	0.000581395	FALSE					
	0.5	0.07	-0.16-0.30	5.78E-01	0.000581395	FALSE					
	1	0.06	-0.17-0.29	5.91E-01	0.000581395	FALSE					
Father Reads	0.01	0.08	0.00-0.15	3.89E-02	0.000581395	FALSE					
	0.1	0.09	0.02-0.16	1.66E-02	0.000581395	FALSE					
	0.2	0.1	0.03-0.17	7.37E-03	0.000581395	FALSE					
	0.3	0.09	0.02-0.16	1.38E-02	0.000581395	FALSE					
	0.4	0.08	0.01-0.15	2.06E-02	0.000581395	FALSE					
	0.5	0.08	0.01-0.15	2.17E-02	0.000581395	FALSE					
	1	0.09	0.02-0.16	1.67E-02	0.000581395	FALSE					
Mother Reads	0.01	-0.02	-0.11-0.08	7.48E-01	0.000581395	FALSE					
	0.1	0.07	-0.01-0.16	1.01E-01	0.000581395	FALSE					
	0.2	0.08	-0.01-0.17	7.80E-02	0.000581395	FALSE					
	0.3	0.08	-0.00-0.17	6.20E-02	0.000581395	FALSE					
	0.4	0.08	-0.01-0.16	8.86E-02	0.000581395	FALSE					
	0.5	0.07	-0.01-0.16	9.37E-02	0.000581395	FALSE					
	1	0.08	-0.01-0.16	8.01E-02	0.000581395	FALSE					
Free School Meals	0.01	0.07	-0.11-0.26	4.42E-01	0.000581395	FALSE					
	0.1	0.08	-0.06-0.22	2.60E-01	0.000581395	FALSE					
	0.2	0.09	-0.09-0.26	3.43E-01	0.000581395	FALSE					
	0.3	0.08	-0.05-0.22	2.32E-01	0.000581395	FALSE					
	0.4	0.08	-0.05-0.22	2.37E-01	0.000581395	FALSE					
	0.5	0.09	-0.09-0.26	3.34E-01	0.000581395	FALSE					
	1	0.08	-0.09-0.26	3.51E-01	0.000581395	FALSE					
MDD											
SES	0.01	-0.06	-0.08--0.03	3.56E-06	0.000581395	TRUE	-0.1	-0.09--0.03	1.49E-05	0.22	6.42E-01
	0.1	-0.05	-0.08--0.03	8.75E-06	0.000581395	TRUE	-0.1	-0.09--0.03	2.71E-05	0.81	3.69E-01
	0.2	-0.05	-0.08--0.03	5.72E-06	0.000581395	TRUE	-0.1	-0.09--0.03	1.48E-05	1.67	1.97E-01
	0.3	-0.05	-0.08--0.03	1.22E-05	0.000581395	TRUE	-0.1	-0.09--0.03	2.69E-05	2.05	1.52E-01
	0.4	-0.05	-0.07--0.03	1.90E-05	0.000581395	TRUE	-0.1	-0.08--0.03	3.92E-05	1.77	1.84E-01
	0.5	-0.05	-0.07--0.03	2.53E-05	0.000581395	TRUE	-0.1	-0.08--0.03	3.85E-05	1.74	1.87E-01
	1	-0.05	-0.07--0.03	4.66E-05	0.000581395	TRUE	-0.1	-0.08--0.03	4.97E-05	2	1.58E-01
Finance Issues	0.01	0.17	0.06-0.28	1.83E-03	0.000581395	FALSE					
	0.1	0.16	0.05-0.26	3.43E-03	0.000581395	FALSE					
	0.2	0.15	0.05-0.26	5.00E-03	0.000581395	FALSE					
	0.3	0.15	0.05-0.26	4.31E-03	0.000581395	FALSE					
	0.4	0.16	0.05-0.26	3.48E-03	0.000581395	FALSE					
	0.5	0.15	0.05-0.26	4.69E-03	0.000581395	FALSE					

	1	0.15	0.05-0.26	4.40E-03	0.000581395	FALSE					
Number of Rooms	0.01	-0.05	-0.07--0.02	2.08E-04	0.000581395	TRUE	-0.1	-0.08--0.03	2.01E-04	1.4	2.36E-01
	0.1	-0.04	-0.07--0.02	3.97E-04	0.000581395	TRUE	-0.1	-0.08--0.02	4.46E-04	2.75	9.75E-02
	0.2	-0.04	-0.07--0.02	4.79E-04	0.000581395	TRUE	-0.1	-0.08--0.02	1.01E-03	2.08	1.49E-01
	0.3	-0.04	-0.07--0.02	3.64E-04	0.000581395	TRUE	-0.1	-0.08--0.02	4.92E-04	2.69	1.01E-01
	0.4	-0.04	-0.07--0.02	3.34E-04	0.000581395	TRUE	-0.1	-0.08--0.02	4.06E-04	3.03	8.17E-02
	0.5	-0.04	-0.07--0.02	4.44E-04	0.000581395	TRUE	-0.1	-0.08--0.02	5.76E-04	2.92	8.75E-02
	1	-0.04	-0.07--0.02	7.68E-04	0.000581395	FALSE	-0.1	-0.08--0.02	7.77E-04	3.32	6.83E-02
Tenure	0.01	0.47	0.26-0.68	9.88E-06	0.000581395	TRUE	0.53	0.29-0.78	2.21E-05	0.03	8.56E-01
	0.1	0.39	0.18-0.59	2.36E-04	0.000581395	TRUE	0.42	0.18-0.67	5.56E-04	0.34	5.62E-01
	0.2	0.34	0.13-0.54	1.31E-03	0.000581395	FALSE	0.39	0.15-0.63	1.54E-03	1.01	3.15E-01
	0.3	0.31	0.11-0.52	2.87E-03	0.000581395	FALSE	0.37	0.13-0.61	2.50E-03	1.43	2.32E-01
	0.4	0.31	0.11-0.52	2.66E-03	0.000581395	FALSE	0.36	0.12-0.60	3.23E-03	1.25	2.64E-01
	0.5	0.31	0.11-0.52	2.76E-03	0.000581395	FALSE	0.36	0.12-0.60	3.22E-03	1.08	2.99E-01
	1	0.29	0.08-0.49	6.02E-03	0.000581395	FALSE	0.35	0.11-0.59	4.57E-03	1.41	2.35E-01
Mother's interest in child's education	0.01	0.17	0.08-0.26	1.81E-04	0.000581395	TRUE	0.18	0.07-0.29	1.02E-03	<0.001	9.90E-01
	0.1	0.14	0.05-0.23	2.18E-03	0.000581395	FALSE	0.13	0.02-0.24	1.84E-02	0.04	8.44E-01
	0.2	0.14	0.06-0.23	1.41E-03	0.000581395	FALSE	0.14	0.04-0.25	8.78E-03	0.18	6.71E-01
	0.3	0.14	0.05-0.23	2.60E-03	0.000581395	FALSE	0.13	0.02-0.24	1.88E-02	<0.001	9.46E-01
	0.4	0.14	0.05-0.23	2.62E-03	0.000581395	FALSE	0.13	0.02-0.23	2.17E-02	0.05	8.21E-01
	0.5	0.13	0.04-0.22	4.61E-03	0.000581395	FALSE	0.12	0.01-0.23	2.71E-02	0.04	8.37E-01
	1	0.12	0.03-0.21	7.13E-03	0.000581395	FALSE	0.11	0.00-0.22	4.44E-02	0.02	8.79E-01
Father's involvement in childcare	0.01	0.05	-0.05-0.16	3.34E-01	0.000581395	FALSE					
	0.1	0.03	-0.08-0.13	6.26E-01	0.000581395	FALSE					
	0.2	0.05	-0.05-0.16	3.25E-01	0.000581395	FALSE					
	0.3	0.06	-0.04-0.17	2.45E-01	0.000581395	FALSE					
	0.4	0.06	-0.05-0.16	2.83E-01	0.000581395	FALSE					
	0.5	0.06	-0.05-0.16	2.95E-01	0.000581395	FALSE					
	1	0.06	-0.05-0.16	2.90E-01	0.000581395	FALSE					
Father's interest in child's education	0.01	0.2	0.10-0.30	1.21E-04	0.000581395	TRUE	0.19	0.07-0.31	1.71E-03	0.12	7.31E-01
	0.1	0.21	0.11-0.31	3.17E-05	0.000581395	TRUE	0.18	0.07-0.30	2.28E-03	0.09	7.59E-01
	0.2	0.21	0.11-0.31	3.29E-05	0.000581395	TRUE	0.19	0.08-0.31	1.25E-03	0.26	6.08E-01
	0.3	0.2	0.10-0.30	9.35E-05	0.000581395	TRUE	0.19	0.07-0.30	2.10E-03	0.08	7.73E-01
	0.4	0.2	0.10-0.30	1.35E-04	0.000581395	TRUE	0.18	0.06-0.29	3.57E-03	0.13	7.14E-01
	0.5	0.19	0.09-0.29	2.04E-04	0.000581395	TRUE	0.17	0.06-0.29	4.07E-03	0.1	7.53E-01
	1	0.18	0.08-0.28	4.73E-04	0.000581395	TRUE	0.16	0.04-0.28	8.00E-03	0.05	8.21E-01
Mother walks	0.01	0.14	-0.01-0.29	5.93E-02	0.000581395	FALSE					
	0.1	0.18	0.03-0.33	2.01E-02	0.000581395	FALSE					

	0.2	0.19	0.04-0.33	1.47E-02	0.000581395	FALSE		
	0.3	0.2	0.05-0.35	8.75E-03	0.000581395	FALSE		
	0.4	0.2	0.05-0.35	9.22E-03	0.000581395	FALSE		
	0.5	0.2	0.06-0.35	7.23E-03	0.000581395	FALSE		
	1	0.21	0.06-0.36	5.07E-03	0.000581395	FALSE		
Father walks	0.01	0.15	0.02-0.27	1.96E-02	0.000581395	FALSE		
	0.1	0.1	-0.02-0.22	1.06E-01	0.000581395	FALSE		
	0.2	0.07	-0.05-0.20	2.37E-01	0.000581395	FALSE		
	0.3	0.1	-0.02-0.22	1.16E-01	0.000581395	FALSE		
	0.4	0.1	-0.03-0.22	1.22E-01	0.000581395	FALSE		
	0.5	0.1	-0.02-0.22	1.10E-01	0.000581395	FALSE		
	1	0.1	-0.02-0.22	9.69E-02	0.000581395	FALSE		
Maternal smoking prior pregnancy	0.01	0.02	-0.04-0.08	4.46E-01	0.000581395	FALSE		
	0.1	0.03	-0.03-0.09	2.87E-01	0.000581395	FALSE		
	0.2	0.03	-0.03-0.08	3.63E-01	0.000581395	FALSE		
	0.3	0.02	-0.04-0.08	4.63E-01	0.000581395	FALSE		
	0.4	0.03	-0.02-0.09	2.30E-01	0.000581395	FALSE		
	0.5	0.03	-0.02-0.09	2.54E-01	0.000581395	FALSE		
	1	0.03	-0.02-0.09	2.69E-01	0.000581395	FALSE		
Maternal smoking during pregnancy	0.01	0.04	-0.02-0.10	1.87E-01	0.000581395	FALSE		
	0.1	0.03	-0.03-0.09	2.88E-01	0.000581395	FALSE		
	0.2	0.03	-0.03-0.09	3.90E-01	0.000581395	FALSE		
	0.3	0.02	-0.04-0.08	5.41E-01	0.000581395	FALSE		
	0.4	0.04	-0.02-0.10	2.46E-01	0.000581395	FALSE		
	0.5	0.03	-0.03-0.09	2.62E-01	0.000581395	FALSE		
	1	0.03	-0.03-0.09	2.66E-01	0.000581395	FALSE		
Parity	0.01	0	-0.02-0.03	7.59E-01	0.000581395	FALSE		
	0.1	0	-0.02-0.03	7.58E-01	0.000581395	FALSE		
	0.2	0.01	-0.02-0.04	4.87E-01	0.000581395	FALSE		
	0.3	0.01	-0.02-0.03	6.24E-01	0.000581395	FALSE		
	0.4	0.01	-0.02-0.03	5.98E-01	0.000581395	FALSE		
	0.5	0.01	-0.02-0.03	6.24E-01	0.000581395	FALSE		
	1	0.01	-0.02-0.03	6.70E-01	0.000581395	FALSE		
Mother's age	0.01	-0.04	-0.06--0.01	1.05E-02	0.000581395	FALSE		
	0.1	-0.02	-0.05-0.01	1.52E-01	0.000581395	FALSE		
	0.2	-0.02	-0.04-0.01	2.65E-01	0.000581395	FALSE		
	0.3	-0.02	-0.05-0.01	1.69E-01	0.000581395	FALSE		
	0.4	-0.02	-0.05-0.01	1.50E-01	0.000581395	FALSE		

	0.5	-0.02	-0.05-0.01	1.74E-01	0.000581395	FALSE		
	1	-0.02	-0.05-0.01	2.02E-01	0.000581395	FALSE		
Father's age	0.01	0	-0.03-0.03	9.72E-01	0.000581395	FALSE		
	0.1	0	-0.03-0.02	7.73E-01	0.000581395	FALSE		
	0.2	0	-0.03-0.03	8.64E-01	0.000581395	FALSE		
	0.3	0	-0.03-0.03	9.57E-01	0.000581395	FALSE		
	0.4	0	-0.03-0.03	8.65E-01	0.000581395	FALSE		
	0.5	0	-0.02-0.03	8.21E-01	0.000581395	FALSE		
	1	0	-0.03-0.03	8.48E-01	0.000581395	FALSE		
Gestational period	0.01	-0.02	-0.05-0.01	2.65E-01	0.000581395	FALSE		
	0.1	-0.01	-0.04-0.02	4.59E-01	0.000581395	FALSE		
	0.2	-0.01	-0.04-0.02	5.64E-01	0.000581395	FALSE		
	0.3	-0.01	-0.04-0.02	5.99E-01	0.000581395	FALSE		
	0.4	-0.01	-0.04-0.02	5.64E-01	0.000581395	FALSE		
	0.5	-0.01	-0.04-0.02	5.77E-01	0.000581395	FALSE		
	1	-0.01	-0.04-0.02	4.95E-01	0.000581395	FALSE		
birth weight	0.01	-0.03	-0.06--0.00	3.09E-02	0.000581395	FALSE		
	0.1	-0.02	-0.04-0.01	2.47E-01	0.000581395	FALSE		
	0.2	-0.02	-0.05-0.01	1.94E-01	0.000581395	FALSE		
	0.3	-0.02	-0.05-0.01	1.59E-01	0.000581395	FALSE		
	0.4	-0.02	-0.05-0.01	2.18E-01	0.000581395	FALSE		
	0.5	-0.02	-0.05-0.01	1.96E-01	0.000581395	FALSE		
	1	-0.02	-0.05-0.01	1.89E-01	0.000581395	FALSE		
Marital status	0.01	0.08	-0.09-0.25	3.39E-01	0.000581395	FALSE		
	0.1	0.03	-0.14-0.19	7.37E-01	0.000581395	FALSE		
	0.2	0.01	-0.16-0.17	9.12E-01	0.000581395	FALSE		
	0.3	0.03	-0.14-0.19	7.53E-01	0.000581395	FALSE		
	0.4	0.04	-0.12-0.21	6.14E-01	0.000581395	FALSE		
	0.5	0.05	-0.12-0.21	5.59E-01	0.000581395	FALSE		
	1	0.04	-0.12-0.21	6.19E-01	0.000581395	FALSE		
Housing Issues	0.01	0.15	0.02-0.28	1.89E-02	0.000581395	FALSE		
	0.1	0.08	-0.04-0.21	2.09E-01	0.000581395	FALSE		
	0.2	0.08	-0.05-0.20	2.12E-01	0.000581395	FALSE		
	0.3	0.09	-0.04-0.21	1.70E-01	0.000581395	FALSE		
	0.4	0.08	-0.04-0.21	1.84E-01	0.000581395	FALSE		
	0.5	0.09	-0.04-0.21	1.65E-01	0.000581395	FALSE		
	1	0.08	-0.05-0.20	2.15E-01	0.000581395	FALSE		
Family Alcohol issues	0.01	0.13	-0.21-0.48	4.39E-01	0.000581395	FALSE		

	0.1	0.15	-0.19-0.50	3.81E-01	0.000581395	FALSE		
	0.2	0.21	-0.13-0.56	2.24E-01	0.000581395	FALSE		
	0.3	0.2	-0.15-0.54	2.63E-01	0.000581395	FALSE		
	0.4	0.23	-0.11-0.57	1.81E-01	0.000581395	FALSE		
	0.5	0.22	-0.12-0.57	1.98E-01	0.000581395	FALSE		
	1	0.23	-0.11-0.58	1.78E-01	0.000581395	FALSE		
Domestic tension	0.01	0.13	-0.01-0.28	7.03E-02	0.000581395	FALSE		
	0.1	0.12	-0.02-0.26	9.93E-02	0.000581395	FALSE		
	0.2	0.12	-0.03-0.26	1.12E-01	0.000581395	FALSE		
	0.3	0.12	-0.02-0.27	8.95E-02	0.000581395	FALSE		
	0.4	0.14	-0.00-0.28	5.78E-02	0.000581395	FALSE		
	0.5	0.12	-0.02-0.27	8.76E-02	0.000581395	FALSE		
	1	0.13	-0.02-0.27	8.26E-02	0.000581395	FALSE		
Employment father	0.01	-0.02	-0.24-0.21	8.77E-01	0.000581395	FALSE		
	0.1	0.17	-0.06-0.39	1.45E-01	0.000581395	FALSE		
	0.2	0.17	-0.06-0.39	1.41E-01	0.000581395	FALSE		
	0.3	0.16	-0.07-0.38	1.69E-01	0.000581395	FALSE		
	0.4	0.21	0.04-0.37	1.26E-02	0.000581395	FALSE		
	0.5	0.16	-0.06-0.38	1.61E-01	0.000581395	FALSE		
	1	0.17	-0.06-0.39	1.45E-01	0.000581395	FALSE		
Father Reads	0.01	0.01	-0.06-0.08	7.68E-01	0.000581395	FALSE		
	0.1	0	-0.06-0.07	9.13E-01	0.000581395	FALSE		
	0.2	0	-0.06-0.07	9.07E-01	0.000581395	FALSE		
	0.3	0	-0.06-0.07	8.94E-01	0.000581395	FALSE		
	0.4	0	-0.06-0.07	9.30E-01	0.000581395	FALSE		
	0.5	0.01	-0.06-0.07	8.44E-01	0.000581395	FALSE		
	1	0	-0.06-0.07	8.98E-01	0.000581395	FALSE		
Mother Reads	0.01	0.01	-0.08-0.09	8.75E-01	0.000581395	FALSE		
	0.1	0.03	-0.05-0.12	4.32E-01	0.000581395	FALSE		
	0.2	0.02	-0.07-0.10	7.11E-01	0.000581395	FALSE		
	0.3	0.02	-0.07-0.10	6.69E-01	0.000581395	FALSE		
	0.4	0.02	-0.06-0.11	5.65E-01	0.000581395	FALSE		
	0.5	0.03	-0.06-0.11	5.53E-01	0.000581395	FALSE		
	1	0.02	-0.06-0.10	6.17E-01	0.000581395	FALSE		
Free School Meals	0.01	0.09	-0.09-0.26	3.31E-01	0.000581395	FALSE		
	0.1	0.08	-0.09-0.25	3.50E-01	0.000581395	FALSE		
	0.2	0.1	-0.07-0.27	2.44E-01	0.000581395	FALSE		
	0.3	0.08	-0.05-0.21	2.41E-01	0.000581395	FALSE		

	0.4	0.11	-0.06-0.28	2.23E-01	0.000581395	FALSE		
	0.5	0.12	-0.05-0.29	1.80E-01	0.000581395	FALSE		
	1	0.12	-0.05-0.29	1.69E-01	0.000581395	FALSE		

Note: All results were corrected for multiple testing using the Bonferroni correction (corrected $p=\alpha/n$ total environments; resulting in $5.81 \times 10^{-4} = 0.05/86$). Sensitivity analysis was performed for all statistically significant results after multiple testing only. Corrected with = refers to whether the maternal or paternal genotype were included as covariates. Interaction statistics refer to the interaction analysis which compared the beta coefficients from the regression analyses and the sensitivity analyses. All regressions were calculated using STATA v12.1 (1).

Appendix 16: *PRS Results for USoc (Chapter 4)*

Environment	Threshold z-scored	Beta	95%CI	P-Value	Bonferroni Correction		Sensitivity			Interaction	
					0.05/30	statistically significant?	Beta	95%CI	P-Value	Wald chi-square	p-value
SCZ											
SES	0.01	-0.02	-0.05-0.01	1.45E-01	1.67E-03	FALSE					
	0.1	-0.02	-0.05-0.01	1.94E-01	1.67E-03	FALSE					
	0.2	-0.02	-0.05-0.01	1.66E-01	1.67E-03	FALSE					
	0.3	-0.02	-0.05-0.01	2.10E-01	1.67E-03	FALSE					
	0.4	-0.02	-0.05-0.01	2.33E-01	1.67E-03	FALSE					
	0.5	-0.02	-0.05-0.01	2.25E-01	1.67E-03	FALSE					
	1	-0.02	-0.05-0.01	2.70E-01	1.67E-03	FALSE					
Number of Rooms	0.01	-0.02	-0.04-0.01	1.72E-01	1.67E-03	FALSE					
	0.1	-0.02	-0.04-0.01	1.36E-01	1.67E-03	FALSE					
	0.2	-0.02	-0.04-0.00	8.60E-02	1.67E-03	FALSE					
	0.3	-0.02	-0.04-0.00	9.32E-02	1.67E-03	FALSE					
	0.4	-0.02	-0.04-0.00	9.62E-02	1.67E-03	FALSE					
	0.5	-0.02	-0.04-0.00	8.94E-02	1.67E-03	FALSE					
	1	-0.02	-0.04-0.00	9.69E-02	1.67E-03	FALSE					
Marital status	0.01	0.08	0.02-0.13	5.42E-03*	1.67E-03	FALSE					
	0.1	0.1	0.04-0.15	**7.96E-04****	1.67E-03	TRUE					
	0.2	0.09	0.03-0.15	1.71E-03*	1.67E-03	FALSE					
	0.3	0.09	0.03-0.15	1.67E-03*	1.67E-03	FALSE					
	0.4	0.09	0.04-0.15	**1.21E-03****	1.67E-03	TRUE					
	0.5	0.09	0.04-0.15	**1.13E-03****	1.67E-03	TRUE					
	1	0.09	0.03-0.15	**1.63E-03****	1.67E-03	TRUE					
Income	0.01	-0.02	-0.04-0.00	1.08E-01	1.67E-03	FALSE					
	0.1	-0.02	-0.04-0.00	6.61E-02	1.67E-03	FALSE					
	0.2	-0.02	-0.04-0.00	7.75E-02	1.67E-03	FALSE					
	0.3	-0.02	-0.04-0.00	7.76E-02	1.67E-03	FALSE					
	0.4	-0.02	-0.04-0.00	7.61E-02	1.67E-03	FALSE					
	0.5	-0.02	-0.04-0.00	7.76E-02	1.67E-03	FALSE					
	1	-0.02	-0.04-0.00	6.57E-02	1.67E-03	FALSE					
Alcohol consumption	0.01	0	-0.02-0.03	9.56E-01	1.67E-03	FALSE					

	0.1	-0.01	-0.03-0.02	6.22E-01	1.67E-03	FALSE		
	0.2	-0.01	-0.03-0.02	5.24E-01	1.67E-03	FALSE		
	0.3	-0.01	-0.03-0.02	5.97E-01	1.67E-03	FALSE		
	0.4	-0.01	-0.03-0.02	6.62E-01	1.67E-03	FALSE		
	0.5	-0.01	-0.03-0.02	5.80E-01	1.67E-03	FALSE		
	1	-0.01	-0.03-0.02	6.42E-01	1.67E-03	FALSE		
Employment	0.01	0.16	0.04-0.27	7.81E-03*	1.67E-03	FALSE		
	0.1	0.15	0.03-0.26	1.23E-02*	1.67E-03	FALSE		
	0.2	0.15	0.04-0.27	1.01E-02*	1.67E-03	FALSE		
	0.3	0.16	0.04-0.27	7.12E-03*	1.67E-03	FALSE		
	0.4	0.15	0.03-0.26	1.10E-02*	1.67E-03	FALSE		
	0.5	0.15	0.03-0.26	1.18E-02*	1.67E-03	FALSE		
	1	0.15	0.04-0.27	8.50E-03*	1.67E-03	FALSE		
Tenure	0.01	0.05	-0.17-0.28	6.48E-01	1.67E-03	FALSE		
	0.1	0.01	-0.22-0.24	9.26E-01	1.67E-03	FALSE		
	0.2	-0.02	-0.25-0.22	8.80E-01	1.67E-03	FALSE		
	0.3	0.01	-0.23-0.25	9.44E-01	1.67E-03	FALSE		
	0.4	0.03	-0.2-0.26	8.11E-01	1.67E-03	FALSE		
	0.5	0.02	-0.22-0.25	8.86E-01	1.67E-03	FALSE		
	1	0.01	-0.22-0.25	9.01E-01	1.67E-03	FALSE		
Finance Issues	0.01	0.12	0.03-0.20	7.99E-03*	1.67E-03	FALSE		
	0.1	0.13	0.04-0.21	3.85E-03*	1.67E-03	FALSE		
	0.2	0.13	0.05-0.22	2.75E-03*	1.67E-03	FALSE		
	0.3	0.13	0.04-0.22	3.55E-03*	1.67E-03	FALSE		
	0.4	0.13	0.05-0.22	2.85E-03*	1.67E-03	FALSE		
	0.5	0.14	0.05-0.22	2.29E-03*	1.67E-03	FALSE		
	1	0.14	0.05-0.22	1.90E-03*	1.67E-03	FALSE		
Education	0.01	0	-0.36-0.37	9.94E-01	1.67E-03	FALSE		
	0.1	-0.04	-0.41-0.33	8.23E-01	1.67E-03	FALSE		
	0.2	-0.04	-0.41-0.33	8.43E-01	1.67E-03	FALSE		
	0.3	-0.06	-0.43-0.32	7.71E-01	1.67E-03	FALSE		
	0.4	-0.05	-0.42-0.32	7.86E-01	1.67E-03	FALSE		
	0.5	-0.05	-0.42-0.32	7.88E-01	1.67E-03	FALSE		
	1	-0.05	-0.42-0.32	7.90E-01	1.67E-03	FALSE		
MDD								
SES	0.01	-0.03	-0.06--0.00	2.62E-02	1.67E-03	FALSE		
	0.1	-0.02	-0.05-0.01	1.39E-01	1.67E-03	FALSE		

	0.2	-0.01	-0.04-0.02	3.72E-01	1.67E-03	FALSE					
	0.3	-0.01	-0.04-0.02	4.00E-01	1.67E-03	FALSE					
	0.4	-0.01	-0.04-0.02	3.76E-01	1.67E-03	FALSE					
	0.5	-0.01	-0.04-0.02	4.94E-01	1.67E-03	FALSE					
	1	-0.01	-0.04-0.02	4.17E-01	1.67E-03	FALSE					
Number of Rooms	0.01	-0.04	-0.07--0.02	**4.36E-04****	1.67E-03	TRUE	-0.04	-0.07--0.02	4.78E-04	1.98	1.60E-01
	0.1	-0.04	-0.06--0.01	1.90E-03*	1.67E-03	FALSE	-0.04	-0.06--0.01	3.22E-03	0.92	3.37E-01
	0.2	-0.02	-0.05--0.00	4.06E-02*	1.67E-03	FALSE	-0.02	-0.05-0.00	7.23E-02	0.21	6.47E-01
	0.3	-0.03	-0.05--0.00	3.59E-02*	1.67E-03	FALSE	-0.02	-0.05-0.00	6.93E-02	0.15	7.01E-01
	0.4	-0.02	-0.05--0.00	4.61E-02*	1.67E-03	FALSE	-0.02	-0.04-0.00	1.02E-01	0.02	8.86E-01
	0.5	-0.03	-0.05--0.00	3.46E-02*	1.67E-03	FALSE	-0.02	-0.05-0.00	8.45E-02	0.01	9.35E-01
	1	-0.03	-0.05--0.00	2.74E-02*	1.67E-03	FALSE	-0.02	-0.05-0.00	6.81E-02	0.01	9.43E-01
Marital status	0.01	0.08	0.03-0.14	2.38E-03	1.67E-03	FALSE					
	0.1	0.05	-0.01-0.10	1.03E-01	1.67E-03	FALSE					
	0.2	0.02	-0.04-0.07	5.70E-01	1.67E-03	FALSE					
	0.3	0.01	-0.04-0.07	6.40E-01	1.67E-03	FALSE					
	0.4	0.01	-0.04-0.07	6.64E-01	1.67E-03	FALSE					
	0.5	0.01	-0.04-0.07	6.00E-01	1.67E-03	FALSE					
	1	0.02	-0.04-0.07	5.18E-01	1.67E-03	FALSE					
Income	0.01	-0.03	-0.05--0.01	**6.72E-04****	1.67E-03	TRUE	-0.04	-0.06--0.02	2.98E-04	2.86	9.08E-02
	0.1	-0.02	-0.04--0.00	1.83E-02*	1.67E-03	FALSE	-0.03	-0.05--0.01	1.09E-02	1.22	2.69E-01
	0.2	-0.02	-0.04--0.00	2.41E-02*	1.67E-03	FALSE	-0.03	-0.05--0.00	1.54E-02	0.86	3.53E-01
	0.3	-0.02	-0.04--0.00	4.11E-02*	1.67E-03	FALSE	-0.02	-0.04--0.00	3.03E-02	0.46	5.00E-01
	0.4	-0.02	-0.04-0.00	5.57E-02*	1.67E-03	FALSE	-0.02	-0.04--0.00	4.51E-02	0.32	5.72E-01
	0.5	-0.02	-0.04--0.00	4.75E-02*	1.67E-03	FALSE	-0.02	-0.04--0.00	3.79E-02	0.36	5.48E-01
	1	-0.02	-0.04--0.00	4.31E-02*	1.67E-03	FALSE	-0.02	-0.04--0.00	2.89E-02	0.61	4.34E-01
Alcohol consumption	0.01	0.01	-0.01-0.04	3.29E-01	1.67E-03	FALSE					
	0.1	-0.01	-0.03-0.02	4.74E-01	1.67E-03	FALSE					
	0.2	-0.01	-0.03-0.02	5.03E-01	1.67E-03	FALSE					
	0.3	0	-0.03-0.02	7.37E-01	1.67E-03	FALSE					
	0.4	-0.01	-0.03-0.02	6.45E-01	1.67E-03	FALSE					
	0.5	0	-0.03-0.02	7.07E-01	1.67E-03	FALSE					
	1	-0.01	-0.03-0.02	6.25E-01	1.67E-03	FALSE					
Employment	0.01	0.2	0.09-0.32	**5.50E-04****	1.67E-03	TRUE	0.18	0.07-0.30	1.68E-03	3.33	6.79E-02
	0.1	0.21	0.10-0.33	**2.63E-04****	1.67E-03	TRUE	0.18	0.06-0.29	2.34E-03	0.7	4.04E-01
	0.2	0.23	0.12-0.35	**5.95E-05****	1.67E-03	TRUE	0.21	0.09-0.32	4.29E-04	0.67	4.14E-01
	0.3	0.22	0.10-0.33	**2.20E-04****	1.67E-03	TRUE	0.17	0.06-0.29	2.94E-03	0.14	7.12E-01

	0.4	0.21	0.09-0.32	**3.86E-04****	1.67E-03	TRUE	0.17	0.05-0.28	4.29E-03	0.28	5.97E-01
	0.5	0.21	0.09-0.32	**3.98E-04****	1.67E-03	TRUE	0.16	0.05-0.28	5.18E-03	0.17	6.80E-01
	1	0.2	0.09-0.31	**5.61E-04****	1.67E-03	TRUE	0.16	0.05-0.28	5.07E-03	0.4	5.30E-01
Tenure	0.01	0.13	-0.10-0.37	2.51E-01	1.67E-03	FALSE					
	0.1	0.13	-0.10-0.35	2.70E-01	1.67E-03	FALSE					
	0.2	0.1	-0.13-0.33	4.07E-01	1.67E-03	FALSE					
	0.3	0.09	-0.15-0.33	4.58E-01	1.67E-03	FALSE					
	0.4	0.09	-0.14-0.32	4.51E-01	1.67E-03	FALSE					
	0.5	0.1	-0.14-0.33	4.15E-01	1.67E-03	FALSE					
	1	0.09	-0.14-0.32	4.29E-01	1.67E-03	FALSE					
Finance Issues	0.01	0.24	0.16-0.33	**2.91E-08****	1.67E-03	TRUE	0.23	0.14-0.32	9.91E-07	2.33	1.27E-01
	0.1	0.22	0.14-0.31	**3.48E-07****	1.67E-03	TRUE	0.19	0.10-0.28	5.67E-05	0.15	6.95E-01
	0.2	0.22	0.14-0.31	**4.09E-07****	1.67E-03	TRUE	0.19	0.10-0.28	5.40E-05	0.13	7.15E-01
	0.3	0.23	0.15-0.32	**1.13E-07****	1.67E-03	TRUE	0.19	0.10-0.28	4.54E-05	0.03	8.71E-01
	0.4	0.23	0.15-0.32	**9.79E-08****	1.67E-03	TRUE	0.19	0.10-0.28	4.49E-05	0.02	9.02E-01
	0.5	0.23	0.14-0.32	**1.52E-07****	1.67E-03	TRUE	0.19	0.10-0.28	6.60E-05	0.02	8.99E-01
	1	0.23	0.15-0.32	**1.36E-07****	1.67E-03	TRUE	0.19	0.10-0.28	5.42E-05	0.02	8.80E-01
Education	0.01	0.2	-0.17-0.57	2.96E-01	1.67E-03	FALSE					
	0.1	0.1	-0.27-0.47	5.93E-01	1.67E-03	FALSE					
	0.2	0.09	-0.27-0.46	6.13E-01	1.67E-03	FALSE					
	0.3	0.09	-0.27-0.46	6.24E-01	1.67E-03	FALSE					
	0.4	0.09	-0.27-0.46	6.11E-01	1.67E-03	FALSE					
	0.5	0.09	-0.27-0.46	6.18E-01	1.67E-03	FALSE					
	1	0.1	-0.27-0.46	6.03E-01	1.67E-03	FALSE					

Note: All results were corrected for multiple testing using the Bonferroni correction (0.05/30 environments = $p \leq 1.67 \times 10^{-3}$). * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results after multiple testing only, except for the one significant SCZ finding due to the lack of available SCZ diagnosis and symptoms in the USoc dataset. All regressions were calculated using STATA v12.1 (1).

Appendix 17: *PRS Results for NCDS (Chapter 4)*

Environment	Threshold z-scored	Beta	95%CI	P-Value	Bonferroni Correction		Sensitivity			Interaction	
					0.05/30	statistically significant?	Beta	95%CI	P-Value	Wald chi-square	p-value
SCZ											
SES	0.01	0	-0.03-0.02	9.04E-01	1.67E-03	FALSE					
	0.1	0.01	-0.01-0.03	3.21E-01	1.67E-03	FALSE					
	0.2	0.02	-0.01-0.04	1.90E-01	1.67E-03	FALSE					
	0.3	0.01	-0.01-0.04	2.18E-01	1.67E-03	FALSE					
	0.4	0.02	-0.01-0.04	1.69E-01	1.67E-03	FALSE					
	0.5	0.02	-0.01-0.04	1.89E-01	1.67E-03	FALSE					
	1	0.02	-0.01-0.04	1.77E-01	1.67E-03	FALSE					
Number of Rooms	0.01	0	-0.03-0.02	6.99E-01	1.67E-03	FALSE					
	0.1	0	-0.02-0.02	7.21E-01	1.67E-03	FALSE					
	0.2	-0.01	-0.03-0.01	4.11E-01	1.67E-03	FALSE					
	0.3	-0.01	-0.03-0.01	3.61E-01	1.67E-03	FALSE					
	0.4	-0.01	-0.03-0.01	3.75E-01	1.67E-03	FALSE					
	0.5	-0.01	-0.03-0.01	3.66E-01	1.67E-03	FALSE					
	1	-0.01	-0.03-0.01	3.92E-01	1.67E-03	FALSE					
Marital status	0.01	0.06	-0.01-0.13	8.36E-02	1.67E-03	FALSE					
	0.1	0.03	-0.03-0.10	3.29E-01	1.67E-03	FALSE					
	0.2	0.03	-0.03-0.10	2.90E-01	1.67E-03	FALSE					
	0.3	0.03	-0.03-0.10	3.34E-01	1.67E-03	FALSE					
	0.4	0.03	-0.03-0.09	3.70E-01	1.67E-03	FALSE					
	0.5	0.02	-0.04-0.09	4.70E-01	1.67E-03	FALSE					
	1	0.02	-0.04-0.09	4.91E-01	1.67E-03	FALSE					
Smoking	0.01	0.06	-0.14-0.27	5.52E-01	1.67E-03	FALSE					
	0.1	0.14	-0.06-0.33	1.68E-01	1.67E-03	FALSE					
	0.2	0.15	-0.05-0.34	1.34E-01	1.67E-03	FALSE					
	0.3	0.15	-0.05-0.34	1.33E-01	1.67E-03	FALSE					
	0.4	0.14	-0.06-0.33	1.71E-01	1.67E-03	FALSE					
	0.5	0.12	-0.07-0.32	2.11E-01	1.67E-03	FALSE					
	1	0.12	-0.07-0.32	2.07E-01	1.67E-03	FALSE					
Employment	0.01	0.08	-0.02-0.18	1.22E-01	1.67E-03	FALSE					

	0.1	0.08	-0.02-0.17	1.34E-01	1.67E-03	FALSE					
	0.2	0.07	-0.02-0.17	1.36E-01	1.67E-03	FALSE					
	0.3	0.09	-0.01-0.18	8.53E-02	1.67E-03	FALSE					
	0.4	0.08	-0.02-0.18	9.87E-02	1.67E-03	FALSE					
	0.5	0.08	-0.01-0.18	8.86E-02	1.67E-03	FALSE					
	1	0.07	-0.02-0.17	1.33E-01	1.67E-03	FALSE					
Tenure	0.01	0.01	-0.11-0.13	8.39E-01	1.67E-03	FALSE					
	0.1	0	-0.11-0.11	9.65E-01	1.67E-03	FALSE					
	0.2	0.01	-0.10-0.12	8.37E-01	1.67E-03	FALSE					
	0.3	0.01	-0.10-0.12	8.11E-01	1.67E-03	FALSE					
	0.4	0.01	-0.10-0.12	8.74E-01	1.67E-03	FALSE					
	0.5	0	-0.11-0.11	9.62E-01	1.67E-03	FALSE					
	1	0.01	-0.10-0.12	9.07E-01	1.67E-03	FALSE					
MDD											
SES	0.01	-0.02	-0.04-0.00	6.29E-02	1.67E-03	FALSE					
	0.1	-0.02	-0.05--0.00	2.86E-02	1.67E-03	FALSE					
	0.2	-0.02	-0.04-0.00	5.21E-02	1.67E-03	FALSE					
	0.3	-0.02	-0.04-0.00	9.59E-02	1.67E-03	FALSE					
	0.4	-0.02	-0.04-0.00	7.95E-02	1.67E-03	FALSE					
	0.5	-0.02	-0.04-0.00	8.95E-02	1.67E-03	FALSE					
	1	-0.02	-0.04-0.00	1.11E-01	1.67E-03	FALSE					
Number of Rooms	0.01	-0.03	-0.04--0.01	8.93E-03*	1.67E-03	FALSE	-0.02	-0.05--0.00	5.00E-02	0.11	7.38E-01
	0.1	-0.03	-0.05--0.01	**5.43E-04****	1.67E-03	TRUE	-0.03	-0.05--0.01	9.02E-03	0.3	5.82E-01
	0.2	-0.03	-0.05--0.01	1.83E-03*	1.67E-03	FALSE	-0.02	-0.05--0.00	3.09E-02	0.19	6.62E-01
	0.3	-0.03	-0.05--0.01	1.72E-03*	1.67E-03	FALSE	-0.02	-0.05--0.00	3.05E-02	0.21	6.48E-01
	0.4	-0.03	-0.05--0.01	**1.16E-03****	1.67E-03	TRUE	-0.03	-0.05--0.00	2.28E-02	0.19	6.62E-01
	0.5	-0.03	-0.05--0.01	**1.51E-03****	1.67E-03	TRUE	-0.02	-0.05--0.00	3.22E-02	0.34	5.58E-01
	1	-0.03	-0.05--0.01	1.84E-03*	1.67E-03	FALSE	-0.02	-0.05--0.00	3.32E-02	0.32	5.72E-01
Marital status	0.01	-0.01	-0.08-0.05	6.89E-01	1.67E-03	FALSE					
	0.1	0	-0.06-0.06	9.39E-01	1.67E-03	FALSE					
	0.2	-0.02	-0.08-0.04	5.20E-01	1.67E-03	FALSE					
	0.3	-0.02	-0.08-0.04	4.55E-01	1.67E-03	FALSE					
	0.4	-0.02	-0.09-0.04	4.29E-01	1.67E-03	FALSE					
	0.5	-0.02	-0.09-0.04	4.29E-01	1.67E-03	FALSE					
	1	-0.02	-0.08-0.04	4.77E-01	1.67E-03	FALSE					

Smoking	0.01	0.21	0.02-0.40	3.06E-02*	1.67E-03	FALSE					
	0.1	0.22	0.03-0.41	2.06E-02*	1.67E-03	FALSE					
	0.2	0.26	0.07-0.44	7.07E-03*	1.67E-03	FALSE					
	0.3	0.26	0.07-0.44	6.57E-03*	1.67E-03	FALSE					
	0.4	0.25	0.06-0.43	9.01E-03*	1.67E-03	FALSE					
	0.5	0.24	0.05-0.42	1.20E-02*	1.67E-03	FALSE					
	1	0.23	0.05-0.42	1.45E-02*	1.67E-03	FALSE					
Employment	0.01	0.08	-0.01-0.18	8.92E-02	1.67E-03	FALSE					
	0.1	0.05	-0.05-0.14	3.18E-01	1.67E-03	FALSE					
	0.2	0.05	-0.04-0.14	2.93E-01	1.67E-03	FALSE					
	0.3	0.05	-0.04-0.15	2.70E-01	1.67E-03	FALSE					
	0.4	0.06	-0.04-0.15	2.47E-01	1.67E-03	FALSE					
	0.5	0.05	-0.04-0.15	2.78E-01	1.67E-03	FALSE					
	1	0.04	-0.05-0.14	3.59E-01	1.67E-03	FALSE					
Tenure	0.01	0.1	-0.01-0.20	8.24E-02	1.67E-03	FALSE	0.05	-0.07-0.18	4.10E-01	0.56	4.54E-01
	0.1	0.19	0.08-0.29	**6.36E-04****	1.67E-03	TRUE	0.11	-0.01-0.23	7.64E-02	0.85	3.58E-01
	0.2	0.16	0.05-0.27	3.08E-03*	1.67E-03	FALSE	0.1	-0.02-0.22	1.04E-01	1.43	2.31E-01
	0.3	0.16	0.05-0.26	4.25E-03*	1.67E-03	FALSE	0.09	-0.03-0.22	1.32E-01	2.23	1.35E-01
	0.4	0.16	0.05-0.27	3.27E-03*	1.67E-03	FALSE	0.1	-0.02-0.22	1.03E-01	1.61	2.04E-01
	0.5	0.16	0.05-0.27	3.33E-03*	1.67E-03	FALSE	0.09	-0.03-0.21	1.39E-01	2.27	1.32E-01
	1	0.15	0.04-0.26	6.04E-03*	1.67E-03	FALSE	0.08	-0.04-0.21	1.79E-01	2.35	1.25E-01

Note: All results were corrected for multiple testing using the Bonferroni correction (0.05/30 environments = $p \leq 1.67 \times 10^{-3}$). * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results after multiple testing only. All regressions were calculated using STATA v12.1 (1).

Appendix 18: *PRS Results for MCS (Chapter 5)*

Environment	Threshold z-scored	SCZ			SCZ Sensitivity			SCZ Wald chi-squared		MDD		
		Beta	95%CI	P-Value	Beta	95%CI	P-Value	chi2	p-value	Beta	95%CI	P-Value
Child SES-by-time	0.01	0.01	0.00-0.01	3.59E-02*						0	-0.00-0.01	1.65E-01
	0.1	0.01	0.00-0.01	2.61E-02*						0.01	0.00-0.01	2.61E-02*
	0.2	0.01	0.00-0.01	2.17E-02*						0.01	-0.00-0.01	5.25E-02
	0.3	0.01	0.00-0.01	3.18E-02*						0.01	0.00-0.01	4.95E-02*
	0.4	0.01	0.00-0.01	3.29E-02*						0.01	-0.00-0.01	5.30E-02
	0.5	0.01	0.00-0.01	3.40E-02*						0.01	0.00-0.01	4.09E-02*
	1	0.01	0.00-0.01	3.32E-02*						0.01	0.00-0.01	3.84E-02*
Child Finance Issues-by-time	0.01	-0.01	-0.06-0.05	8.49E-01						-0.03	-0.09-0.02	2.40E-01
	0.1	-0.01	-0.06-0.04	7.61E-01						-0.02	-0.07-0.03	3.74E-01
	0.2	0	-0.05-0.05	8.50E-01						-0.03	-0.08-0.02	2.84E-01
	0.3	-0.01	-0.05-0.04	8.43E-01						-0.03	-0.08-0.02	3.02E-01
	0.4	-0.01	-0.06-0.04	8.05E-01						-0.03	-0.08-0.02	2.65E-01
	0.5	-0.01	-0.06-0.04	7.81E-01						-0.03	-0.08-0.02	2.60E-01
	1	-0.01	-0.06-0.04	7.96E-01						-0.03	-0.08-0.02	2.82E-01
Child Number of Rooms-by-time	0.01	-0.01	-0.02-0.00	6.06E-02						0	-0.01-0.01	9.60E-01
	0.1	-0.01	-0.01-0.00	1.53E-01						0	-0.01-0.01	9.81E-01
	0.2	-0.01	-0.01-0.00	1.93E-01						0	-0.01-0.01	9.11E-01
	0.3	0	-0.01-0.00	2.71E-01						0	-0.01-0.01	8.25E-01
	0.4	0	-0.01-0.00	2.98E-01						0	-0.01-0.01	7.78E-01
	0.5	0	-0.01-0.00	3.17E-01						0	-0.01-0.01	7.58E-01
	1	0	-0.01-0.00	3.50E-01						0	-0.01-0.01	6.65E-01
Child Tenure-by-time	0.01	-0.12	-0.17--0.07	**1.61E-06****	-0.07	-0.12--0.02	5.58E-03	0.95	3.31E-01	-0.03	-0.08-0.02	2.12E-01
	0.1	-0.11	-0.16--0.06	**2.67E-05****	-0.08	-0.14--0.03	2.83E-03	1.44	2.30E-01	-0.01	-0.06-0.03	5.60E-01
	0.2	-0.1	-0.16--0.05	**5.50E-05****	-0.08	-0.14--0.03	4.46E-03	1.4	2.36E-01	0.01	-0.04-0.06	6.70E-01
	0.3	-0.1	-0.15--0.05	**1.29E-04****	-0.08	-0.13--0.02	6.64E-03	1.83	1.76E-01	0.01	-0.04-0.06	6.58E-01
	0.4	-0.09	-0.15--0.04	**2.34E-04****	-0.08	-0.13--0.02	6.26E-03	1.99	1.59E-01	0.01	-0.03-0.06	6.21E-01
	0.5	-0.09	-0.14--0.04	**2.83E-04****	-0.08	-0.13--0.02	7.47E-03	1.95	1.63E-01	0.01	-0.03-0.06	5.90E-01
	1	-0.09	-0.14--0.04	**3.95E-04****	-0.08	-0.13--0.02	8.34E-03	1.47	2.26E-01	0.02	-0.03-0.06	5.14E-01
Mother taking child	0.01	-0.03	-0.10-0.03	3.23E-01						0.03	-0.04-0.10	3.69E-01
	0.1	-0.03	-0.10-0.03	3.28E-01						0.01	-0.06-0.08	8.23E-01
	0.2	-0.04	-0.10-0.03	2.93E-01						0.01	-0.06-0.08	8.02E-01

for walks-by-time	0.3	-0.04	-0.10-0.03	2.97E-01			0.01	-0.06-0.08	7.33E-01
	0.4	-0.03	-0.10-0.03	3.23E-01			0.01	-0.06-0.07	8.69E-01
	0.5	-0.03	-0.10-0.03	3.33E-01			0	-0.07-0.07	9.86E-01
	1	-0.03	-0.10-0.03	3.29E-01			0	-0.07-0.07	9.45E-01
Father taking child for walks-by-time	0.01	-0.04	-0.14-0.05	3.66E-01			0.02	-0.08-0.11	7.29E-01
	0.1	-0.05	-0.15-0.05	3.27E-01			-0.01	-0.12-0.10	8.27E-01
	0.2	-0.05	-0.16-0.05	3.19E-01			0	-0.11-0.12	9.37E-01
	0.3	-0.05	-0.16-0.05	3.21E-01			0	-0.11-0.12	9.35E-01
	0.4	-0.05	-0.16-0.05	3.31E-01			0.01	-0.11-0.12	9.06E-01
	0.5	-0.05	-0.15-0.06	3.73E-01			0.01	-0.11-0.12	9.04E-01
	1	-0.05	-0.16-0.06	3.58E-01			0	-0.11-0.11	9.65E-01
Smoking Mother-by-time	0.01	0.02	-0.03-0.06	4.94E-01			0.01	-0.03-0.05	6.32E-01
	0.1	0.01	-0.04-0.05	8.04E-01			0.01	-0.04-0.05	7.55E-01
	0.2	0.01	-0.04-0.05	7.09E-01			0.01	-0.04-0.05	7.95E-01
	0.3	0.01	-0.04-0.05	6.97E-01			0.01	-0.04-0.05	7.94E-01
	0.4	0.01	-0.04-0.06	6.86E-01			0.01	-0.04-0.05	7.86E-01
	0.5	0.01	-0.04-0.05	7.14E-01			0.01	-0.04-0.05	7.55E-01
	1	0.01	-0.04-0.05	7.36E-01			0.01	-0.04-0.05	7.90E-01
Parental Marital status-by-time	0.01	0.02	-0.01-0.04	2.44E-01			-0.01	-0.03-0.02	5.27E-01
	0.1	0.01	-0.01-0.04	3.91E-01			-0.01	-0.03-0.02	6.08E-01
	0.2	0.01	-0.02-0.04	4.50E-01			-0.01	-0.04-0.02	4.45E-01
	0.3	0.01	-0.02-0.04	4.21E-01			-0.01	-0.04-0.02	4.81E-01
	0.4	0.01	-0.02-0.04	4.43E-01			-0.01	-0.04-0.02	4.69E-01
	0.5	0.01	-0.02-0.04	4.31E-01			-0.01	-0.04-0.02	5.46E-01
	1	0.01	-0.02-0.04	4.31E-01			-0.01	-0.03-0.02	6.18E-01
Alcohol Consumption Mother-by-time	0.01	0	-0.04-0.03	8.12E-01			-0.02	-0.05-0.01	2.84E-01
	0.1	0	-0.04-0.03	8.39E-01			-0.01	-0.05-0.03	5.94E-01
	0.2	0	-0.04-0.03	8.23E-01			-0.01	-0.06-0.03	5.43E-01
	0.3	0	-0.04-0.03	8.05E-01			-0.01	-0.05-0.03	6.36E-01
	0.4	-0.01	-0.04-0.03	7.75E-01			-0.01	-0.05-0.03	6.21E-01
	0.5	-0.01	-0.04-0.03	7.72E-01			-0.01	-0.05-0.03	6.19E-01
	1	-0.01	-0.04-0.03	7.23E-01			-0.01	-0.05-0.03	6.33E-01
Alcohol Consumption Father-by-time	0.01	0.03	-0.05-0.10	4.82E-01			-0.02	-0.09-0.05	5.29E-01
	0.1	0	-0.08-0.08	9.73E-01			-0.04	-0.13-0.05	4.17E-01
	0.2	-0.01	-0.10-0.07	7.66E-01			-0.05	-0.15-0.04	2.85E-01
	0.3	-0.02	-0.11-0.07	6.19E-01			-0.06	-0.16-0.04	2.19E-01
	0.4	-0.03	-0.11-0.06	5.53E-01			-0.05	-0.15-0.04	2.81E-01

	0.5	-0.02	-0.11-0.06	6.07E-01			-0.06	-0.15-0.04	2.64E-01
	1	-0.02	-0.11-0.07	6.12E-01			-0.06	-0.16-0.04	2.17E-01
Mother reading to child-by-time	0.01	-0.02	-0.11-0.08	7.15E-01	-	-	-0.05	-0.14-0.05	3.12E-01
	0.1	-0.03	-0.13-0.07	5.41E-01			-0.05	-0.14-0.04	2.70E-01
	0.2	-0.03	-0.13-0.06	4.73E-01			-0.04	-0.13-0.06	4.49E-01
	0.3	-0.03	-0.13-0.06	4.96E-01			-0.04	-0.13-0.05	4.24E-01
	0.4	-0.04	-0.13-0.06	4.56E-01			-0.04	-0.13-0.05	4.22E-01
	0.5	-0.04	-0.13-0.06	4.37E-01			-0.04	-0.13-0.05	3.50E-01
	1	-0.04	-0.13-0.06	4.23E-01			-0.05	-0.13-0.04	3.23E-01
Father reading to child-by-time	0.01	-0.09	-0.19-0.01	8.25E-02			-0.04	-0.14-0.06	4.70E-01
	0.1	-0.06	-0.18-0.05	2.83E-01			0.03	-0.09-0.15	6.39E-01
	0.2	-0.06	-0.18-0.05	2.83E-01			0.04	-0.08-0.16	5.42E-01
	0.3	-0.07	-0.19-0.04	2.26E-01			0.05	-0.07-0.17	4.34E-01
	0.4	-0.07	-0.19-0.05	2.42E-01			0.05	-0.07-0.18	3.96E-01
	0.5	-0.07	-0.19-0.04	2.15E-01			0.06	-0.07-0.18	3.76E-01
	1	-0.08	-0.19-0.04	2.13E-01			0.04	-0.08-0.16	5.01E-01

Note: All results were corrected for multiple testing using the Benjamini-Hochberg correction adjusted α = (rank of p-value/number of tests for each threshold) - *α [adjusted α=(rank/560)*0.05]. * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results after multiple testing only. Beta = beta coefficient, CI = Confidence Interval, All regressions were calculated using STATA v12.1 (1).

Appendix 19: *PRS Results for USoc (Chapter 5)*

Environment	Threshold z-scored	SCZ			MDD			MDD Sensitivity			MDD Wald chi-squared	
		Beta	95%CI	P-Value	Beta	95%CI	P-Value	Beta	95%CI	P-Value	chi2	p-value
Adult SES-by-time	0.01	0	-0.00-0.01	6.63E-01	-0.01	-0.01-0.00	6.60E-02	0	-0.01-0	8.24E-02	1.75	1.86E-01
	0.1	0	-0.00-0.01	8.22E-01	-0.01	-0.02--0.01	4.27E-05	-0.01	-0.01-0	2.05E-03**	0.31	5.80E-01
	0.2	0	-0.00-0.01	3.90E-01	-0.01	-0.02--0.00	4.28E-04	-0.01	-0.01-0	1.67E-02**	0.25	6.15E-01
	0.3	0	-0.00-0.01	3.62E-01	-0.01	-0.01--0.00	9.37E-04	-0.01	-0.01-0	2.89E-02**	0.27	6.06E-01
	0.4	0	-0.00-0.01	3.77E-01	-0.01	-0.01--0.00	6.05E-04	-0.01	-0.01-0	1.66E-02**	0.12	7.33E-01
	0.5	0	-0.00-0.01	4.15E-01	-0.01	-0.01--0.00	1.25E-03	-0.01	-0.01-0	2.36E-02**	0.08	7.71E-01
	1	0	-0.00-0.01	4.10E-01	-0.01	-0.01--0.00	1.10E-03	-0.01	-0.01-0	1.98E-02**	0.06	8.08E-01
Adult Number of Rooms-by-time	0.01	0.01	0.00-0.01	**5.21E-04****	0	-0.01--0.00	3.54E-02*					
	0.1	0	0.00-0.01	1.14E-02*	0	-0.01--0.00	1.10E-02*					
	0.2	0	0.00-0.01	1.33E-02*	0	-0.01-0.00	6.01E-02					
	0.3	0	0.00-0.01	3.51E-02*	0	-0.01-0.00	5.92E-02					
	0.4	0	0.00-0.01	4.60E-02*	0	-0.01--0.00	3.98E-02*					
	0.5	0	0.00-0.01	4.32E-02*	0	-0.01-0.00	5.28E-02					
	1	0	-0.00-0.01	7.46E-02	0	-0.01-0.00	5.52E-02					
Adult Tenure-by-time	0.01	0.06	-0.01-0.14	7.29E-02	0.16	0.08-0.23	**6.77E-05****	0.14	0.07-0.22	3.14E-04	8.46	3.60E-03
	0.1	0.06	-0.01-0.13	9.10E-02	0.13	0.06-0.20	**3.70E-04****	0.15	0.07-0.22	8.51E-05	10.76	1.00E-03
	0.2	0.05	-0.02-0.12	1.66E-01	0.14	0.07-0.21	**1.20E-04****	0.16	0.08-0.23	3.39E-05	0.65	4.21E-01
	0.3	0.05	-0.02-0.12	1.43E-01	0.14	0.07-0.21	**1.79E-04****	0.15	0.08-0.23	4.24E-05	1.29	2.56E-01
	0.4	0.05	-0.03-0.12	2.09E-01	0.14	0.07-0.21	**1.38E-04****	0.16	0.09-0.24	2.13E-05	8.1	4.40E-03
	0.5	0.04	-0.03-0.11	2.31E-01	0.14	0.07-0.22	**1.20E-04****	0.16	0.09-0.24	2.04E-05	7.64	5.70E-03
	1	0.05	-0.02-0.12	1.55E-01	0.14	0.07-0.21	**1.63E-04****	0.16	0.09-0.23	2.49E-05	1.15	2.84E-01
Adult Employment-by-time	0.01	-0.02	-0.07-0.03	4.59E-01	0.01	-0.04-0.06	7.88E-01					
	0.1	-0.02	-0.07-0.03	5.01E-01	0.01	-0.04-0.06	6.84E-01					
	0.2	-0.01	-0.06-0.04	6.87E-01	0.02	-0.03-0.07	3.45E-01					
	0.3	-0.01	-0.06-0.04	7.46E-01	0.02	-0.03-0.07	3.96E-01					
	0.4	-0.02	-0.07-0.03	5.30E-01	0.02	-0.03-0.06	5.22E-01					
	0.5	-0.02	-0.07-0.03	4.02E-01	0.02	-0.03-0.06	5.31E-01					
	1	-0.02	-0.07-0.03	4.21E-01	0.02	-0.03-0.07	4.75E-01					
Adult Finance	0.01	0.01	-0.04-0.05	6.76E-01	-0.02	-0.06-0.03	4.43E-01					
	0.1	-0.02	-0.06-0.03	4.92E-01	-0.01	-0.05-0.04	7.80E-01					
	0.2	-0.01	-0.06-0.03	5.46E-01	-0.01	-0.06-0.03	5.77E-01					

Issues-by-time	0.3	-0.01	-0.06-0.03	6.04E-01	-0.02	-0.06-0.02	3.78E-01		
	0.4	-0.02	-0.06-0.03	4.87E-01	-0.03	-0.07-0.02	2.03E-01		
	0.5	-0.01	-0.06-0.03	5.63E-01	-0.03	-0.07-0.02	2.15E-01		
	1	-0.02	-0.06-0.03	4.68E-01	-0.03	-0.07-0.02	2.10E-01		
Adult Income-by-time	0.01	0	-0.00-0.01	7.64E-01	0	-0.01-0.00	3.30E-01		
	0.1	0	-0.00-0.01	4.72E-01	0	-0.01-0.00	6.21E-01		
	0.2	0	-0.00-0.01	3.70E-01	0	-0.01-0.00	2.05E-01		
	0.3	0	-0.00-0.01	5.24E-01	0	-0.01-0.00	1.80E-01		
	0.4	0	-0.00-0.01	6.22E-01	0	-0.01-0.00	2.81E-01		
	0.5	0	-0.00-0.01	6.55E-01	0	-0.01-0.00	3.34E-01		
	1	0	-0.00-0.01	5.71E-01	0	-0.01-0.00	3.88E-01		

Note: All results were corrected for multiple testing using the Benjamini-Hochberg correction adjusted α = (rank of p-value/number of tests for each threshold) - *α [adjusted α=(rank/560)*0.05]. * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results for MDD only (as no SCZ diagnosis is available in USoc) after multiple testing. Beta = beta coefficient, CI = Confidence Interval, All regressions were calculated using STATA v12.1 (1).

Appendix 20: *PRS Results for NCDS – Childhood and Adulthood across Time (Chapter 5)*

Environment	Threshold z-scored	SCZ			MDD		
		Beta	95%CI	P-Value	Beta	95%CI	P-Value
Childhood							
Child SES-by-time	0.01	0	-0.01-0.01	6.42E-01	0.01	-0.00-0.01	2.75E-01
	0.1	0	-0.01-0.01	4.82E-01	0.01	-0.00-0.02	1.76E-01
	0.2	0	-0.01-0.01	6.62E-01	0.01	-0.00-0.01	2.80E-01
	0.3	0	-0.01-0.01	5.19E-01	0.01	-0.00-0.02	2.51E-01
	0.4	0	-0.01-0.01	5.98E-01	0.01	-0.00-0.01	2.69E-01
	0.5	0	-0.01-0.01	5.82E-01	0	-0.00-0.01	3.22E-01
	1	0	-0.01-0.01	5.32E-01	0.01	-0.00-0.01	2.56E-01
Child Finance Issues-by-time	0.01	-0.06	-0.14-0.02	1.42E-01	0	-0.08-0.08	9.67E-01
	0.1	-0.05	-0.13-0.02	1.71E-01	-0.01	-0.09-0.06	7.07E-01
	0.2	-0.05	-0.13-0.03	1.90E-01	0.01	-0.07-0.09	7.67E-01
	0.3	-0.05	-0.13-0.03	2.28E-01	0.01	-0.07-0.09	8.36E-01
	0.4	-0.05	-0.13-0.03	2.32E-01	0	-0.08-0.08	9.85E-01
	0.5	-0.05	-0.12-0.03	2.55E-01	0	-0.08-0.08	9.78E-01
	1	-0.05	-0.12-0.03	2.54E-01	0	-0.08-0.08	9.43E-01
Child Number of Rooms-by-time	0.01	0.01	-0.00-0.02	2.42E-01	0	-0.01-0.01	9.44E-01
	0.1	0.01	-0.00-0.02	6.89E-02	0	-0.01-0.01	5.24E-01
	0.2	0.01	-0.00-0.02	5.65E-02	0.01	-0.00-0.02	2.54E-01
	0.3	0.01	-0.00-0.02	5.41E-02	0.01	-0.01-0.02	3.07E-01
	0.4	0.01	-0.00-0.02	7.34E-02	0.01	-0.00-0.02	2.62E-01
	0.5	0.01	-0.00-0.02	7.55E-02	0.01	-0.00-0.02	1.89E-01
	1	0.01	0.00-0.02	3.93E-02*	0.01	-0.00-0.02	1.87E-01
Child Tenure-by-time	0.01	0.01	-0.07-0.09	8.07E-01	0.03	-0.05-0.12	4.16E-01
	0.1	0.03	-0.05-0.12	4.17E-01	0.03	-0.05-0.11	4.28E-01
	0.2	0.03	-0.05-0.11	4.54E-01	0.06	-0.02-0.14	1.41E-01
	0.3	0.04	-0.04-0.12	3.51E-01	0.04	-0.04-0.12	3.08E-01
	0.4	0.03	-0.05-0.12	4.27E-01	0.05	-0.04-0.13	2.70E-01
	0.5	0.04	-0.05-0.12	3.93E-01	0.04	-0.04-0.12	3.03E-01
	1	0.04	-0.05-0.12	3.75E-01	0.05	-0.04-0.13	2.73E-01
Mother taking child for walks-by-time	0.01	0.02	-0.14-0.19	7.71E-01	0.07	-0.10-0.23	4.09E-01
	0.1	0.01	-0.15-0.18	8.76E-01	0.02	-0.15-0.18	8.43E-01

	0.2	0.01	-0.15-0.18	8.80E-01	0	-0.16-0.17	9.71E-01
	0.3	0	-0.16-0.17	9.58E-01	-0.03	-0.20-0.13	6.93E-01
	0.4	0.01	-0.15-0.18	8.77E-01	-0.04	-0.21-0.13	6.33E-01
	0.5	0.01	-0.15-0.18	8.96E-01	-0.04	-0.20-0.13	6.63E-01
	1	-0.01	-0.17-0.16	9.18E-01	-0.03	-0.20-0.14	7.17E-01
Father taking child for walks-by-time	0.01	-0.05	-0.15-0.05	3.59E-01	0	-0.10-0.10	9.31E-01
	0.1	0.04	-0.06-0.14	4.79E-01	-0.03	-0.13-0.07	6.16E-01
	0.2	0.04	-0.06-0.14	4.16E-01	-0.02	-0.12-0.08	7.14E-01
	0.3	0.04	-0.06-0.14	4.49E-01	-0.04	-0.14-0.06	4.45E-01
	0.4	0.04	-0.06-0.14	4.15E-01	-0.03	-0.13-0.07	4.95E-01
	0.5	0.04	-0.06-0.14	4.51E-01	-0.04	-0.14-0.06	4.51E-01
	1	0.04	-0.06-0.14	4.73E-01	-0.03	-0.13-0.07	5.11E-01
Mother interest in child education-by-time	0.01	0	-0.06-0.07	9.09E-01	0.02	-0.04-0.09	4.52E-01
	0.1	0.02	-0.05-0.08	6.12E-01	0.03	-0.03-0.09	3.45E-01
	0.2	0.01	-0.06-0.07	8.19E-01	0.04	-0.03-0.10	2.63E-01
	0.3	0.01	-0.05-0.08	7.06E-01	0.04	-0.02-0.11	1.73E-01
	0.4	0.01	-0.05-0.08	6.72E-01	0.04	-0.02-0.10	2.16E-01
	0.5	0.01	-0.06-0.07	8.17E-01	0.04	-0.02-0.10	2.14E-01
	1	0	-0.06-0.07	9.01E-01	0.04	-0.02-0.10	2.13E-01
Father involvement in childcare-by-time	0.01	-0.01	-0.09-0.08	8.75E-01	-0.01	-0.10-0.07	7.75E-01
	0.1	-0.02	-0.10-0.07	6.78E-01	0.03	-0.05-0.11	4.86E-01
	0.2	-0.03	-0.11-0.06	5.50E-01	0.04	-0.05-0.12	3.75E-01
	0.3	-0.02	-0.11-0.06	6.20E-01	0.04	-0.05-0.12	3.84E-01
	0.4	-0.01	-0.09-0.07	8.01E-01	0.04	-0.05-0.12	3.69E-01
	0.5	-0.01	-0.09-0.08	8.73E-01	0.04	-0.04-0.13	3.10E-01
	1	-0.01	-0.09-0.08	8.75E-01	0.04	-0.04-0.13	3.22E-01
Father interest in child education-by-time	0.01	0.06	-0.01-0.13	1.13E-01	0.02	-0.05-0.09	6.32E-01
	0.1	0.06	-0.01-0.13	1.06E-01	0.04	-0.03-0.11	3.07E-01
	0.2	0.04	-0.03-0.11	2.42E-01	0.04	-0.03-0.11	2.96E-01
	0.3	0.04	-0.03-0.11	2.29E-01	0.04	-0.03-0.11	2.83E-01
	0.4	0.04	-0.03-0.11	2.61E-01	0.03	-0.04-0.11	3.31E-01
	0.5	0.04	-0.03-0.11	3.12E-01	0.03	-0.04-0.10	3.79E-01
	1	0.04	-0.03-0.11	2.87E-01	0.03	-0.04-0.10	3.53E-01
Father employment-by-time	0.01	0.02	-0.13-0.17	7.74E-01	0.03	-0.12-0.19	6.64E-01
	0.1	-0.02	-0.17-0.13	7.69E-01	0.04	-0.08-0.16	5.28E-01
	0.2	-0.01	-0.16-0.15	9.47E-01	-0.02	-0.18-0.14	8.07E-01
	0.3	0.03	-0.12-0.18	7.05E-01	0	-0.16-0.16	9.81E-01

	0.4	0.03	-0.12-0.18	7.12E-01	-0.03	-0.18-0.13	7.53E-01
	0.5	0.03	-0.12-0.18	6.82E-01	-0.03	-0.18-0.13	7.47E-01
	1	0.03	-0.13-0.18	7.30E-01	-0.01	-0.17-0.14	8.55E-01
Adulthood							
Adult SES-by-time	0.01	0.01	0.00-0.02	4.69E-02*	0	-0.01-0.01	6.27E-01
	0.1	0.01	0.00-0.02	2.94E-02*	0	-0.01-0.01	8.27E-01
	0.2	0.01	-0.00-0.02	6.87E-02	0	-0.01-0.01	5.33E-01
	0.3	0.01	-0.00-0.02	6.01E-02	0	-0.01-0.01	4.24E-01
	0.4	0.01	-0.00-0.02	1.04E-01	0	-0.01-0.01	4.07E-01
	0.5	0.01	-0.00-0.02	8.55E-02	0	-0.01-0.01	3.63E-01
	1	0.01	-0.00-0.02	8.67E-02	0	-0.01-0.01	4.44E-01
Adult Number of Rooms-by-time	0.01	-0.01	-0.02-0.00	2.62E-01	0	-0.01-0.01	7.99E-01
	0.1	-0.01	-0.02-0.01	3.61E-01	-0.01	-0.02-0.00	2.02E-01
	0.2	-0.01	-0.02-0.00	1.62E-01	-0.01	-0.02-0.01	2.87E-01
	0.3	-0.01	-0.02-0.00	1.20E-01	-0.01	-0.02-0.01	2.93E-01
	0.4	-0.01	-0.02-0.00	1.84E-01	0	-0.02-0.01	4.53E-01
	0.5	-0.01	-0.02-0.00	1.57E-01	0	-0.01-0.01	5.32E-01
	1	-0.01	-0.02-0.00	1.39E-01	0	-0.01-0.01	5.55E-01
Adult Tenure-by-time	0.01	-0.02	-0.08-0.03	4.39E-01	0.03	-0.03-0.09	2.79E-01
	0.1	-0.06	-0.12--0.00	4.39E-02*	0	-0.05-0.06	9.38E-01
	0.2	-0.06	-0.11-0.00	5.65E-02	-0.01	-0.07-0.04	6.12E-01
	0.3	-0.06	-0.12--0.00	4.68E-02*	-0.01	-0.07-0.04	6.29E-01
	0.4	-0.06	-0.11--0.00	4.85E-02*	-0.01	-0.07-0.04	6.79E-01
	0.5	-0.06	-0.12--0.00	4.01E-02*	-0.01	-0.07-0.04	6.39E-01
	1	-0.06	-0.12--0.00	3.97E-02*	-0.02	-0.07-0.04	5.67E-01
Adult Employment-by-time	0.01	0.07	-0.04-0.17	2.01E-01	0.07	-0.03-0.17	1.57E-01
	0.1	0.06	-0.03-0.16	2.03E-01	0.04	-0.05-0.14	3.78E-01
	0.2	0.07	-0.03-0.16	1.91E-01	0.04	-0.05-0.14	3.88E-01
	0.3	0.08	-0.02-0.18	1.22E-01	0.04	-0.05-0.14	3.70E-01
	0.4	0.07	-0.02-0.17	1.39E-01	0.05	-0.05-0.14	3.37E-01

	0.5	0.08	-0.02-0.18	1.23E-01	0.04	-0.05-0.14	3.78E-01
	1	0.07	-0.03-0.17	1.80E-01	0.04	-0.06-0.13	4.67E-01
Adult Marital status-by-time	0.01	0.04	0.01-0.08	2.20E-02*	0.02	-0.01-0.06	1.62E-01
	0.1	0.02	-0.02-0.05	3.60E-01	0.05	0.02-0.09	4.71E-03*
	0.2	0.02	-0.01-0.06	2.50E-01	0.04	0.01-0.08	2.28E-02*
	0.3	0.02	-0.02-0.05	3.32E-01	0.04	0.00-0.07	3.60E-02*
	0.4	0.02	-0.02-0.05	3.45E-01	0.04	0.01-0.08	2.19E-02*
	0.5	0.02	-0.02-0.05	3.75E-01	0.04	0.00-0.07	3.67E-02*
	1	0.02	-0.02-0.05	3.73E-01	0.04	0.00-0.07	4.30E-02*
Adult Smoking-by-time	0.01	-0.01	-0.08-0.07	8.90E-01	0.07	-0.01-0.14	7.59E-02
	0.1	0.02	-0.05-0.10	5.25E-01	0.05	-0.03-0.12	2.25E-01
	0.2	0.01	-0.06-0.09	7.19E-01	0.06	-0.02-0.13	1.45E-01
	0.3	0.02	-0.05-0.10	5.40E-01	0.06	-0.02-0.13	1.48E-01
	0.4	0.02	-0.06-0.09	6.33E-01	0.05	-0.02-0.13	1.68E-01
	0.5	0.01	-0.06-0.09	7.07E-01	0.06	-0.02-0.13	1.57E-01
	1	0.01	-0.06-0.09	7.16E-01	0.06	-0.02-0.14	1.29E-01

Note: All results were corrected for multiple testing using the Benjamini-Hochberg correction adjusted α=(rank of p-value/number of tests for each threshold) - *α [adjusted α=(rank/560)*0.05]. * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results after multiple testing only. Beta = beta coefficient, CI = Confidence Interval, All regressions were calculated using STATA v12.1 (1).

Appendix 21: *PRS Results for NCDS – Childhood vs Adulthood (Chapter 5)*

Environment	Threshold	Beta	95%CI	P-Value	Sensitivity			Wald chi-squared	
					Beta	95%CI	P-Value	chi2	p-value
SCZ									
Family SES vs adult SES (0=child, 1=adult)	0.01	0	-0.02-0.02	9.54E-01	0	-0.04	8.82E-01	0.15	7.00E-01
	0.1	0.02	0.00-0.03	1.88E-02*	0.02	0.01-0.04	8.79E-03	0.75	3.88E-01
	0.2	0.02	0.01-0.04	4.97E-03*	0.03	0.01-0.04	1.77E-03	1.71	1.91E-01
	0.3	0.02	0.01-0.04	**2.27E-03****	0.03	0.01-0.05	8.02E-04	1.28	2.59E-01
	0.4	0.03	0.01-0.04	**1.11E-03****	0.03	0.01-0.05	5.44E-04	1.08	2.98E-01
	0.5	0.02	0.01-0.04	**1.96E-03****	0.03	0.01-0.05	8.77E-04	1.17	2.80E-01
	1	0.02	0.01-0.04	**1.75E-03****	0.03	0.01-0.05	7.05E-04	1.19	2.76E-01
Father's employment vs adult employment (0=child, 1=adult)	0.01	0.05	-0.08-0.17	4.43E-01					
	0.1	-0.02	-0.15-0.10	7.24E-01					
	0.2	-0.03	-0.16-0.09	6.00E-01					
	0.3	-0.02	-0.15-0.10	7.08E-01					
	0.4	-0.02	-0.14-0.11	8.09E-01					
	0.5	-0.02	-0.14-0.11	7.90E-01					
	1	-0.02	-0.15-0.11	7.48E-01					
Family number of rooms vs adult number of rooms (0=child, 1=adult)	0.01	-0.01	-0.03-0.00	1.10E-01					
	0.1	0	-0.02-0.02	9.06E-01					
	0.2	-0.01	-0.03-0.01	4.51E-01					
	0.3	-0.01	-0.03-0.01	2.52E-01					
	0.4	-0.01	-0.03-0.01	3.24E-01					
	0.5	-0.01	-0.03-0.01	3.42E-01					
	1	-0.01	-0.03-0.01	3.95E-01					
Family tenure vs adult tenure (0=child, 1=adult)	0.01	0	-0.07-0.07	9.77E-01					
	0.1	-0.04	-0.11-0.03	2.65E-01					
	0.2	-0.04	-0.11-0.03	2.74E-01					
	0.3	-0.05	-0.12-0.02	1.25E-01					
	0.4	-0.05	-0.12-0.02	1.30E-01					
	0.5	-0.06	-0.13-0.01	1.09E-01					
	1	-0.05	-0.12-0.02	1.43E-01					
Parental marital status vs adult	0.01	0.06	-0.12-0.24	5.19E-01					
	0.1	0.1	-0.07-0.28	2.52E-01					
	0.2	0.1	-0.08-0.27	2.97E-01					

marital status (0=child, 1=adult)	0.3	0.11	-0.07-0.28	2.49E-01					
	0.4	0.12	-0.06-0.30	1.84E-01					
	0.5	0.12	-0.06-0.30	1.75E-01					
	1	0.13	-0.05-0.31	1.49E-01					
Maternal smoking prior and during pregnancy vs adult smoking (0=child, 1=adult)	0.01	-0.05	-0.13-0.03	2.27E-01					
	0.1	-0.03	-0.11-0.05	4.68E-01					
	0.2	-0.01	-0.10-0.07	7.61E-01					
	0.3	-0.02	-0.10-0.06	6.49E-01					
	0.4	-0.02	-0.10-0.06	6.36E-01					
	0.5	-0.02	-0.11-0.06	5.79E-01					
	1	-0.02	-0.11-0.06	5.98E-01					
MDD									
Family SES vs adult SES (0=child, 1=adult)	0.01	**Beta**	**95%CI**	**P-Value**	0.04	0.02-0.06	2.31E-06	0.16	6.90E-01
	0.1	0.04	0.02-0.05	**7.12E-06****	0.04	0.02-0.06	4.66E-06	1.29	2.56E-01
	0.2	0.03	0.02-0.05	**6.72E-05****	0.05	0.03-0.06	4.86E-07	2.43	1.19E-01
	0.3	0.04	0.02-0.05	**4.10E-06****	0.05	0.03-0.07	5.18E-08	3.1	7.81E-02
	0.4	0.04	0.02-0.05	**1.04E-06****	0.05	0.03-0.06	1.59E-07	2.73	9.86E-02
	0.5	0.04	0.02-0.05	**3.28E-06****	0.05	0.03-0.07	5.22E-08	2.69	1.01E-01
	1	0.04	0.02-0.05	**2.00E-06****	0.05	0.03-0.07	5.94E-08	3.06	8.01E-02
Father's employment vs adult employment (0=child, 1=adult)	0.01	0.04	0.02-0.05	**3.12E-06****					
	0.1	0.07	-0.06-0.20	2.76E-01					
	0.2	-0.18	-0.31--0.05	5.48E-03*					
	0.3	-0.17	-0.30--0.05	7.08E-03*					
	0.4	-0.16	-0.28--0.03	1.60E-02*					
	0.5	-0.17	-0.29--0.04	1.07E-02*					
	1	-0.16	-0.29--0.04	1.19E-02*					
Family number of rooms vs adult number of rooms (0=child, 1=adult)	0.01	-0.18	-0.31--0.05	6.29E-03*					
	0.1	0.02	-0.00-0.03	6.81E-02					
	0.2	0.01	-0.01-0.03	2.16E-01					
	0.3	0.01	-0.00-0.03	1.46E-01					
	0.4	0.02	-0.00-0.03	1.01E-01					
	0.5	0.01	-0.00-0.03	1.28E-01					
	1	0.01	-0.00-0.03	1.29E-01					
Family tenure vs adult tenure	0.01	0.01	-0.01-0.03	1.65E-01	-0.2	-0.28--0.11	3.76E-06	0.25	6.15E-01
	0.1	-0.14	-0.21--0.07	**1.11E-04****	-0.15	-0.24--0.07	3.22E-04	0.33	5.65E-01
	0.2	-0.07	-0.14-0.00	5.15E-02	-0.14	-0.22--0.05	1.18E-03	1.08	2.98E-01
	0.3	-0.06	-0.13-0.01	8.45E-02	-0.14	-0.22--0.05	1.29E-03	1.5	2.21E-01

(0=child, 1=adult)	0.4	-0.06	-0.13-0.01	1.08E-01	-0.12	-0.20--0.04	3.96E-03	1.28	2.58E-01
	0.5	-0.05	-0.12-0.02	1.43E-01	-0.13	-0.22--0.05	1.55E-03	1.08	2.98E-01
	1	-0.06	-0.13-0.01	1.14E-01	-0.13	-0.21--0.05	1.71E-03	1.43	2.31E-01
Parental marital status vs adult marital status (0=child, 1=adult)	0.01	-0.05	-0.12-0.02	1.48E-01					
	0.1	-0.06	-0.24-0.12	5.25E-01					
	0.2	0.01	-0.18-0.19	9.45E-01					
	0.3	0	-0.18-0.18	9.99E-01					
	0.4	-0.02	-0.21-0.16	7.94E-01					
	0.5	-0.05	-0.23-0.14	6.28E-01					
	1	-0.05	-0.24-0.13	5.62E-01					
Maternal smoking prior and during pregnancy vs adult smoking (0=child, 1=adult)	0.01	-0.04	-0.23-0.14	6.35E-01					
	0.1	0.05	-0.03-0.13	2.35E-01					
	0.2	0.04	-0.05-0.12	3.89E-01					
	0.3	0.06	-0.02-0.15	1.37E-01					
	0.4	0.07	-0.01-0.15	9.99E-02					
	0.5	0.05	-0.04-0.13	2.73E-01					
	1	0.04	-0.04-0.13	2.92E-01					

Note: All results were corrected for multiple testing using the Benjamini-Hochberg correction adjusted α=(rank of p-value/number of tests for each threshold) - *α [adjusted α=(rank/560)*0.05]. * = significant, ** = significant after multiple testing. Sensitivity analysis was performed for all statistically significant results after multiple testing only. Beta = beta coefficient, CI = Confidence Interval, All regressions were calculated using STATA v12.1 (1).

Appendix 22: *Benjamini-Hochberg Correction (Chapter 5)*

Environment	SCZ or MDD	Cohort	Threshold	Beta	CI	p-value	rank	adj alpha	sig?
SES child vs adult	MDD	NCDS	0.3	0.04	0.02-0.05	1.04E-06	1	8.93E-05	yes
Tenure Child	SCZ	MCS	0.01	-0.12	-0.17--0.07	1.61E-06	2	1.79E-04	yes
SES child vs adult	MDD	NCDS	0.5	0.04	0.02-0.05	2.00E-06	3	2.68E-04	yes
SES child vs adult	MDD	NCDS	1	0.04	0.02-0.05	3.12E-06	4	3.57E-04	yes
SES child vs adult	MDD	NCDS	0.4	0.04	0.02-0.05	3.28E-06	5	4.46E-04	yes
SES child vs adult	MDD	NCDS	0.2	0.04	0.02-0.05	4.10E-06	6	5.36E-04	yes
SES child vs adult	MDD	NCDS	0.01	0.04	0.02-0.05	7.12E-06	7	6.25E-04	yes
Tenure Child	SCZ	MCS	0.1	-0.11	-0.16--0.06	2.67E-05	8	7.14E-04	yes
SES Adult	MDD	USoc	0.1	-0.01	-0.02--0.01	4.27E-05	9	8.04E-04	yes
Tenure Child	SCZ	MCS	0.2	-0.1	-0.16--0.05	5.50E-05	10	8.93E-04	yes
SES child vs adult	MDD	NCDS	0.1	0.03	0.02-0.05	6.72E-05	11	9.82E-04	yes
Tenure Adult	MDD	USoc	0.01	0.16	0.08-0.23	6.77E-05	12	1.07E-03	yes
Tenure child vs adult	MDD	NCDS	0.01	-0.14	-0.21--0.07	1.11E-04	13	1.16E-03	yes
Tenure Adult	MDD	USoc	0.5	0.14	0.07-0.22	1.20E-04	14	1.25E-03	yes
Tenure Adult	MDD	USoc	0.2	0.14	0.07-0.21	1.20E-04	15	1.34E-03	yes
Tenure Child	SCZ	MCS	0.3	-0.1	-0.15--0.05	1.29E-04	16	1.43E-03	yes
Tenure Adult	MDD	USoc	0.4	0.14	0.07-0.21	1.38E-04	17	1.52E-03	yes
Tenure Adult	MDD	USoc	1	0.14	0.07-0.21	1.63E-04	18	1.61E-03	yes
Tenure Adult	MDD	USoc	0.3	0.14	0.07-0.21	1.79E-04	19	1.70E-03	yes
Tenure Child	SCZ	MCS	0.4	-0.09	-0.15--0.04	2.34E-04	20	1.79E-03	yes
Tenure Child	SCZ	MCS	0.5	-0.09	-0.14--0.04	2.83E-04	21	1.88E-03	yes
Tenure Adult	MDD	USoc	0.1	0.13	0.06-0.20	3.70E-04	22	1.96E-03	yes
Tenure Child	SCZ	MCS	1	-0.09	-0.14--0.04	3.95E-04	23	2.05E-03	yes
SES Adult	MDD	USoc	0.2	-0.01	-0.02--0.00	4.28E-04	24	2.14E-03	yes
Number of Rooms Adult	SCZ	USoc	0.01	0.01	0.00-0.01	5.21E-04	25	2.23E-03	yes
SES Adult	MDD	USoc	0.4	-0.01	-0.01--0.00	6.05E-04	26	2.32E-03	yes
SES Adult	MDD	USoc	0.3	-0.01	-0.01--0.00	9.37E-04	27	2.41E-03	yes
SES Adult	MDD	USoc	1	-0.01	-0.01--0.00	1.10E-03	28	2.50E-03	yes
SES child vs adult	SCZ	NCDS	0.4	0.03	0.01-0.04	1.11E-03	29	2.59E-03	yes
SES Adult	MDD	USoc	0.5	-0.01	-0.01--0.00	1.25E-03	30	2.68E-03	yes
SES child vs adult	SCZ	NCDS	1	0.02	0.01-0.04	1.75E-03	31	2.77E-03	yes
SES child vs adult	SCZ	NCDS	0.5	0.02	0.01-0.04	1.96E-03	32	2.86E-03	yes
SES child vs adult	SCZ	NCDS	0.3	0.02	0.01-0.04	2.27E-03	33	2.95E-03	yes
Marital status Adult	MDD	NCDS	0.1	0.05	0.02-0.09	4.71E-03	34	3.04E-03	no

SES child vs adult	SCZ	NCDS	0.2	0.02	0.01-0.04	4.97E-03	35	3.13E-03	no
Employment father vs adult	MDD	NCDS	0.1	-0.18	-0.31--0.05	5.48E-03	36	3.21E-03	no
Employment father vs adult	MDD	NCDS	1	-0.18	-0.31--0.05	6.29E-03	37	3.30E-03	no
Employment father vs adult	MDD	NCDS	0.2	-0.17	-0.30--0.05	7.08E-03	38	3.39E-03	no
Employment father vs adult	MDD	NCDS	0.4	-0.17	-0.29--0.04	1.07E-02	39	3.48E-03	no
Number of Rooms Adult	MDD	USoc	0.1	0	-0.01--0.00	1.10E-02	40	3.57E-03	no
Number of Rooms Adult	SCZ	USoc	0.1	0	0.00-0.01	1.14E-02	41	3.66E-03	no
Employment father vs adult	MDD	NCDS	0.5	-0.16	-0.29--0.04	1.19E-02	42	3.75E-03	no
Number of Rooms Adult	SCZ	USoc	0.2	0	0.00-0.01	1.33E-02	43	3.84E-03	no
Employment father vs adult	MDD	NCDS	0.3	-0.16	-0.28--0.03	1.60E-02	44	3.93E-03	no
SES child vs adult	SCZ	NCDS	0.1	0.02	0.00-0.03	1.88E-02	45	4.02E-03	no
SES Child	SCZ	MCS	0.2	0.01	0.00-0.01	2.17E-02	46	4.11E-03	no
Marital status Adult	MDD	NCDS	0.4	0.04	0.01-0.08	2.19E-02	47	4.20E-03	no
Marital status Adult	SCZ	NCDS	0.01	0.04	0.01-0.08	2.20E-02	48	4.29E-03	no
Marital status Adult	MDD	NCDS	0.2	0.04	0.01-0.08	2.28E-02	49	4.38E-03	no
SES Child	MDD	MCS	0.1	0.01	0.00-0.01	2.61E-02	50	4.46E-03	no
SES Child	SCZ	MCS	0.1	0.01	0.00-0.01	2.61E-02	51	4.55E-03	no
SES Adult	SCZ	NCDS	0.1	0.01	0.00-0.02	2.94E-02	52	4.64E-03	no
SES Child	SCZ	MCS	0.3	0.01	0.00-0.01	3.18E-02	53	4.73E-03	no
SES Child	SCZ	MCS	0.4	0.01	0.00-0.01	3.29E-02	54	4.82E-03	no
SES Child	SCZ	MCS	1	0.01	0.00-0.01	3.32E-02	55	4.91E-03	no
SES Child	SCZ	MCS	0.5	0.01	0.00-0.01	3.40E-02	56	5.00E-03	no
Number of Rooms Adult	SCZ	USoc	0.3	0	0.00-0.01	3.51E-02	57	5.09E-03	no
Number of Rooms Adult	MDD	USoc	0.01	0	-0.01--0.00	3.54E-02	58	5.18E-03	no
SES Child	SCZ	MCS	0.01	0.01	0.00-0.01	3.59E-02	59	5.27E-03	no
Marital status Adult	MDD	NCDS	0.3	0.04	0.00-0.07	3.60E-02	60	5.36E-03	no
Marital status Adult	MDD	NCDS	0.5	0.04	0.00-0.07	3.67E-02	61	5.45E-03	no
SES Child	MDD	MCS	1	0.01	0.00-0.01	3.84E-02	62	5.54E-03	no
Number of Rooms Child	SCZ	NCDS	1	0.01	0.00-0.02	3.93E-02	63	5.63E-03	no
Tenure Adult	SCZ	NCDS	1	-0.06	-0.12--0.00	3.97E-02	64	5.71E-03	no
Number of Rooms Adult	MDD	USoc	0.4	0	-0.01--0.00	3.98E-02	65	5.80E-03	no
Tenure Adult	SCZ	NCDS	0.5	-0.06	-0.12--0.00	4.01E-02	66	5.89E-03	no
SES Child	MDD	MCS	0.5	0.01	0.00-0.01	4.09E-02	67	5.98E-03	no
Marital status Adult	MDD	NCDS	1	0.04	0.00-0.07	4.30E-02	68	6.07E-03	no
Number of Rooms Adult	SCZ	USoc	0.5	0	0.00-0.01	4.32E-02	69	6.16E-03	no
Tenure Adult	SCZ	NCDS	0.1	-0.06	-0.12--0.00	4.39E-02	70	6.25E-03	no
Number of Rooms Adult	SCZ	USoc	0.4	0	0.00-0.01	4.60E-02	71	6.34E-03	no
Tenure Adult	SCZ	NCDS	0.3	-0.06	-0.12--0.00	4.68E-02	72	6.43E-03	no
SES Adult	SCZ	NCDS	0.01	0.01	0.00-0.02	4.69E-02	73	6.52E-03	no

Tenure Adult	SCZ	NCDS	0.4	-0.06	-0.11--0.00	4.85E-02	74	6.61E-03	no
SES Child	MDD	MCS	0.3	0.01	0.00-0.01	4.95E-02	75	6.70E-03	no
Tenure child vs adult	MDD	NCDS	0.1	-0.07	-0.14-0.00	5.15E-02	76	6.79E-03	no
SES Child	MDD	MCS	0.2	0.01	-0.00-0.01	5.25E-02	77	6.88E-03	no
Number of Rooms Adult	MDD	USoc	0.5	0	-0.01-0.00	5.28E-02	78	6.96E-03	no
SES Child	MDD	MCS	0.4	0.01	-0.00-0.01	5.30E-02	79	7.05E-03	no
Number of Rooms Child	SCZ	NCDS	0.3	0.01	-0.00-0.02	5.41E-02	80	7.14E-03	no
Number of Rooms Adult	MDD	USoc	1	0	-0.01-0.00	5.52E-02	81	7.23E-03	no
Number of Rooms Child	SCZ	NCDS	0.2	0.01	-0.00-0.02	5.65E-02	82	7.32E-03	no
Tenure Adult	SCZ	NCDS	0.2	-0.06	-0.11-0.00	5.65E-02	83	7.41E-03	no
Number of Rooms Adult	MDD	USoc	0.3	0	-0.01-0.00	5.92E-02	84	7.50E-03	no
SES Adult	SCZ	NCDS	0.3	0.01	-0.00-0.02	6.01E-02	85	7.59E-03	no
Number of Rooms Adult	MDD	USoc	0.2	0	-0.01-0.00	6.01E-02	86	7.68E-03	no
Number of Rooms Child	SCZ	MCS	0.01	-0.01	-0.02-0.00	6.06E-02	87	7.77E-03	no
SES Adult	MDD	USoc	0.01	-0.01	-0.01-0.00	6.60E-02	88	7.86E-03	no
Number of Rooms child vs adult	MDD	NCDS	0.01	0.02	-0.00-0.03	6.81E-02	89	7.95E-03	no
SES Adult	SCZ	NCDS	0.2	0.01	-0.00-0.02	6.87E-02	90	8.04E-03	no
Number of Rooms Child	SCZ	NCDS	0.1	0.01	-0.00-0.02	6.89E-02	91	8.13E-03	no
Tenure Adult	SCZ	USoc	0.01	0.06	-0.01-0.14	7.29E-02	92	8.21E-03	no
Number of Rooms Child	SCZ	NCDS	0.4	0.01	-0.00-0.02	7.34E-02	93	8.30E-03	no
Number of Rooms Adult	SCZ	USoc	1	0	-0.00-0.01	7.46E-02	94	8.39E-03	no
Number of Rooms Child	SCZ	NCDS	0.5	0.01	-0.00-0.02	7.55E-02	95	8.48E-03	no
Smoking Adult	MDD	NCDS	0.01	0.07	-0.01-0.14	7.59E-02	96	8.57E-03	no
Father Reads to Child	SCZ	MCS	0.01	-0.09	-0.19-0.01	8.25E-02	97	8.66E-03	no
Tenure child vs adult	MDD	NCDS	0.2	-0.06	-0.13-0.01	8.45E-02	98	8.75E-03	no
SES Adult	SCZ	NCDS	0.5	0.01	-0.00-0.02	8.55E-02	99	8.84E-03	no
SES Adult	SCZ	NCDS	1	0.01	-0.00-0.02	8.67E-02	100	8.93E-03	no
Tenure Adult	SCZ	USoc	0.1	0.06	-0.01-0.13	9.10E-02	101	9.02E-03	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.3	0.07	-0.01-0.15	9.99E-02	102	9.11E-03	no
Number of Rooms child vs adult	MDD	NCDS	0.3	0.02	-0.00-0.03	1.01E-01	103	9.20E-03	no
SES Adult	SCZ	NCDS	0.4	0.01	-0.00-0.02	1.04E-01	104	9.29E-03	no
Father's interest in child's education	SCZ	NCDS	0.1	0.06	-0.01-0.13	1.06E-01	105	9.38E-03	no
Tenure child vs adult	MDD	NCDS	0.3	-0.06	-0.13-0.01	1.08E-01	106	9.46E-03	no
Tenure child vs adult	SCZ	NCDS	0.5	-0.06	-0.13-0.01	1.09E-01	107	9.55E-03	no
Number of Rooms child vs adult	SCZ	NCDS	0.01	-0.01	-0.03-0.00	1.10E-01	108	9.64E-03	no
Father's interest in child's education	SCZ	NCDS	0.01	0.06	-0.01-0.13	1.13E-01	109	9.73E-03	no
Tenure child vs adult	MDD	NCDS	0.5	-0.06	-0.13-0.01	1.14E-01	110	9.82E-03	no
Number of Rooms Adult	SCZ	NCDS	0.3	-0.01	-0.02-0.00	1.20E-01	111	9.91E-03	no
Employment Adult	SCZ	NCDS	0.3	0.08	-0.02-0.18	1.22E-01	112	1.00E-02	no

Employment Adult	SCZ	NCDS	0.5	0.08	-0.02-0.18	1.23E-01	113	1.01E-02	no
Tenure child vs adult	SCZ	NCDS	0.3	-0.05	-0.12-0.02	1.25E-01	114	1.02E-02	no
Number of Rooms child vs adult	MDD	NCDS	0.4	0.01	-0.00-0.03	1.28E-01	115	1.03E-02	no
Smoking Adult	MDD	NCDS	1	0.06	-0.02-0.14	1.29E-01	116	1.04E-02	no
Number of Rooms child vs adult	MDD	NCDS	0.5	0.01	-0.00-0.03	1.29E-01	117	1.04E-02	no
Tenure child vs adult	SCZ	NCDS	0.4	-0.05	-0.12-0.02	1.30E-01	118	1.05E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.2	0.06	-0.02-0.15	1.37E-01	119	1.06E-02	no
Employment Adult	SCZ	NCDS	0.4	0.07	-0.02-0.17	1.39E-01	120	1.07E-02	no
Number of Rooms Adult	SCZ	NCDS	1	-0.01	-0.02-0.00	1.39E-01	121	1.08E-02	no
Tenure Child	MDD	NCDS	0.2	0.06	-0.02-0.14	1.41E-01	122	1.09E-02	no
Finance Issues Child	SCZ	NCDS	0.01	-0.06	-0.14-0.02	1.42E-01	123	1.10E-02	no
Tenure child vs adult	SCZ	NCDS	1	-0.05	-0.12-0.02	1.43E-01	124	1.11E-02	no
Tenure Adult	SCZ	USoc	0.3	0.05	-0.02-0.12	1.43E-01	125	1.12E-02	no
Tenure child vs adult	MDD	NCDS	0.4	-0.05	-0.12-0.02	1.43E-01	126	1.13E-02	no
Smoking Adult	MDD	NCDS	0.2	0.06	-0.02-0.13	1.45E-01	127	1.13E-02	no
Number of Rooms child vs adult	MDD	NCDS	0.2	0.01	-0.00-0.03	1.46E-01	128	1.14E-02	no
Smoking Adult	MDD	NCDS	0.3	0.06	-0.02-0.13	1.48E-01	129	1.15E-02	no
Tenure child vs adult	MDD	NCDS	1	-0.05	-0.12-0.02	1.48E-01	130	1.16E-02	no
Marital status parents vs adult	SCZ	NCDS	1	0.13	-0.05-0.31	1.49E-01	131	1.17E-02	no
Number of Rooms Child	SCZ	MCS	0.1	-0.01	-0.01-0.00	1.53E-01	132	1.18E-02	no
Tenure Adult	SCZ	USoc	1	0.05	-0.02-0.12	1.55E-01	133	1.19E-02	no
Smoking Adult	MDD	NCDS	0.5	0.06	-0.02-0.13	1.57E-01	134	1.20E-02	no
Employment Adult	MDD	NCDS	0.01	0.07	-0.03-0.17	1.57E-01	135	1.21E-02	no
Number of Rooms Adult	SCZ	NCDS	0.5	-0.01	-0.02-0.00	1.57E-01	136	1.21E-02	no
Number of Rooms Adult	SCZ	NCDS	0.2	-0.01	-0.02-0.00	1.62E-01	137	1.22E-02	no
Marital status Adult	MDD	NCDS	0.01	0.02	-0.01-0.06	1.62E-01	138	1.23E-02	no
Number of Rooms child vs adult	MDD	NCDS	1	0.01	-0.01-0.03	1.65E-01	139	1.24E-02	no
SES Child	MDD	MCS	0.01	0	-0.00-0.01	1.65E-01	140	1.25E-02	no
Tenure Adult	SCZ	USoc	0.2	0.05	-0.02-0.12	1.66E-01	141	1.26E-02	no
Smoking Adult	MDD	NCDS	0.4	0.05	-0.02-0.13	1.68E-01	142	1.27E-02	no
Finance Issues Child	SCZ	NCDS	0.1	-0.05	-0.13-0.02	1.71E-01	143	1.28E-02	no
Mother's interest in child's education	MDD	NCDS	0.3	0.04	-0.02-0.11	1.73E-01	144	1.29E-02	no
Marital status parents vs adult	SCZ	NCDS	0.5	0.12	-0.06-0.30	1.75E-01	145	1.29E-02	no
SES Child	MDD	NCDS	0.1	0.01	-0.00-0.02	1.76E-01	146	1.30E-02	no
Employment Adult	SCZ	NCDS	1	0.07	-0.03-0.17	1.80E-01	147	1.31E-02	no
Income Adult	MDD	USoc	0.3	0	-0.01-0.00	1.80E-01	148	1.32E-02	no
Number of Rooms Adult	SCZ	NCDS	0.4	-0.01	-0.02-0.00	1.84E-01	149	1.33E-02	no
Marital status parents vs adult	SCZ	NCDS	0.4	0.12	-0.06-0.30	1.84E-01	150	1.34E-02	no
Number of Rooms Child	MDD	NCDS	1	0.01	-0.00-0.02	1.87E-01	151	1.35E-02	no

Number of Rooms Child	MDD	NCDS	0.5	0.01	-0.00-0.02	1.89E-01	152	1.36E-02	no
Finance Issues Child	SCZ	NCDS	0.2	-0.05	-0.13-0.03	1.90E-01	153	1.37E-02	no
Employment Adult	SCZ	NCDS	0.2	0.07	-0.03-0.16	1.91E-01	154	1.38E-02	no
Number of Rooms Child	SCZ	MCS	0.2	-0.01	-0.01-0.00	1.93E-01	155	1.38E-02	no
Employment Adult	SCZ	NCDS	0.01	0.07	-0.04-0.17	2.01E-01	156	1.39E-02	no
Number of Rooms Adult	MDD	NCDS	0.1	-0.01	-0.02-0.00	2.02E-01	157	1.40E-02	no
Employment Adult	SCZ	NCDS	0.1	0.06	-0.03-0.16	2.03E-01	158	1.41E-02	no
Finance Issues Adult	MDD	USoc	0.4	-0.03	-0.07-0.02	2.03E-01	159	1.42E-02	no
Income Adult	MDD	USoc	0.2	0	-0.01-0.00	2.05E-01	160	1.43E-02	no
Tenure Adult	SCZ	USoc	0.4	0.05	-0.03-0.12	2.09E-01	161	1.44E-02	no
Finance Issues Adult	MDD	USoc	1	-0.03	-0.07-0.02	2.10E-01	162	1.45E-02	no
Tenure Child	MDD	MCS	0.01	-0.03	-0.08-0.02	2.12E-01	163	1.46E-02	no
Mother's interest in child's education	MDD	NCDS	1	0.04	-0.02-0.10	2.13E-01	164	1.46E-02	no
Father Reads to Child	SCZ	MCS	1	-0.08	-0.19-0.04	2.13E-01	165	1.47E-02	no
Mother's interest in child's education	MDD	NCDS	0.5	0.04	-0.02-0.10	2.14E-01	166	1.48E-02	no
Father Reads to Child	SCZ	MCS	0.5	-0.07	-0.19-0.04	2.15E-01	167	1.49E-02	no
Finance Issues Adult	MDD	USoc	0.5	-0.03	-0.07-0.02	2.15E-01	168	1.50E-02	no
Mother's interest in child's education	MDD	NCDS	0.4	0.04	-0.02-0.10	2.16E-01	169	1.51E-02	no
Number of Rooms child vs adult	MDD	NCDS	0.1	0.01	-0.01-0.03	2.16E-01	170	1.52E-02	no
Alcohol Father	MDD	MCS	1	-0.06	-0.16-0.04	2.17E-01	171	1.53E-02	no
Alcohol Father	MDD	MCS	0.3	-0.06	-0.16-0.04	2.19E-01	172	1.54E-02	no
Smoking Adult	MDD	NCDS	0.1	0.05	-0.03-0.12	2.25E-01	173	1.54E-02	no
Father Reads to Child	SCZ	MCS	0.3	-0.07	-0.19-0.04	2.26E-01	174	1.55E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.01	-0.05	-0.13-0.03	2.27E-01	175	1.56E-02	no
Finance Issues Child	SCZ	NCDS	0.3	-0.05	-0.13-0.03	2.28E-01	176	1.57E-02	no
Father's interest in child's education	SCZ	NCDS	0.3	0.04	-0.03-0.11	2.29E-01	177	1.58E-02	no
Tenure Adult	SCZ	USoc	0.5	0.04	-0.03-0.11	2.31E-01	178	1.59E-02	no
Finance Issues Child	SCZ	NCDS	0.4	-0.05	-0.13-0.03	2.32E-01	179	1.60E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.01	0.05	-0.03-0.13	2.35E-01	180	1.61E-02	no
Finance Issues Child	MDD	MCS	0.01	-0.03	-0.09-0.02	2.40E-01	181	1.62E-02	no
Number of Rooms Child	SCZ	NCDS	0.01	0.01	-0.00-0.02	2.42E-01	182	1.63E-02	no
Father Reads to Child	SCZ	MCS	0.4	-0.07	-0.19-0.05	2.42E-01	183	1.63E-02	no
Father's interest in child's education	SCZ	NCDS	0.2	0.04	-0.03-0.11	2.42E-01	184	1.64E-02	no
Marital status Parents	SCZ	MCS	0.01	0.02	-0.01-0.04	2.44E-01	185	1.65E-02	no
Marital status parents vs adult	SCZ	NCDS	0.3	0.11	-0.07-0.28	2.49E-01	186	1.66E-02	no
Marital status Adult	SCZ	NCDS	0.2	0.02	-0.01-0.06	2.50E-01	187	1.67E-02	no
SES Child	MDD	NCDS	0.3	0.01	-0.00-0.02	2.51E-01	188	1.68E-02	no
Marital status parents vs adult	SCZ	NCDS	0.1	0.1	-0.07-0.28	2.52E-01	189	1.69E-02	no
Number of Rooms child vs adult	SCZ	NCDS	0.3	-0.01	-0.03-0.01	2.52E-01	190	1.70E-02	no

Finance Issues Child	SCZ	NCDS	1	-0.05	-0.12-0.03	2.54E-01	191	1.71E-02	no
Number of Rooms Child	MDD	NCDS	0.2	0.01	-0.00-0.02	2.54E-01	192	1.71E-02	no
Finance Issues Child	SCZ	NCDS	0.5	-0.05	-0.12-0.03	2.55E-01	193	1.72E-02	no
SES Child	MDD	NCDS	1	0.01	-0.00-0.01	2.56E-01	194	1.73E-02	no
Finance Issues Child	MDD	MCS	0.5	-0.03	-0.08-0.02	2.60E-01	195	1.74E-02	no
Father's interest in child's education	SCZ	NCDS	0.4	0.04	-0.03-0.11	2.61E-01	196	1.75E-02	no
Number of Rooms Adult	SCZ	NCDS	0.01	-0.01	-0.02-0.00	2.62E-01	197	1.76E-02	no
Number of Rooms Child	MDD	NCDS	0.4	0.01	-0.00-0.02	2.62E-01	198	1.77E-02	no
Mother's interest in child's education	MDD	NCDS	0.2	0.04	-0.03-0.10	2.63E-01	199	1.78E-02	no
Alcohol Father	MDD	MCS	0.5	-0.06	-0.15-0.04	2.64E-01	200	1.79E-02	no
Tenure child vs adult	SCZ	NCDS	0.1	-0.04	-0.11-0.03	2.65E-01	201	1.79E-02	no
Finance Issues Child	MDD	MCS	0.4	-0.03	-0.08-0.02	2.65E-01	202	1.80E-02	no
SES Child	MDD	NCDS	0.4	0.01	-0.00-0.01	2.69E-01	203	1.81E-02	no
Mother reads to Child	MDD	MCS	0.1	-0.05	-0.14-0.04	2.70E-01	204	1.82E-02	no
Tenure Child	MDD	NCDS	0.4	0.05	-0.04-0.13	2.70E-01	205	1.83E-02	no
Number of Rooms Child	SCZ	MCS	0.3	0	-0.01-0.00	2.71E-01	206	1.84E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.4	0.05	-0.04-0.13	2.73E-01	207	1.85E-02	no
Tenure Child	MDD	NCDS	1	0.05	-0.04-0.13	2.73E-01	208	1.86E-02	no
Tenure child vs adult	SCZ	NCDS	0.2	-0.04	-0.11-0.03	2.74E-01	209	1.87E-02	no
SES Child	MDD	NCDS	0.01	0.01	-0.00-0.01	2.75E-01	210	1.88E-02	no
Employment father vs adult	MDD	NCDS	0.01	0.07	-0.06-0.20	2.76E-01	211	1.88E-02	no
Tenure Adult	MDD	NCDS	0.01	0.03	-0.03-0.09	2.79E-01	212	1.89E-02	no
SES Child	MDD	NCDS	0.2	0.01	-0.00-0.01	2.80E-01	213	1.90E-02	no
Income Adult	MDD	USoc	0.4	0	-0.01-0.00	2.81E-01	214	1.91E-02	no
Alcohol Father	MDD	MCS	0.4	-0.05	-0.15-0.04	2.81E-01	215	1.92E-02	no
Finance Issues Child	MDD	MCS	1	-0.03	-0.08-0.02	2.82E-01	216	1.93E-02	no
Father Reads to Child	SCZ	MCS	0.2	-0.06	-0.18-0.05	2.83E-01	217	1.94E-02	no
Father's interest in child's education	MDD	NCDS	0.3	0.04	-0.03-0.11	2.83E-01	218	1.95E-02	no
Father Reads to Child	SCZ	MCS	0.1	-0.06	-0.18-0.05	2.83E-01	219	1.96E-02	no
Finance Issues Child	MDD	MCS	0.2	-0.03	-0.08-0.02	2.84E-01	220	1.96E-02	no
Alcohol Mother	MDD	MCS	0.01	-0.02	-0.05-0.01	2.84E-01	221	1.97E-02	no
Alcohol Father	MDD	MCS	0.2	-0.05	-0.15-0.04	2.85E-01	222	1.98E-02	no
Number of Rooms Adult	MDD	NCDS	0.2	-0.01	-0.02-0.01	2.87E-01	223	1.99E-02	no
Father's interest in child's education	SCZ	NCDS	1	0.04	-0.03-0.11	2.87E-01	224	2.00E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.5	0.04	-0.04-0.13	2.92E-01	225	2.01E-02	no
Mother walks Child	SCZ	MCS	0.2	-0.04	-0.10-0.03	2.93E-01	226	2.02E-02	no
Number of Rooms Adult	MDD	NCDS	0.3	-0.01	-0.02-0.01	2.93E-01	227	2.03E-02	no
Father's interest in child's education	MDD	NCDS	0.2	0.04	-0.03-0.11	2.96E-01	228	2.04E-02	no
Mother walks Child	SCZ	MCS	0.3	-0.04	-0.10-0.03	2.97E-01	229	2.04E-02	no

Marital status parents vs adult	SCZ	NCDS	0.2	0.1	-0.08-0.27	2.97E-01	230	2.05E-02	no
Number of Rooms Child	SCZ	MCS	0.4	0	-0.01-0.00	2.98E-01	231	2.06E-02	no
Finance Issues Child	MDD	MCS	0.3	-0.03	-0.08-0.02	3.02E-01	232	2.07E-02	no
Tenure Child	MDD	NCDS	0.5	0.04	-0.04-0.12	3.03E-01	233	2.08E-02	no
Number of Rooms Child	MDD	NCDS	0.3	0.01	-0.01-0.02	3.07E-01	234	2.09E-02	no
Father's interest in child's education	MDD	NCDS	0.1	0.04	-0.03-0.11	3.07E-01	235	2.10E-02	no
Tenure Child	MDD	NCDS	0.3	0.04	-0.04-0.12	3.08E-01	236	2.11E-02	no
Father's involvement in childcare	MDD	NCDS	0.5	0.04	-0.04-0.13	3.10E-01	237	2.12E-02	no
Mother reads to Child	MDD	MCS	0.01	-0.05	-0.14-0.05	3.12E-01	238	2.13E-02	no
Father's interest in child's education	SCZ	NCDS	0.5	0.04	-0.03-0.11	3.12E-01	239	2.13E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	1	0.04	-0.04-0.13	3.14E-01	240	2.14E-02	no
Number of Rooms Child	SCZ	MCS	0.5	0	-0.01-0.00	3.17E-01	241	2.15E-02	no
Father walks Child	SCZ	MCS	0.2	-0.05	-0.16-0.05	3.19E-01	242	2.16E-02	no
Father walks Child	SCZ	MCS	0.3	-0.05	-0.16-0.05	3.21E-01	243	2.17E-02	no
SES Child	MDD	NCDS	0.5	0	-0.00-0.01	3.22E-01	244	2.18E-02	no
Father's involvement in childcare	MDD	NCDS	1	0.04	-0.04-0.13	3.22E-01	245	2.19E-02	no
Mother walks Child	SCZ	MCS	0.4	-0.03	-0.10-0.03	3.23E-01	246	2.20E-02	no
Mother walks Child	SCZ	MCS	0.01	-0.03	-0.10-0.03	3.23E-01	247	2.21E-02	no
Mother reads to Child	MDD	MCS	1	-0.05	-0.13-0.04	3.23E-01	248	2.21E-02	no
Number of Rooms child vs adult	SCZ	NCDS	0.4	-0.01	-0.03-0.01	3.24E-01	249	2.22E-02	no
Father walks Child	SCZ	MCS	0.1	-0.05	-0.15-0.05	3.27E-01	250	2.23E-02	no
Mother walks Child	SCZ	MCS	0.1	-0.03	-0.10-0.03	3.28E-01	251	2.24E-02	no
Mother walks Child	SCZ	MCS	1	-0.03	-0.10-0.03	3.29E-01	252	2.25E-02	no
Income Adult	MDD	USoc	0.01	0	-0.01-0.00	3.30E-01	253	2.26E-02	no
Father's interest in child's education	MDD	NCDS	0.4	0.03	-0.04-0.11	3.31E-01	254	2.27E-02	no
Father walks Child	SCZ	MCS	0.4	-0.05	-0.16-0.05	3.31E-01	255	2.28E-02	no
Marital status Adult	SCZ	NCDS	0.3	0.02	-0.02-0.05	3.32E-01	256	2.29E-02	no
Mother walks Child	SCZ	MCS	0.5	-0.03	-0.10-0.03	3.33E-01	257	2.29E-02	no
Income Adult	MDD	USoc	0.5	0	-0.01-0.00	3.34E-01	258	2.30E-02	no
Employment Adult	MDD	NCDS	0.4	0.05	-0.05-0.14	3.37E-01	259	2.31E-02	no
Number of Rooms child vs adult	SCZ	NCDS	0.5	-0.01	-0.03-0.01	3.42E-01	260	2.32E-02	no
Mother's interest in child's education	MDD	NCDS	0.1	0.03	-0.03-0.09	3.45E-01	261	2.33E-02	no
Marital status Adult	SCZ	NCDS	0.4	0.02	-0.02-0.05	3.45E-01	262	2.34E-02	no
Employment Adult	MDD	USoc	0.2	0.02	-0.03-0.07	3.45E-01	263	2.35E-02	no
Number of Rooms Child	SCZ	MCS	1	0	-0.01-0.00	3.50E-01	264	2.36E-02	no
Mother reads to Child	MDD	MCS	0.5	-0.04	-0.13-0.05	3.50E-01	265	2.37E-02	no
Tenure Child	SCZ	NCDS	0.3	0.04	-0.04-0.12	3.51E-01	266	2.38E-02	no
Father's interest in child's education	MDD	NCDS	1	0.03	-0.04-0.10	3.53E-01	267	2.38E-02	no
Father walks Child	SCZ	MCS	1	-0.05	-0.16-0.06	3.58E-01	268	2.39E-02	no

Father walks	SCZ	NCDS	0.01	-0.05	-0.15-0.05	3.59E-01	269	2.40E-02	no
Marital status Adult	SCZ	NCDS	0.1	0.02	-0.02-0.05	3.60E-01	270	2.41E-02	no
Number of Rooms Adult	SCZ	NCDS	0.1	-0.01	-0.02-0.01	3.61E-01	271	2.42E-02	no
SES Adult	SCZ	USoc	0.3	0	-0.00-0.01	3.62E-01	272	2.43E-02	no
SES Adult	MDD	NCDS	0.5	0	-0.01-0.01	3.63E-01	273	2.44E-02	no
Father walks Child	SCZ	MCS	0.01	-0.04	-0.14-0.05	3.66E-01	274	2.45E-02	no
Mother walks Child	MDD	MCS	0.01	0.03	-0.04-0.10	3.69E-01	275	2.46E-02	no
Father's involvement in childcare	MDD	NCDS	0.4	0.04	-0.05-0.12	3.69E-01	276	2.46E-02	no
Income Adult	SCZ	USoc	0.2	0	-0.00-0.01	3.70E-01	277	2.47E-02	no
Employment Adult	MDD	NCDS	0.3	0.04	-0.05-0.14	3.70E-01	278	2.48E-02	no
Father walks Child	SCZ	MCS	0.5	-0.05	-0.15-0.06	3.73E-01	279	2.49E-02	no
Marital status Adult	SCZ	NCDS	1	0.02	-0.02-0.05	3.73E-01	280	2.50E-02	no
Finance Issues Child	MDD	MCS	0.1	-0.02	-0.07-0.03	3.74E-01	281	2.51E-02	no
Father's involvement in childcare	MDD	NCDS	0.2	0.04	-0.05-0.12	3.75E-01	282	2.52E-02	no
Tenure Child	SCZ	NCDS	1	0.04	-0.05-0.12	3.75E-01	283	2.53E-02	no
Marital status Adult	SCZ	NCDS	0.5	0.02	-0.02-0.05	3.75E-01	284	2.54E-02	no
Father Reads to Child	MDD	MCS	0.5	0.06	-0.07-0.18	3.76E-01	285	2.54E-02	no
SES Adult	SCZ	USoc	0.4	0	-0.00-0.01	3.77E-01	286	2.55E-02	no
Employment Adult	MDD	NCDS	0.5	0.04	-0.05-0.14	3.78E-01	287	2.56E-02	no
Finance Issues Adult	MDD	USoc	0.3	-0.02	-0.06-0.02	3.78E-01	288	2.57E-02	no
Employment Adult	MDD	NCDS	0.1	0.04	-0.05-0.14	3.78E-01	289	2.58E-02	no
Father's interest in child's education	MDD	NCDS	0.5	0.03	-0.04-0.10	3.79E-01	290	2.59E-02	no
Father's involvement in childcare	MDD	NCDS	0.3	0.04	-0.05-0.12	3.84E-01	291	2.60E-02	no
Employment Adult	MDD	NCDS	0.2	0.04	-0.05-0.14	3.88E-01	292	2.61E-02	no
Income Adult	MDD	USoc	1	0	-0.01-0.00	3.88E-01	293	2.62E-02	no
Smoking mother prior & during pregnancy vs adult	MDD	NCDS	0.1	0.04	-0.05-0.12	3.89E-01	294	2.63E-02	no
SES Adult	SCZ	USoc	0.2	0	-0.00-0.01	3.90E-01	295	2.63E-02	no
Marital status Parents	SCZ	MCS	0.1	0.01	-0.01-0.04	3.91E-01	296	2.64E-02	no
Tenure Child	SCZ	NCDS	0.5	0.04	-0.05-0.12	3.93E-01	297	2.65E-02	no
Number of Rooms child vs adult	SCZ	NCDS	1	-0.01	-0.03-0.01	3.95E-01	298	2.66E-02	no
Father Reads to Child	MDD	MCS	0.4	0.05	-0.07-0.18	3.96E-01	299	2.67E-02	no
Employment Adult	MDD	USoc	0.3	0.02	-0.03-0.07	3.96E-01	300	2.68E-02	no
Employment Adult	SCZ	USoc	0.5	-0.02	-0.07-0.03	4.02E-01	301	2.69E-02	no
SES Adult	MDD	NCDS	0.4	0	-0.01-0.01	4.07E-01	302	2.70E-02	no
Mother walks	MDD	NCDS	0.01	0.07	-0.10-0.23	4.09E-01	303	2.71E-02	no
SES Adult	SCZ	USoc	1	0	-0.00-0.01	4.10E-01	304	2.71E-02	no
SES Adult	SCZ	USoc	0.5	0	-0.00-0.01	4.15E-01	305	2.72E-02	no
Father walks	SCZ	NCDS	0.4	0.04	-0.06-0.14	4.15E-01	306	2.73E-02	no
Father walks	SCZ	NCDS	0.2	0.04	-0.06-0.14	4.16E-01	307	2.74E-02	no

Tenure Child	MDD	NCDS	0.01	0.03	-0.05-0.12	4.16E-01	308	2.75E-02	no
Tenure Child	SCZ	NCDS	0.1	0.03	-0.05-0.12	4.17E-01	309	2.76E-02	no
Alcohol Father	MDD	MCS	0.1	-0.04	-0.13-0.05	4.17E-01	310	2.77E-02	no
Marital status Parents	SCZ	MCS	0.3	0.01	-0.02-0.04	4.21E-01	311	2.78E-02	no
Employment Adult	SCZ	USoc	1	-0.02	-0.07-0.03	4.21E-01	312	2.79E-02	no
Mother reads to Child	MDD	MCS	0.4	-0.04	-0.13-0.05	4.22E-01	313	2.79E-02	no
Mother reads to Child	SCZ	MCS	1	-0.04	-0.13-0.06	4.23E-01	314	2.80E-02	no
SES Adult	MDD	NCDS	0.3	0	-0.01-0.01	4.24E-01	315	2.81E-02	no
Mother reads to Child	MDD	MCS	0.3	-0.04	-0.13-0.05	4.24E-01	316	2.82E-02	no
Tenure Child	SCZ	NCDS	0.4	0.03	-0.05-0.12	4.27E-01	317	2.83E-02	no
Tenure Child	MDD	NCDS	0.1	0.03	-0.05-0.11	4.28E-01	318	2.84E-02	no
Marital status Parents	SCZ	MCS	1	0.01	-0.02-0.04	4.31E-01	319	2.85E-02	no
Marital status Parents	SCZ	MCS	0.5	0.01	-0.02-0.04	4.31E-01	320	2.86E-02	no
Father Reads to Child	MDD	MCS	0.3	0.05	-0.07-0.17	4.34E-01	321	2.87E-02	no
Mother reads to Child	SCZ	MCS	0.5	-0.04	-0.13-0.06	4.37E-01	322	2.88E-02	no
Tenure Adult	SCZ	NCDS	0.01	-0.02	-0.08-0.03	4.39E-01	323	2.88E-02	no
Marital status Parents	SCZ	MCS	0.4	0.01	-0.02-0.04	4.43E-01	324	2.89E-02	no
Employment father vs adult	SCZ	NCDS	0.01	0.05	-0.08-0.17	4.43E-01	325	2.90E-02	no
Finance Issues Adult	MDD	USoc	0.01	-0.02	-0.06-0.03	4.43E-01	326	2.91E-02	no
SES Adult	MDD	NCDS	1	0	-0.01-0.01	4.44E-01	327	2.92E-02	no
Marital status Parents	MDD	MCS	0.2	-0.01	-0.04-0.02	4.45E-01	328	2.93E-02	no
Father walks	MDD	NCDS	0.3	-0.04	-0.14-0.06	4.45E-01	329	2.94E-02	no
Father walks	SCZ	NCDS	0.3	0.04	-0.06-0.14	4.49E-01	330	2.95E-02	no
Mother reads to Child	MDD	MCS	0.2	-0.04	-0.13-0.06	4.49E-01	331	2.96E-02	no
Marital status Parents	SCZ	MCS	0.2	0.01	-0.02-0.04	4.50E-01	332	2.96E-02	no
Father walks	SCZ	NCDS	0.5	0.04	-0.06-0.14	4.51E-01	333	2.97E-02	no
Number of Rooms child vs adult	SCZ	NCDS	0.2	-0.01	-0.03-0.01	4.51E-01	334	2.98E-02	no
Father walks	MDD	NCDS	0.5	-0.04	-0.14-0.06	4.51E-01	335	2.99E-02	no
Mother's interest in child's education	MDD	NCDS	0.01	0.02	-0.04-0.09	4.52E-01	336	3.00E-02	no
Number of Rooms Adult	MDD	NCDS	0.4	0	-0.02-0.01	4.53E-01	337	3.01E-02	no
Tenure Child	SCZ	NCDS	0.2	0.03	-0.05-0.11	4.54E-01	338	3.02E-02	no
Mother reads to Child	SCZ	MCS	0.4	-0.04	-0.13-0.06	4.56E-01	339	3.03E-02	no
Employment Adult	SCZ	USoc	0.01	-0.02	-0.07-0.03	4.59E-01	340	3.04E-02	no
Employment Adult	MDD	NCDS	1	0.04	-0.06-0.13	4.67E-01	341	3.04E-02	no
Finance Issues Adult	SCZ	USoc	1	-0.02	-0.06-0.03	4.68E-01	342	3.05E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.1	-0.03	-0.11-0.05	4.68E-01	343	3.06E-02	no
Marital status Parents	MDD	MCS	0.4	-0.01	-0.04-0.02	4.69E-01	344	3.07E-02	no
Father Reads to Child	MDD	MCS	0.01	-0.04	-0.14-0.06	4.70E-01	345	3.08E-02	no
Income Adult	SCZ	USoc	0.1	0	-0.00-0.01	4.72E-01	346	3.09E-02	no

Father walks	SCZ	NCDS	1	0.04	-0.06-0.14	4.73E-01	347	3.10E-02	no
Mother reads to Child	SCZ	MCS	0.2	-0.03	-0.13-0.06	4.73E-01	348	3.11E-02	no
Employment Adult	MDD	USoc	1	0.02	-0.03-0.07	4.75E-01	349	3.12E-02	no
Father walks	SCZ	NCDS	0.1	0.04	-0.06-0.14	4.79E-01	350	3.13E-02	no
Marital status Parents	MDD	MCS	0.3	-0.01	-0.04-0.02	4.81E-01	351	3.13E-02	no
Alcohol Father	SCZ	MCS	0.01	0.03	-0.05-0.10	4.82E-01	352	3.14E-02	no
SES Child	SCZ	NCDS	0.1	0	-0.01-0.01	4.82E-01	353	3.15E-02	no
Father's involvement in childcare	MDD	NCDS	0.1	0.03	-0.05-0.11	4.86E-01	354	3.16E-02	no
Finance Issues Adult	SCZ	USoc	0.4	-0.02	-0.06-0.03	4.87E-01	355	3.17E-02	no
Finance Issues Adult	SCZ	USoc	0.1	-0.02	-0.06-0.03	4.92E-01	356	3.18E-02	no
Smoking Mother	SCZ	MCS	0.01	0.02	-0.03-0.06	4.94E-01	357	3.19E-02	no
Father walks	MDD	NCDS	0.4	-0.03	-0.13-0.07	4.95E-01	358	3.20E-02	no
Mother reads to Child	SCZ	MCS	0.3	-0.03	-0.13-0.06	4.96E-01	359	3.21E-02	no
Employment Adult	SCZ	USoc	0.1	-0.02	-0.07-0.03	5.01E-01	360	3.21E-02	no
Father Reads to Child	MDD	MCS	1	0.04	-0.08-0.16	5.01E-01	361	3.22E-02	no
Father walks	MDD	NCDS	1	-0.03	-0.13-0.07	5.11E-01	362	3.23E-02	no
Tenure Child	MDD	MCS	1	0.02	-0.03-0.06	5.14E-01	363	3.24E-02	no
Marital status parents vs adult	SCZ	NCDS	0.01	0.06	-0.12-0.24	5.19E-01	364	3.25E-02	no
SES Child	SCZ	NCDS	0.3	0	-0.01-0.01	5.19E-01	365	3.26E-02	no
Employment Adult	MDD	USoc	0.4	0.02	-0.03-0.06	5.22E-01	366	3.27E-02	no
Income Adult	SCZ	USoc	0.3	0	-0.00-0.01	5.24E-01	367	3.28E-02	no
Number of Rooms Child	MDD	NCDS	0.1	0	-0.01-0.01	5.24E-01	368	3.29E-02	no
Smoking Adult	SCZ	NCDS	0.1	0.02	-0.05-0.10	5.25E-01	369	3.29E-02	no
Marital status parents vs adult	MDD	NCDS	0.01	-0.06	-0.24-0.12	5.25E-01	370	3.30E-02	no
Marital status Parents	MDD	MCS	0.01	-0.01	-0.03-0.02	5.27E-01	371	3.31E-02	no
Employment Father Child	MDD	NCDS	0.1	0.04	-0.08-0.16	5.28E-01	372	3.32E-02	no
Alcohol Father	MDD	MCS	0.01	-0.02	-0.09-0.05	5.29E-01	373	3.33E-02	no
Employment Adult	SCZ	USoc	0.4	-0.02	-0.07-0.03	5.30E-01	374	3.34E-02	no
Employment Adult	MDD	USoc	0.5	0.02	-0.03-0.06	5.31E-01	375	3.35E-02	no
Number of Rooms Adult	MDD	NCDS	0.5	0	-0.01-0.01	5.32E-01	376	3.36E-02	no
SES Child	SCZ	NCDS	1	0	-0.01-0.01	5.32E-01	377	3.37E-02	no
SES Adult	MDD	NCDS	0.2	0	-0.01-0.01	5.33E-01	378	3.38E-02	no
Smoking Adult	SCZ	NCDS	0.3	0.02	-0.05-0.10	5.40E-01	379	3.38E-02	no
Mother reads to Child	SCZ	MCS	0.1	-0.03	-0.13-0.07	5.41E-01	380	3.39E-02	no
Father Reads to Child	MDD	MCS	0.2	0.04	-0.08-0.16	5.42E-01	381	3.40E-02	no
Alcohol Mother	MDD	MCS	0.2	-0.01	-0.06-0.03	5.43E-01	382	3.41E-02	no
Marital status Parents	MDD	MCS	0.5	-0.01	-0.04-0.02	5.46E-01	383	3.42E-02	no
Finance Issues Adult	SCZ	USoc	0.2	-0.01	-0.06-0.03	5.46E-01	384	3.43E-02	no
Father's involvement in childcare	SCZ	NCDS	0.2	-0.03	-0.11-0.06	5.50E-01	385	3.44E-02	no

Alcohol Father	SCZ	MCS	0.4	-0.03	-0.11-0.06	5.53E-01	386	3.45E-02	no
Number of Rooms Adult	MDD	NCDS	1	0	-0.01-0.01	5.55E-01	387	3.46E-02	no
Tenure Child	MDD	MCS	0.1	-0.01	-0.06-0.03	5.60E-01	388	3.46E-02	no
Marital status parents vs adult	MDD	NCDS	0.5	-0.05	-0.24-0.13	5.62E-01	389	3.47E-02	no
Finance Issues Adult	SCZ	USoc	0.5	-0.01	-0.06-0.03	5.63E-01	390	3.48E-02	no
Tenure Adult	MDD	NCDS	1	-0.02	-0.07-0.04	5.67E-01	391	3.49E-02	no
Income Adult	SCZ	USoc	1	0	-0.00-0.01	5.71E-01	392	3.50E-02	no
Finance Issues Adult	MDD	USoc	0.2	-0.01	-0.06-0.03	5.77E-01	393	3.51E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.5	-0.02	-0.11-0.06	5.79E-01	394	3.52E-02	no
SES Child	SCZ	NCDS	0.5	0	-0.01-0.01	5.82E-01	395	3.53E-02	no
Tenure Child	MDD	MCS	0.5	0.01	-0.03-0.06	5.90E-01	396	3.54E-02	no
Alcohol Mother	MDD	MCS	0.1	-0.01	-0.05-0.03	5.94E-01	397	3.54E-02	no
SES Child	SCZ	NCDS	0.4	0	-0.01-0.01	5.98E-01	398	3.55E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	1	-0.02	-0.11-0.06	5.98E-01	399	3.56E-02	no
Employment father vs adult	SCZ	NCDS	0.2	-0.03	-0.16-0.09	6.00E-01	400	3.57E-02	no
Finance Issues Adult	SCZ	USoc	0.3	-0.01	-0.06-0.03	6.04E-01	401	3.58E-02	no
Alcohol Father	SCZ	MCS	0.5	-0.02	-0.11-0.06	6.07E-01	402	3.59E-02	no
Marital status Parents	MDD	MCS	0.1	-0.01	-0.03-0.02	6.08E-01	403	3.60E-02	no
Alcohol Father	SCZ	MCS	1	-0.02	-0.11-0.07	6.12E-01	404	3.61E-02	no
Mother's interest in child's education	SCZ	NCDS	0.1	0.02	-0.05-0.08	6.12E-01	405	3.62E-02	no
Tenure Adult	MDD	NCDS	0.2	-0.01	-0.07-0.04	6.12E-01	406	3.63E-02	no
Father walks	MDD	NCDS	0.1	-0.03	-0.13-0.07	6.16E-01	407	3.63E-02	no
Marital status Parents	MDD	MCS	1	-0.01	-0.03-0.02	6.18E-01	408	3.64E-02	no
Alcohol Mother	MDD	MCS	0.5	-0.01	-0.05-0.03	6.19E-01	409	3.65E-02	no
Alcohol Father	SCZ	MCS	0.3	-0.02	-0.11-0.07	6.19E-01	410	3.66E-02	no
Father's involvement in childcare	SCZ	NCDS	0.3	-0.02	-0.11-0.06	6.20E-01	411	3.67E-02	no
Income Adult	MDD	USoc	0.1	0	-0.01-0.00	6.21E-01	412	3.68E-02	no
Tenure Child	MDD	MCS	0.4	0.01	-0.03-0.06	6.21E-01	413	3.69E-02	no
Alcohol Mother	MDD	MCS	0.4	-0.01	-0.05-0.03	6.21E-01	414	3.70E-02	no
Income Adult	SCZ	USoc	0.4	0	-0.00-0.01	6.22E-01	415	3.71E-02	no
SES Adult	MDD	NCDS	0.01	0	-0.01-0.01	6.27E-01	416	3.71E-02	no
Marital status parents vs adult	MDD	NCDS	0.4	-0.05	-0.23-0.14	6.28E-01	417	3.72E-02	no
Tenure Adult	MDD	NCDS	0.3	-0.01	-0.07-0.04	6.29E-01	418	3.73E-02	no
Father's interest in child's education	MDD	NCDS	0.01	0.02	-0.05-0.09	6.32E-01	419	3.74E-02	no
Smoking Mother	MDD	MCS	0.01	0.01	-0.03-0.05	6.32E-01	420	3.75E-02	no
Mother walks	MDD	NCDS	0.4	-0.04	-0.21-0.13	6.33E-01	421	3.76E-02	no
Alcohol Mother	MDD	MCS	1	-0.01	-0.05-0.03	6.33E-01	422	3.77E-02	no
Smoking Adult	SCZ	NCDS	0.4	0.02	-0.06-0.09	6.33E-01	423	3.78E-02	no
Marital status parents vs adult	MDD	NCDS	1	-0.04	-0.23-0.14	6.35E-01	424	3.79E-02	no

Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.4	-0.02	-0.10-0.06	6.36E-01	425	3.79E-02	no
Alcohol Mother	MDD	MCS	0.3	-0.01	-0.05-0.03	6.36E-01	426	3.80E-02	no
Father Reads to Child	MDD	MCS	0.1	0.03	-0.09-0.15	6.39E-01	427	3.81E-02	no
Tenure Adult	MDD	NCDS	0.5	-0.01	-0.07-0.04	6.39E-01	428	3.82E-02	no
SES Child	SCZ	NCDS	0.01	0	-0.01-0.01	6.42E-01	429	3.83E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.3	-0.02	-0.10-0.06	6.49E-01	430	3.84E-02	no
Income Adult	SCZ	USoc	0.5	0	-0.00-0.01	6.55E-01	431	3.85E-02	no
Tenure Child	MDD	MCS	0.3	0.01	-0.04-0.06	6.58E-01	432	3.86E-02	no
SES Child	SCZ	NCDS	0.2	0	-0.01-0.01	6.62E-01	433	3.87E-02	no
Mother walks	MDD	NCDS	0.5	-0.04	-0.20-0.13	6.63E-01	434	3.88E-02	no
SES Adult	SCZ	USoc	0.01	0	-0.00-0.01	6.63E-01	435	3.88E-02	no
Employment Father Child	MDD	NCDS	0.01	0.03	-0.12-0.19	6.64E-01	436	3.89E-02	no
Number of Rooms Child	MDD	MCS	1	0	-0.01-0.01	6.65E-01	437	3.90E-02	no
Tenure Child	MDD	MCS	0.2	0.01	-0.04-0.06	6.70E-01	438	3.91E-02	no
Mother's interest in child's education	SCZ	NCDS	0.4	0.01	-0.05-0.08	6.72E-01	439	3.92E-02	no
Finance Issues Adult	SCZ	USoc	0.01	0.01	-0.04-0.05	6.76E-01	440	3.93E-02	no
Father's involvement in childcare	SCZ	NCDS	0.1	-0.02	-0.10-0.07	6.78E-01	441	3.94E-02	no
Tenure Adult	MDD	NCDS	0.4	-0.01	-0.07-0.04	6.79E-01	442	3.95E-02	no
Employment Father Child	SCZ	NCDS	0.5	0.03	-0.12-0.18	6.82E-01	443	3.96E-02	no
Employment Adult	MDD	USoc	0.1	0.01	-0.04-0.06	6.84E-01	444	3.96E-02	no
Smoking Mother	SCZ	MCS	0.4	0.01	-0.04-0.06	6.86E-01	445	3.97E-02	no
Employment Adult	SCZ	USoc	0.2	-0.01	-0.06-0.04	6.87E-01	446	3.98E-02	no
Mother walks	MDD	NCDS	0.3	-0.03	-0.20-0.13	6.93E-01	447	3.99E-02	no
Smoking Mother	SCZ	MCS	0.3	0.01	-0.04-0.05	6.97E-01	448	4.00E-02	no
Employment Father Child	SCZ	NCDS	0.3	0.03	-0.12-0.18	7.05E-01	449	4.01E-02	no
Mother's interest in child's education	SCZ	NCDS	0.3	0.01	-0.05-0.08	7.06E-01	450	4.02E-02	no
Smoking Adult	SCZ	NCDS	0.5	0.01	-0.06-0.09	7.07E-01	451	4.03E-02	no
Finance Issues Child	MDD	NCDS	0.1	-0.01	-0.09-0.06	7.07E-01	452	4.04E-02	no
Employment father vs adult	SCZ	NCDS	0.3	-0.02	-0.15-0.10	7.08E-01	453	4.04E-02	no
Smoking Mother	SCZ	MCS	0.2	0.01	-0.04-0.05	7.09E-01	454	4.05E-02	no
Employment Father Child	SCZ	NCDS	0.4	0.03	-0.12-0.18	7.12E-01	455	4.06E-02	no
Father walks	MDD	NCDS	0.2	-0.02	-0.12-0.08	7.14E-01	456	4.07E-02	no
Smoking Mother	SCZ	MCS	0.5	0.01	-0.04-0.05	7.14E-01	457	4.08E-02	no
Mother reads to Child	SCZ	MCS	0.01	-0.02	-0.11-0.08	7.15E-01	458	4.09E-02	no
Smoking Adult	SCZ	NCDS	1	0.01	-0.06-0.09	7.16E-01	459	4.10E-02	no
Mother walks	MDD	NCDS	1	-0.03	-0.20-0.14	7.17E-01	460	4.11E-02	no
Smoking Adult	SCZ	NCDS	0.2	0.01	-0.06-0.09	7.19E-01	461	4.12E-02	no
Alcohol Mother	SCZ	MCS	1	-0.01	-0.04-0.03	7.23E-01	462	4.13E-02	no
Employment father vs adult	SCZ	NCDS	0.1	-0.02	-0.15-0.10	7.24E-01	463	4.13E-02	no

Father walks Child	MDD	MCS	0.01	0.02	-0.08-0.11	7.29E-01	464	4.14E-02	no
Employment Father Child	SCZ	NCDS	1	0.03	-0.13-0.18	7.30E-01	465	4.15E-02	no
Mother walks Child	MDD	MCS	0.3	0.01	-0.06-0.08	7.33E-01	466	4.16E-02	no
Smoking Mother	SCZ	MCS	1	0.01	-0.04-0.05	7.36E-01	467	4.17E-02	no
Employment Adult	SCZ	USoc	0.3	-0.01	-0.06-0.04	7.46E-01	468	4.18E-02	no
Employment Father Child	MDD	NCDS	0.5	-0.03	-0.18-0.13	7.47E-01	469	4.19E-02	no
Employment father vs adult	SCZ	NCDS	1	-0.02	-0.15-0.11	7.48E-01	470	4.20E-02	no
Employment Father Child	MDD	NCDS	0.4	-0.03	-0.18-0.13	7.53E-01	471	4.21E-02	no
Smoking Mother	MDD	MCS	0.1	0.01	-0.04-0.05	7.55E-01	472	4.21E-02	no
Smoking Mother	MDD	MCS	0.5	0.01	-0.04-0.05	7.55E-01	473	4.22E-02	no
Number of Rooms Child	MDD	MCS	0.5	0	-0.01-0.01	7.58E-01	474	4.23E-02	no
Finance Issues Child	SCZ	MCS	0.1	-0.01	-0.06-0.04	7.61E-01	475	4.24E-02	no
Smoking mother prior & during pregnancy vs adult	SCZ	NCDS	0.2	-0.01	-0.10-0.07	7.61E-01	476	4.25E-02	no
Income Adult	SCZ	USoc	0.01	0	-0.00-0.01	7.64E-01	477	4.26E-02	no
Alcohol Father	SCZ	MCS	0.2	-0.01	-0.10-0.07	7.66E-01	478	4.27E-02	no
Finance Issues Child	MDD	NCDS	0.2	0.01	-0.07-0.09	7.67E-01	479	4.28E-02	no
Employment Father Child	SCZ	NCDS	0.1	-0.02	-0.17-0.13	7.69E-01	480	4.29E-02	no
Mother walks	SCZ	NCDS	0.01	0.02	-0.14-0.19	7.71E-01	481	4.29E-02	no
Alcohol Mother	SCZ	MCS	0.5	-0.01	-0.04-0.03	7.72E-01	482	4.30E-02	no
Employment Father Child	SCZ	NCDS	0.01	0.02	-0.13-0.17	7.74E-01	483	4.31E-02	no
Alcohol Mother	SCZ	MCS	0.4	-0.01	-0.04-0.03	7.75E-01	484	4.32E-02	no
Father's involvement in childcare	MDD	NCDS	0.01	-0.01	-0.10-0.07	7.75E-01	485	4.33E-02	no
Number of Rooms Child	MDD	MCS	0.4	0	-0.01-0.01	7.78E-01	486	4.34E-02	no
Finance Issues Adult	MDD	USoc	0.1	-0.01	-0.05-0.04	7.80E-01	487	4.35E-02	no
Finance Issues Child	SCZ	MCS	0.5	-0.01	-0.06-0.04	7.81E-01	488	4.36E-02	no
Smoking Mother	MDD	MCS	0.4	0.01	-0.04-0.05	7.86E-01	489	4.37E-02	no
Employment Adult	MDD	USoc	0.01	0.01	-0.04-0.06	7.88E-01	490	4.38E-02	no
Employment father vs adult	SCZ	NCDS	0.5	-0.02	-0.14-0.11	7.90E-01	491	4.38E-02	no
Smoking Mother	MDD	MCS	1	0.01	-0.04-0.05	7.90E-01	492	4.39E-02	no
Smoking Mother	MDD	MCS	0.3	0.01	-0.04-0.05	7.94E-01	493	4.40E-02	no
Marital status parents vs adult	MDD	NCDS	0.3	-0.02	-0.21-0.16	7.94E-01	494	4.41E-02	no
Smoking Mother	MDD	MCS	0.2	0.01	-0.04-0.05	7.95E-01	495	4.42E-02	no
Finance Issues Child	SCZ	MCS	1	-0.01	-0.06-0.04	7.96E-01	496	4.43E-02	no
Number of Rooms Adult	MDD	NCDS	0.01	0	-0.01-0.01	7.99E-01	497	4.44E-02	no
Father's involvement in childcare	SCZ	NCDS	0.4	-0.01	-0.09-0.07	8.01E-01	498	4.45E-02	no
Mother walks Child	MDD	MCS	0.2	0.01	-0.06-0.08	8.02E-01	499	4.46E-02	no
Smoking Mother	SCZ	MCS	0.1	0.01	-0.04-0.05	8.04E-01	500	4.46E-02	no
Alcohol Mother	SCZ	MCS	0.3	0	-0.04-0.03	8.05E-01	501	4.47E-02	no
Finance Issues Child	SCZ	MCS	0.4	-0.01	-0.06-0.04	8.05E-01	502	4.48E-02	no

Employment Father Child	MDD	NCDS	0.2	-0.02	-0.18-0.14	8.07E-01	503	4.49E-02	no
Tenure Child	SCZ	NCDS	0.01	0.01	-0.07-0.09	8.07E-01	504	4.50E-02	no
Employment father vs adult	SCZ	NCDS	0.4	-0.02	-0.14-0.11	8.09E-01	505	4.51E-02	no
Alcohol Mother	SCZ	MCS	0.01	0	-0.04-0.03	8.12E-01	506	4.52E-02	no
Mother's interest in child's education	SCZ	NCDS	0.5	0.01	-0.06-0.07	8.17E-01	507	4.53E-02	no
Mother's interest in child's education	SCZ	NCDS	0.2	0.01	-0.06-0.07	8.19E-01	508	4.54E-02	no
SES Adult	SCZ	USoc	0.1	0	-0.00-0.01	8.22E-01	509	4.54E-02	no
Mother walks Child	MDD	MCS	0.1	0.01	-0.06-0.08	8.23E-01	510	4.55E-02	no
Alcohol Mother	SCZ	MCS	0.2	0	-0.04-0.03	8.23E-01	511	4.56E-02	no
Number of Rooms Child	MDD	MCS	0.3	0	-0.01-0.01	8.25E-01	512	4.57E-02	no
SES Adult	MDD	NCDS	0.1	0	-0.01-0.01	8.27E-01	513	4.58E-02	no
Father walks Child	MDD	MCS	0.1	-0.01	-0.12-0.10	8.27E-01	514	4.59E-02	no
Finance Issues Child	MDD	NCDS	0.3	0.01	-0.07-0.09	8.36E-01	515	4.60E-02	no
Alcohol Mother	SCZ	MCS	0.1	0	-0.04-0.03	8.39E-01	516	4.61E-02	no
Mother walks	MDD	NCDS	0.1	0.02	-0.15-0.18	8.43E-01	517	4.62E-02	no
Finance Issues Child	SCZ	MCS	0.3	-0.01	-0.05-0.04	8.43E-01	518	4.63E-02	no
Finance Issues Child	SCZ	MCS	0.01	-0.01	-0.06-0.05	8.49E-01	519	4.63E-02	no
Finance Issues Child	SCZ	MCS	0.2	0	-0.05-0.05	8.50E-01	520	4.64E-02	no
Employment Father Child	MDD	NCDS	1	-0.01	-0.17-0.14	8.55E-01	521	4.65E-02	no
Mother walks Child	MDD	MCS	0.4	0.01	-0.06-0.07	8.69E-01	522	4.66E-02	no
Father's involvement in childcare	SCZ	NCDS	0.5	-0.01	-0.09-0.08	8.73E-01	523	4.67E-02	no
Father's involvement in childcare	SCZ	NCDS	1	-0.01	-0.09-0.08	8.75E-01	524	4.68E-02	no
Father's involvement in childcare	SCZ	NCDS	0.01	-0.01	-0.09-0.08	8.75E-01	525	4.69E-02	no
Mother walks	SCZ	NCDS	0.1	0.01	-0.15-0.18	8.76E-01	526	4.70E-02	no
Mother walks	SCZ	NCDS	0.4	0.01	-0.15-0.18	8.77E-01	527	4.71E-02	no
Mother walks	SCZ	NCDS	0.2	0.01	-0.15-0.18	8.80E-01	528	4.71E-02	no
Smoking Adult	SCZ	NCDS	0.01	-0.01	-0.08-0.07	8.90E-01	529	4.72E-02	no
Mother walks	SCZ	NCDS	0.5	0.01	-0.15-0.18	8.96E-01	530	4.73E-02	no
Mother's interest in child's education	SCZ	NCDS	1	0	-0.06-0.07	9.01E-01	531	4.74E-02	no
Father walks Child	MDD	MCS	0.5	0.01	-0.11-0.12	9.04E-01	532	4.75E-02	no
Number of Rooms child vs adult	SCZ	NCDS	0.1	0	-0.02-0.02	9.06E-01	533	4.76E-02	no
Father walks Child	MDD	MCS	0.4	0.01	-0.11-0.12	9.06E-01	534	4.77E-02	no
Mother's interest in child's education	SCZ	NCDS	0.01	0	-0.06-0.07	9.09E-01	535	4.78E-02	no
Number of Rooms Child	MDD	MCS	0.2	0	-0.01-0.01	9.11E-01	536	4.79E-02	no
Mother walks	SCZ	NCDS	1	-0.01	-0.17-0.16	9.18E-01	537	4.79E-02	no
Father walks	MDD	NCDS	0.01	0	-0.10-0.10	9.31E-01	538	4.80E-02	no
Father walks Child	MDD	MCS	0.3	0	-0.11-0.12	9.35E-01	539	4.81E-02	no
Father walks Child	MDD	MCS	0.2	0	-0.11-0.12	9.37E-01	540	4.82E-02	no
Tenure Adult	MDD	NCDS	0.1	0	-0.05-0.06	9.38E-01	541	4.83E-02	no

Finance Issues Child	MDD	NCDS	1	0	-0.08-0.08	9.43E-01	542	4.84E-02	no
Number of Rooms Child	MDD	NCDS	0.01	0	-0.01-0.01	9.44E-01	543	4.85E-02	no
Mother walks Child	MDD	MCS	1	0	-0.07-0.07	9.45E-01	544	4.86E-02	no
Marital status parents vs adult	MDD	NCDS	0.1	0.01	-0.18-0.19	9.45E-01	545	4.87E-02	no
Employment Father Child	SCZ	NCDS	0.2	-0.01	-0.16-0.15	9.47E-01	546	4.88E-02	no
SES child vs adult	SCZ	NCDS	0.01	0	-0.02-0.02	9.54E-01	547	4.88E-02	no
Mother walks	SCZ	NCDS	0.3	0	-0.16-0.17	9.58E-01	548	4.89E-02	no
Number of Rooms Child	MDD	MCS	0.01	0	-0.01-0.01	9.60E-01	549	4.90E-02	no
Father walks Child	MDD	MCS	1	0	-0.11-0.11	9.65E-01	550	4.91E-02	no
Finance Issues Child	MDD	NCDS	0.01	0	-0.08-0.08	9.67E-01	551	4.92E-02	no
Mother walks	MDD	NCDS	0.2	0	-0.16-0.17	9.71E-01	552	4.93E-02	no
Alcohol Father	SCZ	MCS	0.1	0	-0.08-0.08	9.73E-01	553	4.94E-02	no
Tenure child vs adult	SCZ	NCDS	0.01	0	-0.07-0.07	9.77E-01	554	4.95E-02	no
Finance Issues Child	MDD	NCDS	0.5	0	-0.08-0.08	9.78E-01	555	4.96E-02	no
Number of Rooms Child	MDD	MCS	0.1	0	-0.01-0.01	9.81E-01	556	4.96E-02	no
Employment Father Child	MDD	NCDS	0.3	0	-0.16-0.16	9.81E-01	557	4.97E-02	no
Finance Issues Child	MDD	NCDS	0.4	0	-0.08-0.08	9.85E-01	558	4.98E-02	no
Mother walks Child	MDD	MCS	0.5	0	-0.07-0.07	9.86E-01	559	4.99E-02	no
Marital status parents vs adult	MDD	NCDS	0.2	0	-0.18-0.18	9.99E-01	560	5.00E-02	no

Note: Benjamini-Hochberg correction adjusted α=(rank of p-value/number of tests for each threshold) - *α [adjusted α=(rank/560)*0.05]. Beta = beta coefficient, CI = Confidence Interval, adj alpha = adjusted alpha, sig? = significant

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