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Positive Mental Health and Resilience in Young People

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Abstract

The ability to maintain positive functioning in the face of adversity is a concept that has interested researchers for decades. Many refer to this capacity as resilience, although there is yet to be an agreed upon definition of resilience. Some refer to resilience as a trait that permits an individual to handle and overcome stress. Others propose that resilience is a process or outcome that is attained when the necessary resources are in place. In this thesis, I conceptualise and study resilience as a process that emerges from the interaction of protective factors. I use assessments of both positive and negative mental health to determine its presence, and I investigate protective factors at both the genetic and environmental level. In doing so, I attempt to understand the factors that enable individuals exposed to peer victimisation to foster resilience. Peer victimisation occurs when an individual is repeatedly exposed to discomfort at the expense of another person's actions. I focus in particular on experiences in adolescence as this is an important developmental period for later mental health. Overall, the research conducted in this thesis has allowed me to draw three important conclusions. The first is that genetic information can be used to predict the likelihood of experiencing peer victimisation, but is less informative about subsequent resilience. The second is that factors important for resilience after peer victimisation are likely to be in place prior to the victimisation experience. In particular, victims who hold higher perceptions of scholastic competence in childhood maintain greater wellbeing in adulthood than those lower in scholastic competence. Finally, the findings suggest that different interventions will likely be required to both reduce depressive symptoms and improve wellbeing following peer victimisation. As such, the research underscores the importance of investigating predictors of both when determining resilience. Further resilience enquiry will also benefit from adopting a life course perspective and triangulating results from different methodological approaches. This will be key to unveiling more about the complex and dynamic nature of resilience.

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Author declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Publications

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Table of Contents

List of Tables

List of Figures

List of Appendices

Chapter 1: Introduction

1.1 Thesis Motivation

I have always been interested in people and what makes us so different. Why do some succumb to the effects of life's stresses and strains where others do not? It was during my undergraduate degree in psychology that this interest grew further. I became fascinated by genetics and was eager to understand more about its role in predicting individual differences. During my PhD, I therefore set out to learn methods in genetic epidemiology so that I could apply them to the study of resilience and mental health.

Beyond my drive to constantly learn, I also firmly believe in the importance of conducting research on mental health and wellbeing. I hope that my research can contribute to a better understanding of how mental-ill health can be prevented, and positive mental health promoted. I also hope that the work in this thesis will encourage others to consider that research on wellbeing is just as important as the study of mental illness.

1.2 Thesis Overview

The overriding goal of this thesis is to understand the factors that contribute towards resilience following peer victimisation in adolescence. Throughout my projects, I study resilience using assessments of both positive and negative mental health to provide a more complete account of overall functioning. Depressive symptoms are used throughout as an index of mental ill-health. This is because individuals exposed to peer victimisation are at nearly a threefold increase in odds of depression compared to non-victims (Bowes et al., 2010). These odds are larger than estimates for other psychiatric disorders like generalised anxiety disorder

(Stapinki et al., 2014), enabling a larger cohort of individuals to be targeted for possible intervention. Using depressive symptoms rather than depression diagnoses ensured individuals who do not meet diagnostic criteria could be included, and also enabled comparisons with the continuous positive mental health outcome of wellbeing. I focus in particular on depressive symptoms and wellbeing in emerging adulthood, a period that takes place between 18 and 25 years (Arnett, 2000). This allowed me to build upon the current literature to explore further longitudinal outcomes of peer victimisation.

My research predominantly investigates peer victimisation in adolescence as this has been deemed a unique developmental period characterised by several physiological, cognitive, and emotional changes (Troop-Gordon, 2017). These are likely to impact how individuals handle and respond to current and future events in their environment. Understanding the factors that contribute towards more positive outcomes following experiences of peer victimisation in adolescence is thus key to ensuring early intervention and positive mental health in adulthood.

My research projects were conducted using two primary datasets, namely the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Quebec Newborn Twin Study (QNTS). The QNTS was used to first explore whether there are factors that predict a heightened risk of peer victimisation. These findings were then used to inform further study in ALSPAC into factors associated with resilience following peer victimisation.

1.3 Chapter overview

Within this chapter, I introduce the history and development of resilience as a concept, describe the distinctions between resilience and closely related processes, and provide an overview of the different approaches to the study of resilience. I then outline how this has informed my own research on resilience following peer

victimisation, and discuss the importance of investigating predictors of wellbeing in addition to mental illness. I hope that by the end of this chapter, I will have effectively communicated the value of the study of resilience, as well as its implications for not only reducing the risk of mental health problems, but also in promoting wellbeing following adverse events.

1.4 The history and development of resilience

Adverse experiences during childhood and adolescence have a significant negative impact on both physical and mental health across the life-course (Bellis et al., 2015), accounting for up to 30% of mental health problems worldwide (Kessler et al., 2010). Fortunately, there exists great heterogeneity in response to adversity, with early evidence demonstrating the capacity for individuals to avoid problems despite high risk (Garmezy, 1974). This observation, that many at-risk individuals experience relatively typical development, sparked great interest in the concept now recognised as resilience.

Much of our knowledge today about resilience stemmed from early and extensive research within developmental psychology. Studies included those conducted by Rutter (1979) on children from hostile and unsupportive families, as well as longitudinal research by Werner and Smith (1982) on individuals living in poverty in Hawaii. In both cases, it was noted that children growing up in adverse conditions experienced fewer than anticipated adjustment issues. These early investigations, as well as others at that time, tended to focus on the individual qualities of 'invulnerable children' that were believed to support later competence (Anthony, 1974). However, these efforts soon evolved to also consider factors external to the child (Garmezy, 1993; Masten et al., 1990).

The early pioneering research on resilience represents what some have labelled as the first wave of resilience inquiry (Richardson, 2002). Decades of research have

since followed, with a rise in the number of studies dedicated to resilience published in the last two decades (Hjemdal et al., 2007). Following the first wave of resilience research, researchers began to focus less on personal qualities associated with resilience, such as high self-esteem and autonomy (Masten & Garmezy, 1985), and more on the processes and paths by which these factors may lead to resilience (Masten, 2007). This was achieved through the study of interactions between risk and protective factors (Luthar, 2006). Protective factors were those shown to moderate the impact of various adversities. These were found to reside in either the individual, their family, or the community, and included factors such as self-efficacy, close relationships with parents, and a positive school climate (Masten, 2007). The search for moderating protective factors still prevails today, with the most recent wave of resilience inquiry focused on adopting a multi-level perspective to the study of resilience (Vella & Pai, 2019).

The multi-level approach consolidates and builds upon the previous waves of resilience research to understand how different systems may interact to shape functioning. These systems include processes at the genetic, epigenetic, brain, and neurobiological level, as well as behaviour (O'Dougherty-Wright et al., 2013). Investigating these different levels of functioning is grounded on the understanding that resilience is a multidimensional phenomenon, influenced by a dynamic interplay of factors across multiple domains (Masten, 2007). Recent reviews of resilience have supported this and placed great emphasis on studying different protective factors simultaneously (Fritz et al., 2018). It was proposed that exploring the combined effects of protective factors could provide insight into whether they function as a complex interrelated system.

The growth in research on resilience over the last two decades represents an important paradigm shift from a focus on risk and vulnerability, to individual strength and capacity (Panter-Brick & Leckman, 2013). This shift from pathology to

salutogenesis has not only been reflected in the scientific literature (Ager, 2013), but also in clinical settings and policy. Approaches to the treatment and study of psychiatric disorders have moved away from traditional deficit-centred approaches focused on links between risk and psychopathology, to strength-based models that ask why these links occur and how they can be prevented (Panter-Brick, 2014; Zimmerman, 2013). Many have argued that such strength-based approaches focused on building wellbeing should be routinely included in clinical assessments and interventions (Jeste et al., 2015; Rashid & Ostermann, 2009).

In support of this was the policy framework plan published by the World Health Organization in 2017 (WHO, 2017). This outline acknowledged the importance of strengthening resilience and wellbeing and argued that individuals do not develop from deficits, but rather from their strengths and capacities. It was suggested that future planning and delivery of health services should prioritise resilience, but also remain vigilant as not to misinterpret the concept of resilience (WHO, 2017).

1.5 Defining resilience

The word ‘resilience’ originates from the Latin verb ‘resilire’, which means to leap back (Fletcher & Sarkar, 2013). The term has since been adopted and used across many fields of research, including ecology, to denote the capacity of an ecosystem to recover when disturbed, as well as in physics to refer to the elasticity of metals and their ability to resist strain. This latter example of resilience has been used as a metaphor to describe individual differences in response to stress (Lazarus, 1993), however, most use the term resilience today to denote a psychological meaning (Vella et al, 2019).

Many researchers in the field of resilience accept that resilience refers broadly to the ability to adapt successfully and experience positive functioning despite adversity (Southwick et al., 2014). Inherent in this definition, however, is that resilient

functioning requires exposure to an adverse event. There is some confusion in the literature about whether resilience necessitates exposure to adversity, with some proposing that resilience develops as a consequence of trauma, and others suggesting it is a characteristic that can emerge without exposure to trauma (Phillips et al., 2011). Resilience as a construct has therefore been defined as a trait, outcome, and process, with currently no gold standard for assessing resilience (Windle et al., 2011).

1.5.1 Resilience as a trait

Resilience conceptualised as a trait refers to internal qualities of an individual that permit them to overcome stress or adversity (Connor & Davidson, 2003). When investigated from this perspective, resilience is captured using dedicated instruments such as the Connor–Davidson Resilience Scale (CD-RISC) (Connor et al., 2003), the Brief Resilience Scale (Smith et al., 2008), and the Resilience Scale (Wagnild & Young, 1993). These measures aim to assess an individual's general tendency towards resilient functioning. Items included in the different scales have assessed a range of factors including personal competence, acceptance of change and secure relationships, tolerance or humour in the face of stress, confidence, and control (Connor et al., 2003). These often capture many of the characteristics associated with ego-resiliency (Farkas & Orosz, 2015).

Ego-resiliency is a concept that stems from theoretical models of personality. It refers to the ability to adapt and react to changing environmental demands (Block & Block, 1980). Individuals high in ego-resilience are suggested to have a predisposition to resist anxiety and be more flexible when it comes to dealing with novel and potentially stressful circumstances (Block & Kremen, 1996). It has been suggested that such behaviours are under the influence of both genetic and environment factors, and can thus be observed early on through a child's reaction to changing environments (Block et al., 1980). This responsiveness to an individual's

surroundings has been studied in detail in relation to what is known as the Differential Susceptibility Hypothesis (Belsky & Pluess, 2009).

According to the Differential Susceptibility Hypothesis, some individuals are more sensitive to the effects of an environment than others (Belsky & Pluess, 2009). This sensitivity arises from both positive and negative conditions, with individuals more responsive to the beneficial effects of supportive environments also more susceptible to the adverse outcomes of unsupportive ones. Individuals more responsive to such environments who are also able to adapt to changing environmental demands are likely to also be those higher in ego-resilience (Farkas et al., 2015). It is possible that over time, being more susceptible to the effects of both positive and negative environmental conditions allows individuals to demonstrate resilience due to a phenomenon known as 'steeling effects' (Rutter, 2012).

Steeling effects refer to the psychological benefits that can be gained from exposure to moderate or low levels of stress (Liu, 2015). This goes against traditional models of dose–response effects of stress by instead proposing that moderate stress is optimal for mental health (Holtge et al., 2021). Such a proposal means that individuals exposed to no or extreme stress are more at risk of mental health problems. The theory behind this is that moderate stress encourages individuals to seek out resources that help to develop resilience (Liu, 2015). Individuals who experience little stress are thus not presented with the opportunity to prepare for future stressful experiences.

Research on steeling effects in humans is sparse, with findings offering conflicting results. Longitudinal studies on adults have shown that it is not those who experience moderate stress that accumulate more resilience-related resources, but those who experience high stress (Holtge et al., 2021). Such individuals exposed to

high stress were also shown to experience the highest wellbeing one year later. These findings led the authors to argue that resilience may be less related to the experience of stress, but more on the acquired resources (Holtge et al., 2021). In the context of trait resilience, it is possible that due to their natural resourcefulness (Block et al., 1980), individuals high in trait or ego-resilience will be more likely to experience steeling effects when exposed to stress. Such a theory, however, remains to be tested.

Like trait resilience, ego-resilience is assessed using dedicated scales, such as the Ego-Resiliency Scale (Block et al., 1996). However, unlike trait resilience, which captures personal abilities that specifically allow an individual to handle a stressful life event (Oshio et al., 2018), ego-resiliency does not require exposure to adversity (Windle et al., 2011). Instead, measures of ego-resiliency assess more general characterises related to flexibility, temperament, and engagement with the world (Klohnen, 1996). Despite these differences, authors have used the term 'psychological resilience' to refer to both trait resilience (Min et al., 2013) and ego-resilience (Ong et al., 2006), leading to some confusion in the literature.

1.5.2 Resilience as a process or outcome

In contrast to resilience defined as a trait, resilience conceptualised as an outcome or process is never directly measured but inferred from assessments of functioning following risk (Luthar & Zelazo, 2003). Researchers who embrace this view understand resilience to be a frequent phenomenon (Masten, 2001), and one that can be acquired by anyone with the appropriate resources (Fergus & Zimmerman, 2005). From this perspective, resilience is only assessed in the presence of, or following, an adverse event.

A life experience that would qualify as an adversity is one that predicts significant maladjustment (Luthar et al., 2003). Resilience would be inferred following such a

risk if individuals display fewer than expected levels of maladjustment where otherwise expected (Luthar et al., 2015). Such an approach enables the contextualisation for what constitutes positive adjustment across the range of outcomes and adversities studied. Thus, the outcome used to establish the presence of positive adjustment is largely dependent on the risk under study (Luthar et al., 2000). As an example, in the case study of the severely deprived Romanian orphans who received minimal food, stimulation and care when institutionalised, competence in cognitive functioning was viewed as an important determinant of initial adjustment (Rutter, 1998). Later studies on this cohort, however, assessed competence in other domains predicted to be adversely affected by earlier experiences, including developmental and psychological disorders, as well as life outcomes like employment (Sonuga-Barke et al., 2017). Such findings highlight that it is not just the adversity that predicts the appropriate domain of adjustment, but also the time and context.

Although resilience is often indicated by the absence of negative outcomes following adversity, this is distinct from coping, recovery, and competence (Rutter, 2006). Coping describes the process of attempting to deal with difficulties that exceed an individual's resources (Lazarus & Folkman, 1984). The efforts used to cope can be adaptive or maladaptive (Taylor & Stanton, 2007), providing some distinction to resilience which is typically categorised by healthy adjustment efforts. However, it has been noted that the success of coping depends less on adaptive or maladaptive behaviours, and more on the ability to use the strategies in a way that allows a flexible response to the demands of the stressful event (Bonanno & Diminich, 2013). As such, provided the coping facilitates flexible adjustment to the stressor, it may be seen to bolster resilience.

In addition to coping, resilience has also been compared to the concept of recovery (Bonanno & Mancini, 2011). Like resilience, recovery refers to normal functioning

after a traumatic experience (Windle, 2011). However, it has been suggested that resilience is characterised by a more stable trajectory of healthy functioning compared to recovery (Mancini & Bonanno, 2006). Individuals deemed resilient typically suffer mild reactions to the adversity and experience few disruptions to their everyday functioning (Bonanno et al., 2011). Individuals recovering on the other hand, often experience moderate to severe elevations in psychiatric symptoms followed by a gradual decrease (Bonanno et al., 2011). The consequences of recovery and resilience also differ; recovery involves improved emotional, physical, and social functioning, whereas resilience is inferred from specific outcomes based on the type of adversity experienced (Echezarraga et al., 2019). Thus, while it is likely that resilience contributes to the recovery process (Echezarrage et al., 2019), the two are deemed as separate but highly related concepts. Competence on the other hand, may imply resilience, however, it is essential that competence results from overcoming an adverse event to be classified as resilient functioning (Fergus et al., 2005).

A key drawback of viewing resilience as merely an outcome is that it declares the absence of negative adjustment but does not attempt to explain it. This is crucial as there may be some instances in which the absence of maladjustment may be viewed as an atypical or unhealthy response. As an example, losing a loved one is a stressful experience characterised by increased feelings of sadness, anger, and anxiety (O'Connor, 2019). Intense positive emotions following the death of a loved one may therefore not be viewed as an adaptive response. However, over time, an outcome of positive wellbeing after a period of grief may be considered adaptive in the context of protective factors.

Resilience is often viewed as involving three connected components: adversity, outcome, and mediating factors (Gartland et al., 2018). Thus, the idea of resilience being viewed as either an outcome or process has recently been suggested to

cause an unnecessary divide (van Breda, 2018). To avoid separating conceptualisations of resilience, researchers have suggested using the term ‘resilience’ when referring to the process, and ‘resilient’ to the outcome (Ungar, 2004).

In this thesis I conceptualise and explore resilience as a process that emerges from the interaction of various protective factors. Such an approach aligns with the most recent wave of resilience enquiry which focuses on the role of factors across various levels, including individual, family, and community systems (Vella et al., 2019). These protective factors at the individual-level likely overlap with some of the characteristics identified in studies of trait resilience. For example, measures of trait resilience capture factors like self-esteem, social relationships, and problem solving (Connor et al., 2003) which may also be involved in predicting resilient outcomes following adversity (Sapouna & Wolke, 2013). Indeed, studies investigating resilience as either a trait or outcome have found moderate correlations between the two (Stein et al., 2019). Adopting a process view of resilience and considering multiple factors both within and external to the individual may thus prove the most effective means of capturing the complexity of resilience (Rutter, 2012).

In the following sections I outline how different approaches can be used to study resilience when viewed as either a trait, process, or outcome. I then explain how such approaches can be implemented using both observational and genetic data before explaining how such methods can be applied to study resilience following experiences of peer victimisation.

1.6 Approaches to the study of resilience

Due to discrepancies in its operationalisation, various approaches have been taken to the study of resilience (Luthar et al., 2000). Although these differ in their assessment of resilience, most share the common goal of capturing resilience in an

at-risk population by assessing the capacity to avoid the problem for which it is believed to be at risk. For researchers who study the process of resilience and resilient outcomes, one of two approaches have commonly been used within quantitative studies, these are either variable-based or person-based (Masten & Powell, 2003).

1.6.1 Variable-based approach

Variable-based approaches typically use statistical models like multivariate regression to identify protective factors that modify the negative outcomes of a risk (Luthar et al., 2015). This often involves studying the main effects of a protective factor on the outcome of interest, as well as mediating and moderating effects following an adverse experience (Masten et al., 2003). Such an approach derives statistical power from using the full sample and has been used to predict resilience to a range of adversities in childhood and adolescence (Masten et al., 1999). One potential issue with the variable-based approach is that findings are situation-specific. However, given that resilience is likely specific to certain risks and not necessarily generalisable, this is unlikely to be a shortcoming of this approach to the study of resilience.

1.6.2 Person-based approach

Person-based approaches seek to identify and compare groups of individuals, categorised according to their level of risk exposure and adjustment profiles (Luthar et al., 2015). Person-based methods typically involve latent growth mixture modelling which groups participants according to their patterns of growth. Such an approach has been used to study the varying and multiple outcome trajectories following specific adverse events such as loss, divorce, and unemployment (Bonanno et al., 2011). One problem inherent in this approach is that it generates trajectories based only on individuals in the studied sample, meaning generalisation of results are often limited.

Nevertheless, by drawing comparisons between individuals with and without certain factors, or by exploring differences in functioning among individuals with varying levels of risk exposure, both the person-based and variable-based methods have contributed to our understanding of factors predictive of resilience. In the next section I describe how these approaches have been applied and used to study the role of diverse protective factors at both the phenotypic and genetic level.

1.6.3 The role of protective factors

As evident by the variable-based and person-based approaches, a key goal of resilience research is to identify factors that buffer or ameliorate the impact of an adverse event (Masten et al., 2011). Factors that interact with a risk to moderate subsequent consequences have been termed ‘protective factors’, however, the term ‘protective’ has been used somewhat inconsistently in the literature (Luthar et al., 2000). To help clarify different variations in terminology, many now use the term ‘protective’ to refer only to factors that are functional when risk is high, and ‘promotive’ when referring to factors predictive of positive adaptation regardless of risk (Zimmerman et al., 2013). Both types have been suggested to comprise of various assets and resources, with assets referring to factors that reside within the individual, and resources referring to external factors (Fergus et al., 2005). Indeed, a diverse range of factors have been identified within a systematic review as supportive of resilience to the effects of multiple adversities (Fritz et al., 2018). These have spanned processes and factors at the individual, familial, and community level (Vanderbilt-Adriance & Shaw, 2008).

Protective factors shown to be associated with resilience can be considered in relation to the ecological framework described by Bronfenbrenner (1979), see figure 1.1 (taken from Penn, 2005). This acknowledges experiences and interactions between the individual and their environment and proposes different levels in which environments may impact an individual. These are referred to as the microsystem,

the mesosystem, the exosystem, and the macrosystem (Bronfenbrenner, 2005). The microsystem is the first layer of an individual's social ecology and refers to the individual and their immediate setting, such as their home or school. The mesosystem relates to the interaction between two or more microsystems that directly impact the individual, such as between the family at home and peers at school. The exosystem on the other hand, relates to wider structural social settings that do not directly involve the individual but still have an influence, such as the neighbourhood and parent's place of work. At the subordinate level is the macrosystem, this refers to the cultural context and public policy that an individual finds themselves in.

The relevance of these different layers to the study of resilience was highlighted by Ungar (2019) who argued that researchers must consider not only which factors are protective, but for who and in what context. Similar conclusions have been drawn by

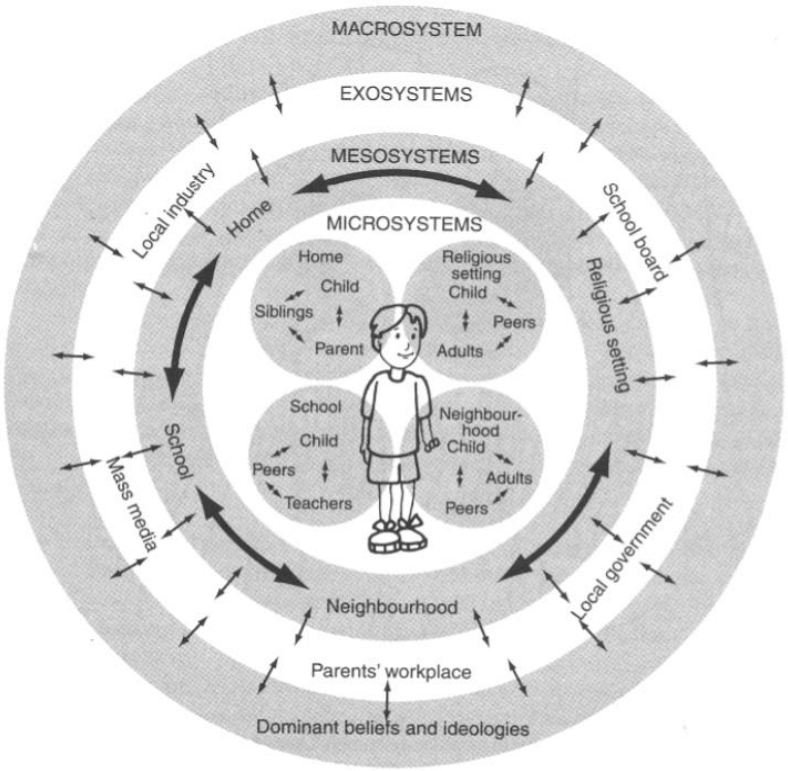

Figure 1.1: *The ecological framework, encompassing micro-, meso-, exo-, and macro-systems*

others who have studied protective factors across various socioecological levels (Gartland et al., 2018). The likelihood of an individual attaining resilience should thus be studied in the context of ecological, psychological, social, and biological systems (Ungar & Theron, 2020).

1.6.4 Genetic contributions to the study of resilience

It is now widely accepted that an individual's response to adversity is mediated by a complex array of factors relating not only to psychosocial and environmental determinants, but also genetic, epigenetic, and neural mechanisms (Feder et al., 2009). Many have therefore advocated for the importance of adopting a multiple-levels-of-analysis perspective when investigating resilience (Cicchetti & Blender, 2006). Such an approach seeks to understand the role of underlying genetic and biological processes, and the extent to which individuals at a high biological risk may be especially vulnerable to the effects of adverse events (Bowes & Jaffee, 2013).

1.6.4.1 Twin research

One approach to understanding the role of genetic and environmental influences is through the twin design. This uses information about phenotypic similarity between different family members to estimate the contribution of genes and environments. Twin studies investigating resilience can thus be used to estimate the degree to which outcomes following stressful life events are heritable. To do this, many have regressed the outcome of interest onto the adverse event and taken the residual scores (Amstadter et al., 2014, 2016; Bowes et al., 2010; De Vries et al., 2021). These scores reflect the difference between actual and predicted outcomes and have been used to study those with fewer than expected problems and thus resilience. Such research has suggested that resilience to cumulative stressful events has a moderate heritability of ~31% (Amstadter et al., 2014), with approximately 40% of this genetic variance unique to resilience, and 60% shared with other traits such as neuroticism (Amstadter et al., 2016). This finding that over

one third of the genetic influences on resilience are unique and not related to genetic influences for mental health has implications for the study of specific genetic variants.

1.6.4.2 Candidate gene studies

To test the role of specific genetic markers, many have conducted candidate gene studies. Two key genetic markers that have been investigated in relation to resilience are the serotonin transporter gene (5-HTTLPR) and the Brain-Derived Neurotrophic Factor (BDNF) (La Greca et al., 2013). Both genes have been implicated in studies of depression and are often explored within a Gene-by-Environment (G×E) design (Aguilera et al., 2009). Such an approach considers genetic vulnerability alongside environmental risk factors, such as family maltreatment, to determine moderating effects on mental health functioning (Comasco et al., 2013).

Gene-by-Environment studies based on candidate genes have been used to test the Differential Susceptibility Hypothesis (Belsky & van IJzendoorn, 2017). Findings have revealed there may be specific genes involved in regulating susceptibility towards positive and negative rearing environments, although outcomes have focused largely on externalising rather than internalising symptoms (Bakermans-Kranenburg & Van I.Jzendoorn, 2011). Overall, studies adopting the candidate G×E design have provided some insight into individual variability in response to stress, however, as with most candidate gene studies (Munafò, 2006), many have failed to replicate findings (Bowes et al., 2013). Most G×E studies to date on specific genes have only considered genetic markers of developmental or mental health disorders. No study has yet explored genes directly affiliated with resilience.

1.6.4.3 Genome-wide association studies

Stein and colleagues (2019) conducted the first genome-wide association study (GWAS) of psychological resilience. Genome-wide association studies (GWASs) are explained in more detail in Chapter 2, however, briefly, GWASs are used to investigate associations between a trait or disorder and hundreds of thousands of genetic variants. In the GWAS of resilience, the researchers separately explored trait resilience and an "outcome-based" measure of resilience among army soldiers (N = 11,492). Trait resilience was determined using a self-assessed questionnaire, while measures of mental health pre- and post- deployment were used to determine 'outcome-based' resilience. Overall, the study identified one genome-wide significant locus associated with trait resilience. For outcome-based resilience, genetic associations were only found when using a smaller sample of individuals reporting extreme stress (Stein et al., 2019).

Despite the small sample size of the resilience GWAS and thus lack of power to detect genetic markers, the study has enabled further investigation into genetic correlates of resilience (De Vries et al., 2021). This has been achieved through creating polygenic scores associated with resilience. Polygenic scores summarise the findings from a GWAS and provide an estimate of an individual's genetic liability to a trait or disease (Sugrue & Desikan, 2019). The process for constructing polygenic scores is explained in detail in Chapter 2. However, it is important to note that unlike the stringent conditions used to detect genetic variants in a GWAS, polygenic scores relax the threshold to consider the role of more generic variants. This has enabled follow-up research to study the predictability of genetic variants associated with resilience, as well as the extent to which these overlap with the variants associated with other closely related traits, like wellbeing.

Findings so far have revealed that the variance in resilience explained by polygenic scores from the resilience GWAS is close to zero (De Vries et al., 2021). However,

such analyses were based on an 'outcome-based' measure of resilience that focused on the absence of psychopathology following adversity. It was concluded that wellbeing may have been a more appropriate indicator of resilience, which was demonstrated by the ability of genetic variants associated with wellbeing to predict resilience (De Vries et al., 2021). Such findings suggest a possible shared genetic aetiology between wellbeing and resilience, which could be used to enhance our understanding of genetic markers of resilience. Further investigations could thus benefit from considering multiple correlated traits in one multivariate GWAS (Choi et al., 2019). Similar approaches have been taken to study the 'wellbeing spectrum' which comprised of traits including life satisfaction, positive affect, depression, and neuroticism (Baselmans et al., 2019). This led to a significant increase in power to detect associated variants and could thus be used to aid our understanding of the genetic underpinnings of resilience (Choi et al., 2019).

It is important to note that the difference between the variance explained by genetic variants identified in the GWAS and the heritability estimates from twin research reflects arises for nearly all common traits. The difference is referred to as the 'missing heritability problem' and has been attributed to several factors, including the absence of rare variants in GWASs (Pallares, 2019) as well as inflated estimates from twin studies due to gene-environment interactions (Young, 2019). Within twin studies, gene–environment interactions that are shared within a family are attributed to the genetic component. This may lead to higher subsequent heritability estimates compared to those from GWASs (Uher, 2014). Understanding how genetic and environmental influences impact the risk of a trait or disorder is thus crucial to informing more about the genetic architecture of complex traits.

1.6.4.4 Gene × Environment research

One complementary approach to investigating resilience is therefore to use genetic proxies for individual traits and vulnerabilities within an interactive Gene by

Environment (G×E) design. Such an approach takes advantage of methods like polygenic scores to investigate whether genetic liability towards a trait or disease influences subsequent resilience following adversity. One advantage of this method is that it provides insight into the processes by which resilience may arise from based on a combination of genetic and environmental factors (Choi et al., 2019).

Findings thus far have provided some evidence that the effects of adversities like childhood trauma, may be moderated by an individual's polygenic risk to depression (Mullins et al., 2016). Adversities occurring in adulthood have also been studied using this interactive polygenic design, including cumulative stressful life events (Colodro-Conde et al., 2018) and the death of a spouse (Domingue et al., 2017). No study, however, has yet applied this G×E framework to explore resilience to adversities specifically in adolescence, or experiences such as peer victimisation. The importance of such research is outlined in the following section.

Overall, our understanding of the genetic underpinnings of resilience is still in its early stages (Maul et al., 2019). However, research thus far has revealed there likely exist genetic contributions to the individual differences in response to adversity. These genetic influences have been shown to overlap with various developmental and emotional traits, including mental health and wellbeing. While there is currently no clear evidence of unique genes associated with self-assessed resilience or 'outcome-based' resilience, further investigation into the genetic aetiology of resilience will benefit from larger genotyped samples, multivariate designs, as well as gene-environment interactive studies.

1.7 Peer victimisation

This thesis focuses on resilience following experiences of peer victimisation. Below I describe peer victimisation and its prevalence, and provide an overview of research investigating its links with mental health. I hope by the end of this section to have

clearly communicated why it is essential that we study resilience to peer victimisation.

1.7.1 Defining victimisation

Peer victimisation describes the experience in which an individual is repeatedly exposed to discomfort at the expense of another person's actions (Olweus, 1993). To be classified as peer victimisation, the perpetrator must be of a similar age to the victim. Instances in which the perpetrator is an adult and the victim a child are referred to as 'maltreatment'.

The term 'peer victimisation' is synonymous with 'bullying', and both are used interchangeably within the literature (Olweus, 2013). This thesis predominately refers to 'peer victimisation' to ensure a clear focus on the victim as opposed to the perpetrator. According to Olweus (2013), the definition of peer victimisation encompasses three key aspects. The first is the presence of a perceived power imbalance between the perpetrator and victim. This can be observed through factors like physical strength or differences in numbers, but can also relate to the victims perceptions of their popularity, status, or self-confidence (Olweus, 2013). This component of peer victimisation has previously been used to distinguish peer victimisation from general conflict (Graham & Bellmore, 2007). The other two defining features of peer victimisation relate to intention and frequency; there must be an underlying intention to cause harm or discomfort which is carried out repeatedly and over time (Olweus, 2013). One-off aggressive incidents between individuals would not be classified as victimisation.

Peer victimisation can manifest in various forms. It can be direct and physical, indirect and relational, or it can be verbal (Stassen Berger, 2007). Direct or physical victimisation involve open attacks such as hitting, kicking, and beating, while indirect or relational victimisation is characterised by behaviours aimed at damaging an

individual's social relationships, such as rumour-spreading or intentional exclusion from a group (Wolke et al., 2000). Verbal victimisation relates exclusively to derogatory and hurtful remarks (Stassen Berger, 2007), however, when words are used to exclude individuals, verbal victimisation can also manifest as relational victimisation.

Research has revealed that the incidence of the different forms of peer victimisation are largely similar (Wolke et al., 2000), with often high correlations reported between direct and indirect experiences (Bowes et al., 2015). Many have therefore combined measures of the two to investigate overall victimisation experiences (Stapinski et al., 2014).

1.7.2 Prevalence of victimisation

Although prevalence rates for peer victimisation vary considerably across nations (Cook et al., 2010; Craig et al., 2009), it is evident that peer victimisation is a prevalent and global public health problem (Biswas et al., 2020). Figures in Europe have ranged from 8.6% in Sweden to 45.2% in Lithuania, with estimates in England around 16.5% (Craig et al., 2009). Studies based in the UK have generally revealed consistent prevalence estimates, particularly in relation to frequent victimisation (Bowes et al., 2015; Bowes et al., 2013; Takizawa et al., 2014). Frequent victimisation can be captured in some questionnaires based on responses to one item alone. This would occur if an individual stated that one form of victimisation, for example "being called nasty names", had occurred at least once per week in the past six months (Wolke et al., 2001). Frequent victimisation can also be inferred if an individual reaches a certain threshold on scores across multiple items. In the commonly used Bullying and Friendship Interview Schedule (Wolke et al., 2001), responses to items could be "seldom", but if at least four of the nine items were "seldom", an individual would be classified as frequently victimised (Lereya et al., 2015).

In one study, approximately 24% of primary school children reported being victimised at least once a week in the last six months (Wolke et al., 2001), suggesting frequent victimisation. In contrast, findings on adolescents have revealed that around 15% are frequently victimised (Bowes et al., 2015; Takizawa et al., 2015). This reduction in prevalence as individuals get older occurs despite using the same victimisation measure, and has been documented both in the UK and worldwide (Biswas et al., 2020). Typically, there is often a peak that occurs in early adolescence (Söderberg & Björkqvist, 2020), with findings to suggest that victimisation among adolescent girls could be on the rise (Cosma et al., 2017).

Individuals more likely to experience victimisation in adolescence are typically those exposed to more severe forms in childhood (Geoffroy et al., 2018). Findings have revealed prevalence estimates for frequent victimisation to be over three times greater for adolescents who reported frequent victimisation in childhood (Bowes et al., 2013). Understanding the factors that contribute to childhood victimisation could thus help to lower the occurrence of victimisation in secondary schools, and could prove crucial to reducing the prevalence of later mental health problems and informing our understanding of resilience. This is because if we can understand predictors of the risk exposure, we can use this information during follow-up investigations to understand whether the same set of risk factors also heighten subsequent resilience (or lack of). I explore this further using data from the Quebec Newborn Twin Study (QNTS) in Chapter 3 to understand predictors of victimisation, and using the Avon Longitudinal Study of Children and Parents (ALSPAC) in Chapter 4. Chapter 4 uses findings from Chapter 3 to understand whether genetic predictors of peer victimisation also modify subsequent mental health after peer victimisation. This is achieved using a gene by environment interaction design.

1.7.3 Resilience to peer victimisation

For over a decade peer victimisation has been recognised as a major public health concern (Srabstein et al., 2008), associated with poorer physical and mental health (Wolke & Lereya, 2015). Mental health problems that have been attributed to peer victimisation have encompassed both internalising and externalising disorders (Arseneault et al., 2010), including depression (Bowes et al., 2015; Ttofi et al., 2011), anxiety (Jadambaa et al., 2020; Stapinski et al., 2014), and suicide ideation or attempt (Brunstein-Klomek et al., 2010). Longitudinal research has revealed many of these problems often extend well into adult life (Takizawa et al, 2014).

Yet despite the large body of research demonstrating that peer victimisation is a significant risk factor for psychopathology, the same research findings have also highlighted the potential for resilience. In particular, it has been shown that although cases of depression are typically higher among victims relative to non-victims (Lund et al., 2009), the percentage of victims with a clinical diagnosis in adulthood has ranged from 10% to 17% (Bowes et al., 2015; Lund et al., 2009). Similar estimates for other disorders among victims have also been reported, with figures for anxiety-related disorders estimated to be around 15% (Stapinski et al., 2014), and approximately 15% for alcohol and marijuana disorders (Copeland et al., 2013). This finding that a substantial proportion of victims do not go on to develop problems has sparked interest in resilience to peer victimisation (Sapouna & Wolke, 2013).

Research to date exploring resilience to peer victimisation, however, has been hindered by a sole focus on mental-ill health (Bowes et al., 2010; Sapouna et al., 2013). Most studies have operationalised resilience following victimisation as the absence or reduction of internalising or externalising symptoms (Bowes et al., 2010; Sapouna et al., 2013). Few have considered how victimisation impacts an individual's quality of life and wellbeing (Flaspohler et al., 2009). Doing so is critical

as peer victimisation not only increases the risk of depressive symptoms in early adulthood, but it also negatively impacts adult wellbeing (Armitage et al., 2021).

1.8 Resilience beyond mental illness

The importance of incorporating measures of positive functioning into assessments of resilience has been previously emphasised (Almedom & Glandon, 2007; Panter-Brick & Leckman, 2013), with some proposing that resilience refers specifically to the ability to harness resources to sustain positive wellbeing (Panter-Brick, 2014; Ungar, 2011), and others suggesting resilience is a key component of wellbeing (Eley et al., 2013) and wellbeing a key component of resilience (De Vries et al., 2021). Nevertheless, in a systematic review of resilience research, it was noted that no study had yet included a measure of wellbeing within assessments of positive adaptation following any adversity (Cosco et al., 2017).

1.8.1 Defining wellbeing

Wellbeing refers broadly to feelings of satisfaction and happiness (Diener, 2000). Many make the distinction between different aspects of wellbeing, namely subjective or hedonic wellbeing, and psychological or eudaimonic wellbeing (Deci & Ryan, 2008). Subjective wellbeing, or hedonic wellbeing, is characterised by high positive affect and low negative affect, as well as a high satisfaction with life (Deci et al., 2008). Life satisfaction is not strictly related to traditional hedonist approaches to wellbeing as it involves a cognitive evaluation of one's life. However, the two affective dimensions closely align with hedonist approaches, explaining why subjective wellbeing is often used synonymously with hedonic wellbeing (Gallagher et al., 2009).

Eudaimonic wellbeing, or psychological wellbeing, relates to the meaning and fulfilment of one's life (Deci et al., 2008). This aspect of wellbeing is less concerned with immediate outcomes and more with broader processes and evaluations of

positive functioning. Models of eudaimonic wellbeing have suggested there are six dimensions that capture what it means to be fully functioning (Ryff & Singer, 2008). These are self-acceptance, purpose in life, personal growth, positive relations with others, autonomy, and environmental mastery (Ryff & Keyes, 1995).

While distinctions between subjective and psychological wellbeing are frequently made, research has also provided evidence of their overlap (Gallagher et al., 2009). This overlap has been observed both at the phenotypic and genetic level, with correlations often higher at the genetic compared to the phenotypic level (Baselmans & Bartels, 2018). Studies investigating genetic correlations with other phenotypes have also revealed similar estimates using different aspects of wellbeing (Fredrickson et al., 2013). This has led some to propose a shared genetic architecture of hedonic and eudaimonic wellbeing (Baselmans et al., 2018), and has resulted in many investigating the two simultaneously (Keyes, 2013; Routledge et al, 2016).

Researchers who investigate the different dimensions of wellbeing together often refer to ‘mental wellbeing’ (Keyes et al., 2010). This term is commonly used in public health and policy when describing overall wellbeing or positive mental health more generally (Regan et al., 2016, WHO, 2013). However, there are dedicated scales for assessing mental wellbeing, such as the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS; Tennant et al., 2007). This scale was developed to ensure a wide conception of wellbeing could be captured, spanning both affective and cognitive dimensions, as well as overall psychological functioning (Tennant et al., 2007). In developing this scale, the authors intended to support the promotion of positive mental health across populations.

Wellbeing in this thesis is defined and investigated as ‘mental wellbeing’, allowing both hedonic and eudaimonic wellbeing to be considered. As such, the WEMWBS is

used as the main outcome measure in chapters using observational data. In analyses based on summary statistics from GWASs, wellbeing is studied using measures related to life satisfaction and positive affect. This is because samples with genotype data and information related to eudaimonic wellbeing are considerably smaller.

1.8.2 The importance of wellbeing

Promoting positive mental health and wellbeing has become integral to public health and policy, particularly in the last two decades (Magyary, 2002). This stemmed from the positive psychology movement initiated by Martin Seligman in 1998 (Fowler et al., 1999). Since then, researchers have challenged some of the proposals made by Seligman and colleagues (2000) relating to positive psychological traits, stating that they failed to consider the context and interplay of processes predicting wellbeing (McNulty & Fincham, 2012). Nonetheless, the importance of wellbeing remains as prominent as ever, as outlined by the World Health Organization (WHO, 2013) in their mental health action plan for the years 2013-2020:

> *"The promotion of mental health and the prevention and treatment of mental disorders are fundamental to safeguarding and enhancing the quality of life, well-being and productivity of individuals, families, workers and communities, thus increasing the strength and resilience of society as a whole".*

Understanding predictors of positive wellbeing is of utmost importance for a multitude of reasons. Firstly, wellbeing is both associated with, and precedes many positive outcomes across major life domains, including work, love, and health (Lyubomirsky et al., 2005). Health outcomes related to higher wellbeing have included both short- and long-term benefits (Howell et al., 2005) as well as increased longevity (Diener & Chan, 2011). These could be driven by underlying

associations between wellbeing and health-related behaviours (Stranges et al., 2014); individuals high in wellbeing may exhibit certain behaviours that lead to more healthy and positive experiences (Wootton et al., 2017). This is likely to contribute to further increases in wellbeing (Lyubomirsky & Layous, 2013) and could prove crucial to mitigating the risk of mental health problems (Layous et al., 2014).

Secondly, although mental health and wellbeing are highly related constructs (Lamers et al., 2015), phenotypic and genetic correlations between wellbeing and mental illness are moderate (Haworth et al., 2017), meaning individuals may show few signs of a mental health problem and still have a poor quality of life. Multiple interventions may therefore be necessary to both prevent mental illness and promote wellbeing. This had led many to advocate for the importance of investigating the two dimensions of mental health, namely depression and wellbeing, as distinct yet related dimensions of functioning (Keyes, 2007; Routledge et al., 2016; Westerhof & Keyes, 2010).

Studies treating wellbeing as a separate construct from depression have provided insight into the independence of the two, with genetically informative studies identifying large genetic overlaps between depression and wellbeing (Bartels et al., 2013), but also genetic factors unique to each (Haworth et al., 2017; Kendler et al., 2011). This means that a strong disposition to depression does not necessarily result in an increased vulnerability to low wellbeing (Kendler et al., 2011). Predictors associated with depression should therefore not be solely relied upon to derive predictions about wellbeing.

Research exploring resilience to adversities beyond peer victimisation has also largely been dominated by a focus on mental illness (Southwick & Charney, 2012). While many refer to the absence of mental health problems as evidence of healthy psychological functioning (Bonanno et al., 2011), wellbeing is rarely assessed. Such

studies thus provide limited insight into predictors of an individual's overall psychological state and resilience. By supplementing findings with assessments of wellbeing, researchers will be able to address more complex questions regarding resilience, such as how, why and for whom protective factors may matter. This will prove vital to ensuring the development of more targeted interventions that suitably support individuals to foster resilience.

1.9 Thesis aims

In this thesis I explore resilience by considering factors that implicate both the risk of depression and mental wellbeing following adolescent victimisation. Investigating predictors of the continuum of outcomes from depressive symptoms through to positive wellbeing (and thus resilience) is grounded on the understanding that there are likely to be similarities and differences in risks for both types of outcome. It was thus hoped that by investigating the two dimensions, an understanding would be attained of how best to support victims of bullying to achieve optimal mental health and resilience despite risk. It was also hoped that my findings would highlight the importance of wellbeing as a separate construct to depression, and would encourage others in the field to consider positive functioning beyond the absence of a mental health disorder. It was also anticipated that my findings would have potential clinical relevance by informing not only why some are at a heightened risk of victimisation, but also why some go on to experience mental health problems and low wellbeing following victimisation, while others remain resilient.

Chapter 2: Methods

2.1 Introduction

Within this chapter I provide an overview of the cohorts used to conduct my analyses and outline the main methods used. I focus on genetic methods, including the creation and use of polygenic scores, which are used in Chapters 3 and 4, as well as Mendelian Randomization (MR), which is applied in Chapter 6 Part 1. Details on specific software, statistical models, and data management are provided in the relevant research chapters.

2.2 Cohort descriptions

The two cohorts predominately used in this thesis are the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Quebec Newborn Twin study (QNTS). The QNTS is used in Chapter 3, while data from ALSPAC is used in Chapters 4, 5, and Chapter 6 Part 2.

2.3 Avon Longitudinal Study of Parents and Children (ALSPAC)

2.3.1 Cohort overview

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a multi-generational prospective cohort investigating multiple influences on health and development (Boyd et al., 2013). Pregnant women residing in the former Avon area of the United Kingdom with an expected delivery date between April 1991 and December 1992 were enrolled for the study. The initial cohort consisted of 14,062 live births but has since increased to 14,901 children who were alive after one year with further recruitment (Northstone et al., 2019).

At the time of recruitment, the 1991 census was used to compare the population of mothers living in the Avon area with infants less than a year old, to those in the rest of Britain (Fraser et al., 2013). Comparisons were also drawn between the ALSPAC

participants and mothers in Avon not enrolled in the study. ALSPAC mothers were more likely to be married than the equivalent populations in Avon and Britain, and were also less likely to be non-White (Fraser et al., 2013). This representation bias remains for those who continue to participate, with ALSPAC children more likely to have higher educational attainment by the age of 16 years compared to the national average and those lost to attrition (Boyd et al., 2013). Studies have also shown that participation rates can be predicted by health-related factors, such as body mass index (BMI) and smoking (Cornish et al., 2021). Below, the representativeness of the ALSPAC cohort in relation to mental health measures is explored in more detail. Despite some loss to attrition, a key advantage of the ALSPAC data set is the breadth of repeat measures assessed at frequent intervals across the life course. These have captured environmental, biological, phenotypic, and genetic information, and have been used to study critical periods of development (Boyd et al., 2013). Data has been collected via questionnaires, clinic assessments and medical records, with informed consent obtained from all participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.3.2 Genotyping of sample

Just over 9,900 children in ALSPAC were genotyped using the Illumina HumanHap550 Quad Array platform (run at the SangerInstitute, Cambridge UK and Laboratory Corporation of America, Burlington, USA). These data were subject to standard quality control measures in which SNPs were excluded if they met the following: a minor allele frequency (MAF) of <0.01, a call rate of <0.95, an individual call rate of <0.97, info <0.80 or if there was evidence of violations of Hardy-Weinberg equilibrium (HWE, $p<5x10^{-7}$). Individual participants were also removed if there were incorrect sex assignments, minimal or excessive heterozygosity, disproportionate missingness (>3%), evidence of cryptic relatedness (proportion of identity by descent >0.125), insufficient sample replication and non-European ancestry. Individuals not of European descent were detected by a multidimensional

scaling analysis seeded with Hapmap II (release 22) individuals. These quality control filters resulted in 9,115 subjects and 500,527 SNPs. Imputation was then performed using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3), resulting in 8,237 eligible children with available genotype data (Taylor et al., 2018).

2.3.3 Victimisation measures

At 13 years, 49% (n=6,838) of the original 14,062 children in ALSPAC attended the research clinic and were assessed for peer victimisation. Participants responded to nine statements taken from the previously validated Bullying and Friendship Interview Schedule (Wolke et al., 2001). These comprised of 5 items relating to direct victimisation, and 4 items relating to indirect experiences of victimisation. Adolescents responded based on the frequency of these experiences within the last six months (0=Never, 1=Seldom, 2=Frequently, 3=Very Frequently). Responses to all nine items can be found in Table 2.1. Overall, the items had good internal consistency (Cronbach's alpha, α=0.72), and correlations between the direct and indirect items were moderate (r=0.52). Analyses in this thesis were therefore conducted using an overall index of peer victimisation, as per previous research (Bowes et al., 2015; Stapinski et al., 2014). Scores from this measure ranged from 0-25 (M= 1.82, SD=2.76), with 0 representing those who had never been bullied. As evident in the histogram in Appendix 2.1, the overall victimisation scores had a high positive skew (skew=2.4). All analyses including the victimisation measure therefore used scores that were log transformed (after adding a constant of 1 to accommodate scores of zero).

Table 2.1: Frequency of victimisation experiences aged 13. Values are numbers (percentages).

		Frequency of victimisation		
Items	**Never**	**Occasional (1-3 times)**	**Frequent (> 4 times)**	**Very Frequent (>1 per week)**
Someone took teenager's belongings	5173 (77.6)	1101 (16.5)	227 (3.4)	166 (2.5)
Someone threatened or blackmailed teenager	6043 (90.6)	472 (7.1)	99 (1.5)	53 (0.8)
Someone hit or beat up teenager	5906 (88.6)	575 (8.6)	118 (1.8)	67 (1.0)
Someone tricked teenager	6155 (92.2)	438 (6.6)	45 (0.7)	35 (0.5)
Someone called teenager nasty names	4264 (64.1)	1230 (18.5)	589 (8.8)	574 (8.6)
Peers would not hang around just to upset teenager	5976 (89.8)	485 (7.3)	124 (1.9)	68 (1.0)
Peers tried to get teenager to do things he or she did not want to do	6112 (92.0)	416 (6.3)	77 (1.2)	41 (0.5)
Peers told lies about teenager	5533 (83.7)	757 (11.4)	217 (3.3)	104 (1.6)
Peers spoilt games to upset teenager	6332 (95.3)	228 (3.4)	49 (0.7)	40 (0.6)

2.3.4 Mental health and wellbeing measures

At 23 years, ALSPAC participants completed a set of wellbeing measures for the first time. A total of 11 different wellbeing measures were included. These covered a diverse range of positive psychological phenotypes, such as subjective happiness and gratitude. This thesis focuses predominantly on wellbeing as assessed using the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS; Tennant et al., 2007). This scale was chosen because of its ability to capture both hedonic and eudaimonic aspects of wellbeing, as well as overall psychological functioning. WEMWBS is also widely used within public health and policy and has proven reliability across populations in Europe (López et al., 2012). This helps to ensure the current findings can be translated into useful recommendations for policy.

The WEMWBS comprises of 14 positively worded items relating to experiences of thoughts and feelings over the last two weeks. An example item is, *"I've been feeling optimistic about the future".* Individuals choose from a 5-point Likert scale that best describes their experience, with answers ranging from "None of the time" to "All of the time". Items are scored positively and summed to produce a minimum score of 14 and a maximum score of 70. Scores in the ALSPAC cohort covered this full range and had a mean of 48.65 (SD=9.06), demonstrating a slight skew (skew = -0.37). The items overall showed extremely good internal consistency (Cronbach's alpha, α=0.93).

Life satisfaction was also assessed in ALSPAC at 23 years and is used in Chapters 5 and 6 of this thesis. Life satisfaction was measured using the Satisfaction with Life Scale (Diener et al., 1985). This is a 5-item scale with excellent psychometric properties, as demonstrated by high internal consistency and high temporal reliability (Diener et al., 1985). Participants respond to each of the five items on a 7-point scale. Answers reflect how much an individual agrees or disagrees with the statement provided, with a higher overall score reflective of greater life satisfaction. Scores in ALSPAC cover the full range (5 to 35), and average 24.06 (*SD*=6.98). As per the WEMWBS, there is a slight negative skew of -0.62. This means more participants score more highly.

In addition to mental wellbeing and life satisfaction, participants aged 23 also completed the Short Mood and Feelings Questionnaire (SMFQ) (Angold, Costello, Messer, & Pickles, 1995). The SMFQ is a 13-item scale derived from the 33-item Moods and Feelings Questionnaire (MFQ) which aims to capture the presence of depression symptoms within the last two weeks (Costello & Angold, 1988). An example item is, *"I didn't enjoy anything at all".* Participants respond to the items by selecting one of the three answers: "Not True", "Somewhat True" or "True". Overall scores range from 0-26, with a score of 12 or above indicative of depression. Scores

in ALSPAC had a mean score of 7.03 (SD=6.05) and were found to have a strong negative correlation (*r*=-0.69) with scores from the WEMWBS.

The sMFQ has proven a reliable and valid measure of depression in both clinical and non-clinical samples (Burleson Daviss et al., 2006), and was shown to have excellent internal consistency in ALSPAC (Cronbach's alpha, α=0.91). Scores did, however, have a skew greater than 1 (skew=1.10), therefore analyses including the sMFQ in this thesis used negative binomial regression models. Negative binomial models were chosen over the Poisson model as the latter assumes that the distribution's mean is equivalent to its variance. This was not the case for the sMFQ (M=7.03, σ^2=36.6). A histogram demonstrating the distribution of these scores and the wellbeing scores can be found in Appendix 2.1

2.3.5 Sample attrition

Of the 9,394 participants sent the mental health and wellbeing questionnaires, 4044 (43.0%) completed the WEMWBS, 4,280 (45.6%) completed the Satisfaction with Life Scale, and 3980 (42.3%) completed the sMFQ. The questionnaires were all made available for the ALSPAC participants to complete online or in paper format. Of those who returned the questionnaires, 2646 (63.2%) had completed them online. Ages of the participants who completed at least one of the wellbeing questionnaires ranged from 22 to 25 years (mean=23.39 years) and comprised of 65% females and 35% males. Sociodemographic information relating to those with complete and missing mental health data can be found in Table 2.2. Individuals who completed either the wellbeing questionnaire or the depressive symptoms scale, or both, were more likely to come from advantaged backgrounds compared to those missing in ALSPAC. This was evident by differences in car and home ownership, as well as differences in the educational background of the mothers. Those who completed the questionnaires, however, were not more likely to be of white ethnicity, and there were no sociodemographic differences between individuals who only

responded to one of the two mental health measures compared to those who completed both. The impact of sample representativeness, however, is discussed further in empirical research chapters using ALSPAC.

Table 2.2: Sociodemographic comparisons of ALSPAC participants with complete and missing mental health and wellbeing data

	Complete Cases[a] (n=3,907)	Wellbeing Responders (n=4,043)	Missing Wellbeing Responders [b] (n=136)	Depression Responders (n=3,979)	Missing Depression Responders [c] (n=72)	ALSPAC Sample (n=15,443)	Missing ALSPAC Sample[d] (n=11,536)
White (%)	95.9	95.9	95.6	96.0	98.5	95.0	94.6
White mother (%)	97.9	97.9	99.1	97.9	100	97.4	97.2
Parents own car (%)	95.2	95.2	95.7	95.3	100	90.8	88.9
Parents married (%)	85.6	85.6	87.0	85.6	85.6	79.5	76.9
Mother was homeowner (%)	85.7	85.6	83.8	85.7	85.5	77.1	73.3
Mother has University degree (%)	20.7	20.6	14.5	20.6	14.3	13.7	10.8

Note:

[a] Complete case responders have data on wellbeing aged 23, depressive symptoms aged 23, as well as the relevant sociodemographic characteristics.

[b] Individuals with complete data on wellbeing and sociodemographic variables but not depression at 23 years.

[c] Individuals with complete data on depressive symptoms and sociodemographic variables but not wellbeing at 23 years.

[d] Core singleton ALSPAC sample not in complete case sample.

2.4 Quebec Newborn Twin study (QNTS)

2.4.1 Cohort overview

The Quebec Newborn Twin Study (QNTS) is an ongoing prospective longitudinal cohort of twins born in the greater Montreal area of Canada (Boivin et al., 2019). Recruitment for the study was initiated by the Quebec Newborn Twin Registry which identified all twin births occurring in the Province of Quebec between April 1995 and December 1998. Names and contact details of the parents of newborn twins were collected from the Registry and contacted by either letter or phone. Of the 989 families contacted, 662 (67%) agreed to participate. Appointments were then scheduled for those who agreed to enrol for when the twins were 5 months of age.

The demographic characteristics of the families were comparable to a single birth sample in the province of Quebec (Brendgen et al., 2013), with 87% of those enrolled of European decent, 3% of African descent, 3% of Asian descent, and 1% of Native Northern Americans. Zygosity was established using a genetic marker analysis, performed on a subsample of 123 and 113 same-sex twin pairs at 5 and 19 months respectively (Forget et al., 2003). In cases where the genetic material was insufficient for genotyping, or where parents refused consent, the pairs were diagnosed using a shortened version of Goldsmith's Zygosity Questionnaire for Young Twins (Goldsmith, 1991). Diagnoses based on this physical similarity measure were accurate in 92% of the cases at 5 months, and in 94% of cases at 19 months (Boivin et al., 2019).

Since the initial laboratory assessment at 5 months, comprising of various cognitive, psychophysiological and behavioural tests, data has been collected at 20, 32, 50 and 63 months of age through home interviews and questionnaires, and through school-based assessments during Kindergarten (average age 6 years), Grade 1 (average age 7 years), Grade 3 (average age 9 years), Grade 4 (average age 10 years) and Grade 6 (average age 12 years). Each assessment comprised of reports from the participants, their peers, and

teachers. Twins have also been followed during adolescence and early adulthood. These assessments took place four times throughout the secondary school period, when participants were on average 13, 14, 15, and 17 years, as well as when participants were 19 and 23 years of age. These assessments included self-reports, parental questionnaires, behavioural observations, and various web-based tests.

Since the original enrolment of 662 families (1,324 twins), the number of participants initially fell to 446 families (892 twins) at the end of preschool. However, figures remained largely stable throughout the primary and secondary school years, with attrition in the sample approximately 1.7% per year on average (Boivin et al., 2019). At 19 years, many of the twins that were lost during follow-up were re-contacted, resulting in an increase of data available for 1,007 twins. Information about sample attrition is presented below.

2.4.2 Genotyping of sample

Genotyping was performed using Illumina's Psych array Beadchip and carried out in two waves. During the first wave, when the twins were approximately 100 months old, a subsample of QNTS families were genotyped, including 407 parents and 581 twins (136 MZ twins, 445 DZ twins). A further 328 twins (including 38 MZ twins) were then genotyped during the second wave at 19 years, increasing the total number of genotyped twins to 909 (Boivin et al., 2019). Data were subject to quality control in which variants with a minor allele frequency (MAF) of <0.01, a SNP genotyping rate of <0.98, and an individual call rate of <0.97 were removed. Variants were also removed if there was evidence of violations of Hardy-Weinberg equilibrium (HWE, $p<1x10^{-6}$). Individuals were also excluded if there were mismatches between genetic and phenotypic sex, or if there was genetic duplication, cryptic relatedness, minimal or excessive heterozygosity, or a potential Klinefelter syndrome diagnosis. After these exclusions, the dataset contained information relating to 443 twins and 588,952 variants. These data were subject to imputation, resulting in a final dataset containing 8,195,349 variants.

2.4.3 Victimisation measures

The QNTS entails detailed and extended assessments of peer relations throughout the primary school years. These were attained using interviews with teachers, ratings from peers, as well as self-reports. From secondary school onwards, participants continued to provide self-reports relating to peer victimisation.

Self-reports of peer victimisation were assessed using structured interviews. The current thesis focuses on assessments at ages 7, 10, 12, 13, 15 and 17 years of age. At each time point, participants answered five questions derived from the previously validated Self-report Victimisation Scale (Ladd & Kochenderfer-Ladd, 2002). Items included in the scale ask participants about their experiences of both direct bullying experiences, for example, “Does it ever happen that some children at school call you names or say bad things to you?” as well as indirect experiences, “Does it ever happen that some children at school say bad things behind your back to other children?”. A list of individual items and their responses can be found in Table 2.3. Responses were recorded on a three-point scale (0=Never, 1=Sometimes, 2=Often) and were averaged across the five items to derive an overall measure of self-reported victimisation. Overall, the five items generally had good internal consistency, with Cronbach’s alpha for each age: 7 years (α=0.67), 10 years (α=0.73) 10 years (α=0.82), 13 years (α=0.57), 15 years (α=0.84), and 17 years (α=0.83). The range and skewness of the scores at each time point can be found in Table 2.4. Here, scores are also reported for individual’s not included in the study due to missing genotype data. There were no significant differences between the victimisation scores of those with complete data compared to those missing.

Teacher reports of peer victimisation were recorded at ages 7-, 10-, and 12-years using responses to the following statements: “In the past 6 months, how often would you say that the child was (1) made fun of by other children, (2) hit or pushed by other children, and (3) called names by other children. All items relate to direct forms of victimisation as these are more likely to be recognised by the teacher than more indirect forms. Such items have been

successfully used previously to assess peer victimisation (Barker et al., 2008). Responses to the three items were recorded on a three-point scale (0=Never, 1=Sometimes, 2=Often) and averaged. Responses can be found in Table 2.3. Despite the skewness of the overall variables at each age (see Table 2.4), each had adequate internal consistency: 7 years (α=0.70), 10 years (α=0.82) and 12 years (α=0.71).

Finally, peer-reported victimisation was assessed through peer nominations at 7 and 10 years of age. Booklets of photographs of all children in a given class were handed out to all participating children in the class. Children were asked to circle photos of two classmates "…who get called names most often by other children", and "…who are often pushed and hit by other children". These statements were adapted from the Victimization subscale of the previously validated modified Peer Nomination Inventory (Perry, Kusel, & Perry, 1988). The total number of nominations received from all classmates for each item was calculated for each participant. Scores for the two statements were highly correlated at both time points (age 7: r=0.50, age 10: r=.65), and were therefore averaged at each age to create an overall measure of peer-reported peer victimisation. According to standard procedures for peer nomination data (Cillessen & Rose, 2005), items were z standardized within classroom to account for differences in classroom size. Peer nominations based on just a single item have proven highly reliable due to being derived from multiple respondents (Hodges, Malone & Perry, 1997).

In chapter 3 I use data from the self-, teacher-, and peer-reports to explore predictors of peer victimisation. Composite scores for each informant are created to explore how self-report measures in childhood and adolescence may be differentially associated with risk factors, and whether these associations vary by informant.

Table 2.3: Item responses from self- and teacher-reported peer victimisation

	Self-reported victimisation responses (childhood), n (%)								
Item	7 years			10 years			12 years		
	Never	Sometimes	Often	Never	Sometimes	Often	Never	Sometimes	Often
Another student has yelled mean things	328 (35.0)	234 (25.0)	374 (40.0)	205 (24.3)	393 (46.7)	244 (29.0)	196 (25.3)	390 (50.3)	189 (24.4)
Another student has said bad things behind your back	476 (51.0)	226 (24.2)	231 (24.8)	269 (32.0)	381 (45.3)	190 (22.7)	244 (31.4)	370 (47.7)	162 (20.9)
Another student prevented you from playing in the group	389 (41.6)	293 (31.4)	252 (27.0)	348 (41.5)	368 (43.9)	122 (14.6)	464 (60.0)	259 (33.5)	50 (6.5)
Another student has pushed, hit, or kicked you	342 (36.8)	272 (29.2)	316 (34.0)	291 (34.7)	380 (45.3)	168 (20.0)	459 (59.2)	232 (30.0)	84 (10.8)
Another student has forced you to do something/give them something you did not want to	495 (53.1)	185 (19.8)	253 (27.1)	681 (81.3)	131 (15.6)	*26* (3.1)	729 (94.1)	41 (5.3)	5 (0.6)
	Self-reported victimisation responses (adolescence), n (%)								
	13 years			15 years			17 years		
	Never	Sometimes	Often	Never	Sometimes	Often	Never	Sometimes	Often
Another student has yelled mean things	322 (39.6)	361 (44.3)	131 (16.1)	456 (57.8)	259 (32.8)	74 (9.4)	538 (67.2)	218 (27.2)	45 (5.6)
Another student has said bad things behind your back	366 (45.1)	337 (41.6)	108 (13.1)	503 (63.7)	222 (28.1)	65 (8.2)	520 (65.1)	222 (27.8)	57 (7.1)
Another student prevented you from playing in the group	658 (81.1)	121 (14.9)	32 (4.0)	729 (92.2)	55 (7.0)	7 (0.8)	745 (92.9)	44 (5.5)	13 (1.6)
Another student has pushed, hit, or kicked you	580 (71.3)	185 (22.8)	48 (5.9)	715 (90.5)	67 (8.4)	9 (1.1)	744 (0.93)	48 (0.06)	8 (0.01)

Another student has forced you to do something/give them something you did not want to	780 (95.9)	27 (3.3)	6 (0.8)	777 (98.2)	13 (1.7)	1 (0.1)	795 (99.2)	7 (0.7)	1 (0.1)

Teacher-reported victimisation responses, n (%)

	7 years			10 years			12 years		
	Never	Sometimes	Often	Never	Sometimes	Often	Never	Sometimes	Often
The student was made fun of by other children	632 (76.0)	188 (22.6)	12 (1.4)	576 (74.1)	182 (23.4)	19 (2.5)	491 (78.1)	116 (18.4)	22 (3.5)
The student was hit or pushed by others	529 (63.7)	283 (34.1)	20 (2.2)	589 (75.7)	179 (23.0)	10 (1.3)	538 (85.5)	83 (13.2)	8 (1.3)
The student was called names by others	691 (82.9)	133 (15.9)	11 (1.2)	583 (75.1)	172 (22.1)	22 (2.8)	514 (81.7)	95 (15.1)	19 (3.2)

Table 2.4: Comparison of peer victimisation scores based on self-, teacher- and peer-reports.

	Individuals with phenotype and genotype data							Individuals with phenotype data only						
	N	Zygosity (% MZ)	Sex (% male)	M (SD)	Min	Max	Skew	N	Zygosity (% MZ)	Sex (% male)	M (SD)	Min	Max	Skew
Self-reported peer victimisation														
Age 7	527	48.4	51.0	0.71 (0.52)	0.00	2.00	0.62	939	42.1	49.1	0.75 (0.52)	0.00	2.00	0.49
Age 10	480	49.4	51.3	0.68 (0.42)	0.00	2.00	0.45	846	41.8	49.5	0.68 (0.43)	0.00	2.00	0.54
Age 12	459	47.5	49.2	0.48 (0.34)	0.00	2.00	1.00	775	40.4	47.5	0.48 (0.36)	0.00	2.00	0.92
Age 13	450	48.2	48.9	0.37 (0.33)	0.00	1.89	1.27	814	39.8	48.5	0.36 (0.33)	0.00	1.89	1.28
Age 15	417	46.8	48.0	0.21 (0.25)	0.00	1.67	1.74	791	38.4	46.7	0.20 (0.24)	0.00	1.67	1.59
Age 17	429	48.3	47.6	0.18 (0.23)	0.00	1.25	1.71	803	38.8	47.1	0.17 (0.21)	0.00	1.44	1.88
Teacher-reported victimisation														
Age 7	476	48.3	51.3	0.26 (0.37)	0.00	2.00	1.44	838	42.7	49.9	0.28 (0.37)	0.00	2.00	1.33
Age 10	436	50.7	50.7	0.25 (0.38)	0.00	2.00	1.63	779	41.7	49.8	0.27 (0.41)	0.00	2.00	1.68
Age 12	375	46.1	46.1	0.21 (0.38)	0.00	2.00	2.17	629	39.0	46.3	0.21 (0.39)	0.00	2.00	2.23
Peer-reported victimisation														
Age 7	465	48.4	50.8	-0.05 (0.96)	-2.19	2.90	0.83	810	42.3	49.1	-0.02 (0.96)	-2.21	3.11	0.78

Age 10	418	50.7	50.7	0.04 (0.95)	-1.35	3.83	1.59	731	42.4	49.1	-0.02 (0.95)	-1.35	4.06	1.75

Note: Peer-reported victimisation scores have been z-standardised within classroom to account for differences in classroom size.

2.4.4 Sample attrition

The current study included twins assessed between 7 and 17 years. Individuals who provided victimisation data at 17 years were more likely to be of white ethnicity and Canadian ancestry compared to those missing (Table 2.5). These individuals were also more likely to have more educated parents and a higher income, but were no more likely to report peer victimisation compared to those with data missing.

Table 2.5: Sociodemographic comparisons of participants from the QNTS with complete victimisation data at 17 years

	Victimisation responders at 17 years (n=803)	**Complete cases (n=429)[a]**	**Victimisation responders with missing genotype (n=374)**	**QNTS Sample (n=1260)[b]**	**Missing QNTS Sample (n=827)[c]**
White (%)	91.2	100	76.1	86.3	79.2
White mother (%)	92.2	100	78.5	88.1	81.7
White father (%)	92.0	100	78.3	93.2	81.2
Canadian ancestors (%)	55.1	63.1	42.6	50.3	44.0
Household income above £50,000 (%)	49.4	53.1	42.3	43.4	37.6
Mother has University degree or higher qualification (%)	30.6	28.1	34.2	27.9	27.6
Father has University degree or higher qualification (%)	34.4	33.7	34.5	29.2	26.3

Note:

[a] Complete cases represent those who provided genotype data and completed the self-reported victimisation scale at 17 years.

[b] Core QNTS sample assessed at 5 months.

[c] Core QNTS sample not included in complete cases due to absent genotype data or victimisation data.

2.5 Genetic methods

Genetic designs involving polygenic scores and Mendelian Randomisation (MR) are used in Chapters 3, 4, and 6 of this thesis to understand predictors of the risk of peer victimisation, resilience to its effects, as well as causal associations with wellbeing. Polygenic scores estimate an individual's genetic liability to a trait or disorder and are generated from genome-wide association studies (GWASs). Here I explain what a GWAS is and how findings from a GWAS can be used to inform further study into mental health and wellbeing using polygenic scores and MR.

2.5.1 Genome-wide Association Study (GWAS)

A central goal of genetics research is to understand how genetic variation is associated with disease and measurable traits. Genome-wide association studies (GWASs) represent a valuable tool in which to do this. GWASs use chip technology to genotype thousands of genetic variants to test these for associations with the outcome of interest. Analyses are carried out using large samples of unrelated individuals and are hypothesis-free, meaning there are no prior assumptions about which genetic variants are involved in predicting the disease.

The genetic variants scanned and investigated within a GWAS are known as single nucleotide polymorphisms, or SNPs. A SNP refers to the variation in the DNA sequence that occurs when a single nucleotide in the genome, either adenine (A), thymine (T), cytosine (C), or guanine (G), differs between individuals. As an example, a DNA sequence for one individual might be GC**C**TATT, but for another it might be GC**T**TATT. Here, there is a difference in a single nucleotide, resulting in two alleles: C and T. Alleles refer to the specific forms of the DNA sequence of a particular gene. When alleles are the same across the two paired chromosomes, they are said to be homozygous with respect to that particular gene. If the alleles are different, they are heterozygous. If two individuals do not carry the same nucleotide at a specific position in the DNA sequence, and if this difference in present in at

least 1% of the population, then this genetic variation is classified as a SNP (Pearson & Manolio, 2008). GWASs are thus grounded on the "common disease, common variant" assumption which argues that genetic influences on common diseases are at least partly attributable to the effects of common genetic variants.

The SNPs identified within a GWAS are those that pass stringent significance thresholds of $p<5x10^{-8}$. This helps to reduce the risk of false positive results. To increase power to detect effects, summary data from a GWAS can be combined with data from multiple other GWASs and meta-analysed. This approach has been widely used to further our understanding of the aetiology of many complex diseases (Begum et al., 2012).

Findings from GWASs thus far have provided evidence that the genetic basis underlying many complex traits is highly polygenic (Shi et al., 2016). This means effects are governed by many genetic variants, each of small magnitude (Dudbridge, 2016). As a result, many have turned to methods that aggregate the effects of many different variants across the genome, including linkage disequilibrium (LD) score regression and polygenic risk scores (Choi et al., 2020). LD score regression estimates and removes confounding biases and polygenicity within a GWAS to provide a more robust account of the degree of inflation (Bulik-Sullivan et al., 2015). This method can be used to study components of heritability and genetic correlations with greater accuracy (Lee et al., 2018a). Polygenic scores, on the other hand, represent the only approach that can estimate genetic liability to a trait at the individual level (Choi et al., 2020).

2.5.2 Polygenic risk scores

To create polygenic scores, it is necessary to have two sources of input data. The first is the base data (GWAS), which holds the necessary summary statistics for the SNP-phenotype associations. These GWAS summary data are often made freely available online, meaning polygenic scores can be constructed for any phenotype in which GWAS summary statistics are available. The second key dataset is the target data. This must contain genotype data

and information relating to at least one phenotype in order to perform the polygenic analysis. The target dataset should be independent of the GWAS sample as this can lead to a substantial inflation of the association between the trait and polygenic scores (Choi et al., 2020).

To construct the scores, the number of independent risk alleles from the discovery GWAS are first assigned a number (0, 1 or 2). Individuals who are homozygous for the risk allele are assigned a score of two, individuals who are heterozygous are assigned a score of 1, and those who are homozygous for the non-risk allele are assigned a score of 0 (Levine et al., 2014). This is done for each SNP. The resulting counts thus reflect the number of risk alleles each individual has. These are each weighted according to their genotype effect estimate, which are the log odd ratios (OR) for binary traits or beta coefficients for continuous traits. The weighted effect sizes are then summed across variants and standardised to derive individual-level scores with a normal distribution. By summing the effects of many genetic variants, polygenic scores assume an additive genetic architecture for complex traits. This is largely consistent with twin research which shows that twin resemblance for up to 69% of traits is due to additive genetic variation (Polderman et al., 2015).

2.5.2.1 Clumping and thresholding

A key challenge in the generation of polygenic scores is the multiple options for creation. One of these is the selection of SNPs for inclusion in the polygenic scores. There are two main approaches to dealing with this, one is to perform shrinkage of the SNPs from a GWAS using techniques such as lassosum (Mak et al., 2017). This involves adjusting the GWAS effect estimates using information related to either prior distributions of the SNPs or knowledge about LD (Choi et al., 2018). Another approach to selecting SNPs is to use only those that met a certain threshold. This is known as clumping and thresholding and represents one of the most common methods (Privé et al., 2019). Unlike shrinkage

techniques, this approach only shrinks excluded SNPs to an effect size estimate of zero, and does not perform any shrinkage on SNPs included in the polygenic score.

The process of clumping involves selecting the most significant variant by removing nearby correlated variants. To do so, researchers must indicate the distance in which correlated variants should be removed, known as the 'window size', as well as the correlation value. Variants within this window and correlation estimate are then subsequently removed. This clumping procedure helps to remove the potential bias of SNPs in LD. LD is inferred if genetic variants on the same chromosome occur more often than would be expected given non-random associations within a large population. However, in doing so, clumping can also remove independently predictive variants in LD (Privé et al., 2019). Figure 2.1 demonstrates an example of a lead SNP (in blue) and SNPs in LD at varying correlation values. This plot was created using SNiPA, a browser for exploring genetic variants (Arnold et al., 2015).

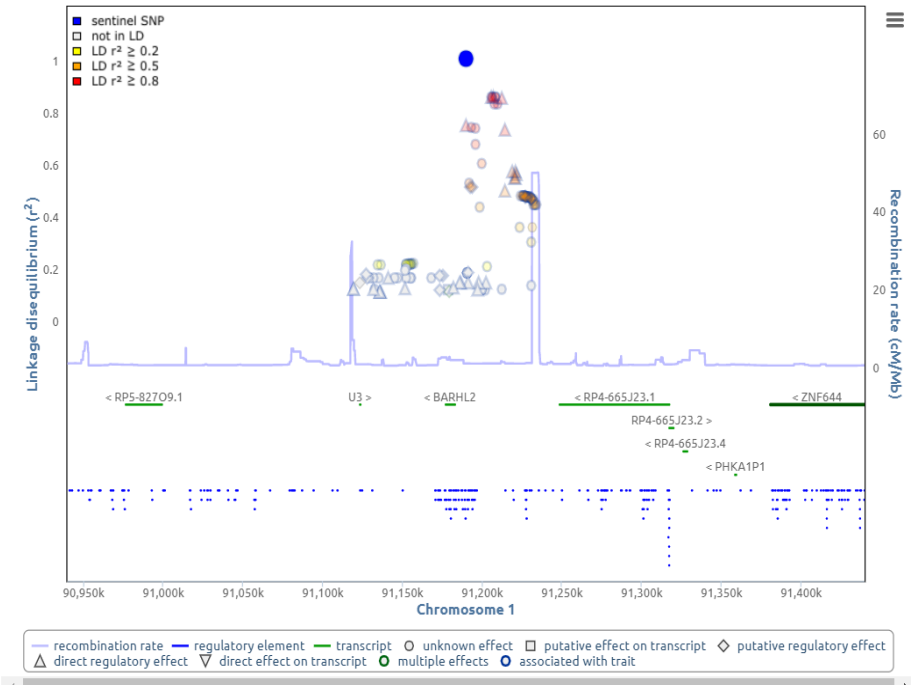

***Figure 2.1**: Linkage disequilibrium plot demonstrating the amount of correlation between the lead SNP and its surrounding variants. The x-axis shows chromosomal position of each SNP, the y-axis shows the correlation coefficient (r^2), and the plot symbols indicate the functional annotation. The plot demonstrates an example of a lead SNP (in blue) on Chromosome 1, and its variants in high LD (r^2 >0.8) plotted in pink.*

The process of thresholding involves extracting SNPs based on a specified p-value threshold. The best-fitting threshold is typically determined using the point at which the most variance is explained. For example, in Figure 2.2, this study chose the *p*-value threshold of $p<1\times10^{-4}$ as this was the point at which the most variance was captured across the two traits using standard polygenic scores (Mostafavi et al., 2020). Since the optimal p-value threshold is unknown a priori, and since strategies for selecting thresholds for polygenic score analyses are still in development, many researchers create polygenic scores using a range of thresholds and then select scores that explain the highest variance in the trait or disease (Anderson et al., 2019). This method is generally preferred over strategies that select a single arbitrary p-value threshold (such as p=1) as this can impair polygenic predictability and lead to false conclusions (Choi et al., 2020). Selecting stringent p-value thresholds, such as those that reach genome-wide significance ($p <5\times10^{-8}$), results in fewer SNPs available for polygenic score calculation. While this can increase signal strength and reduce the potential for random noise (Dudbridge, 2016), including more SNPs and thus covering more of the genome allows more of the variance in the trait or disease to be captured (Purcell et al., 2009). The overall predictability of polygenic scores, however, are a function of multiple factors, including the power of the discovery GWAS, the target data, and the genetic architecture of the trait (Choi et al., 2020). This means that the optimal method for creating the polygenic scores will vary according to the trait under study (Ware et al., 2017).

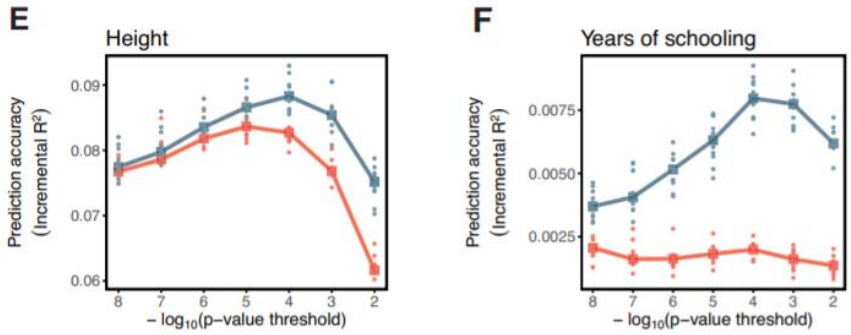

Figure 2.2: *Plot taken from Mostafavi et al. (2020) demonstrating prediction accuracy of standard (grey) and sibling-based (red) polygenic scores at varying p-value thresholds.*

2.5.2.2 Applicability of polygenic scores

Once polygenic scores are created, they are typically used within a linear regression model to predict the measured trait or outcome within the target sample. Covariates can be included as per standard regression analyses, and several polygenic scores can be studied simultaneously. As a result, polygenic scores enable the prediction of diverse phenotypes and experiences based on genetic profile, and allow multivariate approaches to investigate the independent and cumulative impact of multiple genetic vulnerabilities.

By drawing on genetic information for many traits, polygenic scores can provide further insight into genetic correlations and overlap between traits and disorders. This has the potential to increase risk prediction models, particularly if this means studies can draw upon larger samples to study the correlated trait (Baselmans et al., 2020). Such findings may also prove useful in identifying high risk individuals, in helping to select optimal treatment, or in developing new treatments for disorders that share a common genetic basis (Dudbridge, 2016). Before polygenic scores are fit for clinical use, however, there are many challenges to consider. These are discussed in more detail in Chapters 3 and 4.

2.5.2.3 Population stratification

When investigating associations with polygenic scores and measured traits, it is important to account for population stratification. Population stratification refers to the difference in allele frequencies between subpopulations that result from ancestry and non-random mating. If these differences correlate with patterns of environmental variation, it can induce a spurious association between the genetic variants and the outcome of interest. To therefore control for similarity between participants due to population structure, regression models involving polygenic scores are often corrected for genetic structure using principal components analysis (PCA). This is a multivariate method that involves partitioning the genetic variance of the population into uncorrelated PCs that explain it. The first PC accounts for the most variation, with subsequent PCs explaining less and less of the variance. Every individual is

assigned a value that indicates their genetic loading towards each PC, which are included in the regression models as confounders. The number of PCs to include as confounders has been suggested to be ten (Feng et al., 2009), however, this is arbitrary and will depend on the homogeneity of the sample (Anderson et al., 2010).

2.5.3 Mendelian Randomisation (MR)

Mendelian Randomisation (MR) uses natural genetic variation to study the causal effect of an exposure on an outcome. Genetic information is used to compare groups of individuals who should only differ for the variants being studied. In doing so, MR is able to circumvent problems related to confounding that usually compromise tests of association in observational epidemiology (Davey Smith & Ebrahim, 2003).

The principles of MR rely on Mendel's law of segregation such that individuals inherit one of two possible alleles from the mother, and one of two from the father. This random segregation used in MR helps to exercise control over reverse causality. Reverse causality is a form of confounding that is difficult to account for in conventional observational studies. It occurs when an exposure causes a risk factor but is misinterpreted as being caused by the risk factor. For example, an individual with depression may consume more alcohol than those without depression. This would lead to a positive association between the two and may be interpreted as alcohol causing depression. However, it may also be the case that individual's resort to alcohol after depression. By studying risk factors using genetic variants that are fixed from birth, the MR approach allows relationships between two factors to be evaluated for both direction and causality.

In addition to reverse causality, another challenge associated with observational research relates to unmeasured confounding (Davies et al., 2017). This relates to factors that influence both the risk factor and the exposure. Such factors are difficult to control for if they are not known, or if they are large in quantity, and can still be a problem even after statistical adjustment. This is because measurement error can occur if confounders are not

appropriately characterised, resulting in residual confounding (Davies et al., 2017). Although confounders will likely be associated with exposures within an MR study, they cannot influence an individual's genetic predisposition towards that exposure. Thus, by using genetic variants that are largely independent of environmental influences, the MR design is significantly less susceptible to confounding compared to traditional observational studies.

The underlying principles of MR have been compared to those of a Randomised Control Trial (RCT). In a RCT, individuals are randomly assigned to either the intervention or the control group (see Figure 2.3 taken from Davey Smith & Ebrahim, 2008). This randomisation is reflected in the random assortment of alleles in the MR design. In both instances, the random segregation of participants or alleles is independent of any confounding variables, such that confounding factors are assumed to be balanced across the two groups. Any differences that arise are therefore attributed to causal effects of the intervention.

In MR, the intervention refers to differences at the genetic level. While in a RCT, the intervention is typically a treatment that is being proposed for clinical practice. When comparing findings between a RCT and MR, the question therefore arises whether the genetic differences identified in MR reflect the same causal effects being studied in the RCT. There are many reasons why these may not be the same, including differences in time scale and the development of compensatory mechanisms (Burgess et al., 2012). It is possible that over time, individuals develop and use protective factors that help reduce the impact of the risk factor. This would not be captured in MR in which the genetic variants represent lifelong risk. Nevertheless, MR has been proposed as a useful tool for investigating causal effects of modifiable risk factors to aid the selection of targets for intervention (Burgess et al., 2012).

In support of this, a review of the development of new drugs for coronary artery disease (CAD) advocated for the use of MR prior to RCTs (Roberts, 2018). It was argued that the development of new drugs based on RCTs alone has been limited by proposed risk factors being biomarkers rather than causal variants. Using MR has therefore been suggested as an

effective means of detecting causal and genetically supported risk factors for further investigation in RCTs (Nelson et al., 2015; Talmud & Holmes, 2015). This could not only help mitigate some of the time and costs associated with RCTs, but MR investigations can also be conducted where it is not feasible to run a RCT. For example, to investigate the causal impact of alcohol consumption on CAD (Davies et al., 2018).

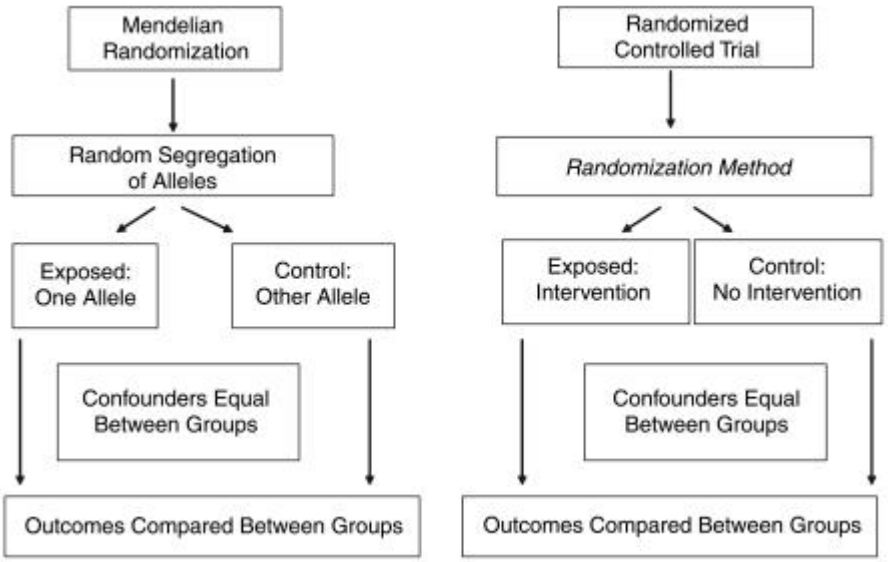

Figure 2.3: *Analogy between MR and a Randomised Controlled Trial (RCT).*

2.5.3.1 Assumptions of MR

MR is based on the assumption that if there is a causal effect of an environmental exposure on an outcome, then genetic variants associated with the exposure should also predict the outcome, through the exposure only (as in Figure 2.4). These genetic variants must be robustly associated with the exposure of interest, and should not be associated with factors that may confound the association between the exposure and the outcome.

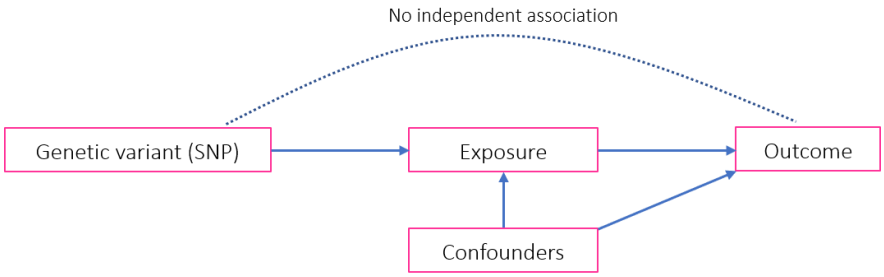

Figure 2.4: *A Directed Acyclic Graph (DAG) demonstrating assumptions of Mendelian Randomisation.*

Some of these assumptions rarely hold in an MR study (Bowden et al., 2016), particularly since most researchers now use summary data from genome-wide association studies (GWAS) as genetic instruments, rather than individual variants. This is because many complex traits are highly polygenic, meaning they are influenced by multiple genetic variants, each of small effect (Visscher et al., 2017).

The causal effects of the exposure on the outcome can be calculated using the following equation:

$$\hat{\beta}_{IV} = \frac{\hat{\beta}_{ZY}}{\hat{\beta}_{ZX}}$$

Here, the effect of the genetic variants on the outcome (β^ZY) are divided by the effect of the genetic variants on the exposure (β^ZX) (Lawlor et al., 2008). Where just one genetic variant

is used as the instrument, the β^IV is known as the Wald estimate. In cases where multiple genetic variants are used as genetic instruments, a two-stage least squares regression (2SLS) is performed. Here, the exposure is first regressed onto the genetic variants to derive predicted values, then the outcome is regressed onto these predicted values. One advantage of investigating the combined effects of multiple variants is that the proportion of variance explained by the genetic instrument in MR is increased (Davey Smith & Hemani, 2014).

2.5.3.2 One and Two sample MR

To conduct MR, researchers can use either a one- or two-sample approach. One sample MR involves using a single sample to test for an association between the genetic instruments for the exposure and the outcome. Such designs can be effective when researchers are interested in multiple outcomes of the same individuals. For example, one study used a one-sample MR design to investigate the degree to which tobacco and cannabis use are causally associated with different aspects of cognitive functioning (Mahedy et al., 2021). In two sample MR, independent study samples are used, with one providing estimates of associations between genetic markers and the exposure, and another used to provide associations between genetic markers and the outcome. This provides researchers with more power and choice in their analyses; however, this does come at the expense of additional assumptions. The two samples are assumed to come from separate samples of participants from similar populations (Davies et al., 2019).

Due to the increase in size of GWASs, with some now including over a million participants (Lee et al., 2018b), it is likely that the two samples will overlap due to participants occurring in more than one consortium (Hartwig et al., 2017). However, it can often be difficult to provide a precise report of overlap as individuals are not identifiable in large summary data. To estimate sample overlap, researchers can calculate a percentage based on included participants in both the exposure and outcome GWASs. This percentage of overlap should

be based on the larger dataset as this includes the overlapping participants and therefore provides the correlation between the association estimates (Burgess et al., 2016). For example, if the exposure dataset is based on 10,000 participants, and the outcome dataset on 100,000, even if all individuals from the exposure dataset participate in the outcome data, sample overlap would still only be 10%. It is important that researchers report estimates of sample overlap as significant overlap can result in a bias towards the exposure-outcome association.

2.5.3.3 MR methods and pleiotropy

In addition to deciding whether to use a one- or two-sample design, researchers must also decide which MR method to use. There exist different variations of MR that make different assumptions about pleiotropy. Pleiotropy occurs when a genetic variant is significantly associated with more than one phenotype. Advances in GWAS discoveries have revealed widespread pleiotropy across many complex traits (Bulik-Sullivan et al., 2015). This can occur through various paths. For example, a variant may predict a primary and a secondary exposure due to the causal effect of the primary exposure on the secondary, a process known as vertical pleiotropy (see A in Figure 2.5). This type of pleiotropy satisfies the principles of MR and therefore would not inflict bias. However, genetic variants may also act on the second exposure via a pathway other than through the primary exposure. This is known as horizontal pleiotropy (see B in Figure 2.5. If this second exposure is a confounder of the relationship between the primary exposure and outcome, then one of the assumptions of MR is violated. Likewise, if the second exposure directly predicts the outcome, then another principle of MR becomes violated. These latter forms of pleiotropy can lead to biased estimates within MR if unaccounted for.

To investigate pleiotropy, variations of the traditional MR method can be compared. These each make different assumptions about pleiotropy and which variants included as genetic instruments are valid (Hartwig et al., 2017). Consistent estimates across the different

methods can help strengthen inferences and make bias less likely. These different methods and their approaches to pleiotropy are described below.

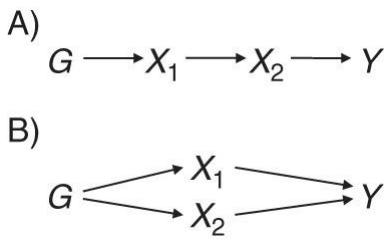

***Figure 2.5**: A Directed Acyclic Graph (DAG) demonstrating vertical (A) and horizontal (B) pleiotropy in associations between exposures (X_1 and X_2) and the outcome (Y).*

2.5.3.3.1 Inverse variance weighted (IVW)

The inverse-variance weighted (IVW) linear regression represents the standard MR approach (Hemani et al., 2018a) and is equal to the estimates derived from the 2SLS method described previously. Within IVW, causal estimates of each SNP are averaged using an inverse-variance weighted formula (Burgess et al., 2013). First, SNPs are regressed onto the exposure and the outcome to derive SNP-exposure and SNP-outcome estimates. A weighted regression is then performed in which the SNP–outcome association estimates are regressed onto the SNP–exposure association estimates, weighted by the inverse of the precision of the IV–outcome coefficients (Bowden et al., 2015). Here the intercept is also constrained to zero, assuming no horizontal pleiotropy.

The weighted estimates within IVW are based on two assumptions. The first is that the SNP-exposure and SNP-outcome association estimates are uncorrelated. The second is that the SNP-exposure association is measured with no measurement error (the NOME assumption) (Hemani et al., 2018a). To estimate the instrument strength, researchers use the F statistic. The F statistic captures the proportion of the variance in the phenotype explained by the genetic variants (R^2), the sample size, and the number of instruments. A general rule of thumb is that the F statistic should generally be larger than 10 (Davies et al., 2017). The

NOME assumption is almost always violated because standard errors are usually non-zero within the SNP-exposure association. However, in instances where this is strongly violated, as evident by a small F-statistic, the resulting IVW estimate would bias results towards the null in two-sample MR (Davies et al., 2019). This is because using weak instruments limits statistical power to test hypotheses. Subsequent interpretations of the results will therefore need to be made with caution.

In addition to weak instruments, biased IVW estimates also occur in the presence of heterogeneity (Bowden et al., 2015). In a typical MR with only vertical pleiotropy, the influence of each SNP on the outcome would be expected to be proportional to the effect of the SNPs on the exposure (Hemani et al., 2018a). These causal estimates should be homogenous, meaning effects are the same across SNPs. When this is not the case, and there is variability in the causal estimates obtained for each SNP, this is known as heterogeneity. Tests of heterogeneity can reveal how consistent the causal estimate is across SNPs, which can be used as an indicator of pleiotropy. Heterogeneity amongst the ratio estimates can be calculated using Cochran's Q statistic.

Understanding the degree of bias resulting from heterogeneity requires testing whether pleiotropic effects are balanced or unbalanced. Balanced pleiotropy occurs if the genetic variants that have pleiotropic effects are independent of the effects of the variants on the exposure. This type of pleiotropy is unlikely to bias the MR result because the genetic effects are in the opposite direction. The two effects therefore cancel one another out. Directional pleiotropy, on the other hand, is likely to inflict bias as the effects of the genetic variants are all in one direction (Plotnikov & Guggenheim, 2019). One way to investigate directional pleiotropy is to supplement findings with other methods, such as MR-Egger regression.

2.5.3.3.2 MR-Egger

In contrast to the IVW method, MR-Egger relaxes the assumptions of MR and does not assume that genetic variants are unaffected by pleiotropy. Instead, MR-Egger is based on

the InSIDE (Instrument Strength Independent of Direct Effect) assumption (Bowden et al., 2015). This assumes that the magnitude of pleiotropic effects on the outcome are independent of the SNPs' association with the exposure, and thus not related to its strength as an instrument (Bowden et al., 2016). Therefore, in contrast to the IVW method, MR-Egger does not constrain the intercept to zero, but instead includes an intercept in the model. An intercept term that differs from zero provides an average of the directional pleiotropic effects across all variants. This pleiotropy is adjusted for in the slope estimate, allowing MR-Egger to provide a sensitivity test for the robustness of the IVW results (Bowden et al., 2015).

The performance of IVW versus MR-Egger varies depending on sample size, the strength of genetic variants, and the heterogeneity of effects. The IVW regression typically has greater power than MR-Egger to reject the causal null hypothesis, while MR-Egger provides a less biased estimate (Bowden et al., 2015). MR-Egger has significantly lower power than IVW regression because of its relaxed assumptions relating to pleiotropy (Hemani et al., 2018a). Because MR-Egger estimates account for heterogeneity and bias due to pleiotropy, power is especially low when the SNP effects are homogenous (Bowden et al., 2017). This is because such analyses are more susceptible to regression dilution bias. The expected magnitude of regression dilution can be estimated using the regression dilution I^2 (Bowden et al., 2016). Where this statistic is lower than 0.9, simulation extrapolation (SIMEX) corrections can be applied.

SIMEX involves the creation of pseudo-data based on the original summary data estimates, but under increasing violations of the NOME assumption (Bowden et al., 2017). Following this, a model is fitted to infer the estimate that would have been obtained if the NOME assumption had been satisfied. As such, SIMEX corrects the MR-Egger coefficients for regression dilution. Any differences in MR-Egger or SIMEX estimates compared to IVW could therefore indicate that either the InSIDE (instrument strength independent of direct effect) assumption is violated, or there is directional pleiotropy. In relation to the previous

example of CAD, MR studies have shown that the impact of a risk factor, known as serum urate, is significantly reduced in MR-Egger estimates relative to IVW (White et al., 2016). Such findings suggest effects of serum urate on CAD risk may be driven by directional pleiotropy and may not necessarily reflect causal effects. This demonstrates the importance of using multiple MR methods to strengthen causal inferences.

2.5.3.3.3 Weighted median and weighted mode

In addition to MR-Egger, other methods exist that are also robust to unsatisfied MR assumptions. These include the weighted median and the weighted mode. Unlike MR-Egger which relaxes the assumption of pleiotropy for all genetic variants, the weighted median makes this assumption for 50% of the variants. This means that the causal estimate derived from a weighted median-based MR will be reliable provided at least half of the genetic variants are valid. For the weighted mode, even if the majority of variants used as instruments are invalid due to pleiotropy, the most common causal effect estimate is considered a consistent estimate of the true causal effect (Hartwig et al., 2017).

When considered together, the IVW, MR-Egger, weighted median, and weighted mode can provide useful insight into the robustness of results against violations of the MR assumption. However, caution should be taken when interpreting results that differ widely across these methods (Plotnikov et al., 2020).

2.6 Chapter summary

This chapter has outlined the two main cohorts used throughout this thesis, as well as the key genetic methods. The MR approach described above is used in Chapter 6 Part 1 to explore possible causal associations with wellbeing, while polygenic scores feature in Chapters 3 and 4. In Chapter 3, polygenic scores are created using data from the Quebec Newborn Twin Study (QNTS) to study predictors of peer victimisation, while in Chapter 4, the

Avon Longitudinal Study of Parents and Children (ALSPAC) is used to study polygenic predictors of resilience in young adulthood.

Chapter 3: A multi-polygenic approach to understanding the risk of peer victimisation[1]

3.1 Chapter overview

In Chapter 2 I provided an overview of the creation and use of polygenic scores. Here, I demonstrate how polygenic scores can be used to predict the risk of experiencing events like peer victimisation. Previous research has identified various traits and vulnerabilities associated with peer victimisation using the polygenic design (Schoeler et al., 2019). However, findings were based on self-report and only included assessments of victimisation in childhood and early adolescence.

In this chapter, I aim to:

- Investigate the aetiology of peer victimisation using genetic information related to multiple traits and vulnerabilities, including mental health, cognition, and physical appearance.
- Build upon previous genetic findings to test whether reports of victimisation from multiple informants can be used to complement predictions.
- Explore whether the same set of genetic vulnerabilities associated with childhood victimisation predict experiences in later adolescence.

3.2 Introduction

Peer victimisation is a prevalent experience in both childhood and adolescence (Biswas et al., 2020), with often long-lasting repercussions for mental health and wellbeing (Armitage et al., 2021). However, as outlined in Chapter 1, many victims also display substantial resilience. To understand and help prevent some of the negative outcomes of peer

[1] This chapter is based on the work conducted during a funded overseas visit to Quebec, Canada. The chapter has been adapted from Armitage, J. M., Morneau-Vaillancourt, G., Pingault, J-B., Andlauer, T. F. M., Paquin, S., & Brendgen, M. et al. (in press). A multi-informant and multi-polygenic approach to understanding predictors of peer victimisation in childhood and adolescence. *JCCP Advances.*

victimisation, it is useful to study factors that predispose an increased vulnerability. Identifying such risk factors could inform further study into whether the same factors confer an added risk to mental health following peer victimisation. Such knowledge could prove crucial to the development of preventive strategies targeted at those most at risk.

3.2.1 Predictors of peer victimisation

Victims of bullying often present certain traits and characteristics that may heighten their risk of peer victimisation. These include, but are not limited to, deficits in executive functioning (Danese et al., 2017), externalising and internalising problems (Cook et al., 2010), being lonely and socially withdrawn (Morneau-Vaillancourt et al., 2021), and being overweight (van Geel et al., 2014). Much of this research exploring correlates of peer victimisation, however, has derived from cross-sectional or longitudinal studies based on phenotypic data. Such designs are subject to confounding and reverse causation, making it difficult to infer if the identified factors predispose subsequent risk. As an example, it is possible that being overweight not only increases the risk of peer victimisation, but also arises as a result of being victimised. To therefore help infer the direction of associations, researchers have used genetically informative designs to study predictors of peer victimisation (Schoeler et al., 2019).

3.2.2 The role of genetics in predicting peer victimisation

Genetically informed methods represent a powerful tool through which the correlational design can be improved (Pingault et al., 2018). This is because the genetic sequence is fixed from birth and largely unaffected by environmental experiences. Problems relating to reverse causality are therefore significantly reduced. In relation to the example of weight, if genetic variants associated with an increased body mass index (BMI) predict peer victimisation, we can be more confident in our inferences relating to the direction of this effect.

Much of the genetic research on predictors of peer victimisation has derived from twin studies. These have been used to investigate the extent to which peer victimisation can be accounted for by genetic and environmental factors (Ball et al., 2008). Findings have revealed that genetic contributions explain between 65% and 77% of the variance in peer victimisation (Johansson et al., 2020; Veldkamp et al., 2019). Part of this genetic liability is shared with genetic vulnerabilities for other risk factors, including disruptive and aggressive tendencies (Boivin et al, 2013b; Musci et al., 2018), as well as physical (Brendgen et al., 2014) and mental health problems (Pergola et al., 2019). This means that individuals with an increased genetic tendency towards aggressiveness for example, are also more likely to experience peer victimisation.

The increased risk of being victimised among individuals with certain genetic vulnerabilities reflects what is known as a gene-environment correlation (rGE). This occurs when exposure to an environment is not entirely random but can be predicted by genetic predispositions. There are three main types of rGE; passive, active, and evocative (Plomin et al., 1977). A passive rGE occurs when the genetically influenced traits of a parent alter the environment of their child. This is largely because parents create environments that are consistent with their genotype. For example, a parent with depressive tendencies might be less emotionally available for their child, resulting in problematic outcomes for the child. Although these effects are genetic in origin, they are environmentally mediated by the parent. An active rGE refers to the environments that the child selects based on their genotype. For example, a child genetically inclined to be more aggressive may also engage in more violent play. An evocative rGE would then arise if these genetically influenced traits evoked a certain reaction from the environment. For example, an aggressive child may evoke more negative treatment from peers.

3.2.2.1 The multi-polygenic approach

Although twin research has provided important insight into the relative contributions of genetic and environmental factors in predicting peer victimisation (Boivin et al., 2013a), such designs are blind to specific genetic variants. This is because twin studies estimate the role of genetic factors by comparing phenotypic similarity between twins with differing degrees of genetic relatedness. To pinpoint sources of genetic variance more directly, polygenic scores can be used.

As explained in Chapter 2, polygenic scores exploit genetic data to provide an estimate of an individual's liability to a trait or disorder. Unlike the latent assessment of genetics and population statistics derived from twin research, polygenic scores provide an indication of the number of risk alleles that an individual carries, allowing individual level analyses (Lewis & Vassos, 2020). These polygenic scores can be used to investigate associations with the original phenotype of interest, or with other traits and exposures to determine possible rGE. Since no large-scale genome-wide association study (GWAS) has been published on peer victimisation, we still know little about the molecular genetic aetiology of victimisation. Using polygenic scores is therefore a relevant tool to do this. Multiple polygenic scores can also be studied in unison to determine their joint and independent predictive power (Krapohl et al., 2018). Such a design is particularly important when investigating exposures like peer victimisation, for which there are multiple associated risk factors (Cook et al., 2010).

One study that employed this multi-polygenic approach to study predictors of peer victimisation was carried out by Schoeler and colleagues (2019). Within their study, polygenic scores related to 35 traits were created and used to test for associations with peer victimisation. The traits related to cognition, personality, physical appearance, and various mental health problems, with these investigated using both single and multi–polygenic regression models. The multi–polygenic regression models were used to explore whether the polygenic scores identified as predictive of peer victimisation also had independent

effects. Overall, the study found that ten polygenic scores were predictive of the risk of peer victimisation, with five also shown to have independent associations (Schoeler et al., 2019). Although limited in magnitude due to the nascent nature of polygenic scores, the pattern of associations was consistent with those previously identified using observational data.

By replicating previous observational studies using genetic data, Schoeler and colleagues (2019) were able to triangulate existing research findings and implicate predisposing risk factors for peer victimisation. This is key to providing a stronger basis for causal inference (Hammerton & Munafò, 2021) and informing early prevention strategies. Some shortcomings of the study, however, need to be acknowledged prior to interpreting the findings.

3.2.3 Limitations of previous research

3.2.3.1 Reports of peer victimisation

The first limitation of the study by Schoeler and colleagues (2019) is that the study relied on self-reports of peer victimisation. Self-reports provide important first-hand accounts of an individual's experience and can thus have some positive implications for intervention. For example, one study found that the relationship between frequent victimisation and mental health service use is mediated by whether victims self-identify as having a mental health problem (Oexle et al., 2020). Such findings highlight the value of understanding the subjective experience to gain insight into support seeking. However, it is also well established that subjective experiences can intensify reactions to events (Reininghaus et al., 2016). This is because self-reports are strongly driven by subjective appraisals of the event.

In support of this, findings have shown that for individuals exposed to child maltreatment, psychopathology later emerges as a function of the subjective experience of the event, even if these subjective reports do not align with more objective measures (Danese & Widom, 2020). This was found after comparing associations between child maltreatment and psychopathology using either self-reports of the maltreatment, or court documented evidence. Such findings again highlight the importance of understanding subjective

experiences and their relevance to informing intervention needs, however, they also highlight a key issue with self-reports which is the potential for self-perception biases.

An example of how self-perceptions may bias outcomes related to peer victimisation has been investigated through study of children with relationship difficulties. Such children often vary in their self-perceptions of both peer status (Boivin & Bégin, 1989) and symptoms of depression (Boivin et al., 1994). It is plausible that for individuals at a greater genetic risk of depression, these self-perceptions will be heightened, making the likelihood of reporting negative peer treatment even more likely. This could mean that associations between self-reported victimisation and genetic proxies for depression are driven by a greater tendency to report victimisation, rather than a greater risk of experiencing victimisation (Schoeler et al., 2019). This is known as the 'shared-rater effect' and has been shown to predict larger associations between victimisation and depression (Schoeler et al., 2018).

To investigate the putative effects of self-reports and complement current findings, researchers have proposed using peer-nominations and teacher-ratings (Ladd & Kochenderfer-Ladd, 2002). Peers become increasingly important throughout childhood and adolescence, with youth spending more time with peers across development (Rubin et al., 2006). Peers are a context for learning skills, attitudes, and behaviours, most of which take place in the school environment (Cillessen & Marks, 2017). Accordingly, peers are key witnesses to social interactions, and are involved in up to 85% of bullying episodes that occur in school (Craig & Pepler, 1997). Peers have therefore been suggested as an ideal reference point from which to assess peer difficulties (Boivin et al., 2013a).

Teachers also play an important role in the school context and management of bullying (Yoon & Bauman, 2014). Because teachers are not direct members of the peer group, they provide more objective accounts of social behaviours (Rubin et al., 2006). However, teachers are not exposed to all social encounters, which may mean that some negative interactions or behaviours go unnoticed (van den Berg et al., 2015). Teacher reports are also

only based on one informant, whereas peer nominations are derived from multiple peers, which increases their reliability (Marks et al., 2013). To therefore attain a more complete understanding of the extent of peer victimisation, it may be necessary to explore reports from the victims, their teachers, and their peers.

It is important to note that different informant reports of peer victimisation should not be expected to yield similar estimates or associations. Many have shown that concordance between self-, teacher-, and peer-reports are often low to moderate when reporting victimisation (Ladd et al., 2002), with agreement typically greater between peer- and teacher-reports than between self- and teacher-reports. Self-reports tend to result in more individuals classified as victims compared to peer-reports (Oldenburg et al., 2015), which likely reflects the different aspects of peer victimisation that is captured by each informant (Ladd et al., 2002). Thus, the goal when using assessments from multiple informants should not be to generate one overarching result (Rubin, 2005), but to determine the extent to which variation specific to each informant is associated with the risk under study (Ladd et al., 2002).

3.2.3.2 Victimisation across childhood and adolescence

Another important consideration when investigating peer victimisation is whether genetic vulnerabilities play out differently across development. The study by Schoeler and colleagues (2019) used an average victimisation score that captured instances between ages 8 to 13 years. This did not allow the authors to investigate whether a genetic vulnerability for a given trait is more of a risk for victimisation in childhood or later adolescence. This is possible because as children progress towards adolescence, significant physical, psychological, and social changes take place (Troop-Gordon, 2017). Such changes may alter an individual's risk of experiencing peer victimisation and may be differentially associated with the risk of victimisation in childhood versus adolescence.

As an example, although individual differences in aggression tend to be stable (Olweus, 2013), the role of aggression as a risk factor for victimisation may differ in childhood and adolescence. Aggressive peers are typically rejected in childhood (Coie & Kupersmidt, 1983) and often at a greater risk of peer victimisation (Brendgen et al., 2011). However, as children move into adolescence, the relationship between peer victimisation and aggression becomes complicated, with aggressive adolescents at less of a risk of peer victimisation if they are rated as more popular (Ferguson et al., 2016). It is possible that this finding reflects a greater acceptance of aggression in adolescence, which could grant protection from peer victimisation by offsetting the likelihood of out-group conflict and retaliation. Accordingly, a genetic vulnerability for aggression may not play out similarly in adolescence versus childhood.

Although genetic variants are fixed from birth, their effects on a phenotype can change over time (Haworth & Davis, 2014). For some traits like intelligence, genetic factors become more important determinants of cognitive ability than in earlier years (Haworth et al., 2010). A polygenic score for intelligence may therefore have a larger impact on peer victimisation experiences in later adolescence relative to those occurring in childhood. No study, however, has yet examined how the impact of genetic vulnerabilities on victimisation may unfold across development.

One way to investigate changes in polygenic predictiveness over time is to use a repeated measures approach like growth-curve modelling (Kwong et al., 2021). Growth-curve modelling involves extracting longitudinal data to study how individual trajectories unfold over time in relation to a population (Goldstein, 2010). This can be used to provide insight into the extent to which associations between genetic liability and traits change across development. Such an approach can also be carried out and performed well where sample sizes are low due to using multiple data points and techniques such as maximum likelihood (McNeish & Matta, 2018). This is explained in more detail in the methods section.

3.3 Current study

The aims of the current study were twofold. The first was to replicate and extend previous research by Schoeler and colleagues (2019) to explore whether teacher- and peer-reports could be used to complement associations based on self-reports. The second was to expand the developmental coverage of previous research by including assessments of peer victimisation beyond childhood.

To achieve the first aim, reports from different informants, including the victims, teachers, and peers, were each investigated separately for associations with previously identified polygenic scores (Schoeler et al., 2019). The second aim was then investigated by taking reports of peer victimisation in childhood and later adolescence, including ages 7, 10, 12, 13, 15, and 17 years. It was hoped that by extending previous findings to document peer victimisation more comprehensively, the current study would provide further insight into the role of pre-existing vulnerabilities. This understanding could be used to inform further study into predictors of resilience following peer victimisation.

3.4 Methods

3.4.1 Sample description

Phenotype and genotype data were taken from the Quebec Newborn Twin Study (QNTS), a prospective longitudinal follow-up of twins that was described in detail in Chapter 2. The current study used participants from twin pairs with available genetic data who also had information relating to experiences of peer victimisation. This was assessed across six different time points: spanning ages 7, 10, 12, 13, 15, and 17 years. At 7 and 10 years, information about peer victimisation was taken using self-, teacher- and peer-reports, while measures at 12 years were based on self- and teacher-reports. Assessments from secondary school onwards were based on self-reports as data from teachers and peers were not available. Self-reports were deemed more appropriate, however, as students have multiple classrooms and teachers during this period.

To maximise available data, the current study used mean composite scores that separately explored predictors of childhood and adolescent peer victimisation, as outlined below. Both twins were included in each twin pair, with family effects modelled in the regression analyses. This resulted in sample sizes that ranged from 448 to 518. Comparisons between monozygotic (MZ) and dizygotic (DZ) twins revealed no significant differences in victimisation scores (see Appendix 3.1). There were also no differences in victimisation scores between included participants and those not included due to missing genotype data, as demonstrated in Chapter 2. However, as noted in Appendix 3.2, those who completed the victimisation assessments at either 7 or 17 years were more likely to be white and from more educated parents.

3.4.2 Measures

Details relating to the peer victimisation measures and how these were assessed were presented in Chapter 2. In Table 3.1, further information about the samples included in the present analyses can be found, alongside average mean scores from the self-, teacher- and

peer-reports. This table also includes victimisation scores that have been z-standardised. Main analyses were conducted using z-standardised scores to facilitate comparisons across the different scales. Results from the unstandardised victimisation scores can be found in Appendix 3.3 and 3.4.

3.4.2.1 Self-reported victimisation

Self-reported victimisation was assessed at each of the included time points. To first replicate previous findings (Schoeler et al., 2019), a self-reported childhood victimisation score was created where data were available from at least two time points from ages 7, 10, and 12 years. To then extend previous research to assess self-reported victimisation in adolescence, the same procedure was run using two or more scores from ages 13, 15, and 17 years. Correlations between the two composite scores was r=0.40 (see Table 3.2 for full correlation matrix).

To facilitate comparisons of victimisation with previous research, scores were converted into percentages representing the proportion of individuals scoring one standard deviation (SD) above the mean. This procedure has been used previously to capture instances of 'frequent victimisation' (Stadler et al., 2010). As evident in Table 3.1, average rates of peer victimisation were largely similar in childhood and adolescence, with 16.8% of individuals scoring one SD above the mean in childhood, and 16.2% in adolescence. These differences were not statistically different according to a two-sample test of equality of proportions (p=0.90).

3.4.2.2 Teacher-reported victimisation

Teacher-reports of victimisation were assessed across three time points, including ages 7, 10, and 12 years. To align with the self-report measure, a mean composite score was created based on scores from at least two time points. Correlations between this composite and the self-reported composite in childhood was r=0.36.

3.4.2.3 Peer-reported victimisation

Peer-reported victimisation was assessed using nominations from peers at ages 7 and 10 years. To create an overall index of victimisation as reported by peers, a mean score was created by averaging the mean scores from ages 7 and 10 years, which correlated at r=0.29. These reports have both been z-standardised to align with standard procedures for peer nomination data (Cillessen & Rose, 2005) and to account for differences in classroom size. As noted in Table 3.2, correlations between the peer-reported composite were greater with teacher-reported victimisation (r=0.48) compared to the self-reports (r=0.36).

Table 3.1: Victimisation scores based on age and informant (raw and z-standardised scores)

				Raw scores						Z-standardised scores			
	N	% Male	% Victimised[a]	M(SD)	Median	Min	Max	Range	Skew	Median	Min	Max	Range
Age 7													
Self-reported	527	51.0	18.4	0.71 (0.52)	0.62	0.00	2.00	2.00	0.62	-0.16	-1.37	2.51	3.88
Teacher-reported	476	51.3	21.2	0.26 (0.37)	0.00	0.00	2.00	2.00	1.44	-0.72	-0.72	4.75	5.47
Peer-reported	465	50.8	18.7	0.00 (1.00)	-0.30	-2.19	2.90	5.09	0.83	-0.30	-2.19	2.90	5.09
Age 10													
Self-reported	480	51.3	19.2	0.68 (0.42)	0.62	0.00	2.00	2.00	0.45	-0.12	-1.60	3.13	4.73
Teacher-reported	436	50.7	22.2	0.25 (0.38)	0.00	0.00	2.00	2.00	1.63	-0.65	-0.65	4.55	5.20
Peer-reported	418	50.7	15.1	0.00 (1.00)	-0.32	-1.35	3.83	5.18	1.59	-0.32	-1.35	3.83	5.18
Age 12													
Self-reported	459	49.2	13.9	0.48 (0.34)	0.44	0.00	2.00	2.00	1.00	-0.10	-1.40	4.40	5.84
Teacher-reported	375	46.1	17.1	0.21 (0.38)	0.00	0.00	2.00	2.00	2.17	-0.55	-0.55	4.77	5.31
Age 13													
Self-reported	450	48.9	13.7	0.37 (0.33)	0.33	0.00	1.89	1.89	1.27	-0.10	-1.09	4.56	5.65
Age 15													
Self-reported	417	48.0	11.5	0.21 (0.25)	0.11	0.00	1.67	1.67	1.74	-0.38	-0.82	5.80	6.62
Age 17													
Self-reported	429	47.6	15.4	0.18 (0.23)	0.11	0.00	1.25	1.25	1.71	-0.30	-0.78	4.57	5.35

Composite scores across ages													
Self-reported childhood[b]	507	50.7	16.8	0.63 (0.32)	0.60	0.00	2.00	2.00	0.61	-0.14	-1.93	4.07	6.00
Teacher-reported childhood[c]	448	50.1	15.1	0.24 (0.29)	0.17	0.00	1.50	1.50	1.44	-0.26	-0.84	4.38	5.22
Peer-reported childhood[d]	518	51.2	14.9	-0.04 (0.81)	-0.26	-1.73	3.72	5.45	1.16	-0.26	-1.73	3.72	5.45
Self-reported adolescence[e]	450	47.3	16.2	0.25 (0.21)	0.19	0.00	1.15	1.15	1.06	-0.30	-1.19	4.22	5.41

Note: Peer-reported victimisation have already been z-standardised, therefore raw and z-standardised scores are the same. Raw scores for self- and teacher-reported victimisation reflect the mean across five items, with each item rated on a three-point scale (0=Never, 1=Sometimes, or 2=Often). A higher overall mean therefore reflects more frequent victimisation.

[a] Percentage victimised reflects those scoring one standard deviation above the mean.

Table 3.2: Correlations between different informant reports of victimisation

Variables	Correlation matrix														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age 7															
1. Self-reported	1	0.20***	0.24***	0..25***	0.11***	0.15***	0.15***	0.11*	0.11***	0.01	0.05	0.75***	0.19***	0.23***	0.07
2. Teacher-reported		1	0.35***	0.12**	0.29***	0.30***	0.20***	0.26***	0.21***	0.16***	0.08*	0.23***	0.73***	0.37***	0.22***
3. Peer-reported			1	0.20***	0.17***	0.29***	0.14***	0.28***	0.22***	0.11*	0.14**	0.34***	0.36***	0.87***	0.22***
Age 10															
4. Self-reported				1	0.29***	0.20***	0.40***	0.22***	0.30***	0.19***	0.12**	0.76***	0.29***	0.27***	0.30***
5. Teacher-reported					1	0.17***	0.25***	0.38***	0.21***	0.15***	0.12***	0.30***	0.80***	0.39***	0.23***
6. Peer-reported						1	0.33***	0.31***	0.29***	0.18***	0.10*	0.34***	0.48***	0.85***	0.25***
Age 12															
7. Self-reported							1	0.34***	0.58***	0.39***	0.31***	0.67***	0.34***	0.27***	0.55***
8. Teacher-reported								1	0.33***	0.24***	0.15***	0.29***	0.77***	0.33***	0.31***
Age 13															
9. Self-reported									1	0.41***	0.34***	0.43***	0.34***	0.31***	0.83***
Age 15															
10. Self-reported										1	0.42***	0.25***	0.24***	0.17***	0.77***
Age 17											1	0.20***	0.16***	0.13***	0.72***
11. Self-reported															
Mean composite scores across ages															

12.	Self-reported childhood[a]	1	0.36***	0.36***	0.40***
13.	Teacher-reported childhood[b]		1	0.48***	0.35***
14.	Peer-reported childhood[c]			1	0.29***
15.	Self-reported adolescence[d]				1

Note*:*

[a] Self-reported childhood composite based on assessments from 7, 10, and 12 years.

[b] Teacher composite based on assessments from 7, 10, and 12 years.

[c] Peer composite based on assessments from 7 and 10 years.

[d] Self-reported adolescent composite based on assessments from 13, 15, and 17 years.

3.4.2.4 Polygenic scores

Publicly available data was taken from ten genome-wide association studies (GWASs) to create ten polygenic scores. These polygenic scores reflect the ten traits and vulnerabilities that were previously identified as predictive of peer victimisation (Schoeler et al., 2019). Information about the GWASs can be found in Appendix 3.5. Where larger and more recent GWASs were available since the study by Schoeler and colleagues (2019), these were used instead to increase power. It is important to note that there was no overlap between the target sample and the GWAS samples.

All polygenic scores were created in PRSice version 2.2.3 (Euesden et al., 2015), a free and efficient software that clumps single nucleotide polymorphisms (SNPs) and performs thresholding against criteria set by the user. All polygenic scores were created by combining the number of risk alleles present for each SNP (0, 1, or 2), weighted by their effect estimates reported in the original GWAS. These were used to construct scores in the QNTS using imputed genotypes, with SNPs removed if they had a minor allele frequency (MAF) < 0.01 and an imputation quality score <0.8. During clumping, SNPs in linkage disequilibrium (LD) at $r^2 > 0.10$ within a 250-base pair window were also removed.

To align with previous procedures (Schoeler et al., 2019), polygenic scores were computed at multiple *p*-value thresholds, from 0.01 to 1 at 0.01 increments. An empirical *p*-value for the best-fit threshold was generated using permutation (10,000 times). This is determined in PRSice using the polygenic score that generates the highest R^2 estimate. Correlations between the final best-fit polygenic scores that were used for the main analysis can be found in Table 3.3. All polygenic scores were standardised to have a mean of 0 and standard deviation of 1. This is to facilitate interpretability (Lewis & Vassos, 2017).

Table 3.3: Genetic correlations between polygenic scores

Variables	Correlation matrix									
	1	2	3	4	5	6	7	8	9	10
1. Major depressive disorder	1	0.15***	-0.03	0.10*	-0.00	-0.17***	0.22***	-0.46***	0.15***	0.12**
2. ADHD		1	0.02	0.13**	-0.12**	-0.21***	0.02	-0.06	0.05	0.05
3. Risk-taking			1	0.08*	0.00	0.01	-0.05	-0.00	0.10*	-0.01
4. BMI				1	-0.09*	-0.15***	0.06	0.04	-0.06	0.32***
5. Intelligence					1	0.35***	-0.10*	.012**	-0.06	-0.02
6. Educational attainment						1	-0.14***	0.17***	0.01	0.07
7. Depressive symptoms							1	-0.32***	-0.07	0.10*
8. Wellbeing								1	-0.08*	-0.12***
9. Schizophrenia									1	0.10*
10. Extreme BMI										1

*p<0.05, **p<0.01, ***p<0.001. ADHD = Attention Deficit Hyperactivity Disorder; BMI=Body Mass Index

Note: Correlations based on a sample of individuals with complete genotype data and the self-reported childhood victimisation composite aged 7 (n=507).

3.4.3 Statistical analyses

3.4.3.1 Main analyses

Mean rates of peer victimisation across all individuals were first compared using t-tests. These were used to estimate whether rates of peer victimisation change over time and by informant. Main analyses then attempted to replicate previous associations between genetic liability and childhood victimisation (Schoeler et al., 2019) using linear regression models. These models explored the ability of the ten polygenic scores to predict peer victimisation using either the self-, teacher-, or peer-reported composite scores. The same set of analyses were then repeated, replacing the self-reported childhood composite with the self-reported adolescent composite.

The contribution of each polygenic score was first investigated separately in single-polygenic score models using the lme4 package (Bates et al., 2014) in R studio 4.05 (R Core Team, 2021). This allowed for the fitting of linear mixed effects models to adjust for the non-independence of the twin data. A linear mixed effects model, sometimes referred to as a multilevel or hierarchical model (Goldstein, 2003; Raudenbush & Bryk, 2002), is used for analysing data that contains clustered structures. It is important to control for clustered data because correlations that may occur within each cluster go against the assumptions of a parametric statistical model which assumes independence. Polygenic scores that were significantly associated with the outcome in these single-polygenic models were then entered into a multi-polygenic score model to assess independent contributions. Multicollinearity was not an issue within the multi-polygenic score models as correlations between the polygenic scores were low (as noted in Table 3.3).

Both the single- and multi-polygenic score models adjusted for sex and 10 principal components (PCs) to control for population stratification. The variance explained by each polygenic score was calculated by first regressing the victimisation variable onto sex and the 10 PCs, and calculating the variance explained by the fixed effects. Pseudo-r-squared

estimates were generated using the “MuMIn” package (Barton, 2020) to estimate the variance explained by the fixed effects. These estimates were then compared to models that included the polygenic scores. The difference in R^2 estimates is referred to as the incremental R^2.

All main analyses corrected for multiple testing using Benjamini-Hochberg False Discovery Rate (FDR; Benjamini & Hochberg, 1995). The Benjamini-Hochberg FDR controls for the probability of making a Type I error on multiple comparisons. This test was chosen over the Bonferroni correction as it allows for the non-independence of repeated tests. The Bonferroni method is too conservative for testing multiple regression coefficients since they are not independent tests (Bland & Altman, 1995). To calculate the FDR, the corresponding p-values are ranked from 1, starting with the smallest p-value. The Benjamini-Hochberg critical value is then calculated as (i/m)*Q, whereby i represents the p-value rank, m represents the total number of tests carried out, and Q the false discovery rate. This was set as 0.05 in the current study. The largest p-value that is smaller than its corresponding Benjamini-Hochberg critical value is deemed significant, as well as the smaller p-values that follow. This can mean that p-values are significant even if they are not smaller than their own Benjamini-Hochberg critical value.

The total number of tests adjusted for in the present study was 49. This reflects the ten single-polygenic score regressions that were conducted for each outcome (4 outcomes in total: self-reported childhood composite, teacher-reported childhood composite, peer-reported childhood composite, self-reported adolescent victimisation), as well as the multi-polygenic score models which were conducted.

3.4.3.2 Mixed effect models for repeated measures

Analyses were then extended to investigate the extent to which associations between polygenic scores and victimisation change across development. To do this, a longitudinal growth curve model was fit to the data using the ‘lme4’ package in R (Bates et al., 2014).

This allowed a mixed effects model to explore mean trajectories of victimisation for the entire sample, as well as individual deviations from the mean for each participant. The default method for accounting for missing data in this package is the restricted maximum likelihood estimation (REML), which is commonly preferred for smaller samples (McNeish et al., 2018).

Within the mixed effects model, the intercept and slope terms for the population trajectory are modelled as fixed effects, and the individual trajectories as random effects. This allows random effects to generate separate growth trajectories for each participant. To examine associations between the polygenic scores and trajectories of victimisation, age was first modelled using all self-reports from ages 7, 10, 12, 13, 15, and 17 years. This allowed analyses to explore whether polygenic scores are associated with both initial victimisation and changes over time. To then test whether polygenic scores had statistically different effects in childhood verse adolescence, a 'period' variable was included in a mixed model for repeated measures. As per the mean composite scores, ages 7, 10 and 12 years were used to represent childhood victimisation, and ages 13, 15, and 17 years captured adolescent victimisation. Ages falling under the 'childhood' category were initially coded as "0" and those in adolescence were coded as "1" to form the period variable. Analyses were then repeated with adolescence coded as "0" and childhood coded as "1" to extract the main effect estimates of adolescent victimisation. All mixed effect models included a main effect of each standardised polygenic score, an interaction term with age (or period), an interaction term between sex and age (or period), as well as the 10 PCs. All models also adjusted for the clustering of twin data.

3.4.4 Power calculations

Power calculations for the main analyses were conducted post-hoc using the 'avengeme' (Additive Variance Explained and Number of Genetic Effects Method of Estimation) package in R studio (Dudbridge, 2013). Within this package, there is a function called 'polygenescore' which is used to estimate the variance explained by polygenic scores based on several input

parameters. These include the sample size of the GWAS and target sample, the SNP-based heritability of the phenotype and the number of variants included in the polygenic score. Different power estimates were therefore attained for each trait and polygenic score, as demonstrated in Appendix 3.6 and 3.7. Power calculations for the longitudinal growth curve models were conducted using simulations based on the 'simr' package in R (Green & MacLeod, 2015). This provided the flexibility necessary for power estimates based on both fixed and random effects (Kumle et al., 2021). It also allowed calculations to compare power for varying effect estimates of the polygenic scores. The results from these calculations are provided in Appendix 3.8.

3.5 Results

3.5.1 Descriptive data

On average across the self-, teacher-, and peer- reports, 15.6% of individuals experienced frequent victimisation in childhood (Table 3.1), based on scoring one SD above the mean (Stadler et al., 2010). T-test comparisons revealed no significant differences between the proportion of individuals identified as frequent victims using either self- or teacher-reports (p=0.55), self- or peer-reports (p=0.46), or teacher- or peer-reports (p=0.99).

Significant decreases in rates of peer victimisation occurred with increasing age, as noted by both the self- and teacher-reports of peer victimisation (see Table 3.4). Such declines were markedly greater when using self- compared to teacher-reports, and were more apparent as age discrepancies increased. This overall trend of decreasing victimisation is consistent with the wider peer victimisation literature (Biswas et al., 2020).

Table 3.4: Comparison of self- and teacher-reported victimisation across time

	Average victimisation scores			**Percentage scoring one SD above mean**		
	Mean (SD)	p^1	p^2	%	p^1	p^2
Self-reported						
Age 7	0.71 (0.52)	-	-	18.4	-	-
Age 10	0.68 (0.42)	0.30	0.30	19.2	0.82	0.82
Age 12	0.48 (0.34)	<0.001	<0.001	13.9	0.07	<0.05
Age 13	0.37 (0.33)	<0.001	<0.001	13.7	0.06	0.99
Age 15	0.21 (0.25)	<0.001	<0.001	11.5	<0.01	0.37
Age 17	0.18 (0.23)	<0.001	<0.05	15.4	0.25	0.12
Teacher-reported						
Age 7	0.26 (0.37)	-	-	21.2	-	-
Age 10	0.25 (0.38)	0.63	0.63	22.2	0.78	0.78
Age 12	0.21 (0.38)	<0.05	0.09	17.1	0.15	0.08

Note: p^1 = Comparison with victimisation score or percentage victimised at age 7. p^2=Comparison with victimisation score or percentage victimised at age assessed prior.

3.5.2 Associations between polygenic scores and childhood victimisation

3.5.2.1 Self-reported peer victimisation

Analyses predicting the self-reported childhood composite revealed significant associations with two of the ten polygenic scores (Table 3.5). These were found for polygenic scores related to major depressive disorder (MDD), which predicted an increased risk of peer victimisation, and polygenic scores related to wellbeing, which reduced the risk of peer victimisation. It is important to note that neither of these associations remained significant in the multi-polygenic score model (see Table 3.6), and neither survived after correction for multiple testing.

3.5.2.2 Teacher-reported peer victimisation

Findings using the teacher-reported victimisation composite revealed associations with three out of the ten polygenic scores. These were different to the polygenic scores identified as predictive of self-reported victimisation. For teacher-reported victimisation, associations were found for polygenic scores related to BMI, intelligence, and educational attainment (Table 3.5). Polygenic scores associated with BMI predicted an increased risk of teacher-reported victimisation, while a higher genetic score for intelligence and educational attainment predicted a reduced risk (see Figure 3.1). Associations with the intelligence and educational attainment polygenic scores both survived after correction for multiple testing, and the educational attainment polygenic score remained associated in the multi-polygenic score model (Table 3.6). Such findings suggest a unique contribution of a genetic propensity for educational attainment on the likelihood of teacher-reported victimisation.

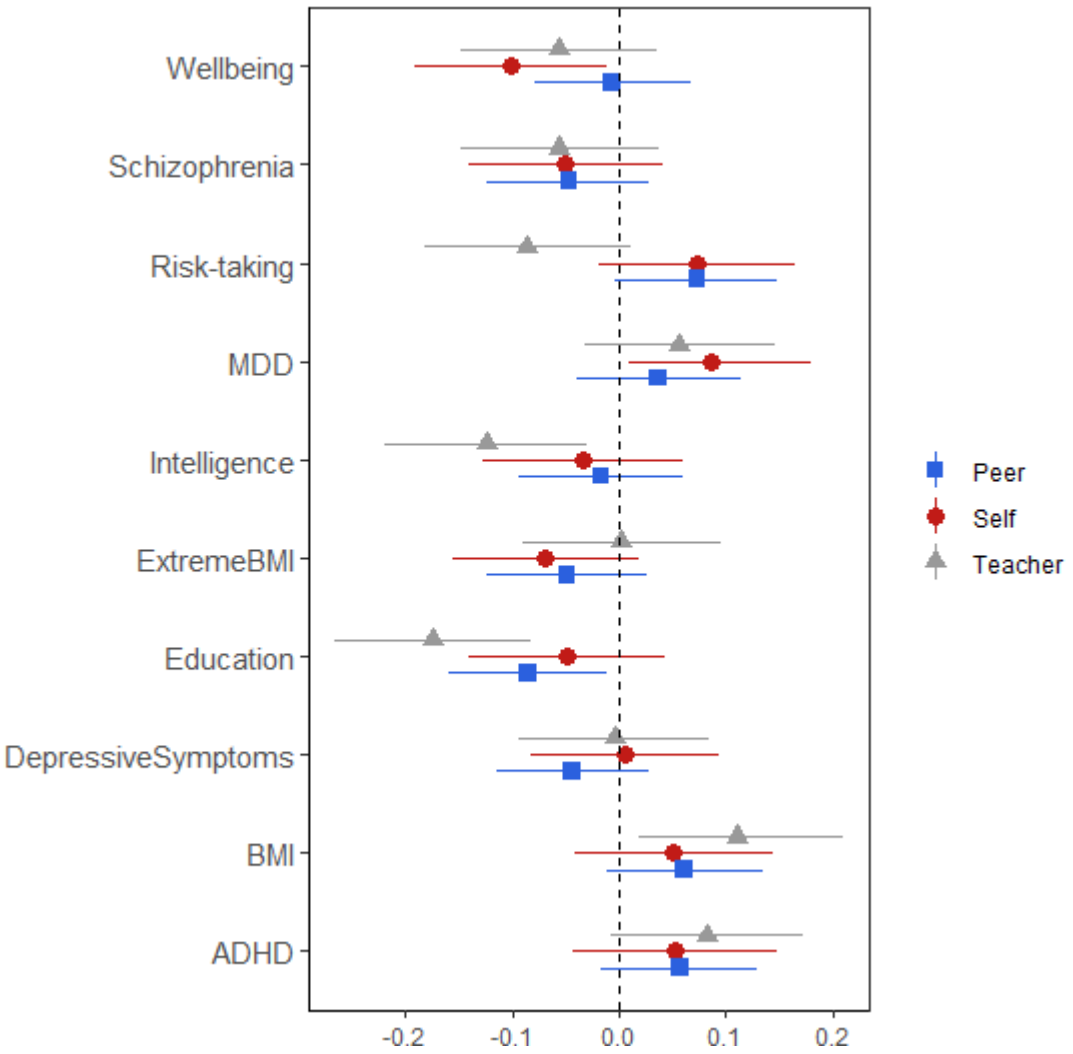

Figure 3.1: *Regression coefficients from single-PGS models predicting victimisation using either self-, teacher-, or peer- reports. Associations between teacher-reported victimisation and the intelligence PGS and the educational attainment PGS survived after correction for multiple testing.*

Table 3.5: Single-polygenic score models investigating associations between polygenic scores and z-standardised self-, teacher-, and peer-reported childhood victimisation

	Self-reported victimisation				Teacher-reported victimisation				Peer-reported victimisation			
PGSs	Coefficient, β(95%,CI)	SE	*p*	R^2	Coefficient, β(95%,CI)	SE	*p*	R^2	Coefficient, *β*(95%,CI)	SE	*p*	R^2
MDD	**0.086 (0.009, 0.181)**	**0.05**	**0.05**	**0.30%**	0.053 (-0.043,0.149)	0.05	0.27	0.91%	0.037 (-0.040,0.114)	0.04	0.35	0.20%
ADHD	0.056 (-0.031, 0.147)	0.05	0.20	0.00%	0.083 (-0.007,0.173)	0.05	0.07	1.36%	0.057 (-0.016,0.129)	0.04	0.13	0.45%
Risk-taking	0.073 (-0.018, 0.166)	0.05	0.11	0.19%	-0.086 (-0.183,0.011)	0.05	0.08	1.27%	0.073 (-0.003,0.149)	0.04	0.06	0.79%
BMI	0.051 (-0.041, 0.145)	0.05	0.28	0.00%	**0.110 (0.019,0.201)**	**0.05**	**0.02**	**1.85%**	0.061 (-0.012,0.135)	0.04	0.10	0.50%
Intelligence	-0.034 (-0.128, 0.060)	0.05	0.47	0.00%	**-0.124 (-0.219,-0.030)**	**0.05**	**<0.001†**	**2.15%**	-0.017 (-0.093,0.060)	0.04	0.66	0.31%
Educational attainment	-0.049 (-0.141, 0.043)	0.05	0.29	0.00%	**-0.174 (-0.267,-0.082)**	**0.05**	**<0.001†**	**3.80%**	**-0.085 (-0.159,-0.011)**	**0.04**	**0.02**	**1.11%**
Depressive symptoms	0.005 (-0.082, 0.093)	0.05	0.90	0.00%	-0.004 (-0.093,0.085)	0.05	0.93	0.63%	-0.044 (-0.115,0.028)	0.04	0.23	0.28%
Wellbeing	**-0.101 (-0.191, -0.011)**	**0.05**	**0.03**	**0.84%**	-0.057 (-0.149,0.035)	0.05	0.22	1.06%	-0.006 (-0.079,0.067)	0.04	0.87	0.00%
Schizophrenia	-0.050 (-0.141, 0.041)	0.05	0.28	0.00%	-0.056 (-0.149,0.038)	0.05	0.24	0.97%	-0.047 (-0.123,0.028)	0.04	0.21	0.31%
Extreme BMI	-0.069 (-0.155, 0.018)	0.05	0.12	0.07%	0.002 (-0.091,0.096)	0.05	0.96	0.63%	-0.049 (-0.123,0.026)	0.04	0.20	0.32%

PGS = Polygenic scores. †FDR.
Note: Analyses based on linear mixed effects model, controlling for sex and 10 principal components. Self-reported victimisation based on mean composite of scores from 7, 10, and 12 years. Teacher-reported victimisation based on mean composite of scores from 7, 10, and 12 years. Peer-reported victimisation based on mean composite of scores from 7 and 10 years.

Table 3.6: Multi-polygenic score models investigating associations between polygenic scores and z-standardised self-, and teacher-reported childhood victimisation

	Self-reported victimisation[a]				Teacher-reported victimisation[b]			
PGSs	Coefficient, β(95%,CI)	SE	*p*	R^2	Coefficient, β(95%,CI)	SE	*p*	R^2
MDD	0.046 (-0.060,0.154)	0.05	0.39	0.97%	-	-	-	4.68%
Wellbeing	-0.080 (-0.181,0.021)	0.05	0.12		-	-	-	
BMI	-	-	-		0.023 (-0.005,0.051)	0.02	0.11	
Intelligence	-	-	-		-0.021 (-0.051,0.009)	0.02	0.18	
Educational attainment	-	-	-		-0.040 (-0.071, -0.010)	0.02	<0.001[†]	

PGS = Polygenic scores. [†]FDR. R^2 = variance explained by the combined effects of the polygenic scores included in the multi-PGS model.
Note: Analyses for each outcome used the PGSs identified in the single-PGS models. All analyses were conducted using linear mixed effects model, controlling for sex and 10 principal components. Self-reported victimisation based on mean composite of scores from 7, 10, and 12 years. Teacher-reported victimisation based on mean composite of scores from 7, 10, and 12 years.

3.5.2.3 Peer-reported peer victimisation

Results from the single-polygenic score models predicting peer-reported victimisation revealed just one significant finding (Table 3.5). This was found using the polygenic score for educational attainment, which as per the teacher-reported victimisation, reduced the risk of peer victimisation. Because just one association was found, there was no need to run a multi-polygenic score model.

3.5.3 Associations between polygenic scores and adolescent victimisation

When investigating whether predictions of childhood victimisation generalise to adolescence, findings revealed some consistent, but also some novel findings (see Table 3.7). Associations between self-reported victimisation in adolescence and polygenic scores related to major depression replicated, and new associations were observed with polygenic scores for BMI, educational attainment, and extreme BMI. No associations survived correction for multiple testing, and none were found in the multi-polygenic score models (see also Table 3.7). Polygenic scores related to major depression and educational attainment did however reach near significance (*p*=0.06).

Table 3.7: Associations between polygenic scores and z-standardised self-reported adolescent victimisation

	Single-PGS regression models				**Multi-PGS regression models**			
PGS	Coefficient, β(95% CI)	SE	*p*	r^2	Coefficient, β(95% CI)	SE	*p*	r^2
MDD	**0.137 (0.033, 0.243)**	**0.05**	**0.01**	**2.64**	0.102 (-0.004, 0.209)	0.05	0.06	5.06
ADHD	0.055 (-0.046, 0.155)	0.05	0.29	1.22	-	-	-	
Risk-taking	-0.055 (-0.165, 0.056)	0.05	0.33	1.19	-	-	-	
BMI	**0.117 (0.013, 0.221)**	**0.05**	**0.03**	**2.23**	0.062 (-0.049, 0.174)	0.06	0.27	
Intelligence	-0.065 (-0.169, 0.004)	0.05	0.22	1.34	-	-	-	
Educational attainment	**-0.117 (-0.218, -0.015)**	**0.05**	**0.02**	**2.36**	-0.101 (-0.207, 0.004)	0.05	0.06	
Depressive symptoms	0.046 (-0.055, 0.147)	0.05	0.37	1.18	-	-	-	
Wellbeing	-0.090 (-0.195, 0.016)	0.05	0.09	1.76	-	-	-	
Schizophrenia	0.082 (-0.024, 0.187)	0.05	0.13	1.56	-	-	-	
Extreme BMI	**0.108 (0.002, 0.214)**	**0.05**	**0.04**	**2.02**	0.093 (-0.020, 0.206)	0.06	0.11	

PGS = Polygenic scores.
Note*:* Analyses were conducted using linear mixed effects model, controlling for sex and the first 10 principal components for stratification.

3.5.4 Mixed effect models for repeated measures

The first set of analyses used growth-curve modelling of all ages. These revealed that the MDD polygenic score was associated with initial levels of victimisation at the intercept (see Table 3.8), but no polygenic scores predicted changes in victimisation across the ten-year period from 7 to 17 years. As previously noted, victimisation was found to decrease over time in the current sample. Therefore, these findings suggest that no polygenic scores are not associated with declines over time.

Table 3.8: Associations between polygenic scores and self-reported victimisation across age

	Single-PGS growth-curve models					
	Intercept			Slope		
PGSs	Coefficient, β(95%,CI)	SE	*p*	Coefficient, β(95%,CI)	SE	*p*
MDD	**0.078 (0.003, 0.157)**	**0.04**	**0.04**	-0.004 (-0.010,0.001)	0.003	0.13
ADHD	0.061 (-0.011, 0.133)	0.04	0.09	-0.004 (-0.009,0.001)	0.003	0.15
Risk-taking	0.034 (-0.041, 0.109)	0.04	0.37	-0.001 (-0.007, 0.004)	0.003	0.59
BMI	0.057 (-0.015, 0.129)	0.04	0.12	-0.003 (-0.008, 0.002)	0.003	0.27
Intelligence	-0.014 (-0.088, 0.061)	0.04	0.72	0.000 (-0.005, 0.006)	0.003	0.82
Educational attainment	-0.042 (-0.115, 0.031)	0.04	0.26	0.002 (-0.004, 0.007)	0.003	0.56
Depressive symptoms	-0.015 (-0.086, 0.057)	0.04	0.69	0.002 (-0.004, 0.007)	0.003	0.57
Wellbeing	-0.068 (-0.141, 0.004)	0.04	0.06	0.004 (-0.002, 0.009)	0.003	0.17
Schizophrenia	-0.052 (-0.125, 0.022)	0.04	0.17	0.004 (-0.001, 0.009)	0.003	0.12
Extreme BMI	-0.048 (-0.118, -0.023)	0.04	0.18	0.003 (-0.002, 0.008)	0.003	0.24

PGS = Polygenic scores.
Note: Analyses based on growth-curve mixed effects models, controlling for interactions between age and the polygenic score, interactions between age and sex, as well as the 10 principal components.
[a] Based on self-reported victimisation at 7, 10, and 12 years.
[b] Based on self-reported victimisation at 13, 15, and 17 years.

To investigate whether associations between the polygenic scores and victimisation significantly differ in childhood versus adolescence, a mixed model for repeated measures was used to investigate associations with the period variable. This characterised trajectories at ages 7, 10, and 12 years into 'childhood', and years 13, 15 and 17 years into 'adolescence'. Findings revealed that childhood victimisation trajectories were predicted by polygenic scores related to MDD, ADHD, and wellbeing, while adolescent victimisation trajectories were associated with the educational attainment polygenic score (see Figure 3.2). Although these differences suggest associations may alter between the two time periods, comparisons between the two revealed that the changes were not statistically

different (see Table 3.9). This means that differences between the polygenic influences across the two trajectories are likely small. This is supported by the overlapping confidence intervals in Figure 3.2.

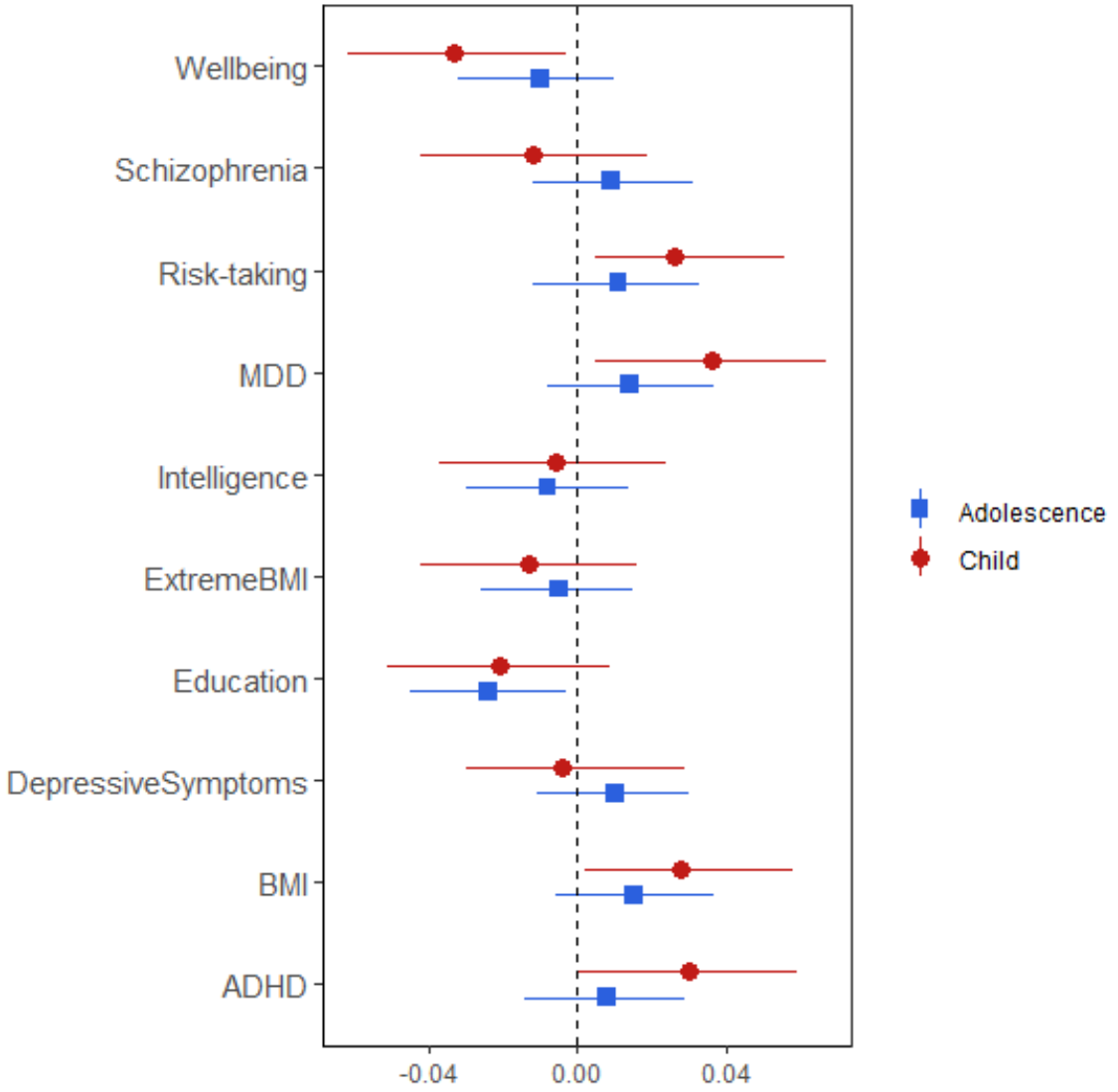

Figure 3.2: *Regression coefficients from single-PGS growth-curve models predicting trajectories in self-reported victimisation in childhood (7, 10, and 12 years) and adolescence (13, 15, 17 years).*

Table 3.9: Associations between polygenic scores and self-reported victimisation across two time periods

	Single-PGS growth-curve models						
	Self-reported childhood victimisation[a]			Self-reported adolescent victimisation[b]			Difference between time periods
PGSs	Coefficient, β(95%,CI)	SE	*p*	Coefficient, β(95%,CI)	SE	*p*	*p*
MDD	**0.036 (0.005, 0.067)**	**0.02**	**0.02**	0.014 (-0.008,0.037)	0.01	0.21	0.89
ADHD	**0.030 (0.00, 0.059)**	**0.02**	**0.05**	0.008 (-0.014,0.029)	0.01	0.47	0.13
Risk-taking	0.026 (-0.005, 0.056)	0.02	0.09	0.011 (-0.012, 0.033)	0.01	0.35	0.31
BMI	0.028 (-0.002, 0.058)	0.02	0.07	0.015 (-0.006, 0.037)	0.01	0.17	0.41
Intelligence	-0.006 (-0.037, 0.024)	0.02	0.69	-0.008 (-0.030, 0.014)	0.01	0.49	0.84
Educational attainment	-0.021 (-0.051, 0.009)	0.02	0.17	**-0.024 (-0.045, -0.003)**	**0.01**	**0.03**	0.76
Depressive symptoms	-0.004 (-0.030, 0.029)	0.02	0.98	0.010 (-0.011, 0.030)	0.01	0.36	0.52
Wellbeing	**-0.033 (-0.062, -0.003)**	**0.02**	**0.03**	-0.010 (-0.032, 0.010)	0.01	0.34	0.14
Schizophrenia	-0.012 (-0.042, 0.019)	0.02	0.45	0.009 (-0.012, 0.031)	0.01	0.41	0.18
Extreme BMI	-0.013 (-0.042, -0.017)	0.02	0.36	-0.005 (-0.026, 0.015)	0.01	0.61	0.63

PGS = Polygenic scores.

Note: Analyses based on growth-curve mixed effects models, controlling for interactions between age period and the polygenic score, interactions between age period and sex, as well as the 10 principal components.

[a] Based on self-reported victimisation at 7, 10, and 12 years.

[b] Based on self-reported victimisation at 13, 15, and 17 years.

3.6 Discussion

This study extends previous findings to investigate for the first time, whether genetic predispositions associated with peer victimisation vary by informant and age. Different vulnerabilities, as indexed by polygenic scores, were associated with exposure to peer victimisation when reported by either the self, the teacher, or peers, with some overlap between teacher- and peer-reports. There were also differences noted in predictors of childhood versus adolescent victimisation, suggesting possible unique vulnerabilities associated with victimisation at both time points. Further investigation using growth curve analyses, however, suggested that these differences between childhood and adolescence were not statistically different.

3.6.1 Predictors of self-, teacher-, and peer-reported victimisation

When investigating genetic liabilities towards self-reported peer victimisation in childhood, findings replicated two of the ten previous associations (Schoeler et al., 2019). These were found using polygenic scores related to mental health, including depression and wellbeing. Despite using different victimisation scales, effect sizes were similar to those reported by Schoeler et al., (2019) for major depression, but were greater than those found previously using the wellbeing polygenic scores. This likely reflects the increase in power gained from using a larger GWAS of wellbeing. It is important to note, however, that these findings did not survive after correction for multiple testing.

Associations between victimisation and genetic markers of mental health were not replicated when using teacher- and peer-reports of victimisation. Teacher-reported victimisation was instead predicted by polygenic scores related to physical and cognitive-related traits, including BMI, intelligence, and educational attainment. These latter two associations survived after correction for multiple testing, and produced effect estimates that were over three times larger than those found using self-reports in both the current and previous study (Schoeler et al., 2019).

The possible discrepancy across informants is reflective of the wider victimisation literature which has reported different predictors (Košir et al., 2020) and outcomes (Scholte et al., 2013) of self- versus teacher- and peer-reported victimisation. In line with the current findings, previous studies have revealed associations between low academic achievement and an increased risk for peer-reported, but not self-reported, peer victimisation (Košir et al., 2020). Similarly, findings have shown that an increased risk of BMI increases the risk for teacher-reported victimisation but not self-reported victimisation (Jansen et al., 2014).

The different genetic vulnerabilities associated with self-, teacher-, and peer-reported victimisation likely reflect the distinct aspects of victimisation that are captured by each. Self-reports tap into subjective appraisals of the event and are more related to internalising problems than peer-reports (Bouman et al., 2012). Teacher- and peer-reports on the other hand, capture popularity and social reputation, and often map onto external markers of maladjustment (Ladd et al., 2002). These different perspectives likely explain the varying associations with the polygenic scores, as well as the low correlations between the informant measures.

Low correspondence between reporters has been noted previously in relation to peer victimisation (Branson & Cornell, 2009), with varying prevalence estimates found between self- and peer-reports (Oldenburg et al., 2015). This may reflect the different methods used to generate the overall scores, with self- and teacher-reports often used to assess the frequency of victimisation experiences, and peer-reports used to capture the number of nominations a child receives. Understanding how and why these differences may lead to discrepant associations with risk factors could be key to informing those at risk of specific adverse outcomes. It is possible that individuals identified as a victim through multiple informants may be those most at risk of adjustment problems (Crick & Bigbee, 1998). However, the current findings suggest it is likely that victims identified through different informant reports will exhibit different problems.

Future studies should carefully consider how informant reports are used. This decision will be dependent largely on the research goals (Bouman et al., 2012; Ladd et al., 2002). If the aim is to understand social maladjustment following victimisation, using teacher- and peer-reports may be more appropriate. However, if the aim is to investigate internalising symptoms, self-reports will be more informative. This was previously advised for researchers interested in understanding psychopathology following childhood maltreatment (Danese et al., 2020). In particular, the authors suggested that interventions aimed at manipulating self-appraisals of an adverse event could help to reduce the potential for psychopathology.

3.6.2 The role of educational attainment

Despite differences in polygenic predictions across the informant measures, the association with the educational attainment polygenic score replicated across teacher- and peer-reports in childhood, as well as self-reports in adolescence. The results suggest that individuals genetically inclined to complete fewer years of schooling may be at an increased risk of peer victimisation compared to those more likely to stay on in higher education. This finding aligns with previous observational findings which have shown that compared to individuals with lower cognitive abilities, individuals with higher cognitive abilities are at a reduced risk of peer victimisation (Verlinden et al., 2014).

The polygenic score for educational attainment was calculated using data from the large Social Science Genetic Association Consortium GWAS for years of education (N=293,723, Okbay et al., 2016). The genetic variants identified in this GWAS have been shown to be predicted by both cognitive and non-cognitive factors (Demange et al., 2021). They have also been shown to relate to family socioeconomic status (SES) and parental education (Wang et al., 2021), with evidence to suggest that one-third of the association between a child's polygenic score and actual educational attainment is explained by the parent's genetic profile and education (Liu, 2018). These genetic influences can occur through both direct genetic transmission from parent to offspring, as well as through gene-environment

correlations. As mentioned previously, this can occur when the genotype of a parent influences the characteristics and outcomes of the child through the environment (Kong et al., 2018). One way in which the genetic predispositions of a parent may influence the educational attainment of the child could be through providing a more stimulating home environment. Such parents may also be more able to financially support their child to continue their learning into higher education. This chain of events may not only explain the current associations between educational attainment and victimisation, but may also confound them.

It is possible that having a lower SES not only increases the risk of victimisation, as noted previously (Tippett & Wolke, 2014), but also reduces the number of years of schooling completed. This could mean that educational attainment does not *directly* influence the risk of peer victimisation. Larger studies should test this confounding and explore a possible gene-by-environment correlation by comparing polygenic predictions both within- and between-family members (Selzam et al., 2019). While the current twin design could have enabled an exploration into within-family effects, analyses would have been unpowered due to sample size.

3.6.3 Predictors of victimisation across time

In addition to highlighting how different informant reports can be used to complement our understanding of predictors of victimisation, the current study also demonstrated the importance of age. Initial analyses investigating predictors of mean victimisation in childhood versus adolescence revealed that both were associated with the polygenic score for major depression. Effect sizes were greater in adolescence, and the polygenic score explained over 2.3% more of the variance in adolescent versus childhood victimisation. However, no associations survived after correction for multiple testing. It is also important to note that differences between associations may reflect the fact that the original GWAS of depression was conducted in a sample of adults (Howard et al., 2018). The resulting genetic variants

are thus more likely to resemble those associated with depression in adolescence compared to in childhood. This could explain why analyses predicting mean victimisation in adolescence but not childhood detected further associations with polygenic scores related to intelligence, educational attainment, and extreme BMI.

In further analyses investigating predictors of trajectories of victimisation, findings revealed that the polygenic score for major depression was associated with initial victimisation but not changes that occur over time. As per previous research (Oncioiu et al., 2020), victimisation in the current study was shown to decline over time. The finding that a higher polygenic risk to depression was only predictive of early instances of victimisation may thus reflect its association with higher frequencies of victimisation.

In support of this, mean victimisation scores were not statistically different at ages 7 and 10 years. This may imply that trajectories of declining victimisation do not occur until adolescence, explaining why the polygenic score for major depression was only associated with victimisation in childhood. It is interesting to note, however, that there were no significant differences between effects of the depression polygenic score on trajectories in childhood versus adolescence. This suggests that while a higher genetic risk to depression may be a more important predictor of victimisation trajectories in childhood, effects are not significantly larger than those on adolescent trajectories. This implies that influences of the depression polygenic score are largely stable over time. Such findings corroborate with the main analyses which revealed associations with mean composite scores in both childhood and adolescence.

In addition to highlighting a role for major depression over time, findings also revealed associations between childhood trajectories and polygenic scores related to ADHD and wellbeing. Associations were in the expected direction such that an increased polygenic risk for ADHD was positively associated with childhood trajectories of victimisation, while higher wellbeing genetic scores were negatively associated. These effects were not found in

analyses predicting trajectories in adolescence, but findings were also not statistically different across the two age periods indicating only weak effects in childhood.

It is important to note that genetic associations are not consistent across the life-course (Haworth & Davis, 2014), so we should expect to find developmental differences between polygenic scores and outcomes at different ages. However, it is likely that larger samples will be needed to detect more subtle effects. Indeed, findings from the power analyses revealed that the current study had just 48% power to detect the current effects of the major depression polygenic score (see Appendix 3.8). Further research using larger cohorts could thus help unveil more about these influences over time. Such research could also consider different types of victimisation trajectories. It is possible that different risk factors are associated with varying trajectories in childhood and adolescence due to some individuals undergoing less chronic experiences. Findings have revealed that while some individual's victimisation experiences are stable across time, for others, high childhood victimisation is followed by either a sharp decline or persistently high victimisation (Oncioiu et al., 2020). Separately exploring associations between polygenic scores and trajectories categorised by chronicity could help to understand predictors of those at the greatest risk. This has the potential to inform more targeted support.

3.6.4 Strengths and limitations

A key strength of the current study is that it is the first to test whether genetic vulnerabilities associated with peer victimisation vary by informant. In doing so, the study was able to identify subtle differences between predictors of self-reported, teacher-reported, and peer-reported victimisation. It also raised awareness into possible differences between risk factors associated with victimisation in childhood and adolescence. Further investigation into factors underlying these effects could prove crucial to informing tailored preventative interventions aimed at different age groups.

Some limitations of the study should be noted. The first is that the sample of twins may limit generalisability to singletons. Although in Quebec, the School Commission Boards encourage separation of twins in classrooms, there are no guidelines to enforce this (White et al., 2018). Having a co-twin in the same class may provide the necessary companionship to help protect against peer victimisation (Veldkamp et al., 2017). This could be through offering physical protection by intervening, or by providing unique social support. Rates of peer victimisation may therefore be expected to be lower than singletons. Drawing comparisons of prevalence to other studies is problematic because of the huge variance across countries (Nansel et al., 2004). Nevertheless, the average percentage of children and adolescents frequently victimised (~16%) in the current study falls within the range of previous reports across nations (Nansel et al., 2004), and is similar to estimates of frequent victims reported in samples based in the UK (Stapinski et al., 2014) and Germany (Stadler et al., 2010). This helps provide reassurance that victimisation estimates in the twin sample are representative. To further ensure this, peer nominations were z-standardised within class to provide an estimate of where the twins stand in comparison to others in their class. Nevertheless, it is still possible that the twin cohort is one explanation why the present study did not replicate all ten associations found previously in a population sample (Schoeler et al., 2019).

Another explanation for the fewer associations found reflects the current sample size, which resulted in some polygenic scores being underpowered to detect associations with victimisation (see Appendix 3.6 and 3.7). Although findings have shown that often just moderate sample sizes are needed to attain sufficient power with polygenic scores (Dudbridge, 2013), an important determinant of predictive power is the sample size of the original GWAS. While the aim of the present study was not to explain the variance in peer victimisation but to study pathways that lead to its occurrence, it is important to consider that the polygenic scores may not adequately capture the original phenotype. This was particularly evident for polygenic scores derived from smaller GWASs.

For example, the original GWAS of depressive symptoms accounted for ~0.5% of the variance in depressive symptoms (Okbay et al., 2016). In comparison, the discovery GWAS of major depression, which included over 600,000 more participants, captured 3.2% of the variance in diagnosed depression. These differences likely explain why associations were detected with major depression, which as can be seen in Appendix 3.6 and 3.7, had over 80% power to explain more of the phenotypic variance than was currently captured, compared to depressive symptoms which had less than 10% power. These differences in GWAS sample size and the variance captured by the lead SNPs may also explain why the most consistent associations were found with educational attainment polygenic score. This was based on a GWAS of over 1 million participants from various countries (Lee et al., 2018). Genetic variants captured by this polygenic score may be more robust to environmental differences in educational institutions across countries, generating more power to detect subtle effects across different informants.

These combined findings highlight the importance of conducting larger GWASs to help develop and evaluate the role of polygenic scores (Murray et al., 2021). In addition, it will be important that new power calculations are created to determine the power of polygenic scores in more complex models. While simulation-based methods were able to estimate power within the growth curve analyses (see Appendix 3.8), this technique does not account for genetic data. Power estimates were therefore only generated for one polygenic score, meaning estimates should be interpreted with some caution.

In addition to sample size limitations, the current findings must also be considered in relation to the construction of the polygenic scores. The number of SNPs included in the polygenic scores was based on the threshold of best fit, which was determined using the highest variance explained. This is common practice in creating polygenic scores (Anderson et al., 2019) and was used previously by Schoeler and colleagues (2019). Using this method helped to avoid selecting one arbitrary threshold for all traits, which is important as the best

fitting threshold is not uniform across traits (So & Sham, 2017). However, it is likely that follow-up research using the same GWASs but different thresholds will lead to different results. This may thus be another explanation why some associations did not replicate from previous research (Schoeler et al., 2019). Indeed, for analyses based on the intelligence polygenic score, Schoeler et al., (2019) used a p-value threshold of $p=0.01$, while the current study used a much less stringent threshold of $p=0.64$ when predicting self-reported victimisation, and $p=0.88$ when predicting teacher-reported (see Appendix 3.6 and 3.7). Such differences in the threshold of best fit were found despite using the same GWAS, suggesting an impact of the different victimisation scales and cohorts used.

Finally, the current study must be interpreted in relation to the sample and measures used. The QNTS cohort and GWASs consisted largely of individuals of white European ancestry. Findings should therefore be cautiously generalised to individuals not in this group. Results must also only be generalised to victims and not bully-victims. Bullying perpetration was not accounted for in the present study due to data unavailability. However, previous findings on victimisation have revealed that associations with polygenic scores related to ADHD and risk taking are no longer apparent after controlling for bullying perpetration (Schoeler et al., 2019). While few associations survived after correction for multiple testing in the present study, it is important that further research investigates associations while accounting for those who also bully others. This could help to inform more specific predictors of the risk of peer victimisation among different groups.

In addition, findings on predictors of peer victimisation using multiple informants should be interpreted with some caution. Peer-reported victimisation was based on nominations from peers that focused on identifying victims in a classroom. This measure did not include questions about the frequency of the victimisation, meaning some peers may have incorrectly commented on infrequent occurrences or minor acts of teasing. According to the definition of peer victimisation, such instances would not be classified as victimisation

(Olweus, 2013). This may explain the low correlation between peer-reported victimisation at ages 7 and 10 years (r=0.29) as it is possible that perceptions of what classifies as victimisation changed over time. In addition, unlike the self-report measure, which covered both direct and indirect forms of victimisation, the teacher and peer assessments focused on direct forms only. Differences between the associated genetic risk factors and the informant reports may therefore reflect underlying differences in the types of victimisation experiences, rather than the unique perspectives captured by each. Future research should investigate this possibility further using larger study samples with diverse assessments of victimisation.

3.6.5 Implications and future directions

Overall, this study provides support for observational findings on predictors of peer victimisation and thus helps to triangulate existing evidence. By using polygenic scores as genetic proxies, the current study was able to implicate pre-existing vulnerabilities and replicate some of the previous genetic findings (Schoeler et al., 2019). When considering the implications of these results, however, it is necessary to acknowledge what the polygenic scores represent. Some polygenic scores may have been limited in power to explore gene-environment correlations with peer victimisation due to an inability to fully capture the original phenotype. Such findings emphasise the importance of follow-up investigation when larger GWASs become available.

Despite possible power issues, this study helps to increase awareness of the impact of the phenotypic assessment of peer victimisation. Findings suggest that different associations will likely be discovered through using self- versus teacher or peer-reports. This has implications for the interpretations of research exploring predictors and outcomes of peer victimisation. In addition, the results suggest that some polygenic scores may be more important predictors of earlier victimisation instances. Further investigation into these early risk factors and possible paths by which they increase the likelihood of victimisation could be key to early prevention. Such research will likely be facilitated by using a combination of genetic and

phenotypic data to understand how genetic contributions to peer victimisation may be moderated by the environment. Such analyses would be bolstered by a GWAS of peer victimisation. A large GWAS would enable researchers to use methods like Mendelian Randomisation (MR) to test whether increased genetic liabilities towards traits like educational attainment are causally associated with peer victimisation and vice versa. This information could then be used to study the effectiveness of protective factors and intervention techniques in moderating both the risk of peer victimisation as well as its causal outcomes.

Studies investigating anti-bullying programmes have revealed that interventions are more effective at reducing bullying perpetration than rates of peer victimisation (Gaffney et al., 2018). Researchers have therefore emphasised that to reduce peer victimisation, it is important to change the behaviours of the bullies and bystanders, rather than make victims "less vulnerable" (Salmivalli et al., 2011a). Although the current findings highlight genetic vulnerabilities of victims, the message is the same. Interventions aimed at reducing the stigma of mental health problems and increasing tolerance of diversity in relation to weight and cognitive abilities could prove useful in moderating the likelihood an individual is subjected to peer victimisation. It is crucial that such interventions are delivered at the school-wide level to ensure there is acceptance across all student populations. This is particularly important as findings have shown that victims who have just one classmate that defends them are significantly less likely to report being frequently victimised (Salmivalli et al., 2011b) and to experience symptoms of depression (Sainio et al., 2011).

Finally, in addition to studying predictors of the occurrence of peer victimisation, research will also greatly benefit from understanding its associated outcomes. Peer victimisation is associated with an increased risk of depression and low wellbeing (Armitage et al., 2021). The current findings thus suggest there could be shared genetic vulnerabilities not only between peer victimisation and its associated predictors, but also its associated outcomes.

This means it is possible that the same vulnerabilities that increase the risk for peer victimisation also increase subsequent problems after peer victimisation. This possibility is investigated further in Chapter 4.

3.7 Chapter summary

This study used polygenic scores to investigate associations between genetic vulnerabilities and the risk of peer victimisation. The findings offer supporting evidence for existing research (Schoeler et al., 2019) and provide novel insight into the role of different informants and the age of the victim. The study revealed that polygenic scores related to educational attainment are consistently associated with multiple informants across childhood and adolescence. However, larger, and more well-powered studies are needed to confirm these findings as some did not survive after correction for multiple testing. Findings also need to be replicated to explore further the subtle differences between predictors of self-, teacher- and peer-reports of victimisation, as well as between instances in childhood and adolescence. Such research could confirm the need to pay close attention to the phenotypic assessment of peer victimisation when assessing its correlates and outcomes.

Chapter 4: A polygenic approach to understanding resilience to peer victimisation[2]

4.1 Chapter overview

Chapter 3 investigated predictors of peer victimisation using genetic information from multiple polygenic scores. This allowed for tests of possible gene-environment correlations (rGE). In this study, polygenic scores are used to investigate risk and resilience following peer victimisation. This is achieved using a gene-environment interaction (G×E) design to understand why some may be at a greater risk of depression and low wellbeing following peer victimisation.

In this chapter, I aim to:

- Investigate whether individuals subjected to peer victimisation are at a heightened risk of depression and low wellbeing if they also have an increased genetic vulnerability to these mental health problems.
- Provide the first insight into whether genetic information can be used to target those more susceptible to the effects of peer victimisation to help foster resilience.

4.2 Introduction

As emphasised in Chapter 3, peer victimisation is considered a major public health concern, associated with adverse outcomes like depression (Arseneault, 2017) and poor wellbeing in adulthood (Armitage et al. 2021). Depression is a common mental health problem characterised by feelings of sadness, low self-worth, and a loss of interest or pleasure (WHO, 2017). Approximately 4% of the population across the globe are depressed each

[2] This chapter has been adapted from Armitage, J. M., R. Wang, A., Davis, O. S. P., & Haworth, C. M. A. (2021). (submitted). A polygenic approach to understanding resilience to peer victimisation. *Behaviour Genetics.*

year (WHO, 2017), with up to 15% suffering across the lifespan (Bromet et al., 2011). For individuals who are frequently victimised in adolescence, the odds of depression in adulthood are twofold greater compared to those not victimised (Bowes et al., 2015). Victims who become depressed also experience significantly poorer wellbeing than their non-depressed, victimised counterparts (Armitage et al., 2021). These effects on wellbeing are independent of the risk of depression, with those avoiding depression after victimisation shown to have significantly lower wellbeing than those with no experiences of victimisation or depression (Armitage et al., 2021). Targeting peer victimisation could therefore be an effective means of not only lowering the risk of depression, but also improving wellbeing in adulthood. It is possible, however, that some individuals are more susceptible to the adverse effects of peer victimisation due to genetics. To test this we can use information about individuals genetic liability to depression and wellbeing and compare their subsequent mental health following experiences of peer victimisation. Such an interactive approach is particularly effective when investigating outcomes like depression and wellbeing, for which there is an established role for genes and environments

4.2.1 The aetiology of depression and wellbeing

Heritability estimates derived from twin studies have revealed that genetic influences explain approximately 37% of the variance in depression (Sullivan et al., 2000) and 36% for wellbeing (Bartels, 2015). These studies, in addition to findings from genome-wide association studies (GWASs), have suggested that the genetic variants underlying these factors are driven by both shared and unique signals (Baselmans et al., 2019). In particular, twin research has suggested that 45% of the genetic influences on life satisfaction are independent of those associated with internalising symptoms, with this figure increasing to 70% when investigating genetic influences on happiness (Haworth et al., 2017). Such findings provide further support for the argument in Chapter 1 that mental illness and wellbeing reflect correlated but distinct dimensions of mental health. As such, investigations

into predictors of the two outcomes would benefit from treating depression and wellbeing as unique constructs.

While genetic findings have implicated a role for both genetic and environment influences in the aetiology of depression and wellbeing, their effects are complex and unlikely to work in isolation. Heritability estimates from the twin design do not capture this gene-environment interplay, therefore researchers have used SNP-based heritability to study more complex paths to depression (Coleman et al., 2020). SNP-based heritability refers to the heritability captured by common genetic variants identified in a genome-wide association study (GWAS). Estimates of SNP-based heritability for depression have been shown to be twice as high among individuals exposed to trauma compared to those not exposed (Coleman et al., 2020). One explanation proposed for this finding was that exposure to trauma heightens genetic influences on depression. This may explain why those exposed to trauma were more likely to be depressed compared to those not exposed. Such a finding provides support for the Diathesis-stress model, which is explained in more detail below, and highlights the importance of considering both the separate and interactive impact of genetic and environmental factors in the aetiology of depression (Assary et al. 2017).

4.2.2 The Diathesis-Stress model and Differential Susceptibility Theory

The crucial role of genetic and environmental influences on mental health is highlighted in the Differential Susceptibility Theory, outlined in Chapter 1 (Belsky & Pluess, 2013), as well as the Diathesis-Stress model (Monroe & Simons, 1991). Both support the idea that genetic or biological factors render some individuals more vulnerable to the effects of the environment (Assary et al., 2018), with the Diathesis-Stress model arguing that the experience of an environmental stress activates an existing genetic vulnerability (Monroe et al., 1991). This then serves to increase the risk of subsequent negative outcomes.

While similar in nature to the Differential Susceptibility Theory, the Diathesis-stress model focuses only on the negative effects of stress. As such, those deemed most at risk are those

with an underlying vulnerability who also experience stress (Ingram & Luxton, 2005). In contrast, the Differential Susceptibility Theory proposes that although genetically at-risk individuals may be more vulnerable to environmental influences, this susceptibility can be both positive and negative (Belsky & Pluess, 2009). This has implications for the study of resilience as it means that at-risk individuals may be those also most responsive to protective and supportive environments.

The genetically driven responses to the environment, whether positive or negative, can be empirically tested through study of interactions between genes and the environment. Using an interaction framework is important as the impact of the environmental factor is argued to be dependent on the pre-existing vulnerability, implying multiplicative effects (Colodro-Conde et al., 2018). This would mean that an individual exposed to peer victimisation would be expected to be at a greater risk of depression if they were also at a high genetic risk of depression. According to the Differential Susceptibility Theory, such individuals would also be anticipated to be just as susceptible to positive influences, such as treatment effects (Keers et al., 2016).

Research to date on the interactive interplay between genetic and environmental factors has focused largely on the Diathesis-stress model of depression (Colodro-Conde et al., 2018). Research investigating Differential Susceptibility in relation to mental health is sparse, with few studies considering the role of genetics (Smith et al., 2021). One study using phenotypic measures found that at-risk individuals exposed to multiple childhood adversities experienced greater reductions in distress over time compared to unexposed individuals (Albott et al., 2018). This was taken as evidence of differential susceptibility; however, such effects were small and based on measures of distress rather than positive functioning. The study also did not assess risk based on genetics, but on exposure to adversities. It was therefore not possible to infer the degree to which susceptibility to adverse events was moderated by an individual's pre-existing genetic liability.

4.2.3 Gene-environment interaction (G×E)

Gene-environment interaction (G×E) studies assess the extent to which psychiatric risk is influenced by genetic predispositions and environmental exposures. The presence of a G×E indicates that the influence of an environment is different for individuals with different genotypes (Ottman, 1996). A G×E can also refer to the different outcomes of a genotype among individuals with differing environmental exposures (Ottman, 1996). While G×E research began using candidate gene studies, which were introduced in Chapter 2, many have now moved towards the use of polygenic scores. This is based on findings of the polygenic nature of most complex traits (Dudbridge et al., 2016).

Studies investigating the moderating role of genetic risk in relation to mental health outcomes have explored polygenic scores for depression in the context of childhood trauma and stressful life events in adulthood. Findings thus far, however, are conflicted within the literature. Some have suggested a heightened risk for individuals exposed to stressful life events in adulthood who also have an increased genetic vulnerability to depression (Colodro-Conde et al., 2018; Shen et al., 2020). Such interactive effects have replicated in some studies when investigating traumatic events in childhood (Shen et al. 2020), although it is important to note that many effects were not robust after correction for multiple testing. Many others have also failed to identify robust interactive effects when investigating polygenic scores for depression and childhood trauma or stressful life events (Musliner et al., 2016; Peyrot et al., 2014, 2018), with some even producing counter evidence (Mullins et al. 2016). In particular, it was found that individuals subjected to childhood trauma were at an increased risk of depression if they had a lower polygenic risk to depression (Mullins et al. 2016). This direction of effect was the opposite to what was predicted and is yet to be replicated in larger cohorts. However, the authors suggested that such findings may reflect the negligible involvement of genetics.

Similar conclusions have been arrived at by researchers investigating outcomes of peer victimisation (Schaefer et al., 2018). It was found that associations between victimisation and

psychopathology remained after accounting for genetic risk, suggesting that adverse outcomes are not merely the result of pre-existing vulnerabilities (Schaefer et al., 2018). While these findings were not derived from a G×E polygenic design but from a twin study, the notion that genetic factors may predict, but not moderate, subsequent outcomes is similar to some of the conclusions from polygenic research (Musliner et al., 2016). These findings in combination with the research on stressful life events (Shen et al., 2020), demonstrate the complex nature of interactions between genetic and environmental factors in predicting psychiatric disorders and highlight the need for further investigation.

4.2.4 Gene-environment correlation (rGE)

Investigating the interplay between genetic and environmental factors when predicting outcomes is important in assessing the degree of confounding (Knafo & Jaffee, 2013). If the same genetic variants not only predict the risk of a disorder but also vulnerability to an environmental experience, associations between the environment and disorder will be obscured. This scenario refers to the gene-environment correlation (rGE, Plomin et al., 1977) which was studied in Chapter 3. It is important that when studying interactions between genetic and environmental factors that possible associations between the two are adjusted for. This is because genetic factors may affect the outcome through multiple pathways simultaneously, such as through increasing liability towards an exposure (rGE) as well as sensitivity towards its effects (G×E) (Eaves et al., 2003). Not accounting for a possible rGE could therefore induce a spurious G×E.

In the context of peer victimisation, it is possible that the increased risk for depression and low wellbeing reflects underlying predispositions towards these mental health outcomes. In particular, genetic variants associated with depression and wellbeing may not only increase susceptibility towards peer victimisation (rGE), as shown previously (Schoeler et al., 2019) and in Chapter 3, but may also moderate subsequent mental health problems (G×E). No study to date, however, has used polygenic scores within a G×E design to test this hypothesis.

Investigating why some individuals subjected to peer victimisation may be at a heightened risk of poorer mental health outcomes could be crucial to ensuring more targeted support for those most at-risk. For instance, if individuals at a higher genetic risk of mental health problems are also more susceptible to the effects of peer victimisation, genetic profiling may be an effective means of detecting the most vulnerable early on. These individuals could then be prioritised for intervention. In addition, investigating those most at risk of poorer mental health outcomes following peer victimisation could also aid our understanding of resilience. It is possible that those more able to avoid mental health problems and exercise resilience are those with lower polygenic scores for depression, or higher polygenic scores for wellbeing.

Just one study to date has used polygenic scores for wellbeing within a G×E design (Domingue et al., 2017). Findings revealed that individuals with higher wellbeing polygenic scores experienced significantly smaller increases in depressive symptoms following the death of a spouse. This study, however, did not assess or compare wellbeing outcomes. Doing so is important as wellbeing represents more than the absence of mental illness (Keyes, 2002) and as already discussed, is influenced by unique genetic factors (Haworth et al., 2017). This means that while individuals may have experienced fewer depressive symptoms following the death of a spouse (Domingue et al., 2017), they may not have had a better quality of life. Understanding predictors of both depression and wellbeing is crucial to determining the true degree of resilience.

4.3 Current study

The goal of this study was to investigate whether the risk of poor adult mental health and wellbeing following peer victimisation can be partly attributed to genetic factors using polygenic scores for depression and wellbeing. In doing so, the study aimed to provide the first insight into whether individual-level genetic data can be used to inform those most at risk following instances of peer victimisation in adolescence. It was hoped that such

knowledge would facilitate our understanding of possible paths to resilience and inform whether genetic profiling could be an effective means of detecting vulnerable children to ensure early intervention.

It was predicted that victims with the most depressive symptoms and lowest wellbeing in early adulthood would be those at a higher genetic risk of depression and low wellbeing. It was also anticipated that those displaying the most resilient outcomes, as evident by fewer depressive symptoms and higher wellbeing, would be those at a lower genetic risk to depression and poor wellbeing. By using continuous polygenic scores, both hypotheses could be simultaneously addressed using an interactive gene-by-environment design. This allowed analyses to test the extent to which mental health outcomes of peer victimisation are moderated by polygenic risk.

4.4 Methods

4.4.1 Sample description

Genotype and phenotype data for this study were taken from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013), which was described in detail in Chapter 2. Individuals included were those who completed the peer victimisation assessment at 13 years (*n*=6,527) and provided genotype data (*n*=4,829). Of these, data were taken from 2,268 individuals who also completed the assessment for depressive symptoms at 23 years, and from 2,299 individuals who completed the wellbeing questionnaire at 23 years. Although the resulting two samples were more likely to be female and white compared to individuals without genotype data (see Appendix 4.1), scores on the victimisation and mental health scales did not significantly differ between these two groups.

4.4.2 Measures

Information about the victimisation and outcome variables were presented in Chapter 2. Briefly, the current study used self-reports from the Bullying and Friendship Interview Schedule to measure peer victimisation at 13 years (Wolke et al., 2001), the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS; Tennant et al., 2007) to assess overall mental wellbeing aged 23, and the shortened version of the Moods and Feelings Questionnaire (sMFQ; Angold et al., 1995) to determine depressive symptoms aged 23. As explained in Chapter 2, analyses were carried out on victimisation scores that had been log-transformed. This was due to high amounts of positive skew (skew=2.4). Results from analyses using the untransformed victimisation scores are presented in the appendices (see Appendix 4.2).

4.4.3 Polygenic scores

Polygenic scores (PGSs) were created using publicly available GWAS summary statistics. ALSPAC was not included in any of discovery GWASs to ensure findings were not biased. For depression, the largest GWAS to date of major depression was used (Howard et al.

2019). This meta-analysed data from the three previous largest GWASs of depression (Howard et al. 2018; Hyde et al, 2016; Wray et al. 2018). Depression was assessed across these studies using different diagnostic instruments, with one using clinically obtained reports and others based on self-reports of clinical depression and help-seeking behaviour. Despite using different assessments, strong genetic correlations were noted between studies, ranging from 0.85 to 0.87. This suggests an overlap in the genetic architecture captured by each GWAS.

Polygenic scores for wellbeing used summary data from a multivariate genome-wide-association meta-analysis (GWAMA, Baselmans et al. 2019). This study introduced two novel methods, the N-weighted multivariate GWAMA (N-GWAMA), and the model-averaging GWAMA (MA-GWAMA) to study genetic variants associated with the wellbeing spectrum. The wellbeing spectrum was a term adopted by the authors to encapsulate four related traits: life satisfaction, positive affect, neuroticism, and depressive symptoms. The N-GWAMA method was used to investigate a unitary effect of all four traits, while the MA-GWAMA relaxed the assumption of a unitary effect to study trait-specific estimates. Polygenic scores within the current study used genetic data derived from the N-GWAMA to investigate variants associated with overall wellbeing.

The depression polygenic scores and wellbeing polygenic scores were created using PRSice (Euesden et al., 2015), which was explained in Chapter 3. For the current study, clumping was set to remove SNPs in linkage disequilibrium (LD) based on an r-squared threshold of 0.10 within a 500kb window. This was to align with the procedures used in both the depression (Howard et al. 2019) and wellbeing GWAS (Baselmans et al. 2019). Each SNP included in the polygenic scores in ALSPAC used best guess imputation genotypes. This means that SNPs with a minor allele frequency (MAF) <1% and an imputation quality score <0.8 have been removed. Further information about the genotyping procedure used in ALSPAC can be found in Chapter 2.

Polygenic scores were initially calculated using *p*-value thresholds of $5x10^{-8}$, $1x10^{-6}$, $1x10^{-4}$, 0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5 and 1. This resulted in polygenic scores with an increasing number of SNPs: 70, 159, 1000, 2197, 12924, 62678, 99128, 127673, 150781, 169733 and 192822 respectively for the depression polygenic scores. For the wellbeing polygenic scores, the number of SNPs were 198, 418, 1628, 4009, 12381, 38939, 55626, 68192, 78160, 86119 and 107155. To facilitate interpretability, all polygenic scores were z-standardised to have a mean of 0 and standard deviation of 1 (Lewis & Vassos, 2017).

4.4.4 Statistical analyses

4.4.4.1 Main effect analyses

Before investigating possible G×E between the polygenic scores and peer victimisation, the main effects of both were examined using linear regressions predicting depressive symptoms and wellbeing. All models controlled for sex as there is evidence to suggest sex differences in the aetiology of both depression (Weissman et al., 1996) and wellbeing (Batz & Tay, 2018). Models also adjusted for the first two genetic principal components (PCs) to reduce confounding by population stratification and to align with previous research (Mullins et al., 2016). The main effect models for the polygenic scores explored all SNP-association thresholds to inform which explained the most variance in the outcome measures. This was determined using the incremental R^2, which was calculated by separately regressing the two outcomes onto sex and the two PCs, and then comparing models to those that included the polygenic scores. Selecting which polygenic scores to use for analyses on the basis of the incremental R^2 is common practice in the field (Anderson et al., 2019). However, to supplement these analyses, polygenic scores were also investigated at the genome-wide significant threshold ($p < 5x10^{-8}$). This helped to ensure scores were specific to the trait of interest and less likely to reflect noise, which can be introduced to scores created at less stringent thresholds. Plots of the variance explained by each polygenic score can be found in Appendix 4.3, and correlations between the selected polygenic scores can be found in Table 4.1.

To determine if the polygenic scores and peer victimisation exert independent effects on depressive symptoms and wellbeing, subsequent regression models explored the main effects of both factors in the same model. Analyses also tested for a potential gene-environment correlation (rGE) by investigating the main effects of the polygenic scores on peer victimisation. These analyses used the polygenic scores that explained the most variance in the outcome measures.

4.4.4.2 Interaction analyses

The presence of a G×E was then examined by including an interaction term (victimisation by the polygenic scores) in regression models predicting depressive symptoms and wellbeing. This was used to provide insight into whether polygenic scores moderate depressive symptoms and wellbeing among individuals subjected to peer victimisation. These analyses used the polygenic scores that explained the most variance, as well as those at genome-wide significance. All interaction models were adjusted for the main effects of the polygenic scores and peer victimisation, as previously recommended (Greenland & Pearce, 2015). To control for the potential effects of sex and the principal components, adjustments were made for all covariate x polygenic score and covariate x victimisation interactions. It has been suggested that modelling confounder interactions is essential to ensuring that any detected G×E effects reflect the specified genetic or environmental variables and not the confounders (Keller, 2014). This is crucial because a covariate related to either the genetic or environmental variable could introduce bias (Moore & Thoemmes, 2016). To illustrate, if females present a higher polygenic risk to depression than males, any apparent G×E between victimisation and the polygenic scores may really represent a sex × E effect. Similarly, if females are at a greater risk of victimisation, any G×E findings may really be driven by an underlying sex × G effect.

Both the main and interaction models were run in R Studio version 4.0.5 (R Core Team, 2021). Analyses predicting wellbeing used standard linear regression while analyses

predicting depressive symptoms used negative binomial regressions. This was to address the negative skew of the depressive symptoms measure. The negative binomial regression was selected over the Poisson model as the Poisson regression assumes identical parameters for the mean and variance, this was not the case for the depressive symptoms measure ($M=6.84$, $\sigma^2=34.8$). To run the negative binomial regressions, the 'MASS' package (Venables & Ripley, 2002) in R was used and the 'rsq' package (Zhang, 2018) to generate R-squared estimates. To control for the probability of making a Type I error on multiple comparisons, Benjamini-Hochberg False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was used as this allows for the non-independence of repeated tests. The procedure for calculating this was described in Chapter 3.

Table 4.1: Correlations between study variables

	Correlation matrix								
Variables	1	2	3	4	5	6	7	8	9
1. Peer victimisation (log)	1	**-0.11*** ** (-0.16, -0.07)	**0.17*** ** (0.13, 0.21)	0.02 (-0.02, 0.06)	0.04 (-0.00, 0.08)	**0.06*** ** (0.02, 0.10)	**0.07*** ** (0.02, -0.09)	**-0.05*** (-0.09, -0.01)	**-0.05*** (-0.09, -0.01)
2. Mental wellbeing		1	**-0.69*** ** (-0.71, -0.67)	**-0.05*** ** (-0.09, -0.01)	-0.03 (-0.07, -0.01)	**-0.10*** ** (-0.14, -0.06)	**-0.11*** ** (-0.15, -0.07)	**0.08*** ** (0.04, 0.12)	**0.14*** ** (0.10, 0.18)
3. Depressive symptoms			1	**0.09*** ** (0.05, 0.14)	0.00 (-0.04, 0.04)	**0.12*** ** (0.08, 0.16)	**0.13*** ** (0.08, 0.16)	**-0.08*** ** (-0.12, -0.04)	**-0.15*** ** (-0.19, -0.11)
4. Sex				.1	0.02 (-0.03, 0.06)	0.03 (-0.02, 0.07)	0.03 (-0.01, 0.07)	-0.03 (-0.07, 0.01)	-.02 (-0.06, 0.02)
5. Depression-PGS (P^T $5x10^{-8}$)					1	**0.18*** ** (0.13, 0.22)	**0.17*** ** (0.13, 0.21)	**-0.62*** ** (-0.64, -0.59)	**-0.34*** ** (-0.38, -0.31)
6. Depression-PGS (P^T 0.1)						1	**0.94*** ** (0.93, 0.95)	**-0.18*** ** (-0.22, -0.14)	**-0.35*** ** (-0.38, -0.31)
7. Depression-PGS (P^T 0.2)							1	**-0.16*** ** (-0.20, -0.12)	**-0.34*** ** (-0.38, -0.30)
8. Wellbeing-PGS (P^T $5x10^{-8}$)								1	**0.51*** ** (0.47,

	0.54)
9. Wellbeing-PGS (P^T 0.001)	1

PGS = polygenic scores. P^T = p-value threshold of the polygenic score. n=2232. ***p<0.001, **p<0.01, *p<0.05.

Note: Mental wellbeing and depressive symptoms were assessed at 23 years and sex was coded as 0=Male and 1=Female.

4.4.5 Power calculations

Power calculations for the main effects of the polygenic scores were conducted using the 'avengeme' package in R studio (Dudbridge, 2013), as per Chapter 3. This was done for both the depression and wellbeing polygenic scores using the thresholds that explained the most variance. For depression, power calculations were based on the GWAS discovery sample of 807,553 (Howard et al., 2019), which explained up to 3.2% of the variance in depression. Using the polygenic score that explained the most variance in the present study, calculations revealed there was 80% power to detect 0.9% of the phenotypic variance. For wellbeing, the discovery sample was 2,370,390, and the study explained up to 1.10% of the variance in wellbeing (Baselmans et al., 2019). This meant the polygenic scores in the current study had 80% power to detect 0.8% of the phenotype variance.

Power for the interaction analyses was determined using G*Power 3.1 (Faul et al., 2009) with $\alpha = 0.05$ and 12 predictors (polygenic risk score, victimisation, sex, principal component 1, principal component 2, polygenic score*victimisation, sex*victimisation, sex*polygenic score, principal component1*victimisation, principal component2*victimisation, principal component1*polygenic score, principal component2*polygenic score). Using the maximum sample of the current study (*n*=2,299), analyses had 80% power to detect effects that explain 0.82% of the phenotypic variance.

4.5 Results

4.5.1 Descriptive data

Approximately 54% of individuals who provided genotype and relevant phenotype information reported some experience of victimisation in adolescence, as indicated by scores of above 0 on the victimisation scale. Of these, 17% had experienced frequent victimisation. This was defined according to a three-level victimisation variable that grouped participants based on their overall victimisation scores. Individuals who scored 0 were classed as never victimised, those scoring between 1 and 3 were classified as occasionally victimised, and those with scores of 4 or more were defined as frequently victimised. This procedure of grouping victims has been used previously to study depression (Bowes et al., 2015) and anxiety (Stapinski et al., 2014) following peer victimisation.

Comparisons of wellbeing scores between individuals with either no or some experiences of peer victimisation revealed significant differences between the two, with non-victims scoring on average 50.04 (range 17-70), and individuals exposed to some victimisation scoring on average 48.53 (range 14-70). Similar results were found for depressive symptoms, with non-victims scoring on average 5.77 (*SD*=5.49) and victims 7.36 (*SD*=5.97). When comparing the percentage of individuals with clinically relevant symptoms, findings revealed that 18.7% of individuals exposed to some peer victimisation had clinically relevant depressive symptoms compared to 12% of non-victims. This figure increased to 22.5% among individuals exposed to frequent victimisation.

Both the depressive symptoms and wellbeing scores were predicted by sex, with females more likely to report reduced wellbeing (ß=-1.08, *SE*=.38, $p<0.001$) and increased depressive symptoms (ß=.172, *SE*=.04, $p<0.001$). Peer victimisation scores, however, were not predicted by sex (ß=-.006, *SE*=.11, $p=.95$), suggesting males and females were equally likely to be victimised.

4.5.2 Main effect analyses

The main effect analyses revealed that both depressive symptoms and wellbeing were predicted by the polygenic scores, with estimates generally stronger when using more liberal thresholds. Polygenic scores derived from the depression GWAS explained the most variance in depressive symptoms at the *p*-value threshold of 0.1 (incremental R^2 = 1.43%), and the most variance in wellbeing at a *p*-value threshold 0.2 (incremental R^2 = 1.21%). The direction of effects was as expected, polygenic scores were positively associated with the risk of depressive symptoms and negatively with wellbeing (see Appendix 4.4 for results across thresholds). When investigating associations using polygenic scores generated from the wellbeing GWAS, associations were in the opposite direction, predicting a lower risk of depressive symptoms and higher wellbeing. These polygenic scores explained more of the variance overall, with the incremental R^2 2.09% for wellbeing and 2.11% for depressive symptoms. These estimates were both derived from polygenic scores at a *p*-value threshold of 0.001 (see Appendix 4.5 for full results).

Associations between the polygenic scores and mental health outcomes remained largely the same after accounting for peer victimisation (see Appendix 4.6), which was associated with a higher risk of depressive symptoms (ß=.193, *SE*=.02, *p*<0.001) and reduced wellbeing (ß=-1.31, *SE*=.24, *p*<0.001). This effect of peer victimisation on mental health and wellbeing also remained after accounting for the polygenic scores (see also Appendix 4.6). Such findings suggest that both the polygenic scores and peer victimisation exert direct and independent effects on depression and wellbeing.

When testing for a possible gene-environment correlation (rGE), analyses revealed that while some of the polygenic scores were associated with peer victimisation (see Appendix 4.7), the variance explained was low, with the depression polygenic scores accounting for up to 0.42% of the variance and the wellbeing polygenic scores explaining 0.45%. Correlations between peer victimisation and the polygenic scores were also low, reaching *r*=0.06

between victimisation and the depression polygenic scores, and *r*=-0.07 with the wellbeing polygenic scores.

4.5.3 Interaction analyses

Despite significant independent effects of both the polygenic scores and peer victimisation in predicting depressive symptoms and wellbeing, no interactions were found between any of the polygenic scores and victimisation (Table 4.2). Findings did reveal a borderline interaction (*p*=0.056) between the depression polygenic scores and victimisation when predicting wellbeing, however, plots of the results suggest that the difference in wellbeing scores between individuals at a high and low polygenic risk was not significantly different (Figure 4.1). This interaction effect was also only found when using the genome-wide significant threshold and was not robust after correction for multiple testing.

It is interesting to note that when entered as an interaction term, peer victimisation was no longer associated with wellbeing (see Table 4.2). This is likely a result of the interactions that were found between peer victimisation and sex in models predicting wellbeing. Such interactions were not found when predicting depressive symptoms which likely explains why victimisation remained associated with depressive symptoms in the interaction models. This leads to the conclusion that while peer victimisation is not predicted by sex, associations with subsequent wellbeing are largely different for males and females. In particular, it was found that females exposed to peer victimisation were more likely to experience reduced wellbeing compared to males. Such findings demonstrate the importance of appropriate control over confounding variables as such effects can lead to misinterpretations of interactive effects (Keller, 2014).

Table 4.2: Impact of log-transformed victimisation scores, polygenic scores, and their interaction on depressive symptoms and wellbeing at 23 years

	Impact on depressive symptoms							
	Polygenic Scores		Victimisation		Interaction			
	β (95% C.I.)	P value	β (95% C.I)	P value	β (95% C.I)	P value	R^2	ΔR^2
Depression-PGS								
P^T=5x10^{-8}	-0.048 (-0.129, 0.033)	0.259	0.188 (0.084, 0.293)	**4.0E-04**†	0.024 (-0.022, 0.070)	0.318	3.1%	0.1%
P^T=0.1	0.100 (0.017, 0.184)	**0.017**	0.177 (0.073, 0.281)	**8.0E-04**†	-0.027 (-0.074, 0.021)	0.271	4.3%	1.3%
Wellbeing-PGS								
P^T=5x10^{-8}	-0.035 (-0.121, 0.050)	0.418	0.181 (0.077, 0.286)	**6.0E-04**†	0.005 (-0.044, 0.054)	0.844	3.6%	0.6%
P^T=0.001	-0.068 (-0.154, 0.018)	0.124	0.176 (0.072, 0.281)	**7.9E-04**†	-0.003 (-0.050, 0.045)	0.911	5.2%	2.2%
	Impact on wellbeing							
Depression-PGS								
P^T=5x10^{-8}	0.091 (-0.702, 0.885)	0.821	-0.014 (-0.979, 1.01)	0.977	-0.452 (-0.916, 0.012)	0.056	2.5%	0.9%
P^T=0.2	-0.365 (-1.17, 0.443)	0.376	-0.022 (-0.969, 1.01)	0.965	-0.085 (-0.554, 0.384)	0.722	3.5%	1.7%
Wellbeing-PGS								
P^T=5x10^{-8}	0.232 (-0.583, 1.05)	0.577	-0.045 (-1.04, -0.949)	0.930	-0.014 (-0.497, 0.468)	0.953	2.9%	1.2%
P^T=0.001	0.074 (-0.743, 0.890)	0.860	0.004 (-0.980, 0.989)	0.993	0.311 (-1.53, 0.776)	0.189	4.6%	2.9%

PGS = Polygenic scores. P^T=p value threshold of the polygenic score. R^2= the variance accounted for by the main and interactive effects of victimisation and the polygenic scores, as well as the covariates. ΔR^2 = the incremental R^2. †FDR

Note: Each row represents a separate multiple regression of either depressive symptoms or wellbeing predicted by the polygenic scores, victimisation, and the gene-environment interaction. Negative binomial regression models were used to investigate depressive symptoms (n=2268), and linear regression models for wellbeing (n=2299)

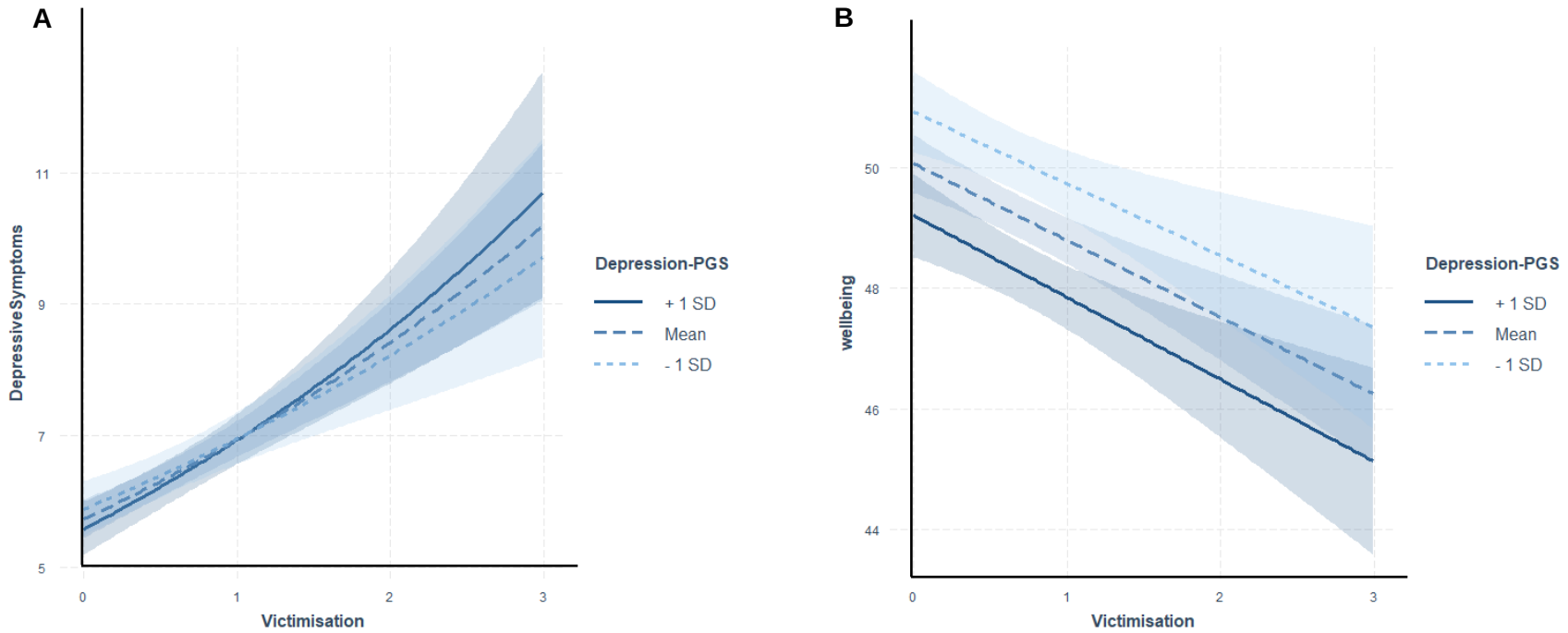

Figure 4.1: *Interactive effects of victimisation and the depression-polygenic scores (PGS) (P-value thereshold=5x10^{8}) on depressive symptoms and wellbeing. Figure A demonstrates no differences in depressive symptoms at $\alpha = 0.05$ among victims with varying polygenic scores. Figure B provides some evidence of an effect of polygenic risk towards depression on wellbeing scores, with those reporting higher victimisation scores and a PGS 1 SD above the mean more likely to report lower wellbeing. This difference in wellbeing scores corresponded to p=0.056.*

Results from analyses using the untransformed victimisation scores can be found in Appendix 4.2. Overall, findings were largely consistent with analyses using the log-transformed victimisation scores, with confidence intervals that overlapped. The interaction between peer victimisation and the depression polygenic scores in predicting wellbeing was also replicated, however, as with the transformed scores, this was not robust after correction for multiple testing. For completeness, results from analyses using the other polygenic score thresholds can be found in Appendix 4.8. Findings were highly consistent across different polygenic thresholds.

4.6 Discussion

This study investigated for the first time, whether mental health problems following peer victimisation can be partly attributed to genetic factors using polygenic scores for depression and wellbeing. Although no G×E was detected, the findings provide important insight into resilience following adolescent victimisation.

4.6.1 Gene-environment interaction (G×E)

Main effect models revealed that both the polygenic scores and peer victimisation had significant independent effects on the risk of depressive symptoms and wellbeing. When entered as an interaction term, however, there was no clear evidence that an individual's polygenic risk moderated the impact of peer victimisation. This means that individuals with a higher genetic risk profile were no more susceptible to the negative effects of peer victimisation than individuals with a lower genetic risk. Such a finding is not consistent with the Diathesis-Stress model (Monroe et al., 1991) or the Differential Susceptibility Theory (Belsky et al., 2013) which would predict a heightened risk for those victimised and at a higher genetic risk (Colodro-Conde et al., 2018). Instead, the results suggest that the increased risk for poorer mental health and wellbeing following peer victimisation is not heightened by genetic differences, as indexed by the current polygenic scores for depression and wellbeing. Genetic profiling is therefore unlikely to be effective in identifying those more vulnerable to the effects of victimisation.

It is possible that no support was provided for the Diathesis-stress model because those at a heightened risk were more susceptible to positive environmental influences. By this, individuals frequently victimised who were also at a higher genetic risk may have also been more receptive to protective factors in the environment. This may have buffered against negative effects of peer victimisation and genetic risk on the likelihood of depression and low wellbeing. Such a finding seems unlikely as the combination of genetic risk and frequent victimisation increased the levels of depressive symptoms and reduced levels of wellbeing.

However, these differences in mental health outcomes were not significantly different to those at a lower risk, providing some support for the Differential Susceptibility Theory. Further investigations could explore this possible differential susceptibility by comparing sensitivity towards protective environments among those at high genetic and environmental risk.

The absence of moderating effects of polygenic risk aligns with some of the existing research on childhood trauma. In particular, previous studies have reported that the likelihood of depression among individuals exposed to trauma is unlikely to be attributable to moderation of genome-wide genetic effects (Musliner et al., 2015; Peyrot et al., 2018). It is possible that such findings indicate that the relationship between peer victimisation and mental health is one in which genetics and pre-existing problems have a negligible effect.

Similar conclusions have been drawn from twin research which has revealed that although pre-existing vulnerabilities predict the likelihood of experiencing peer victimisation or trauma, they cannot solely explain the increased risk of psychopathology (Lewis et al., 2021; Schaefer et al., 2018). These findings were based on the observation that associations between trauma and mental illness, and between peer victimisation and mental illness, remain after accounting for a family history of mental disorders (Schaefer et al., 2018) and pre-existing vulnerabilities (Lewis et al., 2021). The authors interpreted this as suggestive of a causal and direct impact of peer victimisation on mental illness. The findings from the current study provide further evidence of this by demonstrating that peer victimisation predicts a heightened risk of depression and low wellbeing even after controlling for genetic risk towards depression and wellbeing.

4.6.2 Gene-environment correlation (rGE)

When investigating the relationship between peer victimisation and the polygenic scores, there was some evidence of a gene-environment correlation (rGE) (see Appendix 4.5). This aligns with the results from Chapter 3 which noted that polygenic scores for depression and

wellbeing predicted higher self-reported victimisation in participants from the Quebec Newborn Twin Study (QNTS). Such pre-existing vulnerabilities, however, are unlikely to account for the borderline G×E finding in the current study. This is because polygenic scores at genome-wide significance (p=5x10^{8}) were not associated with peer victimisation, the threshold at which this near interaction effect was noted. Such effects are therefore unlikely to reflect a spurious result due to a possible rGE. However, to completely rule out the presence and impact of a potential rGE, future genome-wide association studies (GWASs) will need to include measures of peer victimisation to test for shared genetic variants with mental health outcomes.

4.6.3 Strengths and limitations

Few studies have considered the role of genetic and environmental factors in predicting resilience to the effects of peer victimisation. Those that do exist have explored possible underlying pathways using the twin design (Bowes et al., 2010). While such research has provided meaningful insight into the degree to which genes and environments influence protective factors, the twin design is blind to specific genetic variants. As such, these previous studies were unable to explore moderating effects of genetic liabilities towards certain traits and disorders. This is key to refining our understanding of predictors of resilience following peer victimisation.

The current study also represents the first to use polygenic scores for both positive and negative mental health within a G×E design predicting depression and wellbeing. Correlations between the depression and wellbeing polygenic scores were moderate but not identical (rG~0.62), demonstrating the unique genetic effects that are captured by the two. Polygenic scores derived from the depression GWAS explained up to 1.60% of the variance in depressive symptoms in the current sample, while scores from the wellbeing GWAS explained 2.56% of the variance in wellbeing. These estimates are larger than previous reports of polygenic scores which explained ~1% of the variance in depressive symptoms

(Musliner et al., 2015) and ~0.9% for wellbeing (Okbay et al., 2016). This likely reflects the increase in power gained from using meta-analyses of GWAS data to construct the polygenic scores. It is worth noting, however, that polygenic scores generated from the depression GWAS did not predict depressive symptoms at genome-wide significance ($p<5x10^{-8}$). Power calculations based on this polygenic score revealed that the study would have 80% power to explain phenotypic variance as little as 0.35%. However, the genome-wide significance polygenic scores explained just 0.08% of the variance in depressive symptoms, meaning analyses were underpowered to detect main effects of this small magnitude.

When interpreting the current results, it is also important to be mindful of how the polygenic scores were created. Polygenic scores included SNPs that were selected based on their main effects in the discovery GWAS. It is possible that these SNPs are not the same variants as those involved in any G×E, which may explain the absence of moderating effects. In addition, the wellbeing GWAS used a multivariate approach to combine different traits related to the wellbeing spectrum (Baselmans et al., 2019). One of these measures was depression. Although this was reverse coded in the GWAS to ensure higher scores reflected less negative affect, the resulting wellbeing measure is not strictly positive. This likely explains why the polygenic scores derived from this GWAS explained a similar proportion of the variance in wellbeing and depressive symptoms (see Appendix 4.5). Follow-up research using genetic data related specifically to wellbeing may therefore generate different results.

Other limitations to consider are that both GWASs used to construct the polygenic scores included large samples of individuals from the UKBiobank. Participants from the UKBiobank have been shown to be healthier and less socioeconomically deprived than the general population (Fry et al. 2017). While this may mean that such individuals have fewer mental health problems, research has revealed similar prevalence rates for mental health disorders

among members of the UKBiobank and the general population (Davis et al., 2020). Nevertheless, the extent to which participants from the original GWASs were victimised is not known. It is therefore not currently possible to make deductions about the relative impact on both the genetic estimates and subsequent mental health outcomes.

Finally, mental health and wellbeing were only assessed at one time point in the current study. While this decision was driven by findings on the impact of peer victimisation on mental health and wellbeing at age 23 (Armitage et al., 2021), it is likely that the interplay between genetic and environmental factors is dynamic and subject to change over time. Support for this comes from findings which show that interactions between genes and stressful life events play out differently in early versus later life (Gärtner et al., 2017). It is thus possible that while no strong moderating effects of genetic risk were noted in the current study, interactions with peer victimisation may account for individual differences in mental health and wellbeing at different stages of development.

4.6.4 Implications and future directions

Overall, this study provides a unique insight into resilience following peer victimisation. While genetic dispositions towards depression and wellbeing did not moderate the mental health outcomes of victims, further research is necessary to completely rule this out. Such research will be enhanced by the development of more powerful polygenic scores derived from larger GWASs and deeper phenotyping (Bycroft et al., 2018). Analyses conducted using polygenic scores will always be limited by the phenotypic assessments used in the original GWAS. Research has shown that 'minimal phenotyping', which refers to the reduction of questionnaires or data to fewer items or responses, can result in identifying genetic variants not specific to the phenotype of interest (Cai et al., 2020). These shortcuts are often taken to reduce the time and costs associated with GWASs; however, such techniques may bias our understanding of the genetic architecture of complex traits. It is therefore crucial that any output from genetic research using polygenic scores is carefully considered in relation to

how the phenotype was originally assessed. In addition, research should also carefully consider the threshold used to construct polygenic scores.

Previous studies have tended to use arbitrary SNP p-value thresholds when creating and studying polygenic scores in a G×E framework (Mullins et al., 2016). This is likely one explanation for the lack of consistency within the literature. By using scores that explained the most variance, the current study aligned with the current common practice (de Villiers et al., 2020) and helped avoid 'cherry-picking' results to align with existing hypotheses. Analyses were also supplemented with genome-wide significant polygenic scores. It was hypothesised that using fewer SNPs would help to reduce noise and ensure scores were more specific to the trait of interest. Such an approach, however, can result in an upwards bias, known as 'Winner's Curse' (Shi et al., 2016), which may explain the borderline interactive finding in this study.

It is possible that using different methods to create the polygenic scores could have increased model performance and overall reliability, although findings on the best approach are mixed. While a review of the different polygenic scoring techniques concluded there are methods that outperform the traditional clumping and thresholding approach used in the current study (Pain et al., 2021), others have shown there are no differences in prediction accuracy between the different polygenic score approaches (Allegrini et al., 2019). It has been suggested that retaining and modelling the effects of all genetic variants from the GWAS, instead of removing those in linkage disequilibrium (LD) as per the clumping method, allow the polygenic scores to capture more of the variance (Pain et al., 2021). However, problems can arise when the genetic architecture of a trait is sparse and the sample is large as LD methods cannot accurately address LD structure. Many have therefore suggested that the best approach to creating polygenic scores is dependent on context and trait (de Villiers et al., 2020; Privé et al., 2019). The current study chose to use the clumping and thresholding method to align with previous G×E research (Mullins et al.,

2016; Musliner et al., 2015; Peyrot et al., 2018). However, future studies would benefit from using different polygenic designs to decipher which is most appropriate for modelling moderating effects.

Further research would also benefit from exploring factors beyond polygenic scores for depression and wellbeing as predictive of resilience to the effects of peer victimisation. The current study chose these specific polygenic scores to test the Diathesis-stress model of depression (Colodro-Conde et al., 2018) and whether this transfers to wellbeing. It is likely, however, that factors beyond pre-existing mental health vulnerabilities are important predictors of later functioning and resilience. In support of this, research has shown that a genetic predisposition for anxiety predicts anxiety among children exposed to peer victimisation, but only when certain environmental factors are in place (Guimond et al., 2015). Such findings may explain the absence of moderating effects currently found and demonstrate the importance of factors external to the individual.

Studies investigating the role of the environment have revealed that while interactions between genetic and environmental factors may be absent, interactions between environments may contribute to the risk of peer victimisation (Brendgen et al., 2014). In particular, it was noted that the likelihood of developing physical symptoms following peer victimisation is less dependent on genetic susceptibility for physical health problems, but on non-shared environmental factors. Non-shared environments refer to those that are not shared by individuals living together, such as friendships. Further investigation into protective factors at the environmental level may therefore be necessary to detect moderators of mental health and wellbeing following peer victimisation. Such research could be used to inform further study into more complex interactions between peer victimisation, genetic dispositions, and protective factors in predicting resilience. These more complex models could consider whether interactions between genetic liability and protective factors contribute to an increased or decreased risk of mental health problems following peer

victimisation. Such a design would need to be conducted on large samples of victimised individuals to ensure sufficient power. This may be difficult as the current findings suggest only around 17% of adolescents experience frequent victimisation. Nevertheless, combining data from multiple cohorts may be one approach to increase sample size and thus power to detect more complex interactions between genetic and environmental factors.

4.7 Chapter summary

Overall, the results from this study suggest that the increased risk of depression and low wellbeing observed among victims is unlikely to be explained by a moderating effect of genetic risk, as indexed by the current polygenic scores. This means that having a higher genetic risk towards depression and low wellbeing does not increase the risk of mental health problems following peer victimisation, nor does having a low genetic risk to depression or poor wellbeing predict greater resilience. The reasons why some go on to experience mental health problems and low wellbeing following peer victimisation, while others maintain resilience, therefore requires further investigation. However, this study rules out a major influence of the current polygenic scores.

Chapter 5: Resilience following adolescent victimisation: An exploration into protective factors across development[3].

5.1 Chapter overview

In the previous chapter I explored resilience following peer victimisation using genetic information related to mental health. To provide further insight into possible predictors of resilience, in this chapter I explore the role of 14 protective factors across the individual-, family-, and peer-level. In doing so, I present the first study to consider moderators of adult wellbeing following peer victimisation.

In this chapter, I aim to:

- Build upon existing findings to investigate whether protective factors not only moderate the risk of depressive symptoms following peer victimisation, but also wellbeing and thus resilience.

- Extend previous research to investigate the importance of the timing of the protective factors by studying effects before and after peer victimisation.

5.2 Introduction

As discussed in Chapter 1, resilience researchers are interested in identifying factors that buffer or ameliorate the impact of an adverse event. Many have investigated the role of such factors, referred to as protective factors, in relation to peer victimisation (Ttofi et al., 2014). This research has provided important insight into predictors of more favourable outcomes following both child (Bowes et al., 2010) and adolescent peer victimisation (Vassallo et al., 2014). Most of this research, however, has focused on the reduction of internalising and externalising problems (Sapouna & Wolke, 2013), with just one study considering how wellbeing may be implicated (Flaspohler et al., 2009). While these findings identified

[3] This chapter has been adapted from Armitage, J. M., R. Wang, A., Davis, O. S. P., Collard, P., & Haworth, C. M. A. (2021). Positive wellbeing and resilience following adolescent victimisation: An exploration into protective factors across development. *JCPP Advances, 1*(2), e12024. https://doi.org/10.1002/jcv2.12024

possible protective factors at the peer-level, results were based on correlations between the studied factors and life satisfaction in adolescence. The longitudinal and moderating role of protective factors on adult wellbeing therefore remains largely unknown.

The importance of including assessments of wellbeing in addition to mental illness was outlined in Chapter 1. Here it was noted that although wellbeing and mental illness represent related dimensions of mental health, correlations are not 100% (Haworth et al., 2017). This means that while individuals may not be depressed, they may still be unhappy. Indeed, in relation to peer victimisation, findings have shown that although victims may avoid depression, they still maintain significantly lower wellbeing than their non-victimised counterparts (Armitage et al., 2021). Efforts to support victims should therefore not only consider how mental illness can be prevented, but also how positive wellbeing can be encouraged.

5.2.1 Protective factors

Below I provide an overview of the current literature exploring the role of protective factors in reducing mental illness following peer victimisation. This was used to guide the selection of protective factors to include as potential moderators of wellbeing. Many of the included studies form part of a larger systematic review (Ttofi et al., 2014). This identified common protective factors at the individual-, family-, and peer-level in both childhood and adolescence.

5.2.2 Individual-level protective factors

Factors at the individual-level that have been repeatedly identified as protective for individuals exposed to victimisation include a high self-esteem, good performance at school, and good social skills (Ttofi et al., 2014). Other individual attributes, such as low impulsivity, prosocial attitudes, and moral beliefs, have also been shown to be protective, however, findings are based on reductions in antisocial behaviour and not mental health (Hemphill et

al., 2014; Vassallo et al., 2014). These individual-level protective factors that only predicted reductions in anti-social behaviour were therefore not included in the current study.

5.2.2.1 Self-esteem

Research has repeatedly shown that individuals who are low in self-esteem are at particular risk of both mental health problems (Sowislo & Orth, 2013) and peer victimisation (Tsaousis, 2016). Self-esteem refers to the orientation towards oneself, which is used to evaluate self-liking, self-worth, and competence (Rosenberg, 1979). Many have emphasised the importance of distinguishing between these aspects of self-esteem (Tafarodi & Swann, 1995), with scales designed to separately assess the different dimensions (Harter, 1985). Such scales are based on the assumption that an individual's sense of competency is not a unitary construct, but comprises of feelings towards skills in different domains, including academic, social, and physical (Harter, 1985).

Research investigating different facets of self-esteem in relation to victimisation have shown that perceptions of self-worth may be more protective for mental health than self-competency (Soler et al., 2013). Such findings, however, derived from research on various victimisation experiences, not all of which were inflicted by peers. Studies focused specifically on peer victimisation have explored moderating effects of more global self-esteem (McVie, 2014; Sapouna et al., 2013), assessed using the Rosenberg Self Esteem Scale (Rosenberg, 1965). These have revealed that the risk of depression among adolescent victims is significantly reduced among individuals with higher self-esteem (Sapouna et al., 2013), with moderate interaction estimates reported (McVie, 2014).

No study, however, has discriminated between the different aspects of self-esteem to consider protective effects in relation to peer victimisation, or explored a moderating role in predicting mental health beyond adolescence. This is crucial given the longitudinal impact of victimisation on mental health and wellbeing (Armitage et al., 2021).

5.2.2.2 Academic ability

In addition to high self-esteem, findings have highlighted that doing well in school can protect against some of the negative effects of victimisation (Vassallo et al., 2014). Adolescents who report that they understand the work in their class have been shown to be at lower risk of developing depression six years after experiencing victimisation, with rates dropping by up to 16% (Vassallo et al., 2014). Similar longitudinal research has shown that the risk of depressive symptoms in adulthood drops from 23.1% to 6.9% among low versus high achievers (Hemphill et al., 2014).

Low school achievers typically hold less favourable attitudes towards school (Alves-Martins et al., 2002). Thus, it is possible that understanding schoolwork helps generate more opportunities for engagement, which then serves to increase perceptions of school. Findings have shown that having positive attitudes towards school can help buffer against the negative outcomes of peer victimisation on later mental health (Stadler et al., 2010). One issue with generalising findings on school achievement, however, is that studies to date have relied on single-item assessments of victimisation (Hemphill et al., 2014). Most have also dichotomised factors into protective or non-protective categories (Stadler et al., 2010). The procedure for doing this has varied between studies, with some taking the top 75% of scores to determine the most protective point (Hemphill et al., 2014), and others taking a median split (Stadler et al., 2010) or the best quartile (25%) of high achievers (Vassallo et al., 2014). This has often resulted in small samples of participants, meaning findings should be generalised with caution.

5.2.3 Social skills

A final protective factor at the individual-level is social skills. Individuals at a greater risk of victimisation not only often present lower self-esteem, but are also less socially competent (Cook et al., 2010; Fox & Boulton, 2005). This relationship between social deficits and peer victimisation has been shown to contribute to a heightened risk of depressive symptoms (Perren & Alsaker, 2009).

It has been suggested that a lack of social skills renders individuals more psychologically and socially vulnerable to victimisation and its subsequent effects (Perren et al., 2006). In contrast, good social skills help to build quality relationships and confidence in handling social situations (DeRosier, 2010). Having higher social skills could therefore prove an essential protective factor for victims and may enable problems with others to be more effectively resolved (Lösel et al, 2007). Research in support of this has shown that the prevalence of depression is half as likely among victims who reported higher social skills in adolescence (Vassallo et al., 2014). These findings were based on reports of depression in early adulthood, suggesting longitudinal benefits of having good social skills. As with findings on school performance, however, these findings were based on small samples and are therefore in need of replication.

To summarise, research thus far on individual-level protective factors has suggested that for individuals higher in self-esteem, academic abilities, and social skills, the likelihood of experiencing internalising symptoms after victimisation is reduced (Ttofi et al., 2014). However, the degree to which these factors also promote good wellbeing remains to be tested.

5.2.4 Family-level protective factors

Beyond individual attributes and characteristics, the relationship between an individual and their family has also been noted as important to preventing mental illness following peer victimisation (Averdijk et al., 2014). Studies exploring childhood victimisation have shown that a positive home environment, as well as high maternal and sibling warmth, can moderate the subsequent risk of emotional problems (Bowes et al., 2010). It was proposed that positive family relationships may translate into more opportunities to monitor and guide victims when in need of support. Similar conclusions have been drawn from studies on adolescents exposed to victimisation, with high parental support shown to provide a protective buffer against the risk of later depressive symptoms (Stadler et al., 2010). It was

suggested that greater family security may encourage the victim to turn to the family for support which may serve to reduce internalising problems.

Studies investigating the role of families to date have only assessed negative mental health outcomes up until the age of 18 (Stadler et al., 2010). Thus, much like the individual-level protective factors, it is not yet known whether family influences extend to promoting wellbeing, and whether positive effects of the family continue into later life. It is possible that as individuals progress into early adulthood and move away from the family home, support from family members becomes less important.

5.2.5 Peer-level protective factors

In addition to family relationships, relationships with peers have also been investigated as possible protective factors, however, such research findings are mixed. Some have proposed that the number of friendships are not protective (Averdijk et al., 2014), and the support received from peers can intensify the risk of mental illness among victims (Vassallo et al., 2014). Others, however, have shown a reduction in internalising symptoms among victims with more supportive friends (Papafratzeskakou et al., 2011). Discrepancies between study findings are unlikely to result from different measures as studies have typically used the same scale to capture peer support at a similar age (Vassallo et al., 2011; Papafratzeskakou et al., 2011). Such scales capture the attachment bond between peers by asking about the degree to which they feel understood and respected by their peer, as well as the degree to which their peers are sensitive and responsive to their emotional needs (Armsden & Greenberg, 1987). Thus, it is possible that instead, differences between findings reflect the age at which depressive symptoms were assessed. One study included measures of mental health in early adulthood (Vassallo et al., 2014), and the other focused solely on childhood (Papafratzeskakou et al., 2011). Further research is therefore necessary to clarify the role of peers following peer victimisation.

Just one study has considered how peer support in adolescence may impact the wellbeing of individuals subjected to victimisation (Flaspohler et al., 2009). Findings revealed that adolescents who feel unsupported by their peers and who are exposed to peer victimisation, experience the lowest levels of life satisfaction. Such findings emphasise the need to extend previous findings to explore a possible moderating role of peer support on adult wellbeing.

5.3 Current study

As evident by the review of the literature, research exploring the role of protective factors in relation to peer victimisation and wellbeing is sparse. The current study therefore aimed to address this gap to investigate for the first time, whether factors not only protect against depressive symptoms after peer victimisation, but also promote adult wellbeing. In doing so, the aim of the study was to provide further insight into resilience to peer victimisation, and how this can be fostered.

A second goal of the current study was to extend previous research focused on one stage of development to include protective factors across childhood and later adolescence. Doing so is important as recent findings have revealed that protective factors in early adolescence are more successful in reducing distress compared to those in later adolescence (Fritz et al., 2019). While this study was focused on victims of child abuse, it provides important insight into the dynamic nature of protective factors. No study, however, has yet explored such changes in relation to peer victimisation, or considered whether factors in place prior to victimisation are protective.

The need to adopt a longitudinal perspective has been previously emphasised in the context of resilience (Ungar, 2013). Studying protective factors both before and after exposure to victimisation could help to distinguish those that are specific to increasing resilience after victimisation, and those that are time-independent (Fritz et al., 2018). Identifying protective factors that are time-independent could be especially valuable in allowing preventative programmes to target individuals before exposure to victimisation to help bolster future

resilience. Such an approach could be further enhanced by studying the cumulative effects of protective factors (Fritz et al., 2019). This was achieved in the present study by exploring both the independent and combined impact of protective factors at the individual-, family-, and peer-level.

5.4 Methods

5.4.1 Sample

The longitudinal cohort used to conduct the present analyses was the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013), which was described in detail in Chapter 2. Participants included were those who completed the victimisation assessment at 13 years, as well as the mental wellbeing, life satisfaction, and depressive symptom measures at age 23. Individuals also had available data on various protective factor measures as well as socioeconomic status (SES). A flowchart of those included can be found in Appendix 5.1.

Out of the 6,529 individuals who completed the victimisation assessment, 2,703 (41.4%) completed the wellbeing scale aged 23 and had information relating to their SES. Of these, 97.1% also completed the depressive symptoms scale at age 23. Data were taken from individuals who completed both mental health measures to ensure fair comparisons between models predicting wellbeing or depressive symptoms. In total, complete data for peer victimisation, wellbeing, depression, SES, and all protective factor measures were available for 949 individuals. To maximise the data available in ALSPAC and to avoid problems associated with complete cases, analyses separately explored each protective factor. This resulted in samples that ranged in size from 1,712 to 2,398 participants.

To reduce the potential for bias, possible differences between subsamples were explored. Comparisons revealed no sex differences between samples, and no differences in rates of victimisation, SES levels, or mental health (see Appendix 5.2). Correlations were also conducted between the different protective factors (see Appendix 5.3 for the correlations matrix). These ranged from low to moderate, with the highest correlation observed between social skills in early and late adolescence (r=0.61). The combined findings indicate minimal bias from using separate sub-samples, however, analyses were repeated using multiple imputation to further reduce potential bias. The process for conducting this is explained in

more detail below, and the variables included in the imputation can be found in Appendix 5.4.

5.4.2 Measures

Information about the measures used for the current study are presented in Table 5.1, including information on who was assessed, the age of the participant when the assessment took place, the number of items on each scale and how these were scored. Below I also provide further information about the protective factor measures and the confounding variables. More detailed information about the victimisation and outcome variables were presented in Chapter 2. In summary, the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS; Tennant et al., 2007) was used as the primary outcome, with follow-up analyses conducted using the Satisfaction with Life Scale (Diener et al., 1985). This was to allow comparisons with the only similar study to date on protective factors in relation to wellbeing (Flaspohler et al., 2009). The shortened version of the Moods and Feelings Questionnaire (sMFQ; Angold et al., 1995) was then used to assess depressive symptoms. This allowed me to investigate possible distinctions between protective factors involved in promoting wellbeing and preventing depressive symptoms.

5.4.2.1 Individual-level protective factors

To capture self-esteem, a shortened version of Harter's Self Perception Profile for Children (SPPC; Harter, 1982) was used. This is a 36-item self-report that assesses competence across scholastic, social, athletic, and physical domains, in addition to behavioural conduct and global self-worth. The overall scale has good test–retest stability (Muris et al., 2003) and internal validity, indicated by both previous reports of Cronbach's alpha (α=0.71-0.91; Harter, 2021), and the current findings (Table 5.1). The current study included questions related to global self-worth and one domain of competency as previous findings have suggested distinct effects following victimisation (Soler et al., 2013). The scholastic competence subscale was chosen based on previous research on the role of school ability in relation to peer victimisation (Hemphill et al., 2014). Perceptions of both self-worth and scholastic

competence were based on childhood reports as measures related to self-esteem were not available in adolescence. This was not deemed a limitation, however, as later measures are likely to be negatively affected by peer victimisation (Skues et al., 2005).

Academic ability was captured in the present study using self-ratings of English, Maths, Science, ICT, ART, and Sport ability. These self-perceptions were chosen over test scores to maximise the data available in ALSPAC and to ensure analyses more closely reflected previous procedures (Vassallo et al., 2014). Past research has also shown that self-perceived academic ability is moderately correlated (r=0.45) with actual ability (Greven et al., 2009), leading many to support the use of self-assessed ability as a valid measure of individual differences in academic and intellectual competence (Chamorro-Premuzic et al., 2010).

The final individual-level protective factor, social skills, was assessed using the Social Communication Disorder Checklist (SCDC; Skuse et al., 2005). The SCDC was developed to determine the extent to which a child has difficulties with social reciprocity and verbal and nonverbal communication. It is a 12-item measure that has shown good internal consistency when completed by either teachers or parents (de la Osa et al., 2014). A higher score on the scale is used to indicate greater difficulties interpreting the feelings and moods of others. Items in the current study were therefore reverse coded so that a higher overall score reflected greater social abilities. Log-transformations were also conducted on the social skills scores due to scores having a skew greater than 1 (see Appendix 5.5). Due to the negative skew, analyses were carried out on a reflected and then log-transformed version of the scale. Reflected values were created by subtracting each value from the maximum value and adding 1. To facilitate comparisons with the other protective factors, main results are presented using the untransformed scores. Results from the transformed social skill scores can be found in Appendix 5.6.

5.4.2.2 Family-level protective factors

The role of family relationships and cohesion within the family were assessed using a short-structured interview. This comprised of five questions that captured parental closeness (How close do you feel to your parents?), sibling closeness (How close do you feel to your siblings?), family support (How easy do you find it to discuss problems with people in your family?), family involvement (How often do you do things together as family?) and family cohesion (How well have you been getting along with the family?). All items were responded to on a 4-point scale, with answers reverse coded to ensure a higher score captured more positive family relationships. As evident in Appendix 5.3, inter-item correlations were low to moderate, suggesting each item captures a unique aspect of the family environment. All items were therefore explored separately.

5.4.2.3 Peer-level protective factors

Similar to the family-level protective factors, the protective role of peers was assessed using a short-structured interview. These interviews included five questions taken from the Cambridge Hormones and Moods Project Friendship Questionnaire (Goodyer et al., 1990). This questionnaire captures peer support and includes questions such as, “Do you believe your friends understand you?” and “Are you happy with the number of friends you’ve got?”. Responses were recorded on a 4-point scale, and as per the family relationship measure, answers were reverse coded to ensure a higher score captured more positive peer relationships. Internal consistency fluctuated across ages, as evident in Table 5.1, with the highest alpha noted at 17 years.

5.4.2.4 Confounding variables

All analyses in the current study adjusted for sex. This is because there are sex differences noted in relation to wellbeing, which can fluctuate depending on age (Batz & Tay, 2018). Analyses also controlled for SES as individuals higher in wellbeing are more likely to come from advantageous backgrounds (Kaplan et al., 2008). As indices of SES, parental reports of their occupational status and educational qualifications were used. These two items were

summed for each parent and then combined, generating an overall SES index that ranged from 2 to 11 (*M*=6.08, *SD*=2.00).

Table 5.1. Description of study variables

Construct	Number of items	Sample item	Scoring	Composite creation	Higher score represents	Cronbach's alpha	Completed by	Age
Peer victimisation	9	"Frequency someone tricked teenager"	0-4 ("Never" - ">1/week")	Sum	More victimisation	0.73	Participant	12.5
Mental wellbeing	14	"I've been feeling relaxed"	0-4 ("None of the time" - "All of the time")	Sum	Higher wellbeing	0.93	Participant	23
Depressive Symptoms	13	"I felt miserable or unhappy"	0-3 ("Not at all" - "True")	Sum	More symptoms	0.91	Participant	23
Life Satisfaction	5	"I'm satisfied with my life"	1-7 ("Strongly disagree" - "Strongly agree")	Sum	Higher life satisfaction	0.89	Participant	23
Covariates								
SES	1	"What is your present job? If not working, what was your	9 Social Occupational Classifications	Mean	Lower SES	-	Parent	18 weeks gestation

		most recent job?"						
SES	1	“What is your highest educational qualification?”	0-5 (“Degree” - “None”)	Mean	Lower education	-	Parent	32 weeks gestation
Protective factors: Individual-level								
Scholastic competence	6	“Do well at schoolwork”	1-4 (“Yes, really like me” - “No, not at all like me”)	Sum	Higher competence	0.88	Participant	8
Global self-worth	6	“Happy with self as a person”	1-4 (“Yes, really like me” - “No, not at all like me”)	Sum	Higher self-worth	0.89	Participant	8
Self-perceived academic ability	6	“Rating of maths ability”	1-5 (“Very good” - “Not good at all”)	Mean	Higher perceived ability	0.54	Participant	13
Social skills	12	“Does not realise when	0-3 (“Not true” - “True”)	Sum	Higher social skills	0.88 (all)	Mother	7.5, 13, 16

		others are upset”					
Protective factors: Family-level							
Family support and relationships	5	“How close do you feel to your parents?”	1-4 (“Very close to at least one” - “Not close at all to either”)	Closer relationship	-	Participant	17.5
Protective factors: Peer-level							
Friendships	5	“Believes friends understand them”	1-4 (“Most of the time” - “Not at all”)	Positive friendship	0.50 0.46 0.74	Participant	8, 12.5, 17.5

5.4.3 Missing data and multiple imputation

When using large longitudinal cohorts like ALSPAC, a common problem faced relates to missing data. Missing data occurs for various reasons and is classified as either missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR) (Rubin, 1976). An example of data that is MCAR would be if an individual's questionnaire got lost in the post. This type of missingness does not depend on the observed data, meaning it would not inflict any bias. In this case, the missing data would not need to be imputed. Data that is MAR, however, may be conditional on some other measured variable. For example, an individual may not attend a clinic session due to being unwell. In this instance, there may be other factors in the dataset relating to that individual's health that can be used to predict missingness. In cases where the variable associated with missingness is due to some unmeasured variable, the missingness is categorised as MNAR. However, based on the observed data alone, it is not possible to decipher whether data are MAR or MNAR because the missing data is unknown (Jakobsen et al., 2018).

To increase the chance of data MAR, researchers can run multiple imputation. Multiple imputation accounts for missingness by using potential predictors of missingness. One technique, known as Multiple Imputation by Chained Equations (MICE), involves creating copies of the dataset in which missing values are replaced by conditioning upon other variables in the available data (Van Buuren, 2007). These imputed values are drawn randomly from the predictive distribution of the observed data. Thus, multiple imputation is based on the assumption that the probability of a variable missing depends only on observed data, and not on unobserved variables (Azur et al., 2011).

Multiple imputation by Chained Equations (MICE) was used in the current study to investigate the impact of attrition. This was done using sociodemographic indicators of missing that have previously been used in ALSPAC (Houtepen et al., 2018; Bowes et al., 2015). A list of variables used for imputation can be found in Appendix 5.4.

5.4.4 Statistical analyses

To investigate whether protective factors moderate wellbeing following peer victimisation, regression models included an interaction term (log-transformed victimisation scores by each protective factor). This allowed analyses to ascertain the main and interactive effects of peer victimisation and the protective factors. Peer victimisation scores in the current study were log transformed due to positive skew. As per Chapter 4, a constant of 1 was added as log transforming variables with a zero value is not possible. To confirm that analyses using the log transformed results were representative, analyses were repeated using untransformed victimisation scores. Results from these analyses can be found in Appendix 5.7 and Appendix 5.8.

The main analyses investigated main and interactive effects on mental wellbeing using linear regression models. Follow-up analyses were then carried out to explore whether such findings replicate using measures of life satisfaction and depressive symptoms. For analyses predicting depressive symptoms, negative binomial regression models were used. Negative binomial regression represents a generalised linear model that includes an additional parameter for overdispersion. This was needed due to the skewed depressive symptoms measure. The negative binomial regression model was chosen over the standard Poisson model as the Poisson regression assumes identical parameters for the mean and variance, this was not the case for the depressive symptoms measure ($M=7.03$, $\sigma^2=36.6$).

In further follow-up analyses, Principal Components Analysis (PCA) was used to investigate the combined impact of the protective factors at the individual-, family-, and peer-level. PCA is a statistical method that aims to reduce the dimensionality of data (Lever et al., 2017). To do this, PCA transforms multiple variables into fewer dimensions, known as principal components (PCs) or eigenvectors, that best summarise the data. These are generated by computing a covariance matrix which contains all possible pairings between the included variables. The resulting PCs decrease in order of importance, with the first few components accounting for the most variance. The objective is to generate the smallest number of PCs

that account for the most variation in the original data. The variance explained by each PC is represented by a corresponding eigenvalue. These can be used to determine the number of PCs to retain for further analyses. Most researchers use Kaiser's criterion which asserts that only eigenvalues greater than 1 should be retained (Kaiser 1961). The current study used Kaiser's criterion to decipher which PCs would be entered into the regression models.

As per the previous regression analyses, PCs were entered as an interaction term with peer victimisation. This allowed the main and interactive effects of protective factors across the three levels (individual, family, and peer) to be explored. Following this, the first component from each level was entered into a hierarchical PCA. The resulting component was used to investigate the cumulative impact of components across the three protective factor levels. Loadings of this overall PC and those at the individual-, family- and peer-level can be found in Appendix 5.9.

Multiple imputation was carried out using the Multiple Imputation Chained Equations (MICE) package in R (van Buuren & Groothuis-Oudshoorn, 2010). Based on Rubin's rules (Little & Rubin, 2014), estimates were averaged over 60 imputed datasets. All analyses, including the imputation, were run in R Studio version 4.0.5 (R Core Team, 2021). The 'MASS' package (Venables & Ripley, 2002) was used for the negative binomial regressions and the 'rsq' package (Zhang, 2018) to generate R-squared estimates for these models. For the PCA, the 'prcomp' function within the 'stats' R package was used.

All analyses used z-standardised protective factors to ensure a mean of 0 and standard deviation of 1. This helped facilitate interpretability across the different scales. If a protective factor was assessed more than once, analyses explored the importance of timing of the protective factor by comparing effects before, during and after victimisation. To control for the probability of making a Type I error on multiple comparisons, Benjamini-Hochberg False Discovery Rate (FDR) was used. As described in Chapter 3, this method allows for the non-independence of repeated tests (Benjamini & Hochberg, 1995).

5.4.5 Power calculations

Determining the necessary power for detecting interaction effects is often unclear in epidemiologic studies as power calculations primarily assess the main effects of predictors in a model (Marshal, 2007). Within interaction designs, the variance explained depends on the variance of two predictors, not just one, and often these interactions explain a small proportion of variance (Perugini et al., 2018). Researchers planning to run an interaction study thus face the difficulty of anticipating the effect size of the interaction term.

To overcome this, researchers can use standardised regression coefficients from previous interaction studies to estimate power (Perugini et al., 2018). To run the power calculation, the overall effect estimate (f^2) can be determined using the formula outlined by (Perugini et al., 2018):

$$f^2 \approx \frac{\beta^2_{int}}{1-r^2_{yx}-r^2_{ym}}$$

Here, $ß^2_{int}$ represents the interactive effect estimate, r^2_{yx} represents the correlation between the outcome variable and predictor, and r^2_{ym} represents the correlation between the outcome variable and the moderator. When applied to the current analyses predicting depressive symptoms, self-esteem was used as the moderator as this has been most consistently identified in the literature as having interactive effects (McVie, 2014; Sapouna et al., 2013). Standardised coefficients from the study by Sapouna and Wolke (2013) were used to generate an effect estimate of $f^2 = {}^{0.03066638}$. When plugged into G*Power version 3.1.9.7 (Faul, Erdfelder, Buchner & Lang, 2009) the required sample size to detect effects at 80% power was n=354. Thus, the current study was well-powered to detect interactions between victimisation and the protective factors in predicting depressive symptoms.

Determining the power for analyses predicting wellbeing was made difficult by the fact that this was the first study to use an interaction design to predict wellbeing. It has been

recommended that if interaction effects are not available in the literature, researchers should estimate these using previously reported estimates of correlations between the study variables under the high (or experimental) condition (r_a), and under the low (or control) condition (r_b) (Perugini et al., 2018). Thus, to calculate the power needed to detect an interaction in predicting wellbeing, correlation estimates were taken from the study exploring the impact of peers on life satisfaction among victims (Flaspohler et al., 2009). The interaction was estimated by subtracting the correlation between victimisation and life satisfaction among those with high peer support (r_a=-0.27), from correlations among those with low peer support (r_b=-0.19) (Flaspohler et al., 2009). Running the above formula resulted in f^2 = 0.007320979. When plugged into G*Power, calculations revealed that a sample size of n=1,494 would be necessary to achieve 80% power. The smallest sample size of the current study was n=1,712, meaning there was sufficient power to detect interactive effects.

5.5 Results

5.5.1 Descriptive data

On average across the sub-samples, 63% of participants were female and up to 17.1% had experienced frequent victimisation during adolescence (see Table 5.2). This was defined according to the same three-level victimisation variable used in Chapter 4. Those who scored 0 were classed as never victimised, those scoring between 1 and 3 were classified as occasionally victimised, and those with scores of 4 or more were defined as frequently victimised, as per pervious research (Bowes et al., 2015).

Wellbeing scores in the current study averaged 49.31 (range 14-70). Comparisons of wellbeing scores between individuals with varying experiences of victimisation revealed that wellbeing is significantly higher among non-victims compared to occasional or frequent victims, and significantly higher among occasional victims compared to frequent victims (see Table 5.2). Such differences were not found when comparing the wellbeing of individuals with complete data only (see also Table 5.2), however, this likely reflects the biased sample of participants included.

5.5.2 Main and interactive effects on wellbeing

When investigating the main effects of peer victimisation and the protective factors, it was noted that peer victimisation predicted lower wellbeing across all subsamples accounting for a different protective factor (see Table 5.3). Each protective factor, excluding perceptions of childhood scholastic competence, was positively associated with wellbeing, and remained so after correction for multiple testing.

When investigating possible interactions between victimisation and the protective factors, models revealed a moderating role for perceptions of scholastic competence in childhood, as well as friendships in late adolescence (Table 5.3). However, the direction of these interactive effects was positive for scholastic competence, and negative for friendships.

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Table 5.2: Comparison of wellbeing scores among different protective factor responders in relation to experiences of victimisation

		Never victimised		**Occasionally victimised**		**Frequently victimised**			
Protective Factor	Total N	N (%)	Mean (SD)	N (%)	Mean (SD)	N	Mean (SD)	*p1*	*p2*
Scholastic competence	2302	1053 (45.7)	49.87 (8.73)	857 (37.2)	48.95 (8.86)	392 (17.0)	47.38 (9.27)	**<0.001**	**<0.01**
Global self-worth	2296	1050 (45.7)	49.89 (8.73)	854 (37.2)	48.97 (8.85)	392 (17.1)	47.36 (9.26)	**<0.001**	**<0.01**
Academic ability	2360	1079 (45.7)	49.89 (8.75)	877 (37.2)	48.99 (8.88)	404 (17.1)	47.36 (9.26)	**<0.001**	**<0.01**
Childhood social skills	2330	1073 (46.0)	50.04 (8.75)	864 (37.1)	48.98 (8.81)	393 (16.9)	47.45 (9.00)	**<0.001**	**<0.01**
Adolescent social skills	2339	1084 (46.3)	50.03 (8.77)	867 (37.1)	48.97 (8.89)	388 (16.6)	47.38 (9.12)	**<0.001**	**<0.01**
Late adolescent social skills	2092	964 (46.1)	50.06 (8.76)	778 (37.2)	48.87 (8.91)	350 (16.7)	47.70 (8.84)	**<0.001**	**<0.05**
Closeness to parents	1838	849 (46.2)	50.16 (8.62)	689 (37.5)	49.38 (8.60)	300 (16.3)	47.98 (8.34)	**<0.001**	**<0.05**
Closeness to siblings	1712	804 (47.0)	50.15 (8.58)	633 (37.0)	49.26 (8.65)	265 (16.1)	48.08 (8.38)	**<0.001**	**<0.05**
Family support	1833	848 (46.3)	50.10 (8.63)	688 (37.5)	49.41 (8.57)	297 (16.2)	47.98 (8.34)	**<0.001**	**<0.05**
Parental involvement	1824	842 (46.2)	50.13 (8.63)	686 (37.6)	49.35 (8.62)	296 (16.2)	48.11 (8.30)	**<0.001**	**<0.05**
Relationship with family	1838	849 (46.2)	50.14 (8.61)	689 (37.5)	49.39 (8.62)	300 (16.3)	48.00 (8.34)	**<0.001**	**<0.05**
Childhood friendships	2303	1053 (45.7)	49.96 (8.67)	863 (37.5)	48.87 (8.91)	387 (16.8)	47.41 (9.31)	**<0.001**	**<0.01**
Adolescent friendships	2398	1112 (46.4)	50.01 (8.76)	890 (37.1)	48.98 (8.83)	396 (16.5)	47.43 (9.23)	**<0.001**	**<0.01**
Late adolescent friendships	1811	839 (46.3)	50.12 (8.69)	675 (37.3)	49.42 (8.54)	297 (16.4)	48.05 (8.31)	**<0.001**	**<0.05**
Participants with complete data[a]	949	443 (46.7)	50.28 (8.52)	368 (38.7)	49.75 (8.52)	138 (14.5)	49.33 (8.13)	.23	.37

N = the number of participants who had complete data on the protective factor measure, the victimisation scale, the wellbeing and depression assessments, and SES. p1 = the t-test results comparing the mean wellbeing scores of those never victimised to those frequently victimised. p2 = the t-test results comparing the mean wellbeing scores of those occasionally victimised to those frequently victimised.

Note:

[a] Participants had complete data on all protective factor measures, the victimisation scale, the wellbeing and depression assessments, and SES.

Plots of the findings revealed that as the frequency of victimisation increased, individuals were more likely to have greater wellbeing if they also scored more highly on the scholastic competence scale (Figure 5.1). Such protective effects were shown to account for a further 0.58% of the variance in wellbeing after adjusting for the main effects of victimisation and the confounding variables.

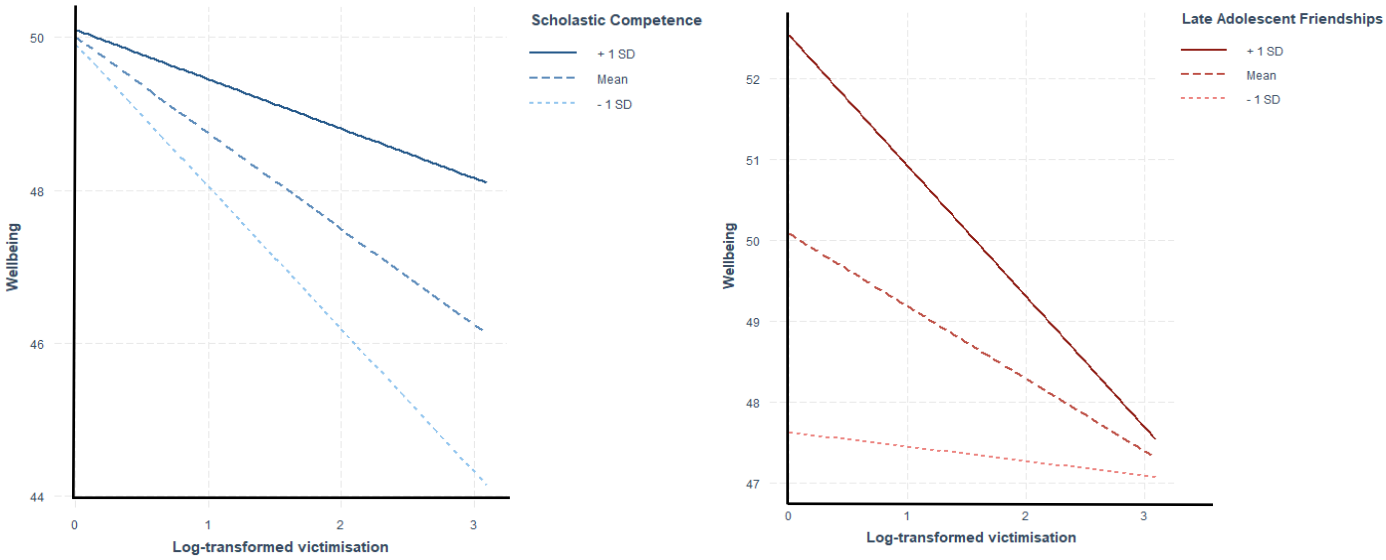

Figure 5.1. *Interactive effects of victimisation and protective factors on wellbeing*

For interactions with friendships in late adolescence, plots of the results revealed that while friendships exerted protective effects for individuals exposed to fewer instances of victimisation, as the frequency of victimisation increased, having more positive friendships did not significantly alter levels of wellbeing (Figure 5.1). Both interactive effects remained after correction for multiple testing and when using the imputed dataset (see Appendix 5.10) and untransformed victimisation scores (see Appendix 5.7). For analyses using the imputed data, significant interactions were also observed with other factors, including late adolescent social skills and family involvement and cohesion. This likely reflects the increase in power gained from using a larger dataset. However, it is important to note that only associations with late adolescent social skills survived multiple testing correction.

Table 5.3: Impact of victimisation (log-transformed), protective factors, and their interaction on wellbeing at 23 years

	Wellbeing											
	Protective Factor				Victimisation			Interaction				
	N	β (95% C.I.)	SE	**P value**	β (95% C.I)	SE	P value	β (95% C.I)	SE	P value	R^2	ΔR^2
Individual-level												
Scholastic competence	2302	0.099 (-0.422, 0.619)	0.265	0.721	-1.31 (-1.78, -0.831)	0.243	**8.20E-08**†	0.631 (0.152, 1.10)	0.244	**0.01**†	2.50%	0.58%
Global self-worth	2296	0.690 (0.162, 1.22)	0.269	**0.01**†	-1.26 (-1.74, -0.782)	0.243	**2.50E-07**†	0.254 (-0.218, 0.727)	0.241	0.291	2.87%	0.88%
Academic ability	2360	1.16 (0.562, 1.75)	0.303	**4.00E-04**†	-1.26 (-1.74, 0.792)	0.241	**1.70E-07**†	-0.049 (-0.549, 0.452)	0.255	0.849	4.37%	2.35%
Childhood social skills	2330	0.952 (0.384, 1.52)	0.290	**1.00E-04**†	-1.26 (-1.73, -0.781)	0.243	**2.40E-07**†	0.393 (-0.094, 0.880)	0.248	0.114	3.08%	1.02%
Adolescent social skills	2339	0.995 (0.417, 1.57)	0.295	**7.6E-04**†	-1.14 (-1.63, -0.637)	0.254	**8.30E-06**†	0.379 (-0.109, 0.867)	0.249	0.128	3.62%	1.65%
Late adolescent social skills	2092	1.30 (0.081, 1.80)	0.254	**3.20E-07**†	-1.26 (-1.72, -0.079)	0.238	**1.40E-07**†	0.161 (-0.296, 0.618)	0.233	0.490	3.86%	2.00%
Family-level												

Closeness to parents	1838	1.34 (0.761, 1.93)	0.297	**6.50E-06**†	-1.05 (-1.56, -0.532)	0.263	**7.10E-05**†	0.007 (-0.520, 0.535)	0.269	0.978	3.67%	2.09%
Closeness to siblings	1712	1.61 (1.02, 2.19)	0.299	**2.10E-08**†	-1.09 (-1.62, -0.550)	0.273	**7.40E-04**†	-0.405 (-0.955, .0146)	0.281	0.150	3.72%	2.11%
Family support	1833	1.52 (0.970, 2.06)	0.278	**5.80E-08**†	-1.02 (-1.54, -0.509)	0.263	**1.00E-04**†	0.004 (-0.523, 0.513)	0.264	0.985	4.33%	2.78%
Family involvement	1824	0.740 (0.188, 1.29)	0.281	**9.0E-04**†	-1.08 (-1.60, -0.556)	0.266	**5.40E-05**†	0.402 (-0.118, 0.922)	0.265	0.130	2.78%	1.35%
Family cohesion	1838	1.35 (0.776, 1.93)	0.293	**1.50E-06**†	-0.900 (-1.42, -0.382)	0.264	**6.70E-04**†	0.108 (-0.406, 0.622)	0.262	0.681	4.06%	2.48%
Peer-level												
Childhood friendships	2303	0.616 (0.082, 1.15)	0.272	**0.024**†	-1.31 (-1.79, -0.827)	0.246	**1.20E-07**†	-0.052 (-0.528, 0.424)	0.243	0.831	2.53%	0.30%
Adolescent friendships	2398	0.913 (0.392, 1.43)	0.266	**6.00E-04**†	-1.38 (-1.63, -0.648)	0.250	**5.60E-06**†	0.040 (-0.395, 0.475)	0.222	0.856	2.97%	0.98%
Late adolescent friendships	1811	2.46 (1.92, 3.01)	0.277	**2.00E-16**†	-0.976 (-1.51, -0.445)	0.271	**3.20E-04**†	-0.745 (-1.25, -0.237)	0.259	**0.004**†	6.81%	5.24%

R^2 = the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the addition of the protective factor. The ΔR^2 was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained. †FDR.

Note: All models adjusted for sex and socioeconomic status.

5.6.3 Main and interactive effects on life satisfaction

When mental wellbeing was replaced with life satisfaction, linear regressions revealed a similar pattern of results for the main effects. All protective factors other than childhood scholastic competence were positively associated with increased life satisfaction at the population level (Table 5.4). When investigating interactions, however, models revealed no moderating effects.

5.6.4 Main and interactive effects on depressive symptoms

Results from analyses predicting depressive symptoms can also be found in Table 5.4. As per the wellbeing measures, all protective factors were shown to predict depressive symptoms at the population level, excluding childhood scholastic competence. Unlike the wellbeing measures, associations were all negative, predicting a reduced risk of depressive symptoms.

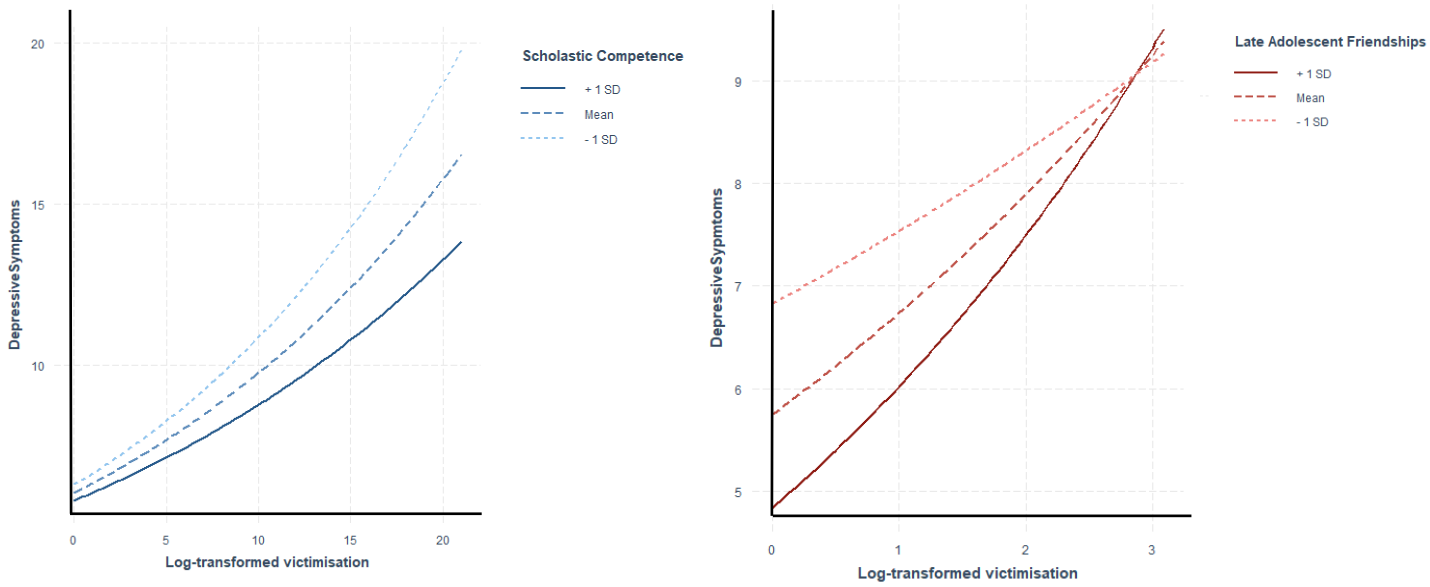

Figure 5.2: *Interactive effects of victimisation and protective factors on depressive symptoms*

When investigating possible interactive effects, findings revealed that scholastic competence did not moderate the level of depressive symptoms following peer victimisation. As represented in Figure 5.2, frequent victims with high perceptions of scholastic competence

were shown to have lower depressive symptoms than frequent victims with low scholastic competence, however this difference was not significant. In contrast, friendships in late adolescence were shown to moderate levels of depressive symptoms (Table 5.4). Plots of the findings revealed similar effects to wellbeing such that friendships appeared protective for those exposed to fewer instances of victimisation (see Figure 5.2). Unlike the results for wellbeing, however, this did not remain after correction for multiple testing.

5.6.5 Principal components analysis (PCA)

After running the PCA and creating the PCs according to Kaiser's criterion, protective factors at the individual-level were captured by the first two components, while protective factors at the family- and peer-level were represented by just one component. Results using these PCs are presented in Appendix 5.11 and 5.12. Findings revealed that the first PC at the individual-level interacted with victimisation to increase both wellbeing and life satisfaction. This PC explained an additional 4.1% of the variance in wellbeing after accounting for victimisation and the confounders, and 4.9% of the variance in life satisfaction. No such protective effects were found for depressive symptoms, or for the PCs capturing the family and peer protective factors. It was also noted that while the component generated from the hierarchical PCA explained a significantly higher amount of the variance in wellbeing, it had no moderating effects on any of the mental health outcomes when interacted with peer victimisation.

Table 5.4: Impact of victimisation (log-transformed), protective factors, and their interaction on life satisfaction and depressive symptoms at 23 years

	Life satisfaction											
	Protective Factor				Victimisation			Interaction				
	N	β (95% C.I.)	SE	P value	β (95% C.I)	SE	P value	β (95% C.I)	SE	P value	R^2	ΔR^2
Individual-level												
Scholastic competence	2310	0.348 (-0.037, 0.733)	0.196	0.076	-1.04 (-1.39, -0.692)	0.179	**6.50E-09**†	0.169 (-0.181, 0.519)	0.179	0.343	2.81%	0.43%
Global self-worth	2304	0.551 (0.160, 0.943)	0.200	**0.006**†	-1.02 (-1.37, -0.670)	0.179	**1.31E-08**†	0.168 (-0.181, 0.517)	0.178	0.345	3.39%	0.94%
Academic ability	2370	0.991 (0.621, 1.36)	0.189	**1.60E-07**†	-1.00 (-1.35, -0.661)	0.175	**1.10E-08**†	-0.057 (-0.395, 0.281)	0.173	0.741	4.15%	1.61%
Childhood social skills	2339	0.954 (0.513, 1.39)	0.225	**2.31E-05**†	-0.953 (-1.30, -0.604)	0.178	**9.11E-08**†	-0.137 (-0.508, 0.235)	0.189	0.471	3.28%	1.07%
Adolescent social skills	2353	0.815 (0.400, 1.23)	0.212	**1.22E-04**†	-0.940 (-1.29, -0.593)	0.212	**1.27E-07**†	0.353 (-0.004, 0.711)	0.182	0.053	4.68%	2.31%
Late adolescent social skills	2100	0.760 (0.333, 1.19)	0.218	**4.84E-04**†	-0.887 (-1.25, -0.522)	0.186	**1.91E-06**†	0.322 (-0.037, 0.681)	0.183	0.079	4.63%	2.29%
Family-level												
Closeness to parents	1850	1.14 (0.702, 1.58)	0.223	**3.40E-07**†	-0.850 (-1.23, -0.465)	0.196	**1.62E-05**†	-0.147 (-0.541, 0.246)	0.201	0.463	3.91%	1.80%
Closeness to siblings	1722	0.854 (0.410, 1.30)	0.226	**1.65E-04**†	-0.952 (-1.35, -0.551)	0.204	**3.41E-06**†	-0.142 (-0.555, 0.271)	0.211	0.500	2.70%	0.70%

Family support	1845	0.888 (0.478, 1.30)	0.209	**2.31E-05**†	-0.837 (-1.22, -0.452)	0.196	**2.19E-05**†	0.218 (-0.169, 0.605)	0.197	0.269	4.10%	1.97%
Family involvement	1836	0.683 (0.272, 1.09)	0.210	**.001**†	-0.890 (-1.28, -0.502)	0.198	**7.20E-06**†	0.244 (-0.141, 0.628)	0.196	0.214	3.28%	1.34%
Family cohesion	1850	1.11 (0.680, 1.55)	0.198	**5.11E-07**†	-0.747 (-1.13, -0.360)	0.198	**1.64E-04**†	-0.038 (-0.424, 0.348)	0.197	0.847	4.22%	2.07%
Peer-level												
Childhood friendships	2313	0.425 (0.028, 0.822)	0.202	**0.036**	-1.08 (-1.44, -0.721)	0.183	**3.98E-09**†	-0.127 (-0.480, 0.225)	0.180	0.478	2.61%	0.12%
Adolescent friendships	2408	0.539 (0.153, 0.925)	0.197	**0.006**†	-0.882 (-1.24, -0.520)	0.184	**1.80E-06**†	0.081 (-0.239, 0.401)	0.163	0.619	2.89%	0.44%
Late adolescent friendships	1823	1.45 (1.04, 1.86)	0.208	**4.71E-12**†	-0.800 (-1.19, -0.412)	0.198	**5.50E-05**†	-0.324 (-0.698, 0.051)	0.191	0.090	5.11%	2.96%
					Depressive symptoms							
Individual-level												
Scholastic competence	2302	-0.036 (-0.089, 0.018)	0.027	0.189	0.178 (0.130, 0.226)	0.024	**3.81E-013**†	-0.030 (-0.076, 0.017)	0.025	0.229	4.01%	.63%
Global self-worth	2296	-0.071 (-1.25, -0.017)	0.028	**0.010**†	0.172 (0.125, 0.220)	0.025	**2.30E-12**†	-0.016 (-0.064, 0.032)	0.024	0.513	4.08%	.92%
Academic ability	2360	-0.114 (-0.165, -0.064)	0.026	**1.41E-05**†	0.187 (0.140, 0.235)	0.024	**1.10E-14**†	0.012 (-0.034, 0.058)	0.024	0.623	5.01%	1.54%
Childhood social skills	2330	-0.109 (-.171, .048)	0.031	**3.91E-04**†	0.187 (0.140, 0.234)	0.024	**1.70E-14**†	0.040 (-0.013, 0.091)	0.026	0.121	4.48%	.59%
Adolescent social skills	2339	-0.134 (-0.194, -0.076)	0.029	**4.51E-05**†	0.178 (0.130, 0.226)	0.025	**4.81E-13**†	0.023 (-0.029, 0.075)	0.025	0.347	5.17%	1.96%
Late adolescent social skills	2092	-0.101 (-0.162, -0.040)	0.030	**7.41E-04**†	0.158 (0.108, 0.208)	0.026	**9.12E-10**†	-0.005 (-0.056, 0.046)	0.025	0.852	4.96%	2.21%

Family-level												
Closeness to parents	1838	-0.092 (-0.154, -0.031)	0.031	**0.003** †	0.158 (0.105, 0.211)	0.027	**5.80E-09**†	-0.018 (-0.071, 0.036)	0.027	0.524	4.45%	1.59%
Closeness to siblings	1712	-0.100 (-0.162, -0.039)	0.031	**3.91E-04**†	0.180 (0.125, 0.235)	0.028	**1.80E-10**†	0.011 (-0.045, 0.067)	0.029	0.701	4.09%	.73%
Family support	1833	-0.108 (-0.165, -0.052)	0.029	**5.11E-04**†	0.161 (0.108, 0.215)	0.027	**3.30E-09**†	-0.009 (-0.062, 0.043)	0.027	0.735	4.57%	1.71%
Family involvement	1824	-0.088 (-0.145, -0.032)	0.029	**2.59E-04**†	0.172 (0.119, 0.225)	0.027	**3.20E-10**†	-0.011 (-0.064, 0.041)	0.027	0.680	4.13%	1.21%
Family cohesion	1838	-0.101 (-0.162, -0.041)	0.030	**9.01E-04**†	0.150 (0.097, 0.204)	0.027	**3.99E-08**†	-0.011 (-0.064, 0.042)	0.027	0.693	4.24%	1.43%
Peer-level												
Childhood friendships	2303	-0.063 (-0.118, -0.009)	0.028	**0.024** †	0.186 (0.137, 0.234)	0.025	**1.30E-13**†	0.015 (-0.033, 0.062)	0.025	0.552	3.77%	.28%
Adolescent friendships	2398	-0.060 (-0.112, -0.008)	0.027	**0.029** †	0.165 (0.116, 0.215)	0.025	**7.17E-11**†	-0.003 (-0.046, 0.039)	0.022	0.890	3.82%	.63%
Late adolescent friendships	1811	-0.176 (-0.233, -0.118)	0.029	**1.91E-09**†	0.163 (0.108, 0.218)	0.028	**1.11E-08**†	0.054 (-0.005, 0.109)	0.027	**0.044**	4.13%	1.55%

R^2 = the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the addition of the protective factor. The ΔR^2 was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained. †FDR.

Note: All models adjusted for sex and socioeconomic status. Results for depressive symptoms were conducted using negative binomial regressions.

5.7 Discussion

This study represents the first to consider potential moderators of adult wellbeing following peer victimisation in adolescence. Findings suggest that victims who hold greater perceptions of scholastic competence in childhood are more likely to maintain higher wellbeing in adulthood. These protective effects were specific to mental wellbeing and were not observed for adult life satisfaction or depressive symptoms. Such findings underscore the importance of investigating predictors of both wellbeing and depressive symptoms when assessing resilience.

5.7.1 Individual-level protective factors

5.7.1.1 Self-esteem

The observed moderating effects of perceived scholastic competence could reflect a number of factors. The first is that individuals with greater perceptions of school competence are more likely to enjoy school and feel satisfied (Verkuyten & Thijs, 2002). These positive feelings towards school may lead victims to become more involved in academic activities, helping to distract them from problematic peers. Having a more positive mindset as a result of increased scholastic competence may also mitigate problems in other domains of life, and may thus lead the victimisation to be experienced as less severe.

It is interesting to note that moderating effects on wellbeing were specific to perceptions of scholastic competence and not self-worth in childhood. It is possible that this reflects the stability of scholastic competence relative to self-worth. Findings have shown that peer victimisation adversely effects global self-esteem (Overbeek et al., 2010), with researchers suggesting that those victimised experience more negative appraisals of how they are evaluated by peers (Lopez & DuBois, 2005). Such appraisals are likely to be specific to their ability to get along with peers rather than their ability to complete schoolwork. Thus, it seems likely that peer victimisation will have less of an impact on perceptions of scholastic ability.

In support of this, research has shown that perceptions of school competence are largely stable across the lifespan, even after accounting for perceptions of self-worth (Putnick et al., 2020). This suggests that while perceptions of self-worth may be negatively influenced by peer victimisation, perceptions related to school competence may be more resistant to change. Higher scholastic competence in childhood may therefore help boost later morale and wellbeing despite self-esteem being damped by victimisation.

Another possible path by which scholastic competence may improve wellbeing could be through academic ability. Findings have shown that unlike global self-esteem, which has no clear impact on academic outcomes, perceptions of scholastic competence have both direct and indirect effects on educational attainment and achievement (Marsh & O'Mara, 2008). Children who have higher perceptions of their ability experience more motivation and persistence which likely leads to their improved academic achievement (Gutman & Schoon, 2013). This is particularly the case for low-attaining students (Gutman et al., 2013). Educational attainment has been shown to increase wellbeing in adulthood (Nikolaev, 2018) and satisfaction in school (Verkuyten et al., 2002), with the latter explained largely by perceptions of scholastic competence. It is therefore possible that scholastic competence is protective for victims because it facilitates greater academic achievement and thus more positive wellbeing.

5.7.1.2 Academic ability

Academic ability in the present study was shown to exert main but not moderating effects on wellbeing. Unlike the scholastic competence scale, which captured perceptions of overall schoolwork, adolescents in the present study rated their academic ability in individual school subjects such as English and Maths. These ratings were then combined to derive an overall measure of academic ability. Such scores are likely to be more affected by performance in specific classes than the perceived scholastic competence scale in childhood, which may

have led to lower overall ratings in adolescence. This could explain why this measure only predicted higher wellbeing at the population level.

It is also possible that no moderating effects were found for adolescent academic ability because it is less related to self-esteem. The scale used to assess perceptions of scholastic competence in childhood captures how individuals evaluate themselves (Harter, 1985). This emphasis on self-concept may be less apparent in more objective questions related to Mathematic ability for example. Future research should consider these findings further by comparing moderating effects of self-worth, perceptions of scholastic competence, and actual educational achievement in adolescence. Using more objective measures of school achievement could also help to shed light on the current absence of protective effects of academic ability in adolescence.

5.7.1.3 Social skills

The final individual-level protective factor explored in the current study was social skills. Much like academic ability in adolescence, this protective factor had main effects on adult wellbeing but did not exert moderating effects among victims. Such findings are consistent with previous research which reported that increased social skills predict fewer problems at the population level, but no moderating effects for victims (Vassallo et al., 2014). Unlike previous research, which used a binary measure of peer victimisation, the current study was based on continuous victimisation scores. This helped to avoid arbitrary cut-offs and subsequent small samples, allowing sufficient power (>80%) to rule out any large interactive effects.

5.7.2 Family-level protective factors

Results from analyses exploring the role of family relationships and support revealed no moderating effects for victims. This stands in contrast to previous research on the protective role of families in predicting internalising symptoms in childhood (Bowes et al., 2010) and adolescence (Stadler et al., 2010). These differences likely reflect the increasing

independence of victims in the current study. While parents play a pivotal role throughout childhood and adolescence, as individuals progress into early adulthood, they may become increasingly less reliant on parental support, particularly if they have moved out of the family home. Indeed, research has shown that support from parents is most effective in moderating internalising problems among younger adolescent victims (Stadler et al., 2010). Such findings lead to the conclusion that family relationships may be protective for victim's mental health during childhood and adolescence, but is less vital to adult wellbeing.

5.7.3 Peer-level protective factors

In contrast to family relationships, some evidence was provided to suggest protective effects of peers for individuals exposed to victimisation. However, such moderating effects were shown to lessen as the frequency of victimisation increased. While these results align with past research which found that peers can exacerbate the risk of mental illness among victims (Vassallo et al., 2014), previous findings compared groups of victims to non-victims. Detecting differences between those exposed to varying frequencies of victimisation was therefore not possible. The present findings suggest that while having positive relationships with peers is beneficial, it is not sufficient to foster resilience among those exposed to frequent and repeated victimisation. This likely reflects the increasingly adverse effects on mental health and wellbeing that occur with greater exposure to victimisation (Armitage et al., 2021). Thus, peers may only be protective against experiences that are less detrimental to mental health and wellbeing.

Another possibility is that the findings reflect the instability of friendships formed. Peer victimisation in one social relationship has been shown to increase the risk of victimisation in a different social context (Vucetic et al., 2021). This means that individuals who are victimised by peers may subsequently be more vulnerable to victimisation by their closer friends. In relation to the current study, it is possible that while victims rated their

relationships as positive at the time of assessment, these relationships may have later altered to negatively impact wellbeing.

The type of friendships formed by individuals exposed to frequent victimisation may also account for the current findings. Research has shown that people generally befriend others who have similar levels of internalised distress (Hogue & Steinberg, 1995). For individuals exposed to frequent victimisation, engaging in discussions with similarly distressed peers may further heighten stress. This is likely due to co-rumination which has been shown to increase the risk of depressive symptoms among victimised adolescents (Guarneri-White et al., 2015). Other negative aspects that can arise from close friendships include emotions such as jealousy. Victims may compare their experiences to others and feel jealous towards their non-victimised peers or those who do not appear to be as adversely affected. These combined findings may explain why relationships with peers do not necessarily provide a buffer against the adverse effects of victimisation on adult mental health and wellbeing.

5.7.4 Cumulative role of individual-, family- and peer-level protective factors

Analyses investigating the cumulative impact of the different factors at the individual-, family- and peer-level revealed that while protective factors at the family- and peer-level had larger main effects on wellbeing, they had no moderating effects on wellbeing following peer victimisation. In contrast, protective factors at the individual-level produced interaction effects that were the same size as their main effects on wellbeing (see Appendix 5.11). These findings highlight the importance of individual characteristics in not only maintaining positive wellbeing at the population level, but also in buffering the adverse outcomes of adolescent victimisation. Such interactive effects accounted for 4.1% of the variance in wellbeing, which was larger than the variance accounted for by the peer-level protective factors, but slightly below that accounted for by the family-level factors.

When investigating the combined impact of protective factors across the three levels, the variance explained increased to 7.1%. However, findings revealed only main effects.

Together these findings suggest that further investigation into individual-level protective factors should take priority over further study into factors at the family- or peer-level. Such research could provide crucial insight into the paths by which individual attributes may allow individuals to maintain resilience in early adulthood. It is important, however, that further investigations do not rule out the role of family- or peer-level factors as these may be important predictors of earlier or later resilience. In particular, findings have shown that the adverse effects of victimisation lessen as individuals get older (Schoeler et al., 2018). It is thus possible that more protective factors may be required at earlier stages of development.

5.7.5 Strengths and limitations

Key strengths of the current study lie in the large sample and longitudinal design. This was the first study to assess protective factors before, during, and after peer victimisation. In doing so, the study was able to provide a unique insight into the importance of timing of the different protective factors. It is possible that the longitudinal cohort may limit the generalisability of results due to selection bias. Participants with available data for peer victimisation and the mental health outcomes may have had fewer problems with their mental health compared to individuals missing. However, previous studies conducted in ALSPAC have shown that even when drop out is associated with the outcome variable, this has a minimal effect on association estimates (Wolke et al., 2009). In addition, findings in the current study were replicated when using an imputed dataset. This imputed dataset also included adolescent depressive symptoms as a predictor of missingness.

Other possible limitations are that due to data availability, some protective factors like adolescent academic ability and peer relations relied on self-reports. While this allowed comparisons with existing research (Vassallo et al., 2014), self-reports may have been biased by negative cognitions and internalising symptoms among victims (Cook et al., 2010). Future research investigating the role of factors like friendships could therefore attempt to distinguish between perceived and actual support using reports from other informants. Such

research, however, would need to carefully consider who to use as informants as close friends may also bully the victim (Vucetic et al., 2021).

Finally, while the current study was well-powered to detect small moderating effects, approximately 17% of participants reported frequent victimisation during adolescence. This figure reflects previous estimates in this sample (Bowes et al., 2015; Stapinki et al., 2014) and resulted in a larger sample of victims than previous studies (Vassallo et al., 2014). However, it is possible that larger samples with more victims may uncover a role for more protective factors.

5.7.6 Implications and future directions

Overall, this study extends the victimisation literature by providing new insight into the role of protective factors in moderating adult wellbeing. Another novelty of the study was the inclusion of protective factors across development. This allowed findings to establish that protective factors most beneficial to adult wellbeing are likely to be in place prior to victimisation, reinforcing the importance of time-independent factors (Fritz et al., 2019). Unlike protective factors that buffer the negative impact of victimisation, time-independent protective factors help build resilience before the occurrence of victimisation. Identifying such factors could therefore be crucial to the development of preventive interventions that target at-risk individuals early on. Doing so could lessen the impact of subsequent negative events and help victims foster more positive wellbeing.

It is possible that time-independent protective factors are more vital to later wellbeing because they are not developed in response to an event but are ingrained early on. The presence of such factors in childhood may allow individuals to build resilience to daily stresses and setbacks, helping to increase the likelihood of responding more favourably to later events like peer victimisation. In the context of the present study, it is possible that individuals with higher perceptions of scholastic competence also had greater confidence to handle adversity. Findings in support of this come from research on trait resilience, a

concept discussed in detail in Chapter 1. Individuals higher in trait resilience perceive themselves as more competent in school and everyday life more generally (Sagone & de Caroli, 2013). Participants who reported higher scholastic competence in the current study may therefore represent a particular resilient profile who are more able to maintain wellbeing in the face of potentially negative events (Hu, Zhang & Wang, 2015).

One way to test such a hypothesis could be to exploit genetic data to investigate whether genetic liabilities towards certain traits are predictive of subsequent resilience. As explained in Chapters 3 and 4, genetic information is fixed from birth and can therefore be used to test the causal direction of effects. Such data could thus be used to triangulate phenotypic findings on the importance of pre-existing protective factors. In the case of scholastic competence, polygenic scores related to this trait could be created using a genome-wide association study (GWAS) of educational attainment (Okbay et al., 2016). If a higher polygenic score for educational attainment predicted more positive functioning after peer victimisation, we could be more confident that a pre-existing tendency towards school competence may be an important determinant of subsequent mental health. Such a design could also be used to tease apart whether findings reflect cognitive or non-cognitive abilities by using GWASs related to these two traits (Demange et al., 2021). Researchers should remain mindful however, to the fact that polygenic scores only capture a small percentage of the variance of most complex traits.

One interesting finding noted in the current study was that perceptions of scholastic competence moderated adult wellbeing, but not life satisfaction or the risk of depressive symptoms. This suggests that while this protective factor may be important for some aspects of adaptation following peer victimisation, it may not be sufficient alone to attain optimal functioning and true resilience. Such findings emphasise the importance of continued investigation into predictors of different dimensions of mental health. They also suggest that

multiple interventions may be necessary to both promote wellbeing and prevent mental illness.

Overall, the findings of this study lead to the conclusion that interventions aimed at increasing perceptions of scholastic competence in childhood could be an efficient means of reducing the burden of peer victimisation. While the ultimate goal is to ultimately alleviate victimisation, and antibullying programs have shown some promise in reducing victimisation in schools (Gaffney et al., 2021), it is widely accepted that eradicating victimisation completely is unlikely (Arseneault, 2017). Thus, efforts to support victims are necessary to ensure positive mental health can still be attained. Such efforts would be best delivered at the school-level as perceptions of competence were specific to school ability. Teachers play an important role in providing feedback to students regarding their schoolwork and are therefore an appropriate target to facilitate changes in student perceptions of ability. School-based interventions can also be delivered to multiple students at a time which is likely to be more efficient than individual family-based interventions.

5.8 Chapter summary

This chapter investigated the role of protective factors across the individual-, family-, and peer-level in moderating the mental health and wellbeing of individuals subjected to peer victimisation. Out of a possible 14 protective factors investigated in ALSPAC, perceptions of scholastic competence was the only factor to exert positive interactive effects on adult wellbeing. Such findings provide unique insight into the importance of timing by demonstrating that protective factors most beneficial to adult wellbeing are likely to be in place prior to victimisation. The path by which perceptions of school ability impact wellbeing, however, remains largely unknown. In the next chapter, I therefore aim to untangle the relationship between educational attainment, intelligence, and wellbeing using methods that enable more causal inferences.

Chapter 6: Part 1: An exploration into the causal relationships between education, intelligence, and wellbeing: A multivariable two-sample mendelian randomization study

6.1 Chapter 6 Part 1 overview

Chapter 5 demonstrated that having higher perceptions of scholastic ability in childhood may increase later wellbeing, particularly among individuals exposed to peer victimisation. One theory proposed for this finding was that those with greater perceptions of school ability may be more likely to stay on and complete further years of schooling. However, the impact of years of schooling on wellbeing remains debated. It is also not yet known whether any effects of years of schooling are driven by intelligence, which also has an unclear relationship with wellbeing. The aim of this Chapter was therefore to test the relationship between years of schooling and wellbeing and the possible role of intelligence. This Chapter is split into two parts, Part 1 includes a Mendelian Randomisation (MR) study which was conducted to determine whether a genetic tendency to complete more years of schooling is causally associated with wellbeing. This MR study also investigated the extent to which any causal association is independent of intelligence. In Part 2 of this Chapter, observational data related to educational attainment, intelligence, and wellbeing is used to further assess these relationships and possible underlying pathways.

In Part 1 of this Chapter I aim to:

- Test whether educational attainment and wellbeing have a causal and bidirectional association.
- Test whether intelligence and wellbeing have a causal and bidirectional association.
- Test whether educational attainment has a causal impact on wellbeing that is independent of intelligence.

- Test whether intelligence has a causal impact on wellbeing that is independent of educational attainment.

6.2 Introduction

Over the last two centuries there has been a dramatic shift in patterns of educational attainment; individuals are completing more years of schooling now than ever before (Lee & Lee, 2016). This change is likely driven by multiple factors, including progressions in economic development and changes in law. In 2013 for example, the UK Government stipulated that all pupils were to remain in full-time education or training until the age of 18. This change was guided by figures released in 2012 which revealed that around 10% of individuals aged 16 to 18 years were either not continuing their education, nor in full-time employment or training (Department for Education, 2012). Although reasons for this likely reflect a range of individual and social factors, previous findings had shown that many individuals not continuing their education came from disadvantaged backgrounds (Rennison et al., 2005). It was thus hoped that by increasing the legal school-leaving age, all young people would have the opportunity to progress and improve their attainment (Department for Education, 2010).

In addition to improving chances of attainment and employment, changes to compulsory schooling were also guided by research on the wider benefits of education (Spielhofer et al., 2007). Educational attainment, which refers to the number of years of schooling completed (Okaby et al., 2016), is associated with a range of positive life outcomes, including marriage (Aughinbaugh et al., 2013), a higher income (Cuñado & Pérez de Gracia, 2012), more prestigious occupational status (Oreopoulos & Salvanes, 2011), greater health (Barcellos et al., 2018), as well as a higher life expectancy (Luy et al., 2019). However, also fundamental

to success is wellbeing (O'Donnell et al., 2014), yet the impact of education on wellbeing remains less clear.

6.2.1 Observational associations between educational attainment and wellbeing

While observational findings have provided evidence of an association between educational attainment and wellbeing, the direction of effects has varied across studies. Some research has shown that individuals who stay on and complete more years of schooling are more likely to report increased levels of happiness (Cuñado et al., 2012; Oreopoulos et al, 2011) life satisfaction (Meeks & Murrell, 2001; Salinas-Jiménez, Artés & Salinas-Jiménez, 2013) and eudaimonic wellbeing (Nikolaev, 2018). Others, however, have suggested there exists a negative relationship between educational attainment and wellbeing (Clark & Jung, 2017; Powdthavee et al., 2015).

It is important to note that discrepancies between findings may reflect differences in design. Studies that have reported a negative impact of staying in school on wellbeing have looked specifically at life satisfaction (Clark et al., 2017; Powdthavee et al., 2015). Such findings should be cautiously interpreted as research has shown subtle differences between predictors of life satisfaction and happiness (Kahneman & Deateon, 2010). Another consideration to note is that one study reporting a negative association used the educational reform (Clark et al., 2017). This involved studying the impact of the one-year rise in compulsory education that occurred in 1972. As a result, the absence of any positive effects may reflect the exclusion of further education, which has been shown to exert a greater positive impact on life satisfaction than secondary school alone (Salinas-Jiménez et al., 2013).

Finally, although some have reported a negative association between educational attainment and wellbeing, this relationship has been shown to reverse after controlling for correlates of educational attainment, including income, occupation, and health (Powdthavee et al., 2015). Such findings suggest that educational attainment may have a positive impact on life

satisfaction, but through several indirect channels. One such channel that is yet to be explored is intelligence.

6.2.2 Educational attainment, intelligence, and wellbeing

Intelligence is a term often used to refer to the many different aspects of cognitive functioning, including memory and learning, visual and auditory perception, processing speed, as well as abstract, verbal, and spatial reasoning (Colom et al., 2010). These different abilities are highly correlated, meaning they can be reliably assessed by standardised tests that determine an individual's intelligence quotient (IQ), or combined into a single underlying latent factor, known as general intelligence or Spearman's g (Spearman, 1904). This has allowed researchers to combine results from different measures and cohorts to study determinants and outcomes of intelligence on a larger scale (Savage et al., 2018).

Intelligence is associated with positive life outcomes like increased career success (Strenze, 2007), higher income (Davies et al., 2019), and better physical heath (Wrulich et al., 2014). It also has both phenotypic and genetic correlations with educational attainment, with evidence to suggest causal effects of intelligence on educational attainment and vice versa (Anderson et al., 2020). Like educational attainment, the evidence surrounding the impact of intelligence on wellbeing is mixed, with studies reporting both positive and negative associations with adult wellbeing (Clark & Lee, 2021). Such results have fluctuated depending on other confounders in the model. Most have shown that the relationship between intelligence and life satisfaction changes from positive to negative after accounting for years of schooling (Clark & Lee, 2021; Flèche et al., 2021). Such findings have led some to argue that the relationship between intelligence and wellbeing is indirect and explained by mediating factors at the societal level, like education (Veenhoven & Choi, 2012). Understanding the role of intelligence is crucial to informing the usefulness of cognitive training. Although intelligence is relatively stable across the lifespan, with up to half of the variance in adult intelligence accounted for by childhood intelligence (Deary et al., 2012),

implicit in these estimates is that half of the variance in intelligence remains unexplained. This suggests there is variation in the stability of intelligence over time, meaning it is subject to change. In support of this, findings have shown that over the last few decades, the average population IQ has increased (Nisbett, 2013). This has been referred to as the 'Flynn effect' and has been estimated to reflect an increase of approximately three IQ points per decade (Bratsberg & Rogeberg, 2018). As noted in Chapter 3, research has also shown that the heritability of intelligence increases over time (Haworth et al., 2010). This has been attributed to gene-environment correlations, whereby as individuals develop, they select and modify their environments to align with their genetic propensities (Plomin & Deary, 2015). Investigating the causal associates of intelligence could thus help to ensure that environments are crafted in a way that allow individuals to develop both cognitively and mentally.

6.2.3 Mendelian Randomisation

To understand the contribution of two highly correlated phenotypes like educational attainment and intelligence, researchers have used multivariable mendelian randomisation (MR) (Davies et al., 2019). Multivariable MR is an extension of univariable MR that was described in detail in Chapter 2. In traditional univariable MR, exposures that are highly related and influenced by the same genetic variants would violate the assumptions of MR. However, it is possible in such instances that the two correlated exposures are still independently associated with the outcome of interest (Burgess & Thompson, 2015). In this scenario, we can estimate such independent effects using multivariable MR.

Unlike univariable MR, multivariable MR requires that genetic variants are not exclusively associated with a single exposure, but with multiple exposures (Burgess et al., 2015). These exposures are allowed to be causally related, however, the effects of the genetic variants must be independent of the outcome. Using the multivariable MR design is thus especially important when testing for causal associations between genetically correlated traits. This is

because genetic confounding can induce spurious associations between exposures and an outcome. For example, educational attainment may appear to predict an outcome, however, this could be in part due to shared genetic effects with intelligence. If associations remain with educational attainment after accounting for intelligence, we can be confident that educational attainment has a direct and independent impact on the outcome of interest.

Previous research using multivariable MR to study educational attainment and intelligence has revealed that the two are differentially associated with health outcomes like BMI and smoking (Davies et al., 2019), as well as neurologic disorders like Alzheimer's (Anderson et al., 2020). The association between educational attainment and Alzheimer's was shown to no longer remain after accounting for intelligence, suggesting a mediating role (Anderson et al., 2020). Such findings provide evidence that although highly correlated, there are likely distinct and unique effects of educational attainment and intelligence. No study, however, has yet explored the causal relationships between educational attainment, intelligence, and wellbeing.

6.3 Current study

The current study aimed to clarify observational research on associations between educational attainment and wellbeing, and between intelligence and wellbeing. Using the multivariable MR approach, the aim was to understand whether educational attainment and intelligence have causal effects on wellbeing, and whether these associations are independent of one another. The study also tested associations for bidirectional effects. This is because wellbeing not only results from successful outcomes, but it also precedes them (Lyubomirsky et al., 2005). Understanding the causal impact of wellbeing on educational attainment and vice versa could thus provide insight into how individuals can reach their full academic potential and optimal wellbeing.

Based on previous phenotypic findings of predictors and outcomes of wellbeing (Lyubomirsky et al., 2005; Nikolaev, 2018), it was predicted that educational attainment would have positive causal effects on wellbeing and vice versa. It was also anticipated that effects of educational attainment on wellbeing would be largely attenuated after accounting for causal effects of intelligence. This is based on the strong bidirectional associations between educational attainment and intelligence (Anderson et al., 2020).

Teasing apart the relative impact of educational attainment and intelligence is important to informing intervention and policy changes. In particular, if associations between educational attainment and wellbeing are shown to be largely accounted for by intelligence, policy makers should focus less on keeping students in higher education, and more on intelligence and cognitive training. If, however, educational attainment exerts a direct positive impact on wellbeing, policy makers and researchers would benefit from further understanding the specific benefits of higher education.

6.4 Methods

This study used summary data from genome-wide association studies (GWASs) to run two variations of MR, univariable and multivariable MR. Univariable MR was described in Chapter 2 and was used in this study to separately test for causal associations between wellbeing and the two exposures: educational attainment and intelligence. Multivariable MR was then used to estimate the direct effects of educational attainment and intelligence on wellbeing, independent of the other. Multivariable MR is run in much the same way as standard univariable MR. When using summary data, the effect of each genetic variant on the outcome is regressed on the effect of each variant on both exposures. These are then used in a multivariable regression to estimate the effect of each exposure on the outcome, conditional on the other exposure included in the model (Sanderson et al., 2019).

6.4.1 GWAS data

Genetic instruments for this MR study used summary data from genome-wide associations studies (GWAS). These were carefully selected to ensure sample overlap was minimal. As noted in Chapter 2, sample overlap can be problematic as it can lead to a bias towards the exposure-outcome association.

6.4.1.1 Educational attainment

Data for educational attainment was taken from the GWAS conducted by the Social Science Genetic Association Consortium (SSGAC; Okbay et al., 2016). This study initially meta-analysed summary statistics from 64 samples, covering 15 different countries. All subjects (*n*=293,723) were of European descent and above the age of 30. Years of schooling was assessed across samples by categorising reports based on the 1997 International Standard Classification of Education (ISCED) scale (UNESCO, 2006). These categories were used to map the equivalent number of years in schooling. The study identified 74 independent genetic variants associated with years of schooling (*m*=14.3, *SD*= 3.6) after adjustment for sex and ancestry principal components. The estimated effect sizes for each SNP ranged

from 0.014 to 0.048 standard deviations per allele (2.7 to 9.0 weeks of schooling), with incremental R^2 values ranging from 0.01% to 0.035%. A polygenic score constructed from the SNPs explained approximately 3.2% of the variance in educational attainment in an independent sample (Okbay et al., 2016).

Following the initial analysis, GWAS data were subsequently combined with those of 111,349 participants from the UK-Biobank (UKB) (Okbay et al., 2016). This replication resulted in a GWAS sample of 405,072 participants, and increased the number of associated SNPs from 74 to 162. The current study, however, used data from the original discovery GWAS as opposed to the larger replication. This is because the original GWAS did not include the UKB which helped to reduce sample overlap. Approximately 9% of participants from the original discovery sample were included in the intelligence GWAS (Savage et al., 2018), this increased to approximately 34% when including both the discovery and replication cohort. To ensure findings were consistent across the two educational attainment samples, analyses were repeated using the larger combined discovery and replication cohort. Results from these analyses are reported in the Appendices.

6.4.1.2 Intelligence

For intelligence, data were derived from the largest GWAS of intelligence to date (*n*=269,867) (Savage et al., 2018). This study was based on 14 cohorts that assessed intelligence using various neurocognitive tests of logical, verbal, spatial, and technical ability. Despite the different assessments, all cohorts extracted a single sum, mean, or factor score which was used to index general intelligence, or Spearman's *g* (Spearman, 1904), and all adjusted analyses for sex, age, and ancestry principal components. These scores were all normally distributed and genetically correlated across cohorts (mean = 0.67). Overall, the GWAS identified 242 lead SNPs associated with intelligence at genome-wide significance. Polygenic scores derived from these SNPs explained up to 5.2% of the variance in intelligence in four independent samples (Savage et al., 2018).

6.4.1.3 Wellbeing

As per Chapter 4, wellbeing data was taken from the multivariate genome-wide-association meta-analysis (GWAMA) (Baselmans et al., 2019). This study used the widely documented genetic overlap between four traits, life satisfaction, positive affect, depression, and neuroticism, to run two novel and complementary methods: An N-weighted multivariate GWAMA (N-GWAMA) and a model-averaging GWAMA (MA-GWAMA). The N-GWAMA was used to investigate a unitary effect of all traits, referred to collectively as the wellbeing spectrum. The MA-GWAMA relaxed the assumption of a unitary effect to study trait-specific estimates for each SNP. Findings from the N-GWAMA revealed 231 independent SNPs associated with the wellbeing spectrum. Polygenic scores generated from these SNPs explained 0.94% of the variance in life satisfaction and 1.10% of the variance in positive affect (Baselman et al., 2019) after adjustment for sex, age, and ancestry principal components. These estimates are larger than the previous GWAS of wellbeing which explained on average 0.7% of the variance in life satisfaction and positive affect (Okbay et al., 2016). Findings from the MA-GWAMA resulted in 148 independent loci for life satisfaction, 191 for positive affect, 239 for depressive symptoms and 263 for neuroticism. The incremental R^2 for these SNPs was slightly lower than those derived from the N-GWAMA, therefore the current study used estimates of the wellbeing spectrum from the N-GWAMA. Follow-up analyses were carried out to explore specific estimates for each trait using the MA-GWAMA results.

Approximately 11% of the wellbeing GWAS were included in the educational attainment GWAS (Okbay et al., 2016), and around 8% in the intelligence GWAS (Savage et al., 2018). These overlap estimates are similar to previous studies investigating wellbeing as the outcome variable within an MR framework (Wootton et al., 2018).

6.4.2 Data harmonisation

To perform MR using summary data, data harmonisation is essential. Data harmonisation checks that the GWAS results have harmonised effect (or coded) alleles. This ensures that the effect of each SNP on the exposure and outcome corresponds to the same allele. Typically, the effect allele in a GWAS is coded on the forward strand (Wang et al., 2017). Therefore, if one GWAS coded the effect allele on the reverse strand, the alleles would not align. For example, one GWAS may report the effects of one SNP as G/T, but the outcome GWAS may report it as C/A. Here, it is evident that one study has reported the effect on the forward strand and the other on the reverse strand. This can be rectified in data harmonisation by flipping the outcome alleles to match those of the exposure alleles (Hemani et al., 2018a). Ensuring that both GWASs are coded using the same strand is crucial to preventing issues with palindromic single nucleotide polymorphisms (SNPs).

Palindromic SNPs refer to those whose alleles are the same letters on the forward and reverse strands. For example, one study may have A/T on forward strand and T/A on the reverse strand. This can be problematic as it introduces ambiguity as to which way round is representative of the effect allele. If the strand is known, this can be interpreted. However, if this information is not available, we can use the effect allele frequencies (EAF). The EAF provides insight into whether the effect allele is the major or minor allele, which can then be used to check allele matching across the exposure and outcome GWASs. Major alleles are those that occur in higher frequencies, while minor alleles have a low allele frequency. Data harmonisation techniques often rely on the minor allele frequency being below 50% to identify ambiguities (Hartwig et al., 2016). Details of the data harmonisation procedure used in the present study is presented below.

6.4.3 Statistical analyses

Both univariable and multivariable MR analyses were conducted using the TwoSampleMR package (Hemani et al., 2018b) in R (R Core Team, 2021). Genetic variants included were

those that passed the genome-wide level of significance ($p<5x10^{-8}$) and clumping. Clumping ensures that included variants are independent and not in linkage disequilibrium (LD). LD refers to the correlation between genetic variants that lie in close proximity on the same chromosome. Estimates that use SNPs in LD can become inflated in MR (Burgess et al., 2013). Clumping was therefore performed at $r^2< 0.001$ within an 10000 kb. This means that only SNPs with the lowest *p*-value above the LD threshold of $r^2 =0.001$, within a 10,000 kb window of the gene were retained. After clumping the variants, data harmonisation was performed.

The current study used the most conservative approach in the TwoSampleMR package for data harmonisation. The positive strand of the alleles was inferred, and allele frequencies were used for palindromic SNPs. If a SNP was palindromic, strands were aligned using a minor allele frequency of 0.42. This means that if the effect allele on the outcome GWAS had a low allele frequency compared to the effect allele on the exposure GWAS, the outcome GWAS was assumed to be presenting the effect on the reverse strand. In this case, the effect allele would be swapped for the outcome GWAS. However, if the minor allele frequency was above 0.42, this SNP would instead be removed as information about the strand and effect allele is less clear.

6.4.3.1 Univariable MR

For all univariable analyses, four different two-sample MR methods were used. As explained in Chapter 2, two-sample MR involves using independent study samples. One sample is used to provide estimates of associations between genetic markers and the exposure, and the other provides association estimates between genetic markers and the outcome. The inverse variance weighted (IVW) method was used as the main analysis, with sensitivity analyses including mendelian randomization-Egger (MR-Egger), weighted median, and weighted mode. Each make different assumptions about pleiotropy, as explained in Chapter 2, with the MR-Egger slope used to provide a pleiotropy-corrected estimate of the causal

effects. A consistent result across these methods would provide the greatest support for a true causal effect.

For all univariable analyses run using the IVW regression, instrument strength was calculated using an F statistic greater than 10 (Staiger & Stock, 1997). The F statistic is a function of how much variance in the trait is explained by the set of genetic instruments (R^2), as well as the number of instruments used and the sample size. For MR-Egger, instrument strength was determined using the regression dilution I^2 (Bowden et al., 2016). Where this statistic was lower than 0.9, simulation extrapolation (SIMEX) corrections were carried out. This was described in detail in Chapter 2.

To further assess the robustness of the results, heterogeneity was estimated using Cochran's Q (Bowden et al., 2018). Heterogeneity refers to the variability in the causal estimates obtained for each SNP. Tests of heterogeneity therefore reveal how consistent the causal estimate is across SNPs, which can be used as an indicator of pleiotropy. Based on previous findings, it was anticipated that heterogeneity would be high (Anderson et al., 2020). A multiplicative random effects IVW regression was therefore chosen to adjust for this. Multiplicative IVW regression provides a more reliable causal estimate as it increases the standard error to reflect the degree of uncertainty due to heterogeneity (Bowden et al., 2018).

To visually assess the degree of heterogeneity, funnel plots were created. These helped to determine whether any pleiotropy is balanced across the SNPs. Asymmetry in the funnel plot indicates directional horizontal pleiotropy, while a larger spread is suggestive of unbalanced pleiotropy. As mentioned in Chapter 2, balanced pleiotropy is unlikely to bias the MR result because effects cancel one another out. To further ascertain the degree of bias resulting from directional pleiotropy, the MR-Egger intercept was investigated. Where the intercept was non-significant, this was taken as evidence of balanced pleiotropy. A leave-one-out analysis was also used to explore if any associations were disproportionately influenced by a

single SNP. Forest plots generated from these represent findings excluding each single SNP in turn. All analyses described above represent the current gold standard methods used in MR (Burgess et al., 2019).

6.4.3.1.1 Univariable analyses: Educational attainment and intelligence

Prior to investigating effects on wellbeing, univariable MR was first used to estimate the bidirectional relationship between educational attainment and intelligence (Anderson et al., 2020). Analyses exploring possible causal effects of educational attainment on intelligence used a total of 63 SNPs that were available following data harmonisation, while analyses exploring the impact of intelligence on educational attainment used 144 SNPs in the genetic instrument.

6.4.3.1.2 Univariable analyses: Educational attainment and wellbeing

Further univariable MR analyses were then run to test for a possible bi-directional association between educational attainment and wellbeing. Analyses exploring the total causal effects of educational attainment on wellbeing used 54 SNPs that were available following data harmonisation. A full list of these SNPs can be found in Appendix 6.1. It was noted that a large proportion (81.4%) of the included variants were not the original 74 genome-wide significant SNPs identified in the GWAS (Okbay et al., 2016). This is due to differences in clumping between the current study and those used in the original GWAS. As a sensitivity test, included SNPs were therefore checked to ensure they were in LD with SNPs from the original GWAS. For analyses exploring total causal effects of wellbeing on educational attainment, there were 147 SNPs available following data harmonisation. Of these, 90 SNPs (61.2%) formed part of the original 232 SNPs identified in the wellbeing GWAS (see Appendix 6.2).

6.4.3.1.3 Univariable analyses: Intelligence and wellbeing

The same set of univariable MR analyses were then conducted using genetic instruments for intelligence. Analyses testing possible causal effects of intelligence on wellbeing used 126

SNPs (see Appendix 6.3 for a full list), of which 12.7% were not the lead SNPs reported in the original GWAS. These were also checked to ensure they were in LD with the original SNPs. Analyses testing for possible causal effects of wellbeing on intelligence used 128 SNPs, of which 71 (55.4%) formed part of the original 232 lead SNPs in wellbeing GWAS (see Appendix 6.4).

6.4.3.2 Sensitivity analyses

As sensitivity tests for the univariable MR analyses, Steiger filtering was conducted. Steiger filtering provides insight into whether the genetic variants used as the instrument explain more of the variance in the exposure compared to the outcome (Hemani et al., 2018a). In doing so, it helps to identify pleiotropic SNPs that likely influence the outcome through a pathway other than the exposure. Where more than one SNP explained more of the variance in the outcome than the exposure, analyses were repeated after removal of these genetic variants.

Follow-up analyses also explored associations with wellbeing using SNPs generated from the MA-GWAMA (Baselmans et al., 2019). This allowed univariable MR analyses to separately test associations with the four individual traits: positive affect, life satisfaction, depression, and neuroticism. Such analyses helped establish the degree to which the original results were driven by positive wellbeing and not negative mental health, and provided insight into whether findings vary as a function of different aspects of wellbeing.

6.4.3.3 Multivariable MR

Multivariable MR was used to estimate the direct independent effects of educational attainment and intelligence on wellbeing. Unlike univariable MR, the instrument assumption within multivariable MR allows a genetic variant to be associated with more than one exposure, provided these are included in the analysis. This allows the regression model to provide an estimate of the causal effects of one phenotype independently of the other. For the current multivariable analyses, the MVMR package (Sanderson et al., 2019) and the

MendelianRandomization package (Rees et al., 2017) were used. As per the univariable MR analyses, variants were selected if they passed the genome-wide level of significance ($p<10x5^{-8}$). Clumping was also performed at $r^2< 0.001$ and 10,000 kb, and palindromic SNPs were aligned using a minor allele frequency of 0.42. This resulted in 151 SNPs available for the multivariable MR analysis, a full list of which can be found in Appendix 6.5.

6.5 Results

6.5.1 Univariable MR: Educational attainment and intelligence

Univariable MR analyses provided evidence of strong causal effects of educational attainment on intelligence, and vice versa (Table 6.1). As per previous findings (Anderson et al., 2020), the effect of educational attainment on intelligence was almost two-fold greater than the magnitude of the effects of intelligence on educational attainment. This was found using both the discovery educational attainment GWAS (*n*=293,723), and the discovery and replication cohort (*n*=405,072) (see Appendix 6.6).

Analyses were unlikely to suffer from weak instrument bias, as indicated by the F statistic of *F*= 38.4 for educational attainment, and *F*=42.7 for intelligence (Table 6.2). However, there was strong evidence of heterogeneity in the causal effect estimates for both directions, as previously found (Anderson et al., 2020). The MR-Egger intercept in analyses predicting intelligence from educational attainment was borderline significant (*p*=0.056), suggesting that directional horizontal pleiotropy may be one possible explanation for this heterogeneity. This was also reflected in the funnel plots which showed some bias in the MR-Egger estimates (see Figure A6.1 in Appendix 6.7). However, there was little evidence of departure from symmetry for causal effects of intelligence on educational attainment, as indicated by the funnel plots (see Figure A6.2 in Appendix 6.7) and MR-Egger intercept. There was also no distortion in the leave-one-out forest plots for either of the univariable analyses (see Figure A6.3 in Appendix 6.7). These findings indicate that associations were not disproportionately influenced by a single SNP.

Table 6.1: Univariable MR analyses assessing bidirectional associations between educational attainment and intelligence

		Causal effect estimates		Heterogeneity statistics		
	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on intelligence						
Inverse variance weighted	63	0.736 (0.647, 0.826)	**4.88E-58**	272.2	62	**8.90E-26**
MR-Egger	63	1.17 (0.724, 1.62)	**3.12E-06**	256.3	61	**3.95E-28**
MR-Egger intercept	63	-0.008 (-0.016, 0.002)	0.056	-	-	-
MR-Egger (SIMEX) [a]	63	1.85 (1.28, 2.42)	**1.44E-08**	-	-	-
Weighted median	63	0.655 (0.566, 0.743)	**1.20E-50**	-	-	-
Weighted mode	63	0.632 (0.410, 0.854)	**1.25E-07**	-	-	-
Intelligence on years of schooling						
Inverse variance weighted	144	0.398 (0.359, 0.438)	**2.40E-85**	466.1	143	**7.11E-36**
MR-Egger estimate	144	0.534 (0.346, 0.721)	**1.17E-07**	459.9	142	**4.16E-35**
MR-Egger intercept	144	-0.003 (-0.006, 0.001)	0.150	-	-	-
MR-Egger (SIMEX)	144	0.815 (0.562, 1.07)	**2.69E-09**	-	-	-
Weighted median	144	0.341 (0.301, 0.381)	**1.92E-65**	-	-	-
Weighted mode	144	0.277 (0.175, 0.379)	**1.56E-06**	-	-	-

Note*:* Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Weighted simulation extrapolation (SIMEX) correction applied.

Table 6.2: F statistic and regression dilution I^2 statistic for the heterogeneity of SNP-exposure effects

Exposure	F	I^2 (unweighted)	I^2 (weighted)
Educational attainment on intelligence	38.44	0.38	0.52
Intelligence on educational attainment	42.72	0.48	0.51
Educational attainment on wellbeing	38.88	0.11	0
Intelligence on wellbeing	43.35	0.45	0.26
Wellbeing on educational attainment	40.78	0.35	0.35
Wellbeing on intelligence	40.83	0.35	0

Note: All based on analyses using educational attainment discovery GWAS (n=293,723).

6.5.2 Univariable MR: Educational attainment and wellbeing

Further univariable analyses provided some evidence of bidirectional effects between educational attainment and wellbeing (see Table 6.3). The IVW results revealed that per every standard deviation (SD) increase in years of schooling, which equates to 3.6 years of schooling, there is a 0.06 (95% CI= 0.04, 0.07) increase in wellbeing. When investigating effects of the wellbeing spectrum, findings revealed that it predicted a 0.21 (95% CI= 0.07, 0.34) increase in the number of years schooling. Such findings suggest that the impact of higher wellbeing on educational attainment is greater than effects of higher educational attainment on wellbeing.

Both the univariable analyses investigating effects of educational attainment on wellbeing and vice versa did not replicate using the MR-Egger; however, this is unlikely to be a result of weak instruments in the IVW or directional pleiotropy (see Table 6.2). Directional pleiotropy is accounted for in MR-Egger, therefore if directional pleiotropy is present, it can result in the removal of any causal effects. This seems unlikely based on the current findings as the MR-Egger intercept did not differ from zero (see Table 6.3) An intercept that differs from zero suggests there is evidence of directional pleiotropy (Bowden et al., 2015). In addition to this, funnel plots provided evidence of balanced pleiotropy (see Figures A6.4 and A6.5 in Appendix 6.8) and there were no outliers or evidence to suggest that associations were strongly driven by a single-SNP (see Figure A6.6 in Appendix 6.8). One SNP located

on Chromosome 5 (rs6882046) showed marginally greater effects than the other SNPs when assessing the impact of educational attainment on wellbeing. However, the difference was minimal. These combined findings therefore suggest that results from the IVW are unlikely to be significantly driven by directional pleiotropy.

Table 6.3: Univariable MR analyses assessing total bidirectional associations between educational attainment and wellbeing, and between intelligence and wellbeing

		Causal effect estimates		Heterogeneity statistics		
	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on wellbeing						
Inverse variance weighted	54	0.057 (0.042, 0.074)	**5.18E-13**	336.7	53	**6.83E-43**
MR-Egger	54	-0.071 (-0.323, 0.180)	5.81E-01	330.1	52	**4.38E-42**
MR-Egger intercept	54	0.002 (-0.002, 0.006)	0.313	-	-	-
MR-Egger (SIMEX) [a]	54	-0.085 (-0.424, 0.252)	0.621	-	-	-
Weighted median	54	0.050 (0.023, 0.077)	**2.29E-04**	-	-	-
Weighted mode	54	0.067 (0.016, 0.119)	**1.26E-02**	-	-	-
Wellbeing on years of schooling						
Inverse variance weighted estimate	147	0.206 (0.071, 0.341)	**2.71E-03**	574.9	146	**3.19E-52**
MR Egger estimate	147	0.049 (-0.651, 0.749)	0.890	574.1	145	**2.15E-52**
MR Egger intercept	147	0.001 (-0.004, 0.004)	0.655	-	-	**-**
MR-Egger (SIMEX) [a]	147	0.528 (-0.265, 1.32)	0.19	-	-	**-**
Weighted median	147	0.187 (0.063, 0.311)	**2.80E-04**	-	-	**-**
Weighted mode	147	0.236 (-0.094, 0.566)	0.163	-	-	**-**
Intelligence on wellbeing						
Inverse variance weighted	126	-0.004 (-0.028, 0.017)	0.713	688.5	125	**7.58E-108**
MR-Egger	126	0.003 (-0.096, 0.103)	0.946	688.4	124	**5.54E-108**

MR-Egger intercept	126	-0.001 (-0.003, 0.001)	0.883	-	-	-
MR-Egger (SIMEX) [a]	126	0.016 (-0.066, 0.098)	0.702	-	-	-
Weighted median	126	-0.001 (-0.018, 0.015)	0.876	-	-	-
Weighted mode	126	0.004 (-0.034, 0.041)	0.844	-	-	-
Wellbeing on intelligence						
Inverse variance weighted estimate	128	0.199 (0.014, 0.390)	**3.48E-02**	665.4	127	**6.72E-74**
MR Egger estimate	128	-0.104 (-1.17, 0.960)	8.47E-01	663.7	126	**5.81E-74**
MR Egger intercept	128	0.001 (-0.006, 0.006)	0.571			
MR-Egger (SIMEX) [a]	128	0.688 (-0.375, 1.75)	0.207	-	-	-
Weighted median	128	0.301 (0.159, 0.443)	**3.40E-05**	-	-	-
Weighted mode	128	0.347 (-0.007, 0.702)	**5.17E-02**	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Unweighted simulation extrapolation (SIMEX) correction applied

6.5.3 Univariable MR: Intelligence and wellbeing

Univariable MR analyses exploring the relationship between intelligence and wellbeing revealed no causal effects of intelligence on wellbeing, but some evidence of a causal effect of wellbeing on intelligence (Table 6.3). In particular, the wellbeing spectrum predicted a 0.20 (95% CI= 0.01, 0.39) increase in intelligence. This did not replicate using MR-Egger; however, the MR-Egger intercept suggested no evidence of bias due to directional horizontal pleiotropy. Funnel plots and the leave-one-out analyses also provided support for balanced pleiotropy (Figures A6.7 and A6.8, Appendix 6.9).

6.5.4 Sensitivity analyses

Steiger filtering was carried out for all three univariable MR analyses to test whether genetic variants used for the exposures had stronger associations with the exposure than with the outcome. For the first analysis, Steiger filtering revealed that all intelligence SNPs explained more of the variance in intelligence than educational attainment. For the educational attainment SNPs, all but 1 SNP (rs8049439) explained more of the variance in educational attainment than intelligence. This SNP has previously been implicated in a GWAS of intelligence (Hill et al., 2019).

For analyses predicting wellbeing, all educational attainment SNPs were more associated with educational attainment than wellbeing, and the same was found for the intelligence SNPs. When investigating causal effects of the wellbeing SNPs on the two exposures, 4 out of a total 147 SNPs (2.7%) were shown to explain more of the variance in educational attainment than wellbeing, and 11 out of a total 128 SNPs (8.6%) explained more of the variance in intelligence than wellbeing. Analyses were therefore repeated after removing these SNPs that explained more of the variance in the outcome than the exposure. Results from these analyses were largely consistent (see Appendix 6.10), suggesting minimal bias from including these SNPs.

In further follow-up analyses, the univariable MR regressions were replicated, replacing the wellbeing SNPs from the N-GWAMA with SNPs generated from the MA-GWAMA. Results from these analyses predicting positive affect, life satisfaction, depression and neuroticism are presented in the Appendices (see Appendix 6.11 to 6.14). Overall, findings using the two indices of wellbeing; positive affect and life satisfaction, revealed a similar pattern of results to those found using the wellbeing spectrum. There was no evidence to suggest a causal effect of intelligence on either life satisfaction or positive affect, but some indication that educational attainment is causally related to the two outcomes. For depression and neuroticism, effect estimates were the opposite direction to those found using the wellbeing outcomes. This helped to confirm that analyses using SNPs generated from the N-GWAMA of the wellbeing spectrum were not strongly driven by these traits.

6.5.5 Multivariable MR

Results from the multivariable MR analysis revealed independent causal effects of both educational attainment and intelligence on wellbeing (Figure 6.1), however findings were in the opposite direction from one another. For educational attainment, a SD increase in years of schooling (3.6 years) predicted a 0.103 (95% CI= 0.05, 0.16) increase in wellbeing, controlling for the effects of intelligence, while intelligence predicted a 0.04 (95% CI= -0.08, -0.01) decrease in wellbeing, controlling for years of schooling. These findings were both larger than those found in the univariable models (see Table 6.4) and were generated despite relatively weak instruments (*F*-statistic=7.94 for intelligence and *F*-statistic=7.23 for educational attainment). These are conditional F-statistics generated by estimating the impact of SNPs on one exposure, conditioning on the other (Sanderson et al., 2019).

Findings from the multivariable MR-Egger analyses produced associations in the same direction for both exposures (Table 6.4), although analyses using years of schooling reached just near significance (p=0.07). This discrepancy is unlikely to reflect directional pleiotropy according to the MR-Egger intercept.

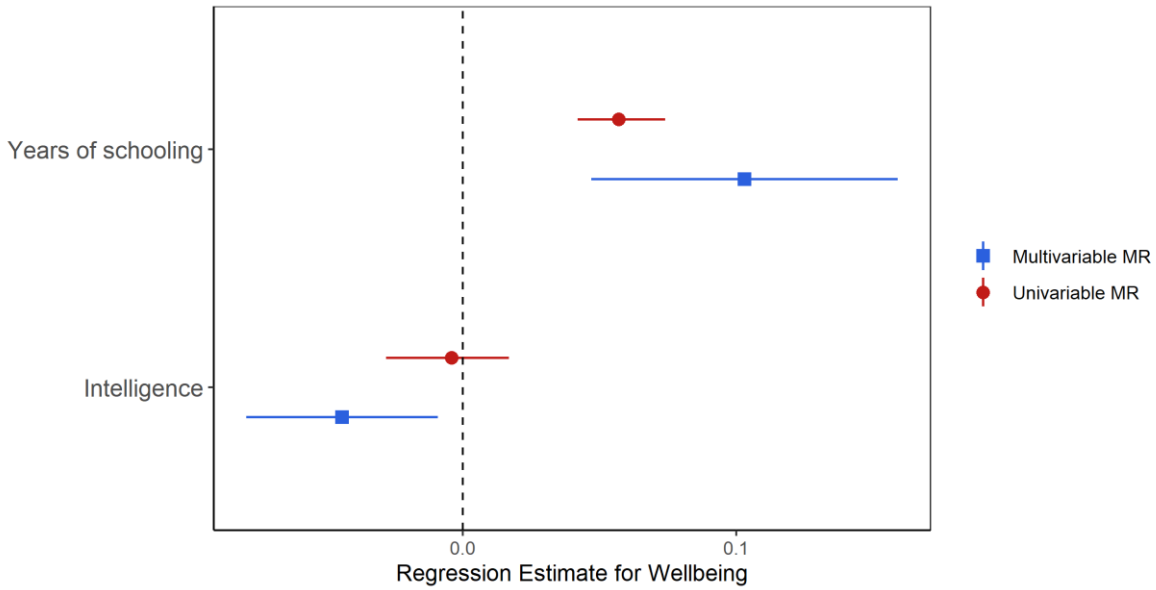

Figure 6.1: *Comparison of univariable and multivariable MR analyses predicting wellbeing based on IVW MR estimates. This figure shows that years of schooling has positive independent (multivariable) and total (univariable) causal effects on wellbeing. In contrast, intelligence has negative independent (multivariable) but not total (univariable) causal effects on wellbeing.*

Table 6.4 Comparison of total and independent effects of educational attainment and intelligence on wellbeing

	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on wellbeing						
Total effects						
Inverse variance weighted	54	0.057 (0.042, 0.074)	**5.18E-13**	336.7	53	**<0.001**
MR-Egger	54	-0.071 (-0.323, 0.180)	5.81E-01	330.1	52	**<0.001**
MR-Egger intercept	54	0.002 (-0.002, 0.006)	0.313	-	-	-
Independent effects						
Inverse variance weighted	151	0.103 (0.047, 0.159)	**4.69E-04**	766.7	149	**<0.001**
MR-Egger	151	0.064 (-0.006, 0.135)	0.075	751.4	148	**<0.001**
MR-Egger intercept	151	0.001 (-0.010, 0.003)	0.082	-	-	-
Intelligence on wellbeing						
Total effects						
Inverse variance weighted	126	-0.004 (-0.028, 0.017)	0.713	688.5	125	**<0.001**
MR-Egger	126	0.003 (-0.096, 0.103)	0.946	688.4	124	**<0.001**
MR-Egger intercept	126	-0.001 (-0.003, 0.001)	0.883	-	-	-
Independent effects						
Inverse variance weighted	151	-0.044 (-0.079, -0.009)	**0.014**	766.7	149	**<0.001**
MR-Egger	151	-0.075 (-0.124, -0.026)	**0.003**	751.4	148	**<0.001**
MR-Egger intercept	151	0.001 (-0.010, 0.003)	0.082	-	-	-

Note: Analyses conducted using the educational attainment discovery and replication cohort (n=293,723). Intercept estimates for the effects of intelligence and years of schooling on wellbeing are the same within the multivariable MR model as there is only one intercept.

In follow-up analyses, the wellbeing outcome was again replaced with life satisfaction and positive affect. These multivariable analyses also revealed a similar pattern of results (Figure 6.2), with independent effects of educational attainment found for both life satisfaction and positive affect using the IVW regression, but not MR-Egger (see Appendix 6.11 and 6.12). Within multivariable MR analyses controlling for educational attainment, there was some evidence of an independent causal effect of intelligence on life satisfaction and positive affect using MR-Egger but not IVW.

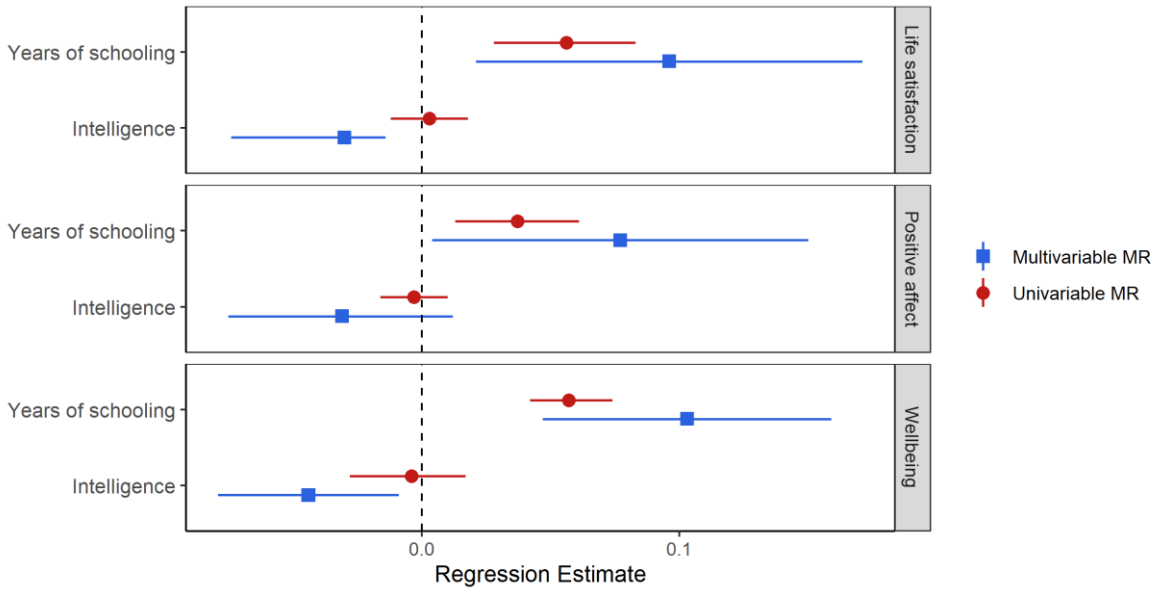

Figure 6.2: *Comparison of univariable and multivariable MR analyses predicting life satisfaction, positive affect, and wellbeing from IVW univariable MR analyses. This figure shows that years of schooling has positive independent (multivariable) and total (univariable) causal effects on all three wellbeing outcomes. In contrast, intelligence has negative independent (multivariable) causal effects on life satisfaction and overall wellbeing but not subjective happiness. Intelligence also has no total (univariable) effects on any of the wellbeing outcomes.*

Finally, as 28 tests were carried out in total, including the univariable MR, multivariable MR, and follow-up MR analyses, the current study adjusted for multiple testing using the false discovery rate (FDR). As these 28 tests were not independent, the Benjamini–Hochberg procedure was used (Benjamini et al., 1995). Just two findings were no longer robust after correction for multiple testing, one of which was the causal effects of wellbeing on intelligence (FDR-adjusted p-value now 0.03), and the other was the effect of educational

attainment on positive affect in the multivariable model (FDR-adjusted p-value now also 0.03). Because the statistical inference for the remaining 26 associations was the same, and because *p*-values alone should not be relied upon for causal inferences (McShane et al., 2019), the raw *p*-values are reported throughout. This is also the approach that has been previously taken in multivariable MR studies (Adams, 2020), helping to ensure the current study is consistent with the wider MR literature.

6.6 Discussion

This study used univariable and multivariable MR to determine whether educational attainment and intelligence have causal and independent effects on wellbeing. Findings provide support for previously reported associations between higher educational attainment and wellbeing (Nikolaev, 2018) and suggest there is a causal, protective effect of staying in school on wellbeing that is independent of intelligence. Associations between intelligence and wellbeing were in the opposite direction, with higher intelligence predictive of reduced levels of wellbeing. This finding was only observed in multivariable models, suggesting causal effects of intelligence that are independent of years of schooling. Such results are consistent with some of the existing literature which has shown direct negative associations with life satisfaction at age 26 (Flèche et al., 2021), and after accounting for educational attainment (Lee et al., 2021). Unlike previous observational research, however, the current findings were able to more directly rule out confounding of educational attainment to establish a causal role for intelligence.

When investigating causal effects of wellbeing on educational attainment and intelligence, findings revealed that wellbeing was associated with both outcomes. Estimates were largely similar for the two outcomes, suggesting that wellbeing has equally positive effects on educational attainment and intelligence. These estimates were greater than those found for analyses predicting wellbeing, suggesting that measures to improve wellbeing may be more beneficial than those aimed at increasing educational attainment or intelligence.

6.6.1 The role of educational attainment

When investigating the role of educational attainment, findings revealed causal associations with wellbeing in both univariable and multivariable models. This finding not only helps to confirm previous observational research, which may have been limited by potential confounding and reverse causation, but it also demonstrates an effect of educational attainment that is not due to pleiotropic effects of intelligence. Such a finding has important

implications for policy as it suggests a unique benefit of staying in school over and above cognitive abilities.

Education has been referred to as an “institutionalised form of social resource” (Yuan et al., 2021). By this, researchers have highlighted that education brings with it both objective resources like books and scientific instruments, as well as attitudes and practices (Yuan et al., 2021). Education is also an important determinant of social relations, which influence both academic and social characteristics (Witkow & Fuligni, 2010) as well as the likelihood of further study (Stadtfelt et al., 2019). Spending more years in education therefore brings increased opportunities for not only developing cognitive skills, but also wider cultural awareness and social networks. It is possible that these broader implications of the learning environment serve to increase wellbeing both directly and indirectly, such as through increased social support and a clearer sense of self (Du et al., 2017).

In addition to providing individuals with social environments and experiences, spending more years in education may also alter habits and health-related choices. Individuals genetically inclined to complete more years of schooling are more likely to engage in vigorous physical activity and less likely to engage in sedentary behaviour (Davies et al., 2019). In comparison, genetic indices of intelligence are negatively associated with vigorous physical activity (Davies et al., 2019). Intense physical activity has been shown to have a positive impact on wellbeing in both adults (Ku et al., 2016) and adolescents (Costigan et al., 2019). Findings have also shown that physical activity, as well as other health- related behaviours such as smoking and alcohol consumption mediate the relationship between educational attainment and depression (Bjelland et al., 2008). These associated behaviours of those who spend more time in education may explain why educational attainment is positively associated with wellbeing, and intelligence negatively associated with wellbeing.

6.6.2 The role of intelligence

Intelligence in the present study was shown to have no main effects on wellbeing when educational attainment was not adjusted for. However, once years spent in schooling was accounted for, significant causal effects were identified. This independent negative effect in the absence of a total effect likely reflects negative confounding. During the univariable MR, the impact of intelligence on wellbeing includes any effects mediated through educational attainment. Any positive effects of educational attainment on wellbeing would therefore have cancelled out influences of intelligence by dragging the result towards the null. Previous studies have produced similar results and shown that the impact of childhood intelligence on adult life satisfaction becomes negative after accounting for outcomes in adulthood like educational attainment (Clark et al., 2021). It was suggested that this may reflect a "residual" effect that occurs among individuals with higher expectations following more years in schooling. Education not only increases happiness, but also desires for happiness (Clark et al., 2015). These aspirations may be higher among those with greater intelligence who may feel greater pressure to succeed in multiple aspects of life. Indeed, compared to adolescents high in creativity, highly intelligent individuals have been known to strive for occupations that require higher training and skills (Getzels & Jackson, 1960). Such careers aspirations may be coupled with heightened stress and anxiety which may serve to reduce wellbeing.

Individuals with high intelligence may also possess certain characteristics that put them at risk of lower wellbeing. Highly intelligent individuals are more prone to rumination and worrying, which can increase susceptibility towards mental health disorders (Karpinski et al. 2018). This has been suggested to reflect what is known as the 'hyper-brain/hyper-body' theory which argues that intelligent individuals have exaggerated physiological, neurological, and psychological responses to environmental stress (Karpinski et al., 2018). Such reactions are likely to be more prevalent among individuals with more extreme intelligence which may explain why analyses using intelligence, but not educational attainment, produced negative associations with wellbeing.

6.6.3 The impact of wellbeing on educational attainment and intelligence

Analyses exploring possible bidirectional associations revealed that higher wellbeing may increase intelligence and the likelihood of completing more years of schooling. These findings align with previous cross-sectional research which demonstrated that individuals high in life satisfaction are more likely to report better grades in school (Gilman & Huebner, 2006). By using a causal design, the current study helps overcome previous limitations related to reverse causality and provides support for improving wellbeing in schools. Such interventions are likely to not only encourage further education and improved cognitive skills, but also more positive wellbeing later in life.

It has previously been argued that in addition to improving academic attainment, schools should prioritise student wellbeing (Bonell et al., 2014). Fostering good wellbeing helps to prevent the development of mental health problems in childhood and adolescence (Cowburn & Blow, 2017), and has been shown to also improve overall school enjoyment and engagement (Seligman et al., 2009). The current study demonstrates an added benefit of wellbeing for increasing the likelihood of further education. In particular, findings point towards the importance of overall wellbeing and life satisfaction rather than positive affect. Analyses conducted with positive affect revealed no impact on the likelihood of completing more years of schooling. Strategies to keep students in education should therefore focus less on making children happy, and more on making them feel satisfied and fulfilled.

6.6.4 Strengths and limitations

A major strength of the current study is that it represents the first to investigate the causal effects of educational attainment and intelligence on wellbeing. By using both univariable and multivariable MR, the study was able to investigate possible mediating effects to infer whether causal relations reflect direct or indirect effects. In doing so, the study revealed distinct, independent effects of both educational attainment and intelligence on wellbeing. The direction of these effects was replicated using two variations of MR, helping to increase

the overall reliability of results. The study also investigated wellbeing using a multivariate genome-wide-association meta-analysis (GWAMA) (Baselmans et al., 2019). This resulted in a significantly larger sample than the previous GWAS of wellbeing (Okbay et al., 2016), helping to increase power and generalisability of the MR analyses. This was also aided by the phenotyping of the educational attainment GWAS (Okbay et al., 2016). The educational attainment GWAS assessed the number of years spent in schooling by using a mapping system that categorised qualifications based on the International Standard Classification of Education (ISCED) (Okbay et al., 2016). This allowed the authors to capture a diverse set of educational systems and qualifications across different countries, helping to increase the generalisability of the findings to different contexts.

There were, however, some limitations of the other phenotypic measures. For intelligence, measures included both neurocognitive tests of ability as well as IQ scales (Savage et al., 2018). It is thus not clear which aspects of intelligence may be specifically related to lower wellbeing. The findings from the GWAS were also based largely on adult samples. Although the genetic variants associated with intelligence in children have similar effects on intelligence in adults (Hill et al., 2016), the longer an individual spends in schooling the greater their adult intelligence (Ritchie & Tucker-Drob, 2018). Thus, it is possible that analyses overestimated associations between intelligence and adult wellbeing. This could be explored using the GWAS of childhood intelligence (Benyamin et al., 2014), however, such analyses will likely be underpowered due to sample size restrictions. The current estimates were also small, therefore, it is unlikely that such analyses would change the interpretation of the results.

Power within the current study was adequate for univariable but not multivariable MR analyses. Tests of instrument strength in multivariable MR are based on the ability of the SNPs to explain the exposure after conditioning on the other exposure (Davies et al., 2019). The low power therefore likely reflects the high correlation between the two exposures in the

current study. It is important to note, however, that power analyses for the multivariable MR are still in their infancy and should be interpreted with some caution (Sanderson et al., 2019). Using multivariable is also the preferred analysis method when investigating highly correlated exposures. Thus, while univariable MR may be more powered, results are likely to suffer from confounding.

Other things to consider when interpreting the current findings are that the multivariable MR estimates do not adjust for bias due to pleiotropic effects other than educational attainment and intelligence. Individuals genetically inclined to spend more years in schooling are more likely to experience increased career success and wealth (Belsky et al., 2018), with similar shared genetic variants also found between intelligence and income (Hill et al., 2019). Income and career success are both associated with higher wellbeing (Judge et al., 2010; Killingsworth, 2021), and may therefore represent a pleiotropic path by which the two exposures impact later wellbeing. This was not explored in the present study as the focus was on academic attainment and abilities, however this will be an important avenue for further research.

Other limitations of the current study relate to the potential for assortative mating and dynastic effects. Assortative mating refers to the non-random selection of a partner who is more phenotypically similar than would be expected by chance (Robinson et al., 2017). Findings have shown this to be the case for educational attainment and intelligence, with individuals more likely to select a mate with a similar educational background (Domingue et al., 2014) and intelligence level (Plomin et al., 2015). This could lead to enriched education-associated SNPs why may inflate subsequent MR estimates (Hartwig et al., 2018). Similarly, dynastic effects, which refer to the influence of the parental genotype on the offspring phenotype via the parent's phenotype (Morris et al., 2020), can also bias MR estimates. Research has provided evidence of dynastic effects in the context of educational attainment by demonstrating that parental educational level and family socioeconomic status predict the

educational outcomes of their offspring (Wang et al., 2021). These dynastic effects as well as assortative mating can be investigated by adjusting analyses for transmitted or non-transmitted SNPs in a within-family design (Munafo et al., 2019). This was not possible in the current study as comparisons in MR are based on unrelated individuals. Follow-up analyses will therefore need to make use of large family-based designs to explore these potential biases.

Finally, the current findings should be considered in relation to the potential selection bias. The wellbeing GWAS used in the current study included large samples from the UK Biobank (Baselmans et al., 2019). Participants in the UK Biobank are generally more educated than the general population, which may have caused an upward bias in the causal effect estimates. Previous MR studies investigating associations with educational attainment, however, have shown that after reweighting analyses for sample selection, there is minimal impact of educational biases on the overall estimates (Davies et al., 2018). Thus, while sample selection is not considered a major drawback, it is important that findings are interpreted in light of this. In addition, findings should also be considered in relation to sample overlap across the GWASs used. While exact estimates of overlap are not possible due to using summary statistics, the large consortiums used in the multivariate meta-analyses included many of the same cohorts. Future research will therefore benefit from larger independent samples to help minimise the potential for bias. Such samples will likely also increase instrument strength and power to detect effects in multivariable MR analyses.

6.6.5 Implications and future directions

Overall, this study demonstrates that individual differences in wellbeing may partly reflect genetic predispositions towards educational attainment and intelligence. Distinct effects were noted for educational attainment and intelligence, as per previous research (Davies et al., 2019), with findings offering unique support for educational policies that raise the school leaving age, but not for cognitive training. Further research would now benefit from

understanding more about predictors of enrolment in higher education, and the degree to which staying in education confers an added benefit over alternative non-academic pathways.

Research should also consider possible intellectual differences between individuals who stay on and complete higher education. It is possible that complex interactions underlie the relationship between educational attainment, intelligence, and wellbeing. For example, while intelligence has a direct negative impact on wellbeing, this effect may be reversed among individuals who attend university. This could be because higher education provides intelligent individuals the platform for them to thrive and fulfil their intellectual needs. It also allows such individuals to be recognised for their abilities which could open opportunities for employment. The current MR design enabled linear and mediating effects to be investigated but not moderating effects. Investigating non-linearity would have been possible if a one-sample MR design had been used (Staley & Burgess, 2017), but this is not yet possible using the two sample MR approach. Further research using observational data may therefore be necessary to investigate both non-linear and interactive effects with adequate power. This is explored further in Part 2 of this chapter.

6.7 Chapter 6 Part 1 summary

This study used Mendelian Randomisation (MR) to investigate possible causal associations between educational attainment and wellbeing, and between intelligence and wellbeing. Findings suggest there may be a positive causal effect of educational attainment on wellbeing such that individuals who complete more years of schooling have greater wellbeing than those with fewer years in education. For intelligence, findings were in the opposite direction, with individuals higher in intelligence more likely to display lower wellbeing, although the effect sizes are small. Further research is now necessary to untangle more about the mechanisms and pathways behind these associations to understand why

influences may differ. This will be key to ensuring more guided recommendations for policy and public health interventions.

Chapter 6: Part 2 – A follow-up investigation into educational attainment, intelligence, and wellbeing

6.8 Chapter Part 2 overview

Part 1 of this Chapter used genetic data to study possible causal relationships between educational attainment and wellbeing, and between intelligence and wellbeing. The study revealed that the direction of effects may be the opposite for these two associations, with educational attainment positively associated with wellbeing, and intelligence negatively. As mentioned in Part 1 of this Chapter, it is possible that these findings reflect non-linear or interactive effects.

Previous research on intelligence has provided evidence of non-linear associations with psychotic symptoms (Horwood et al., 2008), anti-social behaviour (Silver, 2019), and sociability (Major et al., 2014), with the relationship between intelligence and sociability best represented by an inverted U-shape. This means that individuals with both extremely low and extremely high intelligence had lower sociability compared to those with average intelligence. It was speculated that having low intelligence may lead to social ostracizing from peers, while high intelligence may lead to engagement in different activities or interests compared to peers, both resulting in low sociability (Major et al., 2014). Sociability is positively related to wellbeing (Emmons & Diener, 1986). It is therefore possible that there exists a similar trend between intelligence and wellbeing, with low and high intelligence predictive of lower wellbeing, and average intelligence predictive of higher wellbeing. As discussed in Part 1 of this Chapter, this was not possible to investigate using the two-sample MR design.

Another possibility is that the negative effects of intelligence are moderated by educational attainment. While the multivariable Mendelian Randomisation (MR) study was able to estimate the independent and unconfounded effects of educational attainment and intelligence on wellbeing, it was not able to determine the extent to which such effects may

be moderated by the other. For example, it is possible that the negative impact of intelligence on wellbeing is moderated by schooling such that individuals high in intelligence have higher wellbeing if they also spend more time in school compared to those who spend less time in school. This would explain why effects of intelligence were masked in the univariable MR, and could mean there are subtle differences in the effects of intelligence among individuals with and without a university degree. It is also possible that the impact of intelligence or educational attainment differs between males and females. Research has suggested both direct and indirect effects of education on life satisfaction among females, but only indirect or reduced effects among males (Nikolaev, 2018; Salinas-Jiménez & Salinas-Jiménez, 2013). Such findings may also explain why no direct effects of intelligence were identified in the univariable MR. However, investigation into sex differences was not possible using two sample genetic data.

The second part of this study therefore uses observational data to provide further insight into possible underlying pathways driving causal associations between educational attainment and wellbeing, and between intelligence and wellbeing. In particular, Part 2 of this Chapter aims to:

- Replicate associations between educational attainment and wellbeing, and between intelligence and wellbeing using observational data.
- Investigate possible sex differences in effects of educational attainment and intelligence on wellbeing.
- Investigate whether intelligence and wellbeing are best captured by a non-linear relationship.
- Investigate the extent to which the association between intelligence and wellbeing is moderated by educational attainment.

6.9 Methods

6.9.1 Sample

The study used to conduct analyses was the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013). This cohort was described in detail in Chapter 2. Participants included were those who completed a measure of educational attainment at age 26, an intelligence assessment at age 8, as well as relevant wellbeing measures at age 26 (see Figure 6.3). These measured are described in detail in the following section.

Approximately 52% of ALSPAC participants alive at one year of age went on to complete the intelligence assessment at 8 years of age (*n*=7,258). Of these, data on wellbeing were available for 3,179 (44%) participants aged 26. Educational attainment was also assessed at 26 years, with 4,013 participants completing the relevant education questions, and 3,788 completing both the education and wellbeing measures. In total there were 2,844 participants with complete data on intelligence, wellbeing, and educational attainment. The wellbeing of these participants with complete data was not significantly different to those who only completed the wellbeing scales and not the intelligence or educational attainment measures (see Table 6.5). There were also no differences in levels of subjective happiness or life satisfaction between participants with only educational attainment or only intelligence data (Table 6.5). To therefore maximise available data, initial analyses were conducted on separate subsamples of participants with intelligence and wellbeing data (*n*=3,179), and with educational attainment and wellbeing data (*n*=3,788). Comparisons between these two subsamples and individuals missing revealed that those missing were more likely to be male, non-white, and from more disadvantaged backgrounds (Table 6.6). The possible impact of attrition was therefore explored in further analyses, details of which are described below.

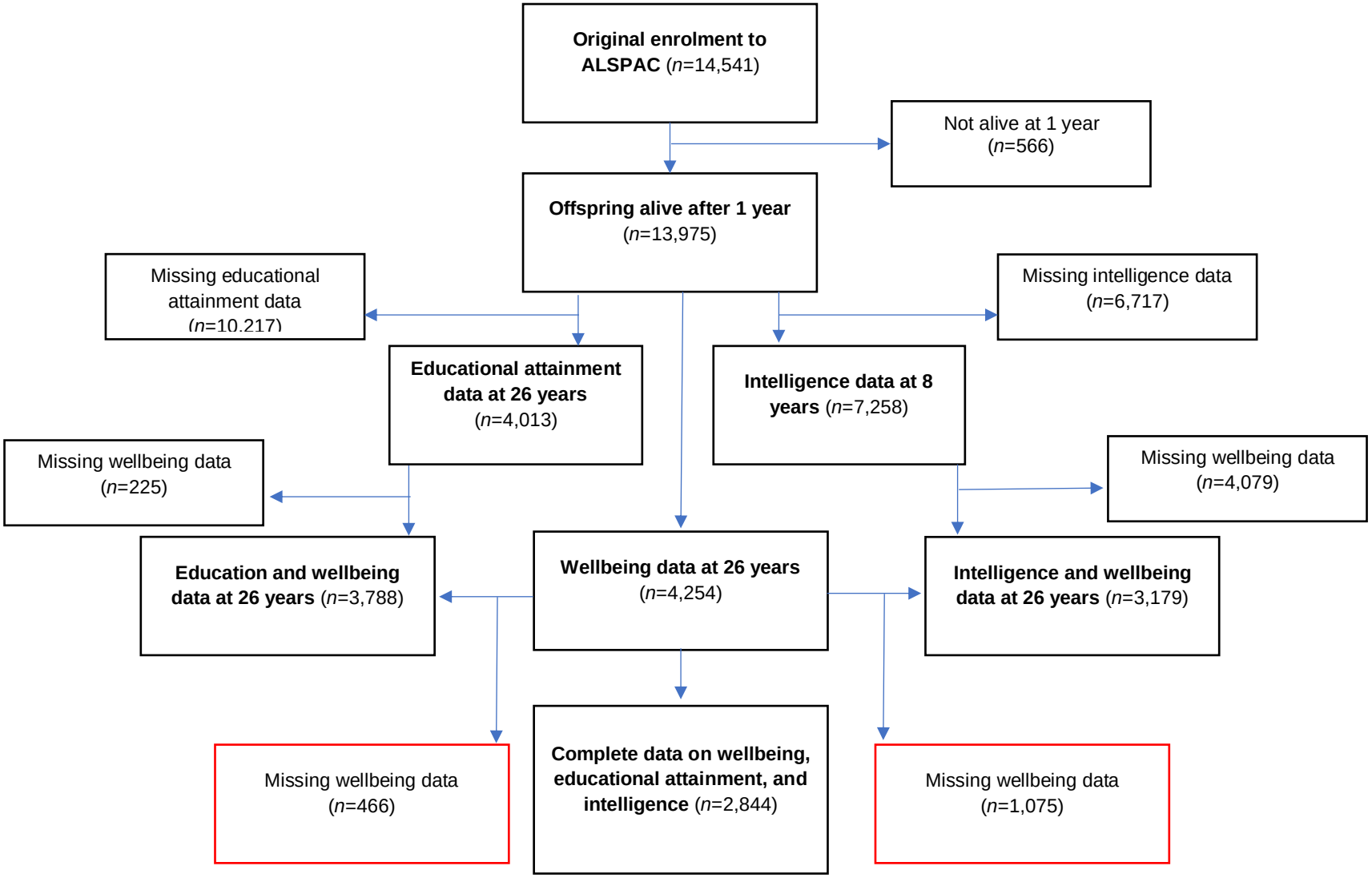

Figure 6.3: *Flowchart of data availability in ALSPAC for the current study. Boxes in red represent data imputed during multiple imputation*

Table 6.5: Comparison of main variables between subsamples

	N	Sex	Subjective Happiness	Life Satisfaction	University degree	Intelligence
Subsample		**% Female**	**Mean, SD**	**Mean, SD**	**% With degree**	**Mean, SD**
Wellbeing only[a]	4,254	65.9	4.88 (1.29)	24.05 (6.98)	-	-
Education and wellbeing[b]	3,788	66.1	4.89 (1.28)	24.17 (6.96)	64.0	
Intelligence and wellbeing[c]	3,179	64.3	4.90 (1.27)	24.33 (6.89)	-	107.68 (16.03)
Complete data[d]	2,844	64.6	4.92 (1.27)	24.37 (6.84)	66.6	107.82 (16.05)

Note:

[a]Data on subjective happiness and life satisfaction at 26 years.

[b]Data on educational attainment, subjective happiness, and life satisfaction at 26 years.

[c]Data on intelligence at 8 years, and subjective happiness and life satisfaction at 26 years.

[d]Data on educational attainment at 26 years, intelligence at 8 years, and subjective happiness and life satisfaction at 26 years.

Table 6.6. Selective attrition for educational attainment and intelligence

	Educational attainment			Intelligence		
	Available[a]	Wellbeing not available[b]	Education and wellbeing not available[c]	Available[d]	Wellbeing not available[e]	Not available in ALSPAC[f]
Variables[±]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Sex						
Male	1,283 (33.9)	169 (36.3)	6,302 (57.0)	1,134 (35.7)	318 (29.6)	6,451 (55.3)
Female	2,505 (66.1)	297 (63.7)	4,755 (43.0)	2,045 (64.3)	757 (70.4)	11,666 (44.7)
Ethnicity						
White	3,236 (96.2)	395 (96.8)	8,619 (94.5)	2,864 (99.7)	767 (94.8)	8,515 (94.4)
Non-white	127 (3.8)	13 (3.2)	476 (5.5)	98 (0.3)	42 (5.1)	505 (5.6)
Mother education						
O level or less	654 (19.3)	80 (19.4)	932 (10.4)	627 (21.0)	107 (13.0)	959 (10.3)
A level	963 (28.3)	99 (24.0)	1,798 (20.1)	900 (30.1)	162 (19.7)	1,861 (19.9)
Degree	1,782 (52.4)	233 (56.6)	6,194 (69.4)	1,460 (48.9)	555 (67.3)	6,516 (69.8)
Partner education						
O level or less	875 (26.2)	91 (22.5)	1,277 (15.0)	796 (27.1)	170 (21.2)	1,356 (15.2)
A level	949 (28.4)	146 (36.1)	2,128 (25.0)	885 (30.1)	210 (26.3)	2,192 (24.6)
Degree	1,514 (45.4)	167 (41.4)	5,102 (60.0)	1,261 (42.8)	420 (52.5)	5,355 (60.2)
Mother occupational status						
Professional	152 (5.0)	14 (3.9)	212 (2.7)	145 (5.4)	21 (3.0)	219 (2.7)
Managerial/technical	1,046 (34.6)	119 (33.1)	2,059 (25.9)	961 (36.0)	204 (28.7)	2,144 (25.8)
Skilled non-manual	1,243 (41.1)	163 (45.3)	3,422 (43.0)	1,092 (40.9)	314 (44.3)	3,573 (43.1)
Skilled manual	100 (3.3)	12 (3.3)	349 (4.4)	92 (3.4)	20 (2.9)	357 (4.3)
Partly skilled	407 (13.5)	44 (12.2)	1,532 (19.3)	328 (12.3)	123 (17.3)	1,611 (19.4)
Unskilled	74 (2.5)	8 (2.2)	374 (4.7)	54 (2.0)	28 (3.8)	394 (4.7)
Marital status						
Single	434 (12.6)	58 (14.0)	2,128 (21.4)	346 (11.5)	146 (17.1)	2,216 (21.4)
First	2,645 (76.6)	310 (74.7)	6,502 (65.5)	2,353 (78.1)	602 (70.5)	6,794 (65.6)
Marriage 2 or 3	237 (6.9)	27 (6.5)	624 (6.3)	195 (6.5)	69 (8.1)	666 (6.4)
Widowed/divorced/separated	137 (3.9)	20 (4.8)	671 (6.8)	120 (3.9)	37 (4.3)	688 (6.6)
Home ownership						
Mortgage/owned	2,891 (84.7)	323 (79.0)	6,855 (69.2)	2,598 (87.2)	616 (73.2)	7,148 (69.1)
Privately rented	174 (5.1)	26 (6.3)	796 (8.0)	130 (4.4)	70 (8.3)	840 (8.1)
Council rented	253 (7.4)	47 (11.5)	1,881 (19.0)	180 (6.0)	120 (14.3)	1,954 (18.9)
Other	96 (2.8)	13 (3.2)	375 (3.8)	73 (2.4)	36 (4.2)	398 (3.9)
Car ownership						
Yes	3,127 (95.5)	373 (93.7)	6,947 (88.8)	2,794 (96.1)	706 (92.4)	7,280 (88.9)
No	146 (4.5)	25 (6.3)	878 (11.2)	113 (3.9)	58 (7.6)	911 (11.1)
Mother depressed						
Yes	227 (7.0)	27 (7.0)	1,058 (11.8)	177 (6.2)	77 (9.8)	1,108 (11.9)
No	3,002 (93.0)	362 (93.0)	7,873 (88.2)	2,653 (93.8)	711 (90.2)	8,222 (88.1)

Smoked during pregnancy						
Yes	556 (16.1)	81 (19.5)	2,760 (28.4)	410 (13.6)	227 (26.5)	2,906 (28.6)
No	2,900 (83.9)	334 (80.5)	6,957 (71.6)	2,605 (86.4)	629 (73.5)	7,252 (71.4)
Parity						
0	3,408 (47.9)	213 (52.2)	4,175 (43.8)	1,477 (49.7)	367 (43.5)	4,320 (43.4)
1	1,201 (35.2)	129 (31.6)	3,303 (34.7)	1,021 (34.4)	309 (36.6)	3483 (34.9)
2+	576 (16.9)	66 (16.2)	2,054 (21.5)	474 (15.9)	168 (19.9)	2,156 (21.7)

Note:

[±] All variables were assessed by the mother of the target participant. Assessments took place between 18 weeks gestation and when the study participant was 8 months of age. More information about these variables is provided in Table 6.7. Parity refers to the number of pregnancies resulting in a live or stillbirth before the target participant was born. [a] Individuals with wellbeing data who also completed the educational attainment question at 26 years (*n*=3,788)

[b] Individuals with educational attainment data but not wellbeing data (*n*=466)

[c] Individuals in rest of ALSPAC without data on educational attainment and wellbeing (*n*=11,655)

[d] Individuals with wellbeing data who also completed the intelligence assessment at 8 years (*n*=3,179)

[e] Individuals with intelligence data but not wellbeing data (*n*=1,075)

[f] Individuals in rest of ALSPAC without data on intelligence and wellbeing (*n*=12,264)

6.9.2 Measures

6.9.2.1 Educational attainment

Educational attainment was captured at 26 years using responses to the item, 'Do you have a university degree?'[4]. This question was included in the Life@26 questionnaire which was sent to 9,230 (66%) participants of the ALSPAC cohort. In total, 4,029 completed the questionnaire, reflecting a 43.7% response rate. Answers to the educational attainment question included 'yes' (*n*=2,452), 'no' (*n*=1,377) or 'still at university' (*n*=200). Those who responded 'still at university' were excluded from analyses. This is because individuals at university at 26 years would not necessarily represent those who followed the typical educational trajectory. For example, individuals may have taken a break from education and returned, or re-taking courses. Including such individuals may therefore have skewed analyses or created noise between the current findings and those from the MR study. This is

4 While data on other educational qualifications were also collected during this questionnaire, this data has not yet been released by ALSPAC.

because the MR study was based on years of schooling, with the highest number of total years coded to reflect those who earned a PhD degree at university. This could not be guaranteed among the current cohort of individual's still studying due to the unavailability of further information.

6.9.2.2 Intelligence

Intelligence was assessed at the "Focus at 8" clinic using the Wechsler Intelligence Scale for Children (WISC-III, Wechsler et al., 1992). This was administered to a total of 7,488 children (average age = 103.8 months) and was the most up to date version at the time. The WISC is now in its fifth addition and remains the most widely used test of individual ability (Wechsler, 2014).

The WISC comprised of ten subtests and a forwards/backwards digit span test. The ten subtests included five verbal tests and five performance tests. The verbal tests aimed to capture the child's knowledge and comprehension by asking them questions about the meaning of different words, similarities between items, as well as mental arithmetic. The performance tests included picture arrangements, block designs and object assembly. The final overall IQ score represents the total scaled scores across verbal and performance tests which were calculated using the WISC manual. For the present analyses, scores were investigated on a continuous scale to explore possible linear and non-linear associations with wellbeing.

6.9.2.3 Wellbeing

Wellbeing measures at age 26 comprised of the Subjective Happiness Scale (Lyubomirsky & Lepper, 1999), the Satisfaction with Life Scale (Diener et al., 1985), and the Meaning in Life Scale (Steger et al., 2006). The current study focused on the Subjective Happiness Scale and the Satisfaction with Life Scale to ensure a close replication of the MR study, which used genetic information related to positive affect and life satisfaction (Baselman et al., 2019). The Subjective Happiness Scale captures global and subjective happiness using 4

items. The first two items ask how individuals characterise their happiness on a 7-point Likert scale ranging from ‘Not a very happy person’ to ‘A very happy person’. The second two items offer brief descriptions of happy and unhappy individuals and ask respondents to rate the extent to which each item describes them. These responses are also recorded on a 7-point Likert scale ranging from ‘Not at all’ to ‘A great deal’. The final item is reverse coded to ensure a higher overall score reflects greater subjective happiness, and a mean is taken across the four items. The scale overall has high internal consistency and test-retest reliability, and is suitable for different age, occupational, and cultural groups (Lyubomirsky et al., 1999).

Life satisfaction was assessed using the Satisfaction with Life Scale (Diener et al., 1985), which was described in detail in Chapter 2. Briefly, this scale is a 5-item measure that was designed to capture cognitive judgments of one’s life satisfaction as opposed to positive affect (Diener et al., 1985). Answers are coded so that a higher overall score reflects greater life satisfaction. Correlations between life satisfaction and subjective happiness were r=0.65. Both wellbeing measures were z-standardised to facilitate comparisons between the two. Results from the unstandardised measures can be found in Appendix 6.15.

6.9.3 Statistical analyses

All analyses were conducted in R studio 4.0.5 (R Core Team, 2021).

6.9.3.1 Main effects

To first replicate the MR findings of an association between educational attainment and wellbeing, and between intelligence and wellbeing, separate linear regression models were first run. These analyses explored effects of educational attainment and intelligence on both subjective happiness and life satisfaction, resulting in 4 linear regression models. Analyses were then repeated including sex as a covariate. This was to align with the MR study which used GWASs that had been adjusted for sex. However, because there were more females in the current subsamples compared to males (see Table 6.5), an interaction term

(sex*exposure) was fit to the models. This enabled analyses to test for possible sex differences. All main effect analyses were corrected for multiple testing using Benjamini-Hochberg False Discovery Rate (FDR; Benjamini & Hochberg, 1995). This was based on a total of 62 tests to include models adjusted for attrition and missing data.

6.9.3.2 Non-linear effects

To check for possible non-linearity in analyses predicting wellbeing from intelligence, subsequent models included either a quadratic, cubic, or quartic polynomial terms. Such analyses were not possible for educational attainment as responses were binary. The decision to include three different polynomial terms was to understand which best described the data, as per previous research focused on mental health in young adulthood (Kwong et al., 2019). The model of best fit was determined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), as previously recommended (Singer & Willett, 2003). Further analyses were then conducted using spline regressions. Polynomial terms may not be flexible enough to capture the relationship between intelligence and wellbeing as they impose a global structure on all of the data. To overcome this, the distribution of the data can be divided into separate portions known as knots, and then a polynomial segment can be fit onto each of these. To run a spline regression, two parameters are needed: the degree of the polynomial and the location of the knots. These can be automatically determined using a Generalised Additive Model (GAM), which was run in the present study using the 'mgcv' R package (Wood, 2006).

6.9.3.3 Interaction effects

To further investigate possible factors driving associations between the exposures and wellbeing, regression models including an interaction term (educational attainment*intelligence) were subsequently run. These were used to provide insight into the extent to which the relationship between intelligence and wellbeing is moderated by

educational attainment and vice versa. Two interaction models were run, one predicting subjective happiness and one predicting life satisfaction.

Power to detect interactive effects was calculated using the same procedure described in Chapter 5 (see formula below). This uses information about predicted interaction effect I ($ß^2_{int}$), the correlation between the outcome variable and predictor (r^2_{yx}), and the correlation between the outcome variable and the moderator (r^2_{ym}). Correlation estimates between educational attainment and wellbeing, and between intelligence and wellbeing were taken from Clark et al., (2021). However, because the current study is the first to investigate interactions between intelligence and educational attainment in predicting wellbeing, interaction estimates were based on correlations in the current sample. In particular, the correlation between intelligence and life satisfaction among those with a university degree (r = 0.049) was subtracted from correlations among those without a degree (r = -0.004). Running the formula below resulted in f^2 =0.01075833. When plugged into G*Power, calculations revealed that a sample size of n=1,018 would be necessary to achieve 80% power. The sample size of the complete cases was n=2,844, meaning there was sufficient power to detect interactive effects.

$$f^2 \approx \frac{\beta^2_{int}}{1 - r^2_{yx} - r^2_{ym}} \longrightarrow f^2 \approx \frac{(0.049 - -0.004)^2}{1 - (0.42^2) - (0.75)^2}$$

6.9.3.4 Sample attrition and selective participation

The number of participants with data on wellbeing and either intelligence or educational attainment was lower than the number of individuals with just the wellbeing data (see Figure 6.3). There are two key approaches to dealing with missing data (Seaman et al., 2012), one is multiple imputation (MI), which was described and used in Chapter 5, and the other is inverse-probability weighting (IPW) (Höfler et al., 2005).

Unlike multiple imputation which uses variables predictive of missingness to impute missing values, IPW uses information related to missingness to investigate the influence on selective participation. This is done by weighting estimates among complete cases by the inverse of their probability of being a complete case (Seaman & White, 2013). These weights are calculated from the full sample and then modelled into the regression to ensure that any effect of the exposure on the outcome is weighed by the likelihood of individuals being selected into the sample. As an example, if the likelihood of completing a measure related to higher education is predicted by parental education, data on parental education could be used from the full sample to calculate weights for the sub-sample of individuals with the outcome data. Such an approach helps to ensure the data is representative of the whole sample and reduces the risk of collider bias. Collider bias can occur when a variable is related to the likelihood of being sampled (Griffith et al., 2020). For example, parental education is related to educational attainment and has been shown to predict the likelihood of participation in ALSPAC (Cornish et al., 2015), conditioning on this variable could therefore introduce collider bias and distort subsequent associations between educational attainment and wellbeing.

Previous studies investigating intelligence in ALSPAC have used both IPW and multiple imputation to example possible effects of attrition (Cornish et al., 2015). Some have suggested that imputing missing values in individuals with near-complete data, as well as adjusting for the exclusion of individuals may be the best approach to overcoming bias (Seaman & White, 2013). Follow-up analyses therefore explored the possible impact of attrition using IPW and multiple imputation. Multiple imputation was conducted using the Chained Equations (MICE) package (van Buuren & Groothuis-Oudshoorn, 2010). Based on Rubin's rules (Little & Rubin, 2014), 60 imputations were conducted. The variables selected to impute data can be found in Table 6.7. These were all variables that have been previously associated with missingness in ALSPAC and include factors such as maternal age and parity, smoking during the first trimester of pregnancy, as well as parental education and

occupational social class (Cornish et al., 2021; Houtepen et al., 2018; Mahedy et al., 2017). For the weighting procedure, the current study followed previous procedures and calculated weights for the IPW from regressions predicting having complete educational attainment or intelligence data using predictors of nonresponse (Schmidt & Woll, 2017). This was done using the 'ipw' package in R (Van der Wal & Geskus, 2011).

Table 6.7: Variables used for IPW and multiple imputation

	N	Question answered by	Age of study child at assessment	No. of items	Item scoring
Maternal age	13,874	Mother	18 weeks gestation	1	Answers range from 15 to 43+
Parity	12,940	Mother	18 weeks gestation	1	Answers range from 0 to 22.
Maternal smoked during first 3 months of pregnancy	13,173	Mother	18 weeks gestation	1	0=No 1=Yes
Mother depressed	12,160	Mother	18 weeks gestation	10	Answers range from 0 to 30, with a higher score meaning more depressed
Marital status	13,378	Mother	14 weeks gestation	1	1=Single, 2= First marriage, 3=Second marriage, 4= Widowed/Separated/Divorced
Mother education	12,323	Mother	32 weeks gestation	1	1=Degree, 2=A level, 3=O level or less
Partner education	11,845	Mother	32 weeks gestation	1	1=Degree, 2=A level, 3=O level or less
Mother occupation	10,970	Mother	18 weeks gestation	1	1=Professional, 2=Managerial and technical, 3=Skilled non-manual, 4=Skilled manual, 5=Partly skilled, 6=Unskilled
Partner occupation	9,407	Partner	18 weeks gestation	1	1=Professional, 2=Managerial and technical, 3=Skilled non-manual, 4=Skilled manual, 5=Partly skilled, 6=Unskilled
Financial difficulties	11,994	Mother	32 weeks gestation	1	0 to 15, with 15 indicating more financial difficulties.
Crowding index	13,084	Mother	14 weeks gestation	1	Calculated by diving number of people living in household by number of bedrooms. Scores range from 0-4, with higher scores indicative of more crowding.
Home ownership	13,321	Mother	14 weeks gestation	1	0=Mortgage/owned, 1=Privately rented, 2=Council rented, 3=Other
Car ownership	11,098	Mother	8 months	1	1=Yes, 2=No

Note: N refers to the number of respondents at the time of assessment in ALSPAC.

6.10 Results

6.10.1 Descriptive data

Among participants with data on educational attainment and wellbeing, approximately 64.5% had a university degree. This figure increased to 66.7% when considering individuals with complete data on intelligence also. These figures are just slightly higher than those derived from the general population at the time of assessment, with approximately 63% of individuals graduating with an undergraduate degree in 2018/19 (HESA, 2020). Of those with complete data, 64.7% of participants who had a university degree were female, and 64.2% of individuals without a university degree were female. Individuals who had a university degree scored significantly higher on the intelligence test at 8 years old (*mean*=112.21, *SD*=14.75, *range*=62-148) compared to individuals without a university degree (*mean*=99.07, *SD*=14.93, *range*=45-138), according to a Welch two sample t-test, $t(1879)=-22.2$, $p<0.001$. Male participants also scored significantly higher on average (*mean*=109.28, *SD*=16.74, *range*=45-148) than females (*mean*=106.79, *SD*=15.55, *range*=49-146), according to a Welch two sample t-test, $t(2197)=4.12$, $p<0.001$, with 17.7% of males scoring 1 SD above the mean compared to 12.9% of females.

Subjective happiness scores in the samples averaged 4.89 (*range* = 1 to 7), while life satisfaction scores averaged 24.25 (*range* = 5 to 35). Happiness scores were not significantly different among those with (*mean*=4.89, *SD*=1.27) or without (*mean*=4.89, *SD*=1.31) a university degree, but those with a degree had significantly higher life satisfaction scores (*mean*=24.78, *SD*=6.65) compared to those without a degree (*mean*=23.09, *SD*=7.36), $t(2591) =6.99$, $p<0.001$. For individuals scoring 1 SD above the mean on the intelligence scale, subjective happiness scores (*mean*=4.79, *SD*=1.27) were significantly lower than those scoring 1 SD below the intelligence mean (*mean*=4.98, *SD*=1.35). For life satisfaction, however, individuals with intelligence scores 1 SD above the mean were significantly higher (*mean*=24.99, *SD*=6.33) than those scoring 1 SD below the

intelligence mean (*mean*=23.78, *SD*=7.27). These combined findings suggest that individuals with a university degree or higher intelligence may not necessary be happier, but more satisfied with life.

6.10.2 Main effect analyses

Linear regression models revealed that having a university degree was not associated with subjective happiness (Table 6.8) but predicted increased life satisfaction. After including an interaction between sex and university degree status into the regression models, analyses revealed significant moderating effects of sex. Plots of the findings showed that females who completed university were more likely to experience increased wellbeing compared to males (see Figure 6.4). For subjective happiness, the direction of effects for the two sexes were in the opposite direction to one another. Females were more likely to experience positive benefits to their subjective happiness if they completed university, and males more likely to experience declines in subjective happiness (see also Figure 6.4). These findings were all closely replicated when using participants who had complete data on intelligence, and after adjusting for attrition using IPW and multiple imputation (see Table 6.8). All findings also remained after correction for multiple testing.

Analyses predicting intelligence revealed that as intelligence scores increased, subjective happiness declined, while life satisfaction increased (Table 6.8). After adding an interaction term between intelligence and sex, analyses revealed moderating effects of sex. In particular, interactions between sex and intelligence predicted increases in subjective happiness and life satisfaction (see Table 6.8). Plots of these findings produced similar patterns to those found for educational attainment, with males more likely to experience declines in subjective happiness as intelligence increases, and females more likely to experience increases. These plots can be found in Figure 6.4.

Overall, results were largely consistent using the complete cases and adjusted models, with analyses predicting subjective happiness more robust to multiple testing after correction for

attrition and missing data. Interactions between sex and intelligence, however, were no longer associated with the two wellbeing outcomes in models adjusted for IPW. To understand why this might be, follow-up analyses used two-proportions z-tests to investigate possible sex differences based on predictors of missingness (see Appendix 6.16). Findings revealed that among participants with intelligence and wellbeing data, females were more likely to have parents with a higher education background and were more likely to live with single-parent mothers. It is possible that after adjusting for such factors, the observed sex differences become less apparent. Such findings may suggest that the educational background of parents largely explains the relationship between higher intelligence and wellbeing among females.

Table 6.8: Linear regression results assessing associations between educational attainment and wellbeing, and between intelligence and wellbeing

	Unadjusted		Adjusted using IPW		Adjusted using multiple imputation (*n*=4,298)		Complete cases (*n*=2,844)	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Subjective happiness								
***Models 1 and 2*[a]**								
University degree	0.003 (-0.063, 0.070)	0.920	-0.020 (-0.102, 0.061)	0.624	-0.016 (-0.078, 0.046)	0.615	-0.022 (-0.098, 0.055)	0.581
Intelligence	-0.002 (-0.004, -0.000)	**.038**	-0.003 (-0.005, -0.002)	**4.58E-06**[†]	-0.003 (-0.004, -0.000)	**0.008**[†]	-0.002 (-0.005, -0.000)	**0.033**
***Models 2 and 3*[b]**								
University degree	-0.226 (-0.339, -0.113)	**9.18E-05**[†]	-0.218 (-0.352, -0.084)	**0.001**[†]	-0.242 (-0.350, -0.136)	**8.54E-06**[†]	-0.219 (-0.347, -0.091)	**7.98E-04**[†]
Sex	-0.186 (-0.298, -0.075)	**0.001**[†]	-0.095 (-0.213, 0.022)	0.111	-0.184 (-0.289, -0.078)	**6.63E-04**[†]	-0.139 (-0.270, -0.009)	**0.036**
University degree * Sex	0.347 (0.208, 0.486)	**1.05E-06**[†]	0.308 (0.139, 0.477)	**3.60E-04**[†]	.344 (.212, .475)	**3.08E-07**[†]	0.307 (0.147, 0.466)	**1.69E-04**[†]
Intelligence	-0.005 (-0.009, -0.002)	**0.003**[†]	-0.003 (-0.005, -0.001)	**0.003**[†]	-.006 (-.009, -.002)	**4.27E-04**[†]	-0.004 (-0.008, -0.000)	**0.027**
Sex	-0.475 (-0.957, 0.006)	0.053	-0.136 (-0.159, 0.423)	0.364	-0.493 (-0.913, -0.072)	**0.022**	-0.253 (0.760, 0.254)	0.329
Intelligence * Sex	0.005 (0.000, 0.001)	**0.029**	0.000 (-0.003, 0.002)	0.670	0.005 (0.001, 0.009)	**.013**[†]	0.003 (-0.002, 0.008)	0.223
Life satisfaction								

***Model 4 and 5*[a]**								
University degree	0.241 (0.176, 0.307)	**7.44E-13**[†]	0.200 (0.118, 0.281)	**1.66E-06**[†]	0.231 (0.169, 0.294)	**3.00E-15**[†]	.223 (.147, .299)	**1.04E-08**[†]
Intelligence	0.005 (0.002, 0.007)	**3.66E-05**[†]	0.004 (0.003, 0.006)	**2.66E-08**[†]	0.004 (0.002, 0.006)	**5.27E-06**[†]	.004 (.002, .006)	**2.40E-04**[†]
***Models 6 and 7*[b]**								
University degree	0.076 (-0.036, 0.188)	0.185	0.015 (-0.119, 0.148)	0.826	0.091 (-0.015, 0.197)	0.092	0.070 (-0.056, 0.197)	0.276
Sex	-0.021 (-0.131, 0.089)	0.701	-0.034 (-0.151, 0.083)	0.568	-0.008 (-0.113, 0.097)	0.883	-0.008 (0.137, 0.121)	0.903
University degree * Sex	0.249 (0.111, 0.388)	**4.07E-04**[†]	0.281 (0.112, 0.449)	**0.001**[†]	0.214 (0.083, 0.345)	**0.001**[†]	0.235 (0.077, 0.393)	**0.004**[†]
Intelligence	0.002 (-0.002, 0.005)	0.340	0.004 (0.002, 0.006)	**4.21E-05**[†]	0.002 (-0.001, 0.005)	0.206	0.002 (-0.001, 0.006)	0.174
Sex	-0.418 (-0.898, 0.061)	0.087	0.182 (-0.115, 0.480)	0.230	-0.304 (-0.723, 0.115)	0.155	-0.199 (-0.703, 0.304)	0.439
Intelligence * Sex	0.005 (0.000, 0.010)	**0.019**[†]	-0.001 (-0.003, 0.002)	0.923	0.004 (0.000, 0.008)	**0.035**	0.003 (-0.001, 0.008)	0.158

[†]FDR.

Note: Sex coded as 0=Male and 1=Female, analyses therefore used male as the reference. In unadjusted models and models adjusted for IPW, n=3,788 for educational attainment and n=3,179 for intelligence.

[a] Analyses included only the exposure.

[b] Analyses included the exposure, sex, and exposure*sex.

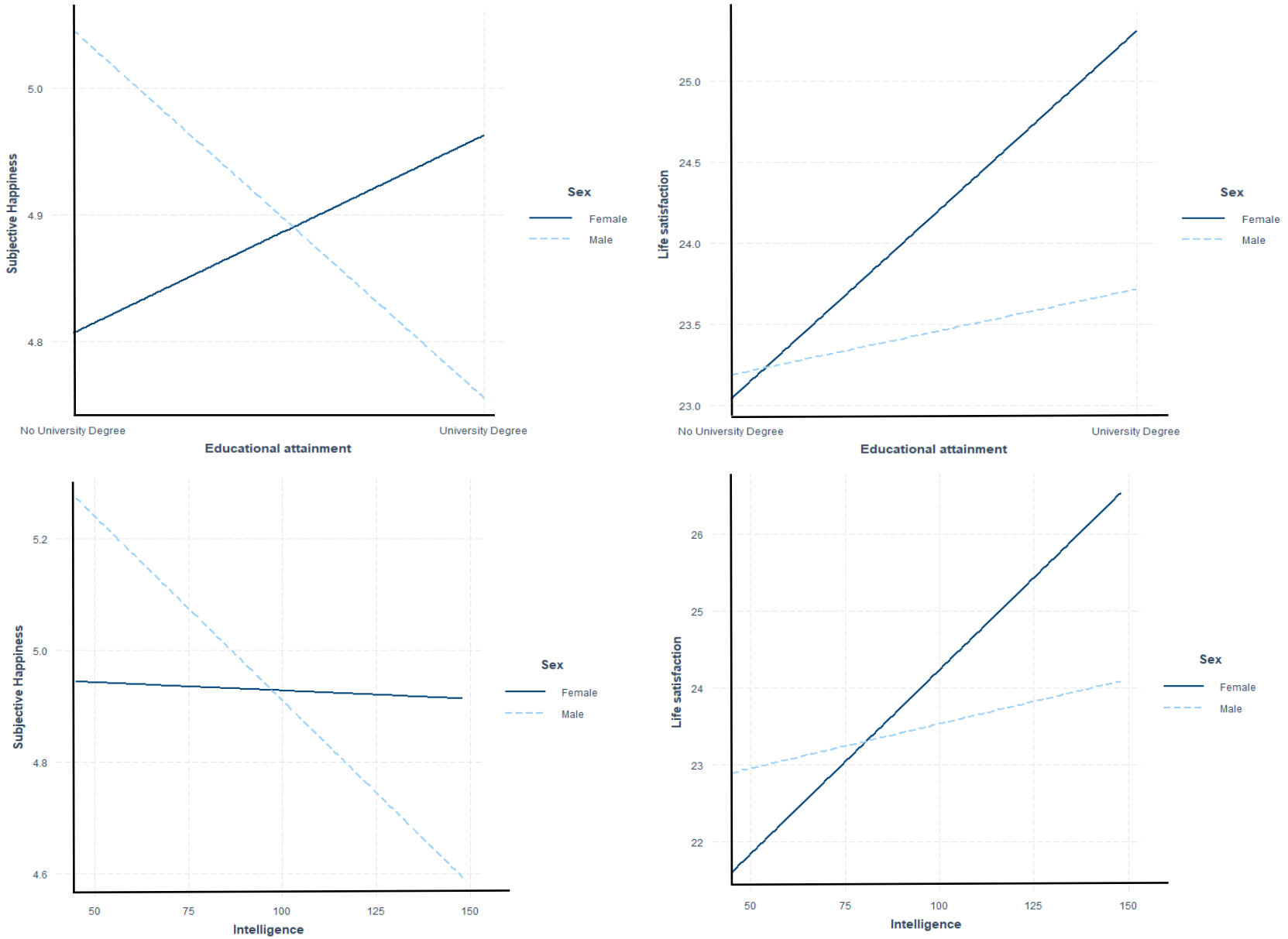

Figure 6.4: *Interactive effects of sex on associations between educational attainment and wellbeing, and between intelligence and wellbeing*

6.10.3 Non-linear effects

In addition to running linear regression models, analyses predicting wellbeing from intelligence also explored non-linearity. While plots of the findings suggested no obvious non-linear effects (see Figures 6.5 and 6.6) these were formally tested in regression models by fitting quadratic, cubic, and quartic terms, as well as running a spline regression. Findings suggested that increases in intelligence were not associated with subjective happiness or life satisfaction in the quadratic, cubic or quartic models (see Table 6.9). There was also no clear evidence that these models fit the data better than the linear models. Similarly, follow-up spline regressions using general additive models (GAM) also revealed no significant improvements in model fit. For subjective happiness, the RSME and R^2 in the GAM model was 0.986 and 0.001 respectively, and for life satisfaction it was 0.984 and 0.005. As evident in Table 6.9, these were not significantly different to the linear models, suggesting the GAM model did not fit the data better, or explain more of the variance.

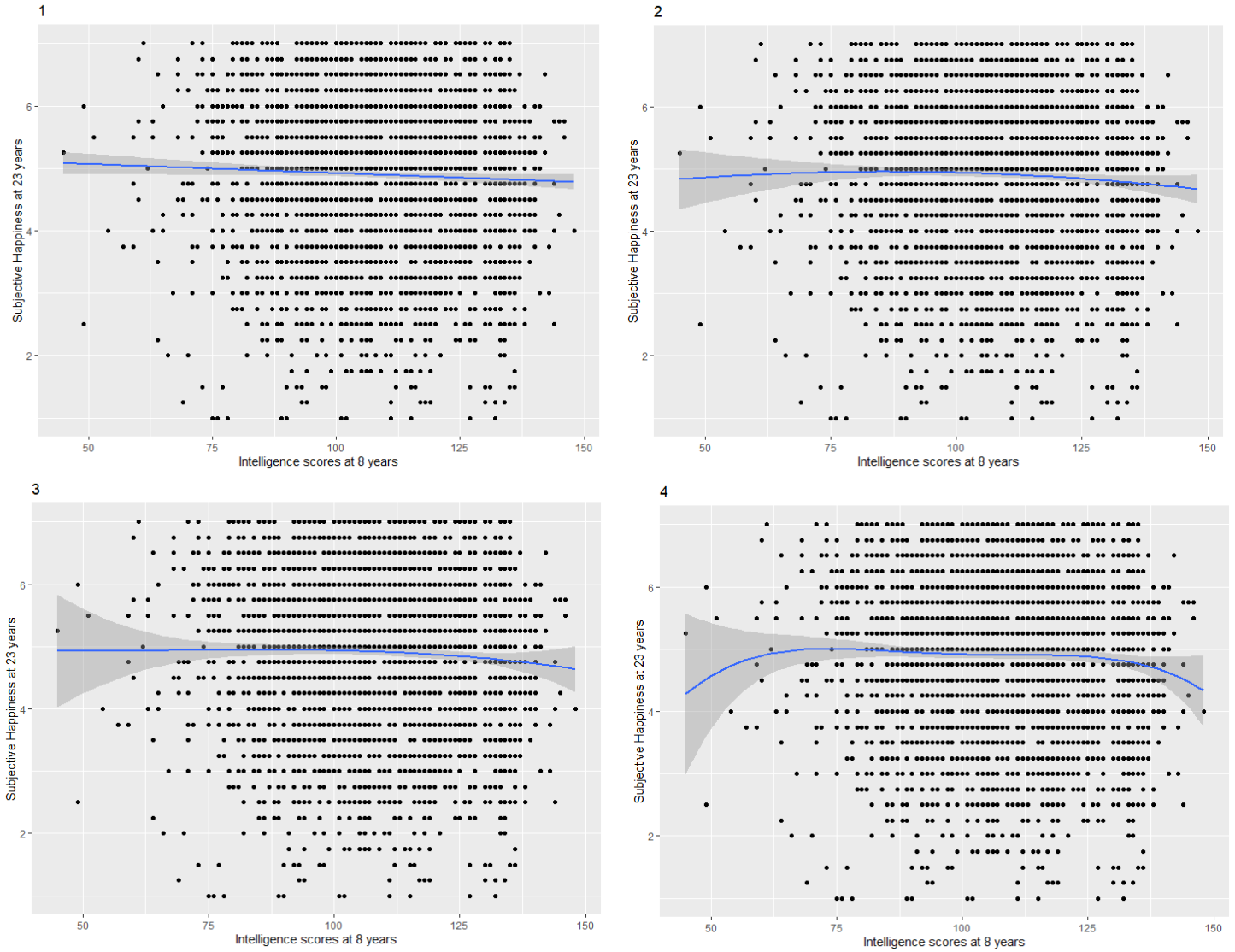

Figure 6.5: *Comparisons between linear (1), quadratic (2), cubic (3), and quartic (4) models for analyses predicting subjective happiness*

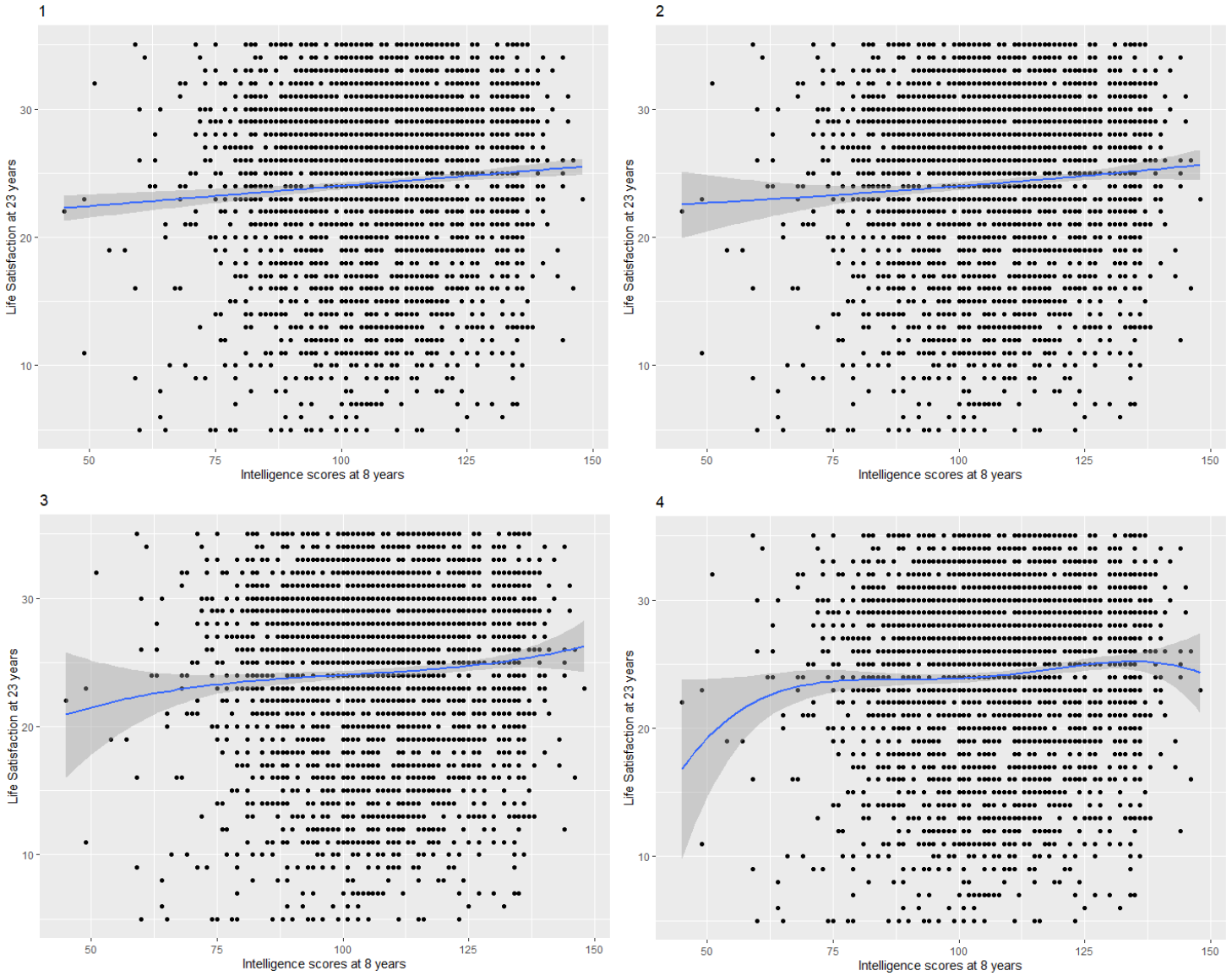

Figure 6.6: *Comparisons between linear (1), quadratic (2), cubic (3), and quartic (4) models for analyses predicting life satisfaction*

Table 6.9: Regression results from linear, quadratic, cubic and quartic models assessing associations between intelligence and wellbeing

	Linear model			Quadratic model			Cubic model			Quartic model		
	β	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**	**β**	**SE**	**P**
Subjective happiness												
Intercept (β0)	0.262	0.119	**0.028**	0.018	0.018	0.295	0.018	0.018	0.295	0.018	0.018	0.295
Intelligence (linear)	-0.002	0.001	**0.038**	-2.05	0.987	**0.038**	-2.05	0.987	**0.038**	-2.05	0.987	**0.038**
Intelligence^2 (quadratic)	-	-	-	-1.09	0.987	0.271	-1.09	0.987	0.271	-1.09	0.987	0.271
Intelligence^3 (Cubic)	-	-	-	-	-	-	-.238	0.987	0.809	-0.238	0.987	0.809
Intelligence^4 (Quartic)	-	-	-	-	-	-	-	-	-	-1.35	0.987	0.172
Adjusted R^2		0.001			0.001			0.001			0.001	
RMSE		0.987			0.986			0.986			0.986	
AIC		**8941.877**			8942.666			8944.607			8944.740	
BIC		**8960.070**			8966.923			8974.929			8981.126	
Life satisfaction												
Intercept	-0.460	0.119	**0.001**	0.025	0.018	0.149	0.025	0.018	0.149	0.025	0.018	0.149
Intelligence (linear)	0.005	0.001	**3.66E-05**	4.07	0.984	**3.67E-05**	4.07	0.984	**3.67E-05**	4.07	0.984	**3.67E-05**
Intelligence^2 (quadratic)	-	-	**-**	0.237	0.984	0.809	0.237	0.984	0.809	0.237	0.984	0.809
Intelligence^3 (Cubic)	-	-	**-**	-	-	**-**	0.769	0.984	0.435	0.769	0.984	0.435
Intelligence^4 (Quartic)	-	-	**-**	-	-	**-**	-	-	**-**	-1.59	0.984	0.106
Adjusted R^2		0.005			0.005			0.005			0.005	

RSME	0.984	0.984	0.984	0.984
AIC	**8925.193**	8927.135	8928.524	8927.904
BIC	**8943.386**	8951.392	89.58.846	8964.290

RMSE = Residual standard error; AIC = Akaike information criterion; BIC = Bayesian information criterion.

6.10.4 Interactive effects

When investigating possible moderating effects of educational attainment on associations between intelligence and wellbeing, findings revealed no interactions in analyses predicting subjective happiness (β=0.001, *SE*=0.003, *p*=0.721) or life satisfaction (β=0.024, *SE*=0.018, *p*=0.197). However, as evident in Figure 6.7 (right hand panel), this effect was not found for those lower in intelligence, providing some evidence of possible moderation. As evident by the y-axis, however, such effects are likely to be small.

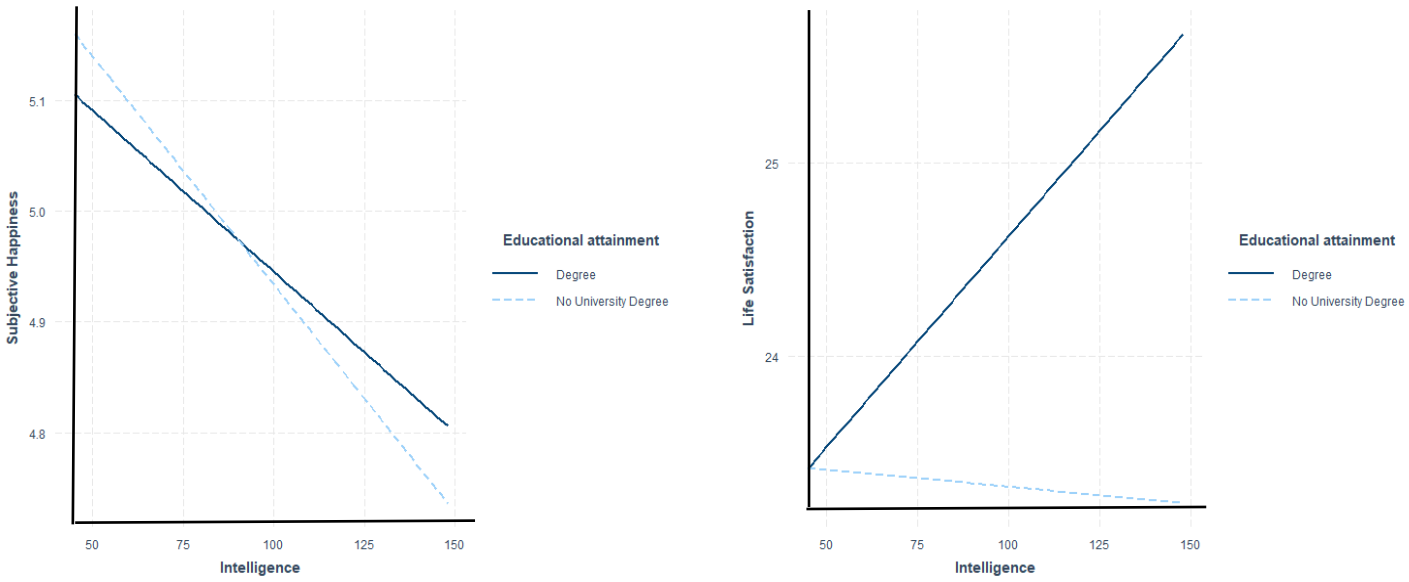

Figure 6.7: *Interactions between educational attainment and intelligence in predicting wellbeing*

6.11 Discussion

This study used observational data to provide further insight into the relationships between educational attainment and wellbeing, and between intelligence and wellbeing. Initial tests of the hypotheses provided some support for the MR study in Part 1 of this Chapter by demonstrating that educational attainment is positively associated with life satisfaction, and intelligence is negatively associated with subjective happiness. Unlike the MR study, the relationship between intelligence and life satisfaction was positive rather than negative. Further exploration into possible sex differences provided some evidence that females benefit more from higher education and intelligence than males in terms of wellbeing. However, there was no evidence to suggest associations were non-linear, or driven by interaction effects. These findings are interpreted in more detail below.

6.11.1 Main effects of educational attainment and intelligence

Analyses exploring the separate main effects of educational attainment and intelligence revealed partly consistent findings to those found in the MR study. In particular, having a university degree was positively associated with life satisfaction, while higher intelligence was negatively associated with subjective happiness. However, findings also revealed no main effects of having a university degree on subjective happiness, and suggested there is a positive association between intelligence and life satisfaction. These two latter findings were not found in the MR study which revealed only positive effects of educational attainment, and negative effects of intelligence, on wellbeing outcomes.

Differences between the current findings and those from the MR study likely arise from a number of factors. Unlike the MR study, which adjusted for mediating effects of years of schooling, the observational findings using intelligence as the predictor may have been confounded by further education. It is possible that higher intelligence encouraged further study, which served to increase satisfaction with life. This may explain the positive associations between intelligence and life satisfaction reported in this study but not in Part 1.

It is also possible that no main effects of having a university degree on subjective happiness were detected due to only assessing one educational qualification. Educational attainment in the MR study was based on total years of schooling. Thus, it is possible that positive effects on subjective happiness are driven by those who continue their education after getting their first degree.

Another fundamental difference between this study and the MR findings is that the observational results are restricted to a specific life stage. In contrast, MR estimates are based on effects of the exposures across the lifetime (Davies et al., 2017). As such, replication of the current study using cohorts assessed at different ages could result in different estimates. This may explain why the current study detected subtle differences between predictors of life satisfaction and subjective happiness where the MR study did not.

Unlike subjective happiness, life satisfaction captures cognitive evaluations of one's life. When reporting on life satisfaction, participants are therefore required to draw comparisons between their actual and desired life situation. It is possible that positive effects of educational attainment and intelligence on life satisfaction therefore reflect the fulfilment of years of hard work. Indeed, findings have shown that factors related to individual prosperity, including income and possessions, predict increased life satisfaction but not feelings of happiness (Diener et al., 2010). Measures of subjective happiness do not require cognitive processing but capture immediate and accessible feelings of pleasure. Such feelings may be less influenced by the accumulation of factors gained from education and more influenced by immediate sensations like perceived general health (Wang et al., 2020). It is possible that young adults in the current study, who may have been transitioning into their new role in either employment, parenthood, or other life domain (Osgood et al., 2005), face increasing stress due to identity changes and a lack of external guidance (Schwartz et al., 2005). This could have resulted in lower happiness levels at that time. Thus, it is possible that further

investigation into the role of educational attainment on subjective happiness at earlier or later stages of life may lead to different estimates.

6.11.2 Sex differences in effects of educational attainment and intelligence

In addition to highlighting potential differences between predictors of life satisfaction and subjective happiness, the current study also provided evidence of possible sex differences. In particular, while similar trends were noted for life satisfaction, models predicting subjective happiness revealed it to be greater among female graduates relative to female participants without a degree, with such effects reversed among males. Males with a university degree were shown to have lower subjective happiness compared to males without a degree. Such opposing results for male and female graduates may have masked any main effects of educational attainment on subjective happiness.

This is supported by the larger effect estimates of the interaction term between sex and educational attainment relative to the main effects in models predicting subjective happiness. Such findings, however, should be interpreted with some caution as it is possible that findings were driven by the representativeness of the samples. Females who provided data on educational attainment were more likely to have parents educated to degree level compared to males (see Appendix 6.16), and there were more female graduates in total (64.7%) relative to male graduates (35.3%). Similar sex differences have emerged previously, with female enrolment at university estimated to be 56.6% in 2018 (Hewitt, 2020). These findings may have biased effects of educational attainment among females towards the exposure-outcome association.

Despite this, sex differences in effects of educational attainment on wellbeing replicated in analyses adjusted for sample attrition and missing data. Similar patterns of sex differences have also emerged previously, with positive associations between years of schooling and happiness shown to be 50% larger in magnitude among females relative to males (Nikolaev, 2018). It is possible that this reflects the increased socialising that occurs in higher

education. Studies have shown that effects of socialising on happiness are greater for females compared to males (Kroll, 2011). While these sex differences were not studied in the context of educational attainment, it is possible that these influences may contribute to greater happiness among female graduates.

Another possibility relates to changes in health behaviours that occur through education. Female graduates have been shown to engage in more physical activity compared to their less educated counterparts (Tran et al., 2021). These health behaviours have been shown to be sex specific, with more educated females but not males at a reduced risk of obesity (Amin et al., 2013; Li & Powdthavee, 2015). Given the positive associations between BMI and wellbeing (Wootton et al., 2018) and the importance of self-rated health on life satisfaction (Wang & Haworth, 2020), it is possible that sex differences in health behaviours contribute to the differential gains in the impact of education on wellbeing.

When considering sex differences in the context of intelligence, findings revealed similar effects in models predicting subjective happiness. Males higher in intelligence were more likely to report lower happiness than males lower in intelligence. The opposite was found for females higher in intelligence, who reported increased subjective happiness. These findings must also be considered in relation to the differences between the sexes as females with intelligence data were also more likely than males to have highly educated parents (see Appendix 6.16. There may also be underlying sex differences in intelligence levels that could have driven effects. Evidence suggests that the average male IQ is four points higher than the average female IQ (Lynn, 1994). The current findings provide support for this by demonstrating higher intelligence scores among males relative to females, with 17.7% of males scoring 1 SD above the mean compared to 12.9% of females. It is possible that such differences generated more power to detect effects of higher intelligence in the male sample. This could explain the stronger negative main effect of intelligence in analyses including sex compared to those based on a combined sample. Such findings, however, should be

interpreted with some caution as there are likely many factors that contribute towards differences between male and female intelligence. The interaction effects between intelligence and sex were also much smaller than those found for educational attainment.

6.11.3 Non-linear and interactive effects

Analyses investigating possible non-linearity revealed that associations between intelligence and wellbeing most likely reflect a linear relationship. Such findings imply that life satisfaction is greatest among those with higher intelligence, while subjective happiness may be greater among those lower in intelligence. These latter effects, however, were small and largely accounted for by sex differences. As such, the combined findings suggest that those at the higher end of the intelligence scale are no more at risk of poorer wellbeing than those with average intelligence. Such a finding does not align with previous research which proposed an added risk for affective and psychological disorders among individuals high in intelligence (Karpinski et al., 2018). This study was based on a sample who had an average age of 53. It is therefore possible that negative effects of intelligence emerge later on. This could also explain why the MR findings, which capture effects of intelligence across the lifespan, detected a negative impact of intelligence on wellbeing. Further research with information on wellbeing in older cohorts could explore this possibility.

When investigating whether having a university degree moderates the impact of intelligence on wellbeing, findings revealed no clear interaction effects. Plots of the findings, however, suggested that life satisfaction is greater among highly intelligent individuals with a degree compared to highly intelligent individuals without. Such differences in wellbeing were not found for those at the lower end of the intelligence scale, suggesting a unique benefit of having a university degree for those high in intelligence. This may be driven by the greater educational accomplishments of those higher in intelligence compared to those with lower intelligence. Intelligent individuals may have been more likely to thrive at university which may have increased perceptions of self-competence and enabled individuals to continue to

succeed post-university. While these interactive effects were small and non-significant, it is possible that there may be subtle moderating effects that may explain why the current influences of intelligence differ to those reported in the MR study.

6.11.4 Strengths and limitations

Key strengths of this study lie in the adjustments for attrition and selective participation. Comparisons between participants and those missing revealed that individuals with educational attainment or intelligence data were more likely to come from socioeconomically advantaged backgrounds (Table 6.6). While the cohort as a whole were less likely to have highly educated parents, comparisons between sexes revealed that females on average had more educated parents compared to males (see Appendix 6.16). As mentioned in Part 1, these parental influences can impact the educational outcomes of the offspring (Wang et al., 2021). By replicating analyses using inverse probability weights, estimates were adjusted such that overrepresented participants were down weighted. Results from these analyses revealed slightly attenuated but consistent findings. This helps to minimise the potential for bias and ensured adjustment for potential collider bias (Griffith et al., 2020).

Some limitations of the study, however, should be noted. First, educational attainment data were only available for university degree completion. While detailed information was collected on educational qualifications in ALSPAC for this age group, this data has not yet been released. Analyses were therefore unable to explore non-linear or cumulative effects of years of schooling, meaning it is not possible to ascertain whether a particular level of education confers an advantage or disadvantage for wellbeing. Such knowledge could have important implications for guiding and supporting students who continue their education to post-graduate level. Previous findings have suggested that more years spent in education predicts marginal positive changes in wellbeing (Nikolaev, 2018). However, such findings were derived from an Australian cohort of males and females combined. It is therefore not known how effects may differ between sexes and across nations.

Replication in other countries is particularly crucial as the average number of years spent in education differs worldwide (Lee et al., 2018), and there exist significant global differences in wellbeing between sexes (Ruggeri et al., 2020). Generalisation across studies may therefore not be appropriate. In addition to this, there are likely cohort effects that may contribute to differences in findings over time. The current study was based on a cohort of participants who were born between 1991 and 1992. As such, those following the typical education trajectory would have graduated from university in either 2012 or 2013. Findings have shown that the time at which an individual graduates can predict wellbeing, with those graduating in times of higher unemployment more likely to have lower life satisfaction (Cutler et al., 2015). Research has also suggested declines in subjective happiness over time (Jebb et al., 2020). It is therefore crucial that when interpreting associative observational results related to wellbeing that researchers are mindful of the time and context in which it was assessed.

As well as acknowledging possible cohort effects, as noted above, it is also important to acknowledge the age at which wellbeing was assessed. Participants in the current study completed wellbeing measures at 26 years. This is four years after most individuals would have graduated from university. Research has shown that the gap in happiness between the educated and less educated widens as individuals age, with happiness starting to increase at around the age of 35 (Nikolaev & Rusakov, 2015). This is suggested to reflect a time at which the uncertainties and student loan debt repayments may be reduced. Such factors may account for the observed negative association between male graduates and wellbeing in the present study. Although, it remains less clear why this effect may be specific to males.

Research could attempt to understand the current results further by considering educational achievement in addition to attainment. Unlike educational attainment, which is captured by years of schooling, educational achievement is assessed using test and examination results. Although highly correlated with cognitive ability (Deary et al., 2007), educational outcomes reflect more than just intelligence (Krapohl et al., 2014). Educational achievement was not

investigated in the present study due to data accessibility. However, it is important that further studies incorporate assessments of achievement to understand its impact on wellbeing, and its possible mediating role in associations between attainment and wellbeing, and between intelligence and wellbeing. Such research could help to identify those at greatest risk and provide further insight into sex differences. For instance, it is possible that individuals high in intelligence but who under achieve in school are most at risk of poorer wellbeing. Such findings may explain the negative impact of intelligence that was noted in the current study among males, who typically underperform in school in comparison to females (Mikk et al., 2012). This understanding of possible paths driving associations between educational attainment and wellbeing, and between intelligence and wellbeing could have important implications for interventions in schools.

6.11.5 Implications and future directions

The current findings encourage further study into possible paths underlying associations between educational attainment and wellbeing, and between intelligence and wellbeing. While the results from Part 1 and Part 2 of this Chapter suggest a small positive impact of educational attainment on wellbeing, the relationship between intelligence and wellbeing remains less clear. The MR study indicated a negative causal impact of intelligence on wellbeing that was independent of years of schooling. However, observational findings suggested this may be driven by underlying sex differences, with males high in intelligence more unhappy than intelligent females. As noted above, the differences between the MR findings and current study likely reflect a number of factors, and each approach has different strengths and limitations. Understanding and acknowledging these as well as the biases of each different method has been suggested as crucial when triangulating results (Hammerton & Munafò, 2021).

Triangulation refers to the use of multiple approaches with varying assumptions. By using both a genetic design and observational data, Part 1 and Part 2 of this Chapter were able to overcome limitations of the other to provide unique insight into the roles of educational attainment and intelligence in relation to wellbeing. While the MR study was able to control for reverse causality, estimates are not time-bound, meaning implications for intervention are less clear. The MR design was also unable to determine the extent to which effects of one exposure moderated the effects of the other, and the impact of possible selection bias. Follow-up research using observational data was therefore necessary to not only confirm the genetic findings, but to also aid understanding of time-specific effects and possible moderating and confounding factors. This provided some context for the causal associations identified in the MR study, and helped to underscore the importance of further study into underlying pathways.

Overall, the combined findings suggest that the path from educational attainment and intelligence to wellbeing is highly complex, with predictors of wellbeing likely to vary according to sex and age. Future research should pay particular attention to the context in which associations arise, and should consider using additional methods to further triangulate the findings. Possible methods could involve the use of structural equation models to further explore direct and indirect paths and possible confounding factors (De Stavola et al., 2015). This could involve tests of mediating and moderating factors beyond those considered in the present study, such as outcomes in adulthood known to moderate the impact of education

on wellbeing, including income, employment, marriage, children, and health (Powdthavee et al., 2015).

6.12 Chapter Part 2 summary

This chapter used observational data to study the relationships between educational attainment and wellbeing, and between intelligence and wellbeing. Findings revealed that higher educational attainment and intelligence predict higher life satisfaction among males and females. In contrast, sex differences likely underlie associations between educational attainment and subjective happiness, and between intelligence and subjective happiness. Further research is now needed to understand the different paths by which educational attainment and intelligence may facilitate improved wellbeing, and to understand how these paths may vary for males and females. This will provide further insight into why results may differ when using genetic and observational data.

Chapter 7: Discussion

The concept of resilience has received increasing attention over the last few decades (Masten, 2021). Yet despite the growing interest in positive adaptation, many have determined resilience by the absence of psychopathology and not the presence of good wellbeing (Cosco et al., 2017). This thesis therefore explored the importance of wellbeing as an indicator of resilience, with a particular focus on functioning after peer victimisation. The key findings from each chapter are summarised in Table 7.1.

In this final chapter, I explore the novel contributions of the research in this thesis and its implications for the study of resilience. I also consider the general limitations of my studies and suggest further directions for the future of resilience research.

Table 7.1: Main findings from each chapter and their implications for the study of resilience

Chapter	Main finding	Implications for resilience
3 - A multi-polygenic approach to understanding the risk of peer victimisation	A genetic tendency to spend more years in schooling is associated with a reduced risk of peer victimisation in childhood and adolescence. Predictors of the risk of peer victimisation may vary depending on the informant and age of the victim. However, further investigation using larger cohorts is necessary to confirm this.	Genetic information can be used to provide some insight into those most at risk of experiencing adverse events like peer victimisation. Targeting individual vulnerabilities, such as depressive tendencies, poor wellbeing, low cognitive abilities, and a higher BMI could help to prevent peer victimisation and thus reduce the risk of subsequent mental health problems.
4 - A polygenic approach to understanding resilience to peer victimisation	The increased risk of depression and poor wellbeing observed following peer victimisation is unlikely to be moderated by	Having a reduced genetic risk towards depression or poor wellbeing does not predict greater resilience following peer

	genetic liabilities towards these traits.	victimisation. The resilience observed among victims may therefore be explained by factors external to the individual.
5 - Resilience following adolescent victimisation: An exploration into protective factors across development	Having higher perceptions of scholastic competence in childhood moderates some of the negative effects of peer victimisation by encouraging greater wellbeing in adulthood. These protective effects were specific to mental wellbeing and were not observed for adult life satisfaction or depressive symptoms.	The findings highlight the importance of timing of protective factors by demonstrating that those most beneficial to adult wellbeing are likely to be in place prior to victimisation. The findings also underscore the importance of investigating predictors of both wellbeing and depressive symptoms when assessing resilience as it is likely that different intervention strategies will be required to reduce depressive symptoms and improve wellbeing.
6 Part 1 - An exploration into the causal relationships between education, intelligence, and wellbeing: A multivariable two-sample mendelian randomization study	Findings from this MR study revealed a positive causal impact of educational attainment on wellbeing, and a negative causal effect of intelligence on wellbeing. Wellbeing was shown to have a positive causal influence on both educational attainment and intelligence, with effects largely similar for the two.	The positive causal effects of wellbeing on educational attainment and intelligence were greater than those found using educational attainment or intelligence as a predictor of wellbeing. Implementing strategies that directly aim to improve wellbeing may therefore be more beneficial than those aimed at increasing wellbeing through educational attainment or intelligence.
6 Part 2 - A follow-up investigation into educational attainment, intelligence, and wellbeing	Having a university degree and higher intelligence predicted greater life satisfaction among male and female young adults. In contrast, sex differences likely underlie associations between educational attainment and subjective happiness, and between intelligence and subjective happiness.	This study provides insight into the importance of triangulation. It also encourages further research into possible paths by which educational attainment and intelligence may implicate wellbeing.

7.1 Genetic predictors of risk and resilience

Chapters 3 and 4 used genetic information to study predictors of risk and resilience. In particular, polygenic scores were used to understand whether a genetic liability towards certain traits can predict both the likelihood of peer victimisation, as well as resilience to its effects. The first study in Chapter 3 provided evidence that individuals genetically inclined to spend fewer years in schooling may be at an increased risk of peer victimisation in childhood and adolescence. Findings also suggested that a genetic liability towards depression, lower wellbeing, lower intelligence, and a higher BMI, may also heighten the risk of peer victimisation. These latter findings were less robust after correction for multiple testing, however, associations between peer victimisation and polygenic scores for depression and wellbeing were replicated in a different cohort in Chapter 4.

Chapter 4 investigated the extent to which polygenic scores for depression and wellbeing could be used to predict resilience following peer victimisation. No strong moderating effects were detected, meaning that the increased risk for poorer mental health and wellbeing following peer victimisation is unlikely to be a result of pre-existing vulnerabilities, as indexed by the included polygenic scores. Together, the results from these chapters imply that while genetic differences may heighten the likelihood an individual experiences an adverse event like peer victimisation, they cannot predict how an individual will react after such events. These findings should be interpreted in relation to the power of polygenic scores and the study design, as discussed below.

Compared to genetic methods like candidate gene studies, polygenic scores allow more of the variance to be explained than any single gene or genetic variant. This helps to increase power in smaller samples to detect gene-environment interactions (G×E). While this is crucial to research on resilience, in which study designs are often limited by smaller samples of participants exposed to adversity, polygenic scores alone currently capture a small percentage of the variance of complex traits (Lewis & Vassos, 2020). Further studies

exploring the interplay between genetic and environmental factors will therefore be bolstered by larger and more diverse genome-wide association studies (GWASs). This will help improve the predictive power of genetic variants and thus the ability to detect more subtle G×E in relation to resilience.

Research attempting to understand the paths to resilience will also benefit from more complex designs that jointly consider genetic susceptibility, adversity, and protective factors. Such research is starting to emerge in the fields of both health and resilience, with studies showing that certain lifestyle habits, such as regular physical activity and a healthy diet, can decrease the risk for cardiovascular disease even among those at a high polygenic risk (Khera et al., 2016). Research on Army soldiers has also revealed that buffering effects of unit cohesion on the likelihood of depression are apparent even among those at a high polygenic risk for depression (Choi et al., 2020). These findings highlight the value of using both genetic and environmental data to identify factors that matter for the most vulnerable. Such research, if applied to the study of peer victimisation, could have important implications for the treatment and support offered to foster resilience. These findings could also be used to inform protective factors that may only be effective for individuals with a certain genetic liability.

It is possible that a low genetic liability towards a risk factor alone is not predictive of resilience, as noted in Chapter 4, but the presence of a lower genetic liability coupled with protective factors in the environment. Chapter 5 provided insight into one possible protective factor in the context of peer victimisation. It was found that wellbeing was greater among victims who had higher scholastic competence in childhood. This was the only protective factor out of a possible 14 to produce such moderating effects. One explanation for this is that just as genetic liability may only take effect in the presence of a protective factor, protective factors may only have buffering effects among individuals with a certain genetic profile.

The Differential Susceptibility hypothesis proposes that some people are more sensitive to both positive and negative environments (Belsky et al., 2009). It is thus possible that genetically at-risk individuals who are subjected to peer victimisation and subsequently develop mental health problems, are also more likely to react more favourably to supportive environments. These protective effects from the environment, however, may only be detected when investigating individuals with increased sensitivity. Further resilience research could explore this possibility by accounting for sensitivity towards positive and negative environments. Such studies should consider using a combination of genetic and environmental measures to determine environmental sensitivity, which is suggested to be 47% heritable (Assary et al., 2020). It is possible that such research could identify environmental sensitivity as an important predictor of responsiveness to protective factors and thus intervention for individuals exposed to peer victimisation.

7.2 Pathways to resilience following peer victimisation

In an attempt to understand the different pathways from peer victimisation to resilience, this thesis used a combination of genetic and phenotypic data. Chapter 4 considered predictors of resilience using polygenic scores for depression and wellbeing, while Chapter 5 explored protective factors at the individual-, family-, and peer-level. In Chapter 6 Part 1 and Part 2, the potential role of two traits, educational attainment and intelligence, were also explored at the genetic and phenotypic level for associations with wellbeing. While findings have informed avenues for further study into factors that may confer increased risk and resilience, it is likely that such research would have been bolstered by combining additional sources of data.

Recent research has suggested there may be biological (Trotta et al., 2021), neurobiological (Quinlan et al., 2020), and epigenetic (Mulder et al., 2020) changes that result from experiences of peer victimisation. Epigenetic mechanisms refer to molecular changes in gene expression that can occur in response to environmental factors. As such, they have

been suggested as one path through which adverse experiences may impact the likelihood of resilience (Smeeth et al., 2021). One study investigating epigenetic changes in relation to peer victimisation revealed opposing patterns of DNA methylation between victims and non-victims (Mulder et al., 2020). While further experimental and longitudinal research is necessary to determine the implications of these differences, recent findings from another study have shown that epigenic changes can mediate the relationship between adversity and subsequent depressive symptoms (Smith et al., 2021). It is thus possible that exposure to peer victimisation results in changes at the epigenetic level, which then serve to heighten the subsequent risk for mental health problems.

In light of this research on peer victimisation, incorporating genetic, epigenetic, biological, neurobiological, and phenotypic data will be necessary to uncover more about the processes that lead to long-term adverse or resilient outcomes. It is likely that complex interrelations underlie these different systems. Thus, further research will need to not only consider the independent effects of these processes on peer victimisation and its associated outcomes, but also how they may operate simultaneously. This will likely require the combination of data from multiple studies with different levels of analysis.

In addition to adopting a multi-systems approach to the study of resilience following peer victimisation, the current findings also encourage further focused attention on the protective factor, scholastic competence. Chapter 5 demonstrated that victims more likely to demonstrate resilience were those who had higher perceptions of school ability in childhood. Chapter 6 Part 1 and 2 therefore tested associations between educational attainment and wellbeing for causality, and explored a possible role for intelligence. Findings revealed that while a tendency to spend more years in education is associated with greater wellbeing, higher intelligence may predict lower wellbeing. Both findings were small in magnitude, and follow-up analyses suggested that some effects may be driven by sex differences. Nevertheless, further investigation of these findings in the context of resilience is warranted

to understand whether individuals who remain in education after being subjected to peer victimisation are more likely to exercise resilience. Such findings could help to underscore the importance of educational attainment as protective for not only reducing the likelihood of peer victimisation, as implied in Chapter 3, but also for subsequent mental health and wellbeing. When combined with the MR findings from Chapter 6, such findings would implicate educational attainment as vital to the wellbeing of both the general population and individuals at risk. This could have important consequences for both policy and interventions to support victims of bullying.

7.3 Resilience as more than the absence of psychopathology

An important implication of the research in this thesis is that measures of both depression and wellbeing are necessary in the assessment of resilience following peer victimisation. This is based on findings from Chapters 4 and 5 which revealed that factors involved in reducing the risk of depression and ensuring positive wellbeing among victims are likely distinct. In Chapter 4, the risk of depressive symptoms following victimisation was not dependent on genetic risk, however, wellbeing was shown to be partially moderated by differences in polygenic scores for depression. These findings suggest the two outcomes of peer victimisation may be governed by unique underlying paths. In support of this, Chapter 5 noted protective effects of scholastic competence for wellbeing but not depressive symptoms following victimisation.

These findings suggest that multiple interventions are needed to both promote wellbeing and prevent mental illness following peer victimisation. This understanding is important as research has shown that individuals who avoid depression following peer victimisation are not necessarily maintaining good wellbeing (Armitage et al., 2021). Efforts to reduce the risk of depression following peer victimisation are therefore not guaranteed to improve wellbeing. Further research should thus continue to investigate moderators of both the risk of depression and wellbeing following peer victimisation to determine how both aspects of

mental health can be targeted. This will be key to supporting individuals to not only avoid depression, but to maintain good wellbeing and thus resilience.

In addition, research should also consider predictors of different levels of mental health functioning after peer victimisation. It is possible that while some protective factors may help individuals to flourish, which is defined as optimal wellbeing and no mental health disorder, other factors may help individuals move from a stage of floundering to languishing (see Figure 7.1 taken from Slade et al., 2010). While the goal of resilience research is to ultimately encourage flourishing, with some describing resilience as the capacity to 'flourish under fire' (Ryff & Singer, 2003), it is possible that some individuals need to progress through stages of floundering and languishing before they reach their complete state of mental health. These steps towards resilience could be investigated through the study of trajectories, which are explained in more detail below.

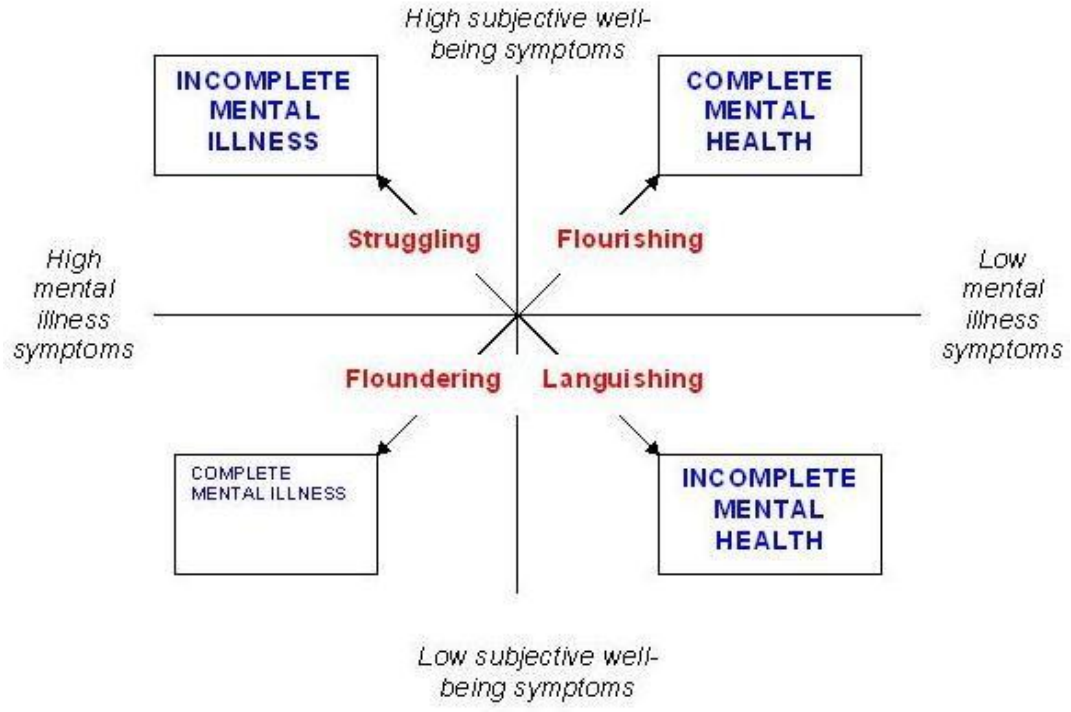

Figure 7.1: *A conceptual framework of the Complete State Model of Mental Health*

7.4 General limitations

While the limitations of each study were described in their respective chapter, this section explores some of the more general limitations of the current methodologies in relation to the study of resilience.

Resilience throughout this thesis has been operationalised as a process that results from the interaction of multiple factors. To study resilience, assessments of both depression and wellbeing were used as outcome variables. While this allowed the studies to overcome previous research focused on the avoidance of psychopathology to understand their translation to wellbeing, other aspects of mental health were not investigated. This limits the generalisation of the current findings as research has shown that peer victimisation not only increases the risk for depression and poor wellbeing (Armitage et al., 2021; Bowes et al., 2015) but also predicts increased anxiety (Stapinski et al., 2015), self-harm (Fisher et al., 2012), psychotic disorders (Wolke et al., 2013), as well as tobacco and illicit drug use (Moore et al., 2017) and poorer academic achievement (Samara et al., 2021). While it would not have been feasible to study all of these outcomes, it is important that further research into resilience following peer victimisation considers adjustment beyond depression and wellbeing. This could provide unique insight into different levels of resilience and could help to identify protective factors specific to certain outcomes. It is important however, that such research carefully considers how different outcomes are investigated. Findings from Chapter 5 pointed towards academic competence as a protective factor for later wellbeing. Studies investigating academic outcomes will therefore likely need to consider protective factors beyond those explored as moderators of mental health.

In addition to exploring outcomes beyond depression and wellbeing, further research is also necessary to determine whether protective factors exert similar effects on resilience in life stages beyond early adulthood. While Chapter 5 used longitudinal data to study the effects

of protective factors across development, investigating their impact at different time points was not possible as wellbeing was assessed for the first time in ALSPAC at 23 years. Investigating effects of risk and protective factors at specific time points is crucial to the development of targeted interventions. However, it may also be useful to study how these effects unfold over time.

Longitudinal research investigating resilience trajectories so far have covered adversities such as loss, military, and major life events (Galatzer-Levy et al., 2018). These studies have identified multiple trajectories of functioning following adversity, with each shown to be predicted by unique individual factors (Galatzer-Levy & Bonanno, 2012). Such findings suggest that different trajectories of mental health functioning after adversity do not share a common aetiology. Investigating heterogeneous trajectories have therefore helped to uncover protective factors that may be specifically involved in fostering resilience for individuals undergoing certain paths (Schultebraucks et al., 2021). No study, however, has yet considered trajectory outcomes following peer victimisation.

Investigating trajectories of mental health functioning both before and after experiences of peer victimisation will likely aid our understanding of time-independent protective factors, which were studied in Chapter 5, as well as steeling effects and post-traumatic growth. Post-traumatic growth is a similar concept to steeling effects and describes the process of benefitting directly from an adverse event (Tedeschi & Calhoun, 1996). Unlike steeling effects, post-traumatic growth involves a significant transformation of the individual from a specific adversity (Ogińska-Bulik & Kobylarczyk, 2016). It is therefore often investigated through the study of cognitive reappraisals, which have been implicated in responses to peer victimisation (Christensen et al., 2017). In contrast, steeling effects describe the desensitisation towards further adverse events, in addition to positive overall adjustment (Rutter, 2012). While studies that include longitudinal data on mental health and different

adversities could explore the potential for steeling effects, it is likely that qualitative designs will be needed to understand individual transformations resulting in post-traumatic growth.

The research in this thesis was predominantly based on two prospective cohort studies: the Quebec Newborn Twin Study (QNTS) and the Avon Longitudinal Study of Parents and Children (ALSPAC). Data from these studies allowed analyses to explore longitudinal associations and the role of genetics, and provided access to larger samples than typically gathered from experimental studies. Nevertheless, it is possible that in addition to investigating post-traumatic growth, an understanding of resilience may also require closer access to subjective experiences. Indeed, previous researchers have advocated for the use of qualitative methods as a means of understanding the construct of resilience (Ungar, 2003). It has been suggested that through offering more detailed descriptions of specific contexts, qualitative enquires help to contextualise resilience findings in relation to the risk, social, and cultural constructs. Such an approach could also be used to inform the degree of exposure to multiple other adversities.

The current research in this thesis focused on resilience following exposure to one particular adversity: peer victimisation. Compared to other forms of victimisation and maltreatment, such as sibling, partner, and sexual victimisation, victimisation by peers is the most common across childhood and early adolescence (Fisher et al., 2015; Radford et al., 2013). Focusing on this form of victimisation thus helped to ensure specific implications for intervention for a larger proportion of affected individuals. Nevertheless, exposure to multiple types of victimisation in adolescence is common (Fisher et al., 2015), with some evidence to suggest a cumulative negative impact of exposure to multiple forms of victimisation (Turner et al., 2006). This has led some to argue that addressing one single adversity is unlikely to have a substantial impact in reducing the risk of mental health problems (Kessler et al., 2010).

It is possible that these findings explain why few protective factors were identified throughout the research in this thesis. Victims exposed to peer victimisation may have also been

exposed to multiple other adversities, and therefore required different forms of support to foster resilience. Future studies could address this by incorporating measures like the Juvenile Victimization Questionnaire (Hamby et al., 2004) to determine exposure to a broad range of maltreatment and victimisation experiences. This could then be used to explore which protective factors may be necessary for individuals exposed to specific or multiple forms of victimisation. It should be acknowledged, however, that exposure to multiple adversities at different time points is likely to lead to a highly heterogenous sample. There is thus unlikely to be a one-size-fits all approach, meaning that personalised interventions are likely to be needed.

It is also important to note that despite findings of cumulative risk, strong independent effects of the different types of victimisation have been found in relation to the risk for mental health problems (Turner et al., 2006). Investigating exposure to specific victimisation experiences is therefore still likely to be important in identifying unique ways to foster resilience. Indeed, it is possible that different protective factors may be required for individuals exposed to either one or multiple adversities. By investigating total sum scores of different victimisation experiences, such distinct effects of protective factors may be masked. In addition, by combining and jointly investigating different forms of victimisation, the researcher assumes that each impacts the risk for mental health and wellbeing through the same underlying mechanisms. Such an approach has been criticised (McLaughlin & Sheridan, 2016), with researchers exploring alternative methods to investigate cumulative risk (Ettekal et al., 2019). The most appropriate model or analysis strategy, however, is likely to depend on the outcome under study and goals of the research (LaNoue et al., 2020). Further resilience research should therefore carefully consider the best approach to modelling exposure to multiple adversities.

7.5 Future of resilience research

The field of resilience has come a long way since interest began around 50 years ago (Garmezy, 1974). One of the key developments has been in the recognition of the multiple and complex interrelated systems that likely support resilience, with many now advocating for the integration of diverse levels of assessments, including biological, genetic, epigenetic, and phenotypic measures (Masten et al., 2021). With more open data available now than ever before, an important next step will be to determine how to use and combine such data to model complex interrelations between systems across time.

The future of resilience enquiry depends largely on researchers adopting a life course perspective. Tracking trajectories of functioning over time is crucial to investigating the dynamic nature of both resilience and the processes that facilitate it (Ioannidis et al., 2020). This will aid understanding of the factors that enable individuals to foster resilience at some time points and not others, and in some contexts but not others. Combining multi-dimensional and multi-level assessment measures within a longitudinal framework will require intricate statistical techniques and integration across disciplines. While complex and timely, this will be vital to facilitating early detection, prevention, and treatment of mental health problems (Ioannidis et al., 2020).

The integration of multiple methodologies and disciplines is fundamental to triangulation (Munafo & Davey Smith, 2018). Triangulation allows different but complementary approaches to test effects for consistency, helping to strengthen causal inferences (Walton et al., 2019). In the case of resilience, reproducible results will help to inform the development of prevention and intervention strategies aimed at vulnerable groups. It could also hold the key to refining our understanding and conceptualisation of resilience as a concept. This is important as the future of resilience relies on authors clearly defining it, whether that be as a trait, process, or outcome. Each definition of resilience likely taps into unique and complementary mechanisms, with factors associated with trait resilience likely to also moderate outcomes following adversity. Explicitly defining resilience, the adversity, and

the criteria for positive adaptation will thus facilitate deeper interpretations and further follow-up investigation.

This thesis has defined and explored resilience as a process that emerges from the interaction of factors at both the genetic and phenotypic level. The presence of resilience was investigated by comparing continuous measures of depressive symptoms and wellbeing in early adulthood, among individuals exposed to varying frequencies of peer victimisation in adolescence. It is important that generalisation of these findings therefore consider these factors when comparing resilient outcomes of victims of bullying.

7.6 Conclusion

In summary, this thesis has investigated the factors that allow individuals exposed to peer victimisation to foster resilience. In doing so, the research has added to the growing literature of both resilience and wellbeing more generally. In maintaining a focus on positive wellbeing and resilience, the research is in keeping with the World Health Organization's policy framework for health and wellbeing (WHO, 2017). This emphasised the importance of strengthening resilience through supportive environments. Such environments should offer protection from factors that may threaten mental health and wellbeing, and should encourage individuals to build their own capabilities. The research in this thesis has strived to identify such factors in the context of peer victimisation. The aim was to uncover ways in which the burden of mental health problems experienced by victims could be prevented, and wellbeing promoted. I hope my findings will encourage further research into factors that may matter for victims of bullying, as well as victims exposed to other adversities. I also hope such research will continue to explore factors that matter for wellbeing as well as mental health, and for individuals living among different populations and cultures. Together, I believe such research could make a significant contribution to the happiness and satisfaction of individuals worldwide.

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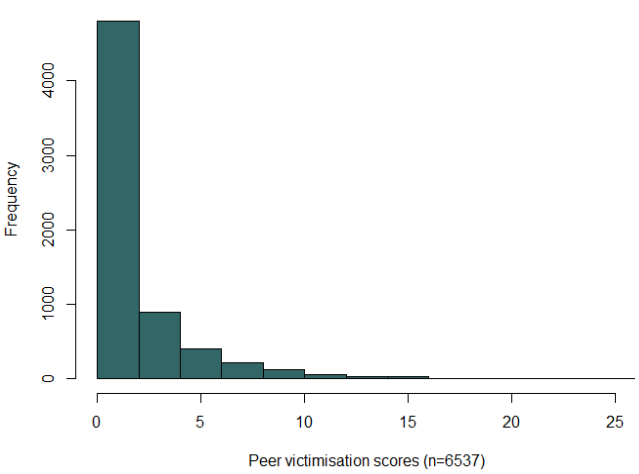
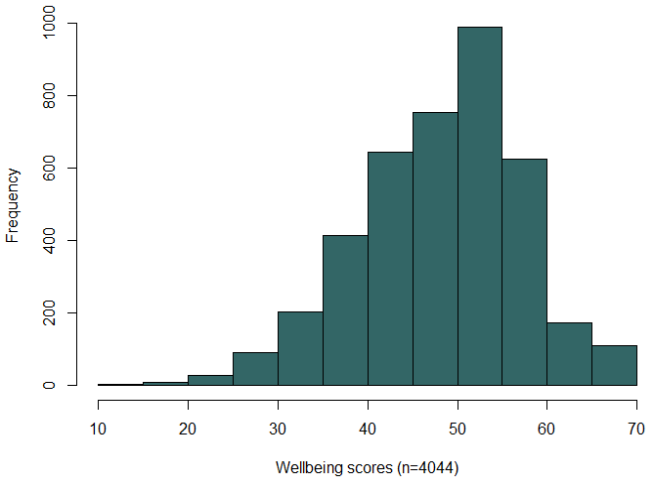
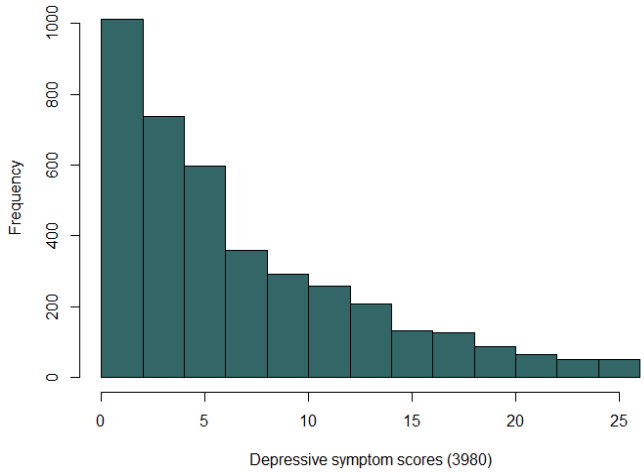
Appendices

Appendix 2.1: Histograms showing the distribution of the peer victimisation, wellbeing, and depressive symptom scores in ALSPAC.







Appendix 3.1: Comparison of victimisation scores by twin zygosity

	Overall sample (MZ and DZ twins)		MZ twins only		DZ twins only		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	p[1]
Self-reported childhood victimisation	507	0.60 (0.32)	250	0.69 (0.52)	257	0.59 (0.31)	0.69
Teacher-reported childhood victimisation	448	0.24 (0.29)	223	0.24 (0.31)	225	0.24 (0.27)	0.94
Peer-reported childhood victimisation	518	-0.04 (0.81)	252	-0.09 (0.74)	266	0.01 (0.87)	0.16
Self-reported adolescent victimisation	450	0.25 (0.21)	212	0.26 (0.21)	238	0.25 (0.21)	0.52

Note: Peer-reported victimisation scores have been z-standardised.

[1]Comparison of mean differences between victimisation scores reported by MZ twin pairs compared to DZ twin pairs.

Appendix 3.2: Socio-demographics comparisons of participants with complete and missing victimisation data at 7 and 17 years

	Victimisation responders aged 7 (n=527)	Victimisation responders aged 17 (n=429)	Victimisation responders missing (n=129)
Victimisation aged 7 (mean,SD)	0.71 (0.52)	0.69 (0.50)	-
White (%)	99.6	100	98.3
White mother (%)	99.6	100	98.3
White father (%)	99.6	100	98.3
Canadian ancestors (%)	66.1	63.1	73.6
Household income above £50,000 (%)	51.8	53.1	46.2
Mother has University degree or higher qualification (%)	27.0	28.1	26.1
Father has University degree or higher qualification (%)	32.5	33.7	25.2

Appendix 3.3: Unstandardised results from single-polygenic score models exploring associations with self-, teacher-, and peer-reported victimisation in childhood

	Self-reported victimisation				Teacher-reported victimisation				Peer-reported victimisation			
PGSs	Coefficient, β(95%,CI)	SE	*p* value	R^2	Coefficient, β(95%,CI)	SE	*p* value	R^2	Coefficient, *β*(95%,CI)	SE	*p* value	R^2
MDD	0.028 (0.003,0.060)	0.02	0.05	0.30%	0.016 (-0.013,0.045)	0.01	0.27	0.91%	0.037 (-0.040,0.114)	0.04	0.35	0.20%
ADHD	0.019 (-0.010,0.049)	0.02	0.20	0.00%	0.025 (-0.002,0.052)	0.01	0.07	1.36%	0.057 (-0.016,0.129)	0.04	0.13	0.45%
Risk-taking	0.025 (-0.006,0.055)	0.02	0.11	0.02%	-0.026 (-0.055,0.003)	0.01	0.08	1.27%	0.073 (-0.003,0.149)	0.04	0.06	0.79%
BMI	0.017 (-0.014,0.048)	0.02	0.28	0.00%	0.033 (0.006,0.061)	0.01	0.02	1.85%	0.061 (-0.012,0.135)	0.04	0.10	0.50%
Intelligence	-0.011 (-0.043,0.020)	0.02	0.47	0.00%	**-0.038 (-0.066,-0.009)**	**0.01**	**<0.001†**	2.15%	-0.017 (-0.093,0.060)	0.04	0.66	0.31%
Educational attainment	-0.016 (-0.047,0.014)	0.02	0.29	0.00%	**-0.053 (-0.081,-0.025)**	**0.01**	**<0.001†**	3.80%	-0.085 (-0.159,-0.011)	0.04	0.02	1.11%
Depressive symptoms	0.002 (-0.027,0.031)	0.02	0.90	0.00%	-0.001 (-0.028,0.026)	0.01	0.93	0.63%	-0.044 (-0.115,0.028)	0.04	0.23	0.28%
Wellbeing	-0.034 (-0.064,-0.004)	0.02	0.03	0.84%	-0.017 (-0.045,0.011)	0.01	0.22	1.06%	-0.006 (-0.079,0.067)	0.04	0.87	0.00%
Schizophrenia	-0.017 (-0.047,0.013)	0.02	0.28	0.00%	-0.017 (-0.045,0.011)	0.01	0.24	0.97%	-0.047 (-0.123,0.028)	0.04	0.21	0.31%
Extreme BMI	-0.023 (-0.052,-0.006)	0.02	0.12	0.07%	0.001 (-0.027,0.028)	0.01	0.96	0.63%	-0.049 (-0.123,0.026)	0.04	0.20	0.32%

Note: PGS = Polygenic scores. †FDR. Analyses based on linear mixed effects model, controlling for sex and 10 principal components. Self-reported victimisation based on mean composite of scores from 7, 10, and 12 years. Teacher-reported victimisation based on mean composite of scores from 7, 10, and 12 years. Peer-reported victimisation based on mean composite of scores from 7 and 10 years.

Appendix 3.4: Unstandardised results from single- and multi-polygenic score models exploring associations with self-reported victimisation in adolescence

	Single-PGS regression models				Multi-PGS regression models			
	Coefficient, β(95% CI)	SE	*p* value	R^2	Coefficient, β(95% CI)	SE	*p* value	R^2
MDD	0.029 (0.007, 0.050)	0.01	0.01	2.64	0.021 (-0.00, 0.043)	0.01	0.06	5.06
ADHD	0.011 (-0.010, 0.032)	0.01	0.29	1.22	-	-	-	
Risk-taking	-0.011 (-0.034, 0.012)	0.01	0.33	1.19	-	-	-	
BMI	0.024 (0.003, 0.046)	0.01	0.03	2.23	0.013 (-0.010, 0.036)	0.01	0.27	
Intelligence	-0.013 (-0.035, 0.008)	0.01	0.22	1.34	-	-	-	
Educational attainment	-0.024 (-0.045, -0.003)	0.01	0.02	2.36	-0.021 (-0.043, 0.000)	0.01	0.06	
Depressive symptoms	0.010 (-0.011, 0.031)	0.01	0.37	1.18	-	-	-	
Wellbeing	-0.019 (-0.041, 0.003)	0.01	0.09	1.76	-	-	-	
Schizophrenia	0.017 (-0.005, 0.039)	0.01	0.13	1.56	-	-	-	
Extreme BMI	0.022 (0.000, 0.045)	0.01	0.04	2.02	0.019 (-0.004, 0.043)	0.01	0.11	

Note: PGS = Polygenic scores.

Analyses were conducted using linear mixed effects model, controlling for sex and the first 10 principal components for stratification.

Appendix 3.5: GWAS information

Phenotype	Reference to GWAS	GWAS discovery sample size	Year GWAS published
Major depressive disorder	Howard, D. M., Adams, M. J., Clarke, T., Hafferty, J. D., Gibson, J., & Shirali, M. et al. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience, 22,* 343-352.	807,553	2019
ADHD	Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., & Agerbo, E., et al. (2017). Discovery of the first genome - wide significant risk loci for attention/deficit hyperactivity disorder. *Nature Genetics, 51*, 63-75.	55,374	2017
Risk-taking	Karlsson Linnér, R., Biroli, P., Kong, E., Meddens, S. F. W., & Wedow, R., et al. (2019). Genome-wide association analyses of risk tolerance and risky behaviors in over one million individuals identify hundreds of loci and shared genetic influences. *Nature Genetics, 51,* 245-257	939,908	2019
BMI	Yengo L, Sidorenko J, Kemper KE, et al. (2018). Meta-analysis of genome-wide association studies for height and body mass index in ~700,000 individuals of European ancestry. bioRxiv, 274654.	456,426	2018
Intelligence	Savage JE, Jansen PR, Stringer S, et al. (2018). Genome-wide association meta - analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature Genetics, 50*(7), 912 -919.	269,867	2018
Educational attainment	Lee, J. J., Wedow, R., Okbay, A., et al. (2018). Gene discovery and polygenic prediction from a genome -wide association study of educational attainment in 1.1 million individuals. *Nature Genetics, 50*(8),1112-1121.	1,131,881	2018
Depressive symptoms	Okbay, A., Baselmans, B. M. L., De Neve, J-E., et al. (2016). Genetic variants associated with subjective well-being, depressive symptoms and neuroticism identified through genome-wide analyses. *Nature Genetics, 48*(6), 624-633.	161,460	2016

Wellbeing	Baselmans, B. M. L., Jansen, R., Ip, H. F., van Dongen, J., Abdellaoui, A., van de Weijer, M. P., & Bao, Y., et al. (2019). Multivariate genome-wide analyses of the well-being spectrum. *Nature Genetics, 51,* 445-451.	2,370,390	2019
Schizophrenia	Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2018). Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. *Cell 173*, 170501715	107,620	2018
Extreme BMI	Berndt SI, Gustafsson S, Mägi R, et al. Genome -wide meta -analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nature Genetics, 45*(5),501-512.	263,407	2013

Appendix 3.6: Power calculations in current study for self-reported childhood victimisation (AVENGEME)

PGS Phenotype	Target sample size[a]	Discovery sample size	Total variance explained by genetic effects in discovery sample	Number of independent SNPs in PGS	P-value threshold of PGS	Power[b]	Phenotypic variance captured by PGS at power level[c]	Variance in victimisation explained by PGS[d]
MDD	507	807,553	3.2%	13,799	0.01	0.91	2.1%	1.47%
ADHD	507	55,374	5.5%	16,907	0.02	0.54	0.84%	0.83%
Risk-taking	507	939,908	1.6%	9,309	0.13	0.61	0.99%	0.88%
BMI	507	456,426	6%	23,776	0.02	0.98	3.2%	0.97%
Intelligence	507	269,867	5.2%	176,145	0.64	0.29	0.38%	0.88%
Educational attainment	507	1,131,881	12%	43,719	0.04	0.99	9.7%	1.05%
Depressive symptoms	507	161,460	0.5%	81,731	0.31	0.07	0.03%	0.68%
Wellbeing	507	2,370,390	1.10%	42,696	0.12	0.31	0.42%	2.06%
Schizophrenia	507	107,620	4.26%	53,909	0.10	0.26	0.33%	0.99%
Extreme BMI	507	263,407	6.4%	5,557	0.02	0.99	4.8%	1.61%

Note: PGS = Polygenic score.

[a]Target sample was based on analyses using the self-reported composite in childhood.

[b]Power estimates for the PGS are based on the parameters provided.

[c]Denotes the phenotypic variance explained by the PGS at the reported power.

[d]The variance in peer victimisation captured by the PGS in current study. This was based on analyses using the self-reported childhood victimisation composite.

Appendix 3.7: Power calculations in current study for teacher-reported childhood victimisation (AVENGEME)

PGS Phenotype	Target sample size[a]	Discovery sample size	Total variance explained by genetic effects in discovery sample	Number of independent SNPs in PGS	P-value threshold of PGS	Power[b]	Phenotypic variance captured by PGS at power level[c]	Variance in victimisation explained by PGS[d]
MDD	448	807,553	3.2%	13,799	0.01	0.87	2.1%	0.91%
ADHD	448	55,374	5.5%	60,336	0.13	0.19	0.26%	1.36%
Risk-taking	448	939,908	1.6%	50,338	0.08	0.25	0.37%	1.27%
BMI	448	456,426	6%	76,505	0.43	0.77	1.58%	1.85%
Intelligence	448	269,867	5.2%	196,506	0.88	0.24	0.35%	2.15%
Educational attainment	448	1,131,881	12%	37,785	0.03	0.99	9.4%	3.80%
Depressive symptoms	448	161,460	0.5%	7,942	0.01	0.07	0.05%	0.63%
Wellbeing	448	2,370,390	1.10%	12,082	0.01	0.50	0.75%	1.06%
Schizophrenia	448	107,620	4.26%	78,126	0.19	0.19	0.24%	0.97%
Extreme BMI	448	263,407	6.4%	35,170	0.23	0.91	4.8%	0.63%

Note:

[a]Target sample was based on analyses using the teacher-reported composite in childhood.

[b]Power estimates for the PGS are based on the parameters provided.

[c]Denotes the phenotypic variance explained by the PGS at the reported power.

[d]The variance in peer victimisation captured by the PGS in current study. This was based on analyses using the teacher-reported childhood victimisation composite

Appendix 3.8: Power calculations in current study based on simulations

	Effect estimate[a]	**Power**
MDD-PGS	0.078	48%
MDD-PGS	0.090	66%
MDD-PGS	0.100	76%
MDD-PGS	0.150	94%

Note:

[a] Power calculation based on effect estimate of MDD-PGS using the growth curve analysis model investigating trajectories over time (n=566). The current effect estimate in the longitudinal growth curve model was 0.078.

Appendix 4.1: Sample characteristics of those in current study compared to those missing

	Victimisation responders (n=6,527) [a]	Victimisation and genotype (n=4,829) [b]	MFQ responders (n=2,268) [c]	Missing MFQ responders (n=2,561) [d]	Wellbeing responders (n=2,299) [e]	Missing wellbeing responders (n=2,530) [f]	ALSPAC Sample (n=15,443) [g]
Female (%)	48.8	51.4	63.9	40.4	63.6	40.4	48.8
Victimised at least once (%)	53.7	54.1	53.7	54.5	53.8	54.4	-
Overall victimisation score, M(SD)	1.82 (2.76)	1.81 (2.69)	1.73 (2.52)	1.88 (2.84)	1.73 (2.53)	1.87 (2.84)	-
Non-white (%)	3.9	0.2	0.3	0.2	0.3	0.2	5.0
Parents own car (%)	94.8	95.3	96.6	94.2	96.5	94.2	90.8
Parents married (%)	83.7	84.9	86.9	83.0	86.8	83.1	79.5
Mother was homeowner (%)	85.1	86.5	89.2	84.1	89.2	84.1	77.1
Mother has University degree (%)	17.2	18.9	23.7	14.5	23.6	14.1	13.7

Note:

[a] Individuals who completed the victimisation assessment at 13 years

[b] Individuals with genotype data who completed the victimisation assessment at 13 years

[c] Individuals with genotype data who completed the victimisation assessment at 13 years and the MFQ at 23 years

[d] Individuals with genotype data who completed the victimisation assessment at 13 years but not the MFQ at 23 years

[e] Individuals with genotype data who completed the victimisation assessment at 13 years and the WEMWBS at 23 years

[f] Individuals with genotype data who completed the victimisation assessment at 13 years but not the WEMWBS at 23 years

[g] Core singleton ALSPAC sample.

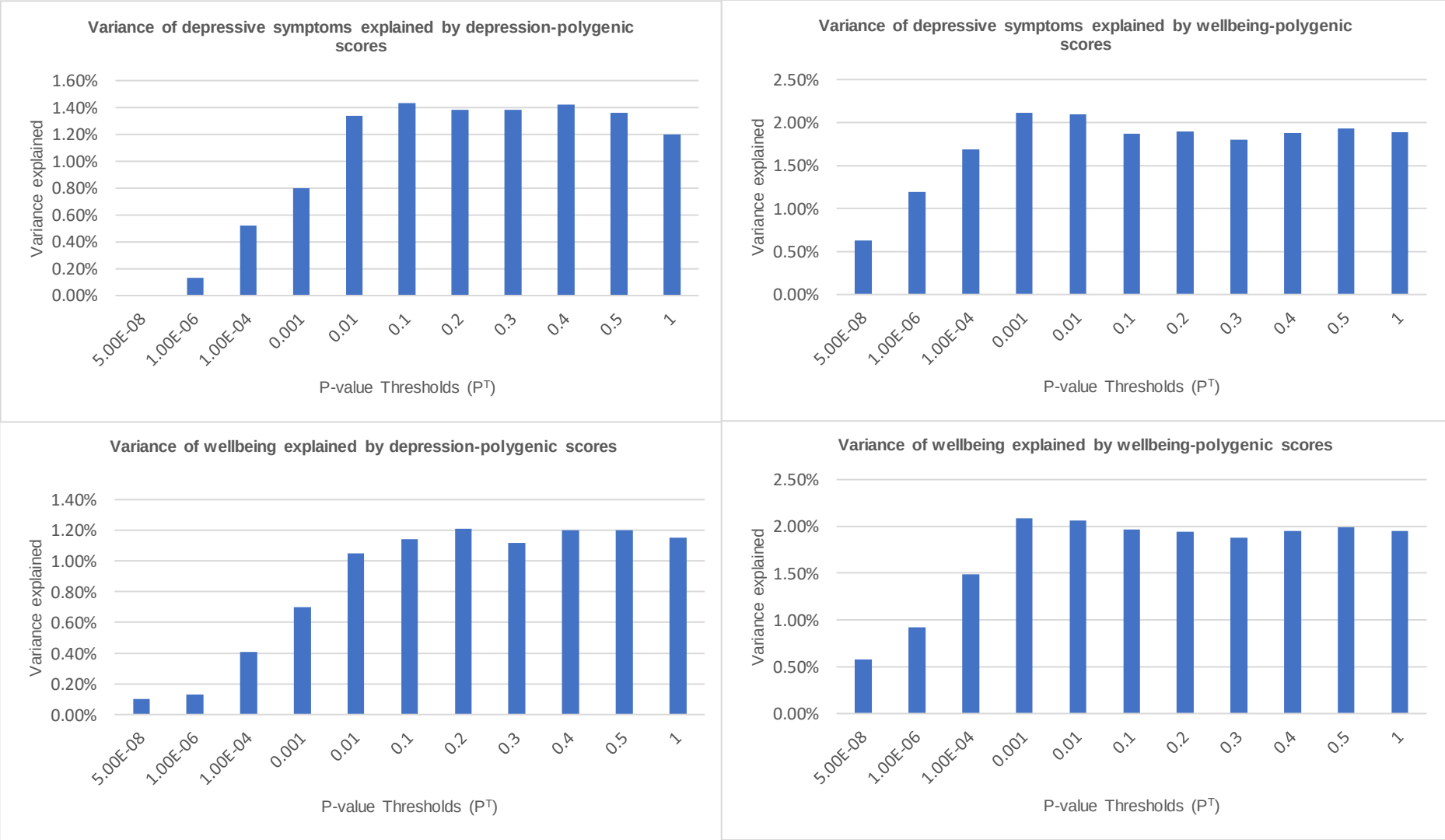
Appendix 4.2: Impact of untransformed victimisation scores, polygenic scores, and their interaction on depressive symptoms and wellbeing at 23 years

	Impact on depressive symptoms							
	Polygenic Scores		Victimisation		Interaction			
	β (95% C.I.)	*p* value	β (95% C.I)	*p* value	β (95% C.I)	*p* value	R^2	ΔR^2
Depression-PGS								
$P^T=5x10^{-8}$	-0.038 (-0.117, 0.040)	0.348	0.045 (0.013, 0.078)	**0.005**	0.005 (-0.009, 0.019)	0.466	2.7%	0.3%
$P^T=0.1$	0.092 (0.011, 0.174)	**0.022**	0.043 (0.010, 0.075)	**0.007**	-0.006 (-0.021, 0.008)	0.370	3.8%	0.8%
Wellbeing-PGS								
$P^T=5x10^{-8}$	-0.037 (-0.120, 0.045)	0.374	0.043 (0.012, 0.076)	**0.006**	0.001 (-0.014, 0.017)	0.864	3.2%	0.2%
$P^T=0.001$	-0.108 (-0.192, -0.024)	**0.011**	0.041 (0.009, 0.073)	**0.009**	0.001 (-0.015, 0.013)	0.850	4.9%	1.9%
	Impact on wellbeing							
Depression-PGS								
$P^T=5x10^{-8}$	0.080 (-0.688, 0.849)	0.838	-0.056 (-0.242, 0.354)	0.713	-0.164 (-0.303, -0.026)	**0.020**	2.6%	0.9%
$P^T=0.2$	-0.329 (-1.11, 0.451)	0.409	-0.054 (-0.244, 0.352)	0.721	-0.044 (-0.184, 0.095)	0.532	3.5%	1.8%
Wellbeing-PGS								
$P^T=5x10^{-8}$	0.149 (-0.638, 0.936)	0.711	-0.018 (-0.279, 0.315)	0.905	0.043 (-0.110, 0.195)	0.582	2.9%	1.3%
$P^T=0.001$	0.384 (-0.400, 1.17)	0.337	-0.030 (-0.264, 0.324)	0.841	0.108 (-0.022, 0.239)	0.104	4.4%	2.8%

Note: PGS = Polygenic scores. P^T=p value threshold of the polygenic score. R^2 = the variance accounted for by the main and interactive effects of victimisation and the polygenic scores, as well as the covariates. ΔR^2 = the incremental R^2. †FDR.

Each row represents a separate multiple regression of either depressive symptoms or wellbeing predicted by the polygenic scores, victimisation, and the gene-environment interaction. Negative binomial regression models were used to investigate depressive symptoms (n=2,268), and linear regression models for wellbeing (n=2,299)

Appendix 4.3: Proportion of variance in depressive symptoms and wellbeing explained by the polygenic scores at each p-value threshold



Appendix 4.4: Association between the depression-polygenic scores and depressive symptoms and wellbeing at 23 years

P^T	Main effects on depressive symptoms[a]			Main effects on wellbeing[b]		
	β (95% C.I.)	*p* value	ΔR^2	β (95% C.I)	*p* value	ΔR^2
$5x10^8$	0.007 (-0.037, 0.035)	0.971	0.00%	-0.271 (-0.625, 0.082)	0.133	0.10%
$1x10^6$	0.028 (-0.008, 0.065)	0.133	0.13%	-0.314 (-0.671, 0.042)	0.084	0.13%
$1x10^4$	0.072 (0.034, 0.110)	**1.8E-04**	0.52%	-0.567 (-0.927, -0.207)	**0.002**	0.41%
0.001	0.086 (0.048, 0.123)	**7.0E-06**	0.80%	-0.741 (-1.10, -0.382)	**5.4E-05**	0.70%
0.01	0.103 (0.067, 0.139)	**2.3E-08**	1.34%	-0.884 (-1.23, -0.534)	**8.1E-07**	1.05%
0.1	0.105 (0.069, 0.140)	**1.2E-08**	1.43%	-0.912 (-1.26, -0.565)	**2.9E-07**	1.14%
0.2	0.110 (0.073, 0.146)	**4.9E-09**	1.38%	-0.954 (-1.31, -0.600)	**1.4E-07**	1.21%
0.3	0.110 (0.073, 0.146)	**4.1E-09**	1.38%	-0.921 (-1.27, -0.567)	**3.5E-07**	1.12%
0.4	0.111 (0.074, 0.147)	**3.2E-09**	1.42%	-0.953 (-1.31, -0.600)	**1.3E-07**	1.20%
0.5	0.107 (0.071, 0.144)	**9.1E-09**	1.36%	-0.953 (-1.31, -0.599)	**1.3E-07**	1.20%
1	0.101 (0.065, 0.138)	**6.2E-08**	1.20%	-0.935 (-1.29, -0.581)	**2.4E-07**	1.15%

Note: P^T = p-value threshold of the polygenic score. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the polygenic risk score. The incremental R^2 was calculated by regressing the outcome on sex and the first two principal components of ancestry, and then including the polygenic scores and comparing the variance explained.

[a] Negative binomial regression models were used to investigate associations between the polygenic scores and depressive symptoms at 23 years (n=2,268)

[b] Linear regression models were used to investigate associations between the polygenic scores and wellbeing aged 23 (n=2,299). To account for possible effects of population stratification, all models controlled for two principal components and sex.

Appendix 4.5: Association between the wellbeing-polygenic scores and depressive symptoms and wellbeing at 23 years

P^T	Main effects on depressive symptoms[a]			Main effects on wellbeing[b]		
	β (95% C.I.)	*p* value	ΔR^2	β (95% C.I)	*p* value	ΔR^2
$5x10^8$	-0.069 (-0.106, -0.032)	**2.6E-04**	0.63%	0.671 (0.313, 1.03)	**2.4E-04**	0.58%
$1x10^6$	-0.097 (-0.134, -0.061)	**3.6E-07**	1.19%	0.850 (0.490, 1.21)	**3.9E-06**	0.92%
$1x10^4$	-0.118 (-0.155, -0.081)	**4.4E-10**	1.69%	1.08 (0.719, 1.43)	**3.9E-09**	1.49%
0.001	-0.134 (-0.172, -0.097)	**1.7E-12**	2.11%	1.28 (0.992, 1.64)	**3.1E-12**	2.09%
0.01	-0.137 (-0.174, -0.100)	**3.4E-13**	2.10%	1.25 (0.899, 1.61)	**4.7E-12**	2.06%
0.1	-0.129 (-0.166, -0.092)	**6.9E-12**	1.87%	1.24 (0.882, 1.59)	**1.2E-11**	1.97%
0.2	-0.128 (-0.165, -0.091)	**1.1E-11**	1.90%	1.23 (0.873, 1.59)	**1.9E-11**	1.94%
0.3	-0.124 (-0.161, -0.086)	**5.6E-11**	1.80%	1.21 (0.891, 1.56)	**3.8E-11**	1.88%
0.4	-0.128 (-0.165, -0.091)	**1.6E-11**	1.88%	1.24 (0.880, 1.60)	**1.6E-11**	1.95%
0.5	-0.129 (-0.166, -0.092)	**9.1E-11**	1.93%	1.25 (0.894, 1.61)	**9.7E-12**	1.99%
1	-0.128 (-0.165, -0.091)	**1.3E-11**	1.89%	1.24 (0.877, 1.59)	**1.7E-11**	1.95%

Note: P^T = p-value threshold of the polygenic score. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the polygenic risk score. The incremental R^2 was calculated by regressing the outcome on sex and the first two principal components of ancestry, and then including the polygenic scores and comparing the variance explained.

[a] Negative binomial regression models were used to investigate associations between the polygenic scores and depressive symptoms at 23 years (n=2,268).

[b] Linear regression models were used to investigate associations between the polygenic scores and wellbeing aged 23 (n=2,299). To account for possible effects of population stratification, all models controlled for two principal components and sex.

Appendix 4.6: Main effects of polygenic scores and log-transformed victimisation scores on depressive symptoms and wellbeing at 23 years

	Main effects on depressive symptoms[a]		Main effects on wellbeing[b]	
Main effects	β (95% C.I.)	*p* value	β (95% C.I)	*p* value
Victimisation (unadjusted)	0.193 (0.144, 0.241)	**8.2E-15**	-1.31 (-1.79, -0.846)	**4.9E-08**
Victimisation (adjusted for dep-PGS, $P^T=5x10^8$)	0.193 (0.145, 0.242)	**7.2E-15**	-1.31 (-1.78, -0.834)	**6.6E-08**
Victimisation (adjusted for dep-PGS, $P^T=0.1$)	0.187 (0.139, 0.236)	**3.3E-14**	-1.26 (-1.73, -0.788)	**1.7E-07**
Victimisation (adjusted for wellbeing-PGS, $P^T=5x10^8$)	0.189 (0.140, 0.237)	**2.6E-14**	-1.28 (-1.75, -0.810)	**1.1E-08**
Victimisation (adjusted for wellbeing-PGS, $P^T=0.001$)	0.183 (0.135, 0.232)	**9.1E-13**	-1.25 (-1.72, -0.780)	**1.9E-07**
Depression-polygenic scores				
$P^T=5x10^8$ (unadjusted)	0.000 (-0.035, 0.037)	0.966	-0.276 (-0.630, 0.077)	0.126
$P^T=5x10^8$ (adjusted for victimisation)	-0.008 (-0.043, 0.028)	0.683	-0.241 (-0.593, 0.111)	0.179
$P^T=0.1$ (unadjusted)	0.105 (0.069, 0.141)	**1.2E-08**	-0.926 (-1.27, -0.578)	**1.9E-07**
$P^T=0.1$ (adjusted for victimisation)	0.099 (0.064, 0.134)	**5.9E-08**	-0.880 (-1.23, -0.534)	**6.5E-07**
Wellbeing-polygenic scores				
$P^T=5x10^8$ (unadjusted)	-0.073 (-0.110, -0.035)	**1.4E-04**	0.685 (0.327, 1.04)	**1.7E-04**
$P^T=5x10^8$ (adjusted for victimisation)	-0.067 (-0.102, -0.029)	**5.0E-04**	0.643 (0.287, 0.999)	**4.0E-04**
$P^T=0.001$ (unadjusted)	-0.136 (-0.174, -0.099)	**1.1E-12**	1.29 (0.937, 1.65)	**1.7E-12**
$P^T=0.001$ (adjusted for victimisation)	-0.128 (-0.165, -0.091)	**1.1E-11**	1.25 (0.898, 1.61)	**6.5E-12**

Note: PGS= Polygenic score. P^T = p-value threshold of the polygenic score.

[a] Negative binomial regression models were used to investigate the main effects of the polygenic scores and victimisation on depressive symptoms aged 23 (n=2,268).

[b] Linear regression models were used to investigate the main effects of the polygenic scores and victimisation on wellbeing aged 23 (n=2,299).

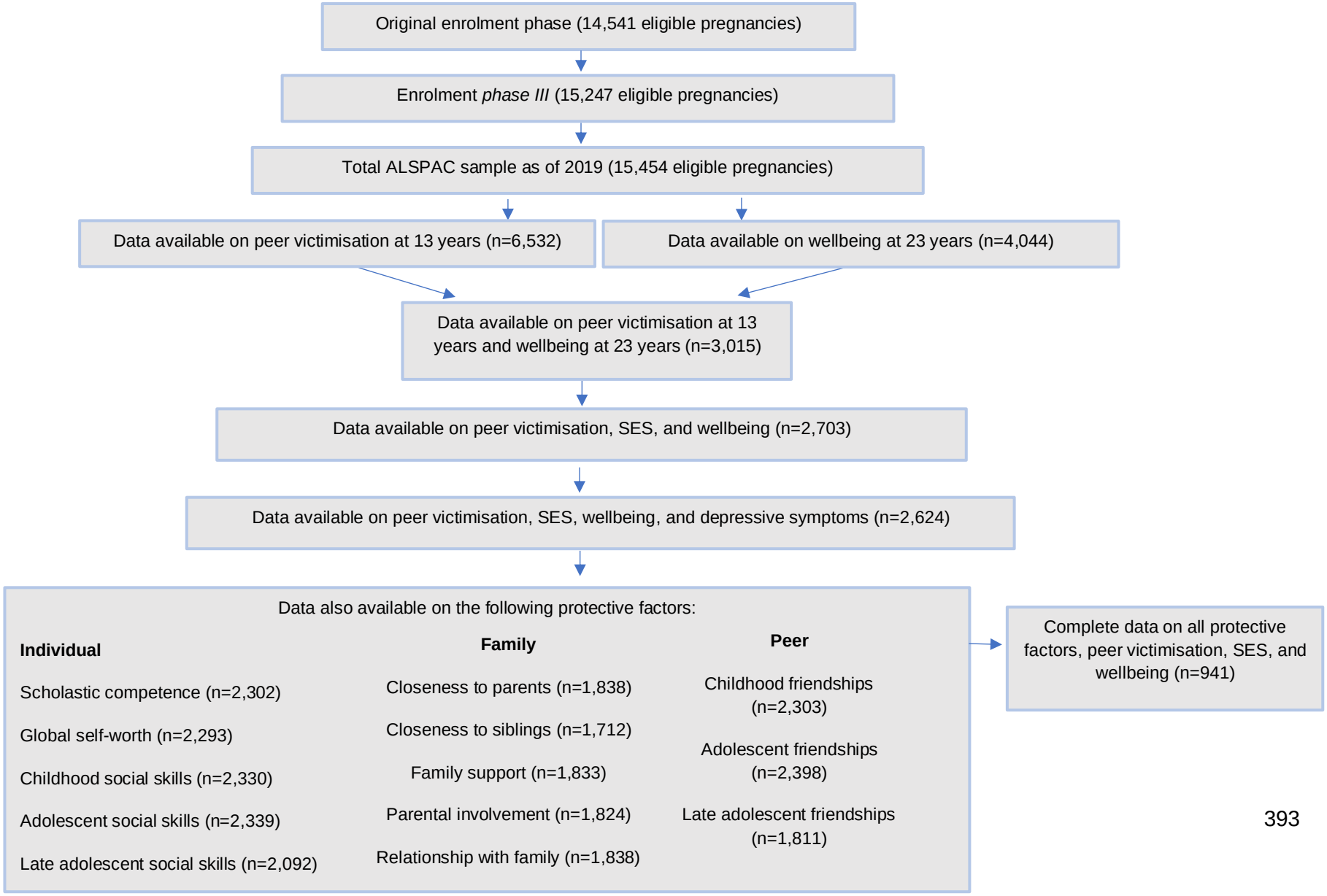
Appendix 4.7: Main effects of polygenic scores on victimisation at 13 years (i.e., gene-environment correlation)

P^T	Main effects of depression-polygenic scores[a]			Main effects of wellbeing-polygenic scores[a]		
	β (95% C.I.)	*p* value	ΔR^2	β (95% C.I.)	*p* value	ΔR^2
$5x10^8$	0.095 (-0.009, 0.198)	0.073	0.14%	-0.125 (-0.230, -0.020)	**0.020**	0.24%
$1x10^6$	0.124 (0.019, 0.228)	**0.020**	0.24%	-0.129 (-0.235, -0.023)	**0.017**	0.26%
$1x10^4$	0.159 (0.053, 0.265)	**0.003**	0.38%	-0.171 (-0.276, -0.065)	**0.002**	0.45%
0.001	0.123 (0.017, 0.229)	**0.022**	0.23%	-0.116 (-0.222, -0.010)	**0.032**	0.21%
0.01	0.161 (0.058, 0.263)	**0.002**	0.42%	-0.128 (-0.232, -0.023)	**0.017**	0.26%
0.1	0.143 (0.041, 0.245)	**0.006**	0.34%	-0.097 (-0.202, 0.008)	0.070	0.15%
0.2	0.161 (0.057, 0.262)	**0.002**	0.41%	-0.077 (-0.182, 0.028)	0.151	0.09%
0.3	0.163 (0.059, 0.266)	**0.002**	0.42%	-0.065 (-0.170, 0.041)	0.228	0.07%
0.4	0.162 (0.058, 0.265)	**0.002**	0.42%	-0.057 (-0.163, 0.049)	0.292	0.05%
0.5	0.159 (0.056, 0.263)	**0.003**	0.41%	-0.059 (-0.165, 0.047)	0.274	0.05%
1	0.157 (0.053, 0.260)	**0.003**	0.39%	-0.058 (-0.163, 0.048)	0.284	0.05%

Note: P^T = p-value threshold of the polygenic score. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the polygenic risk score. The incremental R^2 was calculated by regressing victimisation on sex and the first two principal components of ancestry, and then including the polygenic scores and comparing the variance explained.

[a] Linear regression models were used to separately investigate the main effects of the depression-polygenic scores and wellbeing-polygenic scores on victimisation among individuals with complete victimisation and mental health data (n=2,232). To account for possible effects of population stratification, models controlled for two principal components and sex.

Appendix 5.1: Flowchart of included participants from the Avon Longitudinal Study of Parents and Children



Appendix 5.2: Response patterns across variables

	Full sample in ALSPAC (N)	% with SES data[a]	% with victimisation data[b]	% with wellbeing data[c]	% with victimisation, SES, wellbeing[d]	% with victimisation, SES, wellbeing, depression[c]
Predictor variable						
Peer victimisation	6,529	5,742 (87.9%)	6,529 (100%)	2,975 (45.6%)	2,624 (40.2%)	2,624 (40.2%)
Outcome variables						
Wellbeing (WEMWBS)	4,044	3,458 (85.6%)	3,015 (74.6%)	4,041 (100%)	2,624 (64.9%)	2,624 (64.9%)
Life satisfaction	4,069	3,486 (85.7%)	3,030 (74.5%)	3,993 (98.1%)	2,671 (65.6%)	2,597 (63.8%)
Depressive symptoms	3,977	2,669 (67.1%)	2,975 (74.8%)	2,929 (73.6%)	2,624 (66.0%)	2,624 (66.0%)
Protective factors						
Individual-level						
Scholastic competence	6,854	6,079 (89.0%)	5,292 (77.2%)	2,916 (42.5%)	2,367 (34.5%)	2,303 (33.6%)
Global self-worth	6,843	6,066 (88.6%)	5,283 (77.2%)	2,916 (42.6%)	2,362 (35.5%)	2,296 (33.6%)
Academic ability	6,678	5,937 (88.9%)	5,112 (76.5%)	3,236 (48.6%)	2,904 (43.5%)	2,360 (35.3%)
Childhood social skills	7,818	7,263 (92.9%)	5,154 (65.9%)	3,072 (39.3%)	2,400 (30.7%)	2,330 (29.8%)
Adolescent social skills	6,847	6,169 (90.1%)	5,265 (76.9%)	3,110 (45.4%)	2,833 (41.4%)	2,339 (34.2%)
Late adolescent social skills	5,413	4,924 (91.0%)	4,285 (79.2%)	2,758 (51.0%)	2,516 (46.5%)	2,092 (38.6%)
Family-level						
Closeness to parents	4,030	3,539 (87.8%)	3,431 (85.1%)	2,338 (58.0%)	2,088 (51.8%)	1,838 (45.6%)
Closeness to siblings	3,766	3,312 (87.9%)	3,198 (84.9%)	2,186 (58.0%)	1,954 (51.9%)	1,712 (45.6%)
Family support	4,025	3,528 (87.6%)	3,421 (85.0%)	2,337 (58.1%)	2,084 (51.8%)	1,833 (45.5%)

Parental involvement	3,982	3,498 (86.9%)	3,390 (85.1%)	2,321 (58.3%)	2,074 (52.1%)	1,824 (45.8%)
Relationship with family	4,033	3,539 (87.8%)	3,429 (85.0%)	2,340 (58.0%)	2,089 (51.8%)	1,838 (45.6%)
Peer-level						
Childhood friendships	6,906	6,119 (88.6%)	5,341 (77.3%)	2,926 (42.4%)	2,660 (38.5%)	2,303 (33.3%)
Adolescent friendships	6,157	5,405 (87.8%)	6,004 (97.5%)	2,800 (45.5%)	2,511 (40.8%)	2,398 (38.9%)
Late adolescent friendships	3,963	3,485 (87.9%)	3,375 (85.2%)	2,299 (58.0%)	2,058 (51.9%)	1,811 (45.7%)

Note: SES = Socioeconomic status.

[a] Individuals with complete data on the measured variable, who were also assessed for SES.

[b] Individuals with complete data on the measured variable, who were also assessed for victimisation at 13 years.

[c] Individuals with complete data on the measured variable, who were also assessed for wellbeing at 23 years.

[d] Individuals with complete data on the measured variable, who were also assessed for victimisation aged 13 and wellbeing at 23 years.

Appendix 5.3: Correlations between study variables

Correlation matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	1	-0.12 (-0.16, -0.09)	0.17 (0.14, 0.21)	-0.13 (-0.17, -0.10)	-0.02 (-0.05, 0.00	-0.08 (-0.11, -0.05)	-0.09 (-0.12, -0.06)	-0.12 (-0.15, -0.09)	-0.12 (-0.15, -0.09)	-0.14 (-0.17, -0.11)	-0.03 (-0.06, -0.00)	-0.05 (-0.09, -0.02)	-0.06 (-0.09, -0.03)	-0.07 (-0.11, -0.03)	-0.04 (-0.08, -0.01)	-0.12 (-0.15, -0.08)	-0.10 (-0.13, -0.08)	-0.19 (-0.21, -0.16)	-0.10 (-0.13, -0.06)
2		1	-0.69 (-0.71, -0.67)	0.66 (0.64, 0.68)	-0.07 (-0.10, -0.04)	0.09 (0.06, 0.13)	0.11 (0.08, 0.15)	0.10 (0.06, 0.13)	0.11 (0.08, 0.15)	0.13 (0.10, 0.17)	0.16 (0.13, 0.20)	0.14 (0.10, 0.18)	0.14 (0.10, 0.18)	0.18 (0.14, 0.22)	0.13 (0.09, 0.17)	0.18 (0.14, 0.21)	0.08 (0.04, 0.11)	0.11 (0.08, 0.15)	0.21 (0.17, 0.25)
3			1	-0.58 (-0.60 -0.56)	0.07 (0.04, 0.10)	-0.10 (-0.14, -0.07)	-0.10 (-0.14, -0.07)	-0.80 (-0.12, -0.04)	-0.13 (-0.16, -0.09)	-0.16 (-0.19, -0.12)	-0.14 (-0.17, -0.10)	-0.14 (-0.18, -0.10)	-0.11 (-0.15, -0.07)	-0.16 (-0.19, -0.12)	-0.15 (-0.19, -0.11)	-0.18 (-0.22, -0.14)	-0.08 (-0.12, -0.05)	-0.11 (-0.15, -0.07)	-0.15 (-0.20, -0.11)
4				.1	-0.06 (-0.09, -0.02)	0.09 (0.06, 0.13)	0.11 (0.08, 0.15)	0.12 (0.09, 0.16)	0.16 (0.13, 0.19)	0.15 (0.12, 0.19)	0.14 (0.10, 0.17)	0.15 (0.11, 0.19)	0.12 (0.07, 0.16)	0.18 (0.14, 0.21)	0.14 (0.10, 0.18)	0.18 (0.14, 0.21)	0.08 (0.04, 0.12)	0.13 (0.09, 0.16)	0.19 (0.15, 0.23)
5					1	-0.10 (-0.13, -0.08)	-0.03 (-0.06, -0.01)	-0.06 (-0.08, -0.04)	-0.04 (-0.07, -0.02)	-0.04 (-0.06, -0.01)	-0.12 (-0.15, -0.10)	-0.03 (-0.06, 0.00)	-0.07 (-0.11, -0.04)	-.00 (-.03, .03)	-0.20 (-0.24, -0.17)	-0.05 (-0.08, -0.02)	-0.00 (-0.03, 0.02)	0.06 (0.04, 0.09)	0.03 (-0.00, 0.06)
6						1	0.40 (0.38, 0.42)	0.06 (0.03, 0.09)	0.02 (-0.01, 0.04)	.003 (0.01, 0.06)	0.23 (0.20, 0.26)	0.03 (-0.00, 0.06)	0.05 (0.01, 0.08)	0.07 (0.03, 0.10)	0.06 (0.03, 0.10)	0.05 (0.02, 0.09)	0.17 (0.14, 0.19)	0.08 (0.05, 0.11)	0.02 (-0.02, 0.05)
7							1	0.12 (0.10, 0.15)	0.06 (0.03, 0.08)	0.07 (0.04, 0.10)	0.11 (0.08, 0.14)	0.08 (0.04, 0.11)	0.06 (0.03, 0.10)	0.08 (0.05, 0.12)	0.06 (0.03, 0.10)	0.07 (0.03, 0.10)	0.20 (0.18, 0.23)	0.11 (0.08, 0.14)	0.07 (0.04, 0.11)
8								1	0.54 (0.52, 0.56)	0.43 (0.41, 0.45)	0.08 (0.06, 0.11)	0.12 (0.08, 0.15)	0.11 (0.07, 0.14)	0.06 (0.03, 0.10)	0.06 (0.02, 0.09)	0.10 (0.07, 0.14)	0.09 (0.06, 0.11)	0.05 (0.02, 0.08)	0.03 (-0.02, 0.07)
9									1	0.61 (0.59, 0.63)	0.12 (0.09, 0.15)	0.14 (0.11, .017)	0.09 (0.05, 0.12)	0.07 (0.04, 0.11)	0.06 (0.02, 0.09)	0.15 (0.11, 0.18)	0.04 (0.02, 0.07)	0.03 (0.00, 0.06)	0.02 (-0.01, 0.06)
10										1	0.07 (0.04, 0.10)	0.19 (0.16, 0.23)	0.12 (0.08, 0.15)	0.12 (0.08, 0.15)	0.11 (0.07, 0.14)	0.21 (0.17, 0.24)	0.04 (0.01, 0.07)	0.03 (-0.03, 0.06)	0.01 (-0.03, 0.05)
11											1	0.08 (0.05, 0.12)	0.06 (0.02, 0.10)	0.09 (0.05, 0.12)	0.11 (0.08, 0.14)	0.09 (0.05, 0.12)	0.09 (0.06, 0.11)	0.08 (0.06, 0.11)	0.06 (0.02, 0.09)
12												1	0.45 (0.42, 0.48)	0.53 (0.50, 0.55)	0.27 (0.24, 0.30)	0.61 (0.59, 0.63)	0.07 (0.03, .10)	0.07 (0.04, 0.11)	0.18 (0.14, 0.21)
13													1	0.41 (0.38, 0.43)	0.22 (0.19, 0.25)	0.41 (0.38, 0.44)	0.07 (0.04, 0.11)	0.10 (0.06, 0.14)	0.15 (0.12, 0.18)
14														1	0.29 (0.26, 0.32)	0.54 (0.51, 0.56)	0.09 (0.06, 0.13)	0.10 (0.07, 0.14)	0.22 (0.19, 0.25)

15													1	0.38 (0.35, 0.40)	0.03 (-0.00, 0.06)	-0.03 (-0.07, 0.04)	0.02 (-0.02, 0.05)			
16														1	0.06 (0.03, 0.10)	0.07 (0.04, 0.11)	0.14 (0.11, 0.17)			
17															1	0.18 (0.15, 0.21)	0.14 (0.10, 0.17)			
18																1	0.23 (0.19, 0.26)			
19																	1			

Note: 1= Peer victimisation (log); 2= Mental wellbeing; 3=Depressive symptoms; 4=Life satisfaction; 5=Socioeconomic status; 6=Scholastic competence; 7= Global self-worth, 8=Childhood social skills; 9=Adolescent social skills; 10=Late adolescent social skills; 11= Self-perceived academic ability; 12=Parental closeness; 13=Sibling closeness; 14=Family support; 15=Family involvement; 16=Family cohesion; 17=Childhood friendships; 18=Adolescent friendships; 19=Late adolescent friendships. Colour of cell is used to indicate the strength of the p-value of the correlation. The three shades of red represent $p<0.001$, $p<0.01$ and $p<0.05$ respectively, with white used to denote $p>0.05$. Variables 6-11 comprise of protective factors at the individual level, variables 12-17 comprise of family-level protective factors, and 18-19 are the peer-level protective factors. Correlations were conducted using samples with available information related to the included measures only, therefore samples ranged from n=2185 to n=7261.

Appendix 5.4: Variables included in multiple imputation

Variable	Measure	Age at assessment	Question answered by	Number of items	Sample item	Item response options	Item scoring
Ethnicity of child	1 item	32 weeks gestation	Mother	2	"How would you describe the race or ethnic group of yourself/your partner?"	8 response options, including 'Other (please describe)'.	Child's ethnic background defined as non-white if either mother or father are non-white
Mother's age at first pregnancy	1 item	18 weeks gestation	Mother	1	"How old were you when you became pregnant for the very first time?"	Open response.	Higher score signifies higher age
Homeownership status	1 item	8 months	Mother	1	"Do you currently live in.."	6 response options including "Mortgaged" and "Rented from private landlord"	Higher score signifies greater home ownership
Mother marital status	1 item	32 weeks gestation	Mother	1	"What is your present marital status?	6 response options including "Married" and "Separated"	High score signifies currently married
Mother and partner educational qualifications	2 items	32 weeks gestation	Mother	2	"What educational qualifications do you/your partner have?"	List of qualifications, respondent must tick all that apply	Higher score signifies more educational qualifications
Maternal smoking during pregnancy	1 item	32 weeks gestation	Mother	1	"How many cigarettes per day are you yourself smoking?"	Open response	Greater tar intake
Maternal depression	Edinburgh Postnatal Depression Scale[a]	32 weeks gestation	Mother	10	"Felt sad/miserable in past week"	4-point scale ranging, including 'Yes, most of the time"	Greater depressive symptoms

Adolescent depressive symptoms	Moods and Feelings Questionnaire[b]	13	Child	9	“Teenager felt miserable or unhappy”	3-pont scale ranging from “Not at all” to “True”	Greater depressive symptoms
Childhood IQ	Wechsler Intelligence Scale for Children (WISC)[c]	8	Child	-	-	Responses range from 45 to 151.	Higher IQ

Note: Multiple imputation was conducted using these sociodemographic factors. These were selected as they have previously been associated with missingness in ALSPAC[d]. In total, 60 imputations were ran using Chained Equations (MICE).

[a] Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry, 150,* 782-786.

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Appendix 5.5: Skew of outcome and protective factor variables

Variable	N in full dataset	Skew	N in current study	Skew
Peer victimisation (untransformed)	6537	2.40	2302	2.33
Peer victimisation (transformed)	6537	0.72	2302	0.67
Mental Wellbeing	4044	-0.37	2302	-0.44
Life satisfaction	4072	-0.60	2302	-0.64
Depressive symptoms	3980	1.09	2302	0.86
Scholastic competence	6862	-0.20	2302	-0.28
Global self-worth	6851	-0.69	2296	-0.71
Self-perceived academic ability	6683	-0.35	2360	-0.29
Childhood social skills	7818	-2.20	2330	-2.14
Adolescent social skills	6847	-2.20	2339	-2.41
Late adolescent social skills	5413	-1.90	2092	-2.12
Closeness to parents	4032	-0.97	1838	-0.90
Closeness to siblings	3768	-0.76	1712	-0.73
Family support	4027	-0.38	1833	-0.39
Family involvement	3984	-0.31	1824	-0.41
Family cohesion	4035	-0.70	1838	-0.74
Childhood friendships	6913	-1.02	2303	-0.99
Adolescent friendships	6162	-0.75	2398	-0.77
Late adolescent friendships	3803	-0.89	1726	-0.83

Note: Skew for the peer victimisation and outcome variables were calculated in the current study using the first protective factor.

Appendix 5.6: Impact of victimisation (log-transformed and untransformed), social skills (log-transformed), and their interaction on wellbeing, life satisfaction and depressive symptoms at 23 years

	Wellbeing											
	Protective Factor				Victimisation			Interaction				
	N	β (95% C.I.)	SE	P value	β (95% C.I)	SE	P value	β (95% C.I)	SE	P value	R^2	ΔR^2
Based on victimisation (log-transformed)												
Childhood social skills	2,330	1.06 (0.512, 1.61)	0.279	**1.5E-04**	-1.27 (-1.74, -0.794)	0.241	**1.6E-07**	-0.067 (-0.557, 0.422)	0.250	0.788	3.02%	0.96%
Adolescent social skills	2,339	0.850 (0.314, 1.39)	0.274	**0.002**	-1.23 (-1.71, -0.758)	0.243	**4.0E-07**	0.464 (-0.022, 0.950)	0.248	0.061	3.59%	1.62%
Late adolescent social skills	2,092	0.853 (0.300, 1.41)	0.282	**0.003**	-1.15 (-1.64, -0.647)	0.254	**7.1E-06**	0.449 (-0.043, 0.942)	0.251	0.074	3.63%	1.77%
Based on victimisation (untransformed)												
Childhood social skills	2,330	1.15 (0.679, 1.63)	0.242	**1.9E-06**	-0.385 (-0.522, -0.247)	0.070	**5.2E-08**	-0.080 (-0.208, 0.049)	0.066	0.226	3.11%	0.99%
Adolescent social skills	2,339	1.16 (0.688, 1.62)	0.239	**1.4E-06**	-0.373 (-0.512, -0.233)	0.071	**1.8E-07**	0.024 (-0.109, 0.157)	0.068	0.723	3.55%	1.47%
Late adolescent social skills	2,092	1.12 (0.644, 1.60)	0.244	**4.5E-06**	-0.338 (-0.481, -0.194)	0.073	**4.4E-06**	0.044 (-0.089, 0.178)	0.068	0.517	3.57%	1.66%
	Life satisfaction											
Based on victimisation (log-transformed)												
Childhood social skills	2,339	0.837 (0.432, 1.24)	0.207	**5.3E-05**	-0.962 (-1.31, -0.613)	0.178	**7.0E-08**	-0.156 (-0.519, 0.206)	0.184	0.397	3.32%	0.99%
Adolescent social skills	2,353	0.760 (0.367, 1.15)	0.200	**1.5E-04**	-0.915 (-1.26, -0.567)	0.177	**2.6E-07**	0.404 (0.048, 0.760)	0.182	**0.026**	4.93%	2.43%
Late adolescent social skills	2,100	0.724 (0.318, 1.13)	0.207	**4.8E-04**	-0.889 (-1.25, -0.524)	0.186	**1.9E-06**	0.319 (-0.042, 0.681)	0.184	0.083	4.67%	2.19%
Based on victimisation (untransformed)												

Childhood social skills	2,330	0.906 (0.555, 1.26)	0.179	**4.4E-07**	-0.313 (-0.414, -0.121)	0.051	**1.6E-09**	-0.102 (-0.197, -0.007)	0.049	**0.036**	3.64%	1.30%
Adolescent social skills	2,339	0.963 (0.621, 1.31)	0.175	**3.8E-08**	-0.284 (-0.384, -0.182)	0.051	**3.8E-08**	0.050 (-0.047, 0.147)	0.050	0.314	4.98%	2.49%
Late adolescent social skills	2,092	0.917 (0.566, 1.27)	0.179	**3.3E-07**	-0.275 (-0.380, -0.171)	0.053	**2.5E-07**	0.029 (-0.069, 0.126)	0.050	0.563	4.75%	2.27%
						Depressive symptoms						
Based on victimisation (log-transformed)												
Childhood social skills	2,330	-0.096 (-0.152, -0.040)	0.029	**7.1E-04**	0.188 (0.140, 0.235)	0.024	**1.4E-14**	0.034 (-0.016, 0.084)	0.025	0.171	4.35%	0.47%
Adolescent social skills	2,339	-0.121 (-0.177, -0.067)	0.028	**1.3E-05**	0.177 (0.129, 0.225)	0.025	**7.2E-13**	0.016 (-0.033, 0.066)	0.025	0.510	4.80%	1.60%
Late adolescent social skills	2,092	-0.101 (-0.159, -0.044)	0.029	**4.4E-04**	0.158 (0.108, 0.209)	0.026	**8.9E-10**	-0.004 (-0.055, 0.046)	0.025	0.860	4.65%	1.89%
Based on victimisation (untransformed)												
Childhood social skills	2,330	-0.099 (-0.148, -0.051)	0.025	**5.2E-05**	0.054 (0.040, 0.068)	0.007	**1.8E-14**	0.015 (0.002, 0.029)	0.007	**0.020**	4.47%	0.68%
Adolescent social skills	2,339	-0.133 (-0.181, -0.085)	0.024	**3.9E-08**	0.049 (0.035, 0.064)	0.007	**3.6E-12**	0.011 (-0.003, 0.025)	0.007	0.102	4.94%	1.82%
Late adolescent social skills	2,092	-0.117 (-0.167, -0.068)	0.025	**2.1E-06**	0.043 (0.028, 0.058)	0.007	**4.E-09**	0.004 (-0.010, 0.018)	0.007	0.520	4.56%	1.88%

Note: R^{2} = the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^{2} = the incremental R^{2}. This is the percentage of variance explained by the addition of the protective factor. The ΔR^{2} was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained.

All models adjusted for sex and socioeconomic status. Results for depressive symptoms were conducted using negative binomial regressions.

Appendix 5.7: Impact of victimisation (untransformed), protective factors, and their interaction on wellbeing at 23 years

	Wellbeing											
	Protective Factor				Victimisation			Interaction				
	N	β (95% C.I.)	SE	*p* value	β (95% C.I)	SE	*p* value	β (95% C.I)	SE	*p* value	R^2	ΔR^2
Individual-level												
Scholastic competence	2,302	0.223 (-0.233, 0.678)	0.232	0.337	-0.380 (-0.519, -0.241)	0.071	**9.5E-08**	0.170 (0.038, 0.302)	0.067	**0.011**	2.63%	0.54%
Global self-worth	2,296	0.774 (0.310, 1.24)	0.237	**0.001**	-0.379 (-0.519, -0.238)	0.072	**1.3E-07**	0.048 (-0.086, 0.181)	0.068	0.483	2.97%	0.81%
Academic ability	2,360	1.32 (0.876, 1.76)	0.225	**3.2E-07**	-0.382 (-0.518, -0.247)	0.069	**1.4E-07**	0.049 (-0.080, .0178)	0.066	0.461	4.51%	2.31%
Childhood social skills	2,330	1.29 (0.775, 1.80)	0.261	**8.9E-07**	-0.382 (-0.519, -0.244)	0.070	**5.5E-08**	-0.081 (-0.203, 0.041)	0.062	0.191	3.15%	1.02%
Adolescent social skills	2,339	1.29 (0.796, 1.78)	0.250	**2.9E-07**	-0.379 (-0.518, -0.240)	0.070	**9.6E-08**	-0.005 (-0.132, 0.121)	0.065	0.934	3.61%	1.53%
Late adolescent social skills	2,092	1.29 (0.803, 1.79)	0.251	**2.7E-07**	-0.336 (-0.480, -0.193)	0.073	**4.7E-06**	0.013 (-0.113, 0.139)	0.064	0.836	3.82%	1.91%
Family-level												
Closeness to parents	1,838	1.19 (0.068, 1.69)	0.258	**4.5E-06**	-0.311 (-0.463, -.159)	0.077	**6.3E-05**	0.075 (-0.072, 0.222)	0.075	0.318	3.80%	2.11%
Closeness to siblings	1,712	1.48 (0.096, 1.99)	0.262	**2.1E-08**	-0.339 (-0.497, -.181)	0.081	**2.7E-05**	-0.009 (-0.248, 0.070)	0.081	0.274	3.76%	2.08%
Family support	1,833	1.37 (0.894, .185)	0.243	**2.1E-08**	-0.301 (-0.455, -.147)	0.078	**1.2E-04**	0.066 (-0.076, 0.208)	0.072	0.359	4.46%	2.74%
Family involvement	1,824	0.767 (0.278, 1.26)	0.250	**0.002**	-0.317 (-0.471, -.163)	0.078	**5.7E-05**	0.141 (-0.009, 0.292)	0.077	0.067	2.86%	1.40%
Family cohesion	1,838	1.23 (0.732, 1.73)	0.255	**1.5E-06**	-0.268 (-0.214, -.115)	0.078	**6.0E-04**	0.098 (-0.050, 0.246)	0.075	0.194	4.24%	2.53%
Peer-level												
Childhood friendships	2,303	0.557 (0.101, 1.01)	0.232	**0.017**	-0.401 (-0.545, -0.257)	0.073	**5.1E-08**	0.004 (-0.124, 0.132)	0.065	0.957	2.67%	0.29%
Adolescent friendships	2,398	0.974 (0.523, 1.42)	0.230	**2.4E-05**	-0.382 (-0.536, -0.228)	0.078	**1.2E-06**	-0.020 (-0.140, 0.101)	0.061	0.749	3.14%	0.95%

Late adolescent friendships	1,811	2.29 (1.81, 2.76)	0.245	**2.0E-16**	-0.331 (-0.490, -0.172)	0.081	**4.6E-05**	-0.204 (-0.349, -0.006)	0.074	**0.006**	6.86%	5.13%

Note: R^2 = the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the addition of the protective factor. The ΔR^2 was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained. All models adjusted for sex and socioeconomic status.

Appendix 5.8: Impact of victimisation (untransformed), protective factors, and their interaction on life satisfaction and depressive symptoms at 23 years

	Life satisfaction											
	Protective Factor				Victimisation			Interaction				
	N	β (95% C.I.)	SE	*p* value	β (95% C.I)	SE	*p* value	β (95% C.I)	SE	*p* value	R^2	ΔR^2
Individual-level												
Scholastic competence	2,302	2,302	0.171	**0.040**	-0.320 (-0.422, -0.218)	0.052	**9.0E-10**	0.054 (-0.041, 0.148)	0.048	0.264	3.09%	0.71%
Global self-worth	2,296	2,296	0.175	**3.7E-04**	-0.317 (-0.420, 0.215)	0.052	**1.6E-09**	0.021 (-0.077, 0.119)	0.050	0.677	3.59%	1.14%
Academic ability	2,360	2,360	0.167	**2.4E-09**	-0.314 (-0.413, -0.215)	0.050	**5.4E-10**	-0.030 (-0.126, 0.066)	0.049	0.538	4.39%	1.84%
Childhood social skills	2,330	2,330	0.161	**3.7E-07**	-0.292 (-0.391, -0.192)	0.051	**1.1E-08**	-0.167 (-0.313, -0.021)	0.075	**0.025**	3.46%	1.25%
Adolescent social skills	2,339	2,339	0.183	**1.4E-08**	-0.291 (-0.392, -0.191)	0.051	**1.4E-08**	0.028 (-0.065, 0.121)	0.047	0.553	4.76%	2.39%
Late adolescent social skills	2,092	2,092	0.185	**9.4E-08**	-0.275 (-0.379, -0.170)	0.053	**2.7E-07**	0.021 (-0.071, 0.113)	0.047	0.659	4.70%	2.36%
Family-level												
Closeness to parents	1,838	1,838	0.192	**5.5E-08**	-0.287 (-0.400, -0.175)	0.057	**6.3E-07**	-0.020 (-0.129, 0.090)	0.056	0.726	4.22%	2.11%
Closeness to siblings	1,712	1,712	0.197	**1.9E-05**	-0.328 (-0.446, -0.211)	0.060	**4.9E-08**	-0.050 (-0.168, 0.069)	0.061	0.412	3.17%	1.16%
Family support	1,833	1,833	0.183	**6.7E-07**	-0.276 (-0.389, -0.162)	0.058	**2.2E-06**	0.062 (-0.043, 0.168)	0.054	0.244	4.46%	2.32%
Family involvement	1,824	1,824	0.186	**8.3E-05**	-0.291 (-0.404, -0.177)	0.058	**5.9E-07**	0.066 (-0.044, 0.177)	0.056	0.240	3.56%	1.61%
Family cohesion	1,838	1,838	0.192	**1.1E-07**	-0.257 (-0.371, 0.143)	0.058	**1.1E-05**	0.022 (-0.088, 0.133)	0.056	0.694	4.56%	2.41%
Peer-level												
Childhood friendships	2,303	2,303	0.173	**0.009**	-0.352 (-0.459, -0.246)	0.054	**9.0E-11**	-0.066 (-0.160, 0.028)	0.048	0.171	2.93%	0.20%
Adolescent friendships	2,398	2,398	0.170	**2.0E-4**	-0.306 (-0.418, -0.194)	0.057	**9.8E-08**	-0.017 (-0.105, 0.070)	0.045	0.701	3.13%	0.68%

Late adolescent friendships	1,811	1,811	0.181	**4.7E-14**	-0.292 (-0.407, -0.178)	0.058	**6.3E-07**	-0.096 (-0.198, 0.007)	0.052	0.068	5.51%	3.36%
						Depressive symptoms						
Individual-level												
Scholastic competence	2,302	-0.043 (-0.090, 0.004)	0.024	0.071	0.049 (0.035, 0.063)	0.007	**5.4E-12**	-0.007 (-0.020, 0.006)	0.007	0.303	3.91%	0.65%
Global self-worth	2,296	-0.079 (-0.126, -0.031)	0.024	**0.001**	0.048 (0.034, 0.063)	0.007	**1.8E-11**	-0.001 (-0.015, 0.012)	0.007	0.829	4.06%	0.82%
Academic ability	2,360	-0.112 (-0.158, -0.067)	0.023	**1.2E-06**	0.052 (0.038, 0.066)	0.007	**9.6E-14**	0.004 (-0.009, 0.018)	0.007	0.518	4.83%	1.40%
Childhood social skills	2,330	-0.111 (-0.164, -0.060)	0.026	**2.4E-05**	0.053 (0.039, 0.067)	0.007	**1.9E-14**	0.016 (0.003, 0.028)	0.006	**0.010**	4.63%	0.84%
Adolescent social skills	2,339	-0.146 (-0.198, -0.096)	0.025	**5.8E-09**	0.050 (0.036, 0.064)	0.007	**2.3E-12**	0.013 (0.001, 0.027)	0.006	**0.036**	5.39%	2.28%
Late adolescent social skills	2,092	-0.120 (-0.172, -0.068)	0.025	**2.1E-06**	0.043 (0.028, 0.058)	0.007	**4.8E-09**	0.005 (-0.009, 0.019)	0.006	0.435	4.92%	2.23%
Family-level												
Closeness to parents	1,838	-0.095 (-.0148, -0.041)	0.027	**3.9E-04**	0.043 (0.028, 0.060)	0.008	**3.9E-08**	-0.005 (-0.020, 0.010)	0.008	0.517	4.66%	1.79%
Closeness to siblings	1,712	-0.102 (-.0157, -0.048)	0.027	**1.7E-04**	0.051 (0.035, 0.068)	0.008	**4.4E-10**	0.004 (-0.012, 0.021)	0.008	0.570	4.16%	0.77%
Family support	1,833	-0.104 (-0.154, -0.055)	0.025	**3.9E-05**	0.044 (0.027, 0.060)	0.008	**5.9E-08**	-0.004 (-0.019, 0.011)	0.007	0.598	4.53%	1.65%
Family involvement	1,824	-0.094 (-0.145, -0.043)	0.026	**2.8E-04**	0.049 (0.033, 0.065)	0.008	**9.5E-10**	-0.001 (-0.017, 0.014)	0.008	0.875	4.15%	1.14%
Family cohesion	1,838	-0.102 (-0.155, -0.049)	0.026	**1.0E-04**	0.042 (0.026, 0.058)	0.008	**1.9E-07**	-0.004 (-0.020, 0.012)	0.008	0.629	4.31%	1.47%
Peer-level												
Childhood friendships	2,303	-0.067 (-0.113, -0.021)	0.024	**0.005**	0.054 (0.039, 0.069)	0.007	**2.5E-13**	0.007 (-0.005, 0.020)	0.007	0.256	3.73%	0.18%
Adolescent friendships	2,398	-0.073 (-0.118, -0.028)	0.023	**0.002**	0.049 (0.034, 0.065)	0.007	**3.3E-10**	0.004 (-0.008, 0.016)	0.006	0.506	3.72%	0.64%
Late adolescent friendships	1,811	-0.171 (-0.222, -0.119)	0.026	**3.6E-11**	0.049 (0.032, 0.066)	0.008	**5.2E-09**	0.019 (0.002, 0.034)	0.008	**0.015**	4.13%	1.42%

Note: R^2 = the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^2 = the incremental R^2. This is the percentage of variance explained by the addition of the protective factor. The ΔR^2 was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained. Analyses predicting depressive symptoms were conducted using negative binomial regressions. All models adjusted for sex and socioeconomic status.

Appendix 5.9: Loadings of principal components on the individual, family, and peer-level protective factors

	Loadings	
Protective factor	**PC1**	**PC2**
Individual-level		
Scholastic competence	0.11	-0.65
Global self-worth	0.14	-0.60
Academic ability	0.15	0.13
Childhood social skills	0.48	0.06
Adolescent social skills	0.54	0.14
Late adolescent social skills	0.48	0.12
Family-level		
Closeness to parents	0.49	-
Closeness to siblings	0.41	-
Family support	0.47	-
Family involvement	0.33	-
Family cohesion	0.51	-
Peer-level		
Childhood friendships	-0.49	-
Adolescent friendships	-0.64	-
Late adolescent friendships	-0.59	-
Combined PCA		
Individual-level protective factors	-0.61	-
Family-level protective factors	0.59	-
Peer-level protective factors	-0.52	-

Note: The combined component was created using a hierarchical PCA of PC1 at the individual-level, family, and peer-level. This component accounted for 41.1% of the variance. PC1 at the individual-level accounted for 34.7% of the variance, while PC2 accounted for 21.6% of the variance. The family-level component accounted for 52.7% of the variance and the peer-level component accounted for 45.8%. Analyses predicting the individual-level protective factors used factors 1 and 2 to ensure the variance explained was similar to analyses predicting the family and peer-level protective factors.

Appendix 5.10: Impact of victimisation (log-transformed), protective factors, and their interaction on wellbeing at 23 years (imputed dataset)

	Wellbeing										
	Protective Factor			Victimisation			Interaction				
	β (95% C.I.)	SE	*p* value	β (95% C.I)	SE	*p* value	β (95% C.I)	SE	*p* value	R^2	ΔR^2
Individual-level											
Scholastic competence	0.482 (0.101, 0.866)	0.194	**0.013**	-1.15 (-1.51, -0.781)	0.187	**9.40E-10**	0.448 (0.089, 0.807)	0.183	**0.015**	2.59%	0.94%
Global self-worth	0.841 (0.453, 1.23)	0.198	**2.20E-05**	-1.08 (-1.45, -0.717)	0.187	**7.60E-10**	0.188 (-0.166, 0.543)	0.181	0.297	2.84%	1.19%
Academic ability	1.32 (0.940, 1.70)	0.195	**1.40E-11**	-1.10 (-1.47, -0.740)	0.186	**2.90E-09**	0.087 (-0.270, 0.445)	0.182	0.632	3.93%	2.30%
Childhood social skills	2.65 (1.95, 3.35)	0.359	**1.80E-13**	-1.12 (-1.49, -0.756)	0.187	**1.90E-09**	-0.167 (-0.540, 0.208)	0.190	0.385	2.95%	1.31%
Adolescent social skills	0.886 (0.499, 1.27)	0.197	**7.30E-06**	-1.07 (-1.44, -0.703)	0.187	**1.20E-08**	0.162 (-0.192, 0.515)	0.180	0.371	2.79%	1.16%
Late adolescent social skills	0.717 (0.316, 1.12)	0.204	**4.50E-04**	-0.985 (-1.35, -0.618)	0.187	**1.50E-05**	0.666 (0.305, 1.03)	0.184	**3.00E-04**	3.57%	1.93%
Family-level											
Closeness to parents	1.16 (0.781, 1.54)	0.194	**2.30E-09**	-1.12 (-1.48, -0.755)	0.185	**1.70E-09**	0.376 (0.022, 0.729)	0.181	**0.037**	4.27%	2.63%
Closeness to siblings	1.25 (0.870, 1.62)	0.192	**9.10E-11**	-1.16 (-1.52, -0.798)	0.185	**3.90E-10**	0.127 (-0.227, 0.482)	0.181	0.482	3.82%	2.18%
Family support	1.59 (1.22, 1.96)	0.191	**2.00E-16**	-1.12 (-1.48, -0.755)	0.184	**1.54E-09**	0.129 (-0.223, 0.481)	0.180	0.473	5.09%	3.45%
Family involvement	0.702 (0.319, 1.09)	0.196	**3.40E-04**	-1.18 (-1.54, -0.811)	0.186	**2.90E-10**	0.364 (0.007, 0.721)	0.182	**0.045**	2.88%	1.24%
Family cohesion	1.22 (0.838, 1.60)	0.194	**3.10E-10**	-0.937 (-1.30, -0.573)	0.186	**4.90E-07**	0.471 (0.117, 0.825)	0.180	**9.00E-04**	4.74%	3.10%
Peer-level											
Childhood friendships	0.492 (0.101, 0.883)	0.200	**0.014**	-1.14 (-1.51, -0.767)	0.189	**1.90E-09**	-0.030 (-0.389, 0.330)	0.184	0.872	1.91%	0.26%

Adolescent friendships	0.886 (0.486, 1.29)	0.204	**1.50E-05**	-1.02 (-1.40, -0.646)	0.193	**1.10E-07**	-0.172 (-0.512, 0.169)	0.174	0.323	2.30%	0.65%
Late adolescent friendships	2.02 (1.65, 2.40)	0.191	**2.00E-16**	-0.978 (-1.34, -0.615)	0.185	**1.30E-07**	-0.180 (-0.523, 0.163)	0.175	0.302	5.93%	4.28%

Note: R^2 is the variance accounted for by the main and interactive effects of victimisation and the protective factor, as well as the covariates. ΔR^2 represents the incremental R^2. This is the percentage of variance explained by the addition of the protective factor. The ΔR^2 was calculated by regressing the outcome on victimisation and the covariates, and then including the interaction term with the protective factor and comparing the variance explained. Imputed dataset n=4044. All models adjusted for sex and socioeconomic status.

Appendix 5.11: Impact of victimisation (log-transformed), principal components, and their interaction on wellbeing at 23 years

		Wellbeing			
		Protective factor (PC)	Victimisation	Interaction	
	N	β (95%C.I.)	β (95%C.I.)	β (95%C.I.)	ΔR^2
Individual-level					
PC1	1,571	**0.95 (0.33, .1.6)****	**-1.0 (-1.6, -0.43)*****	**0.94 (0.37, 1.5)****	4.1%
PC2	1,571	0.52 (-0.09, 1.1)	**-1.4 (-1.9, -0.82)*****	-0.00 (-0.54, 0.54)	0.3%
Family-level					
PC1	1,663	**1.7 (1.1, 2.3)*****	**-0.97 (-1.5, -0.43)*****	0.09 (-0.43, 0.61)	4.2%
Peer-level					
PC1	1,476	**-1.9 (-2.5, -1.3)*****	**-0.70 (-1.3, -0.10)***	0.32 (-0.25, 0.89)	3.6%
Combined					
PC1	939	**-2.3 (-3.1, -1.5)*****	-0.03 (-0.78, 0.72)	-0.09 (-0.80, 0.63)	7.2%

Note: ***p<0.001, **p<0.01, *p<0.05. ΔR^2 represents the incremental $R^{2.}$ The combined component was created using a hierarchical PCA of PC1 at the individual-level, family, and peer-level.

Appendix 5.12: Impact of victimisation (log-transformed), principal components, and their interaction on life satisfaction and depressive symptoms

		Life satisfaction				Depressive symptoms			
		Protective factor (PC)	Victimisation	Interaction		Protective factor (PC)	Victimisation	Interaction	
	N	β (95%C.I.)	β (95%C.I.)	β (95%C.I.)	ΔR^2	β (95%C.I.)	β (95%C.I.)	β (95%C.I.)	ΔR^2
Individual-level									
PC1	1,571	**0.82 (0.38, 1.3)*** **	**-0.67 (-1.1, -0.25)*** **	**0.70 (0.29, 1.1)** **	4.9%	**-0.11 (-0.17, -0.05)*** **	**0.16 (0.10, 0.22)*** **	-0.03 (-0.09, 0.03)	3.9%
PC2	1,571	0.41 (-0.04, 0.86)	**-1.0 (-1.4, -0.58)*** **	-0.13 (-0.53, 0.26)	0.3%	**-0.06 (-0.12, 0.00)**	**0.19 (0.14, 0.25)*** **	0.01 (-0.04, 0.06)	0.1%
Family-level									
PC1	1,663	**1.2 (0.80, 1.7)*** **	**-0.78 (-1.2, -0.38)*** **	0.07 (-0.32, 0.46)	3.9%	**-0.12 (-0.18, -0.06)*** **	**0.16 (0.11, 0.22)*** **	-0.02 (-0.08, 0.03)	2.2%
Peer-level									
PC1	1,476	**-1.1 (-1.6, -0.64)*** **	**-0.55 (-1.0, -0.10)***	0.07 (-0.36, 0.49)	2.5%	**0.13 (0.06, 0.19)*** **	**0.12 (0.06, 0.19)*** **	-0.01 (-0.07, 0.05)	1.2%
Combined									
PC1	939	**-1.8 (-2.3, -1.2)*** **	-0.03 (-0.58, 0.51)	-0.19 (-0.33, 0.71)	6.5%	**0.15 (0.08, 0.23)*** **	**0.09 (0.01, 0.18)***	-0.00 (-0.07, 0.07)	3.1%

Note: ***p<0.001, **p<0.01, *p<0.05.

ΔR^2 represents the incremental R^2. The combined component was created using a hierarchical PCA of PC1 at the individual-level, family, and peer-level.

Appendix 6.1: List of SNPs used from the educational attainment GWAS in univariable MR predicting wellbeing

							Association with years of schooling			Association with wellbeing		
SNP	**Inclusion in original 74 SNPs**	**CHR**	**POS**	**A1**	**A2**	**EAF**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**
rs10006235	Not included	4	1.31E+08	C	T	0.7127	0.015	0.003	2.63E-08	1.21E-03	0.0010	0.122
rs1008078	Included	1	9.12E+07	T	C	0.3731	-0.016	0.003	7.88E-11	-9.18E-04	0.0010	0.167
rs1035578	Not included	16	1.25E+07	A	G	0.569	-0.013	0.002	4.71E-08	-6.56E-04	0.0009	0.241
rs10483349	Not included	14	2.96E+07	G	A	0.1698	0.019	0.003	3.02E-09	-3.41E-05	0.0012	0.489
rs10772644	Not included	12	1.34E+07	C	G	0.8713	0.021	0.004	4.11E-08	-1.06E-04	0.0015	0.471
rs10831912	Not included	11	1.29E+07	C	T	0.597	0.015	0.003	1.23E-08	-4.78E-04	0.0010	0.308
rs1106761	Not included	8	1.43E+08	A	G	0.3601	-0.017	0.003	4.08E-11	2.22E-03	0.0010	0.010
rs11130222	Not included	3	4.99E+07	T	A	0.4235	-0.026	0.003	4.58E-25	-2.02E-03	0.0009	0.016
rs11191193	Included	10	1.04E+08	G	A	0.3489	-0.019	0.003	6.97E-13	-1.35E-03	0.0010	0.083
rs12410444	Not included	1	4.42E+07	G	A	0.2817	0.018	0.003	2.14E-11	3.27E-04	0.0010	0.374
rs12514965	Not included	5	1.14E+08	C	T	0.2612	-0.018	0.003	5.12E-10	3.63E-03	0.0011	4.00E-04
rs12761761	Not included	10	1.34E+08	T	C	0.2071	0.017	0.003	3.19E-08	1.85E-03	0.0011	0.045
rs12962421	Not included	18	4.48E+07	G	A	0.4627	0.014	0.002	1.50E-08	-1.36E-03	0.0009	0.074
rs12969294	Included	18	3.52E+07	G	A	0.6213	0.018	0.003	1.11E-11	7.68E-03	0.0010	1.96E-15
rs12987662	Included	2	1.01E+08	A	C	0.3787	0.022	0.003	3.25E-18	2.01E-04	0.0010	0.416
rs13010288	Not included	2	5.18E+07	T	G	0.1119	0.02	0.004	2.21E-08	9.26E-04	0.0014	0.255
rs13421974	Not included	2	1.55E+08	C	T	0.4776	-0.014	0.002	8.96E-09	-6.35E-04	0.0009	0.248

rs1378214	Not included	15	4.76E+07	C	T	0.6175	0.016	0.003	1.20E-10	3.71E-03	0.0010	5.54E-05
rs1424580	Not included	7	1.33E+08	T	C	0.8004	0.018	0.003	9.58E-09	9.67E-04	0.0012	0.205
rs152590	Not included	5	1.07E+08	C	G	0.3433	0.014	0.003	4.83E-08	-2.46E-04	0.0010	0.401
rs16845580	Included	2	1.62E+08	C	T	0.3694	-0.016	0.003	2.07E-10	-2.30E-03	0.0010	0.008
rs17425572	Not included	9	8.80E+07	G	A	0.5597	-0.014	0.002	4.58E-08	-1.19E-03	0.0009	0.102
rs17824247	Included	2	1.44E+08	C	T	0.4198	0.018	0.003	5.29E-13	3.38E-03	0.0009	1.00E-04
rs2456973	Included	12	5.64E+07	C	A	0.3209	0.018	0.003	1.58E-12	-5.40E-04	0.0010	0.292
rs3095075	Not included	4	3.25E+06	G	A	0.4496	0.014	0.002	3.53E-08	2.94E-03	0.0009	8.00E-04
rs320700	Not included	7	1.37E+08	A	G	0.6343	0.016	0.003	1.50E-09	1.82E-03	0.0010	0.031
rs34344888	Not included	14	2.34E+07	G	A	0.6026	0.016	0.003	1.11E-10	7.80E-04	0.0010	0.206
rs35771425	Not included	1	2.12E+08	C	T	0.2052	-0.019	0.003	2.61E-10	2.08E-03	0.0011	0.033
rs4240470	Not included	9	1.25E+08	C	G	0.7071	0.016	0.003	2.63E-09	1.67E-03	0.0010	0.052
rs4244613	Not included	8	1.46E+08	A	G	0.416	-0.014	0.003	9.94E-09	-2.26E-03	0.0009	0.008
rs4468571	Not included	15	7.80E+07	G	A	0.4235	0.014	0.003	2.59E-08	4.99E-03	0.0009	5.30E-08
rs4478846	Not included	1	9.84E+07	T	C	0.8526	0.018	0.003	1.93E-08	-6.19E-04	0.0013	0.312
rs4493682	Included	5	4.52E+07	C	G	0.2034	0.019	0.003	2.27E-08	1.70E-03	0.0012	0.078
rs4800490	Not included	18	2.11E+07	C	A	0.4571	0.015	0.002	2.13E-09	-6.56E-04	0.0009	0.240
rs4863692	Included	4	1.41E+08	T	G	0.334	0.018	0.003	3.80E-12	1.75E-03	0.0010	0.039
rs4974424	Not included	3	1.27E+08	G	A	0.1735	0.019	0.003	2.64E-08	-1.20E-04	0.0013	0.462
rs523934	Not included	11	9.56E+07	A	G	0.416	0.015	0.003	1.09E-08	4.93E-05	0.0009	0.479

rs538628	Not included	17	4.48E+07	C	G	0.2444	-0.018	0.003	2.16E-08	-5.42E-03	0.0011	7.54E-07
rs58694847	Not included	14	8.49E+07	C	G	0.3097	-0.018	0.003	7.41E-11	-2.39E-03	0.0010	0.011
rs61160187	Included	5	6.01E+07	G	A	0.3806	0.018	0.003	5.93E-13	8.90E-04	0.0010	0.176
rs62100767	Not included	18	5.07E+07	G	A	0.3993	-0.014	0.003	1.11E-08	-7.01E-03	0.0010	8.03E-14
rs62263923	Included	3	8.57E+07	G	A	0.3563	0.016	0.003	1.63E-09	-1.70E-04	0.0010	0.431
rs6839705	Not included	4	1.06E+08	C	A	0.6399	-0.017	0.003	1.72E-11	1.33E-03	0.0010	0.086
rs6882046	Not included	5	8.80E+07	G	A	0.3134	0.021	0.003	7.92E-14	-6.86E-03	0.0010	1.87E-11
rs7029201	Not included	9	2.34E+07	A	G	0.4235	0.025	0.003	6.13E-23	2.26E-03	0.0009	0.008
rs7146434	Not included	14	6.47E+07	G	A	0.4347	0.014	0.002	3.74E-08	-3.70E-03	0.0009	3.76E-05
rs7599488	Not included	2	6.07E+07	T	C	0.4254	-0.017	0.002	2.05E-11	-2.77E-04	0.0009	0.384
rs766406	Not included	6	2.63E+07	T	G	0.6194	0.014	0.003	1.89E-08	1.68E-03	0.0010	0.041
rs7757476	Not included	6	1.47E+07	A	G	0.2313	0.02	0.003	9.37E-10	1.19E-03	0.0012	0.154
rs7964899	Not included	12	1.46E+07	A	G	0.4571	0.017	0.002	1.99E-11	-8.33E-04	0.0009	0.187
rs8049439	Not included	16	2.88E+07	C	T	0.3451	-0.015	0.003	2.69E-09	4.68E-04	0.0010	0.312
rs9527702	Not included	13	5.84E+07	G	A	0.2369	-0.023	0.003	4.99E-17	-2.92E-03	0.0011	0.003
rs9556958	Not included	13	9.91E+07	T	C	0.5019	-0.015	0.002	1.89E-09	-5.43E-03	0.0009	2.71E-09
rs9616906	Not included	22	5.11E+07	A	G	0.4515	0.015	0.003	1.73E-09	1.67E-03	0.0009	0.037
rs9739070	Not included	12	1.24E+08	G	A	0.7705	-0.024	0.003	3.95E-16	-1.84E-03	0.0011	0.052

Appendix 6.2: List of SNPs used from the wellbeing GWAS in univariable MR predicting educational attainment

							Association with wellbeing			Association with years of schooling		
SNP	**Inclusion in original 232 SNPs**	**CHR**	**POS**	**A1**	**A2**	**EAF**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**
rs10044064	Not included	5	1.07E+08	G	A	0.283	0.006	0.001	2.88E-08	0.001	0.003	0.744
rs10252771	Not included	7	1.17E+08	G	T	0.320	-0.007	0.001	1.33E-12	-0.005	0.003	0.079
rs10491952	Included	9	11455955	T	C	0.216	0.009	0.001	8.24E-16	0.009	0.003	0.002
rs10497655	Not included	2	1.85E+08	C	T	0.311	0.006	0.001	2.48E-10	-0.005	0.003	0.063
rs10746509	Included	1	2.3E+08	T	C	0.412	-0.005	0.001	9.28E-09	0.002	0.003	0.334
rs10774909	Included	12	1.18E+08	G	C	0.203	-0.009	0.001	1.17E-15	0.005	0.003	0.142
rs10789340	Not included	1	72940273	G	A	0.635	-0.007	0.001	5.03E-14	0.01	0.003	0.000
rs10812851	Included	9	28607877	C	T	0.367	0.006	0.001	4.40E-10	-0.006	0.003	0.014
rs10936879	Included	3	1.76E+08	C	T	0.351	0.006	0.001	3.40E-09	0.004	0.003	0.143
rs10967509	Included	9	26746922	A	G	0.379	0.005	0.001	7.25E-09	-0.001	0.003	0.660
rs111871194	Included	5	1.66E+08	C	T	0.099	0.009	0.002	3.57E-09	0.008	0.004	0.037
rs1150697	Not included	6	28175636	G	C	0.107	-0.009	0.002	6.17E-10	-0.006	0.004	0.173
rs11599236	Included	10	1.06E+08	C	T	0.416	0.008	0.001	4.70E-16	0.007	0.003	0.004
rs11604333	Included	11	57467035	G	C	0.321	-0.007	0.001	1.35E-12	-0.01	0.003	1.19E-04
rs11610143	Included	12	52349071	G	C	0.201	-0.008	0.001	4.61E-12	-0.002	0.003	0.536
rs11675585	Not included	2	24237180	C	T	0.618	0.006	0.001	1.17E-09	0.004	0.003	0.078
rs11693031	Included	2	2.13E+08	G	A	0.331	0.007	0.001	1.01E-12	0.008	0.003	0.004

rs12003380	Not included	9	17135434	C	G	0.448	0.006	0.001	6.69E-10	0.001	0.002	0.814
rs12112864	Not included	7	1.1E+08	A	G	0.152	-0.007	0.001	4.24E-08	0.002	0.003	0.517
rs12374076	Included	3	29764315	G	A	0.505	-0.005	0.001	2.68E-09	-0.002	0.002	0.321
rs12436091	Included	14	30028491	C	T	0.760	-0.007	0.001	6.25E-10	-0.006	0.003	0.055
rs12513440	Included	5	7259853	A	G	0.250	-0.006	0.001	1.66E-08	-0.003	0.003	0.309
rs12521969	Not included	5	61512846	C	A	0.505	-0.006	0.001	6.07E-10	0.006	0.002	0.012
rs12706745	Not included	7	1.26E+08	T	C	0.388	-0.006	0.001	9.65E-12	-0.006	0.003	0.011
rs12788968	Not included	11	1.27E+08	A	G	0.347	-0.005	0.001	2.77E-08	-0.003	0.003	0.251
rs12794371	Included	11	1.27E+08	T	G	0.332	-0.006	0.001	1.10E-09	0	0.003	0.993
rs12910872	Included	15	97169999	T	C	0.121	0.008	0.001	1.48E-08	-0.003	0.004	0.486
rs12958048	Not included	18	53101598	G	A	0.668	0.007	0.001	1.99E-13	0.002	0.003	0.356
rs13072536	Not included	3	52861211	T	A	0.234	0.008	0.001	4.37E-12	-0.002	0.003	0.461
rs1329572	Included	9	37001471	A	T	0.373	-0.005	0.001	7.39E-09	0.001	0.003	0.721
rs13409834	Included	2	22173664	G	A	0.499	0.005	0.001	9.41E-09	0.001	0.003	0.834
rs1371325	Included	4	1.39E+08	G	A	0.597	-0.006	0.001	6.96E-11	-0.001	0.003	0.819
rs1431071	Included	2	2.26E+08	T	G	0.285	0.007	0.001	3.61E-12	0.008	0.003	0.003
rs1551840	Included	3	1.17E+08	A	G	0.386	0.005	0.001	3.09E-08	-0.001	0.003	0.609
rs16958292	Included	15	74097901	G	T	0.135	0.008	0.001	9.45E-09	0.009	0.004	0.017
rs17041417	Included	12	1.03E+08	A	G	0.181	-0.007	0.001	5.34E-10	-0.01	0.003	0.00254
rs1707115	Included	1	1.18E+08	C	T	0.254	0.006	0.001	3.03E-08	0.011	0.003	8.35E-05

rs171697	Included	5	1.04E+08	G	C	0.336	-0.008	0.001	2.84E-15	-0.012	0.003	4.89E-06
rs17186681	Included	15	63988765	T	A	0.198	-0.007	0.001	5.94E-09	0.003	0.003	0.319
rs17583539	Included	2	1.69E+08	G	A	0.225	-0.007	0.001	1.33E-09	-0.001	0.003	0.678
rs17782464	Not included	12	72698280	G	A	0.156	0.008	0.001	3.02E-10	0.003	0.003	0.390
rs1892350	Included	13	68080614	G	A	0.491	-0.005	0.001	1.76E-08	-0.003	0.002	0.279
rs1908643	Not included	10	1.08E+08	A	G	0.110	0.008	0.001	3.46E-08	-0.006	0.004	0.150
rs1940735	Not included	11	1.13E+08	G	T	0.258	-0.007	0.001	4.24E-10	-0.007	0.003	0.014
rs1950835	Included	14	42076640	T	G	0.513	0.005	0.001	1.15E-08	0.002	0.002	0.443
rs198457	Included	11	61471678	T	C	0.187	0.007	0.001	3.66E-09	-0.002	0.003	0.612
rs2071754	Not included	11	31812582	T	C	0.806	0.008	0.001	7.79E-13	0.003	0.003	0.394
rs2093623	Included	10	10922977	A	G	0.489	0.006	0.001	1.21E-11	0.006	0.002	0.014
rs2102341	Included	1	37193908	C	T	0.702	0.007	0.001	1.67E-13	0.004	0.003	0.138
rs2105841	Included	16	13764812	C	T	0.381	-0.007	0.001	2.93E-13	0.007	0.003	0.005
rs210915	Not included	6	11712343	T	C	0.805	0.008	0.001	5.54E-11	-0.001	0.003	0.659
rs2149351	Included	9	1.21E+08	G	T	0.759	0.008	0.001	7.91E-15	0.002	0.003	0.414
rs215816	Not included	1	37667068	A	C	0.298	-0.007	0.001	2.49E-11	-0.004	0.003	0.167
rs2179744	Included	22	41621714	A	G	0.292	-0.007	0.001	5.43E-13	0.002	0.003	0.428
rs2273653	Included	20	47770756	C	A	0.406	0.006	0.001	2.40E-11	-0.012	0.003	4.19E-06
rs2302832	Included	14	75137664	C	T	0.524	-0.008	0.001	1.15E-16	-0.002	0.002	0.515
rs2398144	Included	16	56352854	A	C	0.404	-0.006	0.001	2.53E-11	-0.001	0.003	0.839

rs2458167	Included	11	99500748	C	A	0.686	0.008	0.001	2.99E-14	0	0.003	0.978
rs2589341	Included	8	35425197	C	T	0.343	-0.006	0.001	2.06E-09	-0.004	0.003	0.148
rs261909	Included	12	22874365	C	G	0.436	-0.006	0.001	1.43E-11	-0.003	0.002	0.256
rs2721811	Included	7	24749429	G	A	0.423	-0.006	0.001	2.38E-11	0.007	0.002	0.004
rs28427480	Included	9	98264942	C	A	0.101	-0.011	0.002	1.14E-13	0.004	0.004	0.335
rs285006	Included	16	77077289	A	G	0.342	-0.005	0.001	1.85E-08	-0.004	0.003	0.093
rs2964003	Not included	5	1.53E+08	G	A	0.169	0.007	0.001	3.86E-08	0.003	0.003	0.446
rs297346	Included	11	16355771	G	A	0.637	0.006	0.001	1.32E-09	0.003	0.003	0.304
rs301806	Included	1	8482078	T	C	0.566	0.007	0.001	7.37E-13	-0.005	0.003	0.045
rs306755	Included	20	3099752	C	T	0.465	0.005	0.001	1.45E-08	0.007	0.002	0.003
rs35609938	Included	2	58756729	C	T	0.508	-0.006	0.001	3.76E-12	0.003	0.002	0.222
rs36008138	Not included	17	2559056	T	C	0.262	0.006	0.001	1.61E-08	0.001	0.003	0.703
rs3748400	Not included	16	87445839	T	C	0.766	0.006	0.001	4.82E-08	0.009	0.003	0.002
rs3785234	Included	16	7667392	T	C	0.621	-0.007	0.001	2.71E-13	0.007	0.003	0.007
rs3793577	Included	9	23737627	G	A	0.532	-0.007	0.001	1.22E-13	-0.007	0.003	0.007
rs3811935	Included	5	27025400	G	A	0.497	0.005	0.001	2.17E-09	-0.004	0.002	0.104
rs3846828	Included	6	24282117	A	C	0.108	-0.008	0.001	8.97E-09	0.002	0.004	0.656
rs3936093	Not included	15	78101909	G	A	0.570	-0.006	0.001	1.04E-11	0	0.003	0.934
rs4244117	Not included	1	1.07E+08	A	C	0.742	-0.006	0.001	1.14E-08	0.001	0.003	0.840
rs4362360	Not included	15	86940622	C	T	0.465	0.005	0.001	1.91E-08	0.005	0.002	0.034

rs4461738	Included	6	1.01E+08	C	T	0.464	-0.006	0.001	3.98E-10	-0.001	0.002	0.729
rs4526571	Not included	1	1.76E+08	A	G	0.383	0.006	0.001	2.40E-09	0.003	0.003	0.207
rs4543289	Included	5	1.64E+08	G	T	0.525	-0.007	0.001	3.60E-14	0.004	0.002	0.125
rs45534736	Not included	4	1.23E+08	G	C	0.055	0.011	0.002	2.05E-08	0.015	0.006	0.008
rs4554778	Included	10	68530042	T	C	0.802	0.007	0.001	1.55E-10	0.007	0.003	0.018
rs4654874	Included	1	21156667	G	A	0.563	-0.006	0.001	1.82E-11	-0.005	0.002	0.052
rs4671459	Included	2	63392872	C	A	0.195	0.009	0.001	3.77E-14	0.001	0.003	0.855
rs4739938	Included	8	84259443	G	T	0.086	-0.009	0.002	3.49E-08	-0.002	0.004	0.593
rs4800901	Not included	18	26574983	G	T	0.308	-0.006	0.001	1.23E-09	0.007	0.003	0.008
rs483143	Included	6	27846744	C	G	0.117	0.014	0.001	3.02E-23	0.001	0.004	0.774
rs4836189	Included	5	1.25E+08	G	C	0.406	-0.006	0.001	1.21E-09	-0.002	0.003	0.423
rs4837685	Not included	9	1.23E+08	A	G	0.605	-0.007	0.001	2.60E-12	-0.005	0.003	0.049
rs4895894	Not included	6	1.31E+08	T	C	0.361	-0.005	0.001	4.07E-08	-0.002	0.003	0.526
rs534815	Not included	11	88704918	C	T	0.518	0.008	0.001	1.21E-19	0.002	0.002	0.373
rs550980	Not included	11	74642250	T	C	0.527	0.005	0.001	4.13E-08	-0.004	0.002	0.095
rs55748329	Included	17	79045773	G	A	0.138	0.010	0.001	2.13E-14	-0.002	0.004	0.652
rs56080343	Not included	12	1.19E+08	C	T	0.188	-0.007	0.001	2.01E-10	0.004	0.003	0.254
rs60192801	Not included	2	1.56E+08	A	T	0.293	-0.007	0.001	8.34E-11	0.002	0.003	0.427
rs6072299	Not included	20	39806772	G	A	0.171	-0.007	0.001	3.37E-08	0.007	0.003	0.025
rs6131010	Included	20	44724305	G	A	0.737	0.007	0.001	5.38E-11	0.009	0.003	0.001

rs62041356	Included	16	73710150	C	G	0.133	-0.008	0.001	1.50E-08	0.001	0.004	0.735
rs6589377	Not included	11	1.13E+08	A	G	0.627	-0.010	0.001	7.27E-26	-0.005	0.003	0.046
rs66511648	Included	3	1.18E+08	C	T	0.274	-0.006	0.001	3.10E-09	0.003	0.003	0.331
rs6721577	Included	2	22433763	T	A	0.583	-0.006	0.001	1.58E-10	-0.002	0.003	0.328
rs6771469	Included	3	65173884	C	T	0.402	0.005	0.001	3.98E-08	0.01	0.003	0.000
rs6773869	Included	3	16870340	G	A	0.353	-0.006	0.001	6.76E-10	-0.012	0.003	0.000
rs6776145	Included	3	50316119	C	T	0.121	-0.009	0.001	7.89E-11	0.003	0.004	0.432
rs6925748	Included	6	50930041	G	A	0.420	-0.006	0.001	6.60E-12	0.003	0.002	0.233
rs6943746	Included	7	38907695	G	T	0.386	0.006	0.001	2.23E-11	-0.002	0.003	0.432
rs6988649	Not included	8	1035729	T	C	0.202	-0.006	0.001	2.49E-08	-0.002	0.003	0.431
rs7010590	Included	8	11062882	C	T	0.508	-0.007	0.001	7.49E-16	0.002	0.002	0.380
rs7021901	Included	9	1.28E+08	T	C	0.444	0.005	0.001	7.21E-09	0.001	0.002	0.650
rs703409	Not included	10	1.19E+08	T	C	0.258	0.007	0.001	1.39E-10	0.001	0.003	0.824
rs7107356	Included	11	47676170	G	A	0.507	-0.007	0.001	2.92E-13	-0.005	0.002	0.026
rs7154329	Included	14	41824444	G	A	0.500	0.005	0.001	2.46E-09	-0.003	0.002	0.184
rs716508	Included	16	6336912	T	C	0.683	0.008	0.001	6.04E-16	-0.004	0.003	0.129
rs7396827	Included	11	28577867	C	T	0.534	0.005	0.001	9.95E-09	0.003	0.003	0.236
rs74504435	Included	7	54949256	G	A	0.102	0.009	0.002	6.21E-09	0.006	0.004	0.147
rs7547071	Not included	1	2.27E+08	T	C	0.449	0.005	0.001	3.34E-08	-0.004	0.002	0.149
rs7585722	Not included	2	86819128	C	T	0.150	-0.007	0.001	4.00E-08	0.005	0.003	0.176

rs7703782	Not included	5	87938557	A	T	0.136	-0.010	0.001	1.36E-14	0.016	0.004	1.17E-05
rs77214504	Not included	1	75316394	T	A	0.046	0.012	0.002	1.14E-08	0.02	0.006	0.002
rs7789405	Included	7	82945270	T	C	0.575	0.006	0.001	9.67E-10	-0.001	0.002	0.771
rs779995	Included	2	1.25E+08	C	T	0.374	-0.005	0.001	7.86E-09	-0.005	0.003	0.041
rs7805419	Included	7	12282451	C	T	0.416	-0.007	0.001	1.02E-12	-0.001	0.003	0.685
rs7841297	Included	8	65549342	C	G	0.850	-0.008	0.001	8.64E-11	-0.001	0.004	0.811
rs78962708	Not included	7	4129323	A	G	0.033	-0.014	0.003	2.28E-08	-0.012	0.008	0.116
rs8001600	Included	13	94041035	C	T	0.346	-0.006	0.001	6.35E-10	-0.003	0.003	0.322
rs8070287	Not included	17	1854772	A	G	0.182	-0.006	0.001	4.70E-08	0.011	0.003	0.000802
rs815721	Not included	1	1.9E+08	T	C	0.287	-0.005	0.001	4.69E-08	0.002	0.003	0.498
rs827123	Included	3	1.58E+08	C	T	0.580	-0.006	0.001	1.60E-10	-0.002	0.002	0.329

Appendix 6.3: List of SNPs used from the intelligence GWAS in univariable MR

							Association with intelligence			Association with wellbeing		
SNP	**Inclusion in original 242 SNPs**	**CHR**	**POS**	**A1**	**A2**	**EAF**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**
rs1007934	Included	14	7.35E+07	A	G	0.412	0.016	0.003	1.00E-08	-0.002	0.001	0.007
rs10189857	Included	2	6.07E+07	G	A	0.432	-0.019	0.003	4.91E-12	0.000	0.001	0.457
rs10189912	Included	2	1.44E+08	G	A	0.366	0.019	0.003	1.22E-11	0.003	0.001	4.90E+04
rs1054442	Included	12	4.94E+07	C	A	0.371	0.021	0.003	2.52E-14	0.000	0.001	0.345
rs10779271	Included	1	2.17E+08	G	A	0.307	-0.016	0.003	2.17E-08	0.000	0.001	0.359
rs10917152	Included	1	2.24E+07	T	C	0.137	0.024	0.004	2.23E-09	-0.001	0.001	0.345
rs10954779	Included	8	3.10E+07	T	C	0.551	-0.016	0.003	3.04E-09	-0.001	0.001	0.091
rs11076962	Included	16	5.81E+06	C	T	0.289	-0.017	0.003	2.57E-08	-0.004	0.001	0.000
rs11079849	Included	17	4.71E+07	T	C	0.320	0.017	0.003	2.26E-08	0.001	0.001	0.233
rs112780312	Included	1	1.54E+08	A	G	0.284	-0.018	0.003	3.66E-09	0.001	0.001	0.297
rs1145123	Included	5	1.11E+08	C	T	0.479	-0.021	0.003	1.20E-13	0.000	0.001	0.484
rs115064	Included	7	2.42E+07	C	T	0.398	-0.016	0.003	1.07E-08	0.002	0.001	0.036
rs11605348	Included	11	4.76E+07	A	G	0.349	-0.017	0.003	9.73E-09	0.006	0.001	7.81E-11
rs11623436	Not included	14	3.70E+07	T	C	0.452	-0.016	0.003	9.70E-09	0.002	0.001	0.024
rs11634187	Included	15	4.07E+07	G	T	0.165	-0.022	0.004	1.12E-08	-0.002	0.001	0.044
rs11646221	Included	16	7.67E+06	T	G	0.580	0.018	0.003	1.57E-10	-0.006	0.001	7.82E-12
rs11678106	Included	2	8.24E+07	T	C	0.513	0.016	0.003	4.62E-09	0.001	0.001	0.091

rs11720523	Included	3	7.15E+07	A	C	0.425	0.018	0.003	3.89E-11	0.002	0.001	0.021
rs11793831	Included	9	2.34E+07	T	G	0.420	0.028	0.003	3.25E-23	0.002	0.001	0.007
rs11898362	Included	2	7.36E+07	A	G	0.291	-0.018	0.003	2.25E-09	-0.002	0.001	0.047
rs12026245	Not included	1	1.04E+08	A	G	0.503	-0.018	0.003	6.05E-11	-0.001	0.001	0.200
rs12035012	Included	1	4.18E+07	A	C	0.218	-0.027	0.003	3.68E-16	0.000	0.001	0.403
rs12190777	Not included	6	9.84E+07	G	A	0.281	-0.017	0.003	3.63E-08	0.002	0.001	0.025
rs12470949	Included	2	2.39E+07	C	T	0.722	0.017	0.003	1.32E-08	0.003	0.001	0.003
rs1280049	Included	6	7.65E+07	C	A	0.511	-0.015	0.003	3.92E-08	-0.001	0.001	0.172
rs12886584	Not included	14	4.11E+07	C	T	0.187	-0.021	0.004	9.41E-09	0.000	0.001	0.491
rs13071190	Included	3	1.37E+08	C	T	0.322	-0.018	0.003	5.55E-10	0.001	0.001	0.263
rs13165296	Not included	5	5.96E+07	C	A	0.168	-0.020	0.004	2.44E-08	0.004	0.001	0.002
rs13212044	Included	6	1.27E+08	T	G	0.252	-0.018	0.003	1.46E-08	-0.003	0.001	0.006
rs13223152	Included	7	6.99E+07	G	A	0.401	-0.018	0.003	2.34E-10	0.003	0.001	6.92E-04
rs13253386	Included	8	1.40E+07	G	T	0.501	0.020	0.003	2.37E-13	0.003	0.001	0.002
rs13276212	Included	8	6.64E+07	T	G	0.519	0.015	0.003	4.48E-08	0.001	0.001	0.282
rs1362739	Included	7	1.33E+08	A	C	0.481	0.021	0.003	1.83E-14	0.004	0.001	2.54E-05
rs1369429	Included	15	8.84E+07	C	T	0.687	-0.018	0.003	1.15E-09	0.004	0.001	1.54E-05
rs1408579	Included	10	1.02E+08	T	C	0.487	0.016	0.003	5.23E-09	-0.001	0.001	0.170
rs144246	Included	4	1.73E+07	A	G	0.377	0.015	0.003	4.91E-08	-0.001	0.001	0.194
rs1589652	Included	3	3.55E+07	G	A	0.556	-0.017	0.003	5.82E-10	-0.002	0.001	0.032

rs166820	Included	5	8.94E+07	A	G	0.156	0.024	0.004	1.37E-11	0.002	0.001	0.056
rs17106817	Included	14	6.97E+07	C	T	0.274	-0.017	0.003	2.26E-08	-0.003	0.001	0.004
rs1727307	Included	12	1.24E+08	G	A	0.710	-0.018	0.003	3.10E-09	0.001	0.001	0.270
rs1812587	Included	5	6.30E+07	T	G	0.469	-0.017	0.003	3.68E-10	-0.001	0.001	0.183
rs1831539	Included	1	5.96E+07	C	T	0.477	0.017	0.003	4.72E-10	-0.002	0.001	0.017
rs1840847	Included	5	1.31E+07	A	G	0.331	0.016	0.003	1.44E-08	-0.001	0.001	0.237
rs1906252	Included	6	9.86E+07	A	C	0.490	0.032	0.003	7.48E-31	0.001	0.001	0.095
rs1962047	Included	12	5.83E+07	A	G	0.383	-0.020	0.003	8.89E-12	0.004	0.001	1.60E-05
rs1972860	Included	4	9.46E+07	A	G	0.299	-0.018	0.003	2.09E-09	0.003	0.001	0.003
rs2007176	Not included	2	2.00E+08	C	T	0.445	-0.015	0.003	2.64E-08	-0.001	0.001	0.167
rs2008514	Included	16	2.88E+07	A	G	0.383	-0.029	0.003	1.25E-24	0.001	0.001	0.273
rs2071407	Included	14	1.04E+08	C	T	0.636	0.022	0.003	1.52E-14	-0.006	0.001	8.27E-10
rs2072490	Included	19	1.83E+07	T	C	0.521	0.017	0.003	5.93E-10	0.000	0.001	0.312
rs2239647	Included	14	3.33E+07	C	A	0.551	0.021	0.003	1.14E-13	-0.001	0.001	0.135
rs2268894	Included	2	1.63E+08	T	C	0.530	0.021	0.003	3.98E-14	0.000	0.001	0.464
rs2285640	Included	17	3.50E+07	A	G	0.533	0.018	0.003	2.38E-10	-0.004	0.001	2.49E-05
rs2309812	Included	2	1.01E+08	T	C	0.377	0.023	0.003	9.95E-16	0.001	0.001	0.218
rs2352974	Included	3	4.99E+07	T	C	0.485	-0.031	0.003	3.69E-29	-0.002	0.001	0.006
rs2373353	Included	11	7.92E+07	G	A	0.362	0.016	0.003	1.56E-08	0.000	0.001	0.356
rs2393967	Included	10	6.51E+07	C	A	0.313	0.019	0.003	2.70E-10	0.000	0.001	0.480

rs2450333	Included	5	1.77E+08	A	G	0.528	-0.019	0.003	1.73E-11	0.002	0.001	0.024
rs2457192	Included	16	1.22E+07	A	C	0.695	-0.020	0.003	2.83E-10	0.001	0.001	0.109
rs2558096	Included	2	1.38E+08	G	T	0.601	0.016	0.003	1.74E-08	0.002	0.001	0.013
rs2647995	Included	16	5.16E+07	C	T	0.281	0.020	0.003	8.68E-11	-0.003	0.001	0.005
rs2678210	Included	1	2.02E+08	C	T	0.317	-0.019	0.003	6.97E-10	-0.002	0.001	0.011
rs2721173	Included	8	1.46E+08	T	C	0.469	-0.016	0.003	2.89E-09	-0.002	0.001	0.008
rs2726491	Included	4	1.06E+08	A	G	0.381	-0.028	0.003	4.17E-23	0.004	0.001	1.63E-06
rs2836921	Included	21	4.05E+07	A	G	0.345	0.020	0.003	6.54E-12	-0.001	0.001	0.184
rs28620532	Included	9	9.82E+07	G	A	0.355	0.016	0.003	1.51E-08	-0.003	0.001	0.003
rs287879	Included	6	1.57E+08	G	A	0.301	0.019	0.003	8.47E-10	0.001	0.001	0.149
rs2920940	Included	8	9.32E+07	C	T	0.764	0.025	0.003	2.76E-14	-0.003	0.001	0.001
rs2955280	Included	2	4.41E+07	T	C	0.489	-0.015	0.003	4.90E-08	0.002	0.001	0.005
rs297578	Not included	2	1.57E+08	A	G	0.698	0.018	0.003	1.73E-09	0.001	0.001	0.120
rs3128341	Included	1	7.27E+07	C	T	0.797	0.032	0.003	1.63E-20	-0.001	0.001	0.157
rs329672	Included	11	1.34E+08	T	C	0.622	0.017	0.003	1.00E-09	0.003	0.001	0.000
rs34316	Included	5	8.80E+07	C	A	0.568	-0.021	0.003	2.82E-14	0.004	0.001	9.69E-06
rs35608616	Included	10	1.25E+08	A	G	0.356	-0.018	0.003	7.33E-10	0.001	0.001	0.171
rs35731967	Included	2	2.00E+08	C	T	0.193	-0.022	0.004	2.38E-09	-0.001	0.001	0.194
rs36033	Included	5	6.10E+07	C	T	0.424	-0.016	0.003	1.02E-08	-0.001	0.001	0.231
rs405321	Not included	5	1.14E+08	A	G	0.310	-0.016	0.003	3.32E-08	0.002	0.001	0.01

rs4463213	Included	5	1.40E+08	A	G	0.550	0.019	0.003	3.00E-12	-0.005	0.001	4.47E-07
rs4667954	Not included	2	1.64E+08	C	T	0.279	-0.017	0.003	1.20E-08	0.000	0.001	0.343
rs4725065	Included	7	8.11E+06	G	A	0.505	0.017	0.003	1.52E-09	-0.001	0.001	0.08
rs4731392	Included	7	1.28E+08	G	A	0.313	0.022	0.003	2.69E-13	0.000	0.001	0.344
rs4821995	Included	22	4.15E+07	G	A	0.666	-0.016	0.003	2.62E-08	-0.003	0.001	9.85E-05
rs4852252	Included	2	7.15E+07	C	T	0.557	0.021	0.003	3.84E-14	-0.003	0.001	5.88E-04
rs4976976	Included	8	1.43E+08	A	G	0.406	0.017	0.003	4.53E-10	0.004	0.001	1.71E-05
rs4981713	Not included	14	3.01E+07	G	T	0.393	-0.016	0.003	7.23E-09	-0.005	0.001	5.01E-08
rs55754731	Included	12	1.55E+07	C	T	0.163	-0.021	0.004	6.06E-09	-0.003	0.001	0.006
rs55763037	Not included	5	9.26E+07	G	A	0.212	-0.018	0.003	3.74E-08	-0.002	0.001	0.055
rs566237	Included	6	1.15E+07	G	A	0.316	0.019	0.003	1.82E-10	0.000	0.001	0.413
rs5750830	Included	22	3.98E+07	A	C	0.741	0.023	0.003	2.46E-13	0.000	0.001	0.415
rs58593843	Included	2	6.05E+07	A	G	0.080	-0.028	0.005	2.67E-09	0.001	0.002	0.246
rs59142272	Included	3	1.40E+08	A	G	0.167	0.023	0.004	7.32E-10	-0.003	0.001	0.016
rs600806	Not included	1	1.10E+08	A	G	0.723	-0.019	0.003	3.57E-10	0.002	0.001	0.033
rs6019535	Included	20	4.75E+07	A	G	0.322	0.025	0.003	3.28E-17	-0.006	0.001	8.51E-09
rs60262711	Included	2	1.18E+08	T	C	0.381	0.016	0.003	1.65E-08	0.001	0.001	0.244
rs62181012	Included	2	1.81E+08	C	T	0.205	-0.021	0.004	1.73E-09	0.001	0.001	0.099
rs6508220	Included	18	5.08E+07	G	A	0.491	0.023	0.003	9.56E-17	0.005	0.001	1.49E-08
rs6535809	Included	4	1.53E+08	G	A	0.483	-0.020	0.003	6.65E-13	-0.001	0.001	0.085

rs6539284	Included	12	7.96E+07	C	T	0.424	0.019	0.003	5.56E-12	0.001	0.001	0.087
rs6550835	Included	3	2.41E+07	A	G	0.316	-0.025	0.003	2.44E-17	0.000	0.001	0.349
rs6668048	Included	1	9.62E+07	T	C	0.481	-0.021	0.003	4.24E-15	-0.003	0.001	0.003
rs66954617	Included	17	5.70E+07	G	A	0.624	0.021	0.003	1.72E-13	0.000	0.001	0.407
rs6770622	Included	3	8.52E+07	A	G	0.040	-0.045	0.007	5.76E-11	0.001	0.002	0.265
rs6819372	Included	4	6.80E+07	G	A	0.524	0.020	0.003	4.02E-13	0.003	0.001	0.001
rs6860963	Included	5	1.69E+08	T	C	0.200	0.020	0.003	5.57E-09	-0.002	0.001	0.049
rs6903716	Included	6	2.20E+07	G	A	0.285	-0.018	0.003	2.39E-09	-0.001	0.001	0.174
rs702222	Included	9	2.38E+07	T	C	0.353	-0.020	0.003	5.02E-12	-0.001	0.001	0.151
rs7069887	Included	10	2.96E+07	C	A	0.141	-0.023	0.004	7.44E-09	-0.001	0.001	0.291
rs7116046	Included	11	1.06E+08	T	C	0.386	0.016	0.003	3.27E-08	0.001	0.001	0.092
rs7172979	Included	15	5.18E+07	T	G	0.031	0.061	0.009	2.47E-11	-0.001	0.003	0.413
rs7248006	Included	19	3.19E+07	C	T	0.616	0.019	0.003	1.05E-11	0.000	0.001	0.365
rs72768642	Not included	16	2.47E+07	C	T	0.069	0.031	0.005	1.46E-08	0.005	0.002	0.006
rs7357604	Not included	8	1.43E+08	G	A	0.389	-0.016	0.003	2.56E-08	0.003	0.001	0.004
rs7640196	Not included	3	5.42E+07	T	C	0.231	-0.017	0.003	3.15E-08	-0.002	0.001	0.027
rs7652296	Included	3	8.96E+07	G	A	0.400	-0.017	0.003	3.51E-09	0.001	0.001	0.172
rs7731260	Not included	5	1.08E+08	A	G	0.484	0.015	0.003	2.50E-08	0.000	0.001	0.475
rs7941785	Included	11	6.39E+07	G	A	0.634	-0.016	0.003	4.75E-08	-0.001	0.001	0.084
rs799444	Included	7	4.48E+07	C	T	0.540	-0.018	0.003	2.48E-11	0.000	0.001	0.407

rs80170948	Included	5	6.40E+07	G	T	0.042	-0.045	0.007	7.69E-10	0.000	0.002	0.464
rs8025964	Included	15	8.25E+07	A	G	0.465	0.017	0.003	5.78E-10	-0.002	0.001	0.031
rs8051038	Included	16	7.19E+07	A	G	0.737	0.019	0.003	1.78E-09	0.001	0.001	0.217
rs889169	Included	19	4.75E+07	A	G	0.619	0.016	0.003	2.75E-08	0.000	0.001	0.474
rs9384679	Included	6	1.09E+08	T	C	0.384	-0.027	0.003	7.94E-22	0.000	0.001	0.356
rs9503599	Included	6	3.45E+06	C	T	0.449	0.017	0.003	8.05E-10	0.000	0.001	0.451
rs9516855	Included	13	9.78E+07	G	A	0.052	-0.033	0.006	4.19E-08	-0.008	0.002	0.000
rs967569	Included	2	4.16E+07	T	C	0.645	-0.018	0.003	8.21E-10	-0.001	0.001	0.134
rs9888986	Included	16	6.83E+07	A	G	0.106	-0.024	0.004	3.52E-08	-0.002	0.002	0.059

Appendix 6.4: List of SNPs used from the wellbeing GWAS in univariable MR predicting intelligence

							Association with wellbeing			Association with intelligence		
SNP	**Inclusion in original 232 SNPs**	**CHR**	**POS**	**A1**	**A2**	**EAF**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**
rs10044064	Not included	5	1.07E+08	G	A	0.283	0.006	0.001	2.88E-08	-0.003	0.003	0.325
rs10252771	Not included	7	1.17E+08	G	T	0.320	-0.007	0.001	1.33E-12	0.006	0.003	0.029
rs10491952	Included	9	11455955	T	C	0.216	0.009	0.001	8.24E-16	0.008	0.003	0.025
rs10497655	Not included	2	1.85E+08	C	T	0.311	0.006	0.001	2.48E-10	0.001	0.003	0.688
rs10746509	Included	1	2.3E+08	T	C	0.412	-0.005	0.001	9.28E-09	-0.003	0.003	0.272
rs10789340	Not included	1	72940273	G	A	0.635	-0.007	0.001	5.03E-14	0.014	0.003	6.61E-07
rs10812851	Included	9	28607877	C	T	0.367	0.006	0.001	4.40E-10	0.000	0.003	0.906
rs10936879	Not included	3	1.76E+08	C	T	0.351	0.006	0.001	3.40E-09	-0.006	0.003	0.044
rs10967509	Included	9	26746922	A	G	0.379	0.005	0.001	7.25E-09	0.005	0.003	0.083
rs11082011	Included	18	35145122	T	C	0.661	0.008	0.001	2.13E-17	0.006	0.003	0.035
rs111871194	Included	5	1.66E+08	C	T	0.099	0.009	0.002	3.57E-09	0.020	0.005	1.07E-05
rs11599236	Included	10	1.06E+08	C	T	0.416	0.008	0.001	4.70E-16	0.015	0.003	5.04E-08
rs11675585	Not included	2	24237180	C	T	0.618	0.006	0.001	1.17E-09	0.008	0.003	0.007
rs11693031	Included	2	2.13E+08	G	A	0.331	0.007	0.001	1.01E-12	0.009	0.003	0.003
rs12112864	Not included	7	1.1E+08	A	G	0.152	-0.007	0.001	4.24E-08	-0.007	0.004	0.069
rs12374076	Included	3	29764315	G	A	0.505	-0.005	0.001	2.68E-09	-0.005	0.003	0.057
rs12436091	Included	14	30028491	C	T	0.760	-0.007	0.001	6.25E-10	-0.006	0.003	0.042

rs12513440	Not included	5	7259853	A	G	0.250	-0.006	0.001	1.66E-08	-0.003	0.003	0.286
rs12521969	Not included	5	61512846	C	A	0.505	-0.006	0.001	6.07E-10	-0.008	0.003	0.006
rs12706745	Not included	7	1.26E+08	T	C	0.388	-0.006	0.001	9.65E-12	-0.005	0.003	0.074
rs12788968	Not included	11	1.27E+08	A	G	0.347	-0.005	0.001	2.77E-08	-0.001	0.003	0.610
rs12794371	Included	11	1.27E+08	T	G	0.332	-0.006	0.001	1.10E-09	-0.005	0.003	0.117
rs12910872	Included	15	97169999	T	C	0.121	0.008	0.001	1.48E-08	-0.003	0.004	0.472
rs12958048	Not included	18	53101598	G	A	0.668	0.007	0.001	1.99E-13	0.008	0.003	0.007
rs13165221	Not included	5	93096539	T	C	0.225	0.006	0.001	2.37E-08	0.006	0.003	0.066
rs13409834	Included	2	22173664	G	A	0.499	0.005	0.001	9.41E-09	-0.006	0.003	0.026
rs1371325	Included	4	1.39E+08	G	A	0.597	-0.006	0.001	6.96E-11	0.002	0.003	0.450
rs1431071	Included	2	2.26E+08	T	G	0.285	0.007	0.001	3.61E-12	0.011	0.003	2.54E-04
rs1551840	Included	3	1.17E+08	A	G	0.386	0.005	0.001	3.09E-08	-0.007	0.003	0.017
rs1563245	Included	15	47518807	G	T	0.400	-0.005	0.001	4.13E-08	-0.004	0.003	0.176
rs16958292	Included	15	74097901	G	T	0.135	0.008	0.001	9.45E-09	0.003	0.004	0.499
rs17041417	Included	12	1.03E+08	A	G	0.181	-0.007	0.001	5.34E-10	-0.001	0.003	0.745
rs1707115	Not included	1	1.18E+08	C	T	0.254	0.006	0.001	3.03E-08	0.005	0.003	0.154
rs17583539	Included	2	1.69E+08	G	A	0.225	-0.007	0.001	1.33E-09	-0.006	0.003	0.068
rs17782464	Not included	12	72698280	G	A	0.156	0.008	0.001	3.02E-10	0.001	0.004	0.800
rs1892350	Included	13	68080614	G	A	0.491	-0.005	0.001	1.76E-08	-0.008	0.003	0.005
rs1908643	Not included	10	1.08E+08	A	G	0.110	0.008	0.001	3.46E-08	-0.004	0.004	0.342

rs1940735	Not included	11	1.13E+08	G	T	0.258	-0.007	0.001	4.24E-10	-0.009	0.003	0.002
rs1950835	Included	14	42076640	T	G	0.513	0.005	0.001	1.15E-08	0.003	0.003	0.277
rs198457	Not included	11	61471678	T	C	0.187	0.007	0.001	3.66E-09	-0.003	0.004	0.334
rs2071754	Not included	11	31812582	T	C	0.806	0.008	0.001	7.79E-13	0.000	0.003	0.982
rs2093623	Included	10	10922977	A	G	0.489	0.006	0.001	1.21E-11	0.002	0.003	0.448
rs2102341	Included	1	37193908	C	T	0.702	0.007	0.001	1.67E-13	0.006	0.003	0.037
rs2105841	Not included	16	13764812	C	T	0.381	-0.007	0.001	2.93E-13	0.000	0.003	0.988
rs210915	Not included	6	11712343	T	C	0.805	0.008	0.001	5.54E-11	0.005	0.003	0.184
rs2149351	Included	9	1.21E+08	G	T	0.759	0.008	0.001	7.91E-15	0.002	0.003	0.606
rs215816	Not included	1	37667068	A	C	0.298	-0.007	0.001	2.49E-11	-0.007	0.003	0.018
rs2179744	Included	22	41621714	A	G	0.292	-0.007	0.001	5.43E-13	-0.011	0.003	2.15E-04
rs2273653	Included	20	47770756	C	A	0.406	0.006	0.001	2.40E-11	-0.022	0.003	8.07E-16
rs2302832	Not included	14	75137664	C	T	0.524	-0.008	0.001	1.15E-16	-0.003	0.003	0.206
rs2398144	Included	16	56352854	A	C	0.404	-0.006	0.001	2.53E-11	0.004	0.003	0.153
rs2458167	Included	11	99500748	C	A	0.686	0.008	0.001	2.99E-14	-0.001	0.003	0.761
rs2589341	Included	8	35425197	C	T	0.343	-0.006	0.001	2.06E-09	-0.002	0.003	0.555
rs2721811	Included	7	24749429	G	A	0.423	-0.006	0.001	2.38E-11	0.000	0.003	0.994
rs28427480	Included	9	98264942	C	A	0.101	-0.011	0.002	1.14E-13	0.019	0.005	4.26E-05
rs285006	Included	16	77077289	A	G	0.342	-0.005	0.001	1.85E-08	0.003	0.003	0.330
rs2964003	Not included	5	1.53E+08	G	A	0.169	0.007	0.001	3.86E-08	-0.001	0.003	0.864

rs297346	Included	11	16355771	G	A	0.637	0.006	0.001	1.32E-09	-0.001	0.003	0.744
rs301806	Included	1	8482078	T	C	0.566	0.007	0.001	7.37E-13	-0.009	0.003	7.20E-04
rs306755	Included	20	3099752	C	T	0.465	0.005	0.001	1.45E-08	0.011	0.003	4.72E-05
rs34945223	Included	18	77575871	G	A	0.264	-0.006	0.001	3.35E-08	-0.012	0.003	5.92E-05
rs35609938	Included	2	58756729	C	T	0.508	-0.006	0.001	3.76E-12	-0.001	0.003	0.624
rs36008138	Not included	17	2559056	T	C	0.262	0.006	0.001	1.61E-08	-0.002	0.003	0.546
rs3748400	Not included	16	87445839	T	C	0.766	0.006	0.001	4.82E-08	0.013	0.003	1.66E-05
rs3785234	Not included	16	7667392	T	C	0.621	-0.007	0.001	2.71E-13	0.017	0.003	6.67E-10
rs3793577	Included	9	23737627	G	A	0.532	-0.007	0.001	1.22E-13	-0.006	0.003	0.046
rs3811935	Included	5	27025400	G	A	0.497	0.005	0.001	2.17E-09	-0.007	0.003	0.012
rs3846828	Not included	6	24282117	A	C	0.108	-0.008	0.001	8.97E-09	-0.006	0.005	0.153
rs3936093	Not included	15	78101909	G	A	0.570	-0.006	0.001	1.04E-11	-0.001	0.003	0.651
rs4244117	Not included	1	1.07E+08	A	C	0.742	-0.006	0.001	1.14E-08	-0.003	0.003	0.342
rs4362360	Not included	15	86940622	C	T	0.465	0.005	0.001	1.91E-08	0.000	0.003	0.888
rs4461738	Included	6	1.01E+08	C	T	0.464	-0.006	0.001	3.98E-10	0.002	0.003	0.448
rs4526571	Not included	1	1.76E+08	A	G	0.383	0.006	0.001	2.40E-09	0.007	0.003	0.020
rs4543289	Included	5	1.64E+08	G	T	0.525	-0.007	0.001	3.60E-14	0.002	0.003	0.482
rs4554778	Included	10	68530042	T	C	0.802	0.007	0.001	1.55E-10	0.005	0.003	0.186
rs4654874	Not included	1	21156667	G	A	0.563	-0.006	0.001	1.82E-11	-0.001	0.003	0.824
rs4671459	Included	2	63392872	C	A	0.195	0.009	0.001	3.77E-14	0.015	0.003	2.51E-05

rs4739938	Included	8	84259443	G	T	0.086	-0.009	0.002	3.49E-08	-0.011	0.005	0.015
rs4800901	Not included	18	26574983	G	T	0.308	-0.006	0.001	1.23E-09	-0.007	0.003	0.02
rs4837685	Not included	9	1.23E+08	A	G	0.605	-0.007	0.001	2.60E-12	-0.014	0.003	1.15E-06
rs4895894	Not included	6	1.31E+08	T	C	0.361	-0.005	0.001	4.07E-08	-0.009	0.003	0.002
rs534815	Not included	11	88704918	C	T	0.518	0.008	0.001	1.21E-19	0.003	0.003	0.327
rs550980	Not included	11	74642250	T	C	0.527	0.005	0.001	4.13E-08	0.003	0.003	0.299
rs55748329	Included	17	79045773	G	A	0.138	0.010	0.001	2.13E-14	-0.012	0.004	0.002
rs56080343	Not included	12	1.19E+08	C	T	0.188	-0.007	0.001	2.01E-10	0.007	0.003	0.060
rs6072299	Not included	20	39806772	G	A	0.171	-0.007	0.001	3.37E-08	-0.001	0.004	0.848
rs6131010	Included	20	44724305	G	A	0.737	0.007	0.001	5.38E-11	0.012	0.003	1.40E-04
rs6589377	Not included	11	1.13E+08	A	G	0.627	-0.010	0.001	7.27E-26	-0.001	0.003	0.786
rs66511648	Included	3	1.18E+08	C	T	0.274	-0.006	0.001	3.10E-09	0.006	0.003	0.040
rs6771469	Included	3	65173884	C	T	0.402	0.005	0.001	3.98E-08	0.003	0.003	0.330
rs6776145	Included	3	50316119	C	T	0.121	-0.009	0.001	7.89E-11	-0.003	0.004	0.395
rs6925748	Included	6	50930041	G	A	0.420	-0.006	0.001	6.60E-12	-0.004	0.003	0.193
rs6943746	Included	7	38907695	G	T	0.386	0.006	0.001	2.23E-11	0.002	0.003	0.434
rs6988649	Not included	8	1035729	T	C	0.202	-0.006	0.001	2.49E-08	0.000	0.003	0.996
rs7010590	Included	8	11062882	C	T	0.508	-0.007	0.001	7.49E-16	0.007	0.003	0.010
rs7021901	Included	9	1.28E+08	T	C	0.444	0.005	0.001	7.21E-09	0.005	0.003	0.054
rs703409	Not included	10	1.19E+08	T	C	0.258	0.007	0.001	1.39E-10	-0.002	0.003	0.455

rs7107356	Included	11	47676170	G	A	0.507	-0.007	0.001	2.92E-13	0.007	0.003	0.015
rs7154329	Included	14	41824444	G	A	0.500	0.005	0.001	2.46E-09	0.003	0.003	0.343
rs716508	Included	16	6336912	T	C	0.683	0.008	0.001	6.04E-16	-0.007	0.003	0.019
rs7396827	Included	11	28577867	C	T	0.534	0.005	0.001	9.95E-09	0.007	0.003	0.008
rs74504435	Included	7	54949256	G	A	0.102	0.009	0.002	6.21E-09	0.014	0.005	0.002
rs7547071	Not included	1	2.27E+08	T	C	0.449	0.005	0.001	3.34E-08	0.006	0.003	0.027
rs7585722	Not included	2	86819128	C	T	0.150	-0.007	0.001	4.00E-08	-0.001	0.004	0.754
rs7789405	Included	7	82945270	T	C	0.575	0.006	0.001	9.67E-10	-0.008	0.003	0.004
rs779995	Included	2	1.25E+08	C	T	0.374	-0.005	0.001	7.86E-09	0.000	0.003	0.977
rs7805419	Included	7	12282451	C	T	0.416	-0.007	0.001	1.02E-12	0.004	0.003	0.159
rs78962708	Not included	7	4129323	A	G	0.033	-0.014	0.003	2.28E-08	-0.001	0.009	0.915
rs8001600	Included	13	94041035	C	T	0.346	-0.006	0.001	6.35E-10	-0.002	0.003	0.415
rs8070287	Not included	17	1854772	A	G	0.182	-0.006	0.001	4.70E-08	0.002	0.004	0.596
rs815721	Not included	1	1.9E+08	T	C	0.287	-0.005	0.001	4.69E-08	0.003	0.003	0.303
rs827123	Included	3	1.58E+08	C	T	0.580	-0.006	0.001	1.60E-10	-0.002	0.003	0.390
rs863635	Not included	3	61262414	G	A	0.406	-0.005	0.001	5.68E-09	-0.005	0.003	0.061
rs910187	Included	20	45841052	A	G	0.375	0.006	0.001	6.58E-11	0.004	0.003	0.148
rs9298995	Included	9	4145340	A	G	0.407	0.006	0.001	1.03E-09	-0.007	0.003	0.018
rs9302311	Not included	15	36267960	G	A	0.546	-0.005	0.001	4.82E-08	-0.002	0.003	0.383
rs9332801	Included	11	1.18E+08	C	A	0.063	-0.011	0.002	1.49E-09	0.001	0.006	0.873

rs9380700	Included	6	11991239	A	G	0.249	0.007	0.001	7.35E-10	-0.001	0.003	0.808
rs9427672	Not included	1	1.98E+08	G	A	0.759	-0.007	0.001	1.03E-09	0.003	0.003	0.336
rs942866	Included	14	1.04E+08	T	G	0.660	-0.007	0.001	3.96E-12	0.020	0.003	1.28E-11
rs9592461	Included	13	66941792	G	A	0.516	0.005	0.001	8.17E-09	0.002	0.003	0.5732
rs9601116	Not included	13	79251406	A	G	0.183	-0.007	0.001	1.70E-09	-0.006	0.004	0.092
rs977747	Included	1	47684677	G	T	0.592	0.005	0.001	1.56E-08	-0.014	0.003	5.63E-07
rs9854237	Not included	3	1.55E+08	C	T	0.208	-0.006	0.001	3.69E-08	-0.002	0.003	0.483
rs9855153	Not included	3	18693223	G	A	0.719	-0.006	0.001	3.59E-08	-0.003	0.003	0.296
rs993845	Not included	12	74309749	T	G	0.405	0.005	0.001	8.65E-09	0.001	0.003	0.599
rs9947894	Not included	18	31328720	G	T	0.502	-0.006	0.001	5.49E-12	-0.005	0.003	0.010
rs9992829	Not included	4	1.41E+08	T	C	0.638	0.005	0.001	1.47E-08	0.003	0.003	0.222

Appendix 6.5: List of SNPs used for multivariable MR

			Association with years of schooling			Association with intelligence			Association with wellbeing		
SNP	**A1**	**A2**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**	**BETA**	**SE**	**P**
rs10006235	C	T	0.010	0.002	1.45E-07	**0.003**	0.003	0.304	**0.001**	0.001	0.122
rs1008078	T	C	-0.017	0.002	1.20E-23	**-0.011**	0.003	1.11E-04	**-0.001**	0.001	0.167
rs10189857	G	A	-0.017	0.002	6.70E-24	**-0.019**	0.003	4.91E-12	**0.000**	0.001	0.458
rs10189912	A	G	-0.016	0.002	6.49E-20	**-0.019**	0.003	1.22E-11	**-0.003**	0.001	4.90E-04
rs1035578	A	G	-0.011	0.002	1.33E-10	**-0.009**	0.003	0.002	**-0.001**	0.001	0.241
rs10483349	G	A	0.019	0.002	1.54E-17	**0.013**	0.004	3.28E-04	**0.000**	0.001	0.489
rs10772644	G	C	-0.016	0.003	1.50E-09	**-0.008**	0.004	0.057	**0.000**	0.001	0.471
rs10779271	A	G	0.004	0.002	0.015	**0.016**	0.003	2.17E-08	**0.000**	0.001	0.359
rs10831912	C	T	0.011	0.002	5.19E-11	**0.009**	0.003	0.022	**0.000**	0.001	0.308
rs10917152	C	T	-0.006	0.003	0.0128	**-0.024**	0.004	2.23E-09	**0.001**	0.001	0.345
rs10954779	C	T	0.010	0.002	1.06E-08	**0.016**	0.003	3.04E-09	**0.001**	0.001	0.091
rs1106761	A	G	-0.017	0.002	7.71E-22	**-0.018**	0.003	9.12E-10	**0.002**	0.001	0.010
rs11076962	T	C	0.007	0.002	2.00E-04	**0.017**	0.003	2.57E-08	**0.004**	0.001	2.01E-04
rs11191193	G	A	-0.018	0.002	5.51E-23	**-0.023**	0.003	1.29E-15	**-0.001**	0.001	0.083
rs112780312	G	A	0.007	0.002	1.37E-04	**0.018**	0.003	3.66E-09	**-0.001**	0.001	0.297
rs1145123	C	T	-0.004	0.002	0.020	**-0.021**	0.003	1.20E-13	**0.000**	0.001	0.484
rs115064	C	T	-0.006	0.002	4.95E-04	**-0.016**	0.003	1.07E-08	**0.002**	0.001	0.036

rs11605348	G	A	-0.004	0.002	0.020	**0.017**	0.003	9.73E-09	**-0.006**	0.001	7.81E-11
rs11634187	T	G	0.006	0.002	0.010	**0.022**	0.004	1.12E-08	**0.002**	0.001	0.044
rs11646221	T	G	0.011	0.002	3.01E-11	**0.018**	0.003	1.57E-10	**-0.006**	0.001	7.82E-12
rs11678106	C	T	-0.004	0.002	0.011	**-0.016**	0.003	4.62E-09	**-0.001**	0.001	0.091
rs11720523	C	A	-0.013	0.002	1.54E-14	**-0.018**	0.003	3.89E-11	**-0.002**	0.001	0.021
rs11898362	G	A	0.007	0.002	6.84E-05	**0.018**	0.003	2.25E-09	**0.002**	0.001	0.047
rs12190777	A	G	0.009	0.002	5.45E-06	**0.017**	0.003	3.63E-08	**-0.002**	0.001	0.025
rs12410444	G	A	0.019	0.002	4.86E-24	**0.016**	0.003	9.40E-08	**0.000**	0.001	0.374
rs12470949	C	T	0.003	0.002	0.16	**0.017**	0.003	1.32E-08	**0.003**	0.001	0.003
rs12514965	C	T	-0.015	0.002	5.35E-14	**-0.014**	0.003	1.18E-05	**0.004**	0.001	4.1E-04
rs12535854	G	C	0.005	0.002	0.003	**0.018**	0.003	6.73E-10	**0.001**	0.001	0.245
rs12761761	T	C	0.016	0.002	8.63E-15	**0.018**	0.003	2.44E-08	**0.002**	0.001	0.045
rs1280049	A	C	0.005	0.002	0.002	**0.015**	0.003	3.92E-08	**0.001**	0.001	0.172
rs12886584	C	T	-0.007	0.002	0.002	**-0.021**	0.004	9.41E-09	**0.000**	0.001	0.491
rs12962421	A	G	-0.009	0.002	1.16E-07	**-0.003**	0.003	0.285	**0.001**	0.001	0.074
rs12969294	G	A	0.018	0.002	1.13E-23	**0.005**	0.003	0.120	**0.008**	0.001	1.96E-15
rs13010288	G	T	-0.020	0.003	1.04E-14	**-0.002**	0.004	0.621	**-0.001**	0.001	0.255
rs13071190	T	C	0.007	0.002	3.83E-05	**0.018**	0.003	5.55E-10	**-0.001**	0.001	0.263
rs13212044	G	T	0.009	0.002	1.38E-05	**0.018**	0.003	1.46E-08	**0.003**	0.001	0.006
rs13223152	G	A	-0.006	0.002	2.24E-04	**-0.018**	0.003	2.34E-10	**0.003**	0.001	0.001

rs13253386	T	G	-0.005	0.002	0.005	**-0.020**	0.003	2.37E-13	**-0.003**	0.001	0.002
rs13276212	T	G	0.004	0.002	0.033	**0.015**	0.003	4.48E-08	**0.001**	0.001	0.282
rs13421974	C	T	-0.012	0.002	1.33E-11	**-0.010**	0.003	5.34E-04	**-0.001**	0.001	0.248
rs1362739	A	C	0.010	0.002	1.16E-08	**0.021**	0.003	1.83E-14	**0.004**	0.001	2.54E-05
rs1369429	T	C	0.001	0.002	0.477	**0.018**	0.003	1.15E-09	**-0.004**	0.001	1.54E-05
rs1378214	T	C	-0.013	0.002	1.90E-14	**-0.002**	0.003	0.4367	**-0.004**	0.001	5.54E-05
rs1408579	C	T	-0.007	0.002	1.12E-05	**-0.016**	0.003	5.23E-09	**0.001**	0.001	0.170
rs144246	A	G	0.009	0.002	8.79E-08	**0.015**	0.003	4.91E-08	**-0.001**	0.001	0.194
rs1589652	G	A	-0.002	0.002	0.183	**-0.017**	0.003	5.82E-10	**-0.002**	0.001	0.032
rs166820	G	A	-0.009	0.002	3.12E-05	**-0.024**	0.004	1.37E-11	**-0.002**	0.001	0.056
rs16845580	C	T	-0.014	0.002	1.54E-15	**-0.017**	0.003	1.27E-09	**-0.002**	0.001	0.008
rs17128425	T	A	-0.007	0.003	0.0169	**-0.026**	0.005	1.87E-08	**0.002**	0.002	0.074
rs17425572	G	A	-0.012	0.002	6.89E-13	**-0.011**	0.003	9.06E-05	**-0.001**	0.001	0.102
rs1831539	C	T	0.005	0.002	0.002	**0.017**	0.003	4.72E-10	**-0.002**	0.001	0.017
rs1840847	A	G	0.005	0.002	0.005	**0.016**	0.003	1.44E-08	**-0.001**	0.001	0.237
rs1906252	C	A	-0.022	0.002	6.88E-40	**-0.032**	0.003	7.48E-31	**-0.001**	0.001	0.095
rs1972860	G	A	0.010	0.002	2.05E-08	**0.018**	0.003	2.09E-09	**-0.003**	0.001	0.003
rs2007176	T	C	0.015	0.002	2.29E-18	**0.015**	0.003	2.64E-08	**0.001**	0.001	0.167
rs2008514	A	G	-0.017	0.002	7.43E-22	**-0.029**	0.003	1.25E-24	**0.001**	0.001	0.273
rs2071407	C	T	0.009	0.002	2.25E-07	**0.022**	0.003	1.52E-14	**-0.006**	0.001	8.27E-10

rs2072490	C	T	-0.004	0.002	0.016	**-0.017**	0.003	5.93E-10	**0.000**	0.001	0.318
rs2285640	G	A	-0.006	0.002	5.47E-04	**-0.018**	0.003	2.38E-10	**0.004**	0.001	2.49E-05
rs2309812	T	C	0.021	0.002	1.80E-32	**0.023**	0.003	9.95E-16	**0.001**	0.001	0.218
rs2373353	G	A	0.007	0.002	3.54E-05	**0.016**	0.003	1.56E-08	**0.000**	0.001	0.356
rs2393967	A	C	-0.011	0.002	1.61E-09	**-0.019**	0.003	2.70E-10	**0.000**	0.001	0.480
rs2450333	A	G	-0.012	0.002	1.61E-12	**-0.019**	0.003	1.73E-11	**0.002**	0.001	0.024
rs2456973	C	A	0.017	0.002	2.99E-22	**0.015**	0.003	4.31E-07	**-0.001**	0.001	0.292
rs2478286	G	C	0.009	0.002	9.65E-06	**0.026**	0.003	1.64E-16	**0.000**	0.001	0.446
rs2558096	T	G	-0.005	0.002	0.009	**-0.016**	0.003	1.74E-08	**-0.002**	0.001	0.013
rs2647995	C	T	0.007	0.002	1.71E-04	**0.020**	0.003	8.68E-11	**-0.003**	0.001	0.005
rs2678210	T	C	0.010	0.002	7.43E-08	**0.019**	0.003	6.97E-10	**0.002**	0.001	0.011
rs2726491	G	A	0.013	0.002	1.40E-14	**0.028**	0.003	4.17E-23	**-0.004**	0.001	1.63E-06
rs2836921	A	G	0.005	0.002	0.004	**0.020**	0.003	6.54E-12	**-0.001**	0.001	0.184
rs28620532	G	A	0.004	0.002	0.012	**0.016**	0.003	1.51E-08	**-0.003**	0.001	0.003
rs287879	G	A	0.006	0.002	0.001	**0.019**	0.003	8.47E-10	**0.001**	0.001	0.149
rs2920940	T	C	-0.007	0.002	7.51E-04	**-0.025**	0.003	2.76E-14	**0.003**	0.001	0.001
rs297578	A	G	0.007	0.002	1.34E-04	**0.018**	0.003	1.73E-09	**0.001**	0.001	0.120
rs3095075	A	G	-0.012	0.002	2.10E-12	**-0.008**	0.003	0.006	**-0.003**	0.001	0.001
rs31768	A	T	0.004	0.002	0.026	**0.018**	0.003	2.65E-09	**0.002**	0.001	0.012
rs329672	C	T	-0.007	0.002	2.80E-05	**-0.017**	0.003	1.00E-09	**-0.003**	0.001	2.54E-04

rs34316	C	A	-0.020	0.002	3.35E-30	**-0.021**	0.003	2.82E-14	**0.004**	0.001	9.69E-06
rs34344888	A	G	-0.014	0.002	6.20E-15	**-0.006**	0.003	0.043	**-0.001**	0.001	0.206
rs35731967	T	C	0.007	0.002	0.007	**0.022**	0.004	2.38E-09	**0.001**	0.001	0.194
rs36033	T	C	0.003	0.002	0.059	**0.016**	0.003	1.02E-08	**0.001**	0.001	0.231
rs4240470	G	C	-0.013	0.002	7.44E-13	**-0.009**	0.003	0.003	**-0.002**	0.001	0.052
rs4244613	A	G	-0.010	0.002	2.12E-08	**-0.015**	0.005	0.0042	**-0.002**	0.001	0.008
rs4463213	A	G	0.006	0.002	6.03E-04	**0.019**	0.003	3.00E-12	**-0.005**	0.001	4.47E-07
rs4468571	A	G	-0.013	0.002	5.55E-14	**-0.006**	0.003	0.0375	**-0.005**	0.001	5.30E-08
rs4478846	T	C	0.018	0.002	8.48E-16	**0.013**	0.004	0.005	**-0.001**	0.001	0.312
rs4484297	C	G	0.005	0.002	0.015	**0.018**	0.003	7.45E-09	**0.000**	0.001	0.349
rs4493682	C	G	0.011	0.002	1.70E-06	**0.008**	0.003	0.0165	**0.002**	0.001	0.078
rs4725065	A	G	-0.012	0.002	5.94E-12	**-0.017**	0.003	1.52E-09	**0.001**	0.001	0.080
rs4731392	A	G	-0.009	0.002	5.51E-07	**-0.022**	0.003	2.69E-13	**0.000**	0.001	0.344
rs4800490	C	A	0.014	0.002	3.04E-16	**0.008**	0.003	0.004	**-0.001**	0.001	0.240
rs4821995	A	G	0.005	0.002	0.007	**0.016**	0.003	2.62E-08	**0.003**	0.001	0.001
rs4852252	C	T	0.004	0.002	0.030	**0.021**	0.003	3.84E-14	**-0.003**	0.001	0.001
rs4863692	G	T	-0.014	0.002	3.77E-15	**-0.015**	0.003	4.81E-07	**-0.002**	0.001	0.039
rs4974424	A	G	-0.015	0.002	1.98E-10	**-0.017**	0.004	5.38E-06	**0.000**	0.001	0.462
rs4981713	T	G	0.009	0.002	1.15E-07	**0.016**	0.003	7.23E-09	**0.005**	0.001	5.01E-08
rs523934	A	G	0.015	0.002	1.23E-16	**0.015**	0.003	1.23E-07	**0.000**	0.001	0.479

rs538628	G	C	0.017	0.002	3.94E-15	**0.015**	0.003	2.03E-05	**0.005**	0.001	7.54E-07
rs55754731	C	T	-0.011	0.002	2.20E-06	**-0.021**	0.004	6.06E-09	**-0.003**	0.001	0.006
rs55763037	A	G	0.008	0.002	5.66E-05	**0.018**	0.003	3.74E-08	**0.002**	0.001	0.055
rs566237	G	A	0.003	0.002	0.076	**0.019**	0.003	1.82E-10	**0.000**	0.001	0.413
rs5750830	C	A	-0.008	0.002	6.44E-05	**-0.023**	0.003	2.46E-13	**0.000**	0.001	0.415
rs58694847	C	G	-0.014	0.002	1.37E-12	**-0.010**	0.003	0.001	**-0.002**	0.001	0.011
rs59142272	G	A	-0.011	0.002	1.33E-06	**-0.023**	0.004	7.32E-10	**0.003**	0.001	0.016
rs600806	A	G	-0.012	0.002	1.58E-09	**-0.019**	0.003	3.57E-10	**0.002**	0.001	0.033
rs6019535	G	A	-0.008	0.002	1.56E-05	**-0.025**	0.003	3.28E-17	**0.006**	0.001	8.51E-09
rs60262711	T	C	0.007	0.002	0.002	**0.016**	0.003	1.65E-08	**0.001**	0.001	0.244
rs61160187	A	G	-0.020	0.002	1.17E-30	**-0.012**	0.003	3.01E-05	**-0.001**	0.001	0.176
rs62181012	T	C	0.006	0.002	0.002	**0.021**	0.004	1.73E-09	**-0.001**	0.001	0.100
rs62263923	A	G	-0.015	0.002	6.59E-17	**-0.008**	0.003	0.004	**0.000**	0.001	0.431
rs6508220	G	A	0.011	0.002	9.97E-11	**0.023**	0.003	9.56E-17	**0.005**	0.001	1.49E-08
rs6535809	G	A	-0.009	0.002	1.17E-07	**-0.020**	0.003	6.65E-13	**-0.001**	0.001	0.085
rs6539284	T	C	-0.011	0.002	3.53E-10	**-0.019**	0.003	5.56E-12	**-0.001**	0.001	0.087
rs6550835	G	A	0.006	0.002	9.71E-04	**0.025**	0.003	2.44E-17	**0.000**	0.001	0.349
rs6668048	T	C	-0.012	0.002	6.61E-13	**-0.021**	0.003	4.24E-15	**-0.003**	0.001	0.003
rs66954617	A	G	-0.006	0.002	0.002	**-0.021**	0.003	1.72E-13	**0.000**	0.001	0.407
rs67482514	G	C	0.008	0.002	4.01E-05	**0.018**	0.003	3.21E-08	**-0.002**	0.001	0.025

rs6819372	G	A	0.011	0.002	4.34E-11	**0.020**	0.003	4.02E-13	**0.003**	0.001	0.001
rs6860963	C	T	-0.004	0.002	0.058	**-0.020**	0.003	5.57E-09	**0.002**	0.001	0.049
rs6903716	G	A	-0.006	0.002	6.77E-04	**-0.018**	0.003	2.39E-09	**-0.001**	0.001	0.174
rs702222	C	T	0.006	0.002	6.82E-04	**0.020**	0.003	5.02E-12	**0.001**	0.001	0.151
rs7029201	G	A	-0.024	0.002	1.98E-44	**-0.028**	0.003	9.45E-23	**-0.002**	0.001	0.008
rs7069887	A	C	-0.001	0.002	0.605	**0.023**	0.004	7.44E-09	**0.001**	0.001	0.291
rs7116046	T	C	0.007	0.002	1.16E-04	**0.016**	0.003	3.27E-08	**0.001**	0.001	0.092
rs7146434	G	A	0.011	0.002	2.37E-10	**0.005**	0.003	0.053	**-0.004**	0.001	3.76E-05
rs7172979	T	G	0.017	0.005	0.005	**0.061**	0.009	2.47E-11	**-0.001**	0.003	0.413
rs7248006	C	T	0.005	0.002	0.003	**0.019**	0.003	1.05E-11	**0.000**	0.001	0.365
rs72768642	T	C	-0.006	0.003	0.095	**-0.031**	0.005	1.46E-08	**-0.005**	0.002	0.006
rs73068339	C	G	0.001	0.002	0.432	**0.019**	0.003	5.96E-10	**0.000**	0.001	0.353
rs7312919	C	G	-0.001	0.002	0.726	**0.018**	0.003	4.83E-10	**-0.002**	0.001	0.007
rs7573001	C	G	-0.002	0.002	0.224	**-0.016**	0.003	1.32E-08	**0.001**	0.001	0.201
rs7640196	C	T	0.007	0.002	8.02E-04	**0.017**	0.003	3.15E-08	**0.002**	0.001	0.027
rs7652296	G	A	-0.004	0.002	0.0146	**-0.017**	0.003	3.51E-09	**0.001**	0.001	0.172
rs766406	G	T	-0.014	0.002	3.17E-16	**-0.006**	0.003	0.037	**-0.002**	0.001	0.041
rs7731260	G	A	-0.006	0.002	3.33E-04	**-0.015**	0.003	2.50E-08	**0.000**	0.001	0.475
rs7757476	G	A	-0.019	0.002	1.18E-16	**-0.006**	0.004	0.1	**-0.001**	0.001	0.154
rs7941785	G	A	-0.006	0.002	7.28E-04	**-0.016**	0.003	4.75E-08	**-0.001**	0.001	0.084

rs7964899	G	A	-0.013	0.002	1.33E-14	**-0.010**	0.003	1.64E-04	**0.001**	0.001	0.187
rs799444	T	C	0.006	0.002	0.003	**0.018**	0.003	2.48E-11	**0.000**	0.001	0.407
rs8006700	T	A	0.012	0.002	1.32E-10	**0.018**	0.003	4.96E-10	**0.001**	0.001	0.084
rs80170948	T	G	0.002	0.005	0.656	**0.045**	0.007	7.69E-10	**0.000**	0.002	0.464
rs8051038	A	G	0.009	0.002	3.27E-06	**0.019**	0.003	1.78E-09	**0.001**	0.001	0.217
rs889169	A	G	0.005	0.002	0.007	**0.016**	0.003	2.75E-08	**0.000**	0.001	0.474
rs9384679	T	C	-0.010	0.002	4.88E-08	**-0.027**	0.003	7.94E-22	**0.000**	0.001	0.356
rs9503599	C	T	0.011	0.002	4.90E-10	**0.017**	0.003	8.05E-10	**0.000**	0.001	0.451
rs9516855	A	G	0.012	0.004	0.002	**0.033**	0.006	4.19E-08	**0.008**	0.002	1.08E-04
rs9527702	A	G	0.023	0.002	7.62E-35	**0.013**	0.003	3.49E-05	**0.003**	0.001	0.003
rs9616906	G	A	-0.015	0.002	2.92E-18	**-0.008**	0.003	0.003	**-0.002**	0.001	0.037
rs967569	T	C	-0.006	0.002	0.002	**-0.018**	0.003	8.21E-10	**-0.001**	0.001	0.134
rs9739070	A	G	0.022	0.002	8.95E-26	**0.016**	0.003	2.78E-06	**0.002**	0.001	0.052
rs9888986	G	A	0.008	0.003	0.005	**0.024**	0.004	3.52E-08	**0.002**	0.002	0.059

Appendix 6.6: Univariable MR analyses assessing bidirectional associations between educational attainment (using discovery and replication cohort, n=405,072) and intelligence

		Causal effect estimates		Heterogeneity statistics		
	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on intelligence						
Inverse variance weighted estimate	122	0.775 (0.710, 0.842)	**4.09E-117**	443.2	121	**<0.001**
MR Egger estimate	122	1.06 (0.784, 1.33)	**7.01E-12**	427.7	120	**<0.001**
MR Egger intercept	122	-0.004 (-0.009, -0.002)	**0.042**	-	-	-
MR-Egger (SIMEX) [a]	122	1.36 (1.04, 1.68)	**5.98E-14**	-	-	-
Weighted median	122	0.682 (0.614, 0.751)	**4.56E-84**	-	-	-
Weighted mode	122	0.668 (0.493, 0.844)	**1.45E-11**	-	-	-
Intelligence on years of schooling						
Inverse variance weighted estimate	144	0.436 (0.399, 0.472)	**1.33E-119**	813.5	143	**<0.001**
MR Egger estimate	144	0.510 (0.341, 0.679)	**2.47E-08**	809.1	142	**<0.001**
MR Egger intercept	144	-0.003 (-0.006, 0.001)	0.150	-	-	-
MR-Egger (SIMEX) [a]	144	0.790 (0.552, 1.03)	**9.93E-10**	-	-	-
Weighted median	144	0.339 (0.306, 0.371)	**2.15E-93**	-	-	-
Weighted mode	144	0.296 (0.229, 0.364)	**1.49E-14**	-	-	-

Note: Analyses conducted using the educational attainment discovery and replication cohort (n=405,072).

[a] Weighted simulation extrapolation (SIMEX) correction applied

Appendix 6.7: Funnel and forest plots assessing pleiotropy in univariable MR analyses of years of schooling and intelligence.

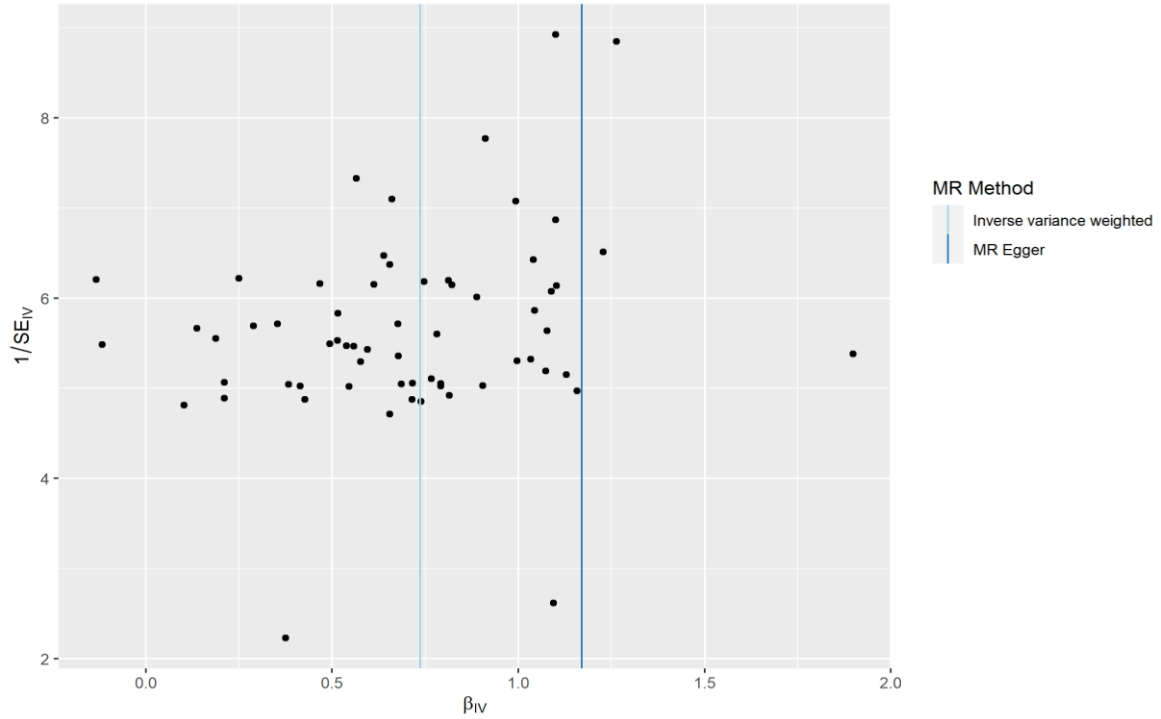


Figure A6.1: *Funnel plot assessing the extent to which pleiotropy is balanced across the set of instruments used in the univariable MR analysis of years of schooling on intelligence. βIV represents the effect size of each SNP, and 1/SEIV represents the inverse standard error for each SNP effect. This plot shows some upward bias in the MR-Egger estimate.*

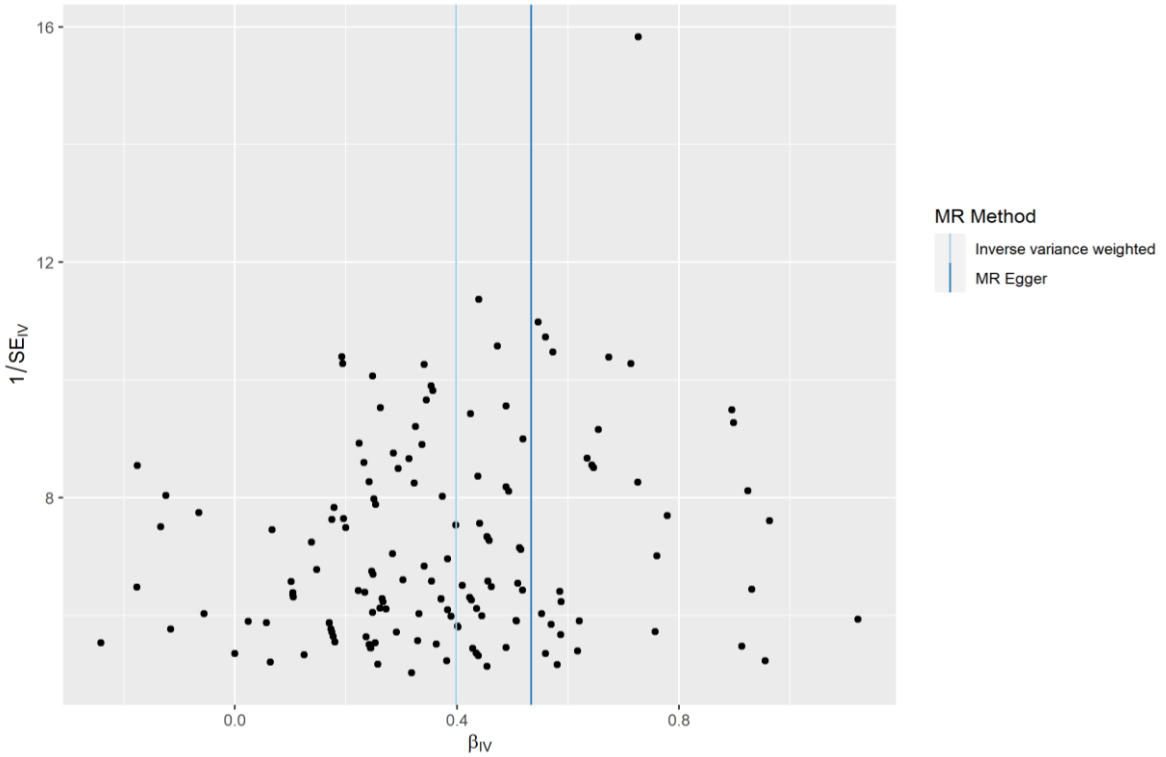
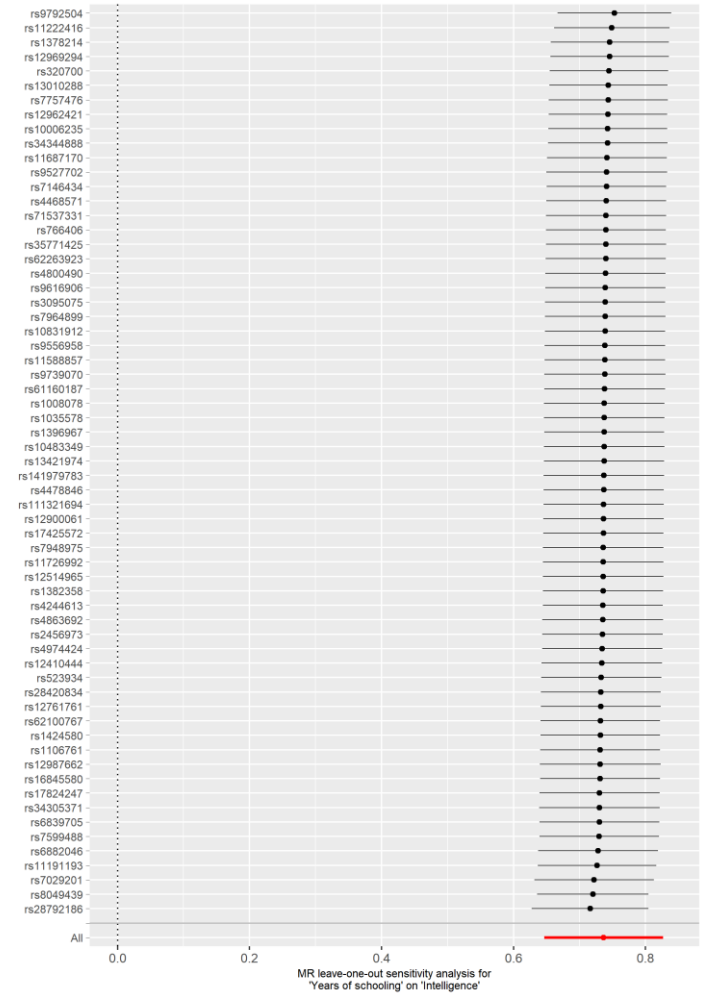


Figure A6.2: *Funnel plot assessing the extent to which pleiotropy is balanced across the set of instruments used in the univariable MR analysis of intelligence on years of schooling. βIV represents the effect size of each SNP, and 1/SEIV represents the inverse standard error for each SNP effect. This plot indicates minimal bias in the MR-Egger estimate.*

A.



B.

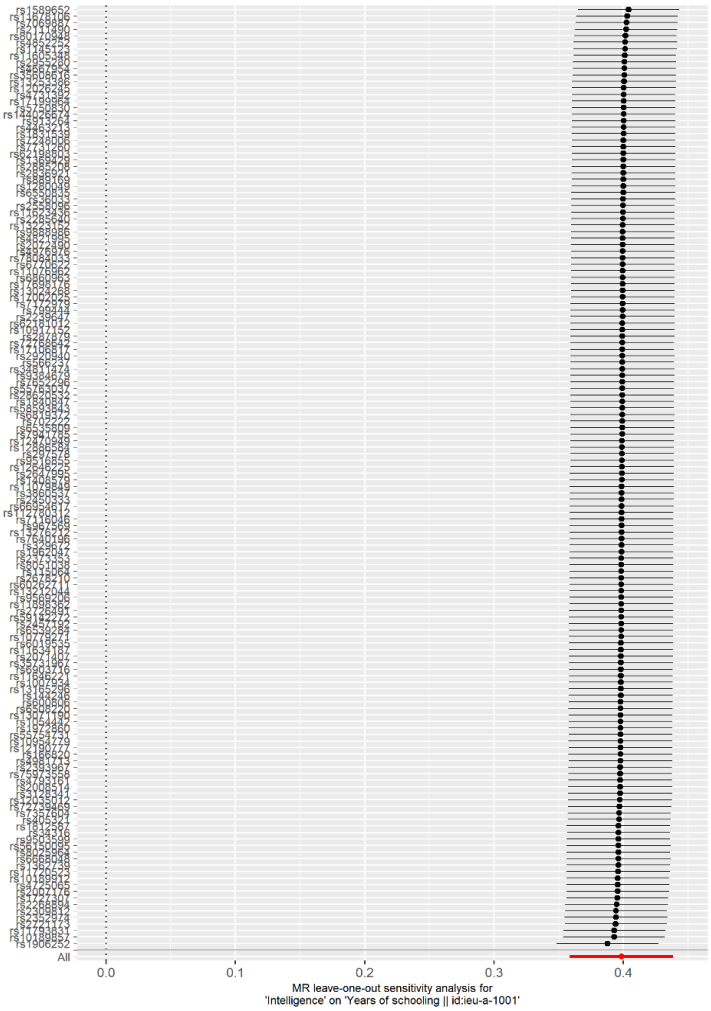


Figure A6.3: *Leave-one-out analyses for A) two-sample univariable MR analysis of years of schooling on intelligence and B) two-sample univariable MR analysis of intelligence on years of schooling. As evident in both forest plots, neither of the univariable associations were driven by a single SNP.*

Appendix 6.8: Funnel and forest plots assessing pleiotropy in univariable MR analyses of years of schooling and wellbeing

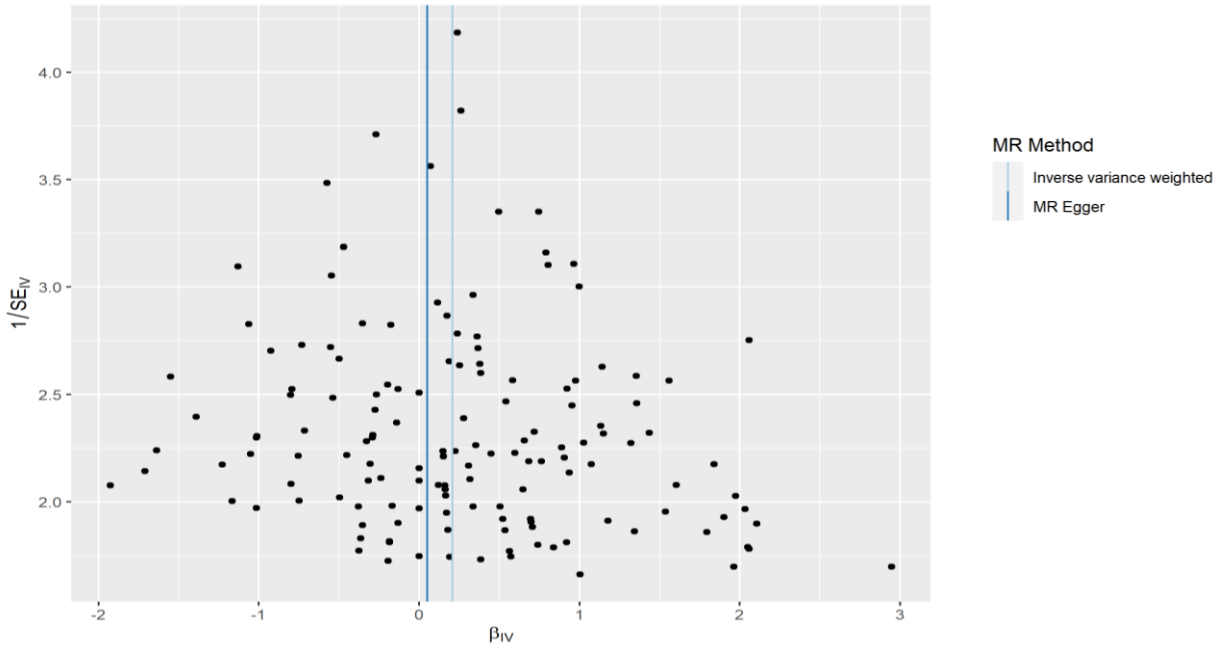
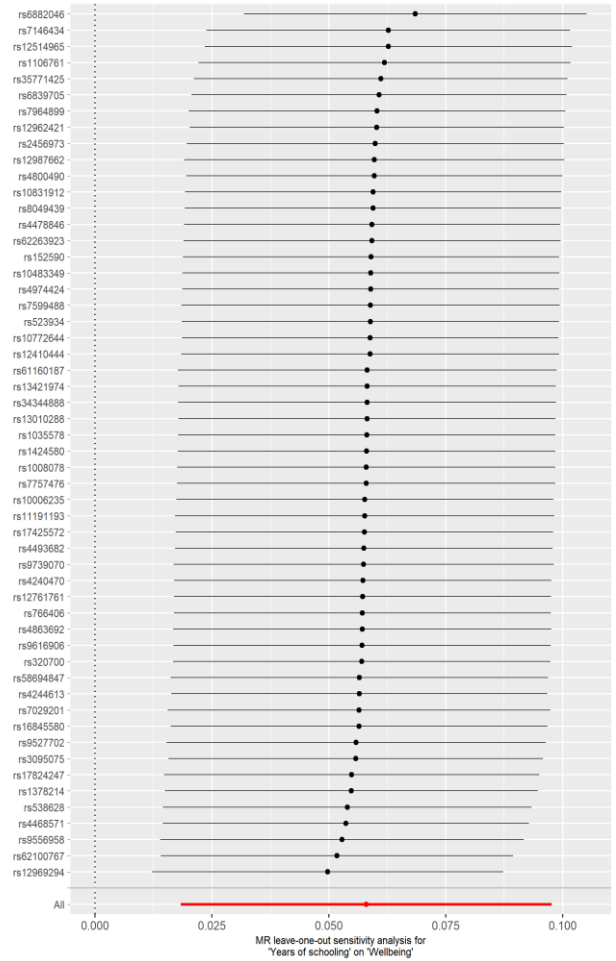


Figure A6.5**:** *Funnel plot assessing the extent to which pleiotropy is balanced across the set of instruments used in the univariable MR analysis of wellbeing on years of schooling. βIV represents the effect size of each SNP, and 1/SEIV represents the inverse standard error for each SNP effect. This plot indicates minimal bias in the MR-Egger estimate.*

A.



B.

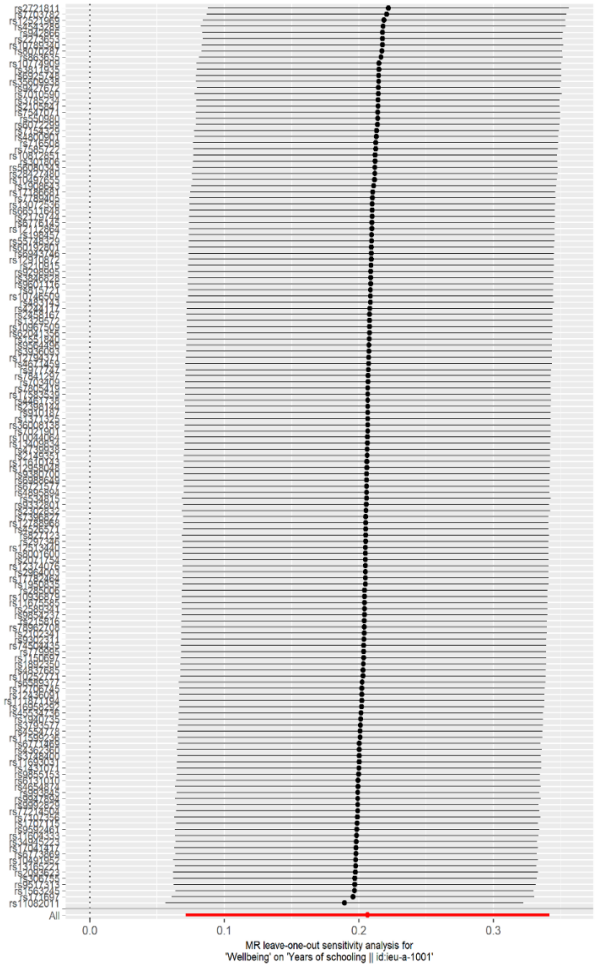


Figure A6.6: *Leave-one-out analyses for A) two-sample univariable MR analysis of years of schooling on wellbeing and B) two-sample univariable MR analysis of wellbeing on years of schooling. As evident in both forest plots, neither of the univariable associations were driven by a single SNP.*

Appendix 6.9: Funnel and forest plots assessing pleiotropy in univariable MR analyses of intelligence and wellbeing

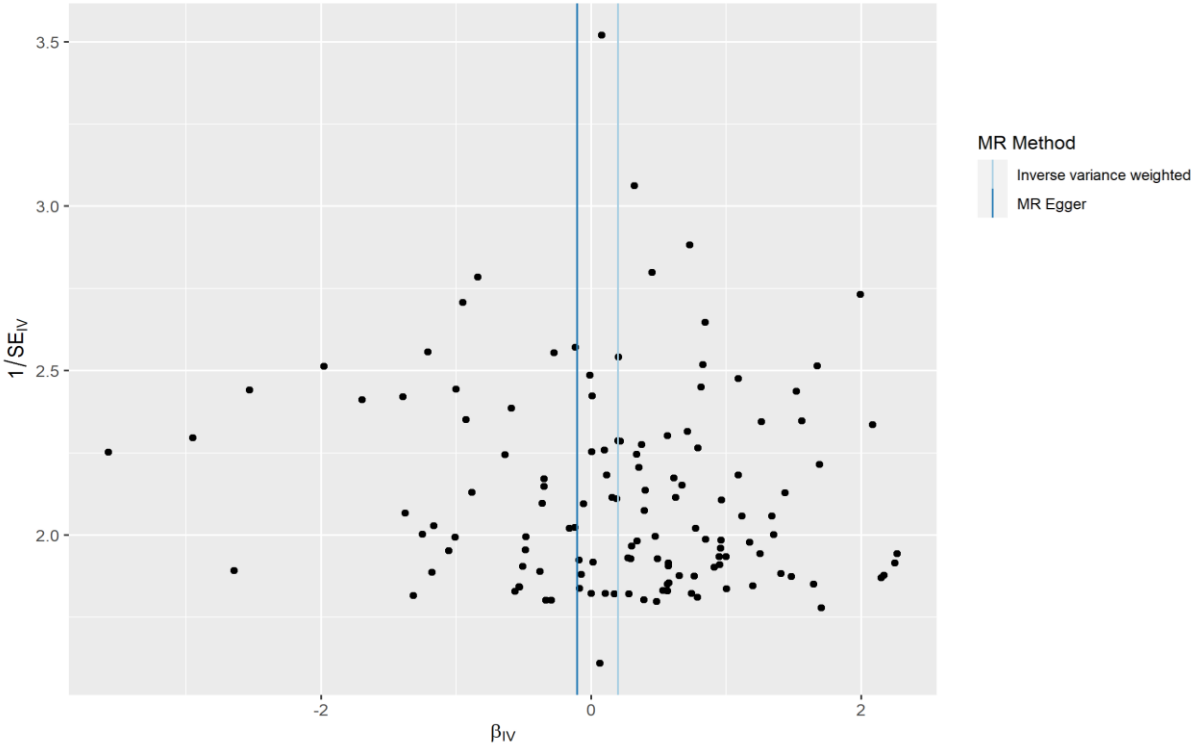


Figure A6.7: *Funnel plot assessing the extent to which pleiotropy is balanced across the set of instruments used in the univariable MR analysis of wellbeing on intelligence. βIV represents the effect size of each SNP, and 1/SEIV represents the inverse standard error for each SNP effect. Findings indicate minimal bias in the MR-Egger estimate.*

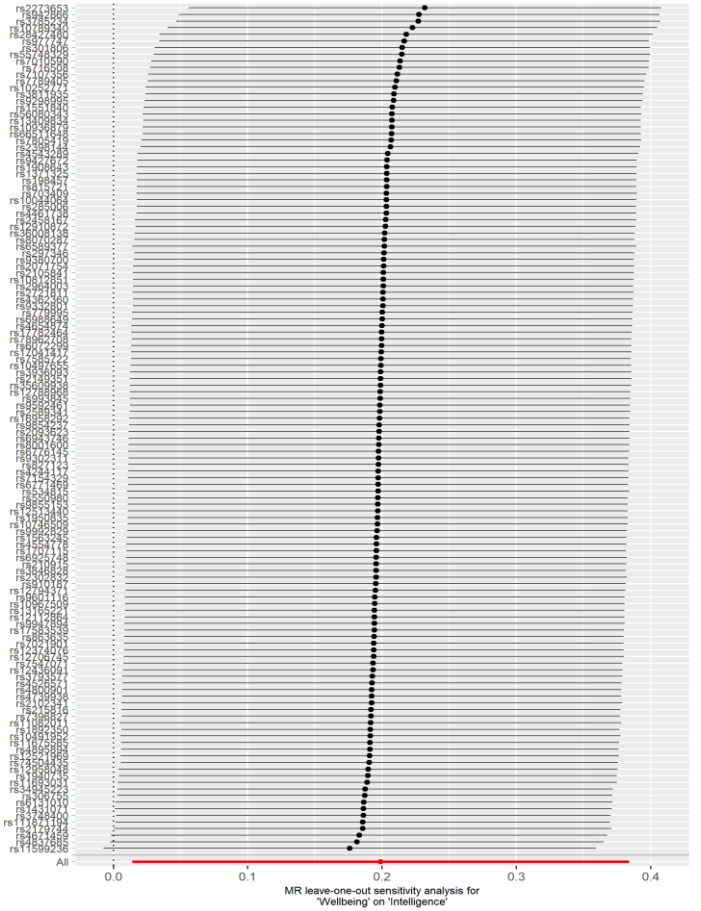


Figure A6.8: *Leave-one-out analysis: each row represents a two-sample univariable MR analysis of wellbeing on intelligence. Findings indicate that no single SNP is driving associations.*

Appendix 6.10: Univariable MR analyses assessing associations between wellbeing and educational attainment, and between wellbeing and intelligence following Steiger filtering

		Causal effect estimates		Heterogeneity statistics		
Total effects	N SNPs	β (95% CI)	P	Q	df	P
Wellbeing on years of schooling						
Inverse variance weighted estimate	143	0.162 (0.033, 0.291)	**0.014**	499.6	142	**1.34E-41**
MR Egger estimate	143	0.065 (-0.605, 0.734)	0.850	499.9	141	**2.28E-41**
MR Egger intercept	143	0.000 (-0.005, 0.005)	0.998	-	-	**-**
Weighted median	143	0.177 (0.056, 0.299)	**0.004**	-	-	**-**
Weighted mode	143	0.236 (-0.107, 0.580)	0.180	-	-	**-**
Wellbeing on intelligence						
Inverse variance weighted estimate	117	0.242 (0.098, 0.386)	**9.66E-04**	334.8	116	**6.35E-23**
MR Egger estimate	117	-0.163 (-0.976, 0.649)	6.95E-01	331.9	115	**4.23E-23**
MR Egger intercept	117	0.003 (-0.002, 0.008)	0.322			
Weighted median	117	0.297 (0.153, 0.441)	**5.47E-05**	-	-	-
Weighted mode	117	0.318 (-0.059, 0.696)	1.01E-01	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

Appendix 6.11: Univariable MR analyses assessing impact of educational attainment and intelligence on positive affect

		Causal effect estimates		Heterogeneity statistics		
Total effects	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on positive affect						
Inverse variance weighted	54	0.037 (0.013, 0.061)	**0.002**	193.6	53	**6.90E-18**
MR-Egger	54	-0.044 (-0.335, 0.247)	0.766	192.4	52	**5.42E-18**
MR-Egger intercept	54	0.001 (-0.004, 0.006)	0.597	-	-	-
MR-Egger (SIMEX) [a]	54	-0.130 (-0.561, 0.302)	0.558	-	-	-
Weighted median	54	0.058 (0.020, 0.097)	**0.003**	-	-	-
Weighted mode	54	0.063 (-0.011, 0.137)	0.101	-	-	-
Positive affect on years of schooling						
Inverse variance weighted estimate	94	0.039 (-0.022, 0.100)	0.217	368.8	93	**1.65E-34**
MR Egger estimate	94	-0.257 (-0.787, 0.273)	0.343	363.8	92	**5.43E-34**
MR Egger intercept	94	0.003 (-0.004, 0.004)	0.263	-	-	-
MR-Egger (SIMEX) [a]	94	-0.254 (-0.985, 0.478)	0.498	-	-	-
Weighted median	94	0.000 (-0.118, 0.118)	1.00	-	-	-
Weighted mode	94	-0.120 (-0.458, 0.219)	0.490	-	-	-
Intelligence on positive affect						
Inverse variance weighted	126	-0.003 (-0.016, 0.010)	0.677	561.9	125	**1.17E-56**
MR-Egger	126	-0.017 (-0.153, 0.119)	0.808	561.8	124	**5.93E-57**

MR-Egger intercept	126	0.000 (-0.002, 0.002)	0.835	-	-	-
MR-Egger (SIMEX) [a]	126	-0.130 (-0.561, 0.302)	0.559	-	-	-
Weighted median	126	-0.001 (-0.023, 0.022)	0.927	-	-	-
Weighted mode	126	0.005 (-0.042, 0.051)	0.842	-	-	-
Positive affect on intelligence						
Inverse variance weighted estimate	83	0.953 (0.022, 0.168)	**0.011**	525.3	82	**7.28E-66**
MR Egger estimate	83	-0.695 (-1.48, 0.088)	0.086	499.8	81	**1.39E-61**
MR Egger intercept	83	0.007 (0.001, 0.01)	**0.045**	-	-	-
MR-Egger (SIMEX) [a]	83	-0.980 (-1.98, 0.02)	0.058	-	-	-
Weighted median	83	0.183 (0.034, 0.332)	**0.016**	-	-	-
Weighted mode	83	0.242 (-0.072, 0.556)	0.135	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Weighted simulation extrapolation (SIMEX) correction applied

[b] Unweighted simulation extrapolation (SIMEX) correction applied

Appendix 6.12: Univariable MR analyses assessing impact of educational attainment and intelligence on life satisfaction

		Causal effect estimates		Heterogeneity statistics		
Total effects	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on life satisfaction						
Inverse variance weighted	54	0.056 (0.028, 0.083)	**6.29E-05**	169.6	53	**3.90E-14**
MR-Egger	54	-0.020 (-0.330, 0.291)	9.01E-01	168.9	52	**2.49E-14**
MR-Egger intercept	54	0.001 (-0.004, 0.006)	0.631	-	-	-
Weighted median	54	0.067 (0.024, 0.111)	**2.41E-03**	-	-	-
Weighted mode	54	0.086 (0.004, 0.169)	**4.54E-02**	-	-	-
Life satisfaction on years of schooling						
Inverse variance weighted estimate	75	0.190 (0.123, 0.256)	**2.06E-08**	270.4	74	**3.56E-24**
MR Egger estimate	75	0.589 (-0.059, 1.24)	**7.93E-02**	264.9	73	**1.38E-23**
MR Egger intercept	75	-0.003 (-0.009, 0.009)	0.223	-	-	-
MR-Egger (SIMEX) [a]	75	0.776 (-0.049, 1.60)	**0.069**	-	-	-
Weighted median	75	0.181 (0.063, 0.299)	**2.68E-03**	-	-	-
Weighted mode	75	0.195 (-0.088, 0.478)	**1.81E-02**	-	-	-
Intelligence on life satisfaction						
Inverse variance weighted	126	0.003 (-0.012, 0.018)	0.687	449.9	125	**3.11E-38**
MR-Egger	126	0.015 (-0.126, 0.157)	0.831	449.8	124	**1.69E-38**
MR-Egger intercept	126	0.000 (-0.002, 0.002)	0.861	-	-	-

Weighted median	126	-0.009 (-0.036, 0.18)	0.510	-	-	-
Weighted mode	126	0.003 (-0.053, 0.060)	0.909	-	-	-
Life satisfaction on intelligence						
Inverse variance weighted estimate	63	0.222 (0.140, 0.304)	**9.98E-08**	332.1	62	**1.41E-38**
MR Egger estimate	63	-0.423 (-1.44, 0.601)	4.21E-01	323.7	61	**1.87E-38**
MR Egger intercept	63	0.006 (-0.002, 0.012)	0.214	-	-	-
MR-Egger (SIMEX) [a]	63	-0.284 (-1.36, 0.793)	0.607	-	-	-
Weighted median	63	0.239 (0.083, 0.395)	**2.59E-03**	-	-	-
Weighted mode	63	0.293 (-0.026, 0.612)	**7.71E-02**	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Weighted simulation extrapolation (SIMEX) correction applied

Appendix 6.13: Univariable MR analyses assessing impact of educational attainment and intelligence on depression

		Causal effect estimates		Heterogeneity statistics		
Total effects	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on depression						
Inverse variance weighted	54	-0.049 (-0.068, -0.032)	**2.72E-08**	252.2	53	**1.03E-27**
MR-Egger	54	0.086 (-0.154, 0.326)	4.84E-01	246.2	52	**5.13E-27**
MR-Egger intercept	54	-0.002 (-0.006, 0.002)	0.265	-	-	-
MR-Egger (SIMEX) [a]	54	0.086 (-0.265, 0.437)	0.633	-	-	-
Weighted median	54	-0.047 (-0.077, -0.018)	**1.39E-03**	-	-	-
Weighted mode	54	-0.019 (-0.071, 0.032)	4.63E-01	-	-	-
Depression on years of schooling						
Inverse variance weighted estimate	114	-0.172 (-0.241, -0.102)	**1.45E-06**	456.2	113	**8.30E-43**
MR Egger estimate	114	-0.176 (-0.871, (0.520)	6.21E-01	456.4	112	**4.09E-43**
MR Egger intercept	114	0.000 (-0.006, 0.006)	0.223	-	-	-
MR-Egger (SIMEX) [a]	114	-0.661 (-1.55, 0.230)	0.149	-	-	-
Weighted median	114	-0.181 (-0.314, -0.049)	**7.28E-03**	-	-	-
Weighted mode	114	-0.261 (-0.609, 0.086)	1.43E-01	-	-	-
Intelligence on depression						
Inverse variance weighted	126	0.001 (-0.004, 0.015)	0.279	632.1	125	**8.97E-69**
MR-Egger	126	0.014 (-0.093, 0.121)	0.799	632.1	124	**4.17E-69**

MR-Egger intercept	126	0.000 (-0.002, 0.002)	0.873	-	-	-
MR-Egger (SIMEX) [a]	126	0.020 (-0.121, 0.161)	0.785	-	-	-
Weighted median	126	0.007 (-0.011, 0.024)	0.451	-	-	-
Weighted mode	126	0.001 (-0.036, 0.039)	0.943	-	-	-
Depression on intelligence						
Inverse variance weighted estimate	98	-0.222 (-0.304, -0.140)	**9.98E-08**	332.1	62	**1.41E-38**
MR Egger estimate	98	0.423 (-0.601, 1.44)	**4.21E-01**	323.7	61	**1.87E-38**
MR Egger intercept	98	-0.006 (-0.012, 0.002)	0.214	-	-	-
MR-Egger (SIMEX) [b]	98	0.788 (-0.491, 2.07)	0.230	-	-	-
Weighted median	98	-0.239 (-0.395, -0.083)	**2.59E-03**	-	-	-
Weighted mode	98	-0.293 (-0.612, 0.026)	**7.71E-02**	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Weighted simulation extrapolation (SIMEX) correction applied

[b] Weighted simulation extrapolation (SIMEX) correction applied

Appendix 6.14: Univariable MR analyses assessing impact of educational attainment and intelligence on neuroticism

		Causal effect estimates		Heterogeneity statistics		
Total effects	N SNPs	β (95% CI)	P	Q	df	P
Years of schooling on neuroticism						
Inverse variance weighted	54	-0.099 (-0.127, -0.072)	**1.56E-12**	360.9	53	**2.11E-47**
MR-Egger	54	0.027 (-0.433, 0.487)	9.07E-01	358.9	52	**1.93E-47**
MR-Egger intercept	54	-0.002 (-0.010, 0.006)	0.587	-	-	-
MR-Egger (SIMEX) [a]	54	-0.089 (-0.704, 0.526)	0.777	-	-	-
Weighted median	54	-0.084 (-0.133, -0.035)	**6.99E-04**	-	-	-
Weighted mode	54	-0.070 (-0.154, 0.014)	1.07E-01	-	-	-
Neuroticism on years of schooling						
Inverse variance weighted estimate	113	-0.126 (-0.171, -0.082)	**3.07E-08**	391.3	112	**1.26E-32**
MR Egger estimate	113	-0.212 (-0.575, 0.151)	2.55E-01	390.5	111	**8.91E-33**
MR Egger intercept	113	0.001 (-0.005, 0.005)	0.636	-	-	-
MR-Egger (SIMEX) [a]	113	-0.568 (-1.06, -0.077)	**0.025**	-	-	-
Weighted median	113	-0.111 (-0.193, -0.030)	**7.37E-03**	-	-	-
Weighted mode	113	0.078 (-0.146, 0.300)	5.01E-01	-	-	-
Intelligence on neuroticism						
Inverse variance weighted	126	-0.015 (-0.030, 0.003)	0.055	632.1	125	**8.97E-69**
MR-Egger	126	-0.041 (-0.208, 0.125)	0.627	632.1	124	**4.17E-69**

MR-Egger intercept	126	0.000 (-0.003, 0.003)	0.751	-	-	-
MR-Egger (SIMEX) [a]	126	-0.052 (-0.188, 0.085)	0.461	-	-	-
Weighted median	126	0.000 (-0.028, 0.029)	0.978	-	-	-
Weighted mode	126	0.004 (-0.057, 0.065)	0.909	-	-	-
Neuroticism on intelligence						
Inverse variance weighted estimate	96	-0.180 (-0.234, -0.126)	**6.31E-11**	332.1	62	**1.41E-38**
MR Egger estimate	96	-0.058 (-0.618, 0.503)	8.40E-01	323.7	61	**1.87E-38**
MR Egger intercept	96	-0.001 (-0.007, 0.005)	0.661	-	-	-
MR-Egger (SIMEX) [b]	96	-0.164 (-0.807, 0.480)	0.619	-	-	-
Weighted median	96	-0.186 (-0.291, -0.082)	**4.85E-04**	-	-	-
Weighted mode	96	-0.152 (-0.431, 0.126)	2.84E-01	-	-	-

Note: Analyses conducted using the educational attainment discovery cohort (n=293,723).

[a] Weighted simulation extrapolation (SIMEX) correction applied

[b] Weighted simulation extrapolation (SIMEX) correction applied

Appendix 6.15: Linear regression results assessing associations between educational attainment and wellbeing, and between intelligence and wellbeing (unstandardised)

	Unadjusted		Complete cases (*n*=2,844)		Adjusted using IPW		Adjusted using multiple imputation (*n*=4,298)	
	b (95% CI)	*p* value	b (95% CI)	*p* value	b (95% CI)	*p* value	b (95% CI)	*p* value
Subjective happiness								
Models 1 and 2[a]								
University degree	0.004 (-0.080, 0.090)	0.920	-0.028 (-0.126, 0.070)	0.581	-0.026 (-0.131, 0.079)	0.624	-0.021 (-0.101, 0.060)	0.615
Intelligence	-0.003 (-0.006, -0.000)	**0.038**	-0.003 (-0.006, -0.000)	**0.033**	-0.004 (-0.006, -0.002)	**4.58E-06**	-0.003 (-0.006, -0.000)	**0.008**
Models 2 and 3[b]								
University degree	-0.291 (-0.436, -0.145)	**9.18E-05**	-0.282 (-0.447, -0.117)	**7.98E-04**	-0.281 (-0.454, -0.109)	**0.001**	-0.313 (-0.450, -0.175)	**8.54E-06**
Sex	-0.239 (-0.382, -0.096)	**0.001**	-0.180 (-0.347, -0.012)	**0.036**	-0.123 (-0.274, 0.028)	0.111	-0.236 (-0.372, -0.100)	**6.63E-04**
University degree * Sex	0.447 (0.268, 0.626)	**1.05E-06**	0.395 (0.189, 0.601)	**1.69E-04**	0.397 (0.179, 0.615)	**3.60E-04**	0.443 (0.274, 0.612)	**3.08E-07**
Intelligence	-0.007 (-0.011, -0.002)	**0.003**	-0.005 (-0.010, -0.000)	**0.027**	-0.004 (-0.006, -0.001)	**0.003**	-0.007 (-0.011, -0.003)	**4.27E-04**
Sex	-0.612 (-1.23, 0.008)	0.053	-0.325 (0.979, 0.328)	0.329	-0.176 (-0.204, 0.557)	0.364	-0.634 (-1.18, -0.093)	**0.022**
Intelligence * Sex	0.006 (0.000, 0.012)	**0.029**	0.004 (-0.002, 0.010)	0.223	0.000 (-0.004, 0.003)	0.670	0.006 (0.001, 0.011)	**0.013**
Life satisfaction								
Model 4 and 5[a]								
University degree	1.68 (1.23, 2.14)	**7.44E-13**	1.55 (1.02, 2.08)	**1.04E-08**	1.39 (0.824, 1.96)	**1.66E-06**	1.61 (1.81, 2.05)	**3.00E-15**
Intelligence	0.031 (0.017, 0.046)	**3.66E-05**	0.029 (0.014, 0.045)	**2.40E-04**	0.029 (0.019, 0.039)	**2.66E-08**	0.030 (0.017, 0.043)	**5.27E-06**

Models 6 and 7[b]								
University degree	0.529 (-0.254, 1.31)	0.185	0.492 (-0.394, 1.38)	0.276	0.104 (-0.828, 1.04)	0.826	0.636 (-0.105, 1.38)	0.092
Sex	-0.147 (-0.917, 0.623)	0.701	-0.056 (0.956, 0.844)	0.903	-0.238 (-1.06, 0.579)	0.568	-0.055 (-0.787, 0.677)	0.883
University degree * Sex	1.74 (0.776, 2.71)	**4.07E-04**	1.64 (0.538, 2.75)	**0.004**	1.96 (0.782, 3.13)	**0.001**	1.49 (0.580, 2.40)	**0.001**
Intelligence	0.012 (-0.012, 0.035)	0.340	0.017 (-0.008, 0.043)	0.174	0.029 (0.015, 0.043)	**4.21E-05**	0.014 (-0.008, 0.035)	0.206
Sex	-2.92 (-6.27, 0.424)	0.087	-1.39 (-4.91, 2.13)	0.439	-1.27 (-0.805, 3.35)	0.230	-2.12 (-5.04, 0.800)	0.155
Intelligence * Sex	0.036 (0.006, 0.067)	**0.019**	0.023 (-0.010, 0.055)	0.158	0.001 (-0.021, 0.019)	0.923	0.029 (0.002, 0.056)	**0.035**

Note: Sex coded as 0=Male and 1=Female, analyses therefore used male as the reference. In unadjusted models and models adjusted for IPW, *n*=3,788 for educational attainment and *n*=3,179 for intelligence.

[a] Analyses included only the exposure.

[b] Analyses included the exposure, sex, and exposure*sex.

Appendix 6.16. Selective attrition for educational attainment and intelligence based on sex

	Educational attainment			Intelligence			Comparison between sexes across groups	
	Female available (*n*=2,505)	Male available (*n*=1,283)	p[1]	Female available (*n*=2,045)	Male available (*n*=1,134)	p[2]	p[3]	p[4]
Ethnicity								
White	2,107 (95.9)	1,129 (96.7)	0.86	1,831 (97.1)	1,033 (96.5)	0.07	0.47	0.88
Non-white	88 (4.1)	39 (3.3)	0.36	67 (2.9)	31 (3.5)	0.45	0.47	0.63
Mother education								
O level or less	407 (18.3)	247 (21.0)	0.06	386 (20.1)	241 (22.6)	0.13	0.15	0.40
A level	602 (27.1)	361 (30.7)	0.**03**	568 (29.6)	332 (31.1)	0.42	0.08	0.89
Degree	1,215 (54.6)	567 (48.3)	**<0.001**	965 (50.3)	495 (46.3)	**0.04**	**<0.001**	0.39
Partner education								
O level or less	537 (24.6)	338 (29.2)	**<0.001**	483 (25.6)	313 (29.8)	**0.02**	0.53	0.80
A level	606 (27.9)	343 (29.6)	0.29	568 (30.0)	317 (30.1)	0.99	0.12	0.82
Degree	1,036 (47.5)	478 (41.2)	**<0.001**	839 (44.4)	422 (40.1)	**0.03**	**0.05**	0.62
Mother occupational status								
Professional	90 (4.6)	62 (5.8)	0.16	85 (5.0)	60 (6.2)	0.24	0.61	0.83
Managerial/technical	662 (33.8)	384 (36.1)	0.22	605 (35.7)	356 (36.5)	0.69	0.26	0.88
Skilled non-manual	816 (41.7)	427 (40.1)	0.43	689 (40.6)	403 (41.3)	0.74	0.53	0.61

Skilled manual	60 (3.1)	40 (3.8)	0.36	55 (3.2)	37 (3.8)	0.52	0.83	0.99
Partly skilled	277 (14.1)	130 (12.2)	0.15	223 (13.1)	105 (10.8)	0.08	0.40	0.34
Unskilled	53 (2.7)	21 (2.0)	0.26	40 (2.4)	14 (1.4)	0.12	0.57	0.45
Marital status								
Single	309 (13.6)	125 (10.5)	**<0.001**	239 (12.3)	107 (9.9)	**0.05**	0.22	0.70
First	1,727 (76.3)	918 (77.2)	0.57	1,508 (77.9)	845 (78.5)	0.73	0.25	0.51
Marriage 2 or 3	147 (6.5)	90 (7.6)	0.26	115 (5.9)	80 (7.4)	0.13	0.50	0.96
Widowed/divorced/separated	81 (3.6)	56 (4.7)	0.13	75 (3.9)	45 (4.2)	0.75	0.68	0.61
Home ownership								
Mortgage/owned	1,873 (83.6)	1,018 (86.8)	**0.02**	1,658 (86.4)	940 (88.5)	0.11	**0.01**	0.24
Privately rented	113 (5.0)	61 (5.2)	0.91	78 (4.1)	52 (4.9)	0.33	0.15	0.82
Council rented	185 (8.3)	68 (5.8)	**0.01**	132 (6.9)	48 (4.5)	**0.01**	0.11	0.21
Other	70 (3.1)	26 (2.2)	0.16	51 (2.6)	22 (2.1)	0.39	0.42	0.93
Car ownership								
Yes	2,037 (95.3)	1,090 (96.0)	0.36	1,795 (95.8)	999 (96.6)	0.35	0.54	0.55
No	101 (4.7)	45 (4.0)	0.36	78 (4.2)	35 (3.4)	0.35	0.54	0.55
Mother depressed								
Yes	149 (7.1)	78 (6.9)	0.88	105 (5.8)	72 (7.0)	0.24	0.12	0.98
No	1,948 (92.9)	1,054 (93.1)	0.88	1,699 (94.2)	954 (93.0)	0.24	0.12	0.98
Smoked during pregnancy								

Yes	369 (16.3)	187 (15.6)	0.64	271 (14.0)	139 (12.9)	0.41	**0.04**	0.07
No	1,892 (83.7)	1,008 (84.4)	0.64	1,664 (86.0)	941 (87.1)	0.41	**0.04**	0.07
Parity								
0	1,039 (46.6)	592 (50.3)	0.05	918 (48.2)	559 (52.4)	0.03	0.32	0.33
1	804 (36.1)	397 (33.7)	0.18	674 (35.4)	347 (32.5)	0.12	0.68	0.59
2+	387 (17.4)	189 (16.0)	0.36	313 (16.4)	161 (15.1)	0.36	0.45	0.57

Note:

[1] Comparison of proportion of males and females with measured variable and educational attainment data.

[2] Comparison of proportion of males and females with measured variable and intelligence data.

[3] Comparison of proportion of females with measured variable across two groups.

4 Comparison of proportion of males with measured variable across two groups.