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Quantifying psychological resilience and elucidating its mechanisms using multivariate modelling

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Abstract

It is estimated that approximately 30% of individuals worldwide are affected by mental health problems during their lifetime. Currently, Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders and a leading cause of non-lethal disability worldwide. However, despite exposure to known risk factors for MDD, human responses to it vary widely. Whilst some individuals develop MDD, others develop only mild and transient symptoms or no depressive symptomology at all. This ability to ‗bounce back' from or ‗escape' the development of psychiatric illness is referred to as *psychological resilience* (Chapter 1). Scientific and clinical interest in resilience has grown exponentially over recent decades, but wide discrepancies are still found in both its definition and measurement. As such, resilience is rarely measured directly, but inferred from the measurement of two specific points of convergence; adversity (its antecedents) and positive adaptation (its consequences). Whilst the study of adversity and positive adaptation has informed our knowledge of resilience it often fails to consider other putative risk factors for MDD (such as genetics), or potential protective factors that may foster resilience despite risk. More recently, examining protective factors have become a focus of research in relation to resilience. This research suggests that numerous protective factors coalesce to contribute to resilient outcomes which give rise to a dynamic resilience process that varies contextually and temporally. Although investigating resilience may be expected to reveal similar findings to studying MDD itself, it does represent a new facet to scientific and clinical research. Specifically, resilience focuses on intervention long before the development of MDD when effects on subsequent suffering may be ameliorated. For this reason, it is imperative to address the concept of resilience, concentrating on the core components of adversity, positive adaptation and protective factors, to move beyond description towards an understanding of individual differences in resilience (Chapter 2). In this thesis, three studies will be presented which aim to examine psychological resilience from multiple perspectives to further delineate the concept.

In Chapter 3, the associations and interactions between neuroticism and general intelligence (*g)* on MDD, and psychological distress were examined in GS:SFHS (Generation Scotland: Scottish Family Health Study) to investigate whether *g* mitigates the detrimental effects of neuroticism on mental health, as such an association has previously been identified for physical health and mortality. A larger replication was also performed in UK Biobank using a self-reported measure of depression. Across two large samples it was found that intelligence provides protection against psychological distress and self-reported depression in individuals high in neuroticism, but intelligence confers no such protection against clinical MDD in those high in neuroticism. In Chapter 4, a new dataset is presented which was designed to investigate psychological resilience and mental health. Specifically, the STRADL (Stratifying Resilience and Depression Longitudinally) dataset aimed to re-contact existing GS:SFHS participants to obtain repeat measures of MDD and psychological distress in addition to obtaining data on resilience, coping style and adverse life experiences. This dataset has the potential to identify mechanisms and pathways to resilience but also elucidate causal mechanisms and pathways of depression sub-types. Chapter 5 investigated whether neuroticism and resilience are downstream mediators of genetic risk for depression, and whether they contribute independently to such risk. Specifically, the moderating and mediating relationships between polygenic risk scores (PRS) for depression, neuroticism, resilience, and

both clinical and self-reported MDD were examined in STRADL. Regression analyses indicated that neuroticism and PRS for depression independently associated with increased risk for both clinical and self-reported MDD, whereas resilience associated with reduced risk. Structural equation modelling suggested that polygenic risk for depression associates with vulnerability for both clinical and self-reported MDD through two partially independent mediating mechanisms in which neuroticism increases vulnerability and resilience reduces it. In Chapter 6, the proportion of phenotypic variance that is attributable to genetic and shared-familial environment was estimated for resilience and three main coping styles; task-, emotion-, and avoidance-oriented coping. Bivariate analyses were conducted to estimate the genetic correlations between these traits and neuroticism. Our results indicate that common genetics affect both resilience and coping style. However, in addition, early shared-environmental effects from the nuclear family influence resilience whereas recent shared-environment effects from a spouse influence coping style. Furthermore, strong genetic overlap between resilience, emotion-oriented coping, and neuroticism suggests a relationship whereby genetic factors that increase negative emotionality lead to decreased resilience. These studies highlight the necessity for complementary multivariate techniques in resilience research to elucidate tractable methodologies to potentially identify mechanisms and modifiable risk factors to protect against psychiatric illness (Chapter 7).

Lay summary

Major Depressive Disorder (MDD) is a leading cause of disease burden worldwide. However, despite exposure to numerous risk factors for depression, not all individuals become unwell. This ability to ‗bounce back' from or ‗escape' MDD is known as *psychological resilience* (Chapter 1). Despite growing scientific interest in resilience, agreement has not been reached as to how best to define and measure it. Instead, resilience has often been inferred from investigating negative life experiences (adversity) and how individuals cope with these events (positive adaptation). Whilst much has been learned from this research, it fails to consider other important facets of resilience such as unobservable risk for depression (e.g., genetic liability), and protective factors which may help an individual overcome the disorder. More recently, research has focused on the protective roles of personality, coping style and genetics to inform our knowledge of resilience. It suggests that multiple factors work together to ‗produce' resilience, which varies throughout the life course, and from situation to situation (Chapter 2).

This thesis presents three studies which aim to investigate resilience from different perspectives to inform a better understanding of the concept. Chapter 3 shows that higher intelligence provides protection against unpleasant emotions and feelings (psychological distress) in individuals that score highly on the personality trait neuroticism. However, intelligence does not provide protection from clinical depression in individuals high in neuroticism. In Chapter 4, a new dataset that was specifically created to investigate psychological resilience is described. Chapter 5 shows that both genetic liability to depression and neuroticism independently increase risk for the disorder, whereas resilience reduces this risk. Furthermore, Chapter 5 demonstrates that the association between genetic liability for depression and the disorder itself is underlain by two partially separate pathways: one in which neuroticism increases risk for depression and one in which resilience reduces such risk, even in individuals genetically susceptible to depression. Chapter 6 shows that in addition to genetic effects, the early environment shared by families contributes to resilience whereas the more recent environment shared between couples' influences coping style. Additionally, Chapter 6 suggests that the genes which lead to unpleasant and negative feelings also reduce psychological resilience. Together, these findings highlight factors that may protect individuals from mental illness, and could potentially be used as part of therapeutic techniques (Chapter 7).

Declaration

I hereby authorise the University of Edinburgh to publish the abstract of this thesis, and to authorise others to do so, for scholarly purposes and with proper acknowledgement of authorship.

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Signed

Lauren Navrady

Date 01/01/2018

Publications

A list of first-author publications that are based directly on the work constituting this thesis are presented below:

Chapter 3:

Navrady, LB., Ritchie, SJ., Chan, SWY., Kerr, D., Adams, MJ., Hawkins, E., Porteous, D., Deary, IJ., Gale, CR., Batty, GD., McIntosh, AM. (2017). Intelligence and neuroticism in relation to depression and psychological distress: Evidence from two large population cohorts. *European Psychiatry*, 43, 58-65.

This study was conceived by LBN, DK, and AMM. LBN wrote the manuscript text and prepared all tables and figures. AMM was the main supervisor for the project, with co-supervision provided by SJR and SWYC. MJA aided in the statistical analysis. LBN and EH contributed to the data entry for the project. All authors reviewed the manuscript for publication.

Chapter 4:

Navrady, LB., Wolters, MK., MacIntyre, DJ., Clarke, T-K., Campbell, AI., Murray, AD., Evans, KL., Seckl, J., Haley, C., Milburn, KK., Wardlaw, JM., Porteous, DJ., Deary, IJ., McIntosh, AM. (2017). Cohort Profile: Stratifying Resilience and Depression Longitudinally (STRADL): A questionnaire follow-up of the Generation Scotland: Scottish Family Health Study (GS:SFHS). *International Journal of Epidemiology,* 47, 13-14g*:* https://doi.org/10.1093/ije/dyx115.

The funding application for this dataset was submitted by senior members of Generation Scotland committee, including AMM, DJP, JMW, and CH. LBN and AI contributed to the data entry and quality control for the project. AMM was the main supervisor for the project. LBN wrote the manuscript text and prepared all tables and figures. MKW aided in the statistical analysis. All authors reviewed the manuscript for publication.

Chapter 5:

Navrady, LB., Adams, MJ., Chan, SWY., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Ritchie, SJ., McIntosh, AM. (2017). Genetic risk of Major Depressive Disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression. *Psychological Medicine,* 1-10: doi:10.1017/S0033291717003415

This study was conceived by LBN, SJR and AMM. LBN wrote the manuscript text and prepared all tables and figures. AMM and SJR were joint supervisors for the project. LBN created the polygenic risk scores. MJA and SJR aided in the statistical analysis. All authors reviewed the manuscript for publication.

Chapter 6:

Navrady, LB., Zeng, Y., Clarke, T-K., Adams, MJ., Howard, DM., Deary, IJ., McIntosh, AMM. Genetic and environmental contributions to psychological resilience and coping. Accepted by *Wellcome Open Research* (awaiting review)

This study was conceived by LBN and AMM. LBN wrote the manuscript text and prepared all tables and figures. AMM was the main supervisor for the project. YZ created the genomic and environmental variance matrices. YZ and T-KC aided in the statistical analysis. All authors reviewed the manuscript for publication.

To acknowledge the contributions of many co-authors, —we" will be used instead of —I" throughout this thesis. A complete list of publications (first- and co-author) received as part of this PhD are presented in **Appendix D**.

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List of abbreviations

AIC	Akaike Information Criterion
AoC	Avoidance-oriented Coping
β	Beta (regression coefficient)
BRS	Brief Resilience Scale
CBT	Cognitive–behavioural therapy
CFI	Comparative Fit Index
CHI	Community Heath Index
CI	95% confidence interval
CIDI-SF	Composite International Diagnostic Interview – Short Form
CISS	Coping Inventory for Stressful Situations
DIC	Deviance Information Criterion
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWLS	Diagonally Weighted Least Squares (estimator)
ECT	Electroconvulsive therapy
EoC	Emotion-oriented Coping
EPQ-SF	Eysenck Personality Questionnaire Short Form-Revised
g	General intelligence
GCTA	Genome-wide Complex Trait Analyses
GHQ	General Health Questionnaire-28
GREML	Genomic-Relationship-Matrix Restricted Maximum Likelihood
GRM	Genetic relationship matrix
GS	Generation Scotland
GS:SFHS	Generation Scotland: Scottish Family Health Study
GWAS	Genome-wide association study
h_n^2	Narrow-sense heritability
HPA	Hypothalamic–pituitary–adrenal axis
ICD	International Classification of Diseases
LMM	Linear Mixed Modelling
LRT	Likelihood Ratio Test
LTE	List of Threatening Experiences
MCMCglmm	Markov Chain Monte Carlo generalised linear mixed model (package in R)
MDD	Major Depressive Disorder
MDS	Multidimensional scaling component
MRI	Magnetic resonance imaging
N	Neuroticism

NASSA(s)	Noradrenaline and specific serotonergic antidepressant(s)
OR	Odds ratio
p	Associated p-value of a test statistic
PC	Principal component
PCA	Principal component analysis
PFC	Prefrontal cortex
PGC	Psychiatric Genomics Consortium
PHQ	Patient Health Questionnaire–9
PRS	Polygenic Risk Score
PRSice	Polygenic Risk Score software
r_g	Genetic correlation from common-variant associated genetic effects
r_k	Genetic correlation from pedigree-associated genetic effects
RMSEA	Root Mean Square Error of Approximation
r_p	Phenotypic correlation
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
SIMD	Scottish Index of Multiple Deprivation
SNP(s)	Single Nucleotide Polymorphism(s)
SNRI(s)	Serotonin-noradrenaline reuptake inhibitor(s)
SSRI(s)	Selective serotonin reuptake inhibitor(s)
STRADL	Stratifying Resilience and Depression Longitudinally
TCA(s)	Tricyclic antidepressant(s)
TLI	Tucker–Lewis Index
ToC	Task-oriented Coping

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Chapter 1
An introduction to Major Depressive Disorder

1.1 Overview

Epidemiological research findings estimate that approximately 30% of the world‘s population are affected by a psychiatric disorder during their lifetime (Kalisch *et al.*, 2015). Major Depressive Disorder (MDD) is among one of the oldest psychiatric disorders to be historically identified (Hippocrates, 1923-1931, Jackson, 1986), and is currently a leading cause of non-lethal disability worldwide (Ferrari *et al.*, 2013). MDD is a highly pervasive and debilitating disorder, with a complex multifactorial interaction of genetic, neurobiological, and environmental components likely contributing to the individual differences seen in clinical liability and depressive symptomology (Otte *et al.*, 2016). However, despite exposure to known risks for MDD, human responses to it vary widely. Indeed, despite significant risk for MDD, many individuals exhibit better than expected adjustment. This ability to ‗bounce back' and ‗escape‘ the development of MDD is widely referred to as *psychological resilience.* Research into resilience is currently in its infancy and a primary aim of this thesis is to better elucidate the underlying causes and mechanisms of the construct which will be addressed empirically in subsequent chapters. The findings from this thesis may have important implications not only for researchers, but for clinicians and policy makers by providing evidence for who is most and least likely to develop MDD, in addition to furthering scientific knowledge for the development of preventative strategies in mental health which may circumvent the need for curative treatments.

Before researchers can begin to investigate protective factors (Chapter 3), protective pathways (Chapter 5), or the genetic and environmental components (Chapter 6) which enable an individual to demonstrate resilience to MDD, a comprehensive knowledge of the disorder itself is needed. This chapter aims to present a brief overview of MDD to familiarise the reader with the disorder, its prevalence and potential causes, as following chapters will employ MDD status as a study variable in order to better illuminate resilience mechanisms. Firstly, a brief historical context of MDD will be outlined before an overview of current diagnostic criteria is detailed. Additionally, current therapeutic techniques for the treatment of MDD will be discussed as a better understanding of psychological resilience may change how current treatments are administered and lead to the development of more efficacious interventions focussing on prevention. Secondly, epidemiological research findings will be discussed in relation to the prevalence of MDD and its impacts at individual and societal levels. An understanding of the impact MDD has on individual suffering and economic burden will likely demonstrate the importance of resilience and how it may alleviate such burden in the future. Finally, the aetiology of MDD will be discussed. Specifically, an overview of putative genetic, neurological, psychological and environmental causes of depression will be presented. A comprehensive understanding of factors which may cause depression may illuminate potential ‗targets‘ in the resilience enquiry.

1.2. Diagnostic criteria and treatment for MDD

The symptoms of depression have been described for millennia, and represent one of the first clear descriptions of neuropsychiatric syndromes in historical texts (Jackson, 1986). Indeed, the history of depression stems as far back as the earliest writings of Hippocrates and Galen in which the symptomatic descriptions of *melancholia* mimic contemporary features of MDD with surprising accuracy (Hippocrates, 1923-1931, Jackson, 1986). Whilst the historic causes of MDD ranged from demonic possession to an imbalance of bodily ‗humors', all descriptions differentiate periods of sadness or bereavement from MDD - a chronic and incapacitating illness. The first serious attempt to categorise and explain melancholic/depressive illness came from the publication of *The Anatomy of Melancholy* by Robert Burton during the seventeenth century (Burton, 1621/2001). In this seminal work, Burton described three key components of melancholia — mood, cognition, and physical symptoms — all of which are distinguishing features in contemporary descriptions of MDD. However, despite the comprehensive descriptions given by Burton, it was the work of diagnosticians such as Kraepelin who identified that modern symptoms of depression likely had the same underlying pathophysiology despite divergent clinical presentations (Kraepelin, 1921/1976). Kraepelin's approach to psychiatric diagnosis has subsequently been credited as the inspiration for the comprehensive manuals used by clinicians today such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) and the International Classification of Diseases (ICD; World Health Organization., 1992).

Table 1.1. DSM-IV Major Depressive Disorder criteria

To meet criteria for MDD, five (or more) of the following symptoms must be present for a minimum of two weeks (sequentially), lasting nearly all day, every day, and represent a change from previous functioning. At least one symptom must be either depressed mood (1) and/or loss of interest/pleasure in daily activities (2)
1. Depressed mood[a]
2. Decreased interest or pleasure is most activities (anhedonia)[b]
3. Fatigue or loss of energy
4. Diminished concentration or indecisiveness[b]
5. Significant (5%) weight change or change in appetite[c]
6. Feelings of worthlessness or excessive/inappropriate guilt[d,e]
7. Hypersomnia/insomnia (changes in sleep)
8. Psychomotor retardation/agitation (changes in activity)[f]
9. Suicidality or recurrent thoughts of death[g]
[a] In children and adolescents this can be irritable mood
[b] As indicated by either subjective account or observation made by others
[c] In children, consider failure to make expected weight gains
[d] Which may be delusional
[e] Not merely self-reproach or guilt about being sick
[f] Observable by others, not merely subjective feelings of restlessness or being slowed down
[g] With or without intent/plan
Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, Major Depressive Disorder
N.B**.** Symptoms must not meet criteria for a Mixed Episode. Symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Symptoms must not be due to the direct physiological effects of a substance or general medical condition. Symptoms must not be better accounted for by bereavement (which must persist > two months)

Currently, MDD is characterised by one or more depressive episodes lasting a minimum of two weeks that involve an impairment in normal functioning. A minimum of five symptoms including low mood and/or anhedonia must be present, lasting nearly all day, every day, for a minimum of two weeks. The current diagnostic criteria for MDD as specified in the DSM-5 (5th edition; American Psychiatric Association, 2013) is

presented in **Table 1.1**. Although it is possible for clinicians to diagnose MDD on the basis of a single depressive episode, the disorder is highly recurrent (American Psychiatric Association, 2013). To illustrate, it has been reported that at least 50% of individuals who recover from a first episode of MDD will have one or more additional episodes in their lifetime, and approximately 80% of individuals with a history of two depressive episodes will experience further recurrence of the disorder (American Psychiatric Association, 2003). A better understanding of psychological resilience may lead to patient interventions which could drastically reduce recurrence rates. A total of nine depressive symptoms are given in the DSM-5 and as such, multiple symptom combinations can each result in an MDD diagnosis, leading to substantial heterogeneity. This heterogeneity has led to the hypothesis that MDD may in fact act as an umbrella term which groups together several causally distinct but symptomatically related syndromes (Kessing, 2007) and as a result, efforts are now being made to stratify the disorder, which could potentially transform current therapeutic outcomes. For example, a large research programme has recently been developed which was specifically designed to investigate the stratification of depression and psychological resilience (STRADL; Navrady *et al.*, 2017a), from which findings from this thesis belong.

Table 1.2. Common psychological treatments used in the treatment of Major Depressive Disorder

Cognitive-behavioural therapy (CBT): CBT is a talking therapy which teaches patients to change negative, distortive thinking patterns which contribute to depression, and teaches skills to manage these thoughts and behaviours in the future
Psychodynamic therapy: This method encourages patients to think about how earlier life experiences have contributed to their current emotions and problems, and aids patients in recognising how these patterns can be changed to facilitate more effective coping strategies.
Problem-solving therapy: This therapy teaches patients the skills needed to identify, address and overcome problems and potential barriers in order to make more effacious decisions in the future.
Interpersonal therapy: This technique focuses on resolving interpersonal conflicts and impoverished relationships
Mindfulness-based therapy: Mindfulness is a contemplative practice commonly involving meditation which encourages patients to pay specific attention to their thoughts, feelings, and experiences to learn acceptance

In managing MDD, two main initial treatment options are utilised: psychological intervention and pharmacotherapy. Psychological treatments include; cognitive–behavioural therapy (CBT), mindfulness-based therapy, and psychodynamic therapy. These interventions broadly focus on changing negative cognitive biases in depressed patients, strengthening effective coping strategies, and illuminating potential sources of stress and/or sadness (Wender and Klein, 2005). A list of common psychological treatments and a brief description of their aims is given in **Table 1.2**. At present, no consistent clinically meaningful differences have been found between the different types of psychological therapy, although they are each more effective than no treatment at all (Cuijpers *et al.*, 2013, Cuijpers *et al.*, 2008, Linde *et al.*, 2015)**.** Despite psychological treatments clearly being effective, patients often experience several barriers to access including cost, time constraints and lack of available services (Mohr *et al.*, 2006, Mohr *et al.*, 2010). To overcome such issues, delivering psychological services over the telephone or through technology-supported mediums have shown to be equally as effective (Mohr *et al.*, 2012). Alternatively, pharmacological treatments have been demonstrated to produce equivalent effects to psychological treatments. For example, the beneficial effects of CBT have been shown to persist for at least 12 months post-treatment, which is similar to the effects seen in individuals who remain on antidepressants

(Hollon *et al.*, 2005). However, effect sizes from psychological and pharmacological treatments cannot be easily compared due to methodological issues (Amick *et al.*, 2015, Weitz *et al.*, 2015).

Antidepressants act to acutely increase levels of monoamine neurotransmitters such as serotonin and noradrenaline. Whilst they have been shown to significantly improve mood and positive affect, and reduce the risk of relapse, how they accomplish these changes is not fully understood (Otte *et al.*, 2016). There are several types of antidepressant medication which are grouped on the basis of their known pharmacological actions, including: selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline and specific serotonergic antidepressants (NASSAs), and tricyclic antidepressants (TCAs). SSRIs such as Citalopram and Fluoxetine are the most widely prescribed MDD medications as they cause fewer side effects than other forms of antidepressant, and are less likely to result in a fatal overdose (López-Muñoz and Alamo, 2009, Zimmerman *et al.*, 2004). Whilst both psychological and pharmacological treatments are effective in the treatment of MDD, it is estimated that 30% of patients do not remit from the disorder, even after several treatment attempts (Rush *et al.*, 2006, Thase *et al.*, 2007). In extreme cases in which treatment resistant patients are severely depressed and/or highly suicidal, electroconvulsive therapy (ECT) is the most widely used and effective non-pharmacological, biological treatment (UK ECT Review Group, 2003). It is likely that our limited knowledge of the biological basis of MDD impedes the development of more efficient treatments for individuals with severe and treatment resistant MDD. However, advancements in resilience research may enable clinicians to develop more efficacious treatments for MDD which could reduce both the recurrence and severity of the disorder. For example, with a better understanding of psychological resilience we may be able to ‗teach' resilience and foster it from childhood across the lifespan and such techniques could be fortified as part of existing therapeutic techniques.

1.3. Epidemiology

In 2011, a multi-national study estimated the 12-month prevalence of MDD to be 6%, based on approximately 90,000 individuals from 18 countries across the globe (Bromet *et al.*, 2011). Whilst the 12-month prevalence for MDD was found to vary between countries (e.g., 2% in Japan and 10% in Brazil), prevalence rates were largely similar across high- and low-income countries. Furthermore, median age of onset, symptomology, disorder severity, and sociodemographic profiles were mostly comparable between countries and cultures (Kendler *et al.*, 2015, Kessler and Bromet, 2013). However, cross-cultural differences are found between high- and low-income countries whereby approximately 60% of individuals with MDD in high-income countries receive treatment for the disorder in comparison to 10% of patients in low-income countries (Wang *et al.*, 2007). The lifetime prevalence of the disorder is estimated to be three times greater than the 12-month prevalence estimates, suggesting that one in six adults will suffer from MDD throughout their lifetime (Bromet *et al.*, 2011). Reports suggest a two-fold increase in MDD risk in women compared to men in adulthood (Seedat *et al.*, 2009). Across genders, the median age of onset for MDD is estimated to be 25 years, with increased risk for MDD onset typically ranging from mid-to-late adolescence to early 40s (Bromet *et al.*, 2011), although generally, MDD prevalence decreases moderately after adulthood, especially in high-income countries (Kessler *et al.*, 2003). However, prevalence rates are often an unreliable metric as they are subject to substantial underestimation and issues surrounding recall bias (Moffitt *et al.*, 2010, Patten, 2009).

MDD is currently the second leading cause of disease burden worldwide (Vos *et al.*, 2015), with significant consequences at individual and societal levels. In 2010, the economic burden associated with MDD was estimated to be $2.5 trillion (Bloom *et al.*, 2011), with this number expected to increase exponentially in coming years. At an individual level, MDD patients are 20-times more likely to die by suicide in comparison to the general population (Chesney *et al.*, 2014), with estimates suggesting that 50% of suicides worldwide (annually) are attributable to the disorder (Otte *et al.*, 2016). Moreover, not only does MDD increase mortality risk in the general population by 60-80% (Cuijpers *et al.*, 2014, Walker *et al.*, 2015), but also has consequences that extend to physical health. Specifically, longitudinal research suggests that MDD increases risk for heart disease, stroke, obesity, diabetes, cancer, cognitive impairment and dementia (Penninx *et al.*, 2013). At present, the mechanisms underlying these comorbidities remain largely unknown, although numerous biological and environmental factors have been suggested (Kessler, 1997, Ripke *et al.*, 2013, Schmaal *et al.*, 2016). The economic burden and individual suffering associated with MDD could potentially be alleviated with the employment of resilience strategies. For example, if individuals can develop resilience before MDD onset, the healthcare system may not need to spend as much money on antidepressant medication or primary care. Furthermore, providing individuals with the tools needed to ‗bounce back' could potentially result in fewer deaths from suicide, or from co-morbid health complications such as heart disease.

1.4. Aetiology

The aetiology of MDD is likely complex and at present nascent mechanisms in MDD remain largely elusive. However, methodological advancements in molecular genetics, neuroimaging and population-based approaches are enabling researchers to learn more about the underpinnings of MDD (Otte *et al.*, 2016). Below, a selection of contemporary methodological approaches to MDD research are reviewed, and relevant gaps in our current knowledge are highlighted.

1.4.1. Genetics

For centuries, it has been observed that MDD clusters within families (Mullins and Lewis, 2017). This familial aggregation hypothesis has been supported by the finding that first-degree relatives of depressed patients are three times more likely to receive an MDD diagnosis than the general population (Geschwind and Flint, 2015), with twin studies reporting narrow-sense heritability estimates of 37% (Geschwind and Flint, 2015, Sullivan *et al.*, 2000). Heritability estimates from family and twin-based studies are generally higher than single-nucleotide polymorphism-derived (SNP) estimates which have been calculated at 21% (Ripke *et al.*, 2013). Estimates of SNP heritability have been found to vary across populations and samples (0.21 ~ 0.32) (Lee *et al.*, 2013, Lubke *et al.*, 2012). Such findings suggest that heritability estimates may be over-estimated which could potentially be due to shared environmental effects, or from unaccounted variance from rare genetic variants, gene interactions or poorly tagged SNPs (Flint and Kendler, 2014, Wray and Maier, 2014). These findings do, however, illustrate the genetic complexity of MDD, and as such make it amenable to many powerful methodologies designed for complex diseases and quantitative traits.

In recent years, genome-wide association studies (GWAS) have been utilised to find specific genetic variants associated with MDD. However, thus far, the search for main genetic effects in MDD have failed to find

consistent or replicable findings (Bosker *et al.*, 2011), as indicated by GWAS meta-analysis (Ripke *et al.*, 2013). This is likely due to the excessive heterogeneity of the disorder and so attempts have now been made to identify genetic loci with a homogeneous phenotypic approach. In 2015, the CONVERGE Consortium published the first GWAS to identify genome-wide significant variants for MDD in a non-European population, in which two replicated loci were associated with recurrent MDD (CONVERGE Consortium, 2015). The subsequent year, a joint analysis of three European samples (n > 75,000), identified 15 genetic loci associated with self-reported clinical MDD (Hyde *et al.*, 2016). One replicated genome-wide significant locus has also been associated with adult-onset MDD (> 27 years) (Power *et al.*, 2017). Furthermore, recent studies have identified several genome-wide significant loci for neuroticism, a personality trait strongly associated with MDD (Okbay *et al.*, 2016, Smith *et al.*, 2016). Whilst significant progress has been made in genetic research, these studies suggest that MDD may be highly polygenic, involving many genes whose cumulative effects may have stronger associations than any one individual locus (Hyman, 2014). Alternatively, the lack of consistent findings may be resultant from complex gene-environment (GxE) interactions whereby genetic variants only confer risk in the presence of specific environmental stressors (Klengel and Binder, 2013, Otte *et al.*, 2016).

1.4.2. The brain

In recent decades, researchers have sought to determine the role of the brain in association with MDD. In particular, the neurological basis of emotion and cognition has received much attention as deficits in these areas are widely implicated in MDD (Bradley *et al.*, 2011, Trivedi, 2006), and are known to be predominately controlled by cortical and subcortical brain regions (Heatherton and Wagner, 2011, Wager *et al.*, 2008). Indeed, numerous studies have identified both morphological and functional abnormalities in association with MDD pathology, most of which focus on the hippocampus (Arnone *et al.*, 2012). For example, structural magnetic resonance imaging (MRI) studies have reported consistent evidence to suggest that hippocampal volume is reduced in MDD patients (Goodkind *et al.*, 2015, Kempton *et al.*, 2011, Schmaal *et al.*, 2016). Specifically, a meta-analysis of 143 imaging studies found MDD patients have smaller hippocampal volumes than healthy controls, in addition to reductions in the thalamus, basal ganglia and several frontal regions (Kempton *et al.*, 2011). Another meta-analysis also found significantly lower hippocampal volumes in MDD patients (Schmaal *et al.*, 2016), although no differences between depressed and non-depressed individuals were found in other subcortical areas. Furthermore, a more recent study also failed to detect significant differences in subcortical volumes between depressed individuals and healthy controls, although the small sample size was recognised as a limiting factor (Shen *et al.*, 2017). At present, contradictory evidence has prevented researchers from determining if small hippocampal volumes are causal in MDD pathology, or if the disorder itself causes morphological changes (Cole *et al.*, 2011, Schmaal *et al.*, 2016). Additionally, findings suggest that significant differences of cortical thinning in the temporal lobes, orbitofrontal cortex, anterior and posterior cingulate, and the insula between MDD patients in comparison to never-depressed controls (Schmaal *et al.*, 2016). It has been proposed that a complex interaction of molecular and cellular mechanisms ultimately contribute to the structural changes found in MDD patients (Otte *et al.*, 2016), but further investigation is needed to confirm this.

Neuroimaging studies have also identified functional abnormalities in MDD, with specific reference to activation and connectivity perturbances within the medial prefrontal–medial parietal default mode network, the

frontoparietal cognitive control circuit, and the affective– salience circuit in MDD patients (Maier *et al.*, 2015, Nusslock and Miller, 2016). The Default Mode Network (DMN) is charactersied by greater neurological activity during ‗resting' states, and has been found to be hyperconnected in MDD (Dutta *et al.*, 2014), which is purported to underlie the symptoms of rumination typical of the disorder (Cooney *et al.*, 2010, Hamilton *et al.*, 2012, Sheline *et al.*, 2009). Conversely, the dynamic coupling between the DMN deactivation and frontoparietal activation is disturbed in MDD (Hamilton *et al.*, 2011, Whitfield-Gabrieli and Ford, 2012), which is hypothesized to underlie (in part) the cognitive deficits seen in MDD. This is unsurprising given the frontoparietal cognitive control circuit is primarily responsible for cognitive tasks (Cole *et al.*, 2013). It has been suggested that the goal-directed attention deficits seen in MDD are due to frontoparietal hypoconnectivity (Kaiser *et al.*, 2015), whereas decreased frontoparietal connectivity has been associated with negative cognitive appraisals (Hamilton *et al.*, 2013, Pizzagalli *et al.*, 2009). One of the most frequently reported findings of functional brain abnormalities in MDD pertain to the heightened activation and increased connectivity of the amygdala (Hamilton *et al.*, 2012), a central component of the affective–salience circuit which is responsible for guiding behaviour. Moreover, hyperactivities have also been found in the anterior insula and anterior cingulate in MDD patients, which potentially explain the increased salience of negative biases typical of the disorder (Hamilton *et al.*, 2012). It is purported that these functional aberrations are due to stress-associated changes in inflammatory and glucocorticoid signalling (Otte *et al.*, 2016) which demonstrate that MDD aetiology is the result of a complex interaction between molecular, neurological and environmental factors.

1.4.3. Psychological and cognitive factors

There is evidence to suggest that personality traits may predispose individuals to MDD (Dunbar, 1943). To illustrate, a recent study has shown that negative affect significantly predicts depressive symptoms longitudinally (Elovainio *et al.*, 2015). Negative affect represents a personality trait characterised by the elevated experience of negative emotions, and as such, it is purported to be highly similar to the personality trait neuroticism (Braithwaite *et al.*, 1984). Neuroticism is a stable personality trait characterised by negative emotional response and stress sensitivity, and has been shown to associate with MDD both cross-sectionally (Chan *et al.*, 2007, Hakulinen *et al.*, 2015, Roelofs *et al.*, 2008), and prospectively (Farmer *et al.*, 2008, Kendler *et al.*, 2006). Further support for the role of neuroticism in depressive illness comes from two large meta-analyses which have demonstrated strong positive associations between neuroticism and mood disorders such as MDD (Kotov *et al.*, 2010, Malouff *et al.*, 2005). However, whilst Malouff and colleagues (2005) found strong associations between neuroticism and mood disorders generally, Kotov et al. (2010) found stronger effects for the association between neuroticism and dysthymia - a more chronic form of MDD. This suggests that MDD severity and chronicity may be associated with exceptionally high levels of neuroticism. The majority of research linking neuroticism and MDD has been cross-sectional, making it difficult to discriminate associative relationships from causal ones. A further difficulty in disentangling the relationship between personality and MDD comes from research which suggests that neuroticism may act as a possible mediator between adversity and indices of mental health (Lardinois *et al.*, 2011). For example, childhood adversity has been found to affect personality development, whereby negative experiences in childhood have been found to promote neuroticism which in turn increases risk for MDD (Roy, 2002). Neuroticism is unlikely to influence developmental

trajectories that lead to MDD in isolation and so it is important to understand the role of potential genetic factors that may influence the association between personality and MDD.

Neuroticism is a partially heritable trait, with numerous family-based and adoption studies reporting estimates of approximately 40% (Birley *et al.*, 2006, Hahn *et al.*, 2013, Vukasović and Bratko, 2015, Wray *et al.*, 2007). Thus far, no evidence for differential heritability has been found when using different measures of neuroticism, or when investigating sex differences (Vukasović and Bratko, 2015, Wray *et al.*, 2007), although phenotypically neuroticism scores are generally higher in women than men (Costa *et al.*, 2001, Soto *et al.*, 2011). It has been suggested that half the genetic variance in neuroticism is attributable to non-additive effects (Hahn *et al.*, 2013, Keller *et al.*, 2005) and so phenotypic differences in neuroticism between sexes is likely resultant from environmental factors, gene-environment interactions, or rare genetic variants (Smith *et al.*, 2016). At a molecular level, research suggests that there may be genetic loci associated with both neuroticism and MDD. For example, a GWAS meta-analysis from the Genetic of Personality Consortium (PGC) identified one genome-wide significant gene - *MAGI1 (de Moor et al., 2015)* which has been previously associated with MDD (Etain *et al.*, 2006, Ferentinos *et al.*, 2014, Karlsson *et al.*, 2012). A subsequent GWAS for neuroticism found nine genome-wide significant loci, two of which have been associated with stress response pathways in MDD (Gray *et al.*, 2015, Lee *et al.*, 2012, Weber *et al.*, 2016). The largest neuroticism GWAS to date identified 11 genome-wide significant loci of which four were nominally significant in a GWAS of MDD (Okbay *et al.*, 2016). Further evidence of a shared genetic aetiology between neuroticism and MDD comes from twin studies which report genetic correlations between neuroticism and MDD of between 0.43 and 0.69 (Hettema *et al.*, 2006, Kendler *et al.*, 2006, Kendler and Myers, 2010). These findings suggest an overlapping genetic architecture in which genes responsible for negative emotions (neuroticism) also increase the risk for MDD.

1.4.4. The environment

Whilst genetic and neuroimaging research has thus far found inconsistent evidence to suggest a definitive preclinical marker for MDD, a number of putative environmental risk factors have been consistently shown to associate with the disorder. For example, marital difficulties, major health issues, job loss, and interpersonal conflicts have been found to substantially associate with an increased risk for MDD onset (Kessler, 1997). These factors occur most often in adulthood and demonstrate that environmental exposures/insults may be closely related to MDD in time, usually in the 12-months preceding onset of the disorder (Kessler, 1997). More recent evidence, however, suggests that difficulties in childhood may be an antecedent of later MDD. Experiences such as physical or sexual abuse, neglect, parental separation or bereavement, and exposure to domestic violence in childhood demonstrate a dose-response relationship whereby the number and severity of early negative life events directly associate with MDD risk, chronicity, and severity (Li *et al.*, 2016). Furthermore, stress *in utero* has also been found to associate with increased MDD risk in later life (Entringer *et al.*, 2015), demonstrating that early life experiences can have profound and long-lasting effects on an individual‘s mental health (Stein *et al.*, 2014), potentially involving epigenetic regulation (Klengel and Binder, 2015). It is likely that - although not definitively proven - genetic liability for MDD may increase an individual‘s propensity for stressful life events which result in the neurological abnormalities described above.

1.5. Chapter conclusions

MDD is a pervasive psychiatric condition characterised, in part, by low mood, anhedonia, cognitive deficits and vegetative symptoms such as disturbed appetite or sleep. Currently, management of depressive symptomology comprises both psychological and pharmacological treatments, the latter of which are used most commonly. However, whilst current treatments for MDD prove effective for some, it is estimated that 30% of patients do not remit from the disorder, even after several treatment attempts (Rush *et al.*, 2006, Thase *et al.*, 2007). Whilst current treatments for MDD are effective for the majority of patients, our limited knowledge of the specific causes of MDD hinder the development of more efficacious treatments, especially for individuals with severe and chronic depression. Current research indicates that the aetiology of MDD likely encompasses a complex interaction of genetic, neurological and environmental factors, although the correlational nature of much of this research means we are unable to infer causality. At present, no underlying mechanism for MDD has been robustly identified which not only limits research for new treatment opportunities, but also ultimately contributes to further disability and suffering. The observation that not all individuals are risk for MDD go on to develop the disorder represents an important area for scientific research. Specifically, the investigation of psychological resilience has the potential not only to alleviate individual suffering but also reduce the economic burden associated with MDD by focussing on prevention rather than cure. Identifying potential factors and mechanisms that may enable individuals to ‗bounce back' and ‗escape' the development of MDD will be the main focus of discussion in subsequent chapters of this thesis.

Chapter 2
The concept of psychological resilience

2.1. History and overview

Negative life events are ubiquitous, and, as outlined in Chapter 1 are potential risk factors for the onset of Major Depressive Disorder (MDD). For example, researchers such as Paykel and colleagues (1969) have long demonstrated the importance of life stress and adversity on the genesis of MDD. However, despite the frequency with which stressful/negative events occur, only a small subset of individuals go on to develop psychopathology (Kalisch *et al.*, 2015). Indeed, it is widely observed that despite exposure to known risks for MDD, most individuals are able to successfully overcome such risk with little or no disruption to their normal functioning (Bonanno, 2004). Specifically, whilst some individuals develop depression in response to MDD risk, others develop only mild and transient symptoms or no depressive symptomology at all. This ability to ‗bounce back' and maintain or regain mental health and ‗escape' the development of MDD is widely referred to as *psychological resilience* (Bonanno and Mancini, 2011, Feder et al., 2011, Luthar et al., 2000, Masten et al., 1990, Sapienza and Masten, 2011).

The origins of resilience can be traced back to the natural sciences whereby researchers noticed that objects – such as a spring - will return to their baseline form despite being previously misshapen (Geller *et al.*, 2003, Lazarus, 1993). Our knowledge of *psychological* resilience, however, emerged from the clinical observation of individuals who were able to effectively negotiate, adapt to, or manage high-risk situations with little or no detriment to their mental health (Richardson, 2002). While initially proposed by psychologists and clinicians (Werner, 1993), interest in psychological resilience has grown substantially over recent decades, motivating a wealth of research across disciplines (Leipold and Greve, 2009, Russo *et al.*, 2012, Southwick and Charney, 2012, Werner, 1982). Although investigations of resilience may be expected to reveal similar risk factors and causality as studying MDD itself, it does represent a new facet to scientific and clinical research. Specifically, resilience focuses on intervention long before the development of MDD when effects on subsequent suffering and its consequences – including its economic burden - may be ameliorated (Sapienza and Masten, 2011). Unlike ‗deficit' models of MDD (Fergus and Zimmerman, 2005), resilience research focuses on understanding healthy functioning despite risk, and on strengths rather than weaknesses (Fergus and Zimmerman, 2005).

The complexities of defining the concept of resilience are widely recognized (Haskett *et al.*, 2006, Luthar *et al.*, 2000, Masten, 2007), leading to wide discrepancies in both its definition and measurement (Bonanno *et al.*, 2015). For this reason, resilience is rarely directly measured (Luthar *et al.*, 2006, Masten and Obradovic, 2006), but inferred from the direct measurement of two specific points of convergence; adversity (its antecedents) and positive adaptation (its consequences) (Windle, 2011). Researchers have also investigated protective factors which could serve as potential moderators and mediators between adversity and positive adaptation (Connor and Davidson, 2003, Wagnild and Young, 1993). Thus far, protective factors in MDD have been assessed from developmental (Garmezy, 1985), dispositional (Bonanno, 2004, Campbell-Sills *et al.*, 2006), genetic (Amstadter *et al.*, 2016, Luthar *et al.*, 2000) and neurobiological (Chan *et al.*, 2016, Russo *et al.*, 2012) viewpoints. This

concept-based perspective indicates that the measurement of resilience needs to consider three fundamental components — adversity, positive adaptation, and protective factors simultaneously (as illustrated in **Figure 2.1**). However, inconsistencies in the specific delineation of these concepts have resulted in confusion over their meaning, and the scientific validity of resilience being questioned (Bodin and Winman, 2004). As the fundamental concepts in resilience are distinct, it is important to address them separately to depict an accurate representation of resilience to MDD. In this chapter, the core components of resilience will be outlined and critically discussed in order to elucidate more effective strategies to examine the aetiology and mechanisms of resilience in this thesis.

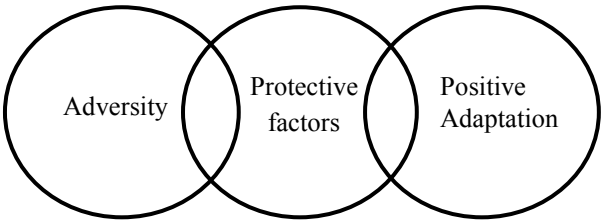

Figure 2.1. The three core components of psychological resilience

2.2 Adversity

It is estimated that 50-60% of individuals will experience a severe trauma during their lifetime, with all individuals experiencing at least one potentially traumatic event (Bonanno and Mancini, 2008, Kessler *et al.*, 1995). The term ‚potentially' is a vital distinction as it draws attention to the individual differences in how people react to negative events. Indeed, despite the frequency with which individuals experience traumatic and distressing events, it is estimated that only 7.8% of psychopathology is resultant from them (Kessler *et al.*, 1995), indicating that resilience is ubiquitous. Luthar and Cicchetti (2000) assert that ‚adversity' incorporates negative life events which are associated with poor functioning. For example, a dose response relationship has been found in which incremental adversity in childhood confers increased risk for depression and suicidality in later life (Cabrera *et al.*, 2007, Felitti *et al.*, 1998). Furthermore, numerous studies report that the number of negative life events experienced greatly increases the risk for MDD across adulthood (Dolan *et al.*, 1985, Ezquiaga *et al.*, 1987, Perris, 1984, Paykel *et al.*, 1969). This threshold-dependent definition of adversity is closely associated with the concept of risk and the statistical probability that an event (or condition) only becomes an indicator of vulnerability when it is strongly associated with maladjustment (Luthar *et al.*, 2000, Masten, 2001). However, the literature pertaining to putative risk factors for MDD is extensive and is not limited only to isolated and highly disruptive events. A constellation of risk factors for depression have been found across biological, psychological, environmental and social domains (for a comprehensive review, see Dobson and Dozois, 2011) and for this reason it is essential to examine adversity in regards to any known risk factor.

The narrow definition of adversity as a negative event/condition which predicts MDD fails to account for the cumulative stress resultant from daily hassles or positive (but stressful) events. Indeed, as suggested in the seminal work of Brown and Harris (1978), environmental risk factors found in daily life often produce cognitive and emotional responses synonymous with MDD. A less stringent definition has been suggested in which

adversity encompasses any hardship or suffering linked to struggle, misfortune or trauma (Jackson *et al.*, 2007), including everyday disruptions and highly stressful, yet still common, events (Davis *et al.*, 2009, Sameroff and Rosenblum, 2006, Paykel *et al.*, 1969). For example, epidemiological research has long examined the depressive effects of chronic work stress (Karasek and Theorell, 1990, Kasl, 1978) and marital difficulties (Beach *et al.*, 1990, Gotlib and McCabe, 1990) with their depressive effects (Kessler *et al.*, 1987, Umberson *et al.*, 1992). Although the connotations associated with ‗adversity' are often negative, positive life events also play a role. For instance, a job promotion will nonetheless necessitate resilience to positively adapt to the new role. Similarly, the birth of new child, which again is unlikely to be considered an adversity, requires a range of resources to navigate a number of novel demands (Neff and Broady, 2011) which could otherwise increase the risk for depressive illness. Hence, resilience mechanisms may differ in regards to their contextual severity (Davydov *et al.*, 2010) and so when examining adversity, we must include not only negative life events, but also everyday stressors and stable, endogenous factors to sufficiently reflect individual differences in resilient outcomes.

Resilience research employs three general approaches to quantify adversity: (1) specific life stressors, (2) multiple-item checklists of negative life events, and (3) the concurrent risk from multiple sources to form an overall adversity estimate (Luthar and Cushing, 1999). Initially, research into adversity focused on specific single life occurrences such as war, death of a loved one or job loss. A psychometric problem in examining distal risk factors for depression is that individuals who demonstrate positive adaptation may not be facing high proximal risk (Richters and Weintraub, 1990). Single risk events (such as witnessing a terror attack) usually precede a negative psychological response (e.g., MDD or post-traumatic stress disorder) but are typically distal in nature. Research suggests that whilst single event adversity confers immediate risk, it can be influenced (and reduced) by proximal variables (Fletcher and Sarkar, 2013). To illustrate, prospective studies investigating children in high-risk environments have found that social support and close interpersonal relationships can ameliorate the detrimental relationship between MDD and adversity (Collishaw *et al.*, 2007, DuMont *et al.*, 2007, Luthar, 2006, Masten *et al.*, 1990, Parker, 1983, Werner and Johnson, 2004). This intimates that resilience is likely the result of protective mechanisms mitigating the negative effects of adversity and so whilst investigating distal risks can illuminate successful outcome in times of adversity, it is equally important to explain their proximal processes (Fletcher and Sarkar, 2013). Furthermore, in studying the time elapsed since the occurrence of an event, the variation in initial impact and length of risk period can be examined. Kessler and Magee (1993, 1994) found that severe adversity in childhood significantly effects early-onset depression, but not late-onset depression, indicating that there is a risk period for adversity after which its depressogenic effects are diminished.

A second approach to investigating adversity focuses on multiple-item inventories such as the Life Events Checklist (Work *et al.*, 1990) and the List of Threatening Experiences (LTE: Brugha *et al.*, 1985) which assess the events in an individual's life which confer adversity such as natural disasters, financial difficulties and marital problems. Although the LTE examines the subjective emotional experiences associated with adverse events, the majority of checklists fail to capture the meaningful variability in adversity which may prevent accurate comparisons between both events and individuals (Seery *et al.*, 2010). Such issues are also relevant

when examining less severe stressors with greater chronicity (e.g., The Daily Hassles Scale; Kanner *et al.*, 1981), and, although studies demonstrate little difference in weighted and unweighted scores according to an individual's impact rating (Swearingen and Cohen, 1985) of negative events, it is important to take account of the heterogeneity of the events in a multiple item inventory (Luthar and Cushing, 1999, Masten *et al.*, 1994). Checklist methodologies also fail to consider the issue of accuracy; depressed individuals consistently demonstrate a negative recall bias (Blaney, 1986). Not adjusting for recall bias may elicit spurious associations between adversity and depression. Indeed, research has found that the experimental induction of depressed mood leads to significantly more reports of past stressful events (Cohen *et al.*, 1988). It is also important to consider measurement confounds such as _controllability' of items within the checklist. Whilst it is relevant to evaluate both _uncontrollable' events (eg., serious injury or sexual assault) and _controllable' events (e.g., detrimental health behaviours such as excessive alcohol consumption or divorce), the inclusion of controllable events may inflate adversity-depression associations (Luthar and Cushing, 1999, Masten *et al.*, 1988) insofar that some events might be attributable to MDD rather than independent of the illness. A differentiation also needs to be made between the characteristics of stressors such as duration (chronic vs. acute), frequency (rare vs. common occurrence), and intensity (high vs. low demand).

Adversity can also be measured by combining specific, distinct risk factors to produce a cumulative approximation of adversity. This approach typically involves computing a total adversity score across a number of high-risk domains, including; genetic liability, low parental income and membership to a minority group (Chang *et al.*, 2014, Gutman *et al.*, 2003, Sameroff *et al.*, 2003, Sameroff and Rosenblum, 2006) to which a count of one or zero is assigned to each index. This methodological approach is gaining increasing popularity as it recognised that adversity rarely occurs in isolation (Fletcher and Sarkar, 2013, Heller *et al.*, 1999, Luthar *et al.*, 2006). Moreover, a summed risk methodology can account for a multitude of known biological and environmental risk factors simultaneously. For example, whilst socioeconomic deprivation is an important risk factor to consider in MDD due to its chronicity and diffuse impact, behavioural genetics research demonstrates that low socioeconomic status has substantive genetic influence (Plomin and Bergeman, 1991, Plomin *et al.*, 1994). Specifically, studies suggest that parents yielding increased genetic risks for their children are more likely to provide sub-optimal environments and upbringing (Clark *et al.*, 2000, Hashima and Amato, 1994, Runyan *et al.*, 1998), decreasing the likelihood of resilient outcomes. Conversely, several studies have reported that children of emotionally warm and nurturant care-givers are found to be more resilient to stressful life events (Egeland *et al.*, 1993, Kim-Cohen *et al.*, 2004, Werner, 1982), even in genetically high-risk, low-income families (Wyman *et al.*, 1999). Together, these studies suggest that some of the risks which are thought to represent environmental adversity actually involve genetic mediation (Plomin *et al.*, 1994), especially in regards to family risk factors. In reflecting the synchronicity of numerous risk factors in real life, the summed risk strategy retains high ecological validity, although causality is difficult to infer. In order to understand how protective factors mediate the relationship between risk or resilience to MDD it may prove more effective to examine factor-analytic or structural models (Catalano *et al.*, 2011, Holahan and Moos, 1991, Schok *et al.*, 2010) rather than simply investigating sum scores.

2.3. Positive adaptation

In conjunction with investigating adversity, resilience to MDD needs also to assess positive adaptation. Positive adaptation has been described by Luthar and colleagues (2000) as ‗behaviorally manifested social competence, or success at meeting stage-salient developmental tasks" (p. 858) and by Masten and Obradovic (2006) as ‗symptoms related to internal well-being" (p. 15) in response to risk. However, competence must be conceptually appropriate to the adversity assessed (Luthar *et al.*, 2000, Luthar *et al.*, 2006). For example, in depressed children an indicator of positive adaptation can be indexed by the attainment of social or educational milestones appropriate to their developmental stage (Luthar *et al.*, 2000, Masten, 2001), whilst in soldiers returning from war the absence of psychopathology would be more fitting. Furthermore, the indicators used to assess positive adaptation must also be appropriately stringent; it is the nature of an adversity that should determine the level of adaptation needed to demonstrate resilience. To illustrate, in individuals with a high genetic risk for MDD or those exposed to a serious adversity, positive adaptation could be defined as a lack of MDD symptomology as opposed to evidence of ‗normal' functioning at work, home and socially from an individual after a relationship breakdown.

Akin to adversity, multiple methodologies are employed to measure positive adaptation with the most common being multiple-item inventories assessing adjustment on a continuum and the presence or absence of psychopathology (Luthar and Cushing, 1999). In using questionnaire measures of adaptation, it is important to ensure they are suitable to the individual(s) being assessed. For example, in psychiatric populations at risk for MDD, it would be fitting to assess self-harm and suicidality, whereas among community samples, it would be appropriate to assess psychological distress (Goldberg and Hillier, 1979) when MDD is suspected. It is often difficult to gauge positive adaptation using multiple-item inventories as they are often administered only to the reference group, and so the individuals reflecting the highest competence within the sample may only illustrate the best of a generally poorly functioning population when compared with a normative group (Mulholland *et al.*, 1991). For instance, when administering the General Health Questionnaire (GHQ; Goldberg and Hillier, 1979) to a group of individuals with a history of MDD, those scoring lowest on psychological distress – i.e. those who are better adapted – may still score statistically higher than individuals who have never been depressed. A similar caveat pertains to the Beck Depression Inventory (BDI; Beck *et al.*, 1961). The BDI is a self-report measure commonly used to make case/control classifications of MDD and to quantify the intensity of depressive symptoms. However, it is well-known that the BDI is heavily weighted towards measuring cognitive aspects of depressive symptomology (Campbell *et al.*, 1984, Carroll *et al.*, 1981, Oliver and Simmons, 1984) and as such low scores (indicative of positive adaptation) may not reflect the multidimensional facets of the disorder but rather favour individuals who meet a specific symptom cluster (Depue and Monroe, 1978).

Psychological resilience encapsulates both a transient period of depressive illness followed by gradual restoration to healthy levels of functioning *and* maintenance of a relative stable trajectory of healthy functioning when depression would otherwise be expected (Fletcher and Sarkar, 2013). However, some researchers assert that the mere absence of depression in the face of risk or adversity is evidence enough of positive adaptation. Bonanno (2004), for example, argues that individuals who experience mild depressive symptomology before returning to baseline exhibit recovery rather than resilience, but to quantify adaptation in such a way is too

simplistic. In particular, individuals who are at sub-threshold for diagnosis of MDD tend to exhibit other threshold and subthreshold forms of psychopathological syndromes (Marshall *et al.*, 2001). In other words, although they are clinically unaffected by MDD they may also be significantly symptomatic and distressed in regard to other psychiatric disorders**.** To overcome this simplification, Amstadter and colleagues (2016) posited that positive adaptation (resilience) should be computed as the residual between actual and predicted psychiatric symptoms, based on the total number of stressful life events one has experienced. Although this method is more rigorous than that proposed by Bonanno (2004) it still relies on assessing positive adaptation and adversity in one domain. Such approaches raise a further caveat in issues of timing. A great deal of variation is likely to be found in positive adaption as a function of the point at which it was measured; recovery periods are typically quite long in depressive illnesses, with research indicating that adverse life events retain their capacity for conferring MDD risk long-term, potentially years post-event (Monroe and Simons, 1991).

As noted previously, it is the nature of an adversity that should determine the level of competence that needs demonstrating. However, positive adaptation needs also be examined across numerous domains to avoid an overly narrow conceptualisation (Luthar and Zelazo, 2003, Luthar *et al.*, 2006), as competence in one particular area does not necessitate generalizability to other domains. At present, resilience is routinely evaluated from a Western perspective, and as such, cross-culturally validated studies are scarce. As positive adaptation is manifest across many contexts, it is vital to be sensitive to the sociocultural factors that contextualize how it is defined. A recent investigation spanning five continents found great variation in adaptation cross-culturally, even in individuals facing similar adversities (Ungar, 2008, Ungar *et al.*, 2007) which demonstrates the necessity for resilience research to be culturally sensitive. In understanding positive adaptation from within the cultural context from which competence emerges, we will be able to take an ecologically valid approach (Ungar, 2008).

2.4. Protective factors

Unlike the risk factors described in Chapter 1 which confer vulnerability to MDD, the field of resilience research has identified several protective factors that enable an individual to maintain a stable mental health trajectory. Limited research has specifically examined the association between protective factors and resilience as agreement on a definition of the concept has yet to be reached. Rather, research has focused on factors that associate with positive mental health outcomes. These factors are not necessarily the antithesis of risk but rather an independent set of variables that could potentially mediate or moderate the relationship between adversity and positive adaptation.

Initially, the resilience enquiry focused on demographic factors which may underlie variability in MDD susceptibility. For example, resilience to MDD has been robustly associated with older age, greater education, and male gender (Bonanno *et al.*, 2007, Murrell and Norris, 1983). Other research suggests that ethnicity may provide a predictive role in resilience whereby African American and Latino groups experience poorer mental health (Adams and Boscarino, 2005) and decreased levels of resilience (Bonanno *et al.*, 2006) in the aftermath of traumatic events, compared to Caucasians. However, the effects of ethnicity are often confounded with low

socioeconomic status (Norris *et al.*, 2002) and when socioeconomic status is adjusted for, the predictive value of race on resilience diminishes (Bonanno *et al.*, 2007).

2.4.1. Personality

An important debate to emerge from extant literature concerns the conceptualisation of resilience as either a trait or a process (Windle, 2011). Initially, resilience was widely regarded as a personality trait (Connor *et al.*, 2003, Schok *et al.*, 2010) and much research was conducted on protective psychological traits such as ‗ego resilience' (Block and Block, 1980). A number of questionnaire measures have now been developed to assess ego resilience (e.g., The ER 89; Block and Kremen, 1996 and Ego Resiliency; Klohnen, 1996), and subsequently, a wealth of personality traits have been associated with positive adaptation. For example, hardiness (Bonanno, 2004) is found to buffer against exposure to risk (Kobasa *et al.*, 1982) by providing individuals with increased confidence and the ability to appraise adversity in a less threatening way (Florian *et al.*, 1995). Similarly, creativity (Simonton, 2000) and humour (Wolin and Wolin, 1993) are also thought to confer resilience by virtue of cognitive flexibility which can exert a stress-inoculation effect (Werner, 1993)**.** Dispositional optimism (Alarcon *et al.*, 2013, Amstadter *et al.*, 2016, Chang and Sanna, 2001) has been shown to positively associate with better life adjustment and negatively correlate with psychiatric illness. Spirituality is also believed to aid individuals in resisting MDD, although this may form one component of a wider belief system that provides meaning, appreciation of oneself and a cohesive life narrative (Bogar and Hulse-Killacky, 2006, Miller *et al.*, 2014, Urman *et al.*, 2001). Self-efficacy (Bachay and Cingel, 1999) and frequent experiences of positive affect, too, are considered protective against the psychological burden of extreme stress (Cohn *et al.*, 2009, Zautra *et al.*, 2005).

Numerous studies have linked the use of positive emotions to resilience as it is thought that positive emotionality and high self-esteem promote habituation to stressors, encouraging efficacious interpersonal behaviours and prompt cognitive reappraisal away from depressive mood states (Amstadter *et al.*, 2016, Buhrmester *et al.*, 2011). Positive emotions provide a multitude of adaptive benefits (Fredrickson, 2001, Kaltman and Bonanno, 2003) crucial in daily life and feature prominently in the context of adversity and risk (Bonanno, 2005, Bonanno, 2004). Extraversion is a personality trait characterised by positive emotionality and assertiveness, which has been hypothesised to protect against MDD by facilitating positive affective (Campbell-Sills *et al.*, 2006). Although empirical evidence specifically demonstrating any relationship between extraversion and resilience is lacking, it stands to reason that extraversion will likely be directly associated with the promotion of mental health (Matthews *et al.*, 2009). Such a hypothesis stems mostly from the observation that traits such as neuroticism which are characterised by negative emotionality are inversely associated with resilience (Amstadter *et al.*, 2016). As discussed in Chapter 1, neuroticism has been extensively associated with psychopathological outcomes (Hettema *et al.*, 2006, Ormel *et al.*, 2013) with strong associations being found between neuroticism and MDD (Lahey, 2009). A current debate in the literature pertains to whether or not resilience and neuroticism are in fact opposite sides of the same construct; that resilience (characterised by positive emotions) is the flip side of neuroticism (charactersied by negative emotions). At present, conflicting findings preclude a definitive answer (Amstadter *et al.*, 2016, Simeon *et al.*, 2007), although subsequent chapters in this thesis will seek to address this question.

Although research has yielded compelling results linking personality traits with positive psychological outcomes (Luthar *et al.*, 2000), their explanatory power is often overestimated (Mischel, 1969). A major caveat of a trait-based conceptualisation of resilience is that it does not necessitate the experience of adversity or risk, an essential element of psychological resilience (Luthar *et al.*, 2000, Rutter, 2006, Windle *et al.*, 2011). Furthermore, personality may be influenced by adversity, especially when it is measured subsequent to occurrence of the adversity (Bonanno and Mancini, 2008).

2.4.2. Interpersonal factors and coping

It is unlikely that any one factor is solely attributable to resilience, but rather numerous factors coalesce, each contributing to the overall likelihood of a resilient outcome (Bonanno *et al.*, 2007, Bonanno and Mancini, 2008). It is important to differentiate between a resilient or favourable outcome, and the resilience factors that predict positive outcomes. Whereas factors such as personality remain relatively stable across time, others will likely fluctuate across the lifespan (Hobfoll, 2002, Hobfoll, 1989). Indeed, it is now widely accepted that resilience varies contextually and temporally, intimating that it is a dynamic process (Kent *et al.*, 2014, Luthar *et al.*, 2000, Norris *et al.*, 2009, Sapienza and Masten, 2011) reflecting active adaptive mechanisms rather than a static property of the individual (Friedman *et al.*, 2014, Mancini and Bonanno, 2009, Russo *et al.*, 2012).

Coping is an active adaptive factor involving direct efforts to modify adverse encounters (Campbell-Sills *et al.*, 2006), and although often used interchangeably, there is a growing body of evidence to suggest that resilience and coping are conceptually distinct constructs (Campbell-Sills *et al.*, 2006, Fletcher and Sarkar, 2013, Tugade and Fredrickson, 2004, Van Vliet, 2008). Numerous studies highlight the importance of coping with resilience (Clauss-Ehlers, 2008, Leipold and Greve, 2009, Sinclair and Wallston, 2004, Tugade and Fredrickson, 2004), but it is crucial to distinguish between coping ‚behaviours' and ‚style'. Whereas specific behaviours are more likely to mediate the link between adversity and depression (Folkman and Moskowitz, 2004), dispositional coping styles may function as a protective factor that moderates components of depressive illness (Campbell-Sills *et al.*, 2006). To illustrate, emotion-oriented coping is characterised by the regulation of distressing emotions, whereas task-oriented coping denotes purposeful efforts aimed at problem solving (Folkman and Lazarus, 1988). Avoidance-oriented coping is defined by behaviours aimed at avoiding difficult circumstances (Cosway *et al.*, 2000). It has been found that task-oriented coping styles associate with better psychological outcomes in comparison to emotion- and avoidance-oriented coping styles which have been associated with poorer outcomes for mental health (Higgins and Endler, 2006). Furthermore, for individuals receiving treatment for MDD, task-oriented coping has been found to associate with less severe symptomology and better prognosis, whereas emotion-oriented coping styles associated with greater psychological dysfunction (Billings and Moos, 1984). It is likely that positive, task-oriented coping styles increase an individual's confidence to appraise adversity with a sense of control, resulting in an increase in positive emotions fostering active problem-oriented behaviours which modify detrimental emotional and neurobiological responses and ultimately buffer against MDD (Southwick and Charney, 2012). These findings suggest that coping style may be an integral factor in resilience, although it is important to note that one's coping style likely consists of a sophisticated repertoire of behavioural manifestations and personality traits (Tugade and Fredrickson, 2004), developed in childhood and fortified across the lifespan

Social support has also been hypothesised as an important proximal factor in the aftermath of severe adversity (Ozer *et al.*, 2003, Rutter, 1987, Werner, 1993). Research associates emotional support with positive adjustment following disaster (Kaniasty and Norris, 2009, La Greca *et al.*, 1996), and multivariate disaster studies have provided compelling evidence for an explicit link between social support and resilient outcomes (Bonanno *et al.*, 2007, Bonanno and Mancini, 2008). However, because social support is the result of a transaction between the individual and their environment, it is not only the number and function of such relationships that are critical, but also the perception of such support (Procidano and Heller, 1983). Feder and colleagues (2009) posit that openness to social support is paramount in ensuring resilience, as a negative view to the support being offered may result in less support being perceived and received. This demonstrates an intrinsic link between personality and social support as positive emotions have been linked to the promotion of resilience (Bonanno, 2004, Luthar *et al.*, 2000, Tugade and Fredrickson, 2004) through openness to support, ease of forming attachments with others, and the ability to seek out social interaction (Campbell-Sills *et al.*, 2006). Extraverted personalities, for example, experience strong positive emotions and tend to have better social networks than individuals scoring highly on neuroticism (Campbell-Sills *et al.*, 2006). Therefore, although social support facilitates resilience to depression, it is a dynamic and reciprocal process that encapsulates one's personal disposition and coping style. Furthermore, research suggests that high levels of social support not only associate positively with active problem-focused coping, self-esteem and optimism, but together these mitigate detrimental neurobiological processes associated with MDD (Kaufman *et al.*, 2006, Southwick and Charney, 2012, Taylor *et al.*, 2011).

2.4.3. The brain

Numerous neurobiological factors are hypothesized to foster resilience to MDD (Russo *et al.*, 2012). For example, a recent brain-imaging study demonstrated that cognitive reappraisal can influence brain regions involved in emotion processing (Ochsner *et al.*, 2002) and therefore may promote resilience to depression. Specifically, cognitive reappraisal of aversive photographs resulted in decreased negative affect which suggests that resilience is dependent on effective prefrontal cortical modulation of emotion-processing systems (e.g., amygdala and medial orbitofrontal cortex). This is supported by the knowledge that the human limbic system is responsible for the regulation of personality, emotional reactivity and social behaviour (Folkman and Moskowitz, 2000, Isen *et al.*, 1987, LeDoux, 1993). Further findings from the limbic system suggest that pre-existing differences in hippocampal volume may partly underlie resilience (Baaré *et al.*, 2010, Chen *et al.*, 2010). Specifically, in individuals with familial risk for MDD, reduced hippocampal volumes were strongly associated with MDD (Baaré *et al.*, 2010, Chen *et al.*, 2010, Cole *et al.*, 2011, Rao *et al.*, 2010). A recent study by Chan and colleagues (Chan *et al.*, 2016) also supports this hypothesis and suggests that larger hippocampal volumes may be a biomarker for resilience. Never-depressed individuals with high risk personality factor for depression showed a significant increase in hippocampal volume, and, because the age of the sample was above that expected for typical age of onset for MDD, participants with a larger hippocampus who remained asymptomatic despite personality risk could be an indicator for psychological resilience (Chan *et al.*, 2016). Furthermore, it has been purported that mesolimbic dopamine pathways in the brain may be more reward responsive and/or stress resistant in individuals who remain optimistic in the face of adversity (Charney, 2004). Together this neural circuitry is believed to mediate successful adaptation (Amstadter *et al.*, 2016, Feder *et al.*,

2009, Fredrickson, 2001). Differences in the balance and interaction of these biological factors may underlie inter-individual variability in resilience to MDD, which is likely mediated by the expression of dispositional traits and coping styles, or by previous adversity (Davidson *et al.*, 2000, Davidson and McEwen, 2012, Feder *et al.*, 2009, Forgeard *et al.*, 2011). Whilst a number of behavioural and psychosocial factors have been associated with neurobiological factors in resilience, it is likely that their covariance is largely attributable to genetics (Miller *et al.*, 2014).

2.4.4. Genetics

Genetic factors may be fundamental in an individual‘s response to adversity (Feder *et al.*, 2009) as our genetic architecture influence the expression of many biological processes and behavioural manifestations. An increasing number of genome-wide studies (GWAS; Ripke *et al.*, 2013) are being conducted to parse the complex genetic contributions to both MDD and resilience, but at present, GWAS have not proven particularly successful in identifying specific genetic risk or protection variants (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, Hek *et al.*, 2013, Sullivan *et al.*, 2009, Wray *et al.*, 2012). To overcome this, researchers are now using candidate genes to focus on individuals at genetic risk for maladaptation who do not develop depression (Luthar *et al.*, 2000). The best-studied genetic factor for resilience pertains to a variation in the serotonin transporter gene (5-HTTLPR) (Caspi *et al.*, 2010). Both the short form of 5-HTTLPR and a single base substitution in the long form of 5-HTTLPR are associated with reduced reuptake of serotonin from the synaptic cleft. As such, lower expression of 5-HTTLPR alleles are associated with increased risk for MDD through changes in the amygdala–ventromedial prefrontal cortex (PFC), a finding demonstrated in children exposed to maltreatment (Karg *et al.*, 2011). It must be noted, however, that the examination of genes related to the hypothalamus-pituitary-adrenal (HPA) axis (Binder *et al.*, 2008, Ressler *et al.*, 2011), and serotonergic systems (Murrough and Charney, 2011, Stein *et al.*, 2009) have thus far yielded only weak to moderate associations with resilient phenotypes, with inconsistent replicability. More compelling results have been found when examining the complex interactions between specific genes and neurochemical stress response systems (for a comprehensive review see Feder et al, (2009) which suggest that an individual‘s genes shape neural and biochemical processes that are expressed psychologically and behaviourally as resilience. Several genetic polymorphisms have been found which directly affect limbic reactivity and prefrontal-limbic connectivity, influencing behavioural responses to adversity in addition to cognitive reappraisal of negative events (de Kloet *et al.*, 2007, Heinz and Smolka, 2006, Ising *et al.*, 2008, Zhou *et al.*, 2008). Furthermore, genetics research also suggests that putative ―risk alleles” operate in a dynamic interplay with the environment (Rende, 2012). To illustrate, social support has been associated with protection to MDD in maltreated children, even in children with the short form 5-HTTLPR gene (Kaufman *et al.*, 2006), although studies suggest that genetic influences on biological responses are far greater than the genetic effects on complex behavioural and psychosocial responses (Feder *et al.*, 2009).

2.5. Resilience measurement

Although research on resilience has substantially increased in the last two decades (Haskett *et al.*, 2006), the confusion over its definition has created considerable difficulty in developing an operational definition of the construct. Divergent approaches to measuring resilience have resulted in inconsistencies regarding the nature of

potential risk factors and protective processes, and prevalence estimates (Haskett *et al.*, 2006, Luthar *et al.*, 2000). For example, the proportion of individuals reported to be resilient ranges from 25% to 84%, even in populations who have experienced similar adversity (Vanderbilt-Adriance and Shaw, 2008). Such diversity raises an important question as to the extent to which resilience is being measured, or an entirely different construct. Currently, there exists no consensus on how resilience should be quantified. As illustrated in **Figure 2.2**, resilience can be measured in a number of ways, although each necessitate a favourable outcome given the presence of underlying risk. Alternatively, several quantitative measures of resilience have now been developed and validated, although they are not widely adopted, and no one scale if preferable over another (Connor and Davidson, 2003).

Psychological resilience is typically defined as a favourable outcome given the presence of underlying risk, and can be quantified as:

1. The absence of psychopathology across diagnostic categories
2. High levels of well-being on a quantifiable scale
3. Better than expected adjustment in comparison to a group ‗average‘

Figure 2.2. Possible ways to quantify psychological resilience

A comprehensive review of resilience scales (Windle *et al.*, 2011) suggests that at present, the Connor-Davidson Resilience Scale (CD-RISC), the Resilience Scale for Adults (RSA) and the Brief Resilience Scale (BRS) are the most preferable quantitative scales for resilience measurement in adult populations, based on extensive criteria. However, it is important to note that not even these three measures thoroughly satisfied all psychometric properties specified in the systematic review (Windle *et al.*, 2011). Currently, resilience measures capture state resilience, rather than assessing resilience across the lifespan. Furthermore, the majority of current inventories focus predominately on assessing the availability of implicit assets and resources which facilitate positive adaptation during times of adversity (Olsson *et al.*, 2003). However, the Brief Resilience Scale aims to assess resilience as an outcome – the ability to *‘bounce back’*. As such, the BRS is a preferable measure to investigate the processes leading to a resilience outcome, or for researchers interested in ascertaining the presence or absence of these resources. It is important to note, however, that the Brief Resilience Scale does reflect a sense of personal agency (Windle *et al.*, 2011), and so no quantitative measure of resilience is entirely perfect.

With increasing evidence to suggest that resilience is an interactive phenomenon which varies across multiple domains, methods with greater explanatory power are needed to investigate psychological resilience. Given the heterogeneity of the construct, it is likely that there are multiple, independent predictors of resilient outcomes which are correlated, and perhaps dependent upon each other. Ultimately, consensus on what resilience is and how it should be measured needs to consider the multidimensional examination of risk, protective factors and positive adaptation in a dynamic fashion.

2.6. Summary and PhD aims

The study of psychological resilience remains at an early stage with no agreement on how it should be defined and measured. However, it is generally assumed that resilience is the ability to ‚bounce back'. Whilst it is widely agreed that both adversity (or risk) and positive adaptation are crucial components in defining resilience to occur, conceptual discrepancies hinder the evaluation and comparison of research findings (Davydov *et al.*, 2010) and the progress of resilience research. There are likely multiple pathways to resilience whereby a combination of factors interact dynamically to enable an individual to cope and function successfully, despite significant risk or adversity (Rutter, 1993). Resilience is a multifaceted phenomenon and so to fully delineate the concept it is imperative to examine adversity/risk, protective factors, and positive adaptation not only at multiple phenotypic levels but also behaviourally, psychologically and biologically. Identifying reliable predictors that could determine who is most likely to be resilient to MDD would enable researchers and clinicians to prospectively forecast the trajectory of an individual's resilience to and recovery from mental illness. This will represent a valuable step towards the development of strategies for protecting individuals prior to disease onset.

It is now imperative to harmonise our approach to resilience, moving beyond description towards an explanation of the individual differences in resilience to MDD. To fully disentangle prediction to resilience, prospective, multivariate designs are necessary. This thesis aims to attempt to quantify psychological resilience and elucidate its mechanisms by investigating resilience from multiple perspectives over three main chapters. Firstly, a study investigating intelligence as a form of resilience will be introduced and discussed (Chapter 3). This chapter aims to provide evidence for the protective effects of intelligence on mental health in high-risk individuals, and ascertain if vulnerability and protection mechanisms in MDD are worthy of independent investigation. A new dataset is introduced in Chapter 4 which was specifically designed to measure psychological resilience. Measures from this dataset will be used in subsequent chapters to examine resilience from multiple perspectives. In Chapter 5, the mediating effects of resilience and neuroticism on the association between genetic liability for MDD and the disorder itself are examined. The study presented within this chapter had two overarching aims; to investigate if neuroticism and resilience are downstream mediators of genetic vulnerability for MDD, and to determine if neuroticism and resilience are independent constructs representing risk and protection mechanisms. The aetiology of resilience will also be investigated (Chapter 6). Specifically, the proportion of the phenotypic variance attributable to genetic and shared-environmental factors will be calculated for resilience and coping style. Additionally, genetic correlations between resilience, coping style and neuroticism will be calculated with the aim of investigating a shared genetic architecture. Finally, a summary of this thesis will be provided in Chapter 7, in addition to the discussion of future directions in resilience research.

Chapter 3
Intelligence as a form of resilience

3.1. Background

As outlined in Chapter 1, mood disorders such as Major Depressive Disorder (MDD) have a long history of association with negative emotions (Jackson, 1986). Not only is MDD characterised by poor modulation of emotional response, the disorder is also highly associated with traits that elicit negative emotions. Specifically, the personality trait neuroticism is strongly positively associated with MDD across the lifespan (Kotov *et al.*, 2010, Malouff *et al.*, 2005). As such, it is widely accepted that high levels of neuroticism confer risk to indices of mental health, including depression and psychological distress (Chan *et al.*, 2007, Fanous *et al.*, 2007, Jylhä and Isometsä, 2006, Lahey, 2009). Although MDD is primarily considered an illness of emotional dysregulation, the disorder is commonly associated with cognitive impairment (Beck *et al.*, 1979). Indeed, deficits in the domains of memory, executive functioning, and processing speed are frequently observed in patients during depressive episodes (Baune *et al.*, 2010, Marazziti *et al.*, 2010). However, a great body of research suggests that despite cognitive deficits at times of illness, higher cognitive ability (intelligence) attenuates the risk for depressive illness throughout the life course (Batty *et al.*, 2005, Gale *et al.*, 2010, Koenen *et al.*, 2009, Scult *et al.*, 2017, Wraw *et al.*, 2016). This suggests that symptoms of MDD effect cognitive performance only at the time of measurement, rather than cognitive ability being a risk factor for depression. Such findings indicate that cognitive ability - specifically intelligence - may act as a protective factor in MDD, and as such is a useful variable to examine in the resilience enquiry.

Studies investigating physical health suggest that higher intelligence mitigates the detrimental effects of neuroticism on indices of physical health and mortality (Leikas *et al.*, 2009, Weiss *et al.*, 2009), although it is not yet known if such an interaction exists for mental health. It is likely that neuroticism and intelligence exert divergent effects on MDD whereby neuroticism increases risk for MDD and intelligence provides protection, as indicated above. To determine if intelligence acts as a moderator in the relationship between neuroticism and MDD, multiple regression analyses can be utilised (e.g., Aguinis, 2004; Jaccard & Turrisi, 2003; Jose, 2013). Such a method would enable researchers to determine if intelligence affects the direction and/or strength of the relationship between neuroticism and MDD. Furthermore, such an analysis may enable researchers to determine the usefulness of examining risk and protective factors simultaneously in regard to resilience. For example, if intelligence is associated with protection against MDD in individuals at high risk for the disorder it would suggest that resilience mechanisms act independently to risk factors.

This chapter introduces an original study and replication examining the protective effects of general intelligence (*g*) on indices of mental health. Specifically, the aim of this study was to determine if *g* would provide protection against both psychological distress and/or MDD in individuals high in neuroticism (a known risk factor for MDD), as such an association has been identified for physical health and mortality (Leikas *et al.*, 2009, Weiss *et al.*, 2009). A subsidiary aim of this study was to ascertain if vulnerability and protection mechanisms are of equal importance when studying resilience. This study is summarized, below, in the

manuscript entitled ‗Intelligence and neuroticism in relation to depression and psychological distress' which has been published in *European Psychiatry*. As first author for this publication, I conceived the experimental design, performed all data analysis and wrote the manuscript for publication. To acknowledge the contributions of co-authors, ―we" will be used instead of ―I" throughout this chapter.

3.2 Paper: Intelligence and neuroticism in relation to depression and psychological distress

3.3 Abstract

Background: Neuroticism is a risk factor for selected mental and physical illnesses, and is inversely associated with intelligence. Intelligence appears to interact with neuroticism and mitigate its detrimental effects on physical health and mortality. However, the inter-relationships of neuroticism and intelligence for major depressive disorder (MDD) and psychological distress have not been well examined.

Methods: Associations and interactions between neuroticism and general intelligence (*g)* on MDD, self-reported depression, and psychological distress were examined in two population-based cohorts: Generation Scotland: Scottish Family Health Study (GS:SFHS, N = 19,200) and UK Biobank (N = 90,529). The Eysenck Personality Scale Short Form-Revised measured neuroticism and *g* was extracted from multiple cognitive ability tests in each cohort. Family structure was adjusted for in GS:SFHS.

Results: Neuroticism was strongly associated with increased risk for depression and higher psychological distress in both samples. Although intelligence conferred no consistent independent effects on depression, it did increase the risk for depression across samples once neuroticism was adjusted for. Results suggest that higher intelligence may ameliorate the association between neuroticism and self-reported depression although no significant interaction was found for clinical MDD. Intelligence was inversely associated with psychological distress across cohorts. A small interaction was found across samples such that lower psychological distress associates with higher intelligence and lower neuroticism, although effect sizes were small.

Conclusions: From two large cohort studies, our findings suggest intelligence acts a protective factor in mitigating the effects of neuroticism on psychological distress. Intelligence does not confer protection against diagnosis of depression in those high in neuroticism.

3.4 Introduction

Major depressive disorder (MDD) is a leading cause of disease burden worldwide (Ferrari *et al.*, 2013). Although MDD aetiology remains elusive, a large proportion of its genetic covariance is attributable to neuroticism (Jardine *et al.*, 1984, Kendler *et al.*, 1993), suggesting a causal relationship. Neuroticism is a partially-heritable personality trait representing high emotionality and stress sensitivity (Matthews *et al.*, 2009), which correlates highly with MDD (Jylhä and Isometsä, 2006)**.** Cross-sectional studies suggest a strong positive association between neuroticism and MDD (Chan *et al.*, 2007, Muris *et al.*, 2005, Roelofs *et al.*, 2008), whilst higher neuroticism prospectively associates with depression longitudinally (Fanous *et al.*, 2007, Farmer *et al.*, 2008, Hirschfeld *et al.*, 1989, Kendler *et al.*, 2006, Kendler *et al.*, 1993)**,** even when controlling for overlapping

criteria (Fergusson *et al.*, 1989, Schmutte and Ryff, 1997, Spijker *et al.*, 2007) and demographics (Kendler *et al.*, 2004, Neeleman *et al.*, 2001)**.** Whist the public health impacts of neuroticism are wide-ranging (for a comprehensive review see Lahey, 2009), neuroticism may be an indirect measure of later MDD risk, rather than the causative risk factor itself. Whilst MDD is often recurrent (Hardeveld *et al.*, 2013), neuroticism is a stable trait (Conley, 1985) suggesting that their correlation is unlikely to be substantially attributable to an effect of MDD on neuroticism.

General intelligence (*g*) is a latent construct theorized to explain the common observation that people who excel in one type of cognitive task tend to excel in others (Humphreys, 1979). When reduced to a single factor (*g*) these correlations explain approximately 50% of the covariance between tests. Lower intelligence in early life has been found to be a risk factor for poor physical health (Wraw *et al.*, 2015) and early mortality in adulthood (Calvin *et al.*, 2011, Deary *et al.*, 2010). Although research specifically regarding MDD is relatively sparse (Gale *et al.*, 2008), there is evidence to suggest that *g* is impaired in depression (Marazziti *et al.*, 2010, Sackeim and Steif, 1988) with longitudinal studies suggesting lower *g* in childhood or adolescence confers vulnerability to psychopathology in adulthood (Gale *et al.*, 2009, Gale *et al.*, 2010, Maccabe, 2008, Zammit *et al.*, 2004).

Psychological distress represents a cluster of emotional symptoms linked to depression (Beck *et al.*, 1979, Goldberg *et al.*, 1987, Snaith, 1987). Although symptoms of distress are common in population samples, (Kessler and Wang, 2008, Singleton *et al.*, 2003) they indicate only subthreshold mental health problems. With self-report measures of distress (Goldberg and Hillier, 1979, Kroencke *et al.*, 2001) freely available in epidemiological research, their measurement provides greater detective power to make distinctions between syndrome and subthreshold symptoms. Longitudinal research suggests neuroticism has a strong, direct effect on psychological distress (Ormel and Wohlfarth, 1991)**.** Low childhood intelligence strongly associates with increased psychological distress in adulthood (Gale *et al.*, 2009, Hatch *et al.*, 2007), which may precede MDD onset (Gulliver *et al.*, 2012). However, this is not a universal observation, particularly in studies accounting for socioeconomic status (SES).

Intelligence and neuroticism may interact to influence indices of health. A longitudinal study of war veterans (Weiss *et al.*, 2009) found high neuroticism and low cognitive ability were separate risk factors for mortality. Specifically, a 1-standard deviation increase in neuroticism resulted in a 33% increase in mortality; a 1-standard deviation decrease in intelligence associated with a 27% increase in mortality. An interaction (hazards ratio of 0.89) suggested that high neuroticism with low cognitive ability associates with high risk of poor health and reduced lifespan. Furthermore, high cognitive ability moderates the adverse effects of neuroticism on adjustment (Leikas *et al.*, 2009). Whether similar interactions exist with regard to their effects on depression remains unknown. No investigation has yet examined how intelligence and neuroticism influence risk for MDD and how they may moderate each other‘s associations in depression and psychological distress. Such an analysis may serve to clarify the mechanisms underlying MDD.

In this study, two large population-based cohorts were examined - Generation Scotland: Scottish Family Health Study (GS: SFHS) (Smith *et al.*, 2013a, Smith *et al.*, 2006) and UK Biobank (Allen *et al.*, 2012, Sudlow *et al.*,

2015). As previous studies suggest strong associations of neuroticism with risk of MDD (Jylhä and Isometsä, 2006, Kendler *et al.*, 1993), the same effect was hypothesised here. We hypothesised that higher intelligence may reduce MDD risk by mitigating the adverse effects of neuroticism, similarly to the interaction identified for mortality (Weiss *et al.*, 2009). This reasoning transfers to psychological distress, hypothesising a positive association between neuroticism and psychological distress would be ameliorated by higher intelligence.

3.5. Method

3.5.1. GS:SFHS Overview

GS:SFHS is a family and population-based cohort recruited throughout Scotland between 2006 and 2011 (Smith *et al.*, 2013a). During clinic assessment, participants aged 18-98 (N = 24,084) provided clinical, cognitive and biological data. Full details are provided elsewhere (Smith *et al.*, 2013a, Smith *et al.*, 2006). The GS:SFHS sample is predominately female (59%), and generally healthier and wealthier than the Scottish population (Smith *et al.*, 2013a). This study includes 19,200 individuals with complete data of interest. Demographic information from this cohort is provided in **Table 3.1** and in **Appendix A**.

3.5.2. Study assessments

During clinic assessment, participants were screened for lifetime history of MDD using a structured clinical interview (First *et al.*, 1997). Diagnosis of MDD follows DSM-IV criteria; if either symptoms of depressive mood or anhedonia are endorsed, a minimum of four further symptoms must also be endorsed. Clinical significance must be endorsed, too (ie., symptoms lasting nearly all day, every day for a minimum of two weeks). This study includes 2,481 individuals meeting criteria for lifetime history of MDD (13%), and 16,719 non-MDD cases (87%).

Four cognitive tests measuring intelligence were administered during clinic assessment (Smith *et al.*, 2013a, Smith *et al.*, 2006). The Wechsler Digit Symbol Substitution Task (Wechsler, 1958) measured processing speed. One paragraph from The Weschler Logical Memory Test I & II (Wechsler, 1945) measured verbal declarative memory. The Verbal Fluency Test measured executive function (Wechsler, 1958) using phonemic lists of C, F and L. Vocabulary was measured with The Mill-Hill Vocabulary Test (Raven, 1958), using combined junior and senior synonyms. General intelligence (*g*) was extracted from these tests, as the first un-rotated principal component (Marioni *et al.*, 2014), explaining 41% of the variance. Loadings for processing speed, vocabulary, verbal declarative memory and executive function were 0.57, 0.68, 0.63 and 0.69 respectively.

The self-reported Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF) (Eysenck, 1991) measured neuroticism. Twenty-four questions assessed neuroticism and extraversion, with total scores on each subscale ranging from 0-12. Higher scores indicate higher levels of each trait. This scale has been concurrently validated (Gow *et al.*, 2005) with high reliability (Eysenck *et al.*, 1985).

Psychological distress was self-reported using the General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1979). Twenty-eight items were scored from 0 ("*not at all*") to 3 ("*much more than usual*") with a total score ranging from 0-84. Higher scores indicate increased psychological distress.

The Scottish Index of Multiple Deprivation (SIMD) (Payne and Abel, 2012) is an official tool which identifies deprivation by combining different indicators (eg., income, crime) into a single index. The SIMD divides Scotland into 6,505 small areas based on participant postcode, and assigns them a relative ranking from 1 (most deprived) to 6505 (least deprived).

3.5.3. UK Biobank Overview

UK Biobank is a population cohort recruited across the UK from 2006-2010. During extensive baseline assessments (Smith *et al.*, 2013b) participants aged 40-69 (N = 502,682) provided biological, physical, and touch-screen questionnaire measures of socio-demographics (e.g., age, sex), psychosocial factors (e.g., mental health), and cognitive function. UK Biobank represents a wide range of exposures typical within the UK population (UK Biobank, 2011), and has been described in detail elsewhere (Allen *et al.*, 2012, Sudlow *et al.*, 2015). In this study, 147 individuals were removed from analysis due to participation in GS:SFHS. In total, 90,529 individuals with complete data of interest were included. Demographic information is provided in **Table 3.1** and in **Appendix A.**

3.5.4. Study assessments

Between 2008-2010, a touch-screen questionnaire was added to the protocol to assess probable depression (N = 172,751) (UK Biobank, 2012). Although depression was not assessed using a precise diagnostic tool, the classification followed a self-report approach within the guidelines of the ICD- 10 (World Health Organisation, 1992) and the DSM-IV (American Psychiatric Association, 1994). Lifetime history of depression was assessed using items relating to the lifetime experience of depressive symptoms and help-seeking for mental health. A detailed description of how this phenotype was derived is provided elsewhere (Smith *et al.*, 2013b). This study included 30,127 (33%) individuals self-reporting lifetime history of depression, and 60,402 (67%) non-depressed cases.

Three novel cognitive tests were administered via touch-screen questionnaire measuring reaction time, verbal-numerical reasoning, and visual memory (Smith *et al.*, 2013b). A timed symbol matching test measured reaction time as the mean response time in *ms* over 12 trials; higher reaction times equate to poorer performance. Thirteen logic/reasoning-type questions assessed verbal-numerical reasoning - the total number of correct answers given within two-minutes was analysed. A visuo-spatial memory task measured the number of errors made when matching card pairs, higher scores reflect poorer cognitive function. From these tests, *g* was extracted as the first un-rotated principal component (Marioni *et al.*, 2014), explaining 44% of the variance in scores. Loadings onto *g* were: -0.61 (verbal-numeric reasoning), 0.57 (visual memory), and 0.55 (reaction time).

Neuroticism was assessed using 12 questions from the Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF) (Eysenck, 1991), administered via a touch-screen questionnaire. A total score from 0-12 was produced, with higher scores reflecting increasing neuroticism.

The first four questions of the Patient Health Questionnaire – 9 (PHQ9; Kroencke *et al.*, 2001) were administered by touch-screen questionnaire to measure psychological distress. Responses on a scale from 0

(*–Not at all"*) to 3 (*–Nearly every day"*) were aggregated and a higher total score denoted higher levels of psychological distress.

The Townsend Deprivation Index (Townsend, 1987) is a census-based measure of deprivation, incorporating unemployment, non-car ownership, non-home ownership and household overcrowding into a single index. Small geographical areas based on postcode information are allocated Townsend Scores. Higher scores represent greater deprivation.

3.6. Statistical analysis

3.6.1. GS:SFHS

In GS:SFHS, the MCMCglmm package was used. The Markov Chain Monte Carlo estimator produces generalised linear mixed models for binary outcomes (using the "threshold" family with a probit link function). The threshold link is unique to MCMCglmm, and although produces very similar results to a logit function, threshold links most closely match the underlying assumptions of latent normal errors in pedigree-based mixed effect models (Lynch and Walsh, 1998). MCMCglmm was essential to control for genetic relatedness of the sample, which was fitted as a random effect using an inverse pedigree matrix. Due to limitations within MCMCglmm with missing predictor variables, only complete data can be used. An interaction was fitted to estimate the moderating effect of *g* on the contribution of neuroticism to MDD. Another model examined this interaction while conditioning on deprivation. Regression coefficients are reported as odds ratios. In a second set of analyses, GHQ was modelled as a normally distributed outcome variable. Neuroticism and GHQ were standardised to have a mean of zero and a standard deviation of 1. Age (standardised) and sex were used as fixed effects throughout.

3.6.2. UK Biobank

In UK Biobank, generalized linear regression analyses were conducted as kinship need not be accounted for. The main effects of neuroticism and *g* were examined as predictors for self-reported depression. The interaction between neuroticism and *g* on depression was modelled. Another model examined this interaction while adjusting for deprivation. Generalized linear regressions were fitted with a logit link function and odds ratios reported. A second set of analyses examined psychological distress (PHQ) using linear regression models. Neuroticism and PHQ were standardised to have a mean of zero and a standard deviation of one. Reaction time was log transformed due to a significantly positive skew. Visual memory was transformed with a log+1 transformation because it was significantly skewed and zero-inflated. All regression analyses co-varied for age, and sex.

3.7. Results

3.7.1. GS:SFHS

As seen in **Table 3.1**, MDD cases were younger, predominately female, and had higher GHQ and neuroticism scores. No group differences were found in general intelligence; ($t(3243.38) = -1.39$, $p = 0.17$, Cohen's $d = .03$). Group differences were found in processing speed and executive function. MDD cases were from less deprived areas; ($t(3171.20) = 9.93$, $p = 2.20 \times 10^{-16}$, Cohen's $d = .22$). Full statistical output can be found in **Appendix A**.

Table 3.1. Demographic, clinical, and cognitive characteristics of GS:SFHS and UK Biobank individuals in the current study

	GS:SFHS			UK Biobank		
	Total (N = 19,200)	Control (N = 16,719)	Lifetime MDD (N = 2,481)	Total (N = 90,529)	Control (N = 60,402)	Lifetime MDD (N = 30,127)
Age	47.16 (14.97)	47.23 (15.27)	46.39 (12.89) *	56.64 (8.13)	57.15 (8.16)	55.60 (7.98) *
Sex (% female)	59	57	72 *	52	46	65 *
Neuroticism	3.84 (3.16)	3.45 (2.94)	6.45 (3.32) *	4.36 (2.86)	2.65 (2.43)	5.09 (2.06) *
GHQ score	15.93 (8.81)	14.93 (7.56)	22.70 (12.77) *	-	-	-
PHQ score	-	-	-	1.36 (1.91)	0.89 (1.33)	2.30 (2.47) *
Wechsler Digit Symbol Substitution Task	72.31 (17.09)	72.45 (17.23)	71.44 (16.06) *	-	-	-
Mill-Hill Vocabulary Test	30.06 (4.76)	30.05 (4.75)	30.15 (4.84)	-	-	-
Wechsler Logical Memory Test I & II	31.01 (8.04)	30.99 (8.09)	31.02 (7.68) *	-	-	-
Verbal Fluency Test	25.68 (8.10)	25.60 (8.11)	26.21 (8.01) *	-	-	-
Reaction Time	-	-	-	564.00 (119.87)	564.70 (119.98)	562.58 (119.66) *
Visual Memory	-	-	-	4.04 (3.21)	4.04 (3.23)	4.04 (3.17)
Verbal-numerical Reasoning	-	-	-	6.09 (2.14)	6.07 (2.16)	6.12 (2.11) *
SIMD	3903.82 (1851.91)	3957.58 (1832.28)	3541.51 (1941.03) *	-	-	-
Townsend score	-	-	-	-1.37 (2.84)	-1.47 (2.77)	-1.06 (2.94) *

Abbreviations: GS:SFHS, Generation Scotland: Scottish Family Health Study; MDD, Major Depressive Disorder; GHQ, General Health Questionnaire; PHQ, Patient Health Questionnaire; SIMD, Scottish Index of Multiple Deprivation

With the exception of sex, value indicate mean (SD)

* Significantly different from controls at $p < .05$

3.7.1.1. Associations of neuroticism and g with MDD status

Higher neuroticism was strongly associated with increased risk for MDD. A 1SD increase in neuroticism increased MDD risk by an odds ratio of 3.61 ([95% CIs = 3.28, 4.01], $p < 1.00x10^{-4}$). Although no age effects were found, being female increased risk for MDD by an odds ratio of 1.76 ([95% CIs = 1.52, 2.03], $p < 1.00x10^{-4}$). *g* had no independent effect on risk for MDD (OR = 1.02, [95% CIs = 0.99, 1.07], $p = 0.53$).

3.7.1.2. Interaction between neuroticism and g on MDD

No interaction was found between neuroticism and *g* (OR = 1.03, [95% CI = 0.98, 1.08], $p = 0.32$), see **Figure 3.1** and **Table 3.2**, even after co-varying for SIMD. However, the main effect of neuroticism was strongly associated with MDD risk (OR = 3.71, [95% CI = 3.37, 4.12], $p < 1.00x10^{-4}$) whilst *g* was associated with a small increase in MDD risk (OR = 1.14, [95% CIs = 1.07, 1.20], $p < 1.00x10^{-4}$). A main effect was found whereby higher deprivation confers risk for MDD (OR = 0.80, [95% CIs = 0.75, 0.86], $p < 1.00x10^{-4}$).

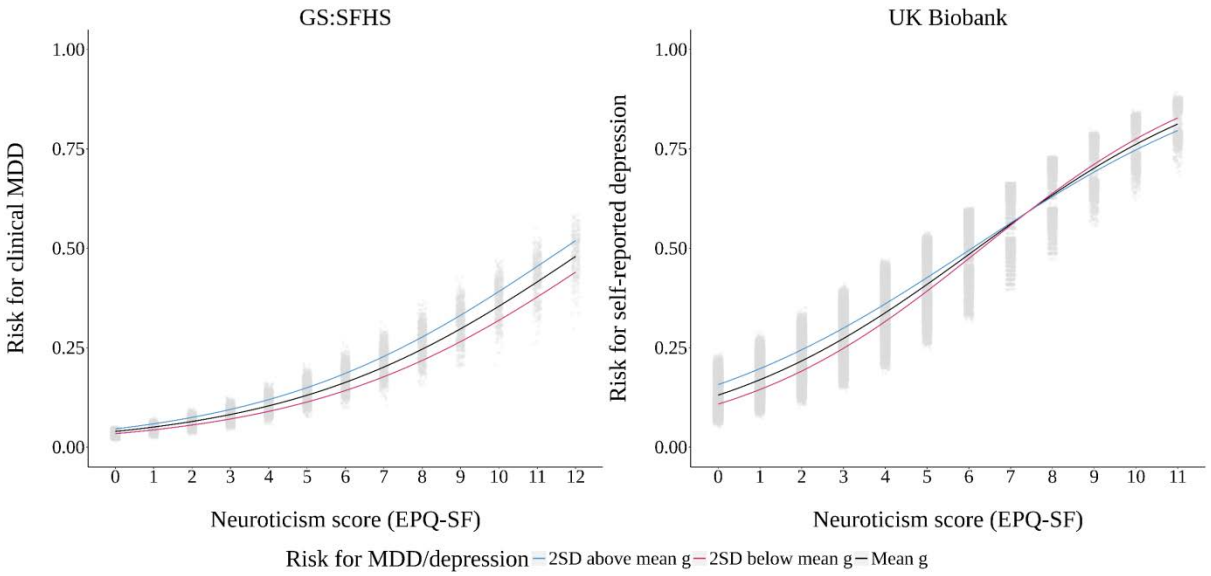

Figure 3.1. Predicted risk for MDD and self-reported depression from the interaction of neuroticism and *g* in both GS:SFHS and UK Biobank

3.7.1.3. Associations of neuroticism and g with psychological distress

Neuroticism was associated with increased psychological distress; a 1SD increase in neuroticism was associated with an increase in GHQ of ß = 0.52 ([95% CIs = 0.50, 0.53], $p < 1.00x10^{-4}$). A small inverse relationship was found whereby higher *g* was associated with decreased levels of psychological distress (ß = -0.08, [95% CIs = -0.09, -0.07], $p < 1.00x10^{-4}$).

3.7.1.4. Interaction between neuroticism and g on psychological distress

A small interaction suggested higher *g* interacts with neuroticism to mitigate neuroticism‘s detrimental association on GHQ (ß = -0.05, 95% [CIs = -0.06, -0.04], $p < 1.00x10^{-4}$), see **Figure 3.2** and **Table 3.2**. This interaction remained after co-varying for deprivation.

Table 3.2. Results of MCMC generalised linear mixed models from GS:SFHS predicting odds ratios for MDD status, beta coefficients for psychological distress (GHQ), p-value, upper and lower 95% confidence intervals and the Deviance Information Criterion AND results of a logistic regression from UK Biobank predicting odds ratios for MDD status, beta coefficients for psychological distress (PHQ), p-value, upper and lower 95% confidence intervals, the Akaike Information Criterion and adjusted R^2 value for the model

Sample	Outcome	Variables	Odds Ratio	β	Lower 95% CIs	Upper 95% CIs	*P* value	DIC	AIC	R^2
GS:SFHS	MDD	Age	1.00	-	0.99	1.01	$9.71x10^{-2}$	12,561.35	-	-
		Sex (F)	1.71	-	1.48	1.97	$< 1.00x10^{-4}$			
		Neuroticism	3.71	-	3.37	4.12	$< 1.00x10^{-4}$			
		g	1.14	-	1.07	1.20	$< 1.00x10^{-4}$			
		Neuroticism * *g*	1.03	-	0.98	1.08	0.32			
UK Biobank	MDD	Age	0.98	-	0.99	0.99	$< 2.00x10^{-16}$	-	98,785.00	-
		Sex (F)	1.34	-	1.32	1.36	$< 2.00x10^{-16}$			
		Neuroticism	2.40	-	2.36	2.44	$< 2.00x10^{-16}$			
		g	1.06	-	1.04	1.07	$5.08x10^{-14}$			
		Neuroticism * *g*	0.96	-	0.95	0.98	$1.09x10^{-7}$			
GS:SFHS	GHQ	Age	-	0.00	0.00	0.00	0.59	47,873.87	-	-
		Sex (F)	-	0.04	0.02	0.07	$2.63x10^{-3}$			
		Neuroticism	-	0.50	0.49	0.52	$< 1.00x10^{-4}$			
		g	-	-0.04	-0.05	-0.03	$< 1.00x10^{-4}$			
		Neuroticism * *g*	-	-0.05	-0.06	-0.04	$< 1.00x10^{-4}$			
UK Biobank	PHQ	Age	-	-0.02	-0.02	-0.01	$< 2.00x10^{-16}$	-	-	0.2976
		Sex (F)	-	-0.02	-0.02	-0.01	1.57x10-8			
		Neuroticism	-	0.51	0.51	0.52	$< 1.00x10^{-4}$			
		g	-	-0.05	-0.06	-0.05	$< 1.00x10^{-4}$			
		Neuroticism * *g*	-	-0.02	-0.03	-0.02	$< 1.00x10^{-4}$			

Abbreviations: MCMC, Markov Chain Monte Carlo; GS:SFHS, Generation Scotland: Scottish Family Health Study; GHQ, General Health Questionnaire; PHQ, Patient Health Questionnaire; DIC, Deviance Information Criterion; *g,* General Intelligence; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion

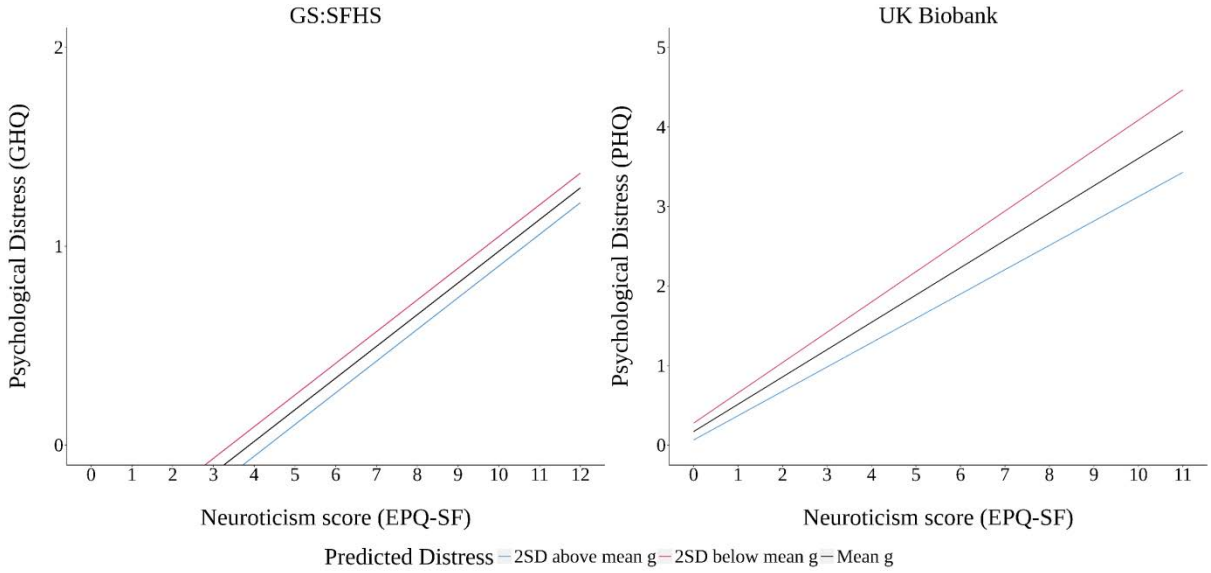

Figure 3.2. Psychological distress scores from the interaction of neuroticism and g in both GS:SFHS (GHQ) and UK Biobank

3.7.2. UK Biobank

As reported in **Table 3.1**, MDD cases were younger, predominately female, and had higher psychological distress (PHQ) and neuroticism scores than non-depressed cases. Significant differences were found in verbal-numerical reasoning (in which non-depressed cases performed better) and reaction time (in which depressed cases performed better). *g* was higher in depressed cases ($t(61357) = -2.65$, $p = 8.12 \times 10^{-3}$, Cohen's $d = .02$). Non-depressed cases had lower deprivation scores than depressed cases; ($t(57110) = -20.08$, $p = 2.2 \times 10^{-16}$, Cohen's $d = .14$), although this difference was small. See **Appendix A** for full statistical output.

3.7.2.1. Associations of neuroticism and g with MDD status

Higher neuroticism was associated with increased likelihood of self-reported depression. For every 1SD increase in neuroticism, the odds for depression increased by 2.39 (95% CIs = [2.35, 2.43], $p < 2.00 \times 10^{-16}$). No main effects of *g* were found (OR = 1.00, [95% CIs = 0.99, 1.01], $p = 0.86$). Small effects of age and sex were found.

3.7.2.2. Interaction between neuroticism and g on MDD

A small interaction was found in which high levels of intelligence and neuroticism associate with reduced self-reported depression (OR = 0.96, [95% CIs = 0.95, 0.98], $p = 1.09 \times 10^{-7}$), see **Table 3.2** and **Figure 3.1**. This interaction remained after co-varying for deprivation.

3.7.2.3. Associations of neuroticism and g with psychological distress

Neuroticism was moderately associated with increased levels of psychological distress. For every 1SD increase in neuroticism, PHQ increased by ß 0.52 ([95% confidence intervals = 0.51, 0.52], $p < 2.00 \times 10^{-16}$). *g* was associated with a small reduction in PHQ (ß = -0.08, [95% CIs = -0.08, -0.07], $p < 2.00 \times 10^{-16}$).

3.7.2.4. Interaction between neuroticism and g on psychological distress

A small interaction was found in which *g* moderates the detrimental effects of neuroticism on psychological distress (ß = -0.02, [95% CIs = -0.03, -0.02], $p < 2.00x10^{-16}$), see **Table 3.2** and **Figure 3.2**. This interaction remained after co-varying for deprivation.

3.8. Discussion

The cross-sectional associations between neuroticism, general intelligence (*g),* MDD, self-reported depression, and psychological distress were examined in two large population based cohorts; GS:SFHS and UK Biobank. Neuroticism was strongly associated with increased risk for both MDD diagnosis and self-reported depression, replicating previous findings (Chan *et al.*, 2007, Muris *et al.*, 2005). Intelligence conferred no consistent independent effects but associated with an increased risk for depression once neuroticism was adjusted for. UK Biobank data suggest an interaction whereby higher *g* has a small effect in reducing the impact of neuroticism on self-reported depression. This interaction was small, both absolutely, and in comparison to the main effects of neuroticism. No such interaction was found in GS:SFHS using a clinical measure of MDD. However, across samples, the risk conferred by neuroticism after co-varying for *g* appears to be increased in terms of the absolute OR value when compared to basic models. Overall, results demonstrate an association whereby intelligence provides modest protection against the risk-conferring effects of neuroticism on self-reported depression, but not clinical MDD.

Consistent and replicable findings were found suggesting higher neuroticism associates with increased psychological distress, whereas higher intelligence associates with reduced psychological distress. A small interaction was found across samples such that lower distress associates with higher intelligence and lower neuroticism. Although these results are of small magnitude, they suggest an important interaction whereby higher *g* lessens the strength of the neuroticism-distress association.

This is the first study of intelligence‘s potential protective influence on MDD (Robinson and Oishi, 2006), self-reported depression, and psychological distress in high neuroticism individuals. Consistent with previous research the strong link between neuroticism with increased risk for depression and psychological distress was replicated with moderate effect sizes. Although longitudinal work suggests intelligence provides protection to mental health (Gale *et al.*, 2010, Gale *et al.*, 2008, Maccabe, 2008), we found *g* increased the risk for depression when adjusted for neuroticism. The magnitude of this risk was very small, however. Across cohorts, intelligence associated with decreased levels of psychological distress. A modest association of intelligence as a mitigating factor in reducing psychological distress in individuals with high neuroticism was found in both cohorts. Although this study suggests intelligence provides a protective function in self-reported depression and psychological distress which mirrors previous research (Calvin *et al.*, 2011, Leikas *et al.*, 2009, Weiss *et al.*, 2009), intelligence was not found to be protective against diagnosis of depression in those high in neuroticism.

It is unclear why intelligence associates with protection to risk for psychological distress, but not MDD. One supposition is that individuals with higher intelligence may be more likely to seek help, and therefore are more likely to receive a clinical diagnosis of depression. Another postulation could be that intelligence has an effect

only during times of depressive episode. A state-dependent association of cognitive ability has been suggested in which variability in intelligence co-varies with depressive episode and remission (for a comprehensive review, see Sackeim and Steif, 1988). As such, subsequent investigations may benefit from addressing the same hypotheses examining individuals with current MDD in comparison to individuals in remission, and controls. Increased psychological distress is an established symptom of depression and often used in clinical diagnosis (Beck *et al.*, 1979, Snaith, 1987). Goldberg (1987) described distress as representing the overall severity of depression and so it is likely that individuals scoring highly on measures of psychological distress may be more likely to self-report the disorder, irrespective of its clinical significance. However, we must be mindful of the complexities of causality; whilst it is likely that the neuroticism trait prospectively predicts later distress and self-reported depression, we cannot be certain that these factors are not manifestations of the same underlying risk.

Intelligence could be a marker of system integrity (Deary, 2012) in which increased intelligence circumvents negative mood biasing in individuals high in neuroticism that may lead to distress and disorder (Hasler *et al.*, 2004). Alternatively, more intelligent individuals may be better able to employ successful coping mechanisms during times of distress: higher intelligence associates with increased resilience to adversity in children (Fergusson *et al.*, 2005). Research suggests that psychosocial factors are associated with resilience to mood disorders (Garmezy *et al.*, 1984). Proactive and psychosocial coping mechanisms may enable individuals to decrease transient feelings of distress and to implement established, effective strategies learned from previous exposure to distress or depression (LeDoux and Gorman, 2001). This possibility is consistent with the finding that whereas *g* and neuroticism interacted to associate with reduced psychological distress, the same interaction was not found in clinical MDD. It would be interesting to explore intelligence‘s influences on coping style (Higgins and Endler, 2006) and subsequent psychological distress and MDD diagnosis in future investigations. Intelligence may influence the adoption of specific coping strategies, and this could be a mediating factor in the ‗depressogenic‘ process.

Some caveats merit comment. Different cognitive tasks were used to generate *g* across our samples. In GF:SFHS, pre-existing, standardized measures were used, whereas UK Biobank used bespoke cognitive tasks. Further replication utilising standardised measures would be beneficial. A second limitation is the differing MDD phenotypes used in each sample. In GS:SFHS, MDD was determined using a semi-structured interview (First *et al.*, 1997), obtaining a robust MDD phenotype based on a standardised diagnostic tool. In UK Biobank, self-reported questionnaires were aggregated to form a depression phenotype; this data is not as comprehensive. Although it is of benefit to have conducted an independent replication within this study, the disparity in depression phenotypes may explain not only the difference in prevalence rates across samples, but also why an interaction was found in UK Biobank and not GS:SFHS. Thirdly, this investigation only examined neuroticism. Personality represents stable individual dispositions in emotional reactivity, behavioural tendencies, and cognitive styles (Deary *et al.*, 2010, Roberts *et al.*, 2007), which may be moderated by intelligence in predicting mental health outcomes. Examining such associations between all major dimensions of personality in subsequent research is advised. As neuroticism and MDD share genetic aetiology (Jardine *et al.*, 1984, Kendler *et al.*, 1993), causality cannot be inferred here, although the associations reported do make a significant

contribution to the literature. Because neuroticism is a stable trait and MDD is a disease with a given age of onset, we can use neuroticism to predict an individual‘s risk for depression, without needing to infer causality.

In conclusion, this study fails to demonstrate that intelligence confers protection to clinical MDD in those with high neuroticism. However, in both samples, a modest interaction was found in which higher intelligence appears to ameliorate the detrimental association between neuroticism and psychological distress. It would be useful to determine this relationship prospectively in a sample where incident cases of MDD can be identified. An important corollary of this work may inform risk and resilience mechanisms in MDD. Future studies to disentangle the mechanisms driving depression are an important next step in further elucidating the aetiology of the disorder.

3.9. Chapter conclusions

This study confirms previous reports which suggest that neuroticism is a risk factor for both psychological distress and depression. It also demonstrates that intelligence can mitigate the detrimental effects of neuroticism in eliciting unpleasant thoughts and feelings at sub-threshold levels, but fails to confer protection against clinical depression. However, whilst *g* was found to act as a protective factor in this study, its effect sizes were small which suggests that other factors are likely to be more important in conferring protection, or mitigating risk, of mental health disorders. These results also indicate that risk and resilience mechanisms are of equal importance to examine in depression research as they may elicit independent and divergent effects on mental health outcomes. Furthermore, given the robust associations between neuroticism and mental health, and resilience and indices of mental health, it is important to understand the mechanisms underlying these associations. This work has laid the foundation for the following chapters of this thesis, where efforts were made to specifically examine the associations between risk and resilience mechanisms in depression, in addition to examining the architecture of psychological resilience.

Chapter 4

A new dataset to examine resilience and mental illness

4.1 Background

In Chapter 2, the three core components of psychological resilience were introduced: adversity, positive adaptation, and protective factors. It is important that any study investigating resilience incorporates these fundamental components as without adversity or risk, an individual cannot demonstrate the ability to ‗bounce back'. Furthermore, as indicated in Chapter 3, the role of protective factors is important to examine as they can ameliorate the negative effects of adversity/risk on mental health outcomes, and may represent a central mediating mechanism in resilience to MDD. At present, few datasets are specifically designed to examine psychological resilience, and as such our knowledge of the concept remains in its infancy. In order to fully elucidate resilience mechanisms and aetiology, it would be preferable to have access to a dataset that contains measures of MDD risk, adversity, mental health incidence, and putative resilience factors such as coping style. Moreover, a dataset which contains a quantitative measure of resilience, in addition to variables which specifically assess adversity, positive adaptation and protective factors would be most optimal.

This chapter introduces a new resource which was designed specifically to investigate psychological resilience. In re-contacting participants from the Generation Scotland: Scottish Family Health Study, this new dataset may enable researchers to prospectively predict which individuals are most likely to be resilient to MDD. Such predictions can be made from the repeated assessment of MDD and psychological distress. Furthermore, this dataset provides researchers the opportunity to assess measures directly related to resilience such as negative life events and coping style. Most importantly, this dataset includes a quantitative self-report measure assessing an individual's ability to ‗bounce back' from adversity which will enable researchers to investigate psychological resilience in a multitude of ways. This new dataset is summarized, below, in the manuscript entitled ‗Cohort Profile: Stratifying Resilience and Depression Longitudinally (STRADL): A questionnaire follow-up of the Generation Scotland: Scottish Family Health Study (GS:SFHS)' which has been published in the *International Journal of Epidemiology*. Whilst the funding application leading to the generation of this dataset was conceived by senior members of Generation Scotland committee, as first author for the publication I was involved in discussions around the development of these questionnaires, and I was responsible for quality control of the raw data and subsequent scoring of questionnaire items. Furthermore, I performed all data analysis and wrote the manuscript for publication. To acknowledge the contributions of co-authors, ―we" will be used instead of ―I" throughout this chapter.

4.2 Paper: Cohort Profile: Stratifying Resilience and Depression Longitudinally (STRADL): A questionnaire follow-up of the Generation Scotland: Scottish Family Health Study (GS:SFHS).

4.3. Why was the cohort set up?

Common health conditions such as heart disease, stroke and depression are a common cause of chronic suffering and economic burden worldwide (Smith *et al.*, 2013). Scotland has a high prevalence of these conditions, and

because of its comparatively stable population (Scottish Government, 2010), it provides a useful citizenry to study their prevalence and impact. Generation Scotland (GS) is a multi-institutional, cross-disciplinary collaboration aiming to promote research into genetics and healthcare throughout Scotland (Generation Scotland). Between 2006-2011 GS undertook its first major study – Generation Scotland: Scottish Family Health Study (Smith *et al.*, 2013, Smith *et al.*, 2006) (GS:SFHS). This large, family-based intensively-phenotyped and genotyped population cohort was designed to examine a diverse range of illnesses such as those aforementioned. The work of GS is especially important to epidemiological research as it provides a means of separating genetic and shared environmental contributions to common non-communicable diseases. Furthermore, the ability to re-contact GS participants and obtain broad consent for future use of their data and samples is especially valuable for prospective studies associated with health outcomes.

In 2015, a strategic award by the Wellcome Trust provided funding for „STRADL: Stratifying Resilience and Depression Longitudinally‘. This project aimed to re-contact participants from GS:SFHS for a further assessment of mental health, specifically depression. Major Depressive Disorder (MDD) is a leading cause of global disease burden with a lifetime prevalence of approximately 10% (Kessler *et al.*, 2003, Levinson, 2006). In coming decades, the prevalence and impact of depression will likely increase (Smith *et al.*, 2006) making the understanding of its aetiology of substantial importance to public health. STRADL was designed to investigate the aetiology of depression and its stratification as it is hypothesised that the diagnosis may group together several causally distinct but symptomatically related syndromes (Kessing, 2007). The increased kinship among STRADL participants created a rich dataset to conduct genetic studies of MDD aetiology in addition to examining the complex genetic and environmental interactions which may increase risk for different depression phenotypes.

STRADL was also designed to investigate psychological resilience (Luthar, 2006, Luthar *et al.*, 2000, Luthar *et al.*, 2006) – the ability to „escape‘ psychopathology despite exposure to known risk factors. Whilst the investigation of resilience may be expected to reveal similar results to studying MDD itself, it has the potential to elucidate protective factors in MDD, even in at-risk individuals. Indeed, examining the variability in response to known MDD risks may not just further our understanding of MDD but a better understanding of resilience mechanisms may also inform future interventions long before the development of the illness (Fergus and Zimmerman, 2005). Ultimately, the work of STRADL has the potential to identify causal mechanisms and pathways of depression sub-types and elucidate mechanisms which give rise to better than expected adjustment.

4.4. Who is in the cohort?

The original GS:SFHS protocol and cohort characteristics has been described extensively elsewhere (Smith *et al.*, 2013, Smith *et al.*, 2006). Between 2006 and 2011, 24,084 participants were extensively phenotyped in addition to providing DNA samples for whole-genome genotyping. GS:SFHS was largely female (59%), and generally healthier and wealthier than the Scottish population.

STRADL sought to recruit GS:SFHS participants for a follow-up assessment of mental health and resilience (N = 24,084). Individuals were eligible to participate if they had taken part in GS:SFHS, had a Community Heath

Index (CHI) number, were alive and living in Scotland, and had given consent for re-contact. A total of 21,525 (89%) individuals from GS:SFHS were eligible for re-contact (**Figure 4.1)**.

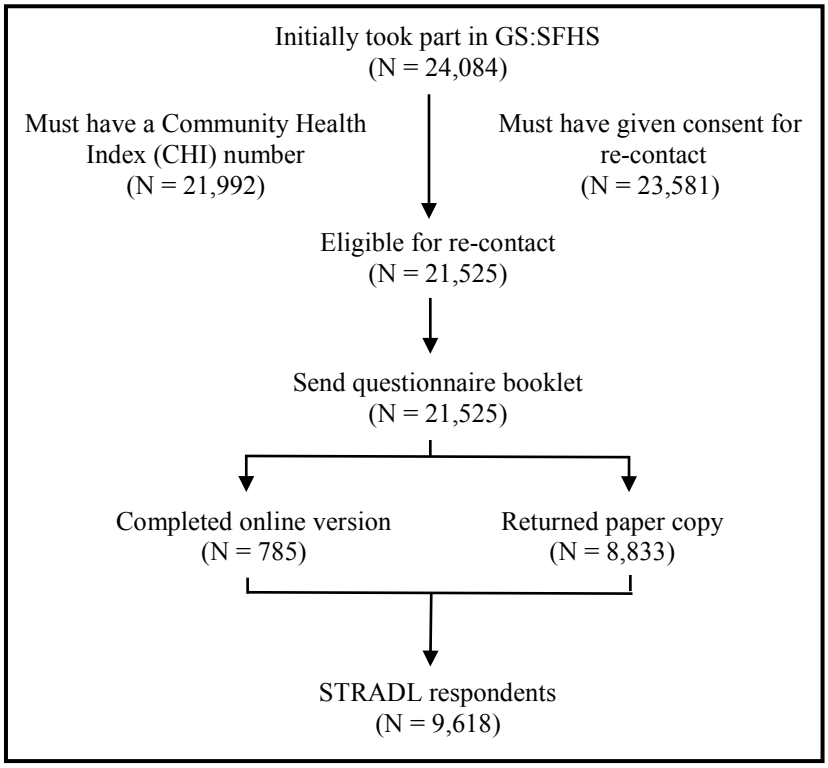

Figure 4.1. STRADL recruitment flow diagram

Study packages were sent to potential participants (N = 21,525) that consisted of a study invitation letter, detailed information sheet and a paper booklet containing the STRADL questionnaires. Study packages were mailed by an independent party. Participants were given the option to complete the questionnaires on paper and return them via Freepost envelope or use a given URL link for online submission. The opportunity to return an email address for further contact was also provided.

'Broad' consent was obtained from participants permitting the use of their data for ‗future medical research into health, illness and medical treatment' without further specification. Participants were informed their data would remain anonymous and be added to that already held by GS.

A total of 9,618 participants responded (45%) at follow-up. A total of 2,460 families (N = 7,158 individuals) of between 2-18 family members and 2,460 unrelated individuals formed the STRADL cohort. The majority completed the paper version of the questionnaire (N = 8,833), and 8% completed online (N = 785). Henceforth, individuals who participated in STRADL will be referred to as ‗respondents' and those who did not reply will be referred to as ‗non-respondents'.

All components of STRADL received formal, national ethical approval from the NHS Tayside committee on research ethics (reference 14/SS/0039).

Whilst age and sex information were collected in STRADL, all other demographic data were obtained from GS:SFHS (**Table 4.1**). The STRADL cohort was predominately female (62%) and were older (Mean = 50.48, SD = 13.41) than non-respondents (Mean = 44.28, SD = 15.70, $t(21457) = -31.25$, $p < .001$, Cohen's $d = .42$) at baseline. STRADL respondents were from less socio-economically deprived areas compared to non-respondents ($t(19812) = -15.15$, $p < .001$, Cohen's $d = .21$) in the Scottish Index of Multiple Deprivation 2009 (SIMD) (Payne and Abel, 2012). The STRADL cohort was generally healthier and wealthier, with a different age–sex profile in comparison to GS:SFHS, although important similarities were apparent (**Table 4.1**). Whilst STRADL may not be truly representative of the Scottish population, the sample includes data on participants from all socio-economic status strata.

Table 4.1. Some baseline comparisons between STRADL respondents and non-respondents and full baseline sample (GS:SFHS)

	Respondents (N = 9,618)	Non-respondents (N = 11,907)	GS:SFHS Total (N = 21,525)
Median age (years)			
Male	54	43	48
Female	52	45	48
Gender (% female)	62	57	59
Employment (those aged up to 75 years) (%)			
Unemployed	4	5	5
Retired	18	13	15
Employed (full or part-time, or self-employed)	71	71	71
Education (%)			
Degree	37	28	32
No qualification	7	9	8
Annual income > £30,000 (%)	63	57	60
SIMD	4123 (1777)	3733 (1875)	3910 (1842)

Abbreviations: STRADL, Stratifying Resilience and Depression Longitudinally; GS, Generation Scotland; GS:SFHS, Generation Scotland: the Scottish Family Health Study; SIMD, the Scottish Index of Multiple Deprivation 2009
With the exception of age and SIMD, values represent percentage
SIMD represents Mean rank (SD)

4.5. What has been measured?

A summary of all data collected and its completeness is shown in **Table 4.2**. All data were anonymised using a barcode system which linked with a unique participant identification number at the time of data analysis. Paper questionnaires were scanned into an electronic database with detailed in-built validity checks.

Although data collection was largely cross-sectional, repeated measures of GS:SFHS measures were collected which enabled longitudinal examination. Pearson's chi-squared (χ^2) tests were conducted to illustrate group differences for categorical data during GS:SFHS. As an alternative to the independent *t*-test, comparisons between respondents and non-respondents at baseline are reported using the Mann–Whitney–Wilcoxon (U) test. Wilcoxon Signed Rank (W) tests have been reported for differences between respondents across GS:SFHS and STRADL as a nonparametric test equivalent to the dependent *t*-test. Calculations for group differences and changes over time have ignored the relatedness of the sample, which will be appropriately controlled for in future publication of the data. These differences are shown in **Table 4.3**.

Table 4.2: Summary of phenotype data available, and percentage providing valid/useable data (N = 9,618)

		Phenotype	%
1.		**Demographics**	
	a.	Age	100
	b.	Sex	100
	c.	Email address	79.99
2.		**Medical History**	
	a.	Stoke or mini stroke (TIA)	98.55
	b.	Heart attack or angina	98.44
	c.	Other heart disease	98.16
	d.	Pains in leg muscles	98.07
	e.	Diabetes (blood sugar problems)	98.54
	f.	High blood pressure	98.47
	g.	High blood cholesterol	98.03
3.		**Brief Resilience Scale (BRS)**	98.00
4.		**List of Threatening Experiences (LTE)**	99.00
5.		**Composite International Diagnostic Interview – Short Form (CIDI-SF)**	97.08
6.		**General Health Questionnaire-28 (GHQ-28)**	93.94
	a.	GHQ somatic	98.09
	b.	GHQ anxiety	98.52
	c.	GHQ social dysfunction	98.53
	d.	GHQ depression	95.96
7.		**Alcohol and tobacco consumption**	
	a.	Have you ever smoked tobacco?	99.12
	b.	Are you a current smoker?	46.20
	c.	If yes, how many cigarettes do you smoke in an average week?	-
	d.	If yes, how many cigars do you smoke in an average week?	-
	e.	If yes, how many 25g packets of tobacco do you smoke in an average week?	-
	f.	Do you currently drink any alcoholic drinks?	98.22
	g.	Have you ever felt you should cut down on your drinking?	80.06
	h.	Have people annoyed you by criticising your dinking?	80.13
	i.	Have you ever felt bad or guilty about your drinking?	80.06
	j.	Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?	80.14
	k.	In an average week, how many units of alcohol do you consume?	79.67
8.		**Coping Inventory for Stressful Situations (CISS)**	
	a.	Task-oriented coping	93.37
	b.	Emotion-oriented coping	94.93
	c.	Avoidance-oriented coping	94.30
	d.	Distraction	95.47
	e.	Social Diversion	96.22

4.5.1. Substance Use

At baseline, 17% of all participants smoked although respondents were less likely to smoke (13%), compared to non-respondents (21%) ($\chi^2(1) = 260.58$, $p < .001$, $r = 0.11$). At follow-up, the percentage of respondents smoking increased to 17% ($\chi^2(1) = 1563.60$, $p < .001$, $r = 0.60$).

At baseline, 90% of participants drank alcohol with respondents more likely to drink alcohol than non-respondents ($\chi^2(1) = 5.23$, $p = 0.02$, $r = 0.02$). Respondents consumed less units per week (Mean = 9.64, SD = 10.79) than did non-respondents (Mean = 10.32, SD = 12.25) at baseline, ($t(13221) = 3.39$, $p < .001$, Cohen's $d = 0.06$) although this difference was small in magnitude. The number of respondents who drink alcohol

decreased at follow-up ($\chi^2(1) = 2575.7$, $p < .001$, $r = 0.53$). Respondent alcohol consumption substantially increased at follow-up (W = 3149600, $p < .001$), although extreme values were reported (Mean = 13.91, SD = 22.42, Range = 0 - 914). Respondent's alcohol consumption was moderately correlated between time points (r = 0.50).

Table 4.3. Repeated measures between respondents and non-respondents during GS:SFHS (baselines) and STRADL (follow-up)

	GS:SFHS		STRADL
	STRADL Non-respondents (N = 11,907)	STRADL Respondents (N = 9,618)	Respondents (N = 9,618)
Currently smoke (%)	21	13 *	17 **
Currently drink (%)	90	91 *	80 **
Alcohol units per week	10.3 (12.3)	9.7 (10.8) *	13.9 (22.4) **
Meets SCID criteria for MDD (%)	13	13	-
Meets CIDI-SF criteria for MDD (%)	-	-	16
Meets CIDI-SF criteria for Bipolar Disorder (%)	-	-	1.3
Meets CIDI-SF criteria for hypomanic episode (%)	-	-	0.4
Total GHQ score	16.4 (9.1)	15.4 (8.4) *	16.9 (9.3) **
GHQ depression score	0.97 (2.4)	0.80 (2.2) *	1.0 (2.2) **
GHQ anxiety score	4.0 (3.8)	3.6 (3.5) *	4.4 (4.2) **

Abbreviations: GS, Generation Scotland; GS:SFHS, Generation Scotland: the Scottish Family Health Study; STRADL, Stratifying Resilience and Depression Longitudinally; SCID, Structured Clinical Interview for DSM-IV; MDD, Major Depressive Disorder; CIDI-SF, Composite International Diagnostic Interview – Short Form; GHQ, General Health Questionnaire
Unless denoted by (%), results represent mean (SD)
GHQ scores calculated using the Likert method
* Significantly different from non-respondents in Wave 1 at $p < .05$
** Significantly different from respondents in Wave 2 at $p < .05$

4.5.2. Mental Health Assessment

GS:SFHS participants were screened for a lifetime history of Major Depressive Disorder (MDD) using the Structured Clinical Interview for DSM-IV Disorders (SCID) (First *et al.*, 2002). Whilst the SCID has the potential to make inferences on an array of Axis I disorders, only case/control classifications for MDD were ascertained. The threshold for lifetime prevalence of MDD follows Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2003) (DSM) criteria. Where either symptoms of either depressed mood or anhedonia were endorsed a minimum of four further symptoms must also be endorsed and their clinical significance confirmed (ie. symptoms lasting nearly all day, every day for a minimum period of two weeks).

STRADL participants completed the Composite International Diagnostic Interview – Short Form (CIDI-SF) (Kessler *et al.*, 1998). The CIDI-SF is a self-report questionnaire measure of psychiatric symptoms developed from the larger CIDI by the World Health Organization (Robins *et al.*, 1988) according DSM-IV (American Psychiatric Association, 2003) criteria. The CIDI-SF used a stem-branch logic in which two symptomatic screening questions (symptoms of depressive mood or anhedonia) must be endorsed and reach clinical significance (lasting nearly all day, every day for two weeks or more). A minimum of four other symptoms must also be endorsed in addition to at least one screening question. Respondents who meet criteria for lifetime history of MDD reliably meet full diagnostic criteria with excellent accuracy if given the long version of CIDI

(Kessler *et al.*, 1998)**.** As the CIDI-SF can be completed in a relatively short period (approximately ten minutes), it is a scalable and acceptable measure for epidemiological studies.

At baseline, an identical proportion of respondents (13%) and non-respondents (13%) met criteria for a lifetime history of MDD as established using the SCID, ($\chi^2(1) = 0.55$, $p = .457$, $r = 0.01$). In STRADL, 16% of respondents met the CIDI-SF criteria for lifetime MDD (N = 1,506) of which 16% reported being currently depressed. Lifetime history of MDD was moderately correlated between the two measures ($r = 0.30$).

4.5.3. Psychological distress

The General Health Questionnaire-28 (GHQ-28) (Goldberg, 1978) was administered across time-points as a tool used to identify milder psychiatric problems in the general population (Snaith, 1987). As psychological distress represents a cluster of emotional symptoms linked to depression, the GHQ-28 was used alongside clinical measures to make better distinctions between syndrome and sub-threshold symptoms (Goldberg and Hillier, 1979, Kroencke *et al.*, 2001). Responses were scored using the Likert method (0-1-2-3) whereby higher scores represent higher levels of psychological distress. Individual domain scores gave information on somatic symptoms, anxiety, social dysfunction and depression.

Non-respondents experienced more psychological distress at baseline than respondents (U = 44888000, $p < .001$) although levels of psychological distress increased over time in STRADL respondents (W = 9713600, $p < .001$). Total GHQ-28 score of respondents across time-points was moderately correlated ($r = 0.46$).

Symptoms of GHQ depression appeared greater in non-respondents than respondents at baseline, (U = 44607000, $p < .001$). GHQ depression scores increased in respondents between time-points (W = 1409700, $p < .001$). GHQ depression scores were moderately correlated ($r = 0.46$) in respondents between assessments.

Symptoms of GHQ anxiety were higher in non-respondents than respondents at baseline, (U = 45042000, $p < .001$). Anxiety scores increased in respondents between time-points (W = 8937100, $p < .001$), and were moderately correlated ($r = 0.45$).

4.5.4. New measures

Questionnaire measures of psychological resilience (Smith *et al.*, 2008), coping style (Endler and Parker, 1990), threatening life experiences (Brugha *et al.*, 1985) and medical conditions were obtained in STRADL, and are summarised in **Tables 4.4**, **4.5 and 4.6**.

4.5.4.1. Brief Resilience Scale

The Brief Resilience Scale (Smith *et al.*, 2008) (BRS) assessed the ability to ‗bounce back' from stress. Six questions were answered on a five-point scale from ―Strongly Disagree" to ―Strongly Agree". A total score was calculated as the mean of the six items, with appropriate reverse scoring of odd-numbered questions. The BRS has previously shown good internal consistency and test-retest reliability (Smith *et al.*, 2008).

Table 4.4 Respondent results of resilience, coping style and psychological distress testing in STRADL

	n	Theoretical maximum score	Mean	SD	Median	Range
BRS	9411	5	2.99	0.36	3	1-5
CISS						
Task-oriented	8980	80	54.33	12.28	56	16-80
Emotion-oriented	9130	80	37.61	12.57	37	16-80
Avoidant-oriented	9070	80	39.41	10.52	40	16-80
Distraction-oriented	9182	40	17.46	6.01	17	8-40
Social Diversion-oriented	9254	25	14.33	4.84	15	5-25
GHQ-28						
GHQ-a[a]	9432	21	4.58	3.76	3	0-21
GHQ-b[a]	9476	21	4.37	4.17	3	0-21
GHQ-c[a]	9477	21	7.60	2.48	7	0-21
GHQ-d[a]	9229	21	1.01	2.24	0	0-15
GHQ total	9035	84	16.88	9.28	14	0-65

Abbreviations: STRADL, Stratifying Resilience and Depression Longitudinally; SD, Standard deviation; BRS, Brief Resilience Scale; CISS, Coping Inventory for Stressful Situations; GHQ-28, General Health Questionnaire-28

[a] GHQ-28 domain scores give information on: (a) somatic symptoms; (b) anxiety/insomnia; (c) social dysfunction; and (d) depression

GHQ scores calculated using the Likert method

4.5.4.2. Coping Inventory for Stressful Situations

The Coping Inventory for Stressful Situations (CISS) (Endler and Parker, 1990) was a self-report questionnaire measuring three coping style scales: task-oriented, emotion-oriented and avoidance-oriented coping. Two sub-scales of avoidance-oriented coping were also derived: distraction and social diversion. Each item was rated on a five-point scale from (1) "Not at all" to (5) "Very much". The CISS has proven a robust measure of assessing situation-specific coping strategies, with a stable factor structure and high construct validity (Cosway *et al.*, 2000, Endler and Parker, 1990).

Table 4.5. Results from respondents completing the List of Threatening Experiences summarizing the number of individuals who endorsed each event and their ratings of its impact

	n^1	n^2	Theoretical maximum score	Mean	SD	Median	Range
Serious injury or assault to yourself	794	783	3	2.18	0.73	2	1-3
Serious injury or assault to a close relative	1880	1831	3	2.19	0.73	2	1-3
Did a parent, spouse, child or sibling die	1145	1126	3	2.40	0.71	3	1-3
Close family friend or other relative die	1841	1798	3	1.75	0.74	2	1-3
Separation due to marital difficulties or break off a steady relationship	427	425	3	2.27	0.73	2	1-3
Serious problem(s) with close friend, neighbour or relative	1059	1047	3	2.13	0.68	2	1-3
Made redundant or sacked from job	301	292	3	1.82	0.81	2	1-3
Seeking work unsuccessfully for more than one month	367	342	3	1.76	0.73	2	1-3
Major financial crisis (such as losing three months income)	436	413	3	2.11	0.79	2	1-3
Problems with the police involving court appearance	111	108	3	2.15	0.83	2	1-3
Something of value lost or stolen	372	361	3	1.91	0.76	2	1-3
Yourself or partner gave birth	393	353	3	2.71	0.61	3	1-3

Abbreviations: SD, Standard deviation

n^1 - The number of participants who indicated they experienced the event within the last six months

n^2 - The number of individuals who subsequently gave criterion contextual threat ratings of the event

4.5.4.3. List of Threatening Experiences

The List of Threatening Experiences (LTE) (Brugha *et al.*, 1985) was a self-report measure consisting of 12 common and threatening life events that may have occurred in the six months prior to completion. For each threatening event endorsed, criterion contextual threat ratings are measured on a scale from 3 ("Very bad") to 1 ("Not too bad"). The LTE has been shown to have excellent test-retest reliability and high sensitivity (Brugha and Cragg, 1990).

Table 4.6. Self-reported diagnosis of common illnesses among respondents

	n	*%*
Stoke or mini stroke (TIA)	302	3
Heart attack or angina	466	5
Other heart disease	382	4
Pains in leg muscles when walking or in bed at night	1703	18
Diabetes (blood sugar problems)	575	6
High blood pressure	2257	24
High blood cholesterol	1887	20

4.6. How often have they been followed up?

STRADL is a mental health questionnaire follow-up of GS:SFHS. Although data collection was cross-sectional STRADL becomes a longitudinal cohort because of NHS data linkage using Community Health Index (CHI) numbers which are allocated to every individual registered with a GP in Scotland. The ability to link with routinely collected NHS data will allow validation of the self-reported illness recorded in the study, and provide information on clinical endpoints and follow-up. Furthermore, the utilisation of NHS linkage converts this two-phase cohort study into a potentially lifelong study of resilience and depression. Future parts of the STRADL study will include DNA methylation analysis and depression-focussed neuroimaging measures of brain structure, function and connectivity.

As with any epidemiological study, a key question is often whether consenting participants are representative of the population from which they are drawn. As indicated in **Table 4.1**, STRADL participants appear to be an older, wealthier and a more affluent, largely female subset of GS:SFHS. This is not surprising as these characteristics are associated with higher response rates to follow-up surveys (Curtin *et al.*, 2000, Koloski *et al.*, 2013). Whilst results from STRADL may under-represent what would be reflected in the general Scottish population, the cohort size results in large amounts of data which represent the full adult spectrum of ages, sex and demography.

Attrition between time-points has been described in **Figure 4.1**. It is possible that the response to STRADL (45%) is due to a response bias whereby individuals with mental health difficulties were more likely to respond to a mental health questionnaire when the purpose has been clearly communicated. Whilst the use of paper questionnaires enabled many near-complete participant responses, it is possible that the majority of potential participants forgot to complete or return their questionnaire booklets.

It is worth noting the disparity in the proportions of paper and online responses. Baseline differences between paper and online respondents are presented in **Table 4.7**. Several reasons have been hypothesized for these

differences. The older demographic of STRADL may have oversampled GS:SFHS participants who did not have access to a personal computer with internet access, or those that were not confident or willing to complete an online survey. Furthermore, the URL provided in the written letter was also very long (53 characters) and it is possible that manually typing a long URL in a browser‘s address bar may have been intimidating or inconvenient for many respondents, especially if IT knowledge was limited.

Table 4.7. Some baseline (GS:SFHS) comparisons between STRADL paper and online respondents

	Paper respondents (N = 8,833)	Online respondents (N = 785)
Median age (years)		
Male	55	50
Female	52	43
Gender (% female)	63	46
Employment (those aged up to 75 years) (%)		
Unemployed	4	3
Retired	16	8
Employed (full or part-time, or self-employed)	73	81
Education (%)		
Degree	36	47
No qualification	7	2
Annual income > £30,000	62	74
SIMD	4115 (1777)	421409 (1781)

Abbreviations: GS:SFHS, Generation Scotland: Scottish Family Health Study; STRADL, Stratifying Resilience and Depression Longitudinally; SIMD, the Scottish Index of Multiple Deprivation 2009
With the exception of age and SIMD, values represent percentage
SIMD represents Mean (SD)

4.7. What has it found? Key findings and publications

Baseline differences between GS:SFHS and STRADL are summarized above (**Tables 4.1** and **4.3)**, whilst differences between online and paper respondents are given in **Table 4.7**. This cohort represents a new and potentially valuable data resource to examine incident depressive symptoms, longitudinal outcomes and mechanisms of psychological resilience. No articles have yet been published with this data but the power of this resource is extensive. Genomic and pedigree based approaches to this data will enable us to estimate trait heritability and the contribution of shared and non-shared environmental effects to depression (Zeng *et al.*, 2016). This data may provide clues to how people can modify behaviour to reduce their risk of depression and psychological distress. Furthermore, STRADL will allow us to conduct genetic epidemiological analysis on indices of mental health, building upon existing data held by GS.

4.8. What are the main strengths and weaknesses?

The STRADL cohort includes important phenotypes to allow population-based genetic and epidemiological research on the stratification of MDD and resilience. The strengths of this cohort lie in the repeated assessment of mood disorders, psychological distress and substance use, making it a valuable dataset to investigate the pathogenic mechanisms that underlie psychopathology in addition to making longitudinal predictions on depression and resilience. As data can be linked anonymously to NHS records STRADL can be converted from a cross-sectional analysis into a longitudinal cohort covering a wide range of clinically-relevant outcomes.

Furthermore, the availability for longitudinal sampling is of benefit in obtaining repeated measures of mental health and resilience, that might be missed by a single measure (Toombs, 1990, von Peter, 2010).

Further, specific limitations of this cohort warrant consideration. Firstly, like other population cohorts such as UK Biobank (Allen *et al.*, 2012, Sudlow *et al.*, 2015), STRADL participants were more likely to be graduates and to come from less socio-economically disadvantaged areas. Nevertheless, participants from all socioeconomic strata were represented in both baseline (GS:SFHS) and follow-up samples.

Differences in prevalence rates of MDD were found in STRADL (using the CIDI-SF), compared to the use of the SCID at baseline. This may be because the SCID is administered face-to-to-face by trained researchers, and may have better psychometric properties than the self-reported CIDI-SF (Ekselius *et al.*, 1994). However, previous research suggests that the diagnostic classifications obtained using the CIDI-SF accurately reflect those made in the larger Composite International Diagnostic Interview (Kessler *et al.*, 1998). In future, the CIDI-SF will be compared to the SCID and to linked NHS records so that a comparison of each technique can be made and potential issues of recall bias can be overcome.

Overall, the GS:SFHS follow-up (STRADL) represents a valuable resource to investigate the stratification of depression and mechanisms of psychological resilience in a large, family-based, cohort.

4.9. Chapter conclusions

This chapter introduced a new resource specifically designed to investigate psychological resilience. The STRADL dataset has several important features that are of particular benefit when studying resilience. Firstly, the inclusion of the List of Threatening Experiences provides a measure of recent adversity, a key component for resilience. Secondly, in re-assessing both depression and psychological distress this dataset enables researchers to potentially make predictions on who is most likely to be resilient by computing the residual for actual and predicted symptoms given the number of life events each individual has experienced. Such a method would encompass two key facets of resilience; adversity and positive adaptation. Finally, this dataset includes a quantitative measure of psychological resilience that assesses an individual‘s ability to bounce back from adversity. Specifically, the Brief Resilience Scale is framed in regard to the negative events an individual has experienced and so negates the necessity to assess adversity simultaneously. Furthermore, the Brief Resilience Scale assumes a trait-based conceptualisation of resilience which infers it is a stable concept over time. Future follow-up of this cohort aims to re-assess resilience using the same methodology and so future investigations can determine if resilience is a stable trait, or a dynamic process which varies temporally. The Brief Resilience Scale will be used in the preceding chapters as a measure of psychological resilience in an attempt to elucidate its mechanisms, determine its genetic architecture, and investigate its environmental contributors.

Chapter 5

Risk and protection as partially independent processes in depressive illness

5.1. Introduction

As discussed in Chapter 1, Major Depressive Disorder (MDD) has a complex genetic aetiology. Current research suggests that the disorder is likely to be polygenic, whereby genetic vulnerability to MDD is resultant from the cumulative effect of many genetic loci which together have a stronger effect on MDD risk than any one individual locus (Hyman, 2014). Such polygenic risk has been confirmed in several studies of MDD (Hyman, 2014, Levine *et al.*, 2014, Ripke *et al.*, 2013) suggesting that genetic liability for the disorder increases risk for disease onset. However, despite greater liability for MDD, not all individuals go on to develop the disorder, as illustrated in family studies of depressed patients which estimate heritability at approximately 37% (Geschwind and Flint, 2015, Sullivan *et al.*, 2000). Such findings demonstrate that genetic factors do not deterministically result in MDD and indicate that there may be mitigating or mediating factors that influence risk or protection to MDD in individuals genetically susceptible to the disorder.

Two factors that may underlie risk and protection in MDD are neuroticism and resilience. Preceding chapters of this thesis have highlighted the risk-conferring effects of neuroticism, and demonstrated that high levels of neuroticism predispose individuals to increased risk for MDD (Kotov *et al.*, 2010, Malouff *et al.*, 2005, Navrady *et al.*, 2017b). Resilience, however, has been found to negatively associate with MDD risk (Campbell-Sills *et al.*, 2006, Wingo *et al.*, 2013). Whilst neuroticism is characterised by negative emotionality, resilience is typified by a range of positive emotions (Amstadter *et al.*, 2016, Campbell-Sills *et al.*, 2006) which could potentially reflect independent mechanisms between risk and protection. However, as discussed in Chapter 2, it has been argued that neuroticism and resilience may represent opposite ends of the same underlying trait and as such reflect a continuum of susceptibility to MDD whereby positive emotionality confers reduced risk and negative emotionality confers increased risk. Such an assertion is supported by a longitudinal twin study which revealed a strong negative phenotypic association between neuroticism and resilience and approximately two-thirds overlap in their genetic aetiology (Amstadter *et al.*, 2016). Furthermore, an additional study found a strong negative genetic correlation between neuroticism and positive affect which has been indirectly related to resilience (Weiss *et al.*, 2016). However, cross-sectional research has revealed an incremental validity of resilience which captures a better prediction of psychiatric symptoms following adversity than does neuroticism alone (Simeon *et al.*, 2007). Specifically, resilience was found to moderate the relationship between childhood emotional neglect and psychiatric symptoms to a greater extent than did the predictive value of neuroticism alone which suggests that neuroticism and resilience may be independent mechanisms in MDD aetiology.

It is important to identify the pathways through which genetic liability for MDD associates with the disorder, as genetic vulnerability does not always result in MDD. Research suggests that neuroticism and resilience could potentially mediate the association between genetic risk and MDD and as such it is important empirical question to address. This chapter introduces an original study which aims to investigate if neuroticism and resilience are

downstream mediators of genetic risk for depression. Furthermore, this chapter aims to examine if neuroticism and resilience are independent mechanisms or represent opposite ends of the same underlying construct. Building upon the work presented in Chapter 3, this chapter will also examine if consistent effects are found across clinical and self-reported measures of MDD, as divergent effects were found previously. This study is summarized, below, in the manuscript entitled ‗Genetic risk of Major Depressive Disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression' which has been published in *Psychological Medicine*. As first author for this manuscript, I conceived the experimental design, performed all data analysis and wrote the manuscript for publication. To acknowledge the contributions of co-authors, ―we" will be used instead of ―I" throughout this chapter.

5.2. Paper: Genetic risk of Major Depressive Disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression

5.3. Abstract

Background: Polygenic risk scores (PRS) for depression correlate with depression status and chronicity, and provide causal anchors to identify depressive mechanisms. Neuroticism is phenotypically and genetically positively associated with depression, whereas psychological resilience demonstrates negative phenotypic associations. Whether increased neuroticism and reduced resilience are downstream mediators of genetic risk for depression, and whether they contribute independently to risk remains unknown.

Methods: Moderating and mediating relationships between depression PRS, neuroticism, resilience and both clinical and self-reported depression were examined in a large, population-based cohort, Generation Scotland: Scottish Family Health Study (N = 4,166), using linear regression and structural equation modelling. Neuroticism and resilience were measured by the Eysenck Personality Scale Short Form Revised and the Brief Resilience Scale, respectively.

Results: PRS for depression was associated with increased likelihood of self-reported and clinical depression. No interaction was found between PRS and neuroticism, or between PRS and resilience. Neuroticism was associated with increased likelihood of self-reported and clinical depression, whereas resilience was associated with reduced risk. Structural equation modelling suggested the association between PRS and self-reported and clinical depression was mediated by neuroticism (43-57%), while resilience mediated the association in the opposite direction (37-40%). For both self-reported and clinical diagnoses, the genetic risk for depression was independently mediated by neuroticism and resilience.

Conclusions: Findings suggest polygenic risk for depression increases vulnerability for self-reported and clinical depression through independent effects on increased neuroticism and reduced psychological resilience. In addition, two partially independent mechanisms—neuroticism and resilience—may form part of the pathway of vulnerability to depression.

5.4. Introduction

Major depressive disorder (MDD) is a pervasive and disabling psychiatric condition characterized by periods of low mood and anhedonia, with an estimated lifetime prevalence of 16% (Levine *et al.*, 2014). MDD has substantial public health implications, with research suggesting the disorder increases mortality risk and exacerbates cognitive decline (Ferrari *et al.*, 2013, Reddy, 2010). Depression is substantially heritable (Sullivan *et al.*, 2000) and has a complex genetic architecture (Liu *et al.*, 2011, Schulze *et al.*, 2014). Whilst modest progress has been made to understand the heterogeneity of genetic risk factors for MDD (Caspi *et al.*, 2003, Duncan and Keller, 2011, Wray *et al.*, 2012), genome-wide association studies have indicated that MDD risk is influenced by a large number of common allelic variations of small effect rather than specific susceptibility loci (Lubke *et al.*, 2012).

A now-commonplace method applied to examine these genetic influences is Polygenic Risk Scores (PRS) (Demirkan *et al.*, 2011) which are used as a measure of "genetic liability" associated with a particular phenotype (Wray *et al.*, 2008). PRS are founded on the assumption that whereas genetic variants with very small individual effects may not meet genome-wide significance thresholds (depending on statistical power), their cumulative associations may have a much stronger effect (Wray *et al.*, 2007, 2008). Polygenic vulnerabilities have been identified in several psychiatric disorders (Purcell *et al.*, 2009, Ripke *et al.*, 2013). Specifically to MDD, PRS have been found to correlate with both the status and chronicity of the disorder (Levine *et al.*, 2014, Ripke *et al.*, 2013). However, to date, PRS typically account for only 1-2% of variance in MDD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, Demirkan *et al.*, 2011, Ripke *et al.*, 2013) suggesting other factors are also influencing risk for the disorder.

Personality is frequently linked with vulnerability to psychiatric illness (Fanous and Kendler, 2004), with one of the strongest associations being between MDD and neuroticism (Kotov *et al.*, 2010). Neuroticism is a partly-heritable personality trait characterised by emotional instability, negative emotional response, and stress sensitivity (Lahey, 2009). Phenotypically, neuroticism is strongly positively associated with MDD both cross-sectionally (Chan *et al.*, 2007, Navrady *et al.*, 2017b, Roelofs *et al.*, 2008), and prospectively (Farmer *et al.*, 2008, Kendler *et al.*, 2006). There is also evidence that neuroticism and depression are strongly genetically correlated (Jardine *et al.*, 1984, Kendler *et al.*, 1993). For example, evidence from twin studies indicates that neuroticism and MDD share up to two thirds of their genetic variance (Carey and DiLalla, 1994, Fanous *et al.*, 2002, Hettema *et al.*, 2006). Furthermore, de Moor and colleagues (2015) found that neuroticism and MDD can be equally well explained by neuroticism PRS (up to 1.05% variance explained), in addition to being able to predict MDD based on neuroticism PRS alone. As neuroticism is a relatively stable trait (Lahey, 2009), it is hypothesised that it may act as an indirect measure of later risk for MDD, and as such is an important phenotype for MDD genetic studies.

Whereas research into MDD risk has dominated the field, interest in psychological resilience has grown substantially over recent decades (Luthar *et al.*, 2006, Russo *et al.*, 2012, Southwick and Charney, 2012). Resilience is often described as the positive pole of individual differences in people's susceptibility to MDD, as it is widely observed that not all individuals at risk for the disorder become unwell (Alim *et al.*, 2008, Collishaw

et al., 2007). Resilience has been related to increased positive and reduced negative affect (Smith *et al.*, 2010), which suggests potentially different mechanisms for vulnerability and protection (Fredrickson, 2001). Cross-sectionally, it was found that individuals scoring higher on self-reported resilience (using The Connor-Davidson Resilience Scale questionnaire) reported fewer psychiatric symptoms following childhood emotional neglect than did those with lower levels of resilience (Campbell-Sills *et al.*, 2006). Using the same measure, higher resilience has been found to mitigate the severity of depressive symptoms in individuals exposed to trauma (Wingo *et al.*, 2013). Furthermore, reports suggest that resilience reduces risk for depression in individuals with high genetic loading for the disorder (Geschwind *et al.*, 2010, Wichers *et al.*, 2008, Wichers *et al.*, 2007).

Current research suggests a positive association between neuroticism and MDD; self-reported resilience and depression show a negative association. However, studies often fail to adequately consider how MDD is measured (Adli *et al.*, 2006, Cameron *et al.*, 2011). Whilst moderate associations between clinical and self-reported measures of MDD suggest the two approaches are interchangeable (Kessler *et al.*, 1998, Rush *et al.*, 2006), important distinctions between clinical and self-reported depression have been found. Specifically, self-reported and clinical measures of depression have each been found to provide unique information about the disorder not captured by the other (Uher *et al.*, 2012) that may help to elucidate underlying mechanisms (Fava *et al.*, 1986, Möller, 2000).

Here, we report a moderation and a mediation analysis of a large population-based cohort (Generation Scotland: Scottish Family Health Study) who completed both self-reported and clinical measures of MDD. First, in a series of moderation analyses, we investigated whether the association between PRS for MDD and clinical and self-reported depression (Levine *et al.*, 2014, Ripke *et al.*, 2013) was moderated by neuroticism or resilience. We predicted that neuroticism would be associated with increased likelihood of both clinical and self-reported depression, whilst resilience would associate in the opposite direction, in line with previous findings. Second, using structural equation modelling, we examined if neuroticism mediates the relationship between PRS for MDD and both clinical and self-reported MDD to increase risk for the disorder, and if resilience would mediate in the opposite direction. The path models we tested are illustrated in **Figure 5.1**.

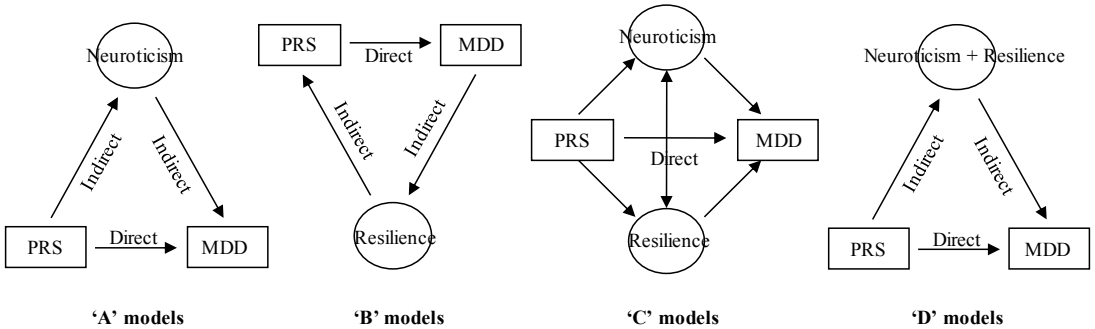

Figure 5.1. The theoretical mediation models tested in the present study

5.5. Methods

5.5.1. Participants

Participants were sampled from the Generation Scotland: Scottish Family Health Study (GS:SFHS) – a family-based epidemiological cohort recruited between 2006 and 2011 (Smith *et al.*, 2013, Smith *et al.*, 2006). At baseline, participants provided extensive data, including personality measures, a structured interview for clinical MDD diagnosis and DNA extraction. In 2014, GS:SFHS participants were re-contacted and asked to take part in a follow-up assessment of mental health and resilience (Navrady *et al.*, 2017a), providing a range of questionnaire measures including resilience and self-reported MDD. Full details of the initial recruitment and follow-up have been given elsewhere (Navrady *et al.*, 2017a, Smith *et al.*, 2013, Smith *et al.*, 2006) and in **Appendix B**. This study includes 4,166 unrelated individuals ($Mean_{age}$ = 56.01, SD = 12.31, N_{female} = 2,634) with complete data of interest.

GS:SFHS received ethical approval from the NHS Tayside Committee (reference 05/S1401/89 and 14/SS/0039). All participants provided written informed consent.

5.5.2. Study assessments

DNA was extracted from participants for whole-genome genotyping, the procedures for which have been reported extensively elsewhere (Smith *et al*., 2006, Zeng *et al*., 2016). Genome-wide genotype data were available for all participants in the current study from which polygenic risk scores (PRS) were created. Using the genotype data and PRCise software (Euesden *et al*., 2015), PRS were calculated by computing the genome-wide sum of trait-associated alleles across genetic loci, weighted by their effect in an independent genome-wide association study (GWAS). The GWAS summary statistics used for these PRS were those from the large, published meta-analysis of MDD from the Psychiatric Genetics Consortium (PGC MDD29; 130,664 MDD cases vs 330,470 controls), although GS:SFHS participants were removed from these summary statistics before calculating PRS. Here, we only report findings using a PRS threshold of 0.50 as preliminary analysis indicated that this threshold was most predictive of both self-reported and clinical MDD in this sample (see **Appendix B**).

Neuroticism was assessed using the self-report questionnaire Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF; (Eysenck, 1991). The neuroticism subsection of the EPQ-SF consists of 12 ‗Yes/No' questions (e.g., ―Are you a worrier?"). Scores range from 0 to 12, with higher scores indicative of higher levels of neuroticism. This scale has been concurrently validated with other quantitative measures of neuroticism (Gow *et al.*, 2005) with high reliability (Eysenck *et al.*, 1985).

Psychological resilience was assessed using the Brief Resilience Scale (BRS; (Smith *et al.*, 2008), a self-report questionnaire used to assess an individual's ability to ‗bounce back' or recover from stress. The BRS consists of six statements (e.g., ―I usually come through difficult times with little trouble") answered on a five-point scale from ―Strongly Disagree" to ―Strongly Agree". After reverse coding of even-numbered questions, a total resilience score was calculated by computing the mean of six questions. The BRS has been found to have a one factor structure, demonstrating good internal consistency and test-retest reliability (Smith *et al.*, 2008).

Participants were screened for clinical diagnosis of MDD at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First *et al.*, 2002). Diagnosis of MDD followed DSM-IV criteria (American Psychiatric Association, 2003); if either symptoms of depressive mood or anhedonia are endorsed, a minimum of four further symptoms must also be endorsed. These symptoms must have lasted nearly all day, every day for a minimum of two weeks. Interview procedures and quality control protocol have been described elsewhere (Fernandez-Pujals *et al.*, 2015). As the interviews were conducted by a trained researcher SCID MDD status can be used as a proxy for clinical MDD. In this sample, 664 individuals met criteria for clinical MDD (16%), and 3,502 were non-MDD cases (84%).

During re-contact, self-reported MDD was assessed using a questionnaire developed by the World Health Organization: the Composite International Diagnostic Interview – Short Form (CIDI-SF; (Kessler *et al.*, 1998). The CIDI-SF evaluates self-reported MDD according to DSM-IV criteria (American Psychiatric Association, 2003) and employs a stem-branch logic to eliminate individuals who fail to endorse a minimum of four symptoms (in addition to depressed mood and/or anhedonia) with clinical significance. Although the CIDI-SF is a self-report measure of MDD, respondents meeting MDD criteria with the CIDI-SF have been shown to reliably meet full diagnostic criteria with excellent accuracy if given the full version of the questionnaire (Kessler *et al.*, 1998). A total of 1,068 individuals in the mental health follow-up sample met criteria for self-reported MDD (26%), with 3,098 classified as non-MDD cases (74%).

5.6. Analyses

All analyses were conducted using R version 3.2.3 (http://www.R-project.org).

5.6.1. Moderation

We performed generalised linear models to examine the moderating associations of both neuroticism and resilience on the relationship between PRS for MDD and clinical and self-reported MDD (SCID and CIDI-SF, respectively). As MDD status is a dichotomous variable, we specified a ~~"b~~inary" family with a logit link function in the analysis. Three moderation models were computed for each MDD category (self-reported and clinical). A basic, first-step model was estimated to examine the validity of the PRS by testing for an association between genetic risk for depression and both clinical and self-reported MDD status. In the second step of the analysis, an interaction model was fitted to estimate the moderating association of neuroticism (total EPQ-SF score) on the contribution of genetic liability to both clinical and self-reported MDD. Another model was then fitted to examine the interaction between PRS and resilience (total BRS score) on susceptibility to clinical and self-reported MDD. Regression coefficients are reported as odds ratios with 95% confidence intervals. The *p*-values presented are raw and uncorrected for multiple testing. All continuous variables have been scaled to have a mean of 0 and a standard deviation of 1. As neuroticism and resilience were measured at different time-points, neuroticism was controlled for age at baseline (Age_{t1}) and resilience was controlled for age at re-contact (Age_{t2}) prior to them entering the moderation models. All models were controlled for four ancestry-informative principal components to take account of possible population stratification; results of these associations are presented in **Appendix B**.

5.6.2. Mediation

The structural equation modelling package ‗lavaan' (Rosseel, 2012) was used in R to estimate and compare models of the types shown in **Figure 5.1**. Diagonally Weighted Least Squares (DWLS) estimation was used in all models to account for MDD being a binary variable. The variance of each latent construct was fixed to 1 so as to identify each model. To assess the absolute fit of each model, a range of model-fit indices are reported (MacCallum *et al.*, 1996, McQuitty, 2006); Root Mean Square Error of Approximation (RMSEA; values indicating good fit <.05), Comparative Fit Index (CFI; values >.95), and Tucker–Lewis index (TLI; values >.95). To calculate the percentage mediation in each model we divided the sum of the indirect paths by the total variance explained by the model (Rosseel, 2012). For comparison of one- and two-factor models, we performed chi-squared tests, as an Akaike Information Criterion (AIC) cannot be computed when using the DWLS method.

As seen in **Figure 5.1**, four mediation models have been produced each for SCID and CIDI-SF MDD status to examine association between PRS and clinical and self-reported MDD, respectively. 'A' models examined the mediating effects of neuroticism (estimated as a latent variable using individual EPQ-SF items) on the relationship between PRS and MDD. A second set of models (‗B') investigated resilience as a latent variable indicated by individual BRS items as a mediator between PRS and MDD. ‗C' models examined neuroticism and resilience as two separate latent mediating variables between PRS and MDD. We also examined the phenotypic correlation between these latent variables within the model. Finally, we created a latent variable, named ‗Neuroticism+Resilience', consisting of all individual EPQ-SF and BRS questionnaire items to determine if one general factor can better explain the relationship between PRS and clinical and self-reported MDD ('D' models).

5.7. Results

Descriptive statistics and a correlation matrix are provided in **Table 5.1.** As illustrated in **Table 5.1**, resilience and neuroticism were moderately negatively correlated (r = -0.48, $p < 0.001$). Further demographic information, a full correlation matrix, and the differences and overlap between clinical and self-reported MDD measures in this study are outlined in **Appendix B**.

5.7.1. Moderation

5.7.1.1. Validity of the MDD PRS

Polygenic risk for MDD was found to be associated with increased likelihood of clinical MDD (see **Table 5.2**). A 1SD increase in genetic liability to depression was associated with an increased likelihood of clinical depression by an odds ratio of 1.20 ([95% CIs = 1.11, 1.31], $p < 0.001$). Age was found to be associated with clinical MDD, and being female increased clinical MDD likelihood by an odds ratio of 1.71 ([95% CIs = 1.42, 2.07], $p < 0.001$).

Similar results were obtained for self-reported MDD, see **Table 5.2**. Specifically, a 1SD increase in polygenic risk for depression increased likelihood of self-reported depression by an odds ratio of 1.18 ([95% CIs = 1.10, 1.27], $p < 0.001$). Age had a small negative association with self-reported MDD, whereas being female increased self-reporting of depression by an odds ratio of 1.94 ([95% CIs = 1.66, 2.28], $p < 0.001$).

Table 5.1. Correlation Matrix and Descriptive Statistics for baseline age, age at re-contact, sex, resilience, neuroticism, clinical and self-reported MDD status

	Age_{t1}	Age_{t2}	Sex (F)	Resilience	Neuroticism	SCID	CIDI-SF	Mean (SD)	N (%)
Age_{t1}	-							50.28 (12.34)	
Age_{t2}	0.99	-						56.01 (12.31)	
Sex (F)	0.09 **	0.09 **	-						2,634 (63)
Resilience	0.05	0.05	-0.10 **	-				3.52 (0.82)	
Neuroticism	-0.14	-0.14	0.17 **	-0.48	-			3.70 (3.17)	
SCID	-0.04 **	-0.04 **	0.18 *	-0.31 **	0.36 **	-			664 (16)
CIDI-SF	-0.08 **	-0.08 **	0.14 *	-0.35 **	0.29 **	0.60 *	-		1,068 (26)

Abbreviations: Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; Resilience, Total score from the Brief Resilience Scale; Neuroticism, Total score from the Eysenck Personality Questionnaire Short-Form; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form representing self-reported MDD

N.B. All p-values significant at $p \leq 0.01$

Demographic information for Sex represent the number and percentage of females in this sample. Demographic details for SCID and CIDI-SF represent the number and percentage of participants meeting criteria for clinical and self-reported MDD, respectively

All coefficients represent Pearson correlations except those denoted by * which represent the tetrachoric coefficient – resultant from both variables being binary, and those denoted by ** which represent point biserial correlations – resultant from binary and continuous variables

Table 5.2. Results of a generalised linear model predicting odds ratios for self-reported and clinical MDD status, p value, upper and lower 95% confidence intervals and the Akaike Information Criterion

MDD Outcome	Variables	Odds ratio	Lower 95% CIs	Upper 95% CIs	*p* value	AIC
SCID	Age_{t1}	0.99	0.99	1.00	0.031	3607.60
	Sex (F)	1.71	1.42	2.07	< 0.001	
	PRS	1.20	1.11	1.31	< 0.001	
CIDI-SF	Age_{t2}	0.99	0.98	0.99	< 0.001	4632.80
	Sex (F)	1.94	1.66	2.28	< 0.001	
	PRS	1.18	1.10	1.27	< 0.001	
SCID	Age_{t1}	0.99	0.99	1.00	0.026	3155.90
	Sex (F)	1.33	1.09	1.63	0.005	
	PRS	1.16	1.05	1.29	0.004	
	Neuroticism	2.49	2.28	2.72	< 0.001	
	PRS * Neuroticism	0.92	0.84	1.00	0.062	
CIDI-SF	Age_{t2}	0.99	0.98	0.99	< 0.001	4366.40
	Sex (F)	1.66	1.41	1.95	< 0.001	
	PRS	1.13	1.05	1.22	0.002	
	Neuroticism	1.81	1.68	1.95	< 0.001	
	PRS * Neuroticism	0.97	0.90	1.04	0.416	
SCID	Age_{t1}	0.99	0.99	1.00	0.030	3251.90
	Sex (F)	1.53	1.26	1.86	< 0.001	
	PRS	1.17	1.06	1.30	0.002	
	Resilience	0.44	0.40	0.48	< 0.001	
	PRS * Resilience	1.06	0.97	1.16	0.211	
CIDI-SF	Age_{t2}	0.99	0.98	0.99	< 0.001	4156.80
	Sex (F)	1.80	1.52	2.12	< 0.001	
	PRS	1.14	1.06	1.24	0.001	
	Resilience	0.43	0.40	0.47	< 0.001	
	PRS * Resilience	1.07	0.99	1.17	0.080	

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score; Age_{t1}, Age at the time of baseline; Age_{t2}, Age at the time of re-contact

N.B. Neuroticism has been controlled for Age_{t1} and resilience has been controlled for Age_{t2} before entering the model. Four principal components controlling for population stratification have been adjusted for and are reported in the supplementary material

5.7.1.2. Interaction between Neuroticism and PRS on MDD

No interaction was found between neuroticism and PRS on clinical MDD status (OR = 0.92, [95% CI = 0.84, 1.00], $p = 0.062$), see **Table 5.2**. PRS remained associated with clinical MDD (OR = 1.16, [95% CIs = 1.05, 1.29], $p = 0.004$), and neuroticism independently associated with increased likelihood of clinical MDD status (OR = 2.49, [95% CI = 2.28, 2.72], $p < 0.001$).

No interaction was found between neuroticism and PRS on self-reported MDD (OR = 0.97, [95% CI = 0.90, 1.04], $p = 0.416$), see **Table 5.2**. PRS remained associated with self-reported depression when co-varying for neuroticism (OR = 1.13, [95% CIs = 1.05, 1.22], $p = 0.002$), and neuroticism also remained strongly independently associated with self-reported MDD status (OR = 1.81, [95% CI = 1.68, 1.95], $p < 0.001$).

5.7.1.3. Interaction between Resilience and PRS on MDD

No interaction was found between PRS and resilience in association with clinical MDD (OR = 1.04, [95% CI =

0.95, 1.14], $p = 0.373$), see **Table 5.2**. The main effect of PRS was associated with clinical MDD (OR = 1.19, [95% CI = 1.08, 1.32], $p = 0.001$). A strong inverse relationship was found between resilience and clinical depression (OR = 0.44, [95% CI = 0.40, 0.48], $p < 0.001$).

No interaction was found between PRS and resilience on self-reported MDD (OR = 1.06, [95% CI = 0.97, 1.16], $p = 0.211$; see **Table 5.2**). Whereas the main effect of PRS was associated with increased likelihood of self-reported depression (OR = 1.17, [95% CI = 1.06, 1.30], $p = 0.002$), resilience was found to be associated with a reduction in self-reported MDD (OR = 0.44, [95% CI = 0.40, 0.48], $p < 0.001$).

5.7.2. Mediation

5.7.2.1. Mediation of Neuroticism

Model 1A showed no direct association between PRS and clinical MDD status ($\beta = 0.04$, $p = 0.077$), although this pathway was estimated to explain 4.4% of the variance. The path from PRS to neuroticism demonstrated a small positive association ($\beta = 0.07$, $p < 0.001$). A larger association between neuroticism and clinical MDD was found ($\beta = 0.87$, $p < 0.001$). This indirect pathway explained 5.8% of the variance. As shown in **Table 5.3**, Model 1A had good fit to the data, and suggested that 57% of the association of genetic liability for depression on clinical MDD was mediated by neuroticism.

In Model 2A, the direct path between PRS and self-reported MDD ($\beta = 0.06$, $p = 0.013$), was estimated to explain 5.5% of the variance. A small association between PRS and neuroticism was found ($\beta = 0.06$, $p < 0.001$), whilst the path from neuroticism to self-reported MDD showed a much stronger association ($\beta = 0.65$, $p < 0.001$). Together, this indirect pathway explained 4.2% of the variance. As shown in **Table 5.3**, Model 2A had good fit to the data. This model suggested that 43% of the association of genetic liability for depression with self-reported MDD was mediated by neuroticism.

5.7.2.2. Mediation of Resilience

In Model 1B, a direct association between PRS and clinical MDD was found ($\beta = 0.06$, $p = 0.008$, explaining 6.4% of the variance). However, a small negative association between PRS and resilience ($\beta = -0.07$, $p < 0.001$), and a larger negative association from resilience to clinical MDD ($\beta = -0.58$, $p < 0.001$), explained 3.8% of the variance. Model 1B‘s fit to the data was also good (see **Table 5.3**), and suggested that 37% of the association between PRS and clinical MDD was mediated by resilience.

A direct association between PRS and self-reported MDD was found in Model 2B ($\beta = 0.06$, $p = 0.008$) which was estimated to explain 5.8% of the variance. A small, negative association between PRS and resilience was found ($\beta = -0.07$, $p < 0.001$), in addition to a larger negative association between resilience and self-reported MDD ($\beta = -0.60$, $p < 0.001$), which together explained 3.9% of the variance. Model 2B‘s fit to the data was also good (see **Table 5.3**), and suggested that 40% of the association between PRS and self-reported MDD was mediated by resilience.

Table 5.3. Fit statistics for the mediation models tested with both clinical and self-reported MDD status as an outcome

Model	MDD outcome	Model description	*df*	χ^2	CFI	TLI	Null RMSEA	RMSEA	RMSEA Lower CI	RMSEA Upper CI
1A	SCID	Neuroticism as a mediator	142	165.97	0.977	0.972	0.038 *	0.006	0.000	0.010
2A	CIDI-SF		155	168.93	0.986	0.983	0.036 *	0.005	0.000	0.009
1B	SCID	Resilience as a mediator	56	159.05	0.992	0.989	0.201	0.021	0.017	0.025
2B	CIDI-SF		49	152.31	0.992	0.989	0.214	0.022	0.019	0.027
1C	SCID	Neuroticism & resilience as separate mediators	281	336.70	0.996	0.996	0.107 *	0.007	0.003	0.010
2C	CIDI-SF		281	336.62	0.997	0.996	0.109 *	0.007	0.003	0.010
1D	SCID	Neuroticism & resilience as one underlying	289	637.17	0.978	0.975	0.107 *	0.017	0.015	0.019
2D	CIDI-SF	mediating factor: Neuroticism+Resilience	289	596.99	0.981	0.978	0.109 *	0.016	0.014	0.018

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker-Lewis index

* TLI and other incremental fit indices may not be that informative, because the RMSEA of the baseline model is lower than 0.158 (Kenny *et al.*, 2011)

5.7.2.2. Mediation of Resilience

In Model 1B, a direct association between PRS and clinical MDD was found (β = 0.06, p = 0.008, explaining 6.4% of the variance). However, a small negative association between PRS and resilience (β = -0.07, p < 0.001), and a larger negative association from resilience to clinical MDD (β = -0.58, p < 0.001), explained 3.8% of the variance. Model 1B's fit to the data was also good (see **Table 5.3**), and suggested that 37% of the association between PRS and clinical MDD was mediated by resilience.

A direct association between PRS and self-reported MDD was found in Model 2B (β = 0.06, p = 0.008) which was estimated to explain 5.8% of the variance. A small, negative association between PRS and resilience was found (β = -0.07, p < 0.001), in addition to a larger negative association between resilience and self-reported MDD (β = -0.60, p < 0.001), which together explained 3.9% of the variance. Model 2B's fit to the data was also good (see **Table 5.3**), and suggested that 40% of the association between PRS and self-reported MDD was mediated by resilience.

5.7.2.3. Two-factor mediation

As shown in **Figure 5.2**, Model 1C found no association between PRS and clinical MDD was found (β = 0.04, p = 0.108), although this direct path was estimated to explain 3.9% of the variance. Whilst a small positive association was found between PRS and neuroticism (β = 0.06, p < 0.001), a small inverse relationship was found between PRS and resilience (β = -0.07, p < 0.001). A positive association was found between neuroticism and clinical MDD (β = 0.68, p < 0.001), whereas a negative association was found between resilience and clinical depression (β = -0.30, p < 0.001). Neuroticism and resilience were moderately negatively correlated (r = -0.25). **Table 5.3** indicates that Model 1C had good fit to the data. Approximately 61% of the association between PRS and clinical MDD was found to be mediated by neuroticism and resilience, as two separate factors.

In Model 2C, we examined the mediating associations of both neuroticism and resilience as separate constructs between PRS and self-reported MDD, within the same model. As shown in **Figure 5.2**, the direct association between PRS and CIDI-SF (β = 0.05, p = 0.033), was estimated to explain 4.7% of the variance. A small positive association was found between PRS and neuroticism (β = 0.06, p < 0.001), and an inverse relationship found between PRS and resilience (β = -0.07, p < 0.001). The same direction of association was evident in the path between neuroticism and self-reported MDD (β = 0.30, p < 0.001) and between resilience and self-reported depression (β = -0.47, p < 0.001). Neuroticism and resilience were found to be negatively correlated (r = -0.25). As shown in **Table 5.3**, Model 2C had good fit to the data, with neuroticism and resilience as two separate factors explaining approximately 52% of the association between PRS and self-reported MDD.

5.7.2.4. Neuroticism and Resilience as one underlying factor

Model 1D examined if neuroticism and resilience reflect opposite ends of the same trait by creating a latent variable (Neuroticism+Resilience) comprising of all the individual item responses from both the EPQ-SF and the BRS. A small association between PRS and clinical MDD was found (β = 0.06, p = 0.023), explaining 6% of the variance. An association between PRS to Neuroticism+Resilience was found (β = 0.04, p < 0.001) in

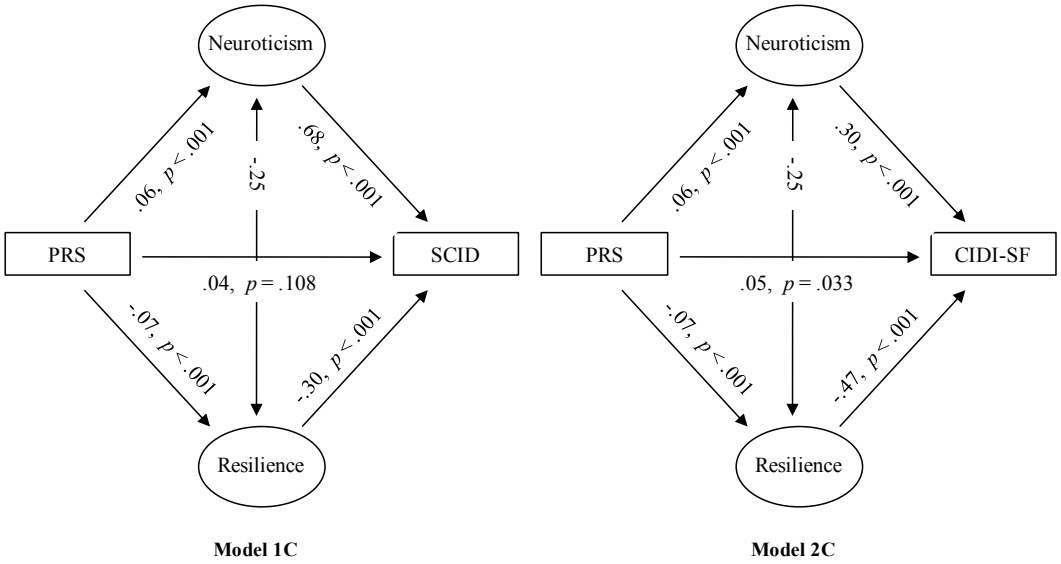

Figure 5.2. Path diagram of Models 1C and 2C, which include a direct bath between PRS and MDD status, an indirect path through neuroticism and an indirect path through resilience

addition to a positive association between Neuroticism+Resilience and clinical MDD (β = 1.19, $p < 0.001$). In total, Model 1D explained 47% of the mediation between PRS and clinical MDD. As shown in **Table 5.3**, Model 1C appears to fit the data much better than does Model 1D $X^2(8) = 300.48$, $p < 0.001$, suggesting that neuroticism and resilience reflected two partially separate constructs independently mediating the relationship between PRS for MDD and clinical depression.

Model 2D also investigated whether one underlying factor can better explain the mediation of the PRS-depression relation by neuroticism and resilience. A small association was found between PRS and self-reported MDD (β = 0.05, $p = 0.025$) which was estimated to explain 4.9% of the variance. A small association between PRS and Neuroticism+Resilience was found (β = 0.04, $p < 0.001$) in addition to a positive association between Neuroticism+Resilience and self-reported MDD (β = 1.21, $p < 0.001$). Together, these indirect paths explained 4.8% of the variance, whilst the model itself explained 49% of the mediation between PRS and self-reported MDD. Model 2D's fit to the data was significantly poorer than that of Model 2C (see **Table 5.3**), $X^2(8) = 260.37$, $p < 0.001$. This suggests neuroticism and resilience should be considered partially independent constructs associated with different mediating mechanisms in the association between genetic liability for MDD and self-reported depression.

5.8. Discussion

Here, we report the first study investigating the moderating and mediating associations of neuroticism and resilience on genetic liability for MDD on both clinical and self-reported depression in a large cohort of individuals. Our results suggest that polygenic risk for MDD is associated with an increased likelihood of both clinical and self-reported depression, replicating previous findings (Levine *et al.*, 2014, Ripke *et al.*, 2013). Consistent with existing literature (Farmer *et al.*, 2008, Navrady *et al.*, 2017b, Roelofs *et al.*, 2008), neuroticism is associated with increased likelihood of both clinical and self-reported MDD, whereas resilience was found to associate in the opposite direction (Geschwind *et al.*, 2010, Wingo *et al.*, 2013). Overall, our moderation analyses demonstrate an association whereby both genetic liability for MDD and neuroticism increases

likelihood of both clinical and self-reported depression, independently, whereas resilience associates with reduced likelihood for both clinical and self-reported depression, even after adjusting for genetic vulnerability. However, neuroticism and resilience did not show a multiplicative relation with the PRS, boosting and reducing the size of its association with depression, respectively. Structural equation modelling of this data suggests that genetic liability for MDD is largely mediated by neuroticism to increase risk for clinical and self-reported depression, whilst resilience mediates PRS to mitigate risk for both clinical and self-reported MDD. Results from this study demonstrate that neuroticism and resilience independently mediate the effects of genetic risk on depression, for both self-reported and clinical measures of MDD.

Whereas the results from our moderation analyses results are consistent with those previously found for PRS (Levine *et al.*, 2014), neuroticism (de Moor *et al.*, 2015), and resilience (Geschwind *et al.*, 2010), our meditational analyses reported novel findings. Consistent with the possibility that polygenic genetic differences shape susceptibility to MDD, our findings further suggest that this relationship is driven by two partially separate mediating mechanisms; one in which neuroticism increases risk for both clinical and self-reported MDD, the other in which resilience reduces the same risk. Evidence for neuroticism and resilience being partially independent mechanisms comes from our finding that the two measures are not perfectly correlated (r = -0.48), in addition to our structural equation models which demonstrate two separate associations.

It is possible that the meditational associations of neuroticism and resilience can be explained by the role of positive and negative emotions. It is well-documented that neuroticism is characterised by a range of negative emotions highly associated with MDD (Chan *et al.*, 2007, Navrady *et al.*, 2017b). Although resilience has received less empirical attention, researchers have hypothesized that resilience is characterised by positive emotionality (Block and Kremen, 1996, Masten, 2001, Wolin and Wolin, 1993) which over time provide individuals with an enduring capacity to ‟bounce back" when MDD would otherwise be expected (Lazarus, 1993, Masten, 2001). Indeed, Fredrickson (2001) has developed the ‟broaden-and-build" hypothesis of positive emotions which posits that whereas negative emotions narrow an individual‘s cognitive biases to increase likelihood of depressive symptoms, positive emotions broaden one‘s though-action repertoires to navigate away from the disorder (Fredrickson, 2004). In the present study, PRS for MDD increased vulnerability to both clinical and self-reported depression. This relationship is mediated and increased by neuroticism as the negative emotions it elicits are congruent with the disorder. Resilience may mediate and ameliorate the relationship between PRS for depression and MDD by promoting habituation to stressors, encouraging efficacious coping behaviours and prompting cognitive reappraisal away from depressive mood states (Amstadter *et al.*, 2016, Buhrmester *et al.*, 2011). These findings may have clinical applications insofar that therapeutic interventions for MDD may benefit from focusing on positive emotions to facilitate recovery and resilience rather than exclusively focused on alleviating psychiatric symptoms (Fredrickson and Joiner, 2002).

Resilient individuals are believed to ‟bounce back‘ from adversity quickly and efficiently, akin to the way a spring stretches but still returns to its original form (Lazarus, 1993). Current resilience measures often fail to assess the concept across the lifespan or recognise that risk or adversity is an essential element of resilience (Windle *et al.*, 2011). Although the Brief Resilience Scale assumes a trait-based conceptualisation of resilience,

the measure is framed in regard to negative events (Smith *et al.*, 2008), which frequently contribute to the onset of the disorder. Moreover, the inclusion of PRS in our analysis provide a measure of MDD risk that precede the outcome. PRS provide a causal anchor for our mediation analyses as they are a biological measure not subject to reverse causality. Whilst the use of genetic factors is unusual in structural equation modelling, they are helpful within this study as we can be more certain of the causal path directions, and as such this is not just a correlational analysis. However, a replication would be beneficial. Furthermore, additional work should fully elucidate the concept of resilience, as wide discrepancies exist in its definition and measurement (Bonanno *et al.*, 2015). We argue that future research needs to assess resilience across the lifespan to fully understand the processes and mechanisms that underlie it, and how it associates with depression.

Some limitations to this study warrant mention. Firstly, our measures of MDD were taken at different time-points. Although our results were robust across the two measures of MDD, we must note the difference in prevalence rates between the clinical (16%) and self-reported (26%) measures. This may be due to a sampling bias at re-contact in which participants with mental health problems were more likely to take part in a study specifically aimed to investigate mental health. Although it has been argued that structured clinical interviews have better psychometric properties than self-report measures of MDD (Ekselius *et al.*, 1994), research does suggest that the diagnostic classifications obtained using measures such as the CIDI-SF accurately reflect those made using the SCID (First *et al.*, 2002). Whilst clinical and self-reported measures have been found to provide unique information on MDD due to disproportionate weighting of symptoms within each measure (Uher *et al.*, 2012), it is widely reported that they each correlate highly when measuring the presence of absence of MDD rather than the severity of symptoms (Fava *et al.*, 1986). For this reason, we believe that the use of a self-reported and clinical measure of MDD is advantageous, despite some limitations. In addition, the concept of resilience was entirely self-reported; there is no consensus on how to measure resilience, and other measures (e.g. the off-diagonal method used by van Harmelen *et al.*, 2017) may have produced different results. It is also possible that MDD and neuroticism may influence the recall of experienced events, and that correlations between these variables, and resilience, may be introduced as a result. However, despite this potential limitation, neuroticism has been demonstrated to be a relatively stable trait in many previous studies and the use of genetic PRS scores—which must come causally prior to behaviours—provides an anchor for study that much previous research does not have available. A final limitation to this study pertains to the differences in time between baseline and re-contact. There is disparity among participants in regard to the time period between their baseline testing and re-contact, with some participants having a longer follow-up period than others. As a result, some participants might have experienced more negative life events, thus increasing their propensity for MDD.

In conclusion, this study suggests that polygenic risk for MDD increases risk for both clinical and self-reported depression through independent effects on increasing neuroticism and reducing resilience. This study suggests that two partially separate mechanisms — neuroticism and resilience — influence vulnerability and protection to MDD.

5.9. Chapter conclusions

This study confirms previous findings that genetic liability for MDD increases risk for the disorder. This work also confirms previous reports which suggest that neuroticism and resilience confer independent effects associated with increased and reduced risk for MDD, respectively. Importantly, this chapter has demonstrated for the first time that neuroticism and resilience represent partially independent pathways. Specifically, this study has provided evidence to suggest that neuroticism mediates PRS-MDD associations to increase risk for the disorder whilst resilience independently mediates in the opposite direction, which suggests neuroticism and resilience are unlikely to be simply polar ends of the same latent construct. Moreover, these associations were consistent across both clinical and self-reported measures of MDD which suggest that resilience and neuroticism may truly reflect divergent risk and protective pathways in mental health susceptibility. However, due to the small negative correlation found between neuroticism and resilience, we can only infer that these pathways are partially independent. As such, further work needs to be done to establish the extent of independence between the two measures. Moreover, as resilience was found to exert a protective effect on MDD in individuals genetically liable to the disorder, it is imperative to investigate the aetiology of resilience. A better understanding of potential ‗causes' of resilience may facilitate the development of more effacious treatment strategies which focus on fostering resilience before the onset of MDD symptomology. In the next chapter, efforts have been made to elucidate the aetiology of psychological resilience and investigate if it is genetically determined, or the result of environmental influences. Additionally, Chapter 5 will also seek to investigate the overlapping genetic architecture of resilience and neuroticism to further determine if they are separate constructs.

Chapter 6
Identification of major variance contributors in resilience and coping

6.1. Introduction

In comparison to Mendelian traits (e.g. Huntingdon's Disease or Cystic Fibrosis) which are determined by a single gene, complex traits have a polygenic architecture, where variation results from the cumulative effects of multiple genetic variants, in addition to environmental effects. The total phenotypic variation of a complex trait (such as psychological resilience) can be determined by separating genetic and environmental components (Lynch and Walsh, 1998). The environmental component, however, can be divided into that unique to the individual, and the environment shared between individuals (Tenesa and Haley, 2013). By calculating the heritability of a trait using this method researchers may be able to quantify to what extent a given trait is the result of genetic factors, or the environment ("nature or nurture"). Accurately partitioning the phenotypic variation of resilience into genetic and environmental components may have important scientific and clinical consequences. Firstly, establishing the genetic heritability of resilience may inform molecular studies which could potentially produce accurate predictions for risk or protection (Makowsky *et al.*, 2011, Tenesa and Haley, 2013). Secondly, it may inform both genetic and environmental interventions (Tenesa and Haley, 2013). Ultimately, the identification of specific genetic loci or contributing environmental exposures in psychological resilience may facilitate the development of interventions for mental health that focus on prevention in addition to cure.

Given that psychological resilience is a complex trait, one of the first steps towards identifying its causes and consequence is to identify the main sources of phenotypic variation. Specifically, it is important to decipher how much of its phenotypic variation is genetic in origin, and how much is influenced by environmental factors. The utilisation of recently developed methods for heritability and variance component analysis can answer such questions. This chapter contains a novel study which partitioned the phenotypic variation of resilience and measured the magnitude of its genetic and environmental components. The aim of this study was to identify the major sources of variation in resilience, and measure the relative contribution of the genetics and environmental components to coping style (which as discussed in Chapter 2 has previously been associated with resilience). Furthermore, this study aimed to disentangle the shared genetic architecture between resilience, coping style, and neuroticism using genetic correlation to further determine if they represent distinct constructs. This study has been summarized, below, into a manuscript entitled 'Genetic and environmental contributions to psychological resilience and coping', which has been accepted by *Wellcome Open Research* and is currently awaiting review. As first author, the study design was conceived by myself, and I analysed the data and wrote the manuscript for publication. To acknowledge the contributions of co-authors, "we" will be used instead of "I" throughout this chapter.

6.2. Paper: Genetic and environmental contributions to psychological resilience and coping

6.3. Abstract

Background: Genetic and environmental factors contribute to psychological resilience and coping style, but estimates of their relative contributions and genetic commonalities with neuroticism are unknown.

Methods: The heritability of resilience and coping style were estimated alongside the variance attributable to early and recent-shared environmental effects in a family-based cohort (GS:SFHS, N = 8,734). Bivariate analyses estimated genetic correlations between resilience, coping style, and neuroticism. Resilience, coping and neuroticism were measured using the Brief Resilience Scale, Coping Inventory for Stressful Situations and Eysenck Personality Scale Short Form-Revised, respectively.

Findings: The greatest proportion of the phenotypic variance for resilience was attributable to common-variant genetic (h_G^2 = .06, SE = .04) and family-shared environmental (h_F^2 = .05, SE = .02) effects. The variance in task- and avoidant-oriented coping was mostly attributable to common genetic, sibling- and couple-shared environment effects. The greatest proportion of the phenotypic variance for emotion-oriented coping was attributable to common genetic, family- and couple-shared environment effects. The estimated genetic correlation between resilience and emotion-oriented coping was high (r_G = -.79, p_{lrt} = .002) as was the correlation between resilience and neuroticism (r_G = -.83, p_{lrt} = .004). Emotion-oriented coping and neuroticism were also highly genetically correlated (r_G = .63, p_{lrt} = .003).

Conclusions: Our results indicate that early environment influences resilience, whereas recent environment effects coping style. Strong genetic overlap between resilience, emotion-oriented coping, and neuroticism suggests a relationship whereby genetic factors that increase negative emotionality lead to decreased resilience. We suggest that genome-wide family-based studies of resilience and coping may help to elucidate tractable methodologies to identify genetic architectures and modifiable environmental risk factors to protect against psychiatric illness.

6.4. Introduction

Aversive life experiences are known risk factors for a broad spectrum of mental health problems (Fergus and Zimmerman, 2005, Haskett *et al.*, 2006, Masten *et al.*, 1990, Werner, 1993). However, despite significant risk for psychopathology, many individuals exhibit better than expected adjustment. This ability to ‚bounce back' and maintain or regain mental health despite significant risk is referred to as *psychological resilience* (Luthar and Zelazo, 2003, Luthar *et al.*, 2006, Smith *et al.*, 2008). Resilience has increasingly become a focus of behavioural and medical research (Amstadter *et al.*, 2014, Bonanno *et al.*, 2015, Davydov *et al.*, 2010) promoting positive mental health and offering an alternative to ‚deficit' models of psychopathology (Fergus and Zimmerman, 2005). The underlying biological mechanisms of resilience are not, however, well understood. Studies seeking to identify the genetic and environmental contributions to resilience are an important starting point from which to build an understanding of its aetiology in addition to identifying treatment strategies focussing on primary prevention which would have significant impacts on several mental health conditions.

Recent studies indicate that genetic factors may be important for understanding individual differences in resilience (Rutter, 2003, Silberg *et al.*, 2001). For example, resilience has been found to attenuate the risk for depression in individuals with high genetic loading for the disorder (Geschwind *et al.*, 2010, Wichers *et al.*, 2008, Wichers *et al.*, 2007, Navrady *et al*., 2017c), although the role of shared environmental factors is not yet known. In a twin study, Boardman and colleagues (Boardman *et al.*, 2008) defined resilience as the residual for positive affect after controlling for social and interpersonal stressors and found resilience is significantly more heritable among men (52%) than women (38%). Similarly, another twin study found modest heritability estimates (24-49%) on measures of well-being and mental health which were indirectly related to resilience (Hansson *et al.*, 2008). A longitudinal twin study (Amstadter *et al.*, 2014) computed resilience as the residual between actual and predicted psychiatric symptoms, based on the total number of stressful life events an individual has experienced, and found moderate heritability estimates at both waves of assessment approximately five years apart (~31%). The relative genetic and environmental contributions to child resilience has been investigated in another twin study (Kim-Cohen *et al.*, 2004) which assessed resilience as the residual from a regression predicting children‘s antisocial behaviour from socioeconomic deprivation. The authors found that 46% of the variance in resilience was attributable to additive genetic effects, with the remainder accounted for by (unexplained) environmental contributors. Together, this research provides strong support for genetic and environmental contributions to resilience, although none accounted for the role of recent environmental factors, which, to our knowledge, have not yet been studied.

It is likely that coping styles also play an important role in resilience (Bonanno *et al.*, 2015). Whereas resilience refers to positive adaptation in the face of adversity, coping encompasses cognitive and behavioural strategies used to manage adversity (Folkman and Moskowitz, 2004). Several well-validated questionnaires have been developed to measure coping (Cosway *et al.*, 2000, Robinson *et al.*, 1997, Vitaliano *et al.*, 1985) which focus on task-, emotion-, and avoidance-oriented coping styles. Emotion-oriented coping is characterised by the regulation of distressing emotions, whereas task-oriented coping denotes purposeful efforts aimed at problem solving (Folkman and Lazarus, 1988). Avoidance-oriented coping is defined by behaviours aimed at avoiding difficult circumstances (Cosway *et al.*, 2000). Coping styles represent strategies and processes sensitive to personal and situational factors (Folkman and Moskowitz, 2004), although evidence from twin studies suggests they may be genetically *and* environmentally mediated. A twin study (Jang *et al.*, 2007) found that, whereas task-and emotion-oriented coping were modestly heritable (17-20%), avoidance-oriented coping was entirely determined by environmental factors. The majority of the variance in coping style was attributable to non-shared environmental influences. Furthermore, Kozak et al. (2005) found modest genetic influences to the variation seen in each coping style (33-39%), in addition to substantial environmental variance. Kendler et al (1991) found that approximately 30% of the total variance in the coping styles of ‗turning to others‘ and ‗problem solving‘ was attributable to genetic effects. Interestingly, however, the variability in the use of ‗denial‘ coping styles was entirely accounted for by environmental influences. Whilst these studies demonstrate that both genetics and environmental influence coping style, no study has yet examined the role of early and recent environmental contributors.

There is evidence to suggest that neuroticism substantially associates with both resilience and coping styles. Neuroticism is a stable, partially-heritable personality trait representing emotional instability and high stress sensitivity (Conley, 1985, Matthews *et al.*, 2009). Unlike resilience and coping style, research suggests neuroticism has a strong genetic determination with little or no shared-environmental influence (see Lahey, 2009 for a review). Neuroticism is negatively associated with resilience (Amstadter *et al.*, 2016, Simeon *et al.*, 2007, Navrady *et al*., 2017c), which is potentially the result of the divergent use of negative and positive emotions. Neuroticism positively correlates with unhealthy and ineffective forms of coping (Drapeau *et al.*, 2016, Endler and Parker, 1990b), and correlates negatively with active, problem-focused coping styles (Carver, 1998, Connor-Smith and Flachsbart, 2007). However, although a longitudinal twin study (Amstadter *et al.*, 2016) has revealed that neuroticism and resilience are genetically correlated (0.67), little is known about the genetic overlap between resilience, coping and neuroticism despite evidence to suggest that are phenotypically associated.

Phenotypically, resilience has been positively correlated with task-oriented coping, and negatively with indices of emotion- and avoidance-oriented coping (Penley *et al.*, 2002, Smith *et al.*, 2008, Zeidner and Saklofske, 1996), however, the genetic and environmental contributions to these relationships are not fully understood. Currently, our knowledge regarding resilience and coping is primarily based on findings from twin studies that assess narrow sense heritability. Family studies with genome-wide genotype data provide an opportunity to disentangle the differential contributions of molecular and non-additive genetic effects whilst simultaneously modelling environmental effects. In the present study we used a family-based genotyped cohort, Generation Scotland: Scottish Family Health Study (GS:SFHS) to investigate genetic and environmental contributions to both psychological resilience and coping style. We drew on the diverse familial relationships within the sample to estimate both molecular and pedigree genetic effects and the contribution of early family environment and recent shared environment by analysing family members/siblings and couples respectively. Furthermore, we tested whether these traits have significant overlapping genetic architectures, and examined their genetic correlations with neuroticism, which has been shown to associate with both resilience and coping style (Connor-Smith and Flachsbart, 2007, Navrady *et al*., 2017c).

6.5. Materials and methods

6.5.1. Generation Scotland: Scottish Family Health Study

The Generation Scotland: Scottish Family Health Study (GS:SHFS) (Smith *et al.*, 2013, Smith *et al.*, 2006) is a family-based population cohort recruited from General Practitioners‘ practices throughout Scotland between 2006 and 2011. Individuals were eligible for participation if they were aged above 18 years and had at least one first-degree relative also willing to participate. A total of 5,628 families spanning up to three generations were recruited. In 2014, GS:SFHS participants were re-contacted and asked to take part in a follow-up study of mental health and resilience (Navrady *et al.*, 2017a). These are the participants included in the current study. Full cohort details and recruitment procedures for baseline and re-contact are described elsewhere (Navrady *et al.*, 2017a, Smith *et al.*, 2013, Smith *et al.*, 2006). All components of GS:SFHS, including its protocol and written study materials have received national ethical approval from the NHS Tayside committee on research ethics (reference 05/s1401/89).

6.5.2. Genotyping and Quality Control procedures

At baseline, blood and salivary DNA samples were collected, stored, and genotyped at the Wellcome Trust Clinical Research Facility, Edinburgh (www.wtcrf.ed.ac.uk). Genome-wide genotype data were generated using the Illumina HumanOmniExpressExome-8 v1.0 DNA Analysis BeadChip (San Diego, CA, USA) and Infinium chemistry (Gunderson, 2009). The details and procedures for DNA extraction and genotyping have been reported extensively elsewhere (Kerr *et al.*, 2013, Nagy *et al.*, 2017). Population outliers were removed from the sample (Amador *et al.*, 2015). Quality control of genotyped SNPs used inclusion thresholds: call rate $\geq$ 98%, missing SNPs per individual $\leq$ 2%, Hardy-Weinberg equilibrium $p > 1x10^{-6}$, and minor allele frequency > 1%. In total, 561,125 autosomal SNPs for 8,734 related individuals remained and were used in subsequent analysis. Multidimensional scaling (MDS) components were created according to the ENIGMA 1000 genomes protocol (ENIGMA Genetics Support Team, 2013) in the software package PLINK (Purcell *et al.*, 2007).

6.5.3. Resilience, coping style and neuroticism

Psychological resilience was assessed at re-contact using the Brief Resilience Scale (BRS) (Smith *et al.*, 2008), (Smith *et al.*, 2008), a self-report questionnaire assessing an individual's ability to "bounce back" or recover from stress. The BRS consists of six statements (e.g., "I usually come through difficult times with little trouble") answered on a five-point scale from "Strongly Disagree" to "Strongly Agree". After reverse coding of even-numbered questions, a total resilience score was calculated by computing the mean of six questions. The BRS has been found to have a one-factor structure, demonstrating good internal consistency (Cronbach's alpha = 0.80-0.91) and test-retest reliability of 0.69 for one month and 0.62 for three months (Smith *et al.*, 2008).

The Coping Inventory for Stressful Situations (CISS) (Endler and Parker, 1990a) was completed at re-contact. The CISS is a 48-item self-report questionnaire in which responders indicate how much they engage in various coping activities "when under stress", on a five-point scale from (1) "Not at all" to (5) "Very much". Scores are summed over three 16-item sub-scales scales measuring task-oriented (e.g. "When under stress I focus on the problem and see how I can solve it"), emotion-oriented (e.g., "When under stress I blame myself for having gotten into this situation") and avoidance-oriented (e.g., "When under stress I take time off and get away from the situation") coping styles. The CISS has proven a robust measure of assessing situation-specific coping strategies, with a stable factor structure, high internal reliability and construct validity (Cosway *et al.*, 2000).

Neuroticism was assessed at baseline using the Eysenck Personality Questionnaire Short Form-Revised (EPQ-SF; Eysenck, 1991) The EPQ-SF is a self-report questionnaire measure consisting of twelve Yes/No questions assessing neuroticism, with scores ranging from 0 to12. Higher scores represent higher levels of neuroticism. This scale has been concurrently validated with other quantitative measures of neuroticism (Gow *et al.*, 2005) with high reliability (Eysenck *et al.*, 1985).

6.6. Statistical Analysis

6.6.1. Narrow-sense heritability

Using univariate GCTA (Yang *et al.*, 2011) (version 1.22) we calculated the narrow-sense heritability of resilience, task-, emotion- and avoidance-oriented coping. Genetic contributions to each trait were measured by

partitioning the phenotypic variance using linear mixed modelling (LMM) techniques. This method employs two variance component matrices that represent common-variant associated genetics (G) and pedigree-associated genetics (K) - details of how these were calculated are provided in **Appendix C**. Narrow-sense heritability (h_n^2) is calculated by the summation of both G and K effects. This method has been demonstrated to reliably estimate heritability in related samples (Zaitlen *et al.*, 2013) overcoming possible confounding effects within family-based cohorts. Each univariate model was adjusted for age, sex, and four MDS components which control for population stratification. As the K estimate could potentially be confounded and inflated by shared environmental effects we also examined the contribution of genetics and shared environment, below.

6.6.2. Contribution of genetics and familial shared environments to phenotypic variance

We re-estimated heritability using a recently developed method based on the genomic-relationship-matrix restricted maximum likelihood (GREML). Using the methods of Xia et al (Xia *et al.*, 2016, Xia *et al.*, 2017), we simultaneously fitted the two genetic components, G and K, alongside three environmental variance components: F (effect shared by nuclear families), S (the effect from the shared sibling environment), and C (environmental effects due to shared couple environments). We estimated the contribution of each component using a linear mixed model (LMM) with statistical significance calculated using likelihood ratio tests (LRT). Age, sex and four MDS components were included in each LMM as fixed effects. Details on the construction of the variance-covariance matrices can be found in the supplemental material.

The initial model was a full model (‗GKFSC') comprising of all genetic and environmental components. However, previous studies (Xia *et al.*, 2016, Zeng *et al.*, 2016) suggest that variance estimates may be confounded due to correlations between components. To overcome this issue, backward stepwise model selection was employed. LRT tests were conducted to test the significance of each variance component, which were removed sequentially if they failed to obtain significance (α = 5%), and had the highest *p*-value. This process was repeated until all the remaining components were significant. This method is described in more detail elsewhere (Xia *et al.*, 2016, Zeng *et al.*, 2016).

6.6.3. Genetic and phenotypic correlations between traits

The genetic correlations of common-variant associated (r_G) and pedigree associated (r_K) genetic effects between resilience, coping style and neuroticism were estimated. Bivariate GREML analysis in GCTA (Lee *et al.*, 2012, Yang *et al.*, 2011) was conducted to estimate the correlations of these genetic components simultaneously. These models were controlled for age, sex, and four MDS components. The significance of each genetic correlation was estimated using the LRT. We also report the phenotypic correlations between these traits (r_p).

6.7. Results

Among the 8,734 participants with genome-wide genotyped data, we recognised 655 couple pairs, 1,925 full sibling pairs and 4,508 nuclear families (minimum two individuals). The number of non-zero elements of the KFSC matrices for whom genotypic and phenotypic information are available for each trait are shown in **Appendix C**. The mean age of the sample was 56.36 years (SD = 13.15), and 5,403 (62%) were female. Demographic details of these individuals are presented within **Appendix C**.

6.7.1. Narrow-sense heritability

The narrow-sense heritability (h_n^2) of resilience was calculated by summing common-variant associated genetic (G) and pedigree-associated genetic (K) effects, and was estimated to be .14 (S.E. = .09, p_{lrt} < 0.001) **(Table 6.1)**. The K component was non-significant, indicating that the total additive genetic variance is primarily due to common-variant associated effects, or that the sample was underpowered to separate common- from pedigree-associated genetic effects.

The h_n^2 of task-oriented coping was .24 (S.E. = .10, p_{lrt} < 0.001), .24 (S.E. = .10, p_{lrt} < 0.001) for emotion-oriented coping, and .23 (S.E. = .10, p_{lrt} < 0.001) for avoidance-oriented coping. Estimates of h_n^2 are potentially inflated as the K component captures both pedigree-associated genetic effects and shared environmental effects. For this reason, we have portioned the phenotypic variance of these traits into genetic and shared environmental components, below.

Table 6.1. Age-, sex-, and population stratification[a]-adjusted univariate GCTA estimates of narrow-sense heritability

Trait	N	h_G^2 (SE)	h_K^2 (SE)	h_n^2 (SE)
Resilience	8555	**0.08 (0.04)**	0.06 (0.05)	**0.14 (0.09)**
ToC	8170	**0.12 (0.05)**	**0.13 (0.06)**	**0.24 (0.10)**
EoC	8306	**0.14 (0.04)**	**0.10 (0.06)**	**0.24 (0.10)**
AoC	8248	**0.14 (0.04)**	0.09 (0.06)	**0.23 (0.10)**

[a] first four MDS components

Abbreviations: ToC, Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented Coping; h_G^2, additive genetic effect from common variants; h_K^2, genetic effect associated with the pedigree; h_n^2, narrow-sense heritability (the sum of h_G^2 and h_K^2)

N.B. text in **bold** indicate LRT p < 0.05 (one-tailed). Values in parentheses represent standard errors.

6.7.2. Full model partitioning phenotypic variation into genetic and shared environmental components

To overcome possible confounding environmental effects, we partitioned the phenotypic variation of each trait by modelling two genetic components (G and K) alongside three environmental components representing the family, sibling, and couple effects (F, S, C) for each trait. The results of these full models are presented in **Table 6.2** and **Appendix C**. Neither genetic nor shared environmental components for resilience were statistically significant in the full model. However, in comparison with the reduced model which does not account for environmental effects (the GK model, above), the full model obtained lower estimates of genetic variance which suggests that the full model effectively reduced confounding environmental effects when calculating heritability estimates.

For task-oriented coping, the full model estimated that 11% (S.E. =.05, p_{lrt} = .006) of the phenotypic variance was attributable to common genetic variants (G). The pedigree-associated (K) component of this model was not significant, and so the proportion of total additive genetic determination was resultant from the effect of common-variant associated genetics (G). Of the three shared-environmental components, both sibling- (e_S^2=.08, SE = .04, p_{lrt} = .019) and couple-shared (e_C^2=.16, SE = .07, p_{lrt} < .001) environmental effects were significant. For emotion-oriented coping, 14% (S.E. = .04, p_{lrt} < 0.001) of its phenotypic variance was determined by

common genetic variants, and 14% (S.E. = .07, p_{lrt} = 0.002) was resultant from couple-shared environmental effects. The environmental effects shared between nuclear family members and full-siblings were not significant. For avoidance-oriented coping, 12% (S.E. = .04, p_{lrt} =0.002) of its phenotypic variance was attributable to common genetic variants (G). Significant effects from sibling- (e_S^2=.05, SE = .03, p_{lrt} = .049) and couple-shared (e_C^2=.14, SE = .07, p_{lrt} < .001) environment were also found. These results are illustrated in **Table 6.2**, and within **Appendix C**.

6.7.3. Backward stepwise model selection to identify major genetic/familial-environmental contributors

Using backward stepwise selection for resilience, only the common-variant associated genetic component and shared nuclear-family component were retained in the final model (the GF model as shown in **Table 6.2** and **Figure 6.1**). Common genetic variants (G) explained 6% (S.E. = .04, p_{lrt} = .041) of the phenotypic variation in resilience and family-shared environmental (F) effects explained 5% (S.E. = .02, p_{lrt} =.020). Using the same methodology, 14% of the variance in task-oriented coping was explained by common-variant associated genetics (h_G^2: S.E. = .03, p_{lrt} < .001). Furthermore, 10% of the variance was explained by sibling-shared environmental effects (e_S^2: S.E. = .03, p_{lrt} < .001), and a further 18% of the variance was explained by couple-shared environmental effects (e_C^2: S.E. = .04, p_{lrt} < .001). Similar patterns were found in avoidance-oriented coping with 15% of the variance explained by common-variant associated genetics (h_G^2: S.E. = .03, p_{lrt} < .001), 7% explained by sibling-shared environmental effects (e_S^2: S.E. = .03, p_{lrt} = .006), and 18% of the variance explained by couple-shared environmental effects (e_F^2: S.E. = .04, p_{lrt} < .001). In examining emotion-oriented coping, it was found that common genetic (h_G^2 = .15, S.E. = .04, p_{lrt} <.001), family-shared (e_F^2 = .05, S.E. = .03, p = .027) and couple-shared environmental effects (e_C^2 = .14, S.E. = .05, p_{lrt} =.002) were most attributable to the phenotypic variance (**Table 6.2** and **Figure 6.1**). These models are presented fully in **Appendix C**.

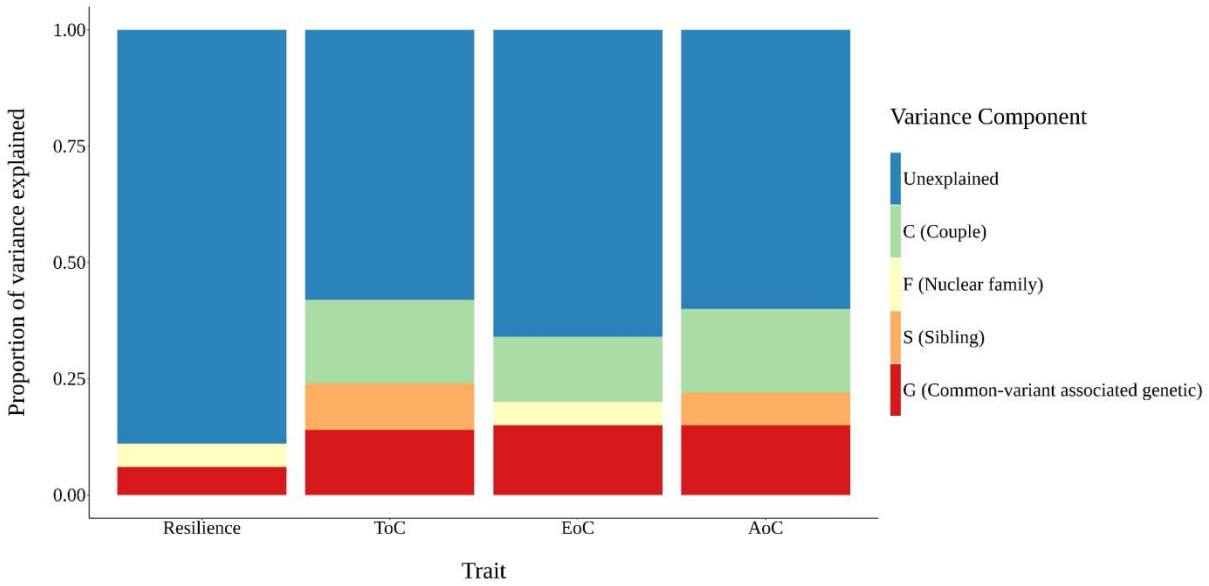

Figure 6.1. Sources of phenotypic variance and the proportion of variance they explained in the most parsimonious backward stepwise selection models for resilience, task-, emotion-, and avoidance-oriented coping styles

Table 6.2. Age-, sex-, and population stratification[a]-adjusted variance component analyses results for Resilience, ToC, EoC, and AoC

				G (common-variant associated genetic)	**K** (pedigree-associated genetic)	**F** (Nuclear family)	**S** (Full sibling)	**C** (Couple)
Trait	n	Model description		h_G^2 (SE)	h_K^2 (SE)	e_F^2 (SE)	e_S^2 (SE)	e_C^2 (SE)
Resilience	8555	Genetics only	GK	**0.08 (0.04)**	0.06 (0.05)			
		Full	GKFSC	0.06 (0.04)	0.00 (0.12)	0.05 (0.06)	0.00 (0.03)	0.01 (0.07)
		Backward selection	GF	**0.06 (0.04)**		**0.05 (0.02)**		
ToC	8170	Genetics only	GK	**0.12 (0.05)**	**0.13 (0.06)**			
		Full	GKFSC	**0.11 (0.05)**	0.02 (0.13)	0.03 (0.06)	**0.08 (0.04)**	**0.16 (0.07)**
		Backward selection	GSC	**0.14 (0.03)**			**0.10 (0.03)**	**0.18 (0.04)**
EoC	8306	Genetics only	GK	**0.14 (0.04)**	**0.10 (0.06)**			
		Full	GKFSC	**0.14 (0.04)**	0.03 (0.12)	0.04 (0.06)	0.00 (0.03)	**0.14 (0.07)**
		Backward selection	GFC	**0.15 (0.04)**		**0.05 (0.03)**		**0.14 (0.05)**
AoC	8248	Genetics only	GK	**0.14 (0.04)**	**0.09 (0.06)**			
		Full	GKFSC	**0.12 (0.04)**	0.00 (0.13)	0.03 (0.06)	**0.05 (0.03)**	**0.14 (0.07)**
		Backward selection	GSC	**0.15 (0.03)**			**0.07 (0.03)**	**0.18 (0.04)**

[a] first four MDS components

Variance component analyses were performed on Resilience, ToC, EoC, and AoC using the genetic model (GK), the model accounting for both genetic and three environmental effects (the full model), and the most parsimonious model selected by backward selection

Abbreviations: ToC, Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented coping

N.B. text in **bold** indicates significant LRT at $p < 0.05$ (one-tailed). Values in parentheses represent standard errors

6.7.4. Phenotypic and genetic correlations between traits

Age-, and sex-adjusted Pearson phenotypic correlations are presented in **Table 6.3.** Resilience was found to positively correlate with task-oriented coping (r_p = .36, SE = .02). Whereas negative associations were found between resilience and emotion-oriented coping (r_p = -.52, SE = .01) and resilience and neuroticism (r_p = -.45, SE = .01), a positive association was found between emotion-oriented coping and neuroticism (r_p = .46, SE = .01).

Table 6.3. Age-, and sex-adjusted phenotypic Pearson correlations

	Resilience	ToC	EoC	AoC	Neuroticism
Resilience	-				
ToC	0.36 (0.01)	-			
EoC	-0.52 (0.01)	-0.17 (0.01)	-		
AoC	-0.05 (0.01)	0.27 (0.01)	0.30 (0.01)	-	
Neuroticism	-0.45 (0.01)	-0.21 (0.01)	0.46 (0.01	0.05 (0.01)	-

Abbreviations: ToC, Task-oriented coping style; EoC, Emotion-oriented coping style; AoC, Avoidance-oriented coping style
All correlations were significant at $p < 0.01$. Values in parentheses represent standard errors

Estimates of common variant-associated and pedigree associated genetic correlations are reported in **Table 6.4**. Since our traits still have contributions from K (based on the full models), we will examine this effect to prevent inflation in our G estimates (Xia *et al.*, 2016, Zeng *et al.*, 2016). Furthermore, because there were no consistent environmental effects across our traits, and because K in the GK models captured a mixture of both pedigree-associated genetic and environmental effects, we have omitted the analysis of environmental correlations.

The estimate of the common-variant associated genetic correlation (r_G) between resilience and emotion-oriented coping was -.79 (S.E. = .19, p_{lrt} = .002) **(Table 6.4)**. The correlation between resilience and emotion-oriented coping explained by additional genetic variation associated with pedigree (r_K) was -.94 (S.E. = .30, p_{lrt} = .033), although this estimate is potentially influenced by the effects of shared-environment. High genetic overlap was found between resilience and neuroticism: r_G = -.83 (SE = .23, p_{lrt} = .004), r_K = -.79 (SE = .28, p_{lrt} = .020); and between emotion-oriented coping and neuroticism: r_G = 0.63 (SE = 0.16, p_{lrt} = 0.003), r_K = 0.74 (SE = 0.21, p_{lrt} = 0.009).

6.8. Discussion

Here, we report a novel study examining the genetic and environmental contributions to resilience and coping style in GS:SFHS, a population and family-based sample comprising close and distant relatives with genome-wide genotyped data. We found that resilience has a relatively low narrow-sense heritability estimate (h_n^2 = 0.14), whilst modest heritability estimates of task-, emotion-, and avoidant-oriented coping style were found (h_n^2 ~ 0.24). However, these estimates are likely inflated as they included shared environmental effects. To overcome this, we re-estimated the heritability of each trait using genetic and shared environmental variance components simultaneously. We demonstrated that variation in resilience has low contributions from genetic and shared environmental factors, with 89% of its phenotypic variance remaining unexplained. We also found that each coping style had substantial genetic (~20%) and shared environmental (20-30%) contributions. We

Table 6.4. Age-, sex-, and population stratification[a]-adjusted bivariate GCTA estimates of genetic correlation

	Resilience	ToC	EoC	AoC	Neuroticism
Resilience	-	.20 (.43)	**-.94 (.30)**	.36 (.54)	**-.79 (.28)**
ToC	.51 (.26)	-	-.46 (.34)	-.08 (.38)	-.06 (.29)
EoC	**-.79 (.19)**	-.05 (.25)	-	-.42 (.54)	**.74 (.21)**
AoC	-.24 (.30)	**.48 (.24)**	**.60 (.21)**	-	.05 (.33)
Neuroticism	**-.83 (.23)**	**-.64 (.21)**	**.63 (.16)**	-.17 (.22)	-

[a] first four MDS components

Abbreviations: ToC, Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented Coping

N.B**.** text in **bold** indicates significant LRT at $p < 0.05$ (one-tailed). Values in parentheses represent standard errors

The genetic correlations between traits resultant from common genetic variance (r_G) are shown on the lower diagonal; the upper diagonal shows the genetic correlations between traits associated with the pedigree (r_K)

Also found large genetic correlations between resilience and emotion-oriented coping for both common-variant associated genetic (r_G = -0.79) and pedigree-associated genetic (r_K = -0.94) effects, which suggests that genetic effects have a shared influence of resilience and emotion-oriented coping styles but in opposite directions. Furthermore, strong positive genetic correlations were found between neuroticism and emotion-oriented coping, whereas strong negative genetic correlations were found between resilience and neuroticism. Together, these findings indicate that genetic factors that increase negative emotionality lead to reduced psychological resilience, which mirror previous reports that which suggest resilience and neuroticism provide partially separate mechanisms to reduce and increase susceptibility to psychopathology, respectively (Navrady *et al.*, 2017c).

The narrow-sense heritability estimate for resilience in the current sample was substantially less than broad-sense estimates derived from twin studies (Boardman *et al.*, 2008, Kim-Cohen *et al.*, 2004). In this study, we have employed the Brief Resilience Scale, a quantitative trait-based measure of resilience, whereas other behavioural genetic studies have found larger genetic effects with both outcome- and process-based approaches (Boardman *et al.*, 2008, Kim-Cohen *et al.*, 2004). It is important to make this distinction clear as this difference may underlie the different heritability estimates reported in the literature. Furthermore, we demonstrate that the heritability of resilience is due to common-variant associated genetic effects, with estimates of pedigree-associated genetics (which include rare and structural genetic variants) having no significant effect. This is a novel finding as previous estimates suggest that for most complex traits over 50% of narrow-sense heritability is attributable to pedigree-associated genetic effects (Xia *et al.*, 2016, Zaitlen *et al.*, 2013). Alternatively, our analysis may have been underpowered or confounded by correlations between components (Xia *et al.*, 2016, Zeng *et al.*, 2016). Narrow-sense heritability estimates of task- and emotion-oriented coping in this study were in line with previous reports (Jang *et al.*, 2007, Kendler *et al.*, 1991, Kozak *et al.*, 2005). Specifically, here we report the narrow-sense heritability of avoidance-oriented coping to be 23%, whereas other researchers have found no genetic effect in avoidance-oriented coping styles. This may be due to our sample being better powered to detect genetic components of avoidance-oriented coping in comparison to previous twin studies (Jang *et al.*, 2007, Kendler *et al.*, 1991, Kozak *et al.*, 2005) which found conflicting results with much smaller samples (n < 1,000). Conversely, our sample may not have had sufficient power to separate out pedigree effects from shared environmental effects, indicated by our study failing to detect any significant pedigree effects.

Backward stepwise model selection of genetic and environmental variance components suggest that common-variant associated genetic and family-shared environmental effects were the most significant contributors of psychological resilience. Within our study, the family effect represents the ‗nuclear' family, an environmental influence associated with living in the same family group. It has been found that children with poor familial relationships are more likely to develop psychopathology in later life (Fearon *et al.*, 2010), whereas positive family relationships have been found to prevent negative mental health outcomes in ‗at-risk' children (Jaffee *et al.*, 2007), which supports our finding that resilience has a substantial family-shared environment component. Behavioural genetics studies suggest that positive familial relationships enable an individual to regulate their behaviour and emotions to perceive their environment as manageable, no matter how challenging (Bakermans-Kranenburg *et al.*, 2004, Bokhorst *et al.*, 2003). Furthermore, previous studies have demonstrated that strong familial attachments in childhood have long-lasting impacts on resilience and general well-being in later life (Masten *et al.*, 1990) which is important within the context of this study which examined adults who may no longer be living within the ‗nuclear' family environment, but whose effects are still apparent.

In examining both genetic and environmental effects simultaneously, we also detected an almost equal contribution from common-variant associated genetic and couple-shared environment effects for all three coping styles. The couple effect reflects the current environment shared between spouses in adulthood, which contrasts with both the full sibling and nuclear family effect which reflects the influence of earlier shared environments. During stressful circumstances, the support of a spouse (living in the same household) is more likely to be sought than support from closely related family members (living in a different household) (Ben-Zur *et al.*, 2001) The major contribution of couple-shared environment to coping could potentially capture the effects of assortative mating (Vinkhuyzen *et al.*, 2012), and other factors leading to spousal similarity. However, this effect may also be explained by couples learning from each other and adapting their coping styles to better face the adversity at hand (Soskolne and Kaplan De-Nour, 1989). Comparatively less variance was accounted for by sibling- and family-shared environmental effects which may be due to the high correlation between the matrices which could potentially impede model fit and estimation (Zeng *et al.*, 2016). Previous simulation of these models (Xia *et al.*, 2016) suggest that true components are detected approximately 80% of the time and so the small sibling- and family-shared environmental effects found could be due to false positives in the model. However, without a larger sample size, it would be difficult to have the power to fully discriminate between these components (Xia *et al.*, 2016), and so we advocate further replication in independent samples.

We also examined the genetic correlations between resilience, coping styles and neuroticism. Our results revealed very high negative correlations between resilience and emotion-oriented coping for both common-variant associated genetic and pedigree-associated genetic components. Furthermore, high negative genetic correlations were found between resilience and neuroticism, which mirror previous findings (Amstadter *et al.*, 2016). These findings suggest that there is a strong shared genetic architecture between resilience, emotion-oriented coping and neuroticism for both common and rare variants whereby genetic factors that increase negative emotionality also lead to decreased resilience. The direction of these findings support previous research which suggests that individuals high in emotion-oriented coping and neuroticism, and low in resilience are at a greater risk for psychopathology (Penley *et al.*, 2002, Smith *et al.*, 2008). We must note, however, that

correlations for pedigree-associated genetic components are likely biased due to the influence of shared-environmental effects which may be contained within the pedigree component, or vice versa. Unfortunately, due to a lack of power and model non-convergence, we were unable to report the environmental correlations between these traits. It would be of benefit to further investigate the genetic and environmental correlations between these traits in a larger sample to underpin important differences between the traits. For example, in further investigating the environmental correlations between resilience and coping style, we may be able to determine if having a resilient spouse is associated with a particular coping style.

A number of limitations to this study deserve mention. Firstly, as noted above we employed a measure of resilience which takes a trait-based conceptualisation. Whilst this is not a problem itself, conceptual discrepancies in resilience measurement will hinder comparison between studies and preclude meta-analysis (Davydov *et al.*, 2010). Secondly, as the re-contact cohort was a sub-set of the larger GS:SFHS sample, we were constrained by a limited number of participants with a reduced familial structure. Future investigation would greatly benefit from a larger sample size with an increased number of familial relationships to fully disentangle environmental components in the relationship between these traits. Furthermore, although we obtained estimates from effects from common-variant and pedigree-associated genetic, our sample is underpowered to detect small effects (Xia *et al.*, 2016) which would be overcome by a larger sample size, either related (using our methodology) or between two independent datasets (using methods such as LD-score regression (Bulik-Sullivan *et al.*, 2015a, Bulik-Sullivan *et al.*, 2015b)). Finally, there may be other major shared and non-shared environmental effects of each of our traits that are not specifically captured in our analysis. For example, a great body of work suggests that resilience may be associated with stressful life events, growing up in adversity, or being raised in care (Beasley *et al.*, 2003, Cicchetti and Rogosch, 2009, Collishaw *et al.*, 2007, Dent and Cameron, 2003, DuMont *et al.*, 2007).

Here, we provide evidence that psychological resilience (quantified by a previously validated ordinal scale), is a heritable trait with a relatively small proportion of its variance explained by genetic factors. Early childhood environment such as that shared by the nuclear family was also found to have a small association with resilience. Task-, emotion- and avoidance-oriented coping styles were found to be moderately heritable, although substantial environmental effects also contributed to their phenotypic variance. Approximately one fifth of the variance in each coping style was attributable to recent environment shared by couples. These results indicate that both genetic and environmental contributors to resilience and coping style need to be considered in future research. Finally, high negative genetic correlations between resilience and both emotion-oriented coping and neuroticism suggests that the traits share an overlapping genetic architecture in which genetic factors that increase negative emotionality lead to reduced resilience. We argue that further work with larger samples sizes is necessary to fully delineate the genetic and environmental contributions of these traits, and the relationships between them to identify modifiable protective factors against psychological distress and illness.

6.9. Chapter Conclusions

This study sought to answer a fundamental question in resilience research: to what extent are individual differences in resilience due to the effect of genetic factors and the environment? Our results indicate that both

genetics and early shared-environmental effects contribute to resilience, which suggest it is the result of both nature and nurture. However, the majority of its phenotypic variance remains unexplained which illustrates a need to further investigate and quantify psychological resilience, so that it can be more reliably measured and the effects of non-shared environment separated from random error and noise. We also demonstrated that coping style was attributable to both genetic and recent shared-environmental factors. Interestingly, this study provided evidence to suggest that resilience, emotion-oriented coping, and neuroticism share an overlapping genetic architecture in which genetic factors that increase negative emotionality lead to reduced resilience. This finding gives rise to further questions regarding resilience as we need to understand *how* these genetic and environmental factors increase an individual‘s resilience as it could inform future clinical intervention. Moving forward, it would be beneficial to use larger samples to replicate these findings and to identify the specific genomic regions that facilitate resilience and/or negative emotional response.

Chapter 7
General Discussion

7.1. Summary

This thesis presented three empirical studies in which multiple and diverse methodological approaches were utilised with the aim to elucidate the aetiology and mechanisms of psychological resilience. The findings from these studies enabled important questions about the nature of resilience to be addressed: firstly, can protective factors mitigate the detrimental effects of known risk factors for Major Depressive Disorder (MDD, Chapter 3); secondly, does resilience represent an independent protective mechanism in vulnerability to MDD separate from risk (Chapter 5); and thirdly, to what extent is resilience the result of genetic or environmental contributions (Chapter 6).

In Chapter 3, moderation analysis suggested that higher general intelligence (*g*) ameliorates the detrimental effects of neuroticism on both psychological distress and self-reported MDD, which suggests that protective factors can ameliorate the effects of risk on mental health outcomes. However, the protective effects of *g* on individuals at risk for MDD (by virtue of high levels of neuroticism) where not found in a clinical measure of MDD. These findings suggested that *g* may act as a resilience factor only at sub-threshold or at-risk levels. Whilst the protective effects of *g* were small, both absolutely, and in comparison to the risk conferring effects of neuroticism, the findings presented in this chapter suggest that protective factors may be important determinants of who is least or most likely to develop psychopathology. This work established a foundation from which to examine psychological resilience in subsequent chapters whereby resilience mechanisms and aetiology were investigated.

Building upon the work presented in Chapter 3, structural equation modelling analysis in Chapter 5 indicated that resilience and risk are partially independent mechanisms in the depressogenic process. Specifically, it was found that resilience mediates the association between genetic risk for depression and the disorder itself to reduce the likelihood of MDD, whereas neuroticism independently mediates in the opposite direction to increase risk for MDD in genetically vulnerable individuals. Importantly, these findings were robust across clinical and self-reported measures of MDD. It is likely that risk and resilience represent partially independent mechanisms through the divergent use of negative and positive emotionality, respectively. However, it is important to determine to what extent these constructs are separate, and, as neuroticism represents a partially heritable personality trait, it is necessary to understand if resilience is also genetically determined.

In Chapter 6, variance component analyses were employed to separate the phenotypic variance of both psychological resilience and coping style into their genetic and shared-environmental components to elucidate their aetiology. Findings suggested that resilience was in part determined by both common-variant associated genetic effects and early shared-environmental effects from the nuclear family. However, a large proportion of the phenotypic variance in resilience remained unexplained. The phenotypic variance in coping style was largely attributable to common-variant associated genetic effects, and recent environmental effects shared by spouses,

although divergent contributions were found across task-, emotion-, and avoidance-oriented coping styles. Strong negative genetic correlations were identified between resilience and emotion-oriented coping style, and between resilience and neuroticism, whereas a strong positive genetic correlation was found between emotion-oriented coping and neuroticism. Such findings suggest an overlapping genetic architecture in which genetic factors that increase negative emotionality also lead to reduced psychological resilience.

Together, these findings provide new insights into psychological resilience, and demonstrate the need to employ diverse multivariate methodologies to disentangle the construct. To illustrate, the use of moderation analysis, structural equation modelling, and variance component analysis have each revealed unique elements pertaining to resilience, and illuminated several important findings that may lay the foundation for future research and clinical practise. For example, the identification of protective factors that may ameliorate the detrimental effects of known risk factors for MDD may provide clinicians a starting point from which to identify which individuals are most likely to ‗bounce back' from mental health problems. Specifically, clinicians may be able to determine which individuals are most likely to respond to treatment, or remit based on the number/intensity/combination of protective factors they possess. Furthermore, as risk and resilience have been found to be partially independent pathways exerting divergent effects on MDD, clinicians may benefit from both fortifying ‗existing resilience' and ‗training' individuals to use a number of resilience techniques (such as positive emotionality and task-oriented coping) which could be used prior to MDD onset and maintained throughout the life course. Moreover, with the identification of genetic architectures and modifiable environmental risk factors, it may be possible to foster resilience in childhood and provide individuals with the tools needed to ‗bounce back' from a young age, which can be strengthened into adulthood. Such work would benefit and build upon existing programmes such as the UK resilience programme (UKRP) which was launched in 2007 in order improve the psychological well-being of school children. Specifically, UKRP aimed to investigate if teaching resilience would affect children's wellbeing, behaviour, attendance and academic attainment and found significant short-term improvements in mental health, school attendance rates and academic attainment in English (Challen *et al,* 2011). A better knowledge of the aetiology and mechanisms underlying resilience may enable researchers to ensure programmes such as UKRP can exert their effect long term, perhaps even into adulthood.

Ultimately, resilience research has the potential not only to alleviate individual suffering but also reduce the economic burden associated with MDD by focussing on prevention rather than cure. However, further replication and advancement is needed in order to generate working hypotheses for psychiatry research and practise. The studies presented within this thesis provide a foundation for future research, and raise more questions than answers. Indeed, despite producing a number of novel and important findings, this body of work is not without its caveats which should be addressed moving forward.

7.2. Limitations

The limitations associated with each individual study within this thesis have already been discussed within their corresponding chapters, and as such, the specific caveats pertaining to each study will not be re-addressed here. Rather, presented below are a number of limitations applicable to this thesis in general.

(1) Firstly, a limitation pertaining to almost all analyses within this thesis is the use of retrospective accounts of lifetime incidence of MDD. Within this thesis, the use self-reported questionnaire measures to estimate life-time prevalence of MDD were used, and whilst common in epidemiological cohort studies they are subject to several caveats regarding their reliability. For example, there is a growing body of evidence to suggest that retrospective accounts of MDD are susceptible to recall bias and distortions of memory. A number of studies have reported diminishing recall of past MDD episodes with increasingly long intervals between episodes of illness (Thompson *et al,* 2004, Wells and Horwood, 2012, Patten *et al,* 2012) which suggest the use of retrospective accounts may underestimate true lifetime prevalence rates. Although unlikely to be a caveat in this thesis, retrospective accounts of MDD may also be impeded in older samples in which recall error is exacerbated by cognitive decline. Further research also suggests that retrospective accounts of MDD may be an unreliable metric based on current mood state, and co-morbid conditions (Baker *et al,* 2004, Knäuper and Turner, 2003, Stone *et al,* 2000). It is important to note this limitation as it is possible our results have not captured a true reflection of MDD prevalence within our samples, despite this being the best method at our disposal. The use of NHS data linkage in future studies may overcome such issues and it would be benefit to compare retrospective accounts of MDD episodes and prevalence with clinical records.

(2) Secondly, the three studies presented within this thesis are based on individuals of White British ancestry, and as such the results may not be generalisable to other populations. As indicated in Chapter 2, there is evidence to suggest that resilience differs between ethnicities (Adams and Boscarino, 2005, Bonanno *et al.*, 2006), a hypothesis that this thesis has not addressed. Furthermore, as the samples used in the studies within this thesis are primarily Caucasian, more affluent, and better educated than the general population in the UK it does not necessarily mean any results can be inferred across all demographic profiles.

(3) Thirdly, the genetic analyses within this thesis are constrained by insufficient power. Specifically, it is likely that the sample sizes used within this thesis have precluded precise heritability estimates, provided insufficient power to reliably detect and differentiate contributors to phenotypic variance, and created uncertainty regarding the generalisability of findings to the general population. Although the sample sizes reported in each chapter are some of the largest reported to date, increasing sample sizes would provide greater predictive power, and as such further replication with larger sample sizes – especially for genetic analysis - is necessary.

(4) This thesis assessed adversity in relatively narrow terms. Whilst both genetic vulnerability and neuroticism are well documented risk factors for MDD (Hyman, 2014, Lahey, 2009, Levine *et al.*, 2014), and important findings have been found demonstrating that resilience can attenuate the detrimental effects of these factors on depression, this thesis has failed to examine the effects of resilience on other risk factors for the disorder. As discussed in Chapters 1 and 2, a wide range of risk factors are associated with MDD (Dobson and Dozois, 2011) across biological, psychological, environmental and social domains. This thesis may have benefited from examining the role of

resilience across a wider range of MDD risk factors. For example, the moderating effects of *g* may be stronger when examining the risk conferring effects of job stress on MDD onset. Additionally, resilience and neuroticism may prove entirely separate mechanisms when mediating the association between negative life events and MDD, compared to partially separate mechanisms when investigating genetic liability for MDD and the disorder. As such, it would be beneficial to conduct further research with an increasing number of risk factors to further elucidate resilience mechanisms across all aspects of adversity.

(5) Finally, this thesis has failed to operationalise psychological resilience, an initial aim of this body of work. Although the findings reported in this thesis are important for guiding future research, they have not provided sufficient insight to be able to define the concept of resilience. This is potentially due to the utilisation of the Brief Resilience Scale (BRS). The BRS is a quantitative measure assessing an individual's ability to _bounce back', and although it is framed in regard to the negative events an individual has experienced it fails to distinguish which protective factors result in high levels of resilience. As denoted in Chapter 2, resilience is likely a process, an outcome, influenced by multiple, independent predictors and this thesis has failed to determine which factors produce resilience across a range of domains (Bonanno *et al.*, 2007, Bonanno and Mancini, 2008). Such a homogenous approach has likely restricted the ability to elucidate resilience factors which would aid in the operationalisation of the construct.

The findings presented in this thesis are constrained due to homogenous sample demographics, the lack of investigating specific resilience factors and the failure to examine resilience to multiple adversities and/or risk. However, despite the above limitations, these studies do provide a starting point from which to further investigate psychological resilience and elucidate its mechanisms and aetiology.

7.3. Future directions

Interest in psychological resilience has grown exponentially in recent decades, with research into this field developing rapidly. Many methodologies have yet to be utilised in the resilience enquiry, and there exists an exciting opportunity for further advancements in the characterisation of resilience phenotypes. Future research investigating resilience has the potential to identify targets for more effacious treatments in MDD which focus on prevention long before the need for curative strategies. A number of potential directions for future study are provided, below.

(1) It is important to recognise that the results presented within this thesis require replication. A first aim for future research would be to replicate the studies discussed here in larger, less homogenous samples. Increased sample sizes would provide researchers additional statistical power to ensure the effects reported are not false positives and would provide scientists the confidence to extrapolate any findings for generalisability in the general population. Furthermore, investigating more diverse samples representing all demographic strata would enable researchers to infer if the results presented here are robust across ethnicity, age, education, and socioeconomic background.

(2) Secondly, it is important that future work investigates resilience from multiple perspectives. As discussed above, this thesis employed only the Brief Resilience Scale as a measure of psychological resilience, although as noted in Chapter 2, several quantitative measures of resilience have been validated (Windle *et al.*, 2011). It would be valuable to compare results across different measures of resilience so as to investigate their underlying similarities with methods such as factor analysis. Such an investigation may further our knowledge of resilience and aid in the quantification of the construct. Furthermore, it would be incredibly valuable to examine resilience as the residual between actual and predicted psychiatric symptoms based on the total number of negative life events an individual has experienced. Such a method is already gaining popularity (Amstadter *et al.*, 2016, van Harmelen *et al.*, 2017) and satisfies two of the core components of resilience; adversity and positive adaptation. Moreover, this methodology would enable researchers to accurately predict which individuals are most likely to be resilience to MDD, in addition to examining the protective factors which influence resilience.

(3) To build upon the work presented in Chapter 6, it would be highly advantageous to further investigate the genetic architecture of psychological resilience so as to elucidate who is most likely to be ‗resilient'. A valuable starting point would be to conduct a genome-wide association study (GWAS) to determine if there are any specific genetic variants associated with resilience. GWAS can be applied to both population- and family-based samples and can be performed on sets of variants categorized by genes, pathways or functional regions and so would be a powerful tool to utilise. Such an analysis was not performed within this thesis as GWAS requires substantial statistical power, which we currently do not have in the GS:SFHS dataset. In future investigation, it would be of benefit to run GWAS on larger sample sizes ($n > 10,000$) and potentially meta-analyse the results across multiple GWAS to overcome issues such as homogenous samples. Furthermore, with the availability to GWAS summary statistics, polygenic risk profiling would be available to researchers. The creation of polygenic risk scores (PRS) provide a quantitative and environmental-free method which can be used to reflect an individual's genetic propensity for resilience. It would be useful in future studies to employ PRS for resilience to investigate how it associates with risks/adversity and mental health outcomes.

(4) Finally, it would be of benefit to examine protective factors in more detail. Specifically, complex structural equation models would enable researchers the opportunity to investigate the multifaceted associations between genetics, the brain, and a comprehensive range of protective factors and how they work together to produce a resilient outcome. Although such an analysis would be largely theoretically determined, it could potentially incorporate all known aspects of psychological resilience. Furthermore, once a better understanding of protective factors and resilience mechanisms has been reached, methodologies such as Machine Learning may provide a suitable way to test proposed causal pathways and illuminate who is most likely to be ‗resilient'.

7.4. General conclusions

Despite significant risk for psychiatric disorders such as MDD, not all individuals become unwell. This thesis is a collection of studies examining *psychological resilience*; the ability to demonstrate better than expected adjustment and ‗bounce back' from adversity. At present, no consensus has been reached as to how resilience should be defined and measured, with debate remaining as to whether the construct is a trait or an outcome. Furthermore, until now, researchers were unsure whether risk and resilience represented independent constructs. This thesis comprises three novel studies which sought to investigate resilience from a number of perspectives with the aim of elucidating its aetiology and mechanisms. Moderation analyses, structural equation modelling, and variance component analysis were each utilised to further understand the facets of resilience. Whilst the concept of resilience was not fully elucidated for the purpose of operationalisation, the use of diverse multivariate methodologies has revealed several important features of resilience. To illustrate, this thesis provides evidence to suggest that risk and resilience are partially independent mechanisms, protective factors such as intelligence can mitigate the detrimental effects of known MDD risks, and resilience has a shared genetic aetiology with traits such as neuroticism and emotion-oriented coping in which genes responsible for negative emotionality reduce resilience. Such results provide an important starting point to build upon our knowledge of resilience and suggest that multivariate approaches are necessary. With further resilience research, scientists may be able to develop preventative strategies in mental health and circumvent the need for curative treatments.

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Appendix A

Supplementary material from Chapter 3

Table A1 Demographic, clinical, and cognitive differences between full GS:SFHS and UK Biobank cohorts and samples within this study

Table A2 Results of a MCMC generalized linear mixed model from GS:SFHS predicting odds ratios of MDD status, p value, upper and lower 95% confidence intervals and the *Deviance Information Criterion*

Table A3 Results of a MCMC generalized linear mixed model from GS:SFHS predicting beta coefficients of psychological distress (GHQ), p value, upper and lower 95% confidence intervals and the *Deviance Information Criterion*

Table A4 Results of a logistic regression from UK Biobank predicting odds ratios for self-reported MDD status, p value, upper and lower 95% confidence intervals and the Akaike Information Criterion

Table A5 Results of a regression from UK Biobank predicting beta coefficients of psychological distress (PHQ), p value, upper and lower 95% confidence intervals and the adjusted R^2 value for the model

Table A1. Demographic, clinical, and cognitive differences between full GS:SFHS and UK Biobank cohorts and samples within this study

	GS:SFHS		UK Biobank	
	Full sample (N = 24,084)	Complete cases (N = 19,200)	Full sample (N ~ 500,000)	Complete cases (N = 90,529)
Age	47.64 (15.41)	47.16 (14.97) *	56.53 (8.09)	56.64 (8.13) *
Sex (% female)	59	59	54	52
MDD (%)	13	13	33	33
Neuroticism	3.87 (3.17)	3.84 (3.16)	3.82 (2.91)	3.46 (2.86) *
GHQ score	16.01 (8.86)	15.93 (8.81)	-	
PHQ score	-	-	1.59 (2.07)	1.36 (1.91) *
Wechsler Digit Symbol Substitution Task	72.23 (17.22)	72.31 (17.09)	-	-
Mill-Hill Vocabulary Test	30.06 (4.76)	30.06 (4.76)	-	-
Weschler Logical Memory Test I & II	30.70 (8.48)	31.01 (8.04) *	-	-
Verbal Fluency Test	22.73 (11.17)	25.68 (8.10) *	-	-
Reaction time	-	-	559.65 (118)	564.00 (119.87) *
Visual memory	-	-	4.15 (3.40)	4.04 (3.21) *
Verbal-numerical reasoning	-	-	5.98 (2.16)	6.09 (2.14) *
SIMD	3909.66 (1846.91)	3903.82 (1851.91)	-	-
Townsend Score	-	-	-1.29 (3.09)	-1.37 (2.84) *

Abbreviations: GS:SFHS, Generation Scotland: the Scottish Family Health Study; MDD, Major Depressive Disorder ; GHQ, General Health Questionnaire; PHQ, Patient Health Questionnaire; SIMD, the Scottish Index of Multiple Deprivation
With the exception of sex and MDD, values represent Mean (SD)
N.B. The UK Biobank samples do not include any individuals who have also taken part in GS:SFHS (N = 147)
* Significantly different to the full sample, using a one-sample *t* test, $p < .05$

Table A2. Results of a MCMC generalized linear mixed model from GS:SFHS predicting odds ratios of MDD status, p value, upper and lower 95% confidence intervals and the *Deviance Information Criterion*

Model	Variables	Odds Ratio	Lower 95% CIs	Upper 95% CIs	*p* value	DIC
1.0	Neuroticism	3.62	3.29	4.03	$< 1.00x10^{-4}$	12428.30
	Age	1.19	1.16	1.23	$< 1.00x10^{-4}$	
	Age²	1.00	1.00	1.00	$< 1.00x10^{-4}$	
	Sex (M)	0.58	0.58	0.66	$< 1.00x10^{-4}$	
1.1	*g*	0.96	0.91	1.01	0.12	13784.89
	Age	1.20	1.16	1.24	$< 1.00x10^{-4}$	
	Age²	1.00	1.00	1.00	$< 1.00x10^{-4}$	
	Sex (M)	0.37	0.32	0.44	$< 1.00x10^{-4}$	
1.2	Neuroticism	3.68	3.33	4.09	$< 1.00x10^{-4}$	12421.57
	g	1.08	1.01	1.14	$1.54x10^{-2}$	
	Age	1.19	1.15	1.23	$< 1.00x10^{-4}$	
	Age²	1.00	1.00	1.00	$< 1.00x10^{-4}$	
	Sex (M)	0.59	0.50	0.68	$< 1.00x10^{-4}$	
	Neuroticism * *g*	1.04	0.99	1.09	0.12	
1.3	Neuroticism	3.61	3.28	4.00	$< 1.00x10^{-4}$	12397.53
	g	1.12	1.05	1.18	$2.05x10^{-4}$	
	SIMD	0.99	0.99	1.00	$< 1.00x10^{-4}$	
	Age	1.19	1.15	1.22	$< 1.00x10^{-4}$	
	Age²	1.00	1.00	1.00	$< 1.00x10^{-4}$	
	Sex (M)	0.60	0.52	0.69	$< 1.00x10^{-4}$	
	Neuroticism * *g*	1.04	0.99	1.09	0.10	

Abbreviations: MCMC, Markov Chain Monte Carlo; GS:SFHS, Generation Scotland: the Scottish Family Health Study; MDD, major depressive disorder; DIC, *Deviance Information Criterion; g*, General Intelligence; SIMD, Scottish Index of Multiple Deprivation

Table A3. Results of a MCMC generalized linear mixed model from GS:SFHS predicting beta coefficients of psychological distress (GHQ), *p* value, upper and lower 95% confidence intervals and the *Deviance Information Criterion*

Model	Variables	β	Lower 95% CIs	Upper 95% CIs	*p* value	DIC
2.0	Neuroticism	0.51	0.50	0.53	$< 1.00x10^{-4}$	47987.62
	Age	0.02	0.01	0.02	$< 1.00x10^{-4}$	
	Age²	-0.00	-0.00	-0.00	$< 1.00x10^{-4}$	
	Sex (M)	-0.03	-0.06	-0.01	$1.66x10^{-2}$	
2.1	*g*	-0.09	-0.10	-0.08	$< 1.00x10^{-4}$	52975.92
	Age	0.03	0.02	-0.03	$< 1.00x10^{-4}$	
	Age²	-0.00	-0.00	-0.00	$< 1.00x10^{-4}$	
	Sex (M)	-0.22	-0.25	-0.20	$< 1.00x10^{-4}$	
2.2	Neuroticism	0.59	0.48	0.51	$< 1.00x10^{-4}$	47795.04
	g	-0.05	-0.06	-0.04	$< 1.00x10^{-4}$	
	Age	0.02	0.02	0.02	$< 1.00x10^{-4}$	
	Age²	-0.00	-0.00	-0.00	$< 1.00x10^{-4}$	
	Sex (M)	-0.94	-0.06	-0.02	$1.58x10^{-3}$	
	Neuroticism * *g*	-0.05	-0.06	-0.04	$< 1.00x10^{-4}$	
2.3	Neuroticism	0.50	0.49	0.51	$< 1.00x10^{-4}$	47754.07
	g	-0.04	-0.05	-0.03	$< 1.00x10^{-4}$	
	SIMD	$2.49x10^{-5}$	$-3.15x10^{-5}$	$-1.81x10^{-5}$	$< 1.00x10^{-4}$	
	Age	0.02	0.02	-0.02	$< 1.00x10^{-4}$	
	Age²	$-2.11x10^{-4}$	$-2.61x10^{-4}$	$-1.65x10^{-4}$	$< 1.00x10^{-4}$	
	Sex (M)	-0.04	-0.06	-0.01	$5.00x10^{-3}$	
	Neuroticism * *g*	-0.05	-0.06	-0.04	$< 1.00x10^{-4}$	

Abbreviations: MCMC, Markov Chain Monte Carlo; GS:SFHS, Generation Scotland: the Scottish Family Health Study; GHQ, General Health Questionnaire; DIC, Deviance Information Criterion; *g,* General Intelligence; SIMD, Scottish Index of Multiple Deprivation

Table A4. Results of a logistic regression from UK Biobank predicting odds ratios for self-reported MDD status, *p* value, upper and lower 95% confidence intervals and the *Akaike Information Criterion*

Model	Variables	Odds ratio	Lower 95% CIs	Upper 95% CIs	*p* value	AIC
3.0	Neuroticism	2.39	2.35	2.43	$< 2.00x10^{-16}$	98707
	Age	1.17	1.14	1.20	$< 2.00x10^{-16}$	
	Age²	1.00	1.00	1.00	$< 2.00x10^{-16}$	
	Sex (M)	0.67	0.66	0.69	$< 2.00x10^{-16}$	
3.1	*g*	0.99	0.98	1.01	0.39	111620
	Age	1.17	1.14	1.20	$< 2.00x10^{-16}$	
	Age²	1.00	0.97	1.02	$< 2.00x10^{-16}$	
	Sex (M)	0.60	0.58	0.61	$< 2.00x10^{-16}$	
3.2	Neuroticism	2.40	2.36	2.44	$< 2.00x10^{-16}$	98649
	g	1.05	1.04	1.07	$5.29x10^{-12}$	
	Age	1.16	1.13	1.20	$< 2.00x10^{-16}$	
	Age²	1.00	1.00	1.00	$< 2.00x10^{-16}$	
	Sex (M)	0.67	0.65	0.68	$< 2.00x10^{-16}$	
	Neuroticism * *g*	0.96	0.95	0.98	$3.44x10^{-7}$	
3.3	Neuroticism	2.39	2.35	2.43	$< 2.00x10^{-16}$	98421
	g	1.07	1.05	1.08	$< 2.00x10^{-16}$	
	Townsend Score	1.04	1.04	1.05	$< 2.00x10^{-16}$	
	Age	1.16	1.10	1.22	$< 2.00x10^{-16}$	
	Age²	1.00	1.00	1.00	$< 2.00x10^{-16}$	
	Sex (M)	0.66	0.65	0.68	$< 2.00x10^{-16}$	
	Neuroticism * *g*	0.97	0.95	0.98	$6.80x10^{-7}$	

Abbreviations: MDD, major depressive disorder; AIC, Akaike Information Criterion; *g*, General Intelligence

Table A5. Results of a regression from UK Biobank predicting beta coefficients of psychological distress (PHQ), *p* value, upper and lower 95% confidence intervals and the adjusted R^2 value for the model

Model	Variables	β	Lower 95% CIs	Upper 95% CIs	*p* value	R^2
4.0	Neuroticism	0.52	0.51	0.52	$< 2.00x10^{-16}$	.2933
	Age	0.00	-0.01	0.01	0.85	
	Age²	-0.00	-0.00	0.00	$3.56x10^{-3}$	
	Sex (M)	0.01	0.00	0.03	$1.89x10^{-5}$	
4.1	*g*	-0.08	-0.08	-0.07	$< 2.00x10^{-16}$	.0420
	Age	0.02	-0.01	0.03	$2.32x10^{-3}$	
	Age²	-0.00	-0.00	0.00	$1.31x10^{-12}$	
	Sex (M)	-0.09	-0.10	-0.08	$< 2.00x10^{-16}$	
4.2	Neuroticism	0.51	0.51	0.52	$< 2.00x10^{-16}$	.2977
	g	-0.05	-0.06	-0.05	$< 2.00x10^{-16}$	
	Age	0.00	-0.00	0.01	0.55	
	Age²	-0.00	-0.00	0.00	$1.88x10^{-4}$	
	Sex (M)	0.02	-0.02	-0.00	$< 6.20x10^{-9}$	
	Neuroticism * *g*	-0.02	-0.03	-0.02	$< 2.00x10^{-16}$	
4.3	Neuroticism	0.51	0.51	0.52	$< 2.00x10^{-16}$	.3045
	g	-0.04	-0.05	-0.04	$< 2.00x10^{-16}$	
	Townsend Score	0.03	0.03	0.03	$< 2.00x10^{-16}$	
	Age	0.00	-0.00	0.02	0.29	
	Age²	-0.00	-0.00	0.01	$8.19x10^{-5}$	
	Sex (M)	-0.00	-0.00	0.00	$1.33x10^{-7}$	
	Neuroticism * *g*	-0.02	-0.03	-0.02	$< 2.00x10^{-16}$	

Abbreviations: PHQ, Patient Health Questionnaire; *g*, General Intelligence

Appendix B

Supplementary material from Chapter 5

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Cohort description

Participants were sampled from the Generation Scotland: Scottish Family Health Study (GS:SFHS) – a family-based epidemiological cohort recruited at random from General Practitioners' practices throughout Scotland between 2006 and 2011 (Smith *et al.*, 2013, Smith *et al.*, 2006). During baseline assessment, participants aged 18-98 (N = 24,090, Mean = 47.64, SD = 15.41) provided a wealth of clinical, phenotypic and biological data, including personality measures such as Neuroticism and a structured interview for clinical MDD diagnosis. Blood and salivary DNA was also taken for 98% of the cohort for genome-wide genotyping (Smith et al, 2006; Smith et al, 2013). In September 2014, GS:SFHS participants were re-contacted and asked to take part in a follow-up assessment of mental health and resilience (Navrady *et al.*, 2017a). A total of 9,618 participants aged 22-100 (Mean = 56.43, SD = 13.37) provided useable re-contact data including questionnaire measures of self-reported MDD and resilience. This study includes 4,166 unrelated individuals (Mean age = 56.01, SD = 12.31, n female = 2,634) with complete data of interest.

Thresholds for MDD Polygenic Risk Scores

Table B1. Results of generalized linear mixed models predicting odds ratios for clinical MDD status (SCID), *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion, from five PRS thresholds

PRS Threshold	Odds Ratio	Lower 95% CI	Upper 95% CI	*p* value	AIC
0.01	1.24	1.14	1.35	< 0.001	3600.90
0.05	1.25	1.15	1.37	< 0.001	3598.40
0.10	1.26	1.16	1.37	< 0.001	3597.50
0.50	1.20	1.11	1.31	< 0.001	3607.60
1.00	1.20	1.10	1.31	< 0.001	3608.20

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score
NB. Each model was adjusted for baseline age (t_1: when the SCID was administered), sex and four principal components which control for population stratification

Table B2. Results of generalized linear mixed models predicting odds ratios of self-reported MDD status (CIDI-SF), *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion, from five PRS thresholds

PRS Threshold	Odds Ratio	Lower 95% CI	Upper 95% CI	*p* value	AIC
0.01	1.13	1.05	1.21	0.001	4642.80
0.05	1.14	1.06	1.22	< 0.001	4640.90
0.10	1.16	1.08	1.25	< 0.001	4636.00
0.50	1.18	1.10	1.27	< 0.001	4632.80
1.00	1.18	1.10	1.27	< 0.001	4633.20

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score
NB. Each model was adjusted for age at follow-up (t_2: when the CIDI-SF was completed), sex and four principal components which control for population stratification

Table B3. Correlation Matrix and Descriptive Statistics

	BRS_1	BRS_2	BRS_3	BRS_4	BRS_5	BRS_6	Resilience	EPQ_1	EPQ_3	EPQ_5	EPQ_7	EPQ_9	EPQ_{11}	EPQ_{13}	EPQ_{15}	EPQ_{17}	EPQ_{19}	EPQ_{21}	EPQ_{23}	Neuroticism	Mean (SD)	N
BRS_1	-																				3.70 (0.96)	
BRS_2	.47	-																			3.40 (1.04)	
BRS_3	.68	.45	-																		3.49 (1.00)	
BRS_4	.56	.63	.51	-																	3.52 (1.04)	
BRS_5	.62	.50	.63	.52	-																3.55 (1.01)	
BRS_6	.60	.61	.54	.69	.57	-															3.64 (1.04)	
Resilience	.81	.77	.79	.82	.80	.84	-														3.52 (0.82)	
EPQ_1	$-.26^{+}$	$-.24^{+}$	$-.27^{+}$	$-.24^{+}$	$-.28^{+}$	$-.24^{+}$	$-.32^{+}$	-														1513
EPQ_3	$-.30^{+}$	$-.26^{+}$	$-.28^{+}$	$-.26^{+}$	$-.29^{+}$	$-.27^{+}$	$-.34^{+}$	$.63^{*}$	-													1310
EPQ_5	$-.15^{+}$	$-.14^{+}$	$-.14^{+}$	$-.13^{+}$	$-.15^{+}$	$-.14^{+}$	$-.18^{+}$	.52*	.36*	-												1105
EPQ_7	$-.22^{+}$	$-.20^{+}$	$-.23^{+}$	$-.23^{+}$	$-.23^{+}$	$-.22^{+}$	$-.27^{+}$	.40*	.42*	.30*	-											1847
EPQ_9	$-.30^{+}$	$-.27^{+}$	$-.27^{+}$	$-.26^{+}$	$-.27^{+}$	$-.27^{+}$	$-.34^{+}$	.70*	.66*	.47*	.45*	-										1276
EPQ_{11}	$-.24^{+}$	$-.24^{+}$	$-.23^{+}$	$-.23^{+}$	$-.24^{+}$	$-.24^{+}$	$-.30^{+}$	.43*	.40*	.36*	.47*	.40*	-									990
EPQ_{13}	$-.27^{+}$	$-.27^{+}$	$-.27^{+}$	$-.27^{+}$	$-.30^{+}$	$-.25^{+}$	$-.34^{+}$	.50*	.47*	.39*	.57*	.49*	.58*	-								2382
EPQ_{15}	$-.23^{+}$	$-.22^{+}$	$-.20^{+}$	$-.20^{+}$	$-.20^{+}$	$-.20^{+}$	$-.26^{+}$	.52*	.43*	.50*	.47*	.44*	.69*	.66*	-							653
EPQ_{17}	$-.23^{+}$	$-.20^{+}$	$-.21^{+}$	$-.22^{+}$	$-.24^{+}$	$-.20^{+}$	$-.27^{+}$	.40*	.42*	.28*	.60*	.43*	.50*	.62*	.46*	-						1796
EPQ_{19}	$-.23^{+}$	$-.24^{+}$	$-.22^{+}$	$-.22^{+}$	$-.24^{+}$	$-.23^{+}$	$-.29^{+}$	.47*	.43*	.38*	.41*	.46*	.75*	.61*	.70*	.43*	-					848
EPQ_{21}	$-.22^{+}$	$-.18^{+}$	$-.19^{+}$	$-.18^{+}$	$-.20^{+}$	$-.21^{+}$	$-.25^{+}$	.57*	.55*	.36*	.44*	.67*	.38*	.42*	.45*	.40*	.43*	-				582
EPQ_{23}	$-.24^{+}$	$-.20^{+}$	$-.24^{+}$	$-.23^{+}$	$-.23^{+}$	$-.21^{+}$	$-.28^{+}$	.49*	.50*	.34*	.51*	.48*	.48*	.59*	.49*	.66*	.48*	.49*	-			1107
Neuroticism	-.41	-.37	-.39	-.38	-.40	-.38	-.48	$.64^{+}$	$.60^{+}$	$.49^{+}$	$.59^{+}$	$.64^{+}$	$.60^{+}$	$.64^{+}$	$.58^{+}$	$.61^{+}$	$.59^{+}$	$.51^{+}$	$.61^{+}$	-	3.70 (3.17)	
Aget1	.04	.04	.04	.03	.04	.05	.05	$-.15^{+}$	$-.13^{+}$	$-.14^{+}$	$-.04^{+}$	$-.14^{+}$	$-.06^{+}$	$-.04^{+}$	$-.04^{+}$	$-.06^{+}$	$-.12^{+}$	$-.02^{+}$	$-.05^{+}$	-.14	50.28 (12.34)	
Aget2	.05	.04	.04	.03	.04	.05	.05	$-.15^{+}$	$-.13^{+}$	$-.13^{+}$	$-.03^{+}$	$-.13^{+}$	$-.06^{+}$	$-.04^{+}$	$-.04^{+}$	$-.06^{+}$	$-.12^{+}$	$-.01^{+}$	$-.04^{+}$	-.14	56.01 (12.31)	
Sex (F)	$-.10^{+}$	$-.06^{+}$	$-.09^{+}$	$-.09^{+}$	$-.11^{+}$	$-.06^{+}$	$-.10^{+}$	.10*	.22*	-.06*	.37*	.06*	.16*	.26*	.15*	.27*	.04*	.20*	.26*	$.17^{+}$		2634
SCID	$-.27^{+}$	$-.23^{+}$	$-.24^{+}$	$-.23^{+}$	$-.28^{+}$	$-.24^{+}$	$-.31^{+}$	.45*	.51*	.22*	.33*	.43*	.37*	.39*	.38*	.32*	.41*	.47*	.42*	$.36^{+}$		664
CIDI-SF	$-.31^{+}$	$-.26^{+}$	$-.29^{+}$	$-.26^{+}$	$-.31^{+}$	$-.28^{+}$	$-.35^{+}$	.35*	.42*	.16*	.22*	.37*	.26*	.26*	.26*	.24*	.29*	.39*	.33*	$.29^{+}$		1068

Abbreviations: Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; BRS, Individual items from the Brief Resilience Scale; Resilience, Total score from the Brief Resilience Scale; EPQ, Individual items from the Eysenck Personality Questionnaire Short-Form; Neuroticism, Total score from the Eysenck Personality Questionnaire Short-Form; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form representing self-reported MDD.

N.B. All p-values significant at $p \leq 0.01$

EPQ items represent the number and percentage of ‗Yes' responses. SCID and CIDI-SF represent the number of individuals meeting criteria for clinical and self-reported MDD, respectively

All coefficients represent Pearson correlations except those denoted by * which represent tetrachoric correlations – resultant from both variables being binary, and those denoted by + which represent point biserial correlations – resultant from binary and continuous variables

Descriptive Statistics for Clinical and Self-reported MDD

Clinical MDD

Based on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First *et al.*, 1997) at baseline assessment (2006-2011), clinically diagnosed MDD cases were predominately female (73%) and younger than non-MDD cases (61% female, M = 49.13, SD = 11.39 and M = 50.49, SD = 12.50, respectively); (t(990.30) = 2.78, $p < 0.001$, Cohen's d = .11). Clinical MDD cases were found to have significantly higher neuroticism scores (M = 6.31, SD = 3.28) than did non-MDD cases (M = 3.20, SD = 2.90); (t(869.91) = 22.75, $p < 0.001$, Cohen's d = 1.00). Clinically diagnosed MDD cases were found to score significantly lower in resilience (M = 2.94, SD = 0.85) in comparison to non-MDD cases (M = 3.63, SD = 0.76); (t(879.19) = 19.48, $p < 0.001$, Cohen's d = .08).

Self-reported MDD

Using the Composite International Diagnostic Interview – Short Form (CIDI-SF; Kessler *et al.*, 1998) at re-contact (2014-2017), a larger proportion of females met criteria for self-reported depression (75%) in comparison to non-MDD cases (59%). Self-reported MDD cases were younger (M = 54.40, SD = 12.28) in comparison to non-MDD cases (M = 56.56, SD = 12.27) at re-contact; (t(1852.70) = 4.96, $p < 0.001$, Cohen's d = .18). Individuals self-reporting MDD scored higher in neuroticism than did non-MDD cases (M = 5.26, SD = 3.45 and M = 3.16, SD = 2.88, respectively); (t(1608) = 17.80, $p < 0.001$, Cohen's d = .66). Significant group differences were found between self-reported MDD cases (M = 3.03, SD = 0.86) and non-MDD cases (M = 3.69, SD = 0.73) in resilience; (t(1617.60) = 22.33, $p < 0.001$, Cohen's d = .83), whereby self-reported MDD cases scored lower on psychological resilience.

Overlap between clinical and self-reported MDD

The two measures of MDD were taken at two separate time-points using two different methods, approximately six years apart. Below is a table detailing the overlap between these two measures in our sample of 4,166 individuals.

Table B4. The overlap of individuals meeting criteria for clinical and self-reported MDD in the current sample (n = 4,166)

		Self-reported MDD (CIDI-SF)	
		Met criteria	Did not meet criteria
Clinical MDD (SCID)	Met criteria	411	253
	Did not meet criteria	6157	2,845

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder

Moderation models for clinical MDD

Table B5. Results of a generalised linear model predicting odds ratios for clinical MDD status, *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion

MDD Outcome	Variables	Odds ratio	Lower 95% CIs	Upper 95% CIs	*p* value	AIC
SCID	Age_{t1}	0.99	0.99	1.00	0.031	3607.60
	Sex (F)	1.71	1.42	2.07	$1.53x10^{-8}$	
	PRS	1.20	1.11	1.31	$1.87x10^{-5}$	
	C1	2.92	0.00	$7.89x10^{24}$	0.969	
	C2	0.01	0.00	$8.63x10^{26}$	0.886	
	C3	0.00	0.00	1.05	0.127	
	C4	$1.83x10^{4}$	0.01	$2.07x10^{10}$	0.169	
SCID	Age_{t1}	0.99	0.99	1.00	0.026	3155.90
	Sex (F)	1.33	1.09	1.63	0.005	
	PRS	1.16	1.05	1.29	0.004	
	Neuroticism	2.49	2.28	2.72	$< 2.00x10^{-16}$	
	PRS * Neuroticism	0.92	0.84	1.00	0.062	
	C1	$1.60x10^{3}$	0.00	$2.18x10^{29}$	0.805	
	C2	0.00	0.00	$2.05x10^{26}$	0.431	
	C3	0.01	0.00	$8.08x10^{2}$	0.516	
	C4	134.63	0.00	$3.43x10^{8}$	0.062	
SCID	Age_{t1}	0.99	0.99	1.00	0.030	3251.90
	Sex (F)	1.53	1.26	1.86	$1.97x10^{-5}$	
	PRS	1.17	1.06	1.30	0.002	
	Resilience	0.44	0.40	0.48	$< 2.00x10^{-16}$	
	PRS * Resilience	1.06	0.97	1.16	0.211	
	C1	0.00	0.00	$1.58x10^{22}$	0.753	
	C2	0.00	0.00	$8.81x10^{22}$	0.629	
	C3	0.00	0.00	$2.42x10^{2}$	0.323	
	C4	$1.03x10^{48}$	0.04	$2.44x10^{11}$	0.124	

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score; Age_{t1}, Age at the time of baseline; C1-4, the principal components which control for population stratification

N.B**.** Neuroticism has been controlled for Age_{t1} and these residuals used within the model. Resilience has been controlled for Age_{t2} before entering the model. Threshold for PRS = 0.50

Moderation models for self-reported MDD

Table B6. Results of a generalised linear model predicting odds ratios for self-reported MDD status, *p* value, upper and lower 95% confidence intervals and the Akaike Information Criterion

MDD Outcome	Variables	Odds ratio	Lower 95% CIs	Upper 95% CIs	*p* value	AIC
CIDI-SF	Age_{t2}	0.99	0.98	0.99	$1.88x10^{-5}$	4632.80
	Sex (F)	1.94	1.66	2.28	$< 2.00x10^{-16}$	
	PRS	1.18	1.10	1.27	$6.01x10^{-6}$	
	C1	$5.87x10^{18}$	0.01	$2.18x10^{40}$	0.082	
	C2	0.63	0.00	$3.17x10^{24}$	0.987	
	C3	0.00	0.00	1.85	0.068	
	C4	$5.41x10^{2}$	0.00	$7.40x10^{7}$	0.298	
CIDI-SF	Age_{t2}	0.99	0.98	0.99	$4.48x10^{-6}$	4366.40
	Sex (F)	1.66	1.41	1.95	$1.03x10^{-9}$	
	PRS	1.13	1.05	1.22	0.002	
	Neuroticism	1.81	1.68	1.95	$< 2.00x10^{-16}$	
	PRS * Neuroticism	0.97	0.90	1.04	0.416	
	C1	$1.81x10^{21}$	0.54	$4.30x10^{43}$	0.058	
	C2	0.07	0.00	$3.19x10^{24}$	0.931	
	C3	0.00	0.00	20.120	0.187	
	C4	19.49	0.00	$3.89x10^{6}$	0.634	
CIDI-SF	Age_{t2}	0.99	0.98	0.99	$4.15x10^{-6}$	4156.80
	Sex (F)	1.80	1.52	2.12	$4.38x10^{-12}$	
	PRS	1.14	1.06	1.24	0.001	
	Resilience	0.43	0.40	0.47	$< 2.00x10^{-16}$	
	PRS * Resilience	1.07	0.99	1.17	0.080	
	C1	$3.75x10^{17}$	0.00	$1.06x10^{41}$	0.134	
	C2	0.00	0.00	$4.61x10^{21}$	0.733	
	C3	0.00	0.00	16.60	0.168	
	C4	$1.28x10^{3}$	0.00	1.17	0.266	

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder; AIC, Akaike Information Criterion; PRS, Polygenic Risk Score; $Age_{t2,}$ Age at the time of re-contact; C1-4, the principal components which control for population stratification N.B**.** Neuroticism has been controlled for Age_{t1} and these residuals used within the model. Resilience has been controlled for $Age_{t2,}$ before entering the model. Threshold for PRS = 0.50

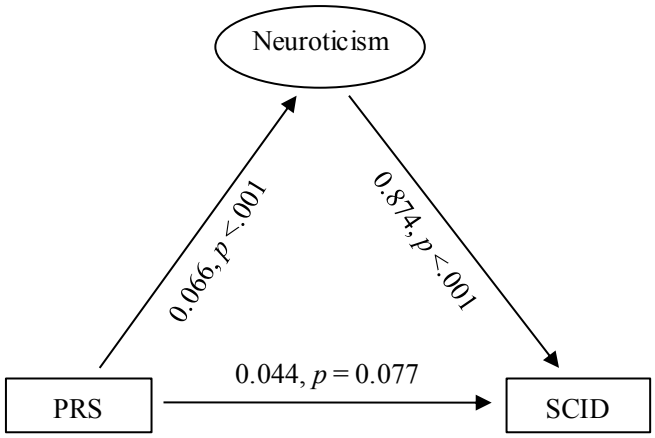

Figure B1. Path diagram of **Model 1A**, which includes a direct path between PRS and clinical MDD status, and indirect path through neuroticism, modelled as a latent variable. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured.
Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder

Table B7. Results of all standardised path coefficients and factor loadings from **Model 1A** examining the mediation of Neuroticism through PRS to clinical MDD status

Model description		ß	S.E	*p* value
SCID ~	PRS	0.044	0.025	0.077
SCID ~	Neuroticism	0.874	0.114	< 0.001
SCID ~	Sex	0.191	0.054	< 0 .001
SCID ~	Age_{t1}	0.003	0.027	0.900
SCID ~	C1	0.004	0.024	0.856
SCID ~	C2	-0.004	0.025	0.868
SCID ~	C3	-0.020	0.025	0.429
SCID ~	C4	0.013	0.025	0.605
Neuroticism ~	PRS	0.066	0.010	< 0 .001
Neuroticism ~	Sex	0.116	0.019	< 0 .001
Neuroticism ~	Age_{t1}	-0.063	0.010	< 0 .001
Neuroticism ~	C1	-0.004	0.005	0.514
Neuroticism ~	C2	0.001	0.005	0.828
Neuroticism ~	C3	-0.020	0.006	0 .001
Neuroticism ~	C4	0.022	0.006	< 0 .001
Neuroticism =~	EPQ1	1.000		
Neuroticism =~	EPQ3	1.012	0.139	< 0 .001
Neuroticism =~	EPQ5	0.631	0.090	< 0 .001
Neuroticism =~	EPQ7	0.695	0.120	< 0 .001
Neuroticism =~	EPQ9	0.967	0.141	< 0 .001
Neuroticism =~	EPQ11	0.853	0.125	< 0 .001
Neuroticism =~	EPQ13	0.803	0.170	< 0 .001
Neuroticism =~	EPQ15	0.829	0.117	< 0 .001
Neuroticism =~	EPQ17	0.808	0.147	< 0 .001
Neuroticism =~	EPQ19	0.859	0.119	< 0 .001
Neuroticism =~	EPQ21	0.803	0.108	< 0 .001
Neuroticism =~	EPQ23	0.916	0.127	< 0 .001

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; C1-4, the principal components which control for population stratification; EPQ, Eysenck Personality Questionnaire Short Form-Revised

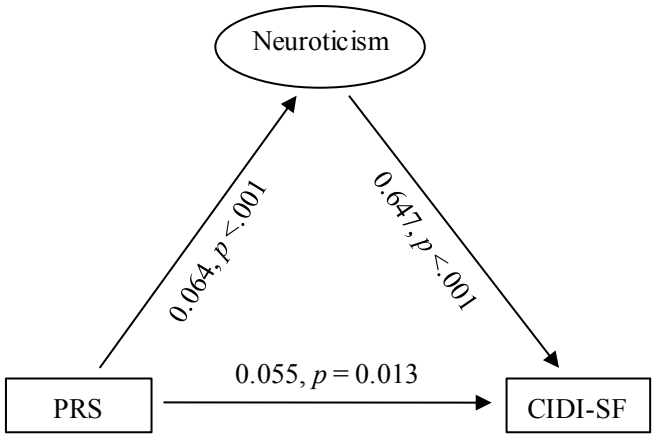

Figure B2. Path diagram of **Model 2A**, which includes a direct path between PRS and self-reported MDD status, and indirect path through neuroticism, modelled as a latent variable. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured
Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder

Table B8. Results of all standardised path coefficients and factor loadings from **Model 2A** examining the mediation of Neuroticism through PRS to self-reported MDD status

Model description		ß	S.E	*p* value
CIDI-SF ~	PRS	0.055	0.022	0.013
CIDI-SF ~	Neuroticism	0.647	0.087	< 0.001
CIDI-SF ~	Sex	0.312	0.047	< 0.001
CIDI-SF ~	Age_{t1}	-0.030	0.188	0.874
CIDI-SF ~	C1	0.045	0.024	0.065
CIDI-SF ~	C2	-0.002	0.022	0.931
CIDI-SF ~	C3	-0.028	0.022	0.203
CIDI-SF ~	C4	0.008	0.022	0.705
Neuroticism ~	PRS	0.064	0.010	< 0.001
Neuroticism ~	Sex	0.119	0.020	< 0.001
Neuroticism ~	Age_{t1}	-0.249	0.055	< 0.001
Neuroticism ~	C1	-0.003	0.005	0.540
Neuroticism ~	C2	0.002	0.005	0.719
Neuroticism ~	C3	-0.020	0.006	0.001
Neuroticism ~	C4	0.021	0.006	0.001
Neuroticism =~	EPQ1	1.000		
Neuroticism =~	EPQ3	1.024	0.143	< 0.001
Neuroticism =~	EPQ5	0.626	0.091	< 0.001
Neuroticism =~	EPQ7	0.758	0.128	< 0.001
Neuroticism =~	EPQ9	0.957	0.143	< 0.001
Neuroticism =~	EPQ11	0.858	0.128	< 0.001
Neuroticism =~	EPQ13	0.845	0.128	< 0.001
Neuroticism =~	EPQ15	0.845	0.179	< 0.001
Neuroticism =~	EPQ17	0.852	0.122	< 0.001
Neuroticism =~	EPQ19	0.790	0.150	< 0.001
Neuroticism =~	EPQ21	0.893	0.121	< 0.001
Neuroticism =~	EPQ23	1.000	0.140	< 0.001

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; C1-4, the principal components which control for population stratification; EPQ, Eysenck Personality Questionnaire Short Form-Revised

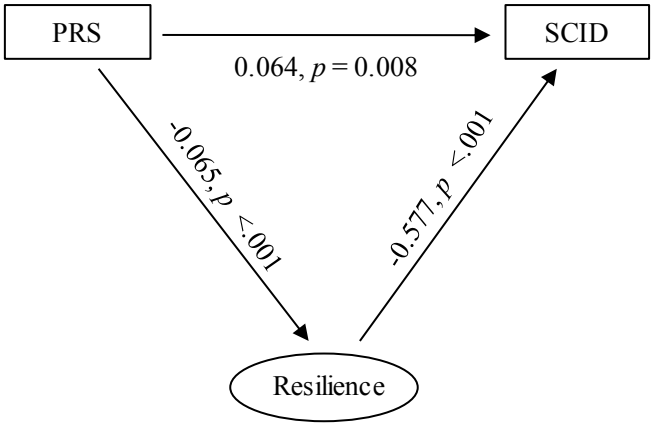

Figure B3. Path diagram of **Model 1B**, which includes a direct path between PRS and clinical MDD status, and indirect path through resilience, modelled as a latent variable. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured

Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; MDD, Major Depressive Disorder

Table B9. Results of all standardised path coefficients and factor loadings from **Model 1B** examining the mediation of Resilience through PRS to clinical MDD status

Model description		ß	S.E	*p* value
SCID ~	PRS	0.064	0.024	0.008
SCID ~	Resilience	-0.577	0.018	< 0.001
SCID ~	Sex	0.197	0.052	< 0.001
SCID ~	Age_{t1}	-0.452	0.201	0.024
SCID ~	C1	-0.008	0.024	0.741
SCID ~	C2	-0.010	0.025	0.697
SCID ~	C3	-0.028	0.025	0.271
SCID ~	C4	0.030	0.025	0.228
Resilience ~	PRS	-0.577	0.018	< 0.001
Resilience ~	Sex	-0.165	0.014	< 0.001
Resilience ~	Age_{t2}	0.010	0.056	0.860
Resilience ~	C1	-0.015	0.007	0.021
Resilience ~	C2	-0.014	0.007	0.040
Resilience ~	C3	0.018	0.007	0.006
Resilience ~	C4	-0.004	0.007	0.531
Resilience =~	BRS1	1.00		< 0.001
Resilience =~	BRS2	0.879	0.022	< 0.001
Resilience =~	BRS3	0.947	0.023	< 0.001
Resilience =~	BRS4	0.974	0.024	< 0.001
Resilience =~	BRS5	0.975	0.024	< 0.001
Resilience =~	BRS6	1.024	0.025	< 0.001

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; BRS, Brief Resilience Scale

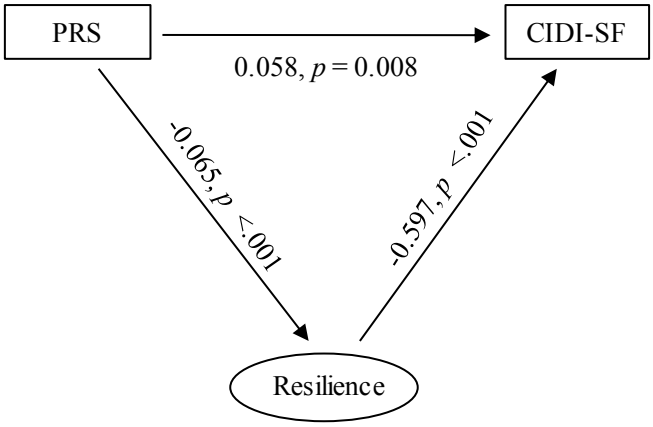

Figure B4. Path diagram of **Model 2B**, which includes a direct path between PRS and self-reported MDD status, and indirect path through resilience, modelled as a latent variable. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured

Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD; MDD, Major Depressive Disorder

Table B10. Results of all standardised path coefficients and factor loadings from **Model 2B** examining the mediation of Resilience through PRS to self-reported MDD status

Model description		ß	S.E	*p* value
CIDI-SF ~	PRS	0.058	0.022	0.008
CIDI-SF ~	Resilience	-0.597	0.018	< 0.001
CIDI-SF ~	Sex	0.290	0.047	< 0.001
CIDI-SF ~	Age_{t1}	-0.070	0.022	0.001
CIDI-SF ~	C1	0.033	0.024	0.171
CIDI-SF ~	C2	-0.009	0.022	0.683
CIDI-SF ~	C3	-0.030	0.022	0.177
CIDI-SF ~	C4	0.019	0.022	0.383
Resilience ~	PRS	-0.065	0.007	< 0.001
Resilience ~	Sex	-0.165	0.014	< 0.001
Resilience ~	Age_{t2}	0.037	0.006	< 0.001
Resilience ~	C1	-0.015	0.007	0.021
Resilience ~	C2	-0.014	0.007	0.040
Resilience ~	C3	0.018	0.007	0.006
Resilience ~	C4	-0.004	0.007	0.531
Resilience =~	BRS1	1.000		< 0.001
Resilience =~	BRS2	0.879	0.022	< 0.001
Resilience =~	BRS3	0.950	0.023	< 0.001
Resilience =~	BRS4	0.972	0.024	< 0.001
Resilience =~	BRS5	0.973	0.023	< 0.001
Resilience =~	BRS6	1.022	0.025	< 0.001

Abbreviations: CIDI-SF, Composite International Diagnostic Interview – Short Form; PRS, Polygenic Risk Score; Age_{t1}, Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; BRS, Brief Resilience Scale

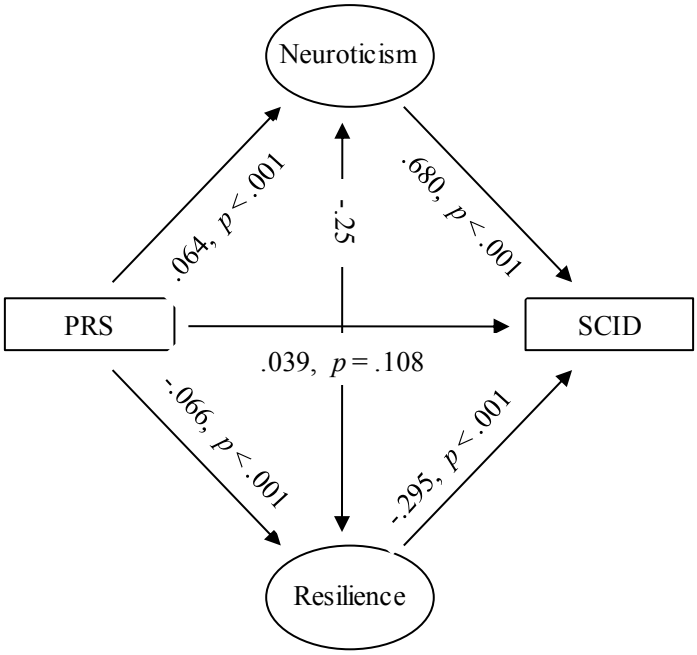

Figure B5. Path diagram of **Model 1C**, which includes a direct bath between PRS and clinical MDD status, an indirect path through neuroticism and an indirect path through resilience, both modelled as latent variables. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured
Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD;MDD, Major Depressive Disorder

Table B11. Results of all standardised path coefficients and factor loadings from **Model 1C** examining the separate mediation of Neuroticism and Resilience through PRS to clinical MDD status

Model description		ß	S.E	*p* value
SCID ~	PRS	0.039	0.024	0.108
SCID ~	Neuroticism	0.680	0.105	< 0.001
SCID ~	Resilience	-0.295	0.044	< 0.001
SCID ~	Sex	0.164	0.053	0.002
SCID ~	Age_{t1}	-0.283	0.205	0.166
SCID ~	C1	-0.001	0.024	0.962
SCID ~	C2	-0.007	0.025	0.784
SCID ~	C3	-0.019	0.025	0.440
SCID ~	C4	0.017	0.025	0.499
Neuroticism ~	PRS	0.064	0.008	< 0.001
Neuroticism ~	Sex	0.116	0.017	< 0.001
Neuroticism ~	Age_{t1}	-0.249	0.052	< 0.001
Neuroticism ~	C1	-0.003	0.005	0.511
Neuroticism ~	C2	0.001	0.005	0.782
Neuroticism ~	C3	-0.020	0.006	< 0.001
Neuroticism ~	C4	0.021	0.006	< 0.001
Neuroticism =~	EPQ1	1.00		< 0.001
Neuroticism =~	EPQ3	1.038	0.102	< 0.001
Neuroticism =~	EPQ5	0.591	0.060	< 0.001
Neuroticism =~	EPQ7	0.801	0.097	< 0.001
Neuroticism =~	EPQ9	1.012	0.107	< 0.001
Neuroticism =~	EPQ11	0.910	0.093	< 0.001
Neuroticism =~	EPQ13	0.899	0.154	< 0.001
Neuroticism =~	EPQ15	0.842	0.082	< 0.001
Neuroticism =~	EPQ17	0.805	0.113	< 0.001
Neuroticism =~	EPQ19	0.886	0.086	< 0.001
Neuroticism =~	EPQ21	0.806	0.075	< 0.001

Neuroticism =~	EPQ23	0.910	0.088	< 0.001
Resilience ~	PRS	-0.066	0.007	< 0.001
Resilience ~	Sex	-0.165	0.014	< 0.001
Resilience ~	Age_{t2}	0.019	0.057	0.733
Resilience ~	C1	-0.016	0.007	0.021
Resilience ~	C2	-0.014	0.007	0.040
Resilience ~	C3	0.018	0.007	0.006
Resilience ~	C4	-0.004	0.007	0.530
Resilience =~	BRS1	1.000		
Resilience =~	BRS2	0.880	0.021	< 0.001
Resilience =~	BRS3	0.947	0.022	< 0.001
Resilience =~	BRS4	0.968	0.023	< 0.001
Resilience =~	BRS5	0.974	0.023	< 0.001
Resilience =~	BRS6	1.014	0.024	< 0.001

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; $Age_{t1,}$ Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; EPQ, Eysenck Personality Short Form-Revised; BRS, Brief Resilience Scale

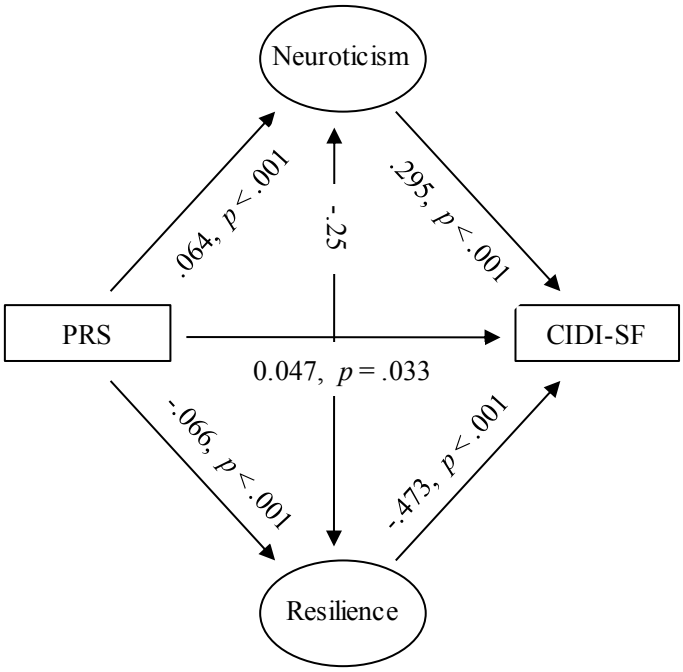

Figure B6. Path diagram of **Model 2C**, which includes a direct bath between PRS and self-reported MDD status, an indirect path through neuroticism and an indirect path through resilience, both measured as latent variables. Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured
Abbreviations: PRS, Polygenic Risk Score; CIDI-SF, Composite International Diagnostic Interview – Short Form, representing self-reported MDD;MDD, Major Depressive Disorder

Table B12. Results of all standardised path coefficients and factor loadings from **Model 2C** examining the separate mediation of Neuroticism and Resilience through PRS to self-reported MDD status

Model description		ß	S.E	*p* value
CIDI-SF ~	PRS	0.047	0.022	0.033
CIDI-SF ~	Neuroticism	0.295	0.070	< 0.001
CIDI-SF ~	Resilience	-0.473	0.035	< 0.001
CIDI-SF ~	Sex	0.276	0.047	< 0.001
CIDI-SF ~	Age_{t1}	-0.016	0.190	0.933
CIDI-SF ~	C1	0.036	0.024	0.136

CIDI-SF ~	C2	-0.008	0.022	0.730
CIDI-SF ~	C3	-0.027	0.022	0.231
CIDI-SF ~	C4	0.013	0.022	0.537
Neuroticism ~	PRS	0.064	0.008	< 0.001
Neuroticism ~	Sex	0.116	0.017	< 0.001
Neuroticism ~	Age_{t1}	-0.249	0.052	< 0.001
Neuroticism ~	C1	-0.003	0.005	0.513
Neuroticism ~	C2	0.001	0.005	0.783
Neuroticism ~	C3	-0.020	0.006	< 0.001
Neuroticism ~	C4	0.021	0.006	< 0.001
Neuroticism =~	EPQ1	1.000		< 0.001
Neuroticism =~	EPQ3	1.039	0.102	< 0.001
Neuroticism =~	EPQ5	0.589	0.060	< 0.001
Neuroticism =~	EPQ7	0.782	0.096	< 0.001
Neuroticism =~	EPQ9	1.020	0.108	< 0.001
Neuroticism =~	EPQ11	0.899	0.922	< 0.001
Neuroticism =~	EPQ13	0.888	0.152	< 0.001
Neuroticism =~	EPQ15	0.834	0.082	< 0.001
Neuroticism =~	EPQ17	0.800	0.112	< 0.001
Neuroticism =~	EPQ19	0.881	0.086	< 0.001
Neuroticism =~	EPQ21	0.809	0.076	< 0.001
Neuroticism =~	EPQ23	0.912	0.088	< 0.001
Resilience ~	PRS	-0.066	0.007	< 0.001
Resilience ~	Sex	-0.166	0.014	< 0.001
Resilience ~	Age_{t2}	0.029	0.057	0.608
Resilience ~	C1	-0.016	0.007	0.021
Resilience ~	C2	-0.014	0.007	0.040
Resilience ~	C3	0.018	0.007	0.006
Resilience ~	C4	-0.004	0.007	0.530
Resilience =~	BRS1	1.000		
Resilience =~	BRS2	0.880	0.021	< 0.001
Resilience =~	BRS3	0.949	0.022	< 0.001
Resilience =~	BRS4	0.967	0.023	< 0.001
Resilience =~	BRS5	0.973	0.022	< 0.001
Resilience =~	BRS6	1.013	0.023	< 0.001

Abbreviations: SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD; PRS, Polygenic Risk Score; $Age_{t1,}$ Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; EPQ, Eysenck Personality Short Form-Revised; BRS, Brief Resilience Scale

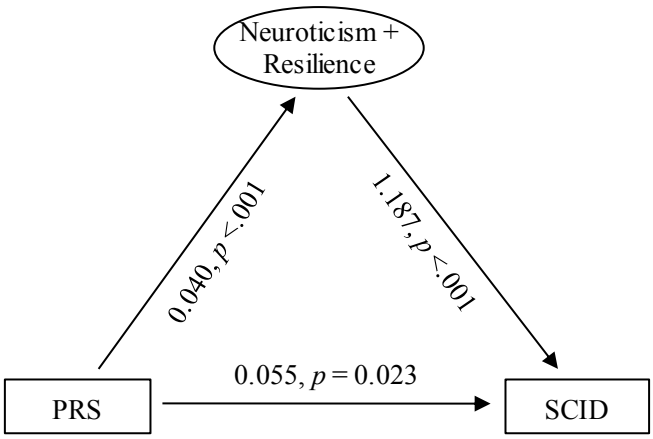

Figure B7. Path diagram of **Model 1D**, which includes a direct path between PRS and clinical MDD status, and an indirect path through the latent variable (Neuroticism+Resilience). Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured
Abbreviations: PRS, Polygenic Risk Score; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD;MDD, Major Depressive Disorder; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale

Table B13. Results of all standardised path coefficients and factor loadings from **Model 1D** examining the mediation of a latent variable Neuroticism+Resilience through PRS to clinical MDD status

Model description		ß	S.E	*p* value
SCID ~	PRS	0.055	0.024	0.023
SCID ~	Neuroticism+Resilience	1.187	0.108	< 0.001
SCID ~	Sex	0.184	0.052	< 0.001
SCID ~	Age_{t1}	-0.371	0.203	0.067
SCID ~	C1	-0.004	0.024	0.856
SCID ~	C2	-0.008	0.025	0.748
SCID ~	C3	-0.024	0.025	0.341
SCID ~	C4	0.023	0.024	0.351
Neuroticism+Resilience ~	PRS	0.040	0.005	< 0.001
Neuroticism+Resilience ~	Sex	0.091	0.010	< 0.001
Neuroticism+Resilience ~	Age_{t1}	-0.068	0.026	0.008
Neuroticism+Resilience ~	Age_{t2}	0.042	0.025	0.093
Neuroticism+Resilience ~	C1	0.005	0.003	0.120
Neuroticism+Resilience ~	C2	0.005	0.003	0.073
Neuroticism+Resilience ~	C3	-0.012	0.003	< 0.001
Neuroticism+Resilience ~	C4	0.008	0.003	0.009
Neuroticism+Resilience =~	EPQ1	1.000		
Neuroticism+Resilience =~	EPQ3	1.030	0.108	< 0.001
Neuroticism+Resilience =~	EPQ5	0.537	0.059	< 0.001
Neuroticism+Resilience =~	EPQ7	0.838	0.110	0.002
Neuroticism+Resilience =~	EPQ9	1.042	0.118	< 0.001
Neuroticism+Resilience =~	EPQ11	0.902	0.098	< 0.001
Neuroticism+Resilience =~	EPQ13	1.208	0.218	< 0.001
Neuroticism+Resilience =~	EPQ15	0.776	0.218	< 0.001
Neuroticism+Resilience =~	EPQ17	0.860	0.130	< 0.001
Neuroticism+Resilience =~	EPQ19	0.852	0.089	< 0.001
Neuroticism+Resilience =~	EPQ21	0.731	0.073	< 0.001
Neuroticism+Resilience =~	EPQ23	0.834	0.086	< 0.001
Neuroticism+Resilience =~	BRS1	-1.939	0.173	< 0.001
Neuroticism+Resilience =~	BRS2	-1.707	0.152	0.001
Neuroticism+Resilience =~	BRS3	-1.834	0.164	0.001

Neuroticism+Resilience =~	BRS4	-1.868	0.167	0.001
Neuroticism+Resilience =~	BRS5	-1.886	0.168	0.001
Neuroticism+Resilience =~	BRS6	-1.956	0.174	0.001

Abbreviations: Structured Clinical Interview for DSM-IV Axis I Disorders, representing clinical MDD ; PRS, Polygenic Risk Score; $Age_{t1,}$ Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience

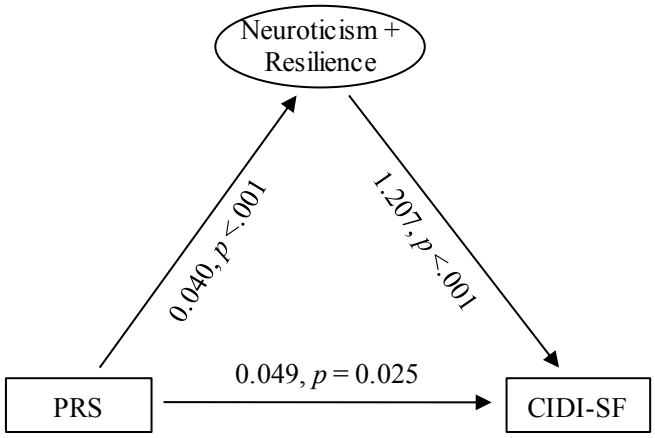

Figure B8. Path diagram of **Model 2D**, which includes a direct path between PRS and self-reported MDD status, and an indirect path through the latent variable (Neuroticism+Resilience). Values are standardised path coefficients. All endogenous variables have been adjusted for population stratification, sex and the age at which the variable was measured
Abbreviations: PRS, Polygenic Risk Score; Composite International Diagnostic Interview – Short Form, representing self-reported MDD;MDD, Major Depressive Disorder; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale

Table B14. Results of all standardised path coefficients and factor loadings from **Model 2D** examining the mediation of a latent variable Neuroticism+Resilience through PRS to self-reported MDD status

Model description		ß	S.E	*p* value
CIDI-SF ~	PRS	0.049	0.022	0.025
CIDI-SF ~	Neuroticism+Resilience	1.207	0.109	< 0.001
CIDI-SF ~	Sex	0.280	0.047	< 0.001
CIDI-SF ~	Age_{t2}	-0.071	0.190	0.708
CIDI-SF ~	C1	0.037	0.024	0.126
CIDI-SF ~	C2	-0.007	0.022	0.752
CIDI-SF ~	C3	-0.027	0.022	0.230
CIDI-SF ~	C4	0.012	0.022	0.569
Neuroticism+Resilience ~	PRS	0.040	0.005	< 0.001
Neuroticism+Resilience ~	Sex	0.090	0.010	< 0.001
Neuroticism+Resilience ~	Age_{t1}	-0.067	0.025	0.009
Neuroticism+Resilience ~	Age_{t2}	0.034	0.025	0.167
Neuroticism+Resilience ~	C1	0.005	0.003	0.116
Neuroticism+Resilience ~	C2	0.005	0.003	0.071
Neuroticism+Resilience ~	C3	-0.012	0.003	< 0.001
Neuroticism+Resilience ~	C4	0.008	0.003	0.010
Neuroticism+Resilience =~	EPQ1	1.000		
Neuroticism+Resilience =~	EPQ3	1.032	0.108	< 0.001
Neuroticism+Resilience =~	EPQ5	0.531	0.059	< 0.001
Neuroticism+Resilience =~	EPQ7	0.816	0.107	< 0.001

Neuroticism+Resilience =~	EPQ9	1.045	0.119	< 0.001
Neuroticism+Resilience =~	EPQ11	0.888	0.097	< 0.001
Neuroticism+Resilience =~	EPQ13	1.187	0.216	< 0.001
Neuroticism+Resilience =~	EPQ15	0.766	0.080	< 0.001
Neuroticism+Resilience =~	EPQ17	0.851	0.128	< 0.001
Neuroticism+Resilience =~	EPQ19	0.846	0.088	< 0.001
Neuroticism+Resilience =~	EPQ21	0.733	0.074	< 0.001
Neuroticism+Resilience =~	EPQ23	0.834	0.086	< 0.001
Neuroticism+Resilience =~	BRS1	-1.959	0.174	0.001
Neuroticism+Resilience =~	BRS2	-1.724	0.154	0.001
Neuroticism+Resilience =~	BRS3	-1.858	0.166	0.001
Neuroticism+Resilience =~	BRS4	-1.887	0.168	0.001
Neuroticism+Resilience =~	BRS5	-1.904	0.170	0.001
Neuroticism+Resilience =~	BRS6	-1.975	0.176	0.001

Abbreviations: Composite International Diagnostic Interview – Short Form, representing self-reported MDD; PRS, Polygenic Risk Score; $Age_{t1,}$ Age at baseline; Age_{t2}, Age at re-contact; C1-4, the principal components which control for population stratification; Neuroticism+Resilience, a latent factor comprised of the individual items from the Eysenck Personality Questionnaire Short Form-Revised and the individual items from the Brief Resilience Scale

Appendix C

Supplementary material from Chapter 6

Table C1 Descriptive data from the individuals in this sample

Table C2 Age-, sex-, and population stratification-adjusted univariate GCTA estimates of narrow-sense heritability

Table C3 Number of non-zero off diagonal entries in the lower triangular part of all variance component matrices

Table C4 Age-, sex-, and population stratification-adjusted variance component analysis results for Resilience, ToC, EoC, and AoC

Table C5 Matrix displaying the genetic correlations (r_G) between Resilience, emotion-oriented coping and neuroticism

Descriptive statistics of the current cohort

Table C1. Descriptive data from the individuals in this sample (n = 8,734)

Variable	n	Mean (SD)	n (%)	Median	Range
Age	8734	56.36 (13.15)		59	22 – 100
Sex (Female)	8734		5,403 (62)		
Resilience	8557	3.56 (0.80)		3.67	1- 5
ToC	8172	54.38 (12.21)		56	16 – 80
EoC	8308	37.62 (12.55)		37	16 – 80
AoC	8250	39.43 (10.49)		40	16 – 80
Neuroticism	8004	3.55 (3.11)		3	0 – 12

Abbreviations: ToC, Task-oriented coping; EoC, Emotion- oriented coping; AoC, Avoidance-oriented coping

Narrow-sense heritability estimates for the four traits examined

Table C2. Age-, sex-, and population stratification[a]-adjusted univariate GCTA estimates of narrow-sense heritability

	n	V_G	V_K	V_e	V_p	V_G/V_P	V_K/V_P	h_n^2
Resilience	8555	0.05 (0.03)	0.04 (0.03)	0.54 (0.02)	0.63 (0.01)	**0.08 (0.04)**	0.06 (0.05)	**0.14 (0.09)**
ToC	8170	17.26 (6.74)	18.56 (8.32)	112.27 (5.21)	148.08 (2.34)	**0.12 (0.05)**	**0.13 (0.06)**	**0.24 (0.10)**
EoC	8306	19.84 (6.46)	14.41 (7.98)	110.45 (5.04)	144.69 (2.26)	**0.14 (0.04)**	**0.10 (0.06)**	**0.24 (0.10)**
AoC	8248	12.91 (4.26)	8.57 (5.31)	73.75 (3.33)	94.75 (1.49)	**0.14 (0.04)**	0.09 (0.06)	**0.23 (0.10)**

[a] first four principal components

Abbreviations: ToC, Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented coping; V_G, variance associated with additive genetic effect from common variants, V_K, variance associated with the pedigree; V_e, residual variance, V_p, phenotypic variance, V_G/V_P, ratio of additive genetic effect from common variants to phenotypic variance; V_K/V_P, ratio of pedigree variances to phenotypic variance; h_n^2, narrow-sense heritability

N.B. text in **bold** indicates LRT $p< 0.05$ (one-tailed). Values in parentheses represent standard error

Construction of Genetic Relationship Matrices (GRMs)

Two GRMs were fitted using the method created by Zaitlen et al (2013). The first GRM comprised of pairwise relationship coefficients of all individuals in the sample. The second GRM included off-diagonal elements of pairs of individuals who has a relationship coefficient < 0.05 set to 0. Assuming inbreeding had not taken place, the second GRM excluded pairs of individuals with a most recent common ancestor of approximately four generations distant. This method has been found to account for potential upward biases due to excessive relationships which allows for the inclusion of closely and distantly related individuals in genetic analyses

Constructing variation-covariance matrices representing different source of variation

G: Genomic relationship matrix: The genetic relationships between individuals were calculated in GCTA using the following formula:

$$Ajk = \frac{1}{N}\sum_{i=1}^{N} \frac{(xij - 2pi)(xik - 2pi)}{2pi(1 - pi)}$$

Yang et al. (2011)

in which i represents a SNP, x is the allele count of the minor allele for individual j or k at i. p_i is the minor allele frequency of SNP i , and N is the total number of SNPs. This matrix was created in GCTA.

K: Kinship relationship matrix: K was calculated by the modification of the G matrix. Relationship co-efficient values less than or equal to 0.05 in the G matrix were set to 0, as this threshold separates closely and distantly related individuals (Zaitlen et al, 2013).

F,S,C: Environmental relationship matrices: To represent different shared environmental effects, familial relationship matrices were designed. Each was created by making an N x N matrix in which all entries were set to 0 and all diagonal entries set to 1. Off-diagonal entries, too, were set to 1 if two families shared the environment of interest. A total of three environmental relationship matrices were created; **F** represents the shared environment of a nuclear family living within the same household, **S** represents the sibling environment, and **C** represents the couple environment.

Estimating the phenotypic variance explained by different source of variation.

The genomic and environment relationship matrices described above were selectively jointly fitted in a Linear Mixed Model (LMM) implemented in GCTA. The models analyzed included all fixed effects and subsets of random effects in the full model:

$$\boldsymbol{Y = Xb + g_g + g_{kin} + e_f + e_s + e_c + \varepsilon}$$

In which Y is a phenotype vector, *b* is a vector of covariates fitted as fixed effects (age, sex, and four principal components derived from the genome-wide genomic relationship matrix). g_g and $g_{kin}$are random genetic effects from SNPs and the extra random genetic effect from the pedigree, respectively. e_f, e_s, e_c represent random environmental effects shared by nuclear family members, full-siblings and couples, respectively. For simplicity, the following codes were used to represent the matrices fitted: for example, ***_GKFSC***‘ was the full model fitting all five matrices as random effects simultaneously, whereas ***_GFC***‘ represents a model in which the genomic relationship matrix, nuclear family and couple environment matrices were simultaneously fitted. The proportion of variance explained by individual component was estimated using REML and tested using Log-likelihood Ratio Test (LRT) in GCTA.

Number of non-zero off diagonal entries for each trait

Table C3. Number of non-zero off diagonal entries in the lower triangular part of all variance component matrices

Matrix	Number of non-zero off diagonal entries				
	Full sample	Resilience	ToC	EoC	AoC
K - pedigree associated genetics	6,015	5,810	5,314	5,501	5,439
F – nuclear family	4,508	4,340	3,982	4,115	4,057
C – couple	655	633	574	588	1,753
S –sibling	1,925	1,863	1,733	1,774	574

Abbreviations: ToC; Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented Coping
N.B**.** As all entries in the G (common-variant associated genetics) matrix are non-zero this matrix is not presented here

Variance component analysis

Table C4. Age-, sex-, and population stratification[a]-adjusted variance component analysis results for Resilience, ToC, EoC, and AoC

Variable	n	Model	h_g^2 (SE)	h_k^2(SE)	e_f^2(SE)	e_s^2(SE)	e_c^2 (SE)
Resilience	8,555	GK	**0.08 (0.04)**	0.06 (0.05)			
		GKFSC	0.06 (0.04)	0.00 (0.12)	0.05 (0.06)	0.00 (0.03)	0.01 (0.07)
		GFSC	**0.07 (0.04)**		0.05 (0.03)	0.00 (0.03)	0.02 (0.05)
		GFC	**0.07 (0.04)**		0.04 (0.03)		0.04 (0.05)
		GF	**0.06 (0.04)**		**0.05 (0.02)**		
ToC	8,170	GK	**0.12 (0.05)**	**0.13 (0.06)**			
		GKFSC	**0.11 (0.05)**	0.02 (0.13)	0.03 (0.06)	**0.08 (0.04)**	**0.16 (0.07)**
		GFSC	**0.12 (0.04)**		0.03 (0.03)	**0.08 (0.04)**	**0.15 (0.05)**
		GSC	**0.14 (0.03)**			**0.10 (0.03)**	**0.18 (0.04)**
EoC	8,306	GK	**0.14 (0.04)**	**0.10 (0.06)**			
		GKFSC	**0.14 (0.04)**	0.03 (0.12)	0.04 (0.06)	0.00 (0.03)	**0.14 (0.07)**
		GFSC	**0.14 (0.04)**		**0.06 (0.03)**	0.00 (0.03)	**0.13 (0.05)**
		GFC	**0.15 (0.04)**		**0.05 (0.03)**		**0.14 (0.05)**
AoC	8,248	GK	**0.14 (0.04)**	0.09 (0.06)			
		GKFSC	**0.12 (0.04)**	0.00 (0.13)	0.03 (0.06)	**0.05 (0.03)**	**0.14 (0.07)**
		GFSC	**0.13 (.04)**		0.03 (0.03)	**0.06 (0.03)**	**0.15 (0.05)**
		GSC	**0.15 (0.03)**			**0.07 (0.03)**	**0.18 (0.04)**

[a] first four principal components
Abbreviations: ToC; Task-oriented Coping; EoC, Emotion-oriented Coping; AoC, Avoidance-oriented Coping; h_g^2, common variants -associated genetic effect; h_k^2, pedigree associated genetic effect; e_f^2, nuclear family environmental effect; e_s^2, full sibling environmental effect; e_c^2, couple environmental effect
N.B. Backward stepwise selection was used to select the most parsimonious model for each trait
Text in **bold** indicates LRT $p < 0.05$ (one-tailed)

Appendix D

List of publications

First author

Navrady, LB., Zeng, Y., Clarke, T-K., Adams, MJ., Howard, DM., Deary, IJ., McIntosh, AMM. Genetic and environmental contributions to psychological resilience and coping. Accepted by *Wellcome Open Research* (awaiting review).

Navrady, LB., Adams, MJ., Chan, SWY., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Ritchie, SJ., McIntosh, AM. (2017). Genetic risk of Major Depressive Disorder: the moderating and mediating effects of neuroticism and psychological resilience on clinical and self-reported depression. *Psychological Medicine*, doi: 10.1017/S0033291717003415.

Navrady, LB., Wolters, MK., MacIntyre, DJ., Clarke, T-K., Campbell, AI., Murray, AD., Evans, KL., Seckl, J., Haley, C., Milburn, KK., Wardlaw, JM., Porteous, DJ., Deary, IJ., McIntosh, AM. (2017). Cohort Profile: Stratifying Resilience and Depression Longitudinally (STRADL): A questionnaire follow-up of the Generation Scotland: Scottish Family Health Study (GS:SFHS). *International Journal of Epidemiology*: dyx115.

Navrady, LB., Ritchie, SJ., Chan, SWY., Kerr, D., Adams, MJ., Hawkins, E., Porteous, D., Deary, IJ., Gale, CR., Batty, GD., McIntosh, AM. (2017). Intelligence and neuroticism in relation to depression and psychological distress: Evidence from two large population cohorts. *European Psychiatry*, 43, 58- 65.

Co-author

Wigmore EM, **Navrady** LB, Hafferty JF, Clarke T-K, Campbell A, Thomson PA, Porteous DJ, Nicodemus KK, Deary IJ, McIntosh AM. Antidepressant treatment resistance and the impact of neuroticism, psychological resilience and coping style. *In submission*.

Wigmore EM, Hafferty JD, Hall LS, Howard DM, Clarke T-K, Fabbri C, Lewis CM, Uher R, **Navrady** LB, Adams MJ, Zeng Y, Campbell A, Gibson J, Thomson PA, Hayward C, Smith BH, Hocking DJ, Mors O, Mattheisen M, Nicodemus KK, McIntosh AM. Genome-wide association study of antidepressant treatment resistance in a population-based cohort using health service prescription data and metaanalysis with GENDEP. *In submission*.

Clarke T-K, Zeng Y, **Navrady** LB, Xia C, Haley C, Campbell A, Navarro P, Amador C, Adams MJ, Howard DM, Hayward C, Thomson PA, Soler AA, Smith BH, Padmanabhan S, Hocking LJ, Hall LS, Porteous DJ, Deary IJ, McIntosh AM. Genetic and environmental determinants of stressful life events and their overlap with depression and neuroticism. Accepted by *Wellcome Open Research* (awaiting review).

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Schweizer S, **Navrady L,** Breakwell L, Howard R, Golden A-M, Werner-Seidler A, Dalgleish T. (2017). Affective Enhancement of Working Memory is Maintained in Depression. *Emotion,* doi: 10.1037/emo0000306.

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interactive effect of gender and moral orientation on altruistic choice. *Social Psychology and Personality Science,* 7, 542-551.

Dalgleish T, **Navrady L**, Bird E, Dunn BD, Golden A-M. (2013). Method-of-loci as a mnemonic device to facilitate access to self-affirming personal memories for individuals with depression. *Clinical Psychological Science,* 1, 156-162.

FeldmanHall O, Mobbs D, Evans D, Hiscox L, **Navrady L**, Dalgleish. (2012). What we say and what we do: The relationship between real and hypothetical moral choices. *Cognition,* 123, 434-441.