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The medium-term course and outcome of Major Depressive Disorder in a youth-aged clinical sample

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Centre for Youth Mental Health
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne

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My girlfriend Katherine, my family and friends

Abstract

Background

Youth (age 15-25) with Major Depressive Disorder (MDD) who present for treatment have a complex range of psychopathology, and multiple areas of functional impairment. The medium-term outcome of this group, over the transition to adulthood, is yet to be prospectively studied.

Prospective studies enable the identification of baseline predictors of poor outcome that can then be targets of future interventions. In prospective studies of clinical samples of adults with MDD, personality disorders and high levels of neuroticism are among the most consistent predictors of poor outcome.

Objectives

This study aimed to describe the medium-term symptomatic and functional course of a clinical sample of youth with MDD. It also aimed to investigate the predictors of the course of MDD, with a focus on personality variables, particularly borderline personality disorder (BPD) pathology and neuroticism. BPD pathology was of specific interest due to its high prevalence in clinical populations of young people, and its established association with functional impairment.

It was hypothesised that dimensional measures of BPD pathology and neuroticism would be independent predictors of the symptomatic and functional course of MDD of the study sample.

Methods

The study followed-up 90 young people who had received treatment for MDD at a specialist psychiatric outpatient service, after an interval of between 6 and 15 years (mean=9.4 years).

At baseline, a detailed assessment of psychopathology and personality had been performed, using the SCID-I, SCID-II and NEO-PI.

The longitudinal symptomatic course of the sample was charted with the Longitudinal Interval Follow-up Evaluation (LIFE). Longitudinal functioning was assessed with the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT), and the Social Adjustment Scale (SAS-SR) was used to measure functioning at follow-up.

The SCID-I was repeated at follow-up to assess mental state disorders over the follow-up period. Both the SCID-II and the NEO-PI were also repeated at follow-up to determine the degree of change in personality and personality pathology

Results

Results indicated that participants experienced a significant symptomatic and functional burden over the medium-term. The mean time to recovery of the presenting Major Depressive Episode (MDE) was 32 months. The study participants were found to be in an MDE for a mean of 42 percent of the follow-up period, this high proportion contributed to by a recurrence rate of 76 percent after recovery from the presenting MDE. 81 percent of the sample also experienced a mental state disorder other than an MDE during the follow-up period.

The mean annual level of functioning of the sample was in the mild impairment range, with Interpersonal Relations the LIFE-RIFT domain recording the greatest impairment. At follow-up, average functioning was in the mildly atypical range.

Both BPD pathology ($r_s=0.25$, $p=0.03$) and neuroticism ($r=0.23$, $p=0.02$) were found to be predictive of the time to recovery of the presenting MDE, and BPD pathology was also predictive of mean annual functioning ($r_s=0.24$, $p=0.03$) over the follow-up period. Neither though were retained as significant predictors in multiple predictor regression analyses.

In regression analyses, a co-occurring anxiety disorder at baseline and baseline functioning (measured by the SOFAS) were the most consistent predictors of the course outcomes. Both of these variables predicted the time to recovery of the presenting MDE (Anxiety disorder $\beta =0.25$, $p=0.03$; SOFAS $\beta =-0.24$, $p=0.03$) and the cumulative duration of time in an MDE over the follow-up period (Anxiety $\beta =0.21$, $p=0.04$; SOFAS $\beta =-0.36$, $p=0.001$). The baseline SOFAS also predicted the overall longitudinal functioning of the sample (LIFE-RIFT mean annual total score) ($\beta =-0.43$, $p=0.002$) and overall functioning at follow-up (SAS-SR overall mean) ($\beta =-0.28$, $p=0.03$). A co-occurring anxiety disorder predicted the Interpersonal Relations domain of the LIFE-RIFT ($\beta =0.30$, $p=0.004$).

Other significant baseline predictors in the multiple predictor analyses were a personality disorder and having had a previous MDE at baseline, Both were predictive of the LIFE-RIFT mean annual total score (Personality disorder $\beta =0.28$, $p=0.02$; Previous MDE $\beta =0.29$, $p=0.02$). Baseline Cluster A personality pathology predicted the overall mean of the SAS-SR at follow-up ($\beta =0.26$, $p=0.04$).

Conclusions

This study describes the significant and enduring symptomatic and functional burden experienced by a clinical sample of youth with MDD over the course of the transition to adulthood. The symptomatic burden consisted of both MDD and a high prevalence of other mental state disorders.

This study identified both functional impairment, and the presence of a co-occurring anxiety disorder at presentation as independently contributing to the symptomatic and functional burden of MDD. Personality pathology in the form of personality disorder or Cluster A pathology independently contributed to the functional burden, as did having had a previous MDE at presentation.

The findings in regard to the course of MDD indicate the need to take a longitudinal perspective in planning for treatment for this population. This would aim to ensure timely and appropriate intervention for recurrent episodes, and for the frequently co-occurring mental state disorders.

In its findings on predictors of course, this study presents a diversity of influential factors. Ideally, these factors would be able to be addressed in an integrated treatment program. Such a program would have the potential to lead to much improved longitudinal outcomes.

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Chapter 1 Thesis overview

Title

“The medium-term course and outcome of Major Depressive Disorder in a youth-aged clinical sample”

1.1 Introduction

This study is of a clinical sample of young people with Major Depressive Disorder (MDD) aged 15 to 24 at baseline followed-up after a period of 5 to 15 years. This study follows a sample of youth over the period of transition to adulthood (Arnett JJ, Zukauskienė, R, & Sugimura, K, 2014).

A youth-age sample brings together two age groups, 15 to 18 year olds and 19 to 24 year olds, which have historically been considered separately in MDD research. Both age groups are significant as they represent the peak periods of onset of the disorder (Hankin et al., 1998; Kessler & Walters, 1998; Newman et al., 1996). Thus far, specific attention to the older age group has been restricted due to it being included in the broad 18 to 65 year age range of adult studies (Buckman et al., 2018).

There has been a movement, particularly in Australia to bring these age groups together in clinical services. A particular spur to this movement is the fact that 75% of mental illnesses have their onset before the age of 25 (Kessler et al., 2005), meaning that the potential benefits of early intervention continue at least to this age (Fusar-Poli 2019). A concern of practitioners has been that having the younger portion of the range receiving treatment from child and adolescent services and the older portion from adult services has meant that youth have not received the treatment that is best suited to them (McGorry & Mei, 2018).

Following up a youth age cohort with MDD provides an opportunity to gain information on the illness course of this group which could then inform the development of treatment in services that are becoming more oriented towards youth.

The study of clinical samples of children and adolescents, the grouping in existing research closest developmentally to youth, demonstrates a significant burden from MDD. The contributors to this burden include mean MDD episode lengths of between 6

and 18 months (Birmaher, Arbelaez, & Brent, 2002), rates of between 44% and 93% of the young people in these samples experiencing co-occurring illnesses such as anxiety and personality disorders (Goodyer, Park, & Herbert, 2001; Karlsson et al., 2008; Rao, Hammen, & Poland, 2010), and mean scores on functioning scales indicating severe impairment in relationship, educational or recreational functioning (Brent et al., 2008; Peters et al., 2015; Rao et al., 1995).

After recovery from a presenting episode, rates of recurrence are high, increasing over time from around 30% at 2 years to 40 to 75% at 5 years (Kennard, Emslie, Mayes, & Hughes, 2006).

One might expect similar experiences for youth but due to the current absence of samples of this age group in the literature, the nature of any similarities or differences is unknown.

The goal of treatment for an MDE is to reduce its burden, across both symptoms and functioning, and ideally to also reduce the risk of further episodes. A step towards treating these components of the disorder is to understand the factors that contribute to them.

A longitudinal study of MDD provides an opportunity to investigate which factors contribute to the severity of its course. Personality, in manifestations as “normal” traits or as personality disorder, has been nominated to be an important influence on both the development and the course of MDD (Klein, Kotov, & Bufferd, 2011; Tyrer 2015).

An interest in the effect of personality on the course of MDD also came from the student researcher’s role as a clinician working with youth with the disorder. It seemed that aspects of patient’s presentations that might be related to personality, particularly the presence of strong negative beliefs about oneself and having difficulties with achieving satisfying relationships, made it difficult to progress in treatment.

It was also considered to be important to include the exploration of functioning and its predictors as a component of this study. There has been a growth in the mental health field of the recognition of the importance of considering functional as well as symptomatic outcomes (Langlieb & Guico-Pabia, 2010; Ro & Clark, 2009). There are multiple reasons for this change. Firstly, functional outcomes are potentially as meaningful or more so than symptomatic outcomes for people with mental health disorders (Figueira & Brissos, 2011). It is also likely that attention to functional recovery enhances symptomatic recovery in MDD (Langlieb & Guico-Pabia, 2010). In addition, a limited functional recovery even with symptomatic recovery indicates a less than optimal quality of life, which might act as a risk factor for future episodes of illness.

To summarise, in following a youth age cohort this study seeks to fill a gap in the current profile of age groups whose longitudinal course of MDD has been explored. It aims to add to the broadening of the types of outcomes that are measured in MDD by including a detailed assessment of functional course. The study will also explore a range of potential predictors of MDD course in order to identify factors that influence its outcome, with a particular focus on personality variables. These predictive factors might be modifiable by treatment, leading to more positive outcomes for young people with MDD.

1.2 Organisation of the thesis

The main focus of Chapter 2 is a review of studies of clinical samples of adolescents with MDD that have been followed longitudinally, generating data on the course of illness and functioning. Participants in these studies provide the closest reference point developmentally for those in the youth age range.

In Chapter 2, the rates of incidence of MDD across age groups are also described to demonstrate the pattern of the illness over the life course. There is also a brief review of longitudinally-studied clinical samples of adults with MDD as a further point of reference and comparison for the study sample.

This chapter includes a discussion of the classification of MDD, and of the current understanding of its relationship with other mental state disorders. Youth with MDD often experience other disorders simultaneously with an episode of the disorder or at other points in their lifetime.

Current conceptualisations of personality and personality disorder, and the evolution of both over the lifespan are described in Chapter 3. This chapter then explores the nature of the relationship of personality factors with MDD prior to the onset of the disorder, during and between episodes.

Chapter 4 provides an overview of the aetiology of MDD in young people. Though an exploration of aetiology was not part of this study, the factors and processes involved in the development of the disorder are the foundations from which the course of the disorder emerges and as such are important elements in understanding its course.

Chapter 5 reviews the study of predictors of MDD course. It initially returns to the longitudinal studies of samples of adolescents with MDD from Chapter 2 to describe their findings on predictive factors. As with Chapter 2, there is also an overview of findings from relevant adult studies. The results of the adult studies provide both a

comparison to the findings in young people, and a potential confirmation of the importance of the factors they find to be predictive.

The existing literature and the gaps identified in it are distilled in the aims and hypotheses of this study contained in Chapter 6.

Chapter 7 details the study methodology. This study draws eligible participants from one treatment sample and two observational studies. The baseline assessment of these samples forms the baseline of this study. Instruments administered at baseline and follow-up are described, as well as the recruitment protocol for the current study and its designated outcomes.

The key sections of Chapter 8 report data on the symptomatic and functional course of MDD for the study sample, and present the analysis of the predictors of these outcomes. This analysis includes univariate and multiple predictor tests.

Supplementing these key sections is data on the incidence of mental state disorders other than MDD over the follow-up period, and on the change in personality and personality disorder variables from baseline to follow-up.

The two other sections of the results chapter are descriptions of the sample at baseline and of the recruitment process. Detailed baseline assessments of the sample provide a description of the study participants and this information is summarised to describe the characteristics of this clinical sample of youth with MDD.

A discussion then follows, as Chapter 9.

Definitions

The diagnostic terms used in this thesis will as defined by the Diagnostic and Statistical Manual IV (DSM-IV) of the American Psychiatric Association (American Psychiatric Association Task Force on DSM-IV 1994a).

Major Depressive Disorder (MDD)

This is the psychiatric condition defined by the occurrence of at least one Major Depressive Episode (MDE).

Age definitions

This thesis will use the age boundaries for these terms adopted by the World Health Organization (WHO 2005).

- Childhood-birth to 9 years
- Adolescence-10 to 19 years of age
- Youth-15 to 24 years

Where studies use alternate definitions, these will be specified. The term “young people” is used for those who fit into any of these categories.

The term Emerging Adulthood is used to refer to people 18 to 29 years of age (Arnett JJ et al., 2014)

Chapter 2 The course of Major Depressive Disorder in clinical samples of young people

2.1 Introduction

This chapter begins with a brief overview of the history of the classification of MDD in children and adolescents, including a description of the developments in the quantitative nosology of the disorder.

Following this, studies of the prevalence and incidence of MDD in children and adolescents, youth and in emerging adults are summarised to provide the broader population context from which the participants in the study sample come.

The bulk of the chapter describes existing research about illness course and psychosocial functioning in clinical samples of adolescents with MDD. This aims to provide a comprehensive summary of existing research of the longitudinal course of the disorder in treatment-seeking young people of a similar age to the participants in the study, to serve as a comparison for the data obtained in this study, and to identify particular areas where further knowledge might be of benefit.

At points throughout the chapter, summary epidemiological data on adult samples are also described to illustrate the characteristics of MDD across the life-course. It also is a further point of reference for the data obtained in the study sample.

2.2 Classification of Major Depressive Disorder in young people

2.2.1 Categorical diagnostic systems

As recently as the 1970s MDD was not considered to be a diagnosis of relevance to children and adolescents (Goldman, S 2012; Kessler, Avenevoli, & Ries Merikangas, 2001; Kovacs 1997). There was a school of thought that mood disturbances were “normative and self-limiting” in this age group (Kessler et al., 2001). The assertion of the influential American psychologist, G. Stanley Hall (1846-1924) that adolescence was inherently a time of “storm and stress” is indicative of the prevailing thinking of the time (Arnett 1999).

From the late 1970s, researchers began to apply the newly developed Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) for adult MDD to children and adolescents. Some held concerns about both the scientific rigour of the process of development of the adult criteria (Kendler, Muñoz, & Murphy, 2010) and also the focus

of field trials on demonstrating the reliability of the criteria rather than testing their validity (Kirk SA, Kutchins H 1992).

Nevertheless, in clinical samples of young people, evidence was found that depressive symptomatology clustered in a manner similar to how it was described in adults (Kovacs, M & Paulauskas, SL, 1984; Roberts, Lewinsohn, & Seeley, 1995; Ryan et al., 1987), and a high level ($\kappa=0.75$) of inter-rater reliability was demonstrated for the diagnosis of MDD (Strober, Green, & Carlson, 1981).

The diagnostic criteria for MDD from the Research Diagnostic Criteria were adopted by the third edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-III) (American Psychiatric Association Task Force on Nomenclature and Statistics 1980).

The exception to their complete adoption was for the DSM-III to have a two week period as opposed to a four week period of symptoms to meet the diagnostic threshold. The sole difference between the specific diagnostic criteria for children and adolescents in DSM was that the mood criterion also allowed a predominantly irritable mood, not only a depressed mood.

The criteria for a Depressive Episode of the International Classification of Diseases (World Health Organization 2004), the other major classificatory system, largely mirror those of the DSM, and the same set of symptoms apply to all ages. One distinction is that the ICD requires two of its designated core symptoms of depressed mood, anhedonia or decreased energy/increased fatigue to be present for diagnosis. A consequence of this is that the DSM is more inclusive, this demonstrated by a Danish study of a clinical sample of children in which only 75% of those meeting DSM-IV criteria for a Major Depressive Episode also met ICD-10 criteria for a Depressive Episode (Sørensen, Mors, & Thomsen, 2005).

2.2.2 Quantitative nosology of psychopathology

The last two decades have seen a rapid development in quantitative nosology in psychiatry through the use of factor analytic techniques. The most extensive area of this analysis has been an exploration of the relationships between the different common mental state disorders (Krueger 1999b; Vollebergh et al., 2001). This work has more recently integrated manic and psychotic experiences, and both personality disorders and personality traits (Kotov et al., 2017).

In the earliest factor-analytic models, initially developed from child and adolescent populations, two factors, an internalising and an externalising dimension were demonstrated (Achenbach & Edelbrock, 1981). This structure has been demonstrated

in children and adolescents, and in adults (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017).

Further analyses in adults divided the internalising dimension into a fear sub-factor, containing the phobic disorders, and a distress sub-factor containing Major Depressive Disorder, Dysthymic Disorder and Generalised Anxiety Disorder (Krueger & Markon, 2006).

In an analysis of correlations of lifetime comorbidities in a child and adolescent population sample, a four factor model emerged in which the internalising dimension split into fear and distress sub-factors, and the externalising dimension into behaviour and substance use disorder sub-factors (Kessler et al., 2012).

Researchers have subsequently included less common disorders in their analyses to explore relationships across the broad range of psychopathology (Andrews et al., 2009; Kotov et al., 2017; Wright et al., 2013).

The HiTOPS consortium of researchers included mental state disorders, personality pathology and personality traits in their analysis (2017). The model developed from their analysis places six “spectra” which integrate these three psychological domains in a level in a hierarchy above sub-factors. At the sub-factor level, in addition to the fear and distress groupings, there are sexual problems, eating pathology and mania, and two externalising sub-factors of substance abuse and antisocial behaviour. Validation of this model remains in its early stages and is yet to include children and adolescents (Conway et al., 2019).

At the top of the HiTOPS hierarchy, above the spectra is a single general psychopathology factor, which has been given the designation of the *p* factor (Caspi & Moffitt, 2018). A significant influence on the development of the concept of the *p* factor was the strength of correlations observed between the higher order dimensions (2018). While most data have come from cross-sectional measurement, there has been some analysis of longitudinal associations. These have demonstrated the continuity of the both the internalising and externalising domains across childhood and adolescence, and of the externalising domain into adulthood (Lahey et al., 2017).

A particular research implication of the identification of these relationships has been for aetiological studies to begin to examine the associations of the higher-order dimensions with potential aetiological agents, with the anticipation that these associations might prove stronger than those found for individual disorders.

It might also be that incorporating the knowledge of higher-order dimensions will enhance the understanding of the course of disorders and their relationship with other disorders over time.

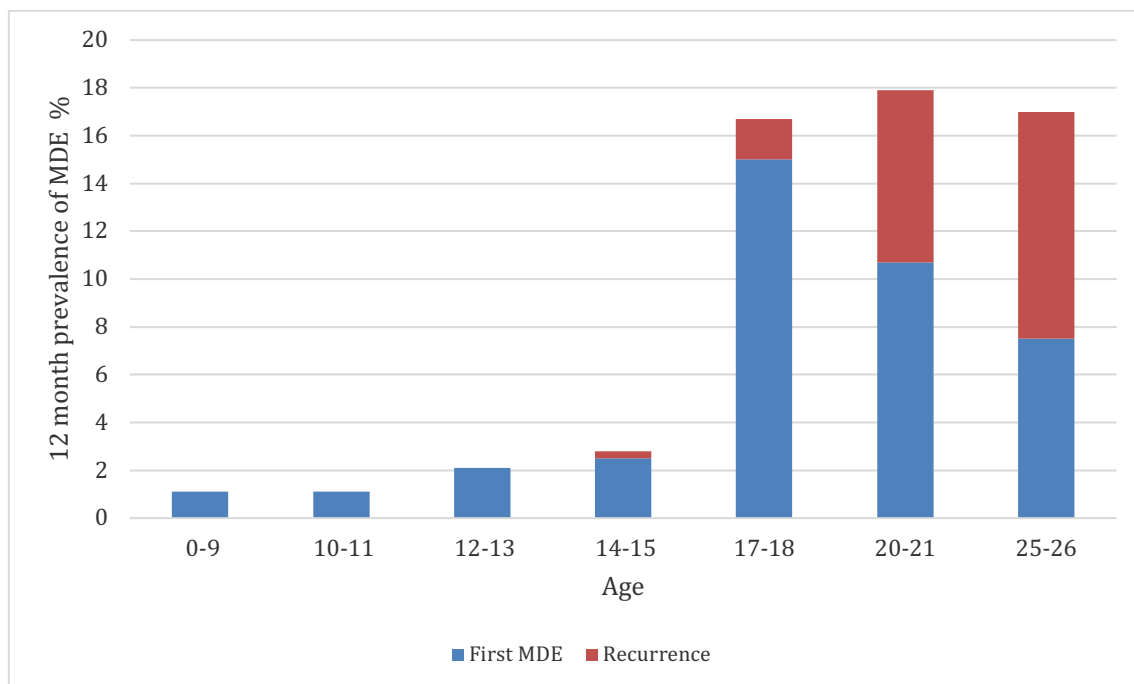
From a clinical perspective, an implication of the quantitative research should be to routinely perform a broader assessment for other dimensionally related pathology of an identified disorder (Hankin 2019). It also holds the promise of a potentially more powerful effect of treatment directed at a dimension, not only at a disorder (Conway et al., 2019) .

2.3 Rates of Major Depressive Disorder in young people

MDD has been found to affect 1% of children before the age of 9 (Kashani et al., 1983). The reported 12 month prevalence of the disorder slowly rises from 1% between ages 10 and 11 (Anderson, Williams, McGee, & Silva, 1987), to rates of 3-4% between age 14 and 15 (Fergusson, Horwood, & Lynskey, 1993; Hankin et al., 1998; McGee & Williams, 1988). There is then a dramatic rise in the 12 month prevalence to 9-13% between 15 and 16 years of age (Fergusson & Woodward, 2002; Kessler & Walters, 1998).

Figure 2.1 illustrates the changing incidence of MDD with age. It presents the 12 month rates for the first episode and recurrent episodes of Major Depressive Disorder in the birth cohort of the New Zealand-based Dunedin Multidisciplinary Health and Development Study. The peak 12 month period for MDD incidence (first episode) was between age 17 and 18, with a rate of 15% (Hankin et al., 1998).

Figure 2-1: 12 month period prevalence of MDE in Dunedin Multidisciplinary Health and Development Study



An overall 12 month prevalence of 15-20% continued up to the mid 20s, with recurrent episodes becoming more common than new onsets (Moffitt et al., 2007b; Newman et al., 1996). A USA-based representative population sample reported its peak 12 month prevalence rate for a Major Depressive Episode of 15.5% between ages 21 and 22 (Kessler & Walters, 1998).

These studies found a divergence in prevalence rates between genders occurring from age 14, peaking between 15 to 18 with girls having a rate 2-4 times that of boys, then gradually returning to close to gender parity in the mid 20s (Hankin et al., 1998; Kessler & Walters, 1998; Moffitt et al., 2007a).

Young people receiving treatment at a specialised mental health service represent a small sub-group of all young people reaching the diagnostic threshold for Major Depressive Disorder in the community.

In an Australian population survey, only 12% of males and 32% of females in the 16-24 year old age group with disorder-level mental health diagnoses had utilised health services for treatment (Slade, T, Johnston A, Teesson M, Whiteford H, Burgess P, Pirkis J, Saw S 2009). Of people of all ages who did receive treatment, only 22% received treatment in specialised settings (2009).

2.4 Longitudinal course of MDD in young people

2.4.1 Literature search strategy

The studies referred to in this section were obtained by a review of Medline and PsychINFO databases from 1978 to June 20th 2019 . This year 1978 was chosen as it was the year that the Research Diagnostic Criteria (Spitzer et al., 1978) were published, meaning that from that year diagnostic terms would have a higher degree of reliability.

The search term “Depressive Disorder” was chosen in preference to “Major Depressive Disorder” in order to capture papers using either DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Diseases) terminology.

“Depressive Disorder” is a MeSH (Medical Subject Heading) term in Medline, but is not a Subject Heading in PsychINFO. This term was linked (using the boolean term “AND”) with “adolescen*” (maps to MeSH term “Adolescent”) or “youth” or “young adult” (MeSH term) to focus on the age group of interest.

To narrow the search to studies of the course of MDD, the terms “course” , “follow-up studies”, “longitudinal studies” or “prospective studies” were added (again using the boolean term “AND”). The latter three terms are both MeSH and PsychINFO Subject Headings.

2.4.2 Inclusion of studies in the review

2.4.2.1 Source of sample

Certain qualitative differences have been found between young people with MDD who are in clinical samples and therefore have received treatment, and young people with MDD in samples which are drawn from the general community.

Studies in the UK and USA have investigated predictors of service usage specifically of young people with MDD (Dunn & Goodyer, 2006; Lewinsohn, Rohde, & Seeley, 1998; Wu et al., 2001). These studies all found that the degree of functional impairment experienced by young people with MDD was associated with service usage.

Other significant predictors of treatment-seeking were the severity of depressive symptoms (Lewinsohn et al., 1998; Wu et al., 2001), the number of previous episodes of depression (Lewinsohn et al., 1998), an earlier age of onset of depression (Dunn & Goodyer, 2006), the presence of co-occurring disorders (Lewinsohn et al., 1998; Wu et

al., 2001), and the history of a suicide attempt (Dunn & Goodyer, 2006; Lewinsohn et al., 1998).

These data indicate that young people with MDD receiving treatment are likely to have a more severe symptomatic presentation and greater functional impairment than those in community samples. As will be explored in detail in Chapter 5, these variables that distinguish clinical and community samples of young people with MDD have been found to affect its course.

The purpose of this chapter is to describe the existing knowledge on the course of MDD in samples similar to the study sample, and therefore it was clinical samples that were selected from the literature search to be the focus of this review.

There are sections throughout this thesis in which the results of studies of prospectively-followed community samples are used to supplement those of the clinical samples. This is done where limited information on a particular subject is available from the clinical samples. Given the differences between community and clinical samples described above, it is not assumed that the findings of either type is completely applicable to the other.

These community samples were not chosen on the basis of a systematic process, rather on their prominence in the literature and their investigation of topics of interest. A requirement of their inclusion was that diagnostic assessments were performed with validated semi-structured or structured instruments. A table presenting the characteristics of these samples, and summary of the assessments performed can be found in Appendix A: Supplementary Tables, at the end of this thesis.

2.4.2.2 Prospective studies

The duration of the participants' index MDE and time to recovery from presentation are two of the symptomatic outcomes of this study. Prospective studies with a rigorous diagnostic assessment at baseline (see 2.4.2.5) would be expected to more accurately establish the timing of the onset of an MDE compared to retrospective assessments. and also better ensure that a participant meets the diagnostic threshold at a study's baseline.

2.4.2.3 Sample size

Only those studies with greater than 20 participants were selected due to the potential risk of small sample size bias reducing the generalisability of any findings.

2.4.2.4 Study duration

The threshold duration of a follow-up period for the inclusion of a study in the review was set at one year in order for there to be sufficient opportunity for a sizeable proportion of participants to at least recover from the index episode, such that the calculation of mean episode durations would be closer to being representative of samples as a whole.

Previous reviews of the course of MDD in clinical samples of children and adolescents have reported mean MDE episode lengths of between four and nine months (Birmaher et al., 2002; Zalsman, Brent, & Weersing, 2006).

2.4.2.5 Diagnostic assessment at baseline

Studies were included in this review if the diagnosis of an MDE at baseline was established according to Research Diagnostic Criteria (Spitzer et al., 1978), DSM criteria of its version III (American Psychiatric Association Task Force on Nomenclature and Statistics 1980) or later, or with corresponding ICD criteria.

2.4.2.6 Outcome parameters

Recovery and recurrence were chosen as the MDD course parameters of interest for the project undertaken for this thesis.

Therefore, in order to enable comparison with the project, it was necessary for at least one of these outcomes to be reported for a previous study to be selected for this review.

The definition of these outcomes also needed to be consistent with the “consensus” definitions proposed for the MDD research field (Frank et al., 1991; Prien, Carpenter, & Kupfer, 1991; Rush et al., 2006).

These definitions identify recovery as a period of prolonged remission, with remission itself defined as a period in which depressive symptoms are in “virtual absence” (2006). A recurrence is a return to meeting the diagnostic threshold for an MDE after recovery (Frank et al., 1991).

2.4.2.7 Age-range at baseline

Studies that contained participants aged between 10 and 24 years old at baseline were eligible for inclusion. This means that studies of adolescents were able to be included, but those of children were not.

It was decided not to include studies of children because of the possibility that age-dependent differences in development would affect the course of Major Depressive Disorder, such that it would not be comparable to that of a youth-aged sample.

2.4.3 Summary of studies selected in the review

There were thirteen studies found that met the inclusion criteria of the review. The baseline characteristics of their samples and the outcomes reported by them are presented in Table 2.1. Ten of the studies were based in the USA, the other three in Canada (Sanford et al., 1995), England (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a), and Finland (Karlsson et al., 2008).

Table 2-1: Longitudinally-followed clinical samples of adolescents with MDD

	Sample size (% retention)	Sample type ¹	Age (mean)	Duration of follow-up (years) (mean)	Functioning	Time to recovery (months)		Recurrence % (Median number, range)	Persistence %
						Mean (sd)	Median		
Strober et al. 1993	52 (90)	I	13-17 (15.3)	2	LIFE -55% with major disruption	6.4 (4.2)	-	-	10
Sanford et al. 1995	67 (100)	I & O	13-19	1		-	-	-	33
Rao et al. 1995	26 (93)	I & O	12-18 (15.4)	6-8 (7)	C-GAS 47.8	-	-	69 (2, 1-6)	-
Clarke et al. 1999	47 (73)	O & C	13-18	2		-	-	25	2.1
Weissman et al. 1999	73 (80)	O	Mean 15.4	10-15 (10.7)		-	-	63	-
Birmaher et al. 2000	104 (97)	O 66% C 33%	13-18 (15.5)	2		-	8.2	31.7	21.1
Fombonne et al. 2001	149 (61)	I & O	Mean 13.9	Mean=20.7		-	-	62.6	
Birmaher et al. 2004	22 (70)	I & O	Mean 13.3	1-11 (4.5)		16.7 (12.5)	6.0		
Hamilton & Bridge 2006	20 (42)	O	13-18	5		-	-	78	10
Karlsson et al. 2008	102 (72)	O	13-18 (16.4)	1		-	6.9	25.2	58.6
Rao et al. 2010	55 (93)	O & C	13-18 (15.3)	5 (3.5)	C-GAS 50.7	9.1	5.0	42.6	7.8
Curry et al. 2011	196 (44)	O 30% C 70%	12-17 (14.3)	5	C-GAS 49.6	-	9	46.6	3.6
Vitiello et al. 2011	164 (51)	I/O 80% C 20%	12-18 (15.9)	1.5	C-GAS 50.3	-	5.6 ³	25.4	38.9

1 I=Inpatient, O=Outpatient, C=Community

2. 87.5% of original sample had MDD, remainder had dysthymic disorder

3. Time to remission (at least three weeks of less than one MDE symptom)

2.4.3.1 Diagnostic instruments

All bar three of the selected studies used the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman, J, Birmaher, B, Brent D, Rao, U, & Ryan N, 1996), a semi-structured interview which establishes diagnoses by Research

Diagnostic Criteria, DSM-III or DSM-IV (American Psychiatric Association Task Force on DSM-IV 1994a) criteria depending on which edition of the instrument is used.

Of the remaining studies, one (Sanford et al., 1995) used a structured diagnostic interview using DSM-III R criteria, the Diagnostic Interview Schedule for Children-Revised (Shaffer et al., 1993).

The two other studies used a symptom checklist to make a diagnosis of a Major Depressive Episode according to DSM-IV criteria. One had a two-stage process in which participants were first seen by an allied health mental health clinician, then by a psychiatrist (Hamilton & Bridge, 2006, 1999). In the other, a child psychiatrist reviewed the clinical files of potential study participants (Fombonne et al., 2001a).

2.4.3.2 Measurement of outcomes

Both the K-SADS and the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller, Shapiro, Lavori, & Wolfe, 1982a), which were the instruments used over the follow-up periods of the selected studies, define the symptomatic threshold to reach remission as being the presence of less than or equal to two symptoms of a Major Depressive Episode.

Both instruments define recovery as when this level of symptomatology has been present for at least eight consecutive weeks.

Both the K-SADS and the LIFE in their initial editions used the Research Diagnostic Criteria criterion of 4 weeks for the duration of symptoms necessary for an MDE. This changed to two weeks in their later editions which they used the criteria of the DSM-III (American Psychiatric Association Task Force on Nomenclature and Statistics 1980), III-R (American Psychiatric Association 1987) and IV (American Psychiatric Association Task Force on DSM-IV 1994a).

A variable that was not necessary to be present in order for a study to be included in the review, but that was frequently reported, is persistence. This defines an episode that is present from the baseline assessment continuously until the follow-up assessment of a study. Given varying follow-up periods between studies, the meaning and significance of persistence varies from study to study.

One of the included studies had the outcome of remission, not recovery (Vitiello et al., 2011). It defined remission as having at least three consecutive weeks of one or no symptoms of an MDE. This study was included as its sample size of 154 participants makes it significant in the field.

Participants in the samples were recruited from inpatient and outpatient treatment settings. Five samples, four of which were treatment studies (see following paragraph) also contained adolescents recruited from the community, at rates from 20 to 67% of their total sample. As noted above, as clinically-sourced participants are likely to have characteristics that can lead to a more severe course of illness, the presence of community-sourced participants in a sample might be associated with more benign overall outcomes.

2.4.3.3 Type of studies

Four of the studies followed up participants of randomised trials, two having tested antidepressant medication and cognitive-behavioural therapy alone and in combination (Curry et al., 2011; Vitiello et al., 2011), the other two having compared individual cognitive-behavioural therapy and family therapy (Birmaher et al., 2000; Clarke, Rohde, Lewinsohn, Hops, & Seeley, 1999). The other studies were naturalistic.

2.4.3.4 Exclusion criteria

There were exclusion criteria applied in all but three of the included studies, with the treatment studies being the most selective. Such exclusions limit how representative a study is of a “true” clinical sample.

Most commonly excluded were those with particular comorbid disorders. Substance use disorders led to exclusion across the treatment studies (Birmaher et al., 2000; Clarke et al., 1999; Curry et al., 2011; Vitiello et al., 2011) and in two of the naturalistic samples (Karlsson et al., 2008; Rao et al., 2010). Next most commonly excluded were potential participants with eating disorders (Birmaher et al., 2000; Karlsson et al., 2008; Vitiello et al., 2011) and pervasive developmental disorders (Curry et al., 2011; Rao et al., 1995; Vitiello et al., 2011).

In one of the naturalistic studies, the exclusions were not for all participants with an identified disorder, rather for the most severe eating disorders and for those with a primary as opposed to a secondary substance use disorder (Karlsson et al., 2008). Four studies excluded potential participants if they were taking psychotropic medication (Birmaher et al., 2000, 2004; Clarke et al., 1999; Rao et al., 2010). Suicidality was a cause for exclusion in two of the treatment studies, in one for an attempt within six months (Curry et al., 2011), in the other for an attempt during the course of treatment (Vitiello et al., 2011). A third treatment study (Clarke et al., 1999) excluded potential participants on the basis of them needing immediate treatment. Suicidality might have been part of the reason for this necessity.

Although the range of follow-up periods was wide, from 1 to almost 21 years, nine of the thirteen studies were between 1 and 5 years in duration.

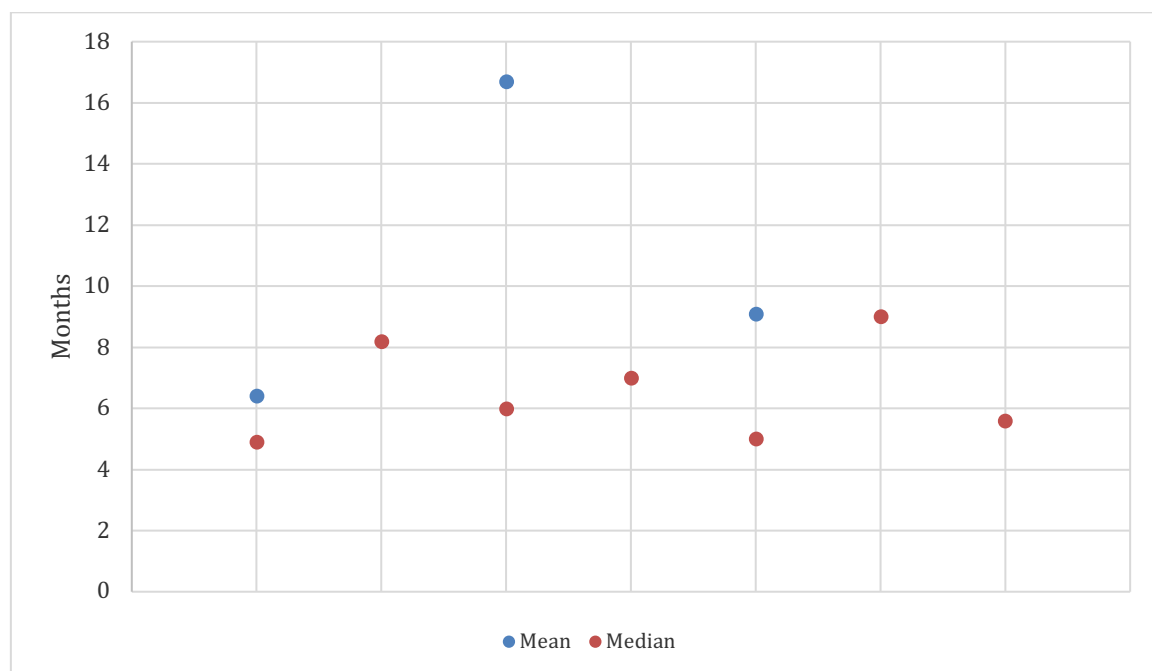
2.4.4 Outcomes of reviewed studies

2.4.4.1 Length of episode

There are two parameters that studies use to describe the length of an Major Depressive Episode for which a person presents for treatment. “Duration of episode” measures from the point at which someone meets criteria for an Major Depressive Episode prior to presentation to when they enter recovery, while “time to recovery”, as the name implies only measures from the point of presentation for treatment to the recovery.

Time to recovery was more commonly reported and the findings of the studies are presented in Figure 2.2.

Figure 2-2: Time to recovery of index MDE in longitudinally studied samples of adolescents



The median time to recovery was more commonly reported than the mean of this outcome. It had a range between 6 and 9 months. The related variable of time to remission in the study that did not report time to recovery was 5.6 months (Vitiello et al., 2011).

Durations for the less commonly reported outcome of mean time to recovery were 6.4, 9.1 and 16.7 months (Birmaher et al., 2004; Rao et al., 2010; Strober, Lampert,

Schmidt, & Morrell, 1993). The study with the longest mean time to recovery also had the longest, though variable length follow-up period, with this ranging from 1 to 11 years (2004). Therefore the mean value for time to recovery would be able to include participants with protracted episodes.

This study was the only one to report the duration of the index episode, and its mean was 18.3 months (2004).

One might assume that the range of episode lengths underestimates the time to recovery in a clinical sample without any exclusion criteria, given the range of exclusions across the selected studies. However, due to the fact that comorbid disorders such as substance use disorders and eating disorders are often excluded in these longitudinal studies, it is difficult to know their true impact.

The one study that tested the association of substance use disorders with time to recovery did not demonstrate an association (Karlsson et al., 2008), while no studies tested the role of eating disorders as a predictor of episode length.

Another of the common exclusion criteria across the studies reporting median time to recovery was the use of psychotropic medication (Birmaher et al., 2000, 2004; Rao et al., 2010). This exclusion may have diluted the overall severity of a sample should adolescents with more severe depression be more likely to be taking medication.

Treatment guidelines for adolescents do recommend the use of antidepressants in adolescents with more severe (or psychotherapy-resistant) depression (*Depression in Children and Young People: Identification and Management* 2005/2017; McDermott B 2010).

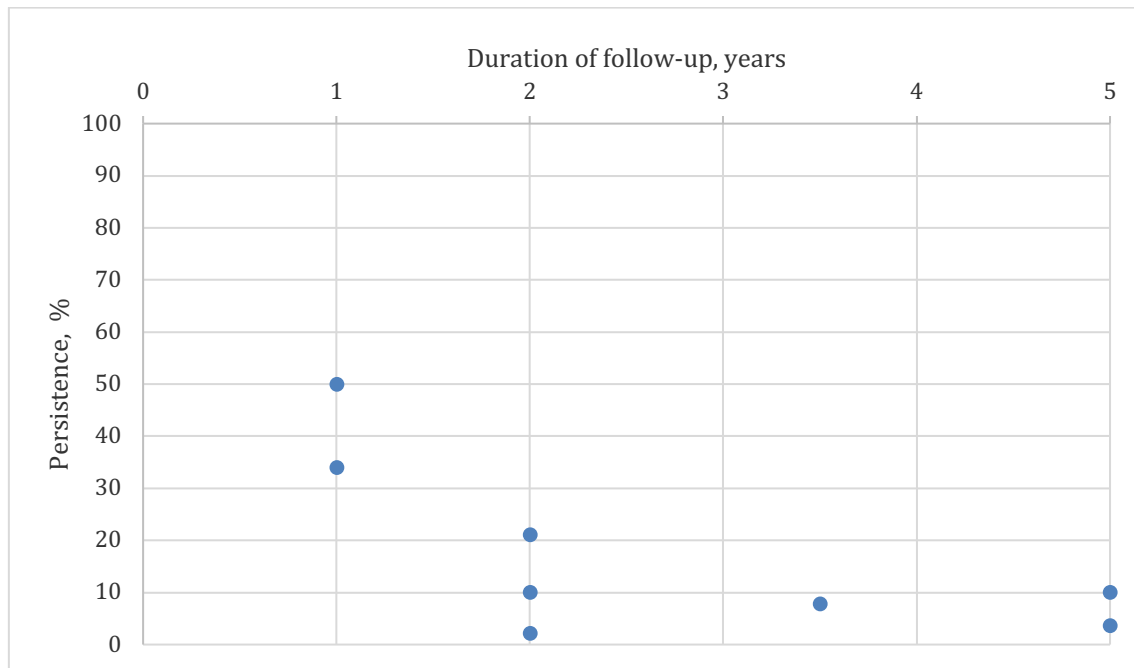
As will be examined in more detail in Chapter 5, while severity is a robust predictor of episode length in longitudinal clinical samples of adults with Major Depressive Disorder (Ilardi, Craighead, & Evans, 1997; Keller et al., 1984; Melartin et al., 2004; Viinamäki et al., 2006; Vuorilehto, Melartin, & Isometsä, 2009), it has been little studied in adolescent samples.

2.4.4.2 Recovery and persistence

A number of studies also report the persistence of a Major Depressive Episode. This was generally defined as not experiencing a recovery over the course of the study.

One study (Birmaher et al., 2000) defined persistence as the absence of a sustained recovery, with a recovery classified as sustained if there were a 6 month period in which only one or no symptoms of MDE were experienced

Figure 2-3: Rates of persistence of index MDE in adolescent clinical samples



Studies measured recovery from the time of presentation for treatment. At one year, rates of persistence were 33% (Strober et al., 1993) and 59% (Karlsson et al., 2008). At two years, rates of persistence ranged from 2 to 21% (Birmaher et al., 2000; Clarke et al., 1999; Strober et al., 1993). In the two studies with uniform 5 year follow-up periods, 3.6% (Curry et al., 2011) and 10% (Hamilton & Bridge, 2006) of participants were yet to recover at follow-up.

To summarise, most treatment-seeking adolescents will recover from their index MDE within two years of presentation. However, for a small percentage of these adolescents, an MDE can be very protracted, sometimes lasting beyond five years.

2.4.4.3 Recurrence

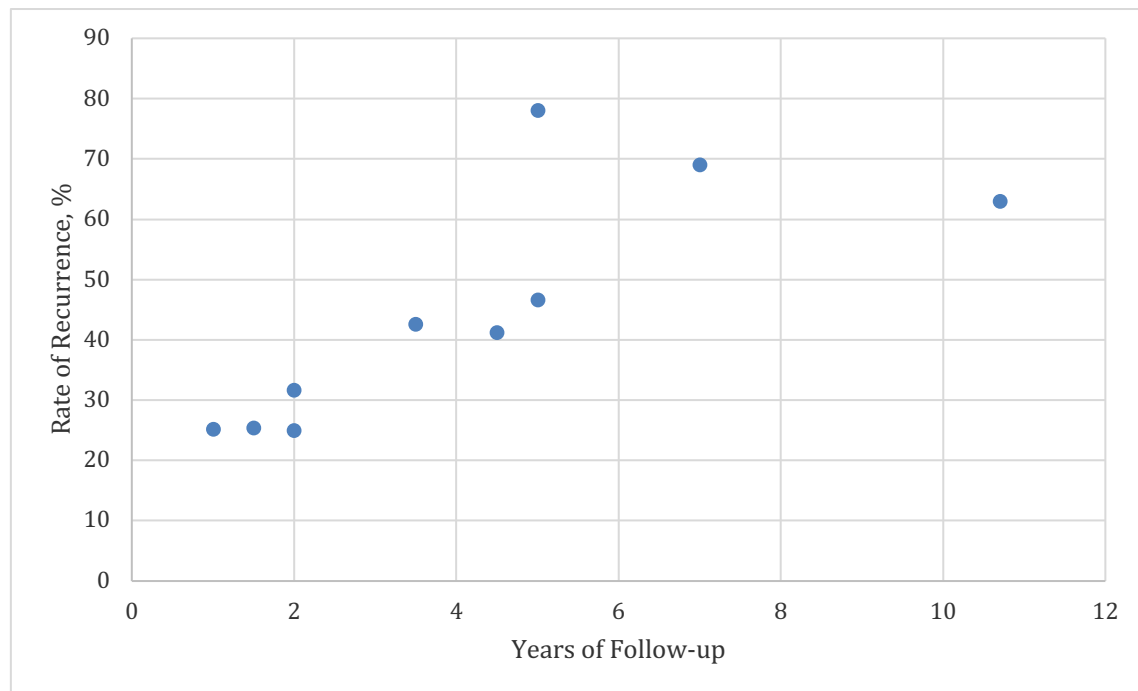
The reporting of and interpretation of the data on recurrence is complicated by a number of issues. Firstly, there are non-uniform lengths of follow-up periods within some samples, such that data on a particular rate over a specified period may not be available.

Secondly, recurrence rates are dependent on recovery rates, as a recurrence can only occur after recovery. With regard to this point, given increasing rates of recovery over time, the longer the study, the closer the recurrence rate for the entire sample will be to the true recurrence rate.

A further issue is that most studies report times to recurrence for the entire period of follow-up, rather than timing these from the point of recovery.

The studies that did report mean time to recurrence from recovery found a wide range of mean durations for this variable, ranging from 1.86 (Curry et al., 2011) to 3.1 years (Rao et al., 2010).

Figure 2-4: Rates of MDD recurrence in clinical samples of adolescents with MDD



Studies of uniform follow-up length found rates of recurrence of 31% in 2yrs (Birmaher et al., 2000), and 46.6% (Curry et al., 2011) and 78% (Hamilton & Bridge, 2006) in 5 years. Rates of recurrence reported in studies with non-uniform follow-up periods are generally concordant with these, with a rate of 42% in a study with 3.5 year mean follow-up (Rao et al., 2010), 41.2% in a study with a 4.5 year mean (Birmaher et al., 2004), and 69% in a study with a 7 year mean follow-up period (Rao et al., 1995). The rate of recurrence did not further increase in the three studies of greater than 10 years duration (Fombonne et al., 2001a; Weissman et al., 1999). This may be due to a percentage of people having very sustained periods prior to a recurrence, or never having a recurrence. It is possible also that the long duration of the study mitigates against recall of distant past episodes, falsely lowering the recurrence rate. Among those individuals that had recurrences, one recurrence was the most common number of recurrences to have.

2.4.5 Adult samples

2.4.5.1 Search strategy

Throughout this thesis, the findings from studies of MDD in adult clinical samples are used to supplement those from samples of young people. This has been done as the relevant research in young people is often limited, and as a point of comparison. Rather than performing a complete review of adult studies, the most recent systematic review of a particular topic was sought, then studies published since that time were searched systematically.

The most recent systematic review of longitudinal studies of clinical samples of adults with MDD found in MEDLINE was from 1994 (Piccinelli & Wilkinson, 1994), reviewing 16 studies published between 1970 and 1993. Searching for subsequent studies was focussed on those with larger sample sizes ($n > 50$) in order to maximise the generalisability of their findings. Otherwise the strategy and selection criteria were as for adolescent studies, as described in 2.4.1 and 2.4.2 above.

2.4.5.2 Longitudinal clinical samples of adults with MDD

Data for the studies published since 1994 and the earlier review are summarised in Table 2-2 and Table 2-3 below. The studies, although sharing similar definitions of time to recovery or duration of episode had a wide range of outcomes with median episode lengths of 6, 7, 12 and 24 months (Hoencamp, Haffmans, Griens, Huijbrechts, & Heycop ten Ham, 2001; Kennedy, Abbott, & Paykel, 2003; Penninx et al., 2011). Adolescent studies, as reported above, have generally reported durations at the lower end of this range.

The studies with longer episodes had associated rates of persistence of 39% at 3.5 years (Hoencamp et al., 2001), and 31% at 5 years (Bukh, JD, Andersen, PK, & Kessing, LV, 2016). A number of the earlier studies reported persistence rates at 10 years, these ranging from 8% to 15% {AngstJules 1986;KilohLg 1988;LeeAs 1988}. Rates of recurrence in the adult samples are generally higher or at the higher end of the range of those of adolescent samples over comparable periods.

Two of the studies measured the proportion of time their participants spent at various levels of MDE symptoms over their follow-up periods. A five-year study found that its participants spent on average 20% of time meeting full MDE criteria, and 31% experiencing between one and four symptoms (Holma, Holma, Melartin, Rytsälä, & Isometsä, 2008).

In a longer study, at means of 8.7 (Judd et al., 1998) and 18.4 years (Judd 2012) of follow-up, 15% of the time period was spent meeting full MDE criteria. In this study, the researchers investigated the proportion of time its participants met the full criteria for an MDE while in an episode, finding that that the median proportion of an episode spent at full criteria was 32% (Keller et al., 1992). They also found that the transition to recovery was characterised by a gradual reduction of symptoms.

Table 2-2: Selected longitudinal clinical samples of adults with MDD

	Sample characteristics	Duration of follow-up	Length of episode	Persistence	Recurrence	Proportion of follow-up period in MDE
Collaborative Depression Study Keller et al. 1992 Mueller & Leon 1996 Judd et al. 1998 Mueller et al. 1999 Judd 2012	Inpatient & outpatient n=431	20yrs	Time to recovery Median 4.4 mths	2 yrs-19% 5 yrs-12%	2yrs-46% 5yrs-74% 10yrs-85%	12 yr mean MDE 15.3% Minor Depression 26.7% Subsyndromal 16.5% No symptoms 41.5%
Hoencamp et al. 2001	Outpatient n=95	3.5-7.5yrs	Time to recovery Median 24 mths	3.5yrs-36.8%	39.3% (at 3.5 yrs)	-
Kennedy, Abbot & Paykel 2003	Inpatient & outpatient n=69	10yrs	Time to recovery Median 7.0 mths Mean 12.3 mths	8%	66%	-
Vantaa Melartin et al. 2004 Holma et al. 2008	Inpatient & outpatient n=198	5yrs	Time to remission ¹ Median 8.1 mths	18mths-37% 5 yrs -11.6%	18mths 38% 5yrs 71%	5 yr mean MDE 20.2% Partial remission 31% Full remission 48.7%
NESDA Penninx et al. 2011	Mixed primary care and outpatient n=1104	2yrs	Time to remission ² Non-comorbid MDD: Median 6 mths Comorbid MDD and Anxiety disorder: Median 12 mths	MDD gp 21% Comorbid gp. 25.5%	22% (of remitters)	-
Bukh et al. 2016	Inpatient & outpatient n=301	5yrs	Duration of episode Median 20 mths	1 yr 71.2% 2 yr 41.6% 5 yr 16.7%	31.5%	-

1-No MDE symptoms for 2 consecutive months 2-Defined as symptom-free for 3 consecutive months, includes anxiety symptoms if comorbid disorder

Table 2-3: Summary of data from Piccinelli & Wilkinson 1994 review

Duration of follow-up	% Recovery Mean (range)	% Recurrence Mean (range)	% Persistence Mean (range)
6 mths	53 (49-56)	-	-
1 year	64 (28-75)	26 (25-27)	15 (8-17)
2-5 years¹			
Giles et al. 1989 (3 yrs)		59	
Copeland 1983 (5 yrs)		57	
10 years		Mean =76	Mean=12
Angst 1986		-	13
Kiloh et al. 1988		63	8
Lee & Murray 1988		95	15

¹ Defined as not meeting criteria for MDD for "at least a few weeks"

2.4.6 Comorbidity

2.4.6.1 Mental state disorders

Table 2-4 displays the rates of comorbid mental state disorders detected at baseline, and also, where measured, the rates over the follow-up periods of the reviewed studies of samples of adolescents with MDD.

Anxiety disorders were the most common with rates at baseline ranging from 22.5% to 71.5%, with a mean rate of 36%. Dysthymic, Disruptive behaviour and Substance use disorders also had wide-ranging prevalences, generally falling between 10% and 40% of the study participants at baseline. These rates all represent a marked elevation from those seen in general population samples of adolescents.

Lifetime prevalence rates for adolescents for experiencing any anxiety disorder have been found to be 15-20% (Beesdo, Knappe, & Pine, 2009). Dysthymic disorder has been reported to occur in 1-1.5% of the population over the adolescent period (Charlson, Ferrari, Flaxman, & Whiteford, 2013). A review of epidemiological studies of disruptive behaviour disorder calculated pooled prevalence rates in for Oppositional Defiant Disorder and Conduct Disorder of 3.3% and 3.2% respectively in children and adolescents (Canino, Polanczyk, Bauermeister, Rohde, & Frick, 2010). Lifetime prevalence rates in adolescents in the USA for alcohol use disorders and substance use disorders were measured at 6.5% and 8.9% respectively (Merikangas & McClair, 2012).

Table 2-4: Rates of mental state disorder comorbidity at study baseline and over follow-up in child and adolescent clinical MDD samples

	Age (mean)	Duration of follow-up, yrs (mean)	Rate of comorbidity (% of sample)	Rates of disorder types % at baseline (follow-up prevalence %)			
				Dysthymic disorder	Anxiety disorders	Disruptive behaviour	Substance use disorder
Sanford et al. 1995	13-19	2	-	36.1	60.7	39	37.7
Rao et al. 1995	12-18 (15.4)	6-8 (7)	-	21 (26.9)	32 (38.5 ¹)	7 (-)	- (34.6)
Weissman et al. 1999	Mean 15.4	10-15 (10.7)	-	- (5.5)	SAD ² , 37 OCD 11 (19.2)	11 (8.2)	- (Alcohol 31.5 Drug 30.1)
Birmaher et al. 2000	13-18 (15.5)	2	-	22	32	21	-
Fombonne et al. 2001	Mean 13.8	Mean 20.7	56	- (9.4)	34 (36.5)	36 (-)	12 (Alcohol 26 Drug 1.0)
Birmaher et al. 2004	Mean 13.3	1-11 (4.5)	-	-	71.4	-	-
Hamilton & Bridge 2006	13-18	5	-	- (-)	- (OCD 29 ¹ PTSD 18 Social Phobia 23.5)	- (-)	- (Alcohol abuse 30 Marijuana abuse 45)
Karlsson et al. 2008	13-19 (16.4)	1	74.1	6.9	57.5	10.9	16.7
Rao et al. 2010	13-18 (15.3)	5 (3.5)	43.6	-	-	-	-
Curry et al. 2011 Peters et al. 2015	12-17 (14.3)	5	- (54.6)	7.7 (-)	22.5 (15.8)	21.9 (9.2)	- (10.2)
Vitiello et al. 2011 ¹	12-18 (15.9)	1.5	-	29.1	36.4	7.0	-

1 With exception of disruptive behaviour disorder rates are for entire baseline sample: only 56% completed follow-up

2 Separation anxiety disorder

* Rate of disorder significantly higher than in non-clinical control group

Five of the selected studies collected data on the prevalence of mental state disorders other than MDD in their samples over follow-up periods ranging from five to twenty years (Fombonne et al., 2001a; Hamilton & Bridge, 2006; Peters et al., 2015; Rao et al., 1995; Weissman et al., 1999). The disorders that were most common were anxiety and substance use disorders. Rates of both disorder types were generally in the range of 25% to 35% across these studies. Of the other disorder types reported, rates of dysthymic disorder were between 5.5% and 26.9% (Fombonne et al., 2001a; Rao et al., 1995; Weissman et al., 1999), while behavioural disorders occurred at rates of 8.2% and 9.2% (Peters et al., 2015; Weissman et al., 1999). Only one study reported an overall mental state disorder comorbidity rate, of 54.6%, over a five-year follow-up period (2015).

2.4.6.2 Personality disorders

Only one of the selected adolescent MDD studies reported the rates of personality disorder in its sample (Karlsson et al., 2008). To supplement that study, data was sought from clinical adolescent MDD samples that did not meet this review's selection criteria.

Three samples reporting rates of personality disorders were found, two of which were of outpatients (Ramirez, Ekselius, & Ramklint, 2015) or predominantly so (Marton, P et al., 1989), and one of inpatients (Grilo, Walker, Becker, Edell, & McGlashan, 1997).

The data from these studies is presented in Table 2-5.

Table 2-5: Personality disorders in clinical samples of young adults and adolescents with depressive disorders

	Ramirez et al. 2013	Karlsson et al. 2008	Marton et al. 1989	Grilo et al. 1997
Sample	Consecutive referrals to public outpatient clinic	Consecutive depressive disorder referrals to public psychiatry outpatient service	Consecutive MDD referrals to range of services, mostly outpatients	Consecutive MDD admissions to private inpatients service
Diagnostic method	SCID-II ¹	SCID-II	Personality Disorders Examination ²	Personality Disorders Examination
Number of participants	148	174 (38 with Dysthymic disorder or Minor depression)	35	87
Age (mean)	18-25 (22.4)	13-19yo (16.4)	14-19yo (16.7)	12-18yo (15.6)
Rate of PD (%)	30	41.3	65	71 (Borderline 57%)
Clusters (% of total sample)	A 8 B 11 C 16	A 2 B 13 C 14 Mixed 12	A 0 B 29 (Borderline 20) C 23 Mixed 14	A 13 B 59 (Borderline 57) C 36

1(First, MB, Gibbon, M, Williams, JBW, & Benjamin LS, 1997) 2(Loranger, A, Susman, V, & Oldham, J, 1985)

Among the outpatient samples, it can be seen that there was variation in the rate of having any personality disorder, with the highest rate at 65% (Marton, P et al., 1989). One factor contributing to the higher rate of Cluster C disorders in this and the inpatient sample (Grilo et al., 1997) was the inclusion of Passive Aggressive personality disorder in this group. This accounted for 50% of the Cluster C disorders in the inpatient sample (1997).

Borderline personality disorder is a common diagnosis in adolescent inpatient samples. Two studies of consecutive admissions to adolescent inpatient units reported prevalence rates of Borderline personality disorder of 33% (Ha, Balderas, Zanarini, Oldham, & Sharp, 2014) and 28% (Pedersen & Aarkrog, 2001) among all patients. Therefore the higher rate in the inpatient sample (Grilo et al., 1997) in Table 2-5 is not unexpected.

The overall rates of personality disorder in these samples, ranging from 30% to 71% compare to a point prevalence of personality disorder of 12.7% at age 16 in a general population sample (Johnson, Cohen, Kasen, & Brook, 2005).

A meta-analysis of studies of clinical samples of outpatient and inpatient adults with MDD reported an overall rate of personality disorder of 45% (Friborg et al., 2014),. Rates for individual clusters were 9% for A, 19% for B, and 30% for C. Within cluster B, Borderline PD was most common (14% of total sample), while Avoidant PD was the most prevalent in cluster C (16% of total sample).

2.4.7 Suicidality

It can be seen in Table 2-6 below that rates of suicidal ideation at presentation in longitudinal clinical studies of adolescent MDD are mostly above 35%, with a range from 26-66%. Rates of lifetime history of suicide attempts in these clinical samples, at presentation, range from 2.2 to 34%.

When followed prospectively, for periods between one and 20 years, rates of suicide attempts were between 7% and 26%. Completed suicide was uncommon in these samples, with no suicides in five of the seven studies reporting this outcome. The suicides occurred in the two studies of longest duration (Fombonne et al., 2001a; Weissman et al., 1999).

The larger literature of longitudinal studies of MDD in adult clinical populations adds some relevant information. There is some indication that younger onset of MDD may not define a higher risk group for suicide, with earlier age of onset not found to be a risk factor for suicide in a large (n>36000) Danish registry study, which included patients from the age of 15 (Nordentoft, Mortensen, & Pedersen, 2011).

Both this study (median follow-up 18 years) and the longitudinal study of Angst (range of follow-up 20 to 30 years) found a persistent risk of suicide over time, with Angst describing this as being linear from the point of presentation (Angst, Angst, & Stassen, 1999). Hence it is understandable that the longer of the studies commencing in adolescence or childhood would be more likely to detect the occurrence of suicide.

Table 2-6: Suicidality in longitudinal adolescent clinical MDD samples

	<i>At presentation</i>		<i>Follow-up period</i>		
	Suicidal ideation %	Past suicide attempt %	Duration	Suicide attempt %	Suicide %
Strober et al. 1993	-	-	2 yrs	10	0
Rao et al. 1995	39	-	6-8 yrs	-	0
Weissman et al. 1999	-	34	10-15 yrs	26	7.7
Birmaher et al. 2000	36	23	2 yrs	-	-
Fombonne et al. 2001	54	-	20.7 yrs	22	2.5
Birmaher et al. 2004	35.2	11.8	1-11 yrs (mean=4.5)	12	0
Rao et al. 2010	29	-	1-5 yrs (mean=3.5)	-	-

2.4.8 Functional impairment and outcome

2.4.8.1 Conceptualisation of functioning

There is increasing attention being given to the ways in which mental illness impacts on an individual beyond the experience of symptoms (Langlieb & Guico-Pabia, 2010; Ro & Clark, 2009). In the research field, this is reflected by measures of functional impairment being more commonly included in assessment batteries, in addition to symptom measures.

Defining functioning is complex. As noted by theorists in the field, “it is literally about what we do daily and throughout life, and defining it is indeed a challenging task.” (Ro & Clark, 2009).

In its International Classification of Functioning, Disability and Health (World Health Organization 2001), the World Health Organization does not provide a broad definition of functioning, but identifies three domains. These are body, which includes physical and psychological functioning, activity, the ability to perform tasks, and participation, which is defined as involvement in life situations (Rapee, Bögels, van der Sluis, Craske, & Ollendick, 2012; World Health Organization 2001).

A matter of ongoing debate is whether quality of life should be included in the assessment of functioning. One position is that the construct of functioning should measure more “overt and objective aspects” (2012), while another is that it is a necessary component, particularly in describing higher-level functioning (Ro & Clark, 2009).

Another way in which the concept has been divided is between its more day to day activity-related features and a more “macro” level which includes longer-term goals and values (2009).

A challenge in the assessment of functioning in clinical populations has been whether to include symptoms in this assessment. The initial functioning measure used in the DSM, the Global Assessment of Functioning (GAF) (Association 2000) did include symptoms, but there has been a movement away from this practice, demonstrated by the DSM adopting the Social and Occupational Assessment Scale (SOFAS) (Spitzer, Gibbon, & Endicott, 2000), which assesses functioning independently of symptoms (Rybarczyk 2011).

The use of “affect-laden” (Ro & Clark, 2013) terminology in functioning scales is also an issue in clinical populations, as it leads to correlations of functioning with levels of psychopathology and also with dimensional scores of personality traits such that these variables may confound results.

Examples of such terminology in the widely-used Social Adjustment Scale Self-Report (SAS-SR) (Weissman, Myrna M, Prusoff, Brigitte A, Thompson, Douglas, Harding, Pamela S, & Myers, Jerome K, 1978) include terms such as ashamed, upset, and worried. It has been argued though that it is difficult to not use such terms when assessing functioning above a basic task level (Ro & Clark, 2013).

Ro and Clark have taken an approach of theoretical inclusivity in the conceptualisation of functioning in their factor analysis of commonly-used functioning measures in both community and clinical samples (Ro & Clark, 2009, 2013; Ro, Eunyoe 2010). The purpose of these studies was to empirically develop a comprehensive model of functioning.

Analyses in both types of sample indicated a three-factor structure, consisting of Well Being, Social/Interpersonal Functioning, and Basic Functioning. The first factor is named Well Being as it included items assessing how a person evaluates themselves and their life, but also contains items measuring positive relations with other people and performance of daily work, social and leisure tasks.

The second factor has been influential in the development of the concept of personality functioning contained in the alternative personality disorder classification of the DSM-5 (American Psychiatric Association 2013). It contains items that measure identity, self-concept, intimacy and empathy (Ro & Clark, 2013).

The items loading on the third factor, Basic Functioning were behaviourally-oriented and assessed the ability to care for one's physical needs as well as mobility and communication skills.

A gap in this structure is the absence of educational functioning, which was not included as it was not relevant across the samples that were analysed.

2.4.8.2 Baseline functioning in longitudinal clinical samples of young people with MDD

All the studies measuring baseline functioning found evidence of impairment in their participants. Four of the studies used a global rating scale, the C-GAS (Shaffer, D, Gould, MS, & Brasic, J, 1983), and their mean ratings ranged from 47.8 to 50.9 (Peters et al., 2015; Rao et al., 2010; Rao et al., 1995). These ratings are at the upper end (better functioning) of the 50-41 segment, defined as "obvious impairment in most areas, or severe impairment in one". The segment above (60-51) is defined as "some noticeable problems in more than one area".

Only one study had a non-psychiatric control group at baseline (Weissman et al., 1999). It was found, using the Psychosocial Schedule for School-Age children (Lukens et al., 1983) that compared to control adolescents the functioning of their participants was on average one standard deviation poorer in a range of relationship and school performance domains (Puig-Antich et al., 1993). Many participants had specific areas of higher dysfunction, with 90% performing two standard deviations worse than controls in at least one domain.

Table 2-7: Baseline and follow-up functioning in clinical samples of adolescents with MDD

			Baseline		Follow-up	
	Control group	Measure	Score/Rating	vs. Control	Scale	Non-scale
Adolescent						
Strober et al. 1993 2 yrs	Inpatients with depression with psychotic features	Longitudinal Interval Follow-up Evaluation ¹ (LIFE)	Severe impairment School 10% Social 22.5% Major functional disruption 25%	Severe impairment School 50%* Social 66%* Major functional disruption 55.6%*	Any impairment (mild to severe) 6/24 mths School 40/30% Interpersonal 53/35% Overall 88/40%	-
Rao et al. 1995 6-8yrs (mean=7yrs)	Non-patient age-matched	Children’s global assessment score ² (C-GAS)	Mean=47.8 (sd=9.8)	-		vs. controls –lower SES -higher Parenthood No difference –Education
		LIFE Base Psychosocial	-	-	vs. controls Worse	

		Schedule ¹ (controlled for SES)			-Global rating*** -Friends* -Life satisfaction* No difference -Vocation -Family -Recreation -Sexual	
		GAF ³ (controlled for SES)	-	-	Control 79.8 MDD recurrent 65.7*** Non-recurrent 75.3*	
Weissman et al. 1999 10-15 yrs (mean=10.7)	Adolescents with no history of psychiatric illness	Psychosocial schedule for school-age children ⁴ -assesses family and peer relationships, school performance	-	On average one standard deviation below participants on all domains (ie. higher functioning)	-	<i>vs. controls</i> Lower -Education achievement -Social class No difference -Employment -Income -Marital status
		SAS interview ⁵	-	-	Greater impairment -Overall*** -Work*** -Social*** -Family*** -Parental* No difference -Marital	
Fombonne et al. 2001 20.7 yrs	Nil	Adult Personality Functioning Assessment (APFA ⁶)	-	-	Pervasive social dysfunction 48%	-
Rao et al. 2010	Nil	C-GAS	50.7 (sd=7.3)	-	-	-
Peters et al. 2015 (SOFTADS) 5 yrs	Nil	C-GAS/GAF ³	50.2	-	74	-

1 (Keller et al., 1987) 2 (Spitzer et al., 2000) 3 (Association 2000) 4 (Lukens et al., 1983) 5 (Weissman & Bothwell, 1976b)

6 (Hill, Harrington, Fudge, Rutter, & Pickles, 1989)

***p<0.001, **p<0.01, *p<0.05

2.4.8.3 Functional outcome

All but one of the studies that measured baseline functioning also made assessments of the level functioning of their participants at the time of their follow-up interviews.

There was ongoing impairment detected in all of the samples, though with a degree of improvement in functioning shown in the two studies that had repeated measurements of their instruments (Peters et al., 2015; Strober et al., 1993).

In two studies with non-psychiatric control groups, divergences of the MDD cohort on categorical non-scale measured functional outcomes were uncommon. These two studies could be described as medium-term in length, one with follow-up period of a

mean of 7 years (Rao et al., 1995), the other with a follow-up period between 10 and 15 years (Weissman et al., 1999).

Both adolescent MDD cohorts were at a lower socio-economic status point at follow-up than their controls, but neither study clearly controlled for baseline SES. The only other individual functioning variable difference between participants and controls from these studies was a lower level of educational achievement for MDD participants in the 10-15 year study, with fewer attending college (1999).

These studies did however detect differences in scale scores with overall ratings of functioning lower for the MDD groups compared to controls. These were on the Social Adjustment Scale interview (Weissman, Sholomskas, & John, 1981) and the Longitudinal Interval Follow-up Evaluation psychosocial schedule (Keller et al., 1987). It may be that the differences between the control and MDD groups detected by these scales are not sufficiently large to translate to categorical functional outcomes.

For relationship functioning, greater impairment in relationships with friends, measured on the “Social/Leisure” scale in the SAS Interview, was consistent across the two studies while one reported impairment in family relationship functioning (Weissman et al., 1999). One of the two studies study reported greater impairment in vocational functioning (1999).

In the study with the longest follow-up period, 20.7 years, almost half (48%) of the sample were assessed as having “pervasive social dysfunction” at follow-up (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001b). This is defined as having “major problems” in at least two domains of the Adult Personality Functioning Assessment (Hill et al., 1989). The six domains cover work, interpersonal relationships, and functioning in daily tasks. Of the domains, the participants’ functioning was worst in those assessing interpersonal relationships.

2.4.8.4 Longitudinal studies of community samples of young people with MDD

The previous section revealed the small number of clinical studies examining functioning and due to this limited data it was considered worthwhile to supplement the findings of the clinical studies with those of community populations, bearing in mind that these are not matching groups.

The data in this section is not the product of a systematic review, rather a presentation of the findings of a number of the larger studies in the community field. A particular feature of the studies selected is the attention paid in analyses to the presence of possible sub-groups of interest and potential confounding variables.

All of the studies listed found worse adult functioning in those who had experienced an MDE in adolescence compared to matched controls. However, in all studies this result was qualified by the analysis of subgroups or by the detection of potentially confounding variables in multi-variate analyses.

A particular focus of one study was to examine whether functional impairment in adulthood of those with a history of adolescent MDD represented a “scar” of the adolescent illness (Beevers, Rohde, Stice, & Nolen-Hoeksema, 2007). It was found that the level of functioning in adulthood was no lower than it was prior to the adolescent MDE, suggesting that poor functioning was a precursor to, rather than a consequence of the MDE.

This finding was not however consistent across all these studies, with another reporting lower functioning in its participants with a history of an MDE remaining despite controlling for baseline functioning (Wilson, Hicks, Foster, McGue, & Iacono, 2014). In this case identical measures were not used at both time points. This study reported both worse intimate relationship and work functioning in adulthood to be associated with having recurrent MDEs up to age 29, with the relationship finding being limited to those with onset of MDD prior to age 17.

Another study found almost all significant associations of having an MDE before the age of 19 with functioning at age 24 to be eliminated by controlling for the presence of an MDE recurrence or the presence of another mental state disorder between the age of 19 and 23 (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003).

In their stepwise model, baseline functioning was introduced next as a covariate, and a further association was removed, with having a smaller social network the sole significant association remaining. This was then removed in the final step of the analysis, the introduction of a measure of current depressive symptoms, the Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977).

An additional element examined in the remaining study in Table 2-8 was the contribution of social and familial factors to adult functioning in MDD (Fergusson & Woodward, 2002). Disruption to the parental relationship, low level of maternal education and deviant peer affiliation were identified as significant covariates across the educational outcomes.

Table 2-8: Longitudinal community studies of MDD in young people

Study name and sample type	Assess - ment points	Sample	Comparison/ Variable of interest	Outcome & Scale	Univariate findings for MDE group	Multivariate findings
CHDS (Fergusson & Woodward 2002, 2007) Birth cohort	T1:15yo T2:16yo T3:18yo T4: 21yo T5: 25yo	Total=1265 MDE age 14-16=124 Episodes of MDE age 16-21 1-4: 248 5-9: 59 10+: 38	MDE age 14-16yo vs. no MDE in this period	Educational status age 18-21 -Completed school -Tertiary education or training -University	Worse outcome on all variables	Difference no longer present when controlled for social, familial and comorbidity factors up to T1.
				Work status age 18-21 -Prolonged unemployment	Higher rate	As above
			Frequency of MDE age 16-21	Educational status age 21-25 -Tertiary qualification -University degree	Frequency of recurrence associated with fewer qualifications	Differences no longer present with controlled for social, familial and comorbidity factors up to T3.
				Work -Welfare dependency - Unemployed >1mth -Income	Frequency of recurrence associated with worse outcomes on all variables	As above
OADP (Lewinsohn et al. 2003) High School students	T1:14-18yo T2: 1 yr later T3: 24yo	Total=1709 T2 lifetime history of MDE=351 T2 lifetime history of non-affective disorder=293 T3 total=941	MDD<19yo vs. no MDD <19yo	Global functioning -GAF	Lower GAF	Control for Age 19-23 MDE recurrence or comorbid mental state disorders & T1 GAF Sole remaining association -Smaller social network No longer present when current CES-D score controlled for
				Quality of relations -Family -Friends Small social network	Lower quality family relations Smaller social network	
				Education -Total years	Fewer years	
				Work -Wks unemployed in past yr -Household income	Greater wks unemployed	

AADS (Beevers et al. 2007) Female high-school students	T1:12-15 yo T2-7: annual follow-up	Total=496 MDE T2-7 & recovery=49 Never MDE =430	MDE T2-7 & recovery vs. Never MDE (random selection of 98)	Social Adjustment Scale (SAS)	Worse functioning	
				Peer support –Networks of Relationships Inventory	Lower scores	
Minnesota Twin (Wilson et al. 2014) Same-sex twins	T1: 17yo T2: 20yo T3: 29yo	Total=1252 MDD onset <17yo=166 MDD onset >17yo=247	No MDE vs. 1. Onset<17y o 2. Onset>17y o 3. Single episode vs. Recurrent	Intimate Relationship -Dyadic Adjustment Scale	Onset<17yo & Recurrent	
				Work -Social Adjustment Interview	Recurrent (both onset ages)	

2.5 Summary

As there have not been previous longitudinal studies of clinical samples of youth with MDD with which to compare this study's sample, longitudinal studies of the closest matching age-group, adolescents, have been reviewed in this chapter.

These studies demonstrate that these young people often have a complex presentation, experiencing a wide range of psychopathology and functional impairment across multiple areas of their lives.

The longitudinal symptomatic course of MDD in these samples was characterised by a narrow range of median recovery times of 5-9 months. However, up to 20% of adolescents at two years, and up to 10% at five years had yet to recover from their index MDE. Recurrences were common, with rates approaching a linear pattern, from 25% at two years. to 47% at 5 years, and 70% at 7 years. The sample participants continued to have other mental state disorders over the study follow-up periods. Anxiety and substance use disorders were the most common among these, each occurring at rates of around 30%.

The exploration of the course of functioning in these adolescent clinical samples has been limited to cross-sectional assessment at follow-up. These studies reported impairment at follow-up points up to 21 years on a range of functioning scales. Most consistently and severely affected among the specific domains was relationship functioning.

Chapter 3 Personality, personality pathology and their relationship to Major Depressive Disorder in young people

3.1 Introduction

The aim of this chapter is to present the current understanding of the nature of the interaction between Major Depressive Disorder and a young person's personality. The reason for interest in this interaction is that personality variables have been found to be associated with negative outcomes for adults with Major Depressive Disorder. Prominent among these findings are associations between these poor outcomes and higher levels of neuroticism (Klein, DN et al., 2018) or personality disorder (Newton-Howes, Tyrer, & Johnson, 2006).

Firstly, a summary is provided on how personality and personality pathology are conceptualised. Particular attention will be given to young people and to the models upon which the instruments used to assess personality and personality pathology in this study are based.

In this study, personality traits were assessed with the NEO Personality Inventory, which is based on the Five Factor Model of personality (McCrae 1991). Personality pathology was assessed with the Structured Clinical Interview for DSM-IV personality disorders (SCID-II) (First, MB et al., 1997), which uses the model of personality disorders developed for the earlier DSM-III (American Psychiatric Association Task Force on Nomenclature and Statistics 1980).

The second part of the chapter describes theory and empirical data relating to the interaction between personality and personality disorder and Major Depressive Disorder.

3.2 Personality

3.2.1 Definition

A definition of personality that is inclusive of a number of strands of personality theory is that it is "the set of psychological traits and mechanisms within the individual that are organised and relatively enduring and that influence his or her interactions with, and adaptations to, the intrapsychic, physical and social environments" (Larsen, RJ & Buss, DM, 2005).

3.2.2 Conceptualisation of personality

Personality theory is a complex and evolving field, with many components potentially belonging under its broad umbrella. This summary will describe its most prominent strands.

3.2.2.1 *Temperament*

This component of personality theory draws on the observational study of children from infancy to early adulthood by Thomas and Chess (Compas, Connor-Smith, & Jaser, 2004; Thomas, A, Chess, S, & Birch, HG, 1970). The term has come to refer to characteristics that are “largely inherited, evident early in life, and relatively stable across development” (Frick, PJ & Morris, AS, 2004). It is believed that these temperamental characteristics have a close relationship with biological processes (Shiner, RL & Allen, TA, 2018).

The instruments developed to measure temperament based on theoretical reflection, further observational studies and the factor analysis of this observation “have all provided for some measure of emotionality, most particularly negative emotionality, adaptability, activity, sociability, and attention regulation” (Hertzig 2012).

Longitudinal studies have demonstrated significant correlations of measures of temperament over time (Rettew & McKee, 2005). These have been shown to be higher over shorter time intervals, with correlations of 0.25 reported from infancy to age 5, and 0.82 from 5 to 7 years of age (Prior M 1992).

The Dunedin Multidisciplinary Health and Development Study analysed the correlation of temperament types at age 3 with related constructs up to the age of 21 and reported small to medium effect sizes, with regression coefficients from the multiple regression analyses between 0.25 and 0.48 (Caspi 2000). It has been observed that these correlations are strongest at the extremes of temperament measures (Hertzig 2012).

3.2.2.2 *Factorial traits*

Personality traits have been defined as “the relatively enduring patterns of thoughts, feelings and behaviours that reflect a tendency to respond in certain ways in certain circumstances” (Roberts 2009). They have been conceptualised as being a later-occurring and more differentiated form of temperamental dispositions (Shiner, RI 2015). Models of personality traits have been developed from population-level patterns of co-variation of inter-individual differences in behaviour (Baumert et al., 2017).

The five-factor model (FFM) of personality traits which is used in this study has its origins in the factor analysis of personality-related adjectives extracted from an

unabridged English dictionary. These terms had been initially clustered and analysed by Cattell who reduced them to 12 factors (Cattell, RB 1943, 1947). An early five factor model was produced from Cattell's variables shortly after this (Fiske, DW 1949).

The FFM of Costa and McCrae (McCrae & Costa, 1987) is comprised of five dimensions of personality; neuroticism, extroversion, openness to experience, conscientiousness and agreeableness, with these dimensions further sub-divided into 30 "facets". The structure of the model was developed largely through factor-analytic methods in adult community samples (McCrae 1991).

In Table 3-1 the facets of the FFM as delineated in the NEO-Personality Inventory of Costa and McCrae (Costa & McCrae, 1995) are listed as well as an alternative description of the lower order facets of each factor (Shiner, RL & DeYoung, CG, 2013). Affective components of neuroticism are anxiety, fearfulness, anger and irritability, therefore containing both internalising and externalising dimensions (Shiner, RL & Allen, TA, 2018). Individuals with high neuroticism have a tendency to low self-esteem, self-consciousness and guilt (McCrae & John, 1992). The behavioural manifestations of this trait also have internalising and externalising dimensions, with avoidance and impulsivity characteristic of those with high neuroticism (McCrae & John, 1992; Shiner, RL & Allen, TA, 2018).

Extraversion has been described as reflecting "an individual's preference to actively engage with or approach novelty in the environment" (2018), with a key aspect of this environment being other people. The associated "positive emotions" include being cheerful and enthusiastic.

The trait of conscientiousness combines a tendency to be governed by conscience and to diligence and thoroughness (McCrae & John, 1992).

One's approach to interpersonal situations links a number of the facets of agreeableness, with high degree of concern for others' feelings manifest in characteristics such as empathy and altruism (Tackett, JL, Hernández, MM, & Eisenberg, N, 2019). Aligned with such a concern are tendencies to self-regulation and self-discipline (2019).

The final trait of the FFM, openness to experience has been defined as capturing "individual differences in the motivation to approach and create novel stimuli, as well as in patterns of convergent and divergent thought" (Schwaba, T 2019). Convergent thought refers to intelligence.

Table 3-1: Personality factors and lower-level facets of the FFM of personality

Personality factor	Lower-level facets	
	NEO-PI facets	Shiner and DeYoung
Neuroticism	Anxiety Depression Self-consciousness Impulsivity Vulnerability Hostility	Fearfulness Insecurity/low self-confidence Anxiousness Anger/irritability Sadness
Extraversion	Positive emotion Activity Excitement seeking Warmth Gregariousness Assertiveness	Sociability Positive emotions Assertiveness Approach Activity level/energy
Conscientiousness	Order Achievement-striving Competence Deliberation Self-discipline Dutifulness	Achievement striving Orderliness Self-control Attention
Agreeableness	Modesty Straightforwardness Trust Altruism Compliance Tendermindedness	Hostility/aggression Empathy Compliance Prosocial behaviour
Openness to experience	Fantasy Aesthetics Feelings Ideas Values Actions	Creativity Curiosity Intellect Perceptual sensitivity

The FFM has been replicated in adolescents (De Fruyt, F, Mervielde, I, Hoekstra, HA, & Rolland, J-P, 2000; John, Caspi, Robins, Moffitt, & Stouthamer-Loeber, 1994).

However a weakness identified in this research is that this finding has relied mostly on a “top-down” approach in which instruments designed for the FFM have been tested in

this age group, rather than a more “bottom-up” strategy where instruments without this theoretical orientation are used (de Pauw, S 2017).

Factor analytic studies of the FFM in children and adolescents have found that there is some differentiation from adults in the allocation of facets to particular domains. (Shiner & Caspi, 2003b). A narrower Neuroticism domain has been defined, containing facets describing anxious distress and low self-worth. The facets of impulsivity and angry-hostility, found in the adult Neuroticism domain, have been found to cluster in the Conscientiousness and Agreeableness domains respectively (de Pauw, S 2017). A more recent “bottom-up” factor analytic study identified a six-factor model, with Activity the additional domain (Soto & John, 2014). This contains facets reflecting motor activity, energy level, motivation and competitive drive. It was found that this domain became less prominent over ages 15 to 20, with the FFM providing a better fit for 18 to 20 year olds. In her review of childhood personality and temperament, de Pauw comments that more developmental research is needed to further clarify personality structures in young people (de Pauw, S 2017).

The FFM was chosen as the trait model to be used in this study due to its solid scientific foundations, which contribute to it being described as the consensus model of personality traits (Klein, DN et al., 2018). Its structure has been replicated by multiple researchers, both by those using Cattell’s variables, and others analysing alternative sets of variables (Goldberg 1990; Wright, AGC 2017). This structure has also been replicated across a range of cultures (Allik, J & Realo, A, 2017; John, OP, Naumann, LP, & Soto, CJ, 2008).

It has also been found to be a comprehensive model of personality, being able to replicate the factor structures of other scales “using data derived solely from scale associations with the five-factor model” (O’Connor 2002).

There is evidence that the domains of the FFM are enduring representations of inter-individual differences. The rank-order correlation of the trait domains of the FFM has been demonstrated to range from 0.61 to 0.8 for individuals from age 25 to 75 at intervals from 4 to 20 years (Costa, McCrae, & Löckenhoff, 2019; Costa, PT & McCrae, R, 2017).

In general there is less stability of traits at a younger age, with rank correlations of 0.47 between ages 12 to 18, 0.51 between ages 18 to 22, and 0.57 between ages 22 to 29 (Roberts & DelVecchio, 2000).

There is also evidence of normative change in personality over the life-course. This was examined in a meta-analysis of 92 prospective studies of personality using the

FFM taxonomy (Roberts, Walton, & Viechtbauer, 2006). This found a reduction in mean-level neuroticism from adolescence into middle age, with an increase in facets of extraversion relating to independence and self-confidence over the same period.

Both openness and conscientiousness increased over young adulthood (age 18-22), with the increases in conscientiousness extending into middle age. The only period of statistically significant change for agreeableness was between the ages of 60 to 70, which saw an increase in this trait.

In a brief discussion on the mechanism of this change, the authors of this review suggest it is due to “normative change”, that is a change that most people would experience in a particular life period, potentially driven by a combination of biological and social processes.

3.2.2.3 Big three model

Another trait model that is often applied by researchers in the Major Depressive Disorder field is the PEN model of Eysenck. This model has diverse theoretical foundations, drawn from disciplines such as “learning theory, genetics, physiology, perception, psychopharmacology...” (van Kampen 2009).

The PEN model contains the traits negative emotionality and positive emotionality, which have been found to correlate highly with the FFM traits neuroticism and extraversion respectively (Kentle 2002; Markon, Krueger, & Watson, 2005). In a student sample negative emotionality had a correlation of 0.83 with neuroticism, and positive emotionality had a correlation of 0.78 with extraversion (Clark, LA & Watson, D, 1999).

The third trait of the PEN model was originally named “psychoticism” by Eysenck, but latterly has been known as disinhibition vs. constraint to differentiate it from psychosis. Eysenck proposed that disorders with psychotic symptoms were both on a continuum from least to most severe and also that they were continuous with a spectrum of other “abnormal states” namely “schizoid disorders, psychopathy, alcoholism, criminality” (van Kampen 2009). These propositions have been criticised and questions raised on the adequacy of the psychometric properties of the P dimension (Zuckerman, Kuhlman, & Camac, 1988).

This trait has been found to have negative correlations of a moderate strength with two FFM traits, -0.54 with conscientiousness, and -0.50 with agreeableness (Clark, LA & Watson, D, 1999). Openness has been found to have a moderate degree of correlation

with positive emotionality (Digman 1997), though in one analysis was mostly independent from the Big Three (Markon et al., 2005).

Tellegen developed a similar three-factor model, and labelled the third dimension constraint (Tellegen, A 1985). Subsequently, the positive emotionality dimension was divided into “agentic” items, measuring dominance and assertion, and “communal” items measuring sociability and affiliation (Patrick, Curtin, & Tellegen, 2002).

3.2.2.4 Other trait models

A distinguishing feature of the lexical HEXACO six-factor model is its development by factor analysis of personality descriptors of a range of European and Asian languages (Ashton & Lee, 2007; Ion et al., 2017).

Two of its factors, Extraversion and Conscientiousness are very similar to those of the FFM. A third factor, Openness to Experience is also similar to its same-named factor of the FFM, but has a “prominent element” of unconventionality.

Its Emotionality factor shares features of Neuroticism of the FFM, but excludes items related to anger and adds those related to sentimentality. The Agreeableness factor of HEXACO is similar to that of the FFM, but with (low) anger included and sentimentality excluded. The additional trait, beyond the FFM is named Honesty-Humility, and contains traits such as sincerity, fairness, unpretentiousness and lack of greed.

The authors of the model theorise that the Honesty-Humility, Agreeableness and Emotionality factors are important in reciprocal and kin altruism. Each of the other three factors are related to engagement in particular types of endeavours, social for Extraversion, task-related for Conscientiousness, and idea-related for Openness to Experience.

In two studies of comparative validity in general populations samples with the FFM, the HEXACO model has demonstrated similar strengths of correlation with behavioural outcomes, informant reports and clinical measures (Grucza & Goldberg, 2007; Thalmayer, Saucier, & Eigenhuis, 2011).

3.2.2.5 Further elements of personality theory

Personality theorists are also interested in the processes that contribute to the personality structures described above as well the development of personality over the life-course (Baumert et al., 2017; McAdams, DP 2019).

In his conceptualisation of personality development over the life-course, McAdams proposes overlapping stages of being a social actor, then to being a motivated agent, with the third stage as an autobiographical author (2019).

This conceptualisation highlights the dynamic relationship between social roles and temperament and traits, proposing in adult years that increasing mean levels of agreeableness and conscientiousness and decreasing mean levels of neuroticism are related to the responsibilities of being a parent or paid employee (Donnellan, MB, Hill, PL, & Roberts, BW, 2015; McAdams, DP 2019). Such a relationship of adaptation between social roles and traits is captured by the quotation "...the mind has the structure it has because the world has the structure it has" (Anderson 1991). Motivation has been identified as a potential underlying process in personality development (McAdams, DP 2019). Drives to competence and affiliation in young adulthood are examples of such guiding motivations (Freund, AM & Riediger, M, 2006). Functionalist frameworks of personality "predict that individuals will gravitate towards trait levels that allow them their most valued outcomes" (Baumert et al., 2017). Such dynamic interactions are central to the systemic model of personality offered by Larocco (Larocco 2015). In this model, personality is viewed as an open, hybrid system with constituents including "affective tendencies, feeling rules, cognitive frames, semiotic repertoires, forms of memory, senses of embodiment as well as the semioaffective and cognitive maps and channels that link such phenomena and structures"(2015). This large number of constituents illustrates the complexity of personality as a phenomenon, and the many areas to be elucidated by further research.

3.2.2.6 Cloninger

The "psychobiological" model of Cloninger is another model of personality whose relationship with Major Depressive Disorder has been explored, most often in testing its association with treatment outcome. The development of this model was informed particularly by genetic studies and theories of learning and identity development (Cloninger, Svrakic, & Przybeck, 1993).

Two Identifying features are its explicit division of personality into temperament (four domains) and character (three domains), and its inclusion of personality pathology within these domains, such that it straddles both pathological and "normal" personality. Its temperament domains are Harm avoidance, Novelty seeking, Reward dependence and Persistence, and its character domains are Self-directedness, Self-transcendence and Cooperativeness.

Cloninger's model has been operationalised in the Temperament and Character Inventory (TCI). In regard to its psychometric properties, low levels of internal

consistency for some scales in an early version were improved in its revised form (Brändström, Richter, & Nylander, 2003). It was also proposed that patterns of scores on the TCI dimensions would relate to specific personality disorders, but evidence for such associations has been mixed (Trull & Durrett, 2005).

3.3 Personality pathology

The period of the last two decades has been a particularly intense phase of theoretical reflection and empirical research in the field of personality pathology, catalysed by the publication of revisions of the main classificatory systems, the fifth version of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) and the 11th version of the International Classification of Diseases (ICD-11).

A significant development of this period has been a recognition of dimensional characteristics of personality pathology, and the parallel recognition of the limitations of the categorical system used in DSM-IV and ICD 10.

3.3.1 Personality disorder

3.3.1.1 Definition

This term designates a threshold at which the impact of elements of a person's personality becomes sufficiently problematic as to warrant psychiatric treatment. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorder, DSM-5 identifies the cause of this impact as being the deviation of a person's personality, "markedly from the expectations of the individual's culture" (American Psychiatric Association 2013).

Personality is defined as defined by the DSM-5 as "an enduring pattern of inner experience and behaviour". DSM-5 identifies four areas of personality in which the marked deviation is manifested: cognition, affectivity, interpersonal functioning and impulse control. Two of these areas must be affected to reach the diagnostic threshold. The problematic impact that the disorder must cause is "clinically significant distress" or "impairment in social, occupational, or other important areas of functioning" (2013). The DSM-5 definition is very similar to that proposed for the 11th edition of the International Classification of Diseases (ICD-11), which defines personality disorder as being a "...disturbance in how an individual experiences and thinks about the world, manifested in maladaptive patterns of cognition, emotional experience, emotional expression, and behaviour" (Tyrer, Reed, & Crawford, 2015).

As would be expected given it is a disorder of personality, both classifications stipulate the pervasiveness, inflexibility and stability of the divergent/maladaptive patterns (American Psychiatric Association 2013; Tyrer et al., 2015).

3.3.1.2 Categorical model of personality disorder

The categorical model of personality disorder has been prominent in psychiatric research and practice since the publication of DSM-III (American Psychiatric Association Task Force on Nomenclature and Statistics 1980). It has been posited that the contemporaneous “neo-Kraepelinian” movement (Blashfield, RK 1984) which asserted a medical model of psychiatry had a significant influence on the categorical conceptualisation of personality disorders in DSM-III (Livesley, WJ 2018).

Two particularly relevant propositions of the neo-Kraepelinian “credo” to the conceptualisation of personality disorders were that there is a boundary between the normal and the sick, and that there are discrete mental illnesses (2018).

The ten specific personality disorders, organised into three clusters, that were defined in DSM-III have been retained by successive versions of the DSM, including DSM-5.

These are the Cluster A disorders: schizoid, paranoid, schizotypal, the Cluster B disorders: borderline, histrionic, narcissistic, antisocial, and the Cluster C disorders: avoidant, dependent and obsessive-compulsive. Each has specified criteria, and to qualify for a diagnosis, one must meet a specific number of these, in addition to the general criteria for personality disorder described in 3.3.1.1.

Clinical observations and theoretical reflections provided the content that led to conceptualisation of these disorders, drawing on a range of theoretical traditions, particularly classical European phenomenologists and psychoanalysts (Livesley, WJ 2018; Trull & Durrett, 2005). Important among contributory thinkers were the early to mid 20th century psychiatrists Schneider, Freud, Reich and Kohut (Crocq 2013; Livesley, WJ 2018) .

A number of criticisms of the categorical model, and the DSM personality disorder diagnostic structure have come from epidemiological studies.

The status of a personality disorder (as defined by DSM) as a distinct entity is weakened by findings such as comorbid personality disorder diagnoses being present in more than 50% of patients (Oldham et al., 1992; Zimmerman, Rothschild, & Chelminski, 2005) and remission rates from diagnostic status of up to 60% in 2 years (Grilo et al., 2004).

Other aspects of the DSM structure affecting its validity include the arbitrary cut-offs of numbers of criteria to meet the personality disorder diagnostic threshold and also the heterogeneity of an individual disorder that is allowed by the many possible combinations of traits (Johansen, Karterud, Pedersen, Gude, & Falkum, 2004; Ofrat, S, Krueger, RF, & Clark, LA, 2018; Trull & Durrett, 2005).

One further limitation of the categorical system is that it dispenses with potentially useful information when the sum of traits is subthreshold for a categorical disorder diagnosis (Skodol 2012; Trull & Durrett, 2005).

Critical observations have also been made of the clinical utility of the categorical system. The large overall number of criteria and detailed assessment needed to accurately establish the presence of an individual trait contributed to a time consuming and complex diagnostic process (Tyrer et al., 2015). Also, with the exception of borderline and to a lesser extent anti-social personality disorder, the model has not led to the development of treatment for the disorders (Newton-Howes, Clark, & Chanen, 2015).

3.3.1.3 Dimensional models of personality pathology

Part of the impetus for the development of dimensional models of personality disorder came from the concerns about the limitations of the categorical model as described above (Widiger & Simonsen, 2005).

The particular advantages of a dimensional approach, especially if it includes the assessment of both “normal” and pathological personality are its breadth of description of an individual and the conciseness delivered by eliminating the issue of “comorbid” personality disorders (De Clercq 2018; Ofrat, S et al., 2018).

Three approaches to developing a dimensional model of personality pathology have been to to organise the traits of the categorical model dimensionally, and to integrate these traits either with symptoms of mental state disorders or with existing models of general personality structure (Widiger & Simonsen, 2005).

All of these approaches have produced a structure of four similar domains, with some having a fifth (Kotov et al., 2017; Widiger & Simonsen, 2005). The four consistent domains are negative affectivity, detachment, antagonism, and disinhibition, the fifth, psychoticism.

The four consistent domains can be conceptualised as representing maladaptive variants of four of the domains of the FFM (Verbeke, De Caluwé, & De Clercq, 2016). Negative affectivity is the extreme high variant of Neuroticism, while detachment,

antagonism and disinhibition are extreme low variants of Extraversion, Agreeableness and Conscientiousness respectively.

The relationship of psychoticism to Openness to Experience has been a topic of debate, with concern about how well it can incorporate schizotypy (Ofrat, S et al., 2018). A study attempting to resolve this issue concluded that “psychoticism can be understood as a related construct within the structural system of some Openness to Experience/Intellect conceptualisations” (Chmielewski, Bagby, Markon, Ring, & Ryder, 2014).

3.3.1.4 Dimensional models in classificatory systems

The DSM-5 has included an alternative model of personality disorders (AMPD) in its Section III Emerging Measures and Models (American Psychiatric Association 2013). One part of this model is a taxonomy of pathological personality traits, with the broad domains being those listed in 3.3.1.3 above. Beneath these domains lie twenty five facets, listed in Table 3-2 below.

Table 3-2: Domains and facets of DSM-5 III personality disorder model

Domain	Facets
Negative affectivity	Emotional lability Anxiousness Separation insecurity Perseveration Restricted Affectivity (-)
Detachment	Restricted Affectivity Withdrawal Anhedonia Depressivity Intimacy avoidance Risk taking
Antagonism	Manipulativeness Deceitfulness Grandiosity Attention seeking Calmness Hostility
Disinhibition	Depressivity Impulsivity Risk taking Distractibility

	Rigid perfectionism (-)
Psychoticism	Perseveration Eccentricity Perceptual dysregulation Unusual beliefs

ICD-11 contains only a dimensional model of personality disorder. It differs from the DSM-V AMPD model in that it does not have a psychoticism domain, and that it does not contain obsessiveness within its disinhibition domain, rather having its own domain of anankastia (Widiger, TA 2018). The reason for not having a psychoticism domain is that schizotypal personality disorder is considered a form of schizophrenia (2018). Its remaining three domains mirror three of the DSM-V AMPD: negative affectivity, detachment and dissociality (analogue of “antagonism”) (Tyrer et al., 2015). One issue identified with the ICD-11 trait model is the absence of a lower facet level, the details of which would be expected to guide clinical treatment (Herpertz et al., 2017).

There is some evidence for the validity of these new models, with less empirical data available for the more recently published ICD-11 (Mulder & Tyrer, 2019). The instrument that assesses the DSM-V AMPD trait model, the Personality Inventory for DSM-V (PID-5) has been reported as having adequate psychometric properties (2019). Researchers have also found the DSM-V AMPD traits to be associated with psychosocial impairment (Simms & Calabrese, 2016), and relatively stable across periods up to more than a year (Zimmermann, Kerber, Rek, Hopwood, & Krueger, 2019).

3.3.1.5 Severity in classificatory systems

Both the DSM-5 (in its Section III) and the ICD-11 include a measure of the severity of the personality disorder. In the DSM-5, personality functioning is measured in the domains of sense of self, divided into identity and self-regulation, and interpersonal relatedness, divided into empathy and intimacy. Each sub-domain is scored on a five point severity scale. These domains have been criticised as being too aligned with a psychodynamic theoretical model of personality disorder, as opposed to being more theoretically neutral (Widiger, TA 2018).

The ICD-11 rates severity on a spectrum from a sub-threshold category of “personality difficulty” through mild, moderate and severe levels. In its description of these levels, it has broad descriptions of the degree of impairments in interpersonal relationships and

the performance of social and occupational roles, and the level of harm to self and others (Tyrer et al., 2015). The researchers and clinicians critical of the lack of detail of the ICD-11 trait model have also expressed concern about the reliability and utility of this approach to defining severity (Herpertz et al., 2017).

3.3.1.6 Personality pathology in young people

Both the categorical and dimensional models of personality pathology have had some exploration in young people, with research into the categorical model having been limited by uncertainty about the validity of and the potential stigma resulting from a personality disorder diagnosis prior to adulthood (Newton-Howes et al., 2015; Sharp, Vanwoerden, & Wall, 2018).

The relevance of the traits of the categorical model to young people has been indicated by their mean level being shown to peak in early to mid-adolescence in a community sample assessed for these traits over 9 years into early adulthood (Johnson et al., 2000). Borderline personality disorder is the disorder most often assessed in clinical samples of adolescents, and prevalence rates of 11% in outpatients (Chanen et al., 2004) and up to 49% inpatients demonstrate its importance (Levy et al., 1999).

A perception that adolescent personality was too unstable was one of the reasons for the reluctance to diagnose personality disorders in this age group (Sharp et al., 2018). Longitudinal studies indicate a greater stability for the overall level of personality disorder traits that an individual has, and the level of traits within the DSM-defined clusters, than for specific disorders for which there is a wide range of stability (Chanen et al., 2004; Johnson et al., 2000) .

Over two years in a clinical sample the absolute stability of trait scores was 0.44 (intra-class correlation coefficient), and rank-order stability 0.47 (Pearson's correlation), while the corresponding scores for individual disorders ranged from 0.23 to 0.71, and 0.27-0.76 (2004).

An attenuation in the overall level of personality disorder traits from adolescence to early adulthood has been observed, with the level of these being found to fall by 48% over 9 years in the above-mentioned community sample (Johnson et al., 2000).

Significant improvement is not however a universal experience. In that study, the presence of a personality disorder diagnosis as an adolescent was predictive of the number of personality disorder traits one had as a young adult, which was a mean of 17 for that group (2000).

The dimensional model of personality pathology outlined in 3.3.1.4 has been replicated in adolescents, an example being the initially four-domain Dimensional Personality Symptom Item pool (DIPSI: (De Clercq, De Fruyt, Van Leeuwen, & Mervielde, 2006)) (Verbeke et al., 2016).

Its development took a “bottom-up” approach as its name implies, with the use of a maladaptive trait item pool which was developed from parental descriptions of childhood personality (Kushner, Tackett, & De Clercq, 2013).

In this model a fifth dimension named “Oddity” was subsequently added and contains the facets Oversensitivity to feelings, Extreme fantasy, Daydreaming and Odd thoughts and behaviour (Verbeke & De Clercq, 2014).

There is evidence of convergent validity of the DIPSI model with a similar four factor domain emerging from the youth version of the Schedule for Nonadaptive and Adaptive Personality (Linde, Stringer, Simms, & Clark, 2013), developed by a “top-down” approach from the adult version of this instrument (Kushner et al., 2013).

3.3.1.7 Affective temperaments

Central to the origins of this concept is the theory of Kraepelin that particular personality patterns were precursors of affective illness, namely depressive, manic, irritable and cyclothymic temperaments (Klein et al., 2011; Kraepelin, E 1921). An important contributor to this theory was his observation that the relatives of people with affective illness appeared to possess these temperaments.

Contemporary echoes are evident in the work of Akiskal and colleagues (Rihmer, Akiskal, Rihmer, & Akiskal, 2010), and also the presence of diagnoses of cyclothymic and dysthymic disorders, and depressive personality disorder in versions of the DSM. Akiskal operationalised his conception of affective temperaments in the TEMPS instrument (Akiskal et al., 1998), and has used this to explore the relationship of its designated temperaments to affective disorders. The TEMPS added an “anxious” temperament to the four proposed by Kraepelin.

Studies with the instrument have found an aggregation of related temperaments in those with affective disorders and their families, and that a cyclothymic temperament is predictive of the later development of hypomanic symptoms in patients with Major Depressive Disorder (Rihmer et al., 2010).

In regard to non-clinical populations, a Gaussian distribution of these temperaments has been reported (Rovai et al., 2013). A number of studies in community samples

have found significant positive correlations between the temperament types, raising questions about their independence (Vázquez, Tondo, Mazzarini, & Gonda, 2012). Kraepelin's observation regarding the presence of related temperaments in family members of those with mood disorders has received empirical support in the case of depressive personality disorder. Research has shown elevated rates of this disorder in first degree relatives of people with MDD (Klein 1999), and a genetic basis for this finding has been suggested by a large twin study that showed shared genetic variance for these conditions (Ørstavik, Kendler, Czajkowski, Tambs, & Reichborn-Kjennerud, 2007).

Depressive personality disorder has however not been included in the DSM-5, with its features judged to be best represented on the dimensional traits of anxiousness, depressivity and anhedonia (Huprich 2013).

In his review on depression and personality, Klein comments that affective temperaments as currently conceived contain complex cognitive and interpersonal characteristics, such that they are unlikely to reflect "basic temperamental processes", but rather an interaction between such processes and environmental factors (Klein et al., 2011).

3.3.1.8 Clinical traits

There is a small body of research investigating the relationship of individual personality "traits" with MDD (Klein, DN, Durbin E, Shankman, SA, & Santiago, NJ, 2002).

Although named traits, facets may be a title that is more consistent with current terminology. The most studied are dependency, obsessionality, self-criticism, sociotropy and autonomy. Sidney Blatt (Blatt, SJ 1974), Aaron Beck (Beck, AT n.d.) and David Zuroff (Zuroff, Mongrain, & Santor, 2004) have been prominent theorists in this field.

It has been hypothesised that specific "traits" would interact with specific stressors to increase the risk of an MDE, an example being that a dependent person would be at particular risk of an MDE following a relationship breakdown.

3.4 The relationship of personality variables to MDD in young people

This section begins with an overview of the models that have been developed to describe the relationship of personality variables to MDD. The focus of this section as a whole will not be on proving a particular model, but rather on providing evidence of the interaction between personality and MDD.

As this is a study of young people with established MDD, most attention will be paid to the evidence of the impact of personality on the course of illness. A circumscribed review of the published literature was performed on this topic, the search strategy described in 3.4.4 below.

There will be some exploration of the role of personality in the development of MDD, which would otherwise be presented in the following chapter on the aetiology of the disorder.

3.4.1 Classical models

A range of models have historically been proposed by theorists to describe the relationship between personality variables and Major Depressive Disorder (Bagby, Psych, Quilty, & Ryder, 2008; Klein, DN et al., 2002; Klein, DN et al., 2018). The term personality variable is being used here to include both “normal” and pathological personality. Two models have prominent positions on aetiology. Of these, the vulnerability model identifies personality variables as having a role in the development of MDD, while the common cause model hypothesises that a third factor has a role in the causing both.

Other models focus on non-causative influences. In the pathoplastic model, personality affects the presentation of MDD, its course and its response to treatment. The scar or complication model is oriented in the other direction, positing an effect of MDD on personality.

Two other models place personality and MDD on a spectrum as well as incorporating a potential causative role for personality and third common factors. The precursor model contains a spectrum of time, having personality temporally preceding MDD. Severity forms the spectrum of the continuum model, with parallel dimensions of increasing personality disturbance and increasing severity of depressive illness.

One could summarise these models as collectively describing personality and MDD as dynamic entities, each affecting the evolution of the other, with other factors potentially playing a mediating role in this relationship (Durbin, EC 2019).

3.4.2 Contemporary contributions to models

Contemporary developments in research and thinking on personality and MDD that add to the classical models of their relationship are the multiple levels aetiological model (Hankin 2012), and the categorisation of MDD as part of the broader dimension of internalising disorders or an internalising spectrum (Kotov et al., 2017) or in relation to a general psychopathology factor (Tackett et al., 2013) in the quantitatively-developed nosologies.

The multiple levels model of the aetiology of MDD presents MDD as arising through the dynamic interaction between factors grouped broadly into those within an individual and those in the environment, with each broad grouping having further subdivisions. An aetiological agent therefore exists in a complex system with many other agents with which it can interact.

Consideration of MDD as part of a internalising dimension or spectrum or a general psychopathology factor logically leads to locate its relationship with personality at least to some degree through its relationship with these broader structures.

3.4.3 Mechanism and mediators of the relationship between personality variables and MDD

The classical models described above provide information about the possible structure and direction of the relationship between personality variables and MDD. Consideration of potential third factors and of the details of the mechanism of the relationship add a further degree of depth to the understanding of this interaction.

Genetic factors have been nominated as potential contributors to the relationship. Twin studies have found that the covariation between neuroticism and MDD was due to a large degree to common genetic effects (Fanos, Gardner, Prescott, Cancro, & Kendler, 2002). More recently, genome-wide association studies in adults have demonstrated associations between neuroticism and MDD, both as a single disorder, and also as part of the dimension of internalising psychopathology (Lo et al., 2017; Sanchez-Roige, Gray, MacKillop, Chen, & Palmer, 2018).

Theorists in the developmental psychology field have described the processes that might link personality traits to MDD (Durbin, EC 2019; Shiner & Caspi, 2003a). Shiner

and Caspi nominate the learning processes, patterns of comparison with others, and the nature of the interactions with the environment that are characteristic of particular personality dispositions as important mediators of the relationship between childhood personality and later psychopathology (Shiner & Caspi, 2003a).

Durbin cites experiences of “developmental pressure” such as at life-stage transitions as loci for these interactions to occur (Durbin, EC 2019). An example that is relevant to the study sample is the potential impact of low extraversion on a transition from primary to secondary school in regard to the social environment that it might elicit. Adolescents with low levels of this trait are less likely to attract peers to play with, with the potential consequence of the stress of loneliness contributing to the onset of an MDE.

These processes would also seem applicable to personality pathology, and to the maintenance of MDD as much as its development.

3.4.4 Search strategy for literature reporting association of personality variables on course of MDD

For adolescent samples, information on a predictive effect of personality variables were sought from the clinical and community studies reviewed in Chapter 2.

This was also done for the adult clinical samples reviewed in that chapter. In addition, the studies selected as described in 5.3 are included in this chapter if they included personality variables as a predictor.

As the number of studies of adult samples that were able to be cited according to the criteria described in 5.3 was only six, and as the investigation of the effect of personality variables a key priority of this study, the selection criteria were adjusted. The adjusted minimum requirements for these studies were that they were at least 6 months in duration, and that both the baseline diagnostic and outcome evaluations of MDD were made according to diagnostic criteria. The methodological limitations of these additional studies were having clinical rather than structured assessments, not adhering to the consensus definitions of recovery and recurrence, or having relapse or remission as outcomes. Studies of fewer than 50 participants were also able to be selected.

As with the strategy described in 2.4.5.1 the first step in this search was to find the most recent relevant systematic reviews of adult samples. Those found on the predictive effect on the course of MDD of personality traits and personality disorder covered studies published up to 2008 (Morris, Bylsma, & Rottenberg, 2009) and 2007

(Newton-Howes et al., 2014) respectively. The studies within these reviews meeting the selection criteria of the search are included in the discussion below.

Research subsequent to these reviews were sought using the search terms “depression” AND “neuroticism” OR “negative affectivity” AND “predict*” for trait studies, and “depressive disorder” AND “personality disorder” for studies of personality pathology. The terms “neuroticism” and “negative affectivity” were used rather than “personality” in order to narrow the search, with the expectation that most relevant studies would contain one of these terms, being the most prominent among traits.

3.4.5 Personality traits and MDD

3.4.5.1 Cross-sectional studies of trait models of personality and MDD

A meta-analysis has been performed on 175 cross-sectional studies testing the association of FFM personality traits in adults experiencing an MDE (Kotov, Gamez, Schmidt, & Watson, 2010). There is the potential for the strength of any such association to be inflated by a state effect, as well as by any enduring effect of MDD on personality.

The meta-analysis revealed a large effect size of 1.33 for the association of Neuroticism with having an MDE, an association that was in fact stronger with Dysthymic Disorder ($d=1.93$) and with anxiety disorders ($d=1.91$). The review authors hypothesize that the relatively weaker association with MDD may be due to heterogeneity within the MDD population, including those who have only had a single episode, who may have lower levels of neuroticism.

Among facets, one of the studies reviewed in the meta-analysis demonstrated that items measuring the stress reaction components of neuroticism had a specific association to anxiety and depressive disorders (Krueger, Caspi, Moffitt, Silva, & McGee, 1996).

Extroversion and Conscientiousness had a moderate negative associations with MDEs ($d=-0.62$, -0.90), also having more strongly negative associations (>1.0) with the other disorder types.

The authors of the review comment that the same constellation of traits are associated across the internalising disorders: high neuroticism, low conscientiousness and low extroversion, and suggest that environmental factors account for the differentiation into particular disorders.

3.4.5.2 Prospective studies of personality traits and the development of MDD

Table 3-3: Prospective studies investigating the association of personality traits and MDD in young people

Study	Instrument/s	Association with onset of MDD
Dunedin Multidisciplinary Health and Development Study (Krueger et al. 1999a)	MPQ ¹	NE (high) PE (low)
Minnesota Twin Family Study (Wilson et al. 2014)	MPQ	NE (high) PE (low) Constraint (low)
Northwestern-UCLA Youth Emotion Project (Kendall et al. 2015)	MASQ-AD Big 5-E NEO-PI-R BIS Big 5 N	N (high) PE (low)
Christchurch Health and Development Study (Newton-Howes et al. 2015)	EPI	NE (high) PE (low)

¹ (Tellegen, A & Waller, NG, 1995)

Each of the above-mentioned models would gain support from the evidence of particular personality factors temporally preceding the development of MDD. Such evidence is found in four studies in young people, all community samples that had baseline assessments performed in mid-teenage years, then followed their participants to young adulthood for between three and sixteen years.

The projects were situated in Dunedin, New Zealand (Krueger 1999a), Minnesota (Wilson, DiRago, & Iacono, 2014) Los Angeles and Chicago (Kendall et al., 2015) and Christchurch, New Zealand (Newton-Howes, Horwood, & Mulder, 2015).

All of these studies investigated Neuroticism/Negative Emotionality (N/NE) and Extroversion/Positive Emotionality (E/PE).

To measure personality traits, the Dunedin and Minnesota studies used the Multidimensional Personality Questionnaire (MPQ) (Tellegen, A & Waller, NG, 1995), which also rates “Constraint”, the third factor of the three-factor personality model. The Christchurch study assessed personality with the short form of the Eysenck Personality Inventory (Eysenck, HM & Eysenck, SBG, 1964), while the other USA study used five different instruments. Only the Christchurch study tested a range of co-variate psychosocial risk factors.

The baseline neuroticism or negative emotionality score was predictive of a future MDE in each study. This relationship was maintained in the multi-variate analysis of the Christchurch study. An interesting finding of the Minnesota study was that the group of people with either chronic or recurrent MDD failed to show the age-related normative decrease in neuroticism. This could mean such a persistence is a risk factor for a more severe course and/or represents a “scar” effect of a more severe course.

Lower levels of Extroversion or Positive Emotionality or related sub-scales were associated with the later development of MDD in all of the studies, but the magnitude of this effect was reduced when tested with co-variates. The Los Angeles/Chicago study found that Positive Emotionality no longer had a significant effect when Neuroticism was introduced in their analysis. Their interpretation of this result is that the predictive ability of low Positive Emotionality was due to its overlap with Neuroticism.

Of the two studies testing Constraint, the Minnesota study found lower levels of this to be predictive of later MDD, but did not test it in a multivariate model with the other factors.

The Christchurch and Los Angeles/Chicago studies were also interested in whether the personality dimensions had unique associations with depressive disorders. Such a unique association was not detected, with high neuroticism predicting the occurrence of anxiety disorders in both studies, and low extroversion predicting substance dependence in the Christchurch sample and anxiety disorders in the Los Angeles/Chicago study.

3.4.5.3 Prospective studies of personality traits and MDD course

There have been few studies testing the impact of personality on the severity of MDD course or functional course in young people with MDD. None of the clinical longitudinal studies that have been reviewed included personality trait variables among the predictors that were tested.

One prospective community study found a significant negative association of Positive Emotionality (measured on the MPQ) at age 17 with the presence of any recurrence between 17 and 29 year of age, but no association of this outcome with Negative Emotionality or Constraint (Wilson, Vaidyanathan, Miller, McGue, & Iacono, 2014).

A further finding from this study was those with a recurrent course of MDD did not experience the normative reduction in Negative Emotionality seen with age. The study

authors suggested that this persistent level of Negative Emotionality might represent a scar of a recurrent course of MDD.

There is evidence from prospective studies in general population samples of adolescents of an impact of neuroticism on functioning, indicating investigation of this relationship is worth pursuing in youth with MDD. These studies have found neuroticism or the related construct of negative emotionality to be predictive of a range of aspects of relationship and vocational functioning.

In the relationship domain, neuroticism at age 19 has been shown to be predictive of poorer relationship functioning with friends, family and romantic partners at age 23 (Deventer, Wagner, Lüdtke, & Trautwein, 2019). Negative emotionality (measured on the MPQ) at age 18 predicted lower levels of relationship quality and higher levels of conflict and abuse at age 26 (Robins, Caspi, & Moffitt, 2002).

Vocational functioning was also assessed in the cohort of the last mentioned study, and it was found that negative emotionality at age 18 was predictive of poorer occupational status, work satisfaction and financial security at age 26 (Roberts, Caspi, & Moffitt, 2003).

As mentioned above, there were two tiers of adult samples selected. Those of the higher methodological standard are presented in Table 3-4. Italicised variables are those that were significant univariate but not multivariate predictors. Bold variables are significant multivariate predictors. Variables in normal type are significant univariate predictors that were not entered in a multivariate analysis. Shaded boxes indicate that the particular outcome was not assessed in that study.

Table 3-4: First tier longitudinal adult clinical samples with personality variables as an outcome predictor

Study & Duration	Sample	Baseline assessment of personality	Outcomes and Significant predictors			
			Duration of episode	Chronicity	Recurrence	Functioning Instrument or Outcome
<i>CLPS</i> 2 years Grilo et al. 2005 Markowitz et al. 2007	Inpatient & Outpatient n=302	DIPD-IV ¹ (Schizotypal Borderline Avoidant Obsessive-Compulsive)	Schizotypal PD Borderline PD Avoidant PD Any PD	Non-remission of PD		GAF ² Persistent PD LIFE ³ Persistent PD Baseline PD
Hopwood et al. 2007 4 years	n=104	NEO-PI-R ⁴ SNAP ⁵				GAF -N+E+A+C - Negative Temperament + Positive Temperament -Disinhibition

6 years Grilo et al. 2010	n=303	DIPD-IV (Schizotypal Borderline Avoidant Obsessive- Compulsive)	Schizotypal PD Borderline PD Any PD		Borderline PD Obsessive- Compulsive PD Any PD	
<i>Vantaa</i> 18 month Melartin et al. 2004 Leskelä et al. 2009	Inpatient & Outpatient n=269	EPI ⁶ -N, E IMSR ⁷ PSSS-R ⁸	+ <i>N</i> (MVA -MDD severity -anxiety severity (BAI))		+ <i>N</i> (MVA -MDE severity -number of c-m disorders)	Subjective social support - <i>N</i> + <i>E</i>
		SCID-II ⁹ -Any PD -Cluster	<i>Personality disorder</i>		<i>Personality disorder</i>	
5 years Holma et al. 2008		EPI-N, E	- <i>E</i> (MVA -preceding DD -cluster C PD -DUD)		(Social phobia)	Disability support - <i>E</i>
		SCID-II -Any PD -Cluster	Cluster C PD		<i>Not predictive</i>	<i>Not predictive</i>
Viinamäki et al. 2003, 2006 2 years	Outpatients n=104 (137)	SCID-II -Any PD		Personality disorder Cluster C PD		
<i>NESDA</i> 2 year Spinhoven et al. 2011	Primary care/ Specialist n=722	NEO-FFI ¹⁰ -N, E	+ <i>N</i> - <i>E</i> (MVA -MDD severity -negative life events)	+ <i>N</i> - <i>E</i> (MVA Age of onset-older DUD IDS NLE PLE		
4 year Boschloo et al. 2014		NEO-PI-R		+ <i>N</i> - <i>E</i> - <i>C</i> (MVA Severity Severity childhood trauma		
Riihimäki et al. 2014 5 years	Primary care n=89 (137)	SCID II -Any PD -Cluster	<i>Not predictive</i>		Cluster C PD Personality disorder	Unemployed Cluster B Personality Disorder Time on sick leave DSP Sheehan Disability Scale ¹¹

						SOFAS <i>Not predictive</i>
Bukh et al. 2016 5 years	Inpatient & Outpatient n=301	EPQ ¹² -N,E, P		+ N	<i>Not predictive</i>	
		SCID II -Any PD -Clusters -Individual disorders		Any PD Cluster C PD	Cluster C PD Avoidant PD	

1 Diagnostic Interview for DSM-IV Personality Disorders (Zanarini, MC, Frankenburg, FR, Sickel, AE, & Yong, L, 1996)

2 Global Assessment of Functioning (Association 2000)

3 Longitudinal Interval Follow-up Evaluation (Keller et al., 1987)

4 NEO Personality Inventory-Revised (Costa & McCrae, 1997)

5 Schedule for Nonadaptive and Adaptive Personality (Clarke, LA 1993)

6 Eysenck Personality Inventory (Eysenck, HM & Eysenck, SBG, 1964)

7 The Interview Measure of Social Relationships (Brugha et al., 1987)

8 Perceived Social Support Scale-Revised (Blumenthal et al., 1987)

9 Structured Clinical Interview for DSM-IV axis II Personality Disorders (First, MB et al., 1997)

10 NEO Five Factor Inventory (Costa, PT & McCrae, RR, 1992)

11 (Sheehan & Sheehan, 2008)

12 Eysenck Personality Questionnaire (Eysenck, HJ & Eysenck, SBG, 1975)

Neuroticism was the most frequently assessed personality trait in the adult clinical samples selected, followed by extraversion, while other traits were assessed in only one study.

These studies demonstrate consistent associations, positive for neuroticism (Melartin et al., 2004; Scott, Eccleston, & Boys, 1992; Scott, Williams, Brittlebank, & Ferrier, 1995; Spinhoven et al., 2011), and negative for extraversion (Holma et al., 2008; Kasch, Rottenberg, Arnow, & Gotlib, 2002; Spinhoven et al., 2011) with the duration of episode of a presenting MDE. This means that higher neuroticism is associated with longer episodes, and higher extraversion with shorter ones.

While neuroticism was also consistently associated with chronicity (Boschloo et al., 2014; Bukh, JD et al., 2016; Duggan, Lee, & Murray, 1990; Hirschfeld, Klerman, Andreasen, Clayton, & Keller, 1986; Rhebergen et al., 2012; Weissman, Prusoff, & Klerman, 1978), the effect of extraversion was close to evenly split between a negative association (Boschloo et al., 2014; Parker, G et al., 1992; Spinhoven et al., 2011) and no association (Bukh, JD et al., 2016; Duggan et al., 1990; Hirschfeld et al., 1986; Weissman et al., 1978), with all of the latter but Bukh et al. being lower rigour studies. Neuroticism was found to be associated with recurrence over the shorter term, in studies of 12 (Berlanga, Heinze, Torres, Apiquián, & Caballero, 1999) and 18 months (Melartin et al., 2004), but not in the two 5 year long studies (Bukh, JD et al., 2016; Holma et al., 2008). None of four studies showed an effect for extraversion on

recurrence (Berlanga et al., 1999; Bukh, JD et al., 2016; Holma et al., 2008; Melartin et al., 2004).

In five of eight multivariate analyses of these studies finding a univariate association of neuroticism with MDD course outcomes, neuroticism was found not to have a significant association with these outcomes in multi-variate analyses. Four of these analyses found a measure of depression severity to be an independent predictor of outcome (Boschloo et al., 2014; Melartin et al., 2004; Spinhoven et al., 2011), two reported significant associations of outcomes with negative life events (Spinhoven et al., 2011), and one found the number of comorbid disorders to be associated with recurrence risk (Melartin et al., 2004).

These results indicate that the effect of neuroticism on MDD course may be mediated at least in part by it causing an increased severity of depression. Another interpretation of the relationship is that an elevated neuroticism score is caused by the severity of the depressive episode, and may not relate to the relative strength of the neuroticism trait. There is evidence from a number of studies that levels of neuroticism are elevated during a depressive episode (Griens, Jonker, Spinhoven, & Blom, 2002; Jylhä, Melartin, Rytsälä, & Isometsä, 2009; Karsten et al., 2012; Ormel et al., 2004). Such elevations though have been found to relate to a moderate to high degree to trait levels of neuroticism, with test re-test correlations of 0.48 (Clark, Vittengl, Kraft, & Jarrett, 2003), 0.55 (Morey et al., 2010) and 0.70 (Costa, Bagby, Herbst, & McCrae, 2005) for neuroticism levels across phases of illness.

Some researchers have advocated for the separation of affect-influenced “state” components of personality and more stable trait-like components in predictor research (Clarke, LA 1993; Vittengl, Clark, Thase, & Jarrett, 2014).

Of the other traits, conscientiousness had a negative association with chronicity in one study, in which neither agreeableness nor openness to experience were found to have an effect (Boschloo et al., 2014).

In the three of four studies assessing a relationship of personality traits with functioning, extraversion predicted better functioning, doing so on a single item overall scale (GAF) (Hopwood et al., 2007), as well as on a specific measure of subjective social support (Melartin et al., 2004), and had a negative association with receiving disability support (Holma, Holma, Melartin, Rytsälä, & Isometsä, 2012). Neuroticism predicted worse functioning on the first of these two measures (Hopwood et al., 2007; Melartin et al., 2004).

Neither neuroticism nor extraversion predicted social functioning at 18 years from study baseline (Duggan et al., 1990) on an early version of the Social Adjustment Scale (Paykel, Weissman, Prusoff, & Tonks, 1971).

Agreeableness and Conscientiousness, in the one study in which they were assessed predicted a higher GAF score (Hopwood et al., 2007).

Table 3-5: Second-tier prospective studies of personality as a predictor in adult clinical MDD samples

	Sample	Instrument	Duration	Outcome	Findings
<i>Duration of episode</i>					
Scott et al. 1992	Inpatients/ Outpatients n=46	EPQ-N ¹	Mean 12 months	Time to recovery	+ Neuroticism
Scott et al. 1995	Inpatients/ Outpatients n=20	EPQ-N	12 months	Time to recovery	+ Neuroticism (controlled for severity)
<i>Persistence</i>					
Kasch et al. 1992	Outpatient/ Community n=62	BAS/BIS ²	8 months	Remission	BAS subscales -Reward responsiveness -Drive
de Winter et al. 2005	Inpatients/ Outpatients n=70	EPQ-N	2 yrs	Time to remission	Not predictive
Weissman et al. 1978	Female outpatients n=150	EPI-N,E ³ (after one month of treatment)	4 yrs	Chronicity to A.20 months B.48 months	A + Neuroticism
Hirschfeld et al. 1986	Inpatients/ Outpatients n=38	N,E ⁴	2 yrs	Non-recovery	+ Neuroticism
Duggan, Lee & Murray 1990	Inpatients n=80	EPI-N,E LOI ⁵	18 yrs	A.2 yrs of unremitting symptoms B.Global poor outcome C.Social adjustment (SAS ⁶)	A + Neuroticism B + Neuroticism + Obsessionality (LOI) C + Obsessionality
Parker et al. 1992	Inpatients/ Outpatients n=168	EPI-N,E ISM ⁷	12 months	Caseness	- Extroversion
<i>Recurrence</i>					
Berlanga et al. 1999	Outpatients n=42	EPI-N,P	12 months	Recurrence	+ Neuroticism

1 Eysenck Personality Questionnaire (Eysenck, HJ & Eysenck, SBG, 1975)

2 Behavioral Activation System/Behavioral Inhibition System Scales (Carver, CS & White, TL, 1994)

3 Eysenck Personality Inventory (Eysenck, HM & Eysenck, SBG, 1964)

4 Instrument developed by study authors

5 Leyton Obsessional Inventory (Cooper, J 1970)

6 Social Adjustment Scale (Paykel, Weissman, Prusoff, & Tonks, 1971)

7 Interpersonal Sensitivity Measure (Boyce & Parker, 1989)

3.4.5.4 Cloninger's model

The focus of work on Cloninger's model of personality and MDD has been on treatment response, rather than illness course. Morris et al. review reported the findings of four studies which failed to show an association of baseline Harm Avoidance with treatment response (Morris et al., 2009). A later review however was more positive about its predictive ability, with high levels across seven studies mostly predicting a poor treatment response (Kampman & Poutanen, 2011).

3.4.5.5 Summary of the relationship of personality to MDD course and functioning

As the number of relevant studies in young people is so small, any meaningful summary can only be made of the adult studies. The two findings for young people, both from community studies were that low Positive Emotionality and high Dependency can predict a recurrent course.

Perhaps the standout finding from the above-reported adult studies is the consistent relationship of neuroticism with MDD chronicity with findings from the high quality studies further supported by those with methodological limitations.

Although only one time point in one high quality study found a significant association of neuroticism with MDE duration, two of the lower quality studies also did. The only quality issue of these studies was sample size, with one with a cohort of 46 participants being just below the 50 benchmark.

The very few studies assessing functioning, both globally and by more specific parameters have been supportive of a relationship with personality, including the less frequently tested traits of conscientiousness and agreeableness.

In both the NESDA (Boschloo et al., 2014; Spinhoven et al., 2011) and Vantaa specialist studies (Melartin et al., 2004), neuroticism was not retained as an independent predictor in multi-variate analyses in which MDE severity was retained. This raises the possibility that the observed effect of neuroticism on MDD course is due to its relationship with severity and it may be in fact that the raised in-episode neuroticism score is a consequence of episode severity.

In regard to variables other than neuroticism, the findings for (low) extroversion generally paralleled those of neuroticism, though with slightly fewer positive findings. Conscientiousness was only measured in three studies, and a related variable in a fourth. Low levels of this trait were found to have one positive association with both of MDE duration and chronicity. Low conscientiousness and the related variable were also predictive of worse global functioning in two studies.

In the three studies testing Agreeableness and Openness, no positive findings were made for Openness, with Agreeableness found to have an association with global functioning, but not with chronicity.

3.4.6 Pathological personality and MDD

3.4.6.1 Prospective studies of DSM-defined personality pathology and the development of MDD

Similar to the personality literature, there are few prospective studies in young people investigating the relationship of pathological personality to MDD. The most detailed prospective data is from the Children in the Community study, which assessed a representative community sample of adolescents in New York state for DSM-IV defined personality disorder traits at ages 14 and 16 (Johnson et al., 1999).

At age 22 participants were assessed for the presence of mood disorders in the preceding 12 months, with MDD, Dysthymic Disorder and Bipolar Disorder clustered in this category. Controlling for co-morbid personality disorders and other Axis I disorders in adolescence, it was found that all personality disorders, including the Appendix B diagnoses of Depressive and Passive-Aggressive PD were associated with an increased risk for mood disorders at age 22, with odds ratios ranging from 3.6 to 5.6. This study also analysed the dimensional association of PD symptoms with mood disorder diagnoses, finding mean trait numbers in adolescence for Paranoid, Borderline, Histrionic and Dependent PDs were associated with mood disorders at age 22. It is perhaps worthy to note these results are based on a relatively small number of people with a mood disorder, this being fifty-three people from the total sample of 717. The prospective association of Conduct Disorder with MDD has been investigated in three studies. Conduct Disorder is an imperfect marker of Antisocial Personality Disorder (ASPD) as only a small percentage of people with this disorder will have ASPD in adulthood (Tyrer 2015), and therefore it is reasonable to assume that an association with later MDD may be for reasons other than enduring personality characteristics.

Both the Dunedin and Christchurch birth cohort studies found an association of a dimensional measure of conduct problems in childhood with MDD in young adulthood (Fergusson, Horwood, & Ridder, 2005; Moffitt et al., 2007a), while the Great Smoky Mountain Study did not (Copeland, Shanahan, Costello, & Angold, 2009).

A small number of studies in adults provide support for the prospective relationship of personality pathology with MDD. The large (n>35,000) NESARC community study in

the USA found that Borderline and Schizotypal PDs were predictive a first onset MDE over a three-year follow-up period (Grant et al., 2008).

In a study of a clinical population of adults with a personality disorder diagnosis, 44% had a new onset MDD over a six year follow-up period (Gunderson et al., 2008).

Though lacking a control group to enable the calculation of relative risk, this points to an association given this rate is well above most estimates of the lifetime community prevalence of MDD.

3.4.6.2 Other personality pathology models and the development of MDD

Prospective disorder-level research investigating the association of first-episode MDEs with personality pathology models other than that of the DSM is sparse, with only dependency having been shown to be predictive of a first episode MDE in three adult samples (Hirschfeld et al., 1989; Rohde, Lewinsohn, & Seeley, 1990; Sanathara, Gardner, Prescott, & Kendler, 2003). A recent review described studies in adults with established MDD that tested the matching of traits and stressors as having inconsistent findings and a number of methodological limitations (Klein, DN et al., 2002).

3.4.6.3 Prospective studies of personality pathology and the course of MDD in young people

There has been limited investigation of the interaction of pathological personality with the course of MDD in young people, the relevant studies presented in Table 3-6. Only one of the clinical adolescent longitudinal studies selected by this review assessed the association of the categorical personality disorder model with MDD course (Karlsson et al., 2008), while three community studies have done so, but by representing the personality disorders dimensionally (Craighead, Sheets, Craighead, & Madsen, 2011; Hart, Craighead, & Craighead, 2001; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Sheets, Duncan, Bjornsson, Craighead, & Craighead, 2014).

Table 3-6: Prospective studies assessing effect of personality pathology on MDD in young people

	Number of participants	Age at baseline	Period	Instrument	Domains tested	Recurrence associations
<i>Clinical</i>						
Karlsson et al. 2008	174 (74 with PD)	13-18 (Mean =16.4)	12 months	SCID II	DSM-IV Categorical PD diagnosis	Any personality disorder
<i>Community</i>						
Lewinsohn et al. 2000	274	19	4 years	PDE ¹	Dimensional scores for DSM-IV Borderline PD Antisocial PD	Borderline personality score
Hart et al. 2001	65	Mean 18.7	18 months	IPDE ²	1.Dimensiona scores for DSM-IV PD Clusters 2.Total IPDE score	Cluster B score Total IPDE score
Craighead et al. 2011 Sheets et al. 2014	130	18-21	18 months	IPDE	1.Eight empirically developed PD Factors 2.Dimensiona scores for DSM-IV PD Clusters and Total IPDE score	3 PD Factors Interpersonal hypersensitivity Antisocial conduct Social anxiety Total IPDE score

1 Personality Disorder Examination (Loranger, A, Susman, VL, Oldham, JM, & Russakoff, L, 1987)

2 International Personality Disorder Examination (World Health Organization 1996)

The one clinical study found that having any personality disorder increased the risk of having a recurrence, with an odds ratio in their multivariate analysis of 3.35 (95% CI 1.16-9.65) (Karlsson et al., 2008). Given the relatively brief 12 month duration of this study, this is a small subgroup (n=22) who have had a short episode (median length for entire study population= 59 weeks) and a rapid recurrence. Having a personality disorder did not however predict MDE persistence over the course of the study, nor episode duration.

The community studies, one in a sample originally selected in high school (Lewinsohn et al., 2000), and two of undergraduate students (Craighead et al., 2011; Hart et al., 2001; Sheets et al., 2014) all found an association of a baseline dimensional measurement of the categorical personality disorder model and the recurrence of Major

Depressive Disorder in early adulthood. All of the members of these samples had previously had an MDE, but were in recovery at their study baselines.

In two of the community samples, the association was specifically with Cluster B traits, and more specifically with Borderline personality traits in the 4 year follow-up of the Oregon Adolescent Development Project (Hart et al., 2001; Lewinsohn et al., 2000). The other undergraduate sample (Craighead et al., 2011; Sheets et al., 2014) performed a factor analysis on the responses to the assessment instrument that they administered, the International Personality Disorder Examination (World Health Organization 1996). Three of the factors were predictive of a recurrence, two of which included Cluster B traits. “Interpersonal hypersensitivity” contains the Borderline personality trait of hypersensitivity to abandonment, while “Antisocial Conduct” as its title implies is composed of behavioural antisocial characteristics. The third predictive item was “Social Anxiety”, and the study authors describe it as measuring feelings of inadequacy and social inhibition.

3.4.6.4 Prospective studies of personality pathology and MDD course in adults

The longitudinally-followed clinical samples of adults selected for this review are displayed in Table 3-4 and Table 3-7 with the latter containing the second tier studies. These demonstrate a consistent effect of baseline personality disorder across the MDD course outcomes: with longer index episodes (Grilo et al., 2005, 2010; Holma et al., 2008; Melartin et al., 2004), higher rates of chronicity (Bukh, JD et al., 2016; Szádóczy, Rózsa, Zámori, & Füredi, 2004; Viinamäki et al., 2006), an increased risk of recurrence (Alnaes & Torgersen, 1997; Bukh, JD et al., 2016; Melartin et al., 2004; Riihimäki, Vuorilehto, Melartin, & Isometsä, 2014), and a shorter time to recurrence (Grilo et al., 2010).

The dynamic nature of personality disorder was addressed in the CLPS study, and it was found at its 2 year follow-up that if a personality disorder remitted, MDD was more likely to remit (Markowitz et al., 2007).

Most of the studies analysed the effect of personality disorder at the level of any disorder, or at the cluster level. Cluster C was the sole of the three to demonstrate an effect on the MDD outcomes as a cluster, which it did for one of each of the outcomes in four studies (Bukh, JD et al., 2016; Holma et al., 2008; Riihimäki et al., 2014; Viinamäki et al., 2003), and in multi-variate analyses in all four.

Two studies performed analyses at the level of individual disorders, one finding a significant association of Schizotypal, Borderline and Avoidant personality disorders

with the duration of index MDE at both 2 and 6 years of follow-up (Grilo et al., 2005, 2010), the other of Borderline personality disorder with the risk of relapse (Alnaes & Torgersen, 1997).

The CLPS study also found that Borderline and Obsessive-Compulsive disorders predicted a shorter-time to recurrence at its 6 year follow-up (Grilo et al., 2010).

In eight of the ten multi-variate analyses performed in these studies, personality disorder variables remained significant, indicating their independence among the included variables (Bukh, JD et al., 2016; Grilo et al., 2005, 2010; Holma et al., 2008; Riihimäki et al., 2014).

It was in a study of 18 months duration in which personality disorders were not retained in the multivariate model, with measures of depression and anxiety severity predictive of episode duration, and depression severity and the number of comorbidities predictive of recurrence (Melartin et al., 2004).

Table 3-7: Lower methodological quality adult longitudinal clinical studies of personality disorder

	Sample type and size	Instrument	Follow-up period	Outcome	Predictors
Szádóczy et al. '04	117 inpatients or outpatients	Semi-structured interview for DSM IV personality disorders developed by study authors	2 years	Chronicity	Any Personality Disorder Cluster C Personality Disorder
Alnaes & Torgersen 1997	88 outpatients	SIDP-I ¹	6 years	Relapse	Borderline Personality Disorder

¹ Structured Interview of DSM-III Personality Disorders (Stangl, D, Pföhl, B, Zimmerman, M, Bowers, W, & Corenthal, C, 1985)

As mentioned above, the CLPS study assessed the impact of the remission of personality disorder in its participants with an MDD (Markowitz et al., 2007). It found that the remission of a personality disorder led to the improvement of functioning, such that at 12 months, those with such a remission had equivalent functioning on global measures, the GAF (American Psychiatric Association Task Force on DSM-IV 1994a) and the LIFE global social adjustment scale (Keller et al., 1987), to participants without a personality disorder at baseline.

However at 2 years those with a baseline personality disorder continued to have worse functioning than those who did not on some specific measures of functioning. These measures were the employment, recreation and relationship domains of the LIFE.

The Vantaa study looked specifically at disability support payments and found that having a personality disorder at baseline was not associated with receiving this payment at 5 years (Holma et al., 2012).

3.4.6.5 Clinical traits and MDD course

The sole finding on clinical traits and MDD course in young people comes from the Oregon Adolescent Depression Project. In this study, the authors developed a scale measuring excessive emotional reliance (on others), a feature of dependency. Scores on the scale independently predicted the recurrence of Major Depressive Disorder over a 6 year follow-up period (Lewinsohn et al., 2000).

A small number of longitudinal studies investigating clinical traits were detected in the review, and are presented in Table 3-8 below. These were not specifically targeted in the search strategy so it is not known what proportion of relevant published studies these represent.

Dependency was assessed in three studies, and was found to predict relapse over a 6 year follow-up period (Alnaes & Torgersen, 1997), but did not predict non-recovery in studies of 6 months (Klein, Harding, Taylor, & Dickstein, 1988) and 2 years duration (Hirschfeld et al., 1986).

In a 6 month study of a small sample, autonomy had a negative association with non-recovery (Scott, J, Harrington, J, House, R, & Ferrier, IN, 1996).

Table 3-8: Adult clinical longitudinal MDD samples and clinical traits

	Sample type and size	Instruments	Follow-up period	Outcome	Predictive
Hirschfeld et al. 1986 (CDS)	Inpatients and Outpatients n=38	Dependency scale ¹	2 years	Non-recovery	<i>Not predictive</i>
Scott et al. 1996	Patients ¹ n=16	Sociotropy/ Autonomy Scale ³	6 months	Non-recovery	- Autonomy
Klein et al. 1998	Outpatients n=48	DEQ- Dependency, Self-criticism ⁴	6 months	Non-recovery	<i>Not predictive</i>
Alnaes & Torgersen 1997	Outpatients n=88	BCI ⁵	6 yrs	Relapse	Dependency

1 Scale developed by study authors

2 Inpatient or outpatient not specified

3 (Beck, A, Epstein, N, & Harrison, R, 1983)

4 Depressive Experiences Questionnaire (Blatt, SJ, D'Affliti, JP, & Quinlan, DM, 1976)

5 Basic Character Inventory {Torgersen 1980}

3.4.6.6 Summary of impact of personality pathology on MDD course and functioning

As described above, there is evidence for personality pathology, measured as a discrete category or dimensionally having an effect on the severity of MDD symptomatic and functional course in both young people and adults.

It would appear that traits belonging to Cluster B or C are most influential. However it is possible that their stronger observed association reflects their higher prevalence in the MDD population relative to Cluster A traits, with studies simply underpowered for detecting a Cluster A influence. That said, the higher prevalence of Cluster B and C traits dictates that they need to be attended to.

Of the individual disorders, Borderline and Avoidant personality disorders have been found to have significant impacts on the severity of MDD course in multiple studies. More global measures of personality pathology, namely the presence of any personality disorder, and dimensional measures of total pathology have also been shown to be important. In most studies where this was the case, there were also relationships detected with more specific personality measures. In one community sample only such a global measure was found to have a significant relationship with MDD course, with this likely reflecting the low level of personality pathology in the sample such that it was necessary for a global measure to distill what was present (Craighead et al., 2011).

An issue raised by this study is the potential utility of alternative classifications of personality pathology in understanding the course of MDD as it found independent dimensional associations of non-DSM based classifications of personality pathology with having a relapse or recurrence of MDD.

A final point to be made is the potential for a “mood state effect” for the measurement of personality disorder traits during an MDE (Klein, DN et al., 2002; Morey et al., 2010). The implication of this is that a measurement of personality disorder pathology during an MDE may be inflated and thus not be a true measure, such that any association with the further course will be a distortion of any real effect.

Some studies have found that the number of disorder criteria or PD diagnoses met change with improvement in depressive symptoms (Fava et al., 2002; Melartin, Haukka, Ryttsälä, Jylhä, & Isometsä, 2010), while others have not (Lopez-Castroman et al., 2012; Loranger et al., 1991). The evidence available appears to support there being greater stability for trait counts than for categorical diagnoses (Durbin & Klein, 2006; Lopez-Castroman et al., 2012; Melartin et al., 2010)

Chapter 4 Aetiology of Major Depressive Disorder in young people

4.1 Introduction

This chapter reviewing the aetiology of MDD in young people has been included in this thesis to provide a summary of an important part of the context of the course of the disorder.

It is believed that there is a degree of age-related specificity to the aetiological processes in MDD, such that child, adolescent or adult-onset are often considered separately in theoretical models of MDD aetiology and in related empirical research (Ingram, RE, Siegle, GJ, & Steidtmann, D, 2014). As most of the young people in the sample had their illness onset in adolescence, that developmental stage will be the focus of this chapter. A small number of participants in the sample had their first MDE in childhood, therefore there will also be some exploration of the aetiology of childhood-onset MDD.

There has been a movement towards creating integrative models of the aetiology of MDD in adolescence, bringing together and organising variables and processes that have often been investigated in isolation from each other (Hagan et al., 2015; Rudolph, KD & Flynn, M, 2014).

Perhaps the most detailed integrative aetiological model is that proposed by Hankin (Hankin 2012), and the divisions of this model have been used as a template for the structure of this chapter.

In this model, an individual is placed within their environment which is divided into three systems of scaled proximity from the individual. The closer “micro” and “meso” systems contain closer, interpersonal influences such as one’s family and peers, while the more distal “macro” system contains community, ethnicity, economic status and culture.

The structure of the factors within an individual draws on the National Institute of Mental Health’s Research Diagnostic Criteria project’s “units of analysis” (Cuthbert & Insel, 2013). These were selected from the units of measurement commonly used in psychopathology research (Kozak & Cuthbert, 2016).

The three groups of factors within an individual in Hankin’s model are genetic and cellular processes, intermediate processes and endophenotypes (information processing, stress physiology, and neural anatomy) and observable behaviours, emotions and cognitions.

In terms of the direction of interaction between these groups of factors within an individual, the Research Diagnostic Criteria project conceives the genetic and cellular functions as influencing the intermediate processes, which are then manifest in the observable behaviours, emotions and cognitions (Insel et al., 2010).

The interaction between the characteristics of the different factors in the model for a particular individual contributes to the onset of an MDE, as well as its maintenance and recurrence (Hankin 2012).

The purpose of this chapter is to provide a broad description of the current knowledge of the aetiology of MDD in adolescents, by means of a narrative review. Hankin's model has been used to structure the chapter as its detail allows this breadth, being inclusive of a range of potential aetiological factors and processes.

Importantly also, through its integration of concepts of the Research Domain Criteria it is aligned with influential contemporary thinking on the development of psychopathology.

In the sections below, the theory behind the inclusion of the different factors in the aetiological model will be described. Evidence supporting a role for the factors in the development of MDD in adolescents and will also be cited. Studies of participants with a categorical disorder-level diagnosis of MDD, as opposed to a dimensional measure, were preferentially sought as these are likely to be more relevant to the project sample. Most of the evidence presented below comes from research on one or a small number of related proposed aetiological factors, indicative of the fact that theories on the nature of the relationships between different factors generally remain to be substantiated.

4.2 Individual differences

4.2.1 Genetics

Family studies provided early evidence of the likely role of genetic factors in the development of MDD in children and adolescents. In their meta-analysis, Rice et al. reported an odds ratio for having MDD of 2.3 for first-degree relatives of children and adolescents with the disorder, and an odds ratio of 4 for children and adolescents having MDD when their parents had the disorder (Rice, Harold, & Thapar, 2002).

Such studies cannot distinguish between genetic and environmental aspects of family influence, with this task being performed by twin studies (Plomin & Daniels, 2011). The study of Glowinski et al., the Minnesota Adolescent Female Twin Study (MOAFTS) reported the liability to MDD in their sample as 40% due to genetic effects, and 60%

due to non-shared environmental influences. This result is similar to that found in studies of adults with MDD, which have described heritability estimates of 40-50% (Levinson 2006).

Estimates of heritability in studies of depressive symptoms in young people range from 30-50% in adolescents (Rice 2010), but are much lower and in fact non-significant in children (Rice et al., 2002).

In regard to specific genes responsible for the heritability, no candidate genes thus far selected have been found to have a significant effect (Rice 2010; Wilson et al., 2014). The authors of an adult genome-wide association study that also did not find candidate genes for MDD proposed that this outcome may be due to the moderate heritability of MDD, its likely genetic heterogeneity, and the heterogeneity of non-genetic aetiological factors (Levinson et al., 2014). Consequently, it is currently thought that the genetic risk for MDD is likely to arise from small effects of multiple susceptibility genes (Lau, JYF, Lester, KJ, Hodgson, K, & Eley, TC, 2014). Genome-wide association studies in recent years in adults with MDD have taken significant steps towards identifying relevant genes, with these yielding 80 replicated loci (Ormel, Hartman, & Snieder, 2019). Others have suggested, given high levels of comorbidity of other mental state disorders with MDD, it would be worthwhile looking for shared susceptibility loci for anxiety and depressive disorders (Waszczuk, Zavos, Gregory, & Eley, 2014). Waszczuk et al. found high genetic correlations of depressive and anxiety symptoms in adolescence and young adulthood.

An area of increasing interest is the exploration of the nature of the relationship between genes and environmental factors in the development of MDD (Lau, JYF et al., 2014). Most prominent among studies of this type with young people with MDD has been work on gene by environment (GxE) effects related to stress and allele variants of the serotonin transporter gene. Replicated findings of significant GxE associations for the serotonin transporter gene have been found though these have been mixed in regard to the particular allele causing the effect (Dunn et al., 2011). It has been suggested that this is due to varying quality of methodology of stress measurement (Karg, Burmeister, Shedden, & Sen, 2011).

Other strands of this type of research are gene-environment correlation (rGE), investigating the association between genetic factors and the risk of particular environmental exposures, and epigenetics, the study of the effects of environmental factors on gene expression.

4.2.2 Intermediate processes and endophenotypes

4.2.2.1 *Biological stress physiology*

Abnormalities in hypothalamic-pituitary axis (HPA) function have been found across the age-range of people experiencing an MDE (Stetler & Miller, 2011). As will be described in section 4.4.1.1 below, experiences of adversity in childhood are a risk factor for a later MDD. Researchers are continuing to attempt to link these two findings, having detected changes in HPA function in children who have had adverse life events, and determined that similar changes in other samples are a risk factor for future MDD (Wilkinson & Goodyer, 2011).

There are a number of hypotheses on how stress hormones could lead to the development of MDD in young people, with some supportive evidence from cross-sectional studies and animal models (Hagan et al., 2015).

One proposes that chronic stress in childhood affects hippocampal development, such that its inhibitory effect on stress is impaired, making it more likely for depressive symptoms to emerge on exposure to stress (Goodyer 2008). Another suggests the association of stress with a later onset of MDD may be mediated by reduced neuroplasticity (Pittenger & Duman, 2008). It has also been posited that the HPA system could moderate the above-mentioned interaction between childhood adversity and the serotonin transporter polymorphism (Wilkinson & Goodyer, 2011).

4.2.2.2 *Neuroanatomy, activation, connectivity*

Adolescence is a period of significant brain re-modelling, with differential rates of maturation between those systems responsible for emotions and reward, and those involved in cognitive and impulse control (Casey et al., 2010; Weir, Zakama, & Rao, 2012).

It has been theorised that both the remodelling itself (Forbes & Dahl, 2005) and the maturation mismatch, between systems (Nelson, Leibenluft, McClure, & Pine, 2005) may contribute to the vulnerability to MDD in this life period, as might an exaggeration of the mismatch (Hagan et al., 2015).

Strong emotional responses paired with a less mature capacity to plan regulate behaviour have the potential to damage relationships, leading to stressful interpersonal consequences including relationship breakdowns or social isolation that could contribute to the development of a depressive episode (Henje Blom et al., 2016; Nelson et al., 2005).

Researchers have investigated whether there are associations between neurological structure or function and the development of MDD in young people. Most studies have been of samples of young people with established MDD, limiting the strength of any hypotheses of causality. Both structural and functional cross-sectional studies of the brains of young people with MDD have shown differences compared to control groups, specifically in the pre-frontal cortex and the related sub-cortical areas of the amygdala and hippocampus (Hulvershorn, Cullen, & Anand, 2011; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014)

Among the limited prospective studies there are contrasting findings. One study found an association of volume changes in the hippocampus, amygdala and putamen and the onset of MDD in adolescence (Whittle et al., 2014). Another study, of a familial high-risk youth-aged cohort found no relationship between the patterns of development of subcortical structures and a subsequent MDD (Papmeyer et al., 2016).

A review suggested that brain changes may be intermediate phenotypes of MDD, citing the association of the volumes of the above-mentioned subcortical regions with serotonin transporter and BDNF polymorphisms (Weir et al., 2012).

4.2.2.3 Information processing

This refers to brain patterns of attention information selection, storage and retrieval, Information processing biases could be the “lower order” phenomena that lead to cognitive vulnerabilities such as those described in 4.3.2 below (Jacobs, Reinecke, Gollan, & Kane, 2008).

A recent review examined the evidence for information processing biases in children and adolescents with an established MDD (Lau & Waters, 2017). The particular types of processing that were analysed were attention, discrimination between threat and safety, and memory. No differences were found between those with and MDD and control participants on threat-safety tests, while the results for the other two variables were mixed.

In the attention testing, there was a stronger tendency for those samples with an MDD to be more consistently biased to negative stimuli when they were longer in duration, suggesting voluntary attention allocation. For memory, samples of young people with an MDD were variable in their tendency to preferentially recall negative information, while most MDD samples recalled less specific autobiographical memories than matched controls.

There unfortunately haven't yet been prospective studies that have explored whether any of the observed, or other biases precede the onset of MDD (Hankin, BL, Snyder, HR, & Gulley, LD, 2015; Lau & Waters, 2017).

4.3 Observable, Accessible Behaviours, Emotions and Cognitions

4.3.1 Other mental state disorders

In section 0 above, it was described how the rates of other mental state disorders in young people with MDD in clinical samples exceeded those found for the individual disorders in the general population. Such a finding points to either one disorder increasing the risk of the other occurring, and or the presence of a common underlying factor or factors, environmental or genetic, causing elevated vulnerabilities for both disorders (Cummings, Caporino, & Kendall, 2014)

Chronological precedence would be one indication of a potential aetiological role for another disorder in MDD development (Kendler 2012). There is evidence for each of the higher prevalence disorder groups, namely anxiety, behavioural and substance use disorders temporally preceding the development of MDD in young people (Costello, Copeland, & Angold, 2011; Marmorstein, Iacono, & Malone, 2010; Rutter, Kim-Cohen, & Maughan, 2006) .

An alternative explanation suggested for such precedence is that different disorders at different ages represent the manifestation of the same underlying disorder in a particular developmental context (Costello et al., 2011). One argument against this being the case is that, for all disorder groups there are studies that have also found MDD to be the preceding disorder, though these studies appear to be in the minority. In the subsections below, detail will be provided on the nature of the evidence linking particular disorders to MDD, as well as proposed mechanisms of the association.

4.3.1.1 Anxiety disorders

Anxiety disorders have been found to be comorbid with MDD in both clinical and community samples of young people. Rates of comorbidity from 23 to 71% have been reported in clinical samples of young people with MDD as described earlier, and community sample rates of comorbidity are well above those for individual disorders (2011), ranging from 25 to 50% (Garber & Weersing, 2010).

In regard to possible common underlying factors, there is evidence as previously mentioned of a shared genetic vulnerability of anxiety and depressive symptoms in young people, with differing findings on whether this vulnerability is for a single

internalising dimension, two dimensions of fear and distress disorders, or for single disorders with a degree of shared genetic vulnerability between them (Franić, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Waszczuk et al., 2014).

A number of community studies in young people have shown a prospective relationship between anxiety disorders in childhood or adolescence and subsequent depressive disorders in adolescence or young adulthood (Avenevoli, Stolar, Li, Dierker, & Ries Merikangas, 2001; Beesdo, Pine, Lieb, & Wittchen, 2010; Mathew, Pettit, Lewinsohn, Seeley, & Roberts, 2011; Moffitt et al., 2007b; Pine, Cohen, Gurley, Brook, & Ma, 1998). In their review of disorder continuity between developmental stages, Costello et al. found an odds ratio of 2.7 for an anxiety disorder in childhood predicting a depressive disorder in adolescence (Costello et al., 2011).

The specific disorders for which such a relationship has been found in these studies are Overanxious disorder of childhood, Generalised Anxiety Disorder (GAD), Specific Phobia, Social Phobia, and Panic Disorder, with the distress-type disorders most consistently predictive.

In regard to the mechanism behind this relationship, Silk et al. propose that social-evaluative threat and reward processing provide the link between anxiety disorders and subsequent MDD in young people (Silk, Davis, McMakin, Dahl, & Forbes, 2012).

Drawing on the work of Davey et al, they suggest that a sense of threat reduces the involvement of young people with anxiety disorders in reward-seeking activity, with the consequence that repeated failure to achieve social rewards causes suppression of the reward system, resulting in anhedonia (Davey, Yücel, & Allen, 2008).

In their review, Cummings et al. assert a less specific pathway, this being that the psychosocial impairment resulting from an anxiety disorder would act as a risk factor for a depressive disorder (Cummings et al., 2014). Further more specific mediators of the relationship that have been suggested include increased HPA axis activity, negative cognitions and stressful life events (Rutter et al., 2006).

4.3.1.2 Behavioural and substance use disorders

Specific evidence for childhood and early adolescent behavioural problems preceding MDD in a person's early to mid 20's comes from both the Christchurch and Dunedin birth cohorts (Fergusson et al., 2005; Kim-Cohen et al., 2003). The finding from the Christchurch cohort was drawn from a dimensional measure of conduct problems at age 7-9, while that of Dunedin was for a diagnosis of Conduct or Oppositional Defiant Disorder at age 11 or 13.

In their review of continuities of psychopathology, Rutter et al. draw on the findings of a 20 year follow-up of school children (Champion, Goodall, & Rutter, 1995) to comment on the specific impairments observed in those with conduct disorders, namely “failures in relationships and academic settings”, and draw a link between these and consequent depressive thinking (Rutter et al., 2006).

Prospective studies of young people with substance use disorders have also demonstrated an increased risk of a later MDD. These have shown a relationship between substance abuse in the mid or late teenage years and a diagnosis of MDD in the late teens (Stice, Burton, & Shaw, 2004) or early twenties (Marmorstein et al., 2010; Rao, Daley, & Hammen, 2000; Rohde, Lewinsohn, Kahler, Seeley, & Brown, 2001).

Similar to the case with conduct problems, the authors of the above studies on substance use suggest that a subsequent MDD may be a consequence of psychosocial impairment resulting from the substance use. A specific mechanism of substance use leading to MDD proposed is via physiological effects, and Stice et al. hypothesised that reduced positive affect could be the result of recurrent substance use causing the down-regulation of mesolimbic dopaminergic pathways.

The Minnesota Twin study reported an additive effect of substance use (not necessarily disorder) and problems with the police before the age of 15, on the risk of MDD at age 17 or 20 (McGue & Iacono, 2005). The presence of four “problem behaviours” were associated with a 57% rate of MDD in young women, and 33% in young men, and led the study authors to suggest that having both early substance and conduct problems placed people in a particularly high risk group.

4.3.2 Cognitive vulnerabilities

The three dominant theories in this field are Hopelessness Theory, Beck’s Cognitive Theory and Responses Style Theory (Abela, JRZ & Hankin, BL, 2008; Jacobs et al., 2008). The first two of these posit that the nature of the content of one’s appraisal of negative events predisposes a person to developing depressive symptoms. In the testing of Hopelessness Theory, the bulk of studies have focussed on patterns of attribution of negative events, with the theory being that a style of believing that such events are due to global and stable causes is depressogenic.

Responses-style theory distinguishes between those who respond to depressive symptoms by ruminating, or by distraction, proposing that ruminators will experience problems of greater severity and duration.

The majority of studies in this field focus on increases in depressive symptoms, with only a small number examining the relationship of cognitive vulnerabilities to the onset of MDD in children or adolescents (Hammen, Adrian, & Hiroto, 1988; Lewinsohn, Joiner, & Rohde, 2001).

The Oregon Adolescent Development Project, of Lewinsohn et al. found a trend for the interaction of dysfunctional assumptions (testing Beck's theory) and negative life events to be associated with first episode MDE. Contrary to what would be expected theoretically, it found a significant association of the interaction of attribution patterns and fewer negative life events with first episode MDE, but not with a high level of negative events.

Hammen et al. found no association of attributional style with first episode MDE in children of depressed mothers.

Two studies have examined the relationship between rumination and future MDE (not specifically first episode) (Abela & Hankin, 2011; Nolen-Hoeksema, Stice, Wade, & Bohon, 2007). Both found a significant association between rumination and a future MDE, with the Abela et al. study also demonstrating an association of the interaction between high rumination and high negative life events and future MDE.

Using high levels of intercorrelation of "negative" cognitive styles as a rationale, a recent study tested a composite measure of these, emphasising self-worth and attributional style in its content (Carter & Garber, 2011). This 6 year prospective study of adolescents demonstrated that high levels of either interpersonal stress or negative cognitions in combination with either high or low levels of the other were predictive of first episode MDE.

4.4 Micro and meso-systems

4.4.1 Relationships

Adolescence is a developmental period of complex demands across relationship domains, including one's internal relationship with oneself. The stress associated with negotiation of these demands can be particularly high, and the attendant consequences of difficulties with them, such as family discord and peer exclusion potentially significant (Furman, W, McDunn, C, & Young, BJ, 2008; Platt, Cohen Kadosh, & Lau, 2013). It is understandable therefore that managing relationships in adolescence can be a source of emotional distress. This could be expected to be the

case especially for those with vulnerabilities such as attachment difficulties, negative views of oneself, and problems with affect regulation.

4.4.1.1 Early abusive experiences

Having adverse experiences in childhood has been identified as a risk factor for developing MDD in adolescence and young adulthood, as well as in later adulthood (Oldehinkel, Ormel, Verhulst, & Nederhof, 2014; Scott, Smith, & Ellis, 2010; Weich, Patterson, Shaw, & Stewart-Brown, 2009; Widom, DuMont, & Czaja, 2007). Such an effect is not specific to MDD among common psychiatric disorders (Keyes et al., 2012; McLaughlin et al., 2012).

There is evidence that the more severe the adversity, the greater the risk of subsequent MDD. The Weich et al. review of prospective studies found severe child abuse and neglect more consistently associated with later MDD than features of family relationships such as emotional unresponsiveness and general discord.

It has been proposed that a mechanism by which early adverse experiences lead to MDD in adolescence is via increased sensitivity to the effects of later stress, and there is some empirical support for this proposition (Oldehinkel et al., 2014). Possible underlying biological mechanisms have been mentioned in 4.2.2.1 above.

4.4.1.2 Family

Experiences within families from as early as infancy have been explored for their relationship to later MDD. Often the family is the context in which abusive experiences occur. There is also evidence that problematic family relationships of a less severe nature impact on the risk for future MDD. The diversity of theory, terminology and measurement methods has produced a rich volume of research, but constrains the ability of this research to lead to clear conclusions.

A small number of prospective studies assessing different aspects of the parent-child relationship in childhood have demonstrated associations with MDD in adolescence, specifically with ambivalent attachment in infancy (Sroufe, LA, Carlson, EA, Levy, AK, & Collins, WA, 2005), deficits in parental support (Stice, Ragan, & Randall, 2004), affectionless control (Nomura, Wickramaratne, Warner, Mufson, & Weissman, 2002), and maternal criticism (Silk et al., 2009). Of note is the finding that the association with ambivalent attachment has only been found in families with other risk factors for MDD, pointing to the complexity of the relationships between risk factors, and the likely interaction of multiple factors in leading to MDD (Restifo & Bögels, 2009).

The authors of a review on childhood attachment and later MDD propose a mechanism by which these are related (Morley & Moran, 2011). They suggest that problematic early attachment affects the internal representation of onself such that helpless responses occur when confronted by later difficulties. A caveat they provide is that the bulk of research supporting such a process is from retrospective assessment of adults with MDD.

Restifo and Bögels review the association of adolescent MDD with other aspects of family relationships, specifically parent factors, marital conflict and the whole family system. With the exception of parent factors, for which they report an association of parental MDD with adolescent MDD (Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997), relevant prospective studies they review have assessed depressive symptoms rather than disorder.

Two prospective longitudinal studies continuing into young adulthood have reported significant associations with later MDD of family factors other than the parent-child relationship. The USA-based Simmons Longitudinal Study found such an association with negatively-perceived role in the family and low family cohesion (Reinherz, Giaconia, Hauf, Wasserman, & Silverman, 1999), while the Dunedin birth cohort study reported an association between parental disagreement about discipline and having an MDE between ages of 18 and 26 (Jaffee et al., 2002).

Parental separation or divorce can also influence the development of MDD as found by the National Collaborative Perinatal Project (USA), which found an association of separation occurring before the age of 7 and the onset of MDD before age 14 (Gilman, Kawachi, Fitzmaurice, & Buka, 2003).

4.4.1.3 Peer and romantic relationships

The Oregon Adolescent Depression Project (OADP) is one disorder-level prospective study that had demonstrated an association of peer relationships with depression, finding that a lack of pleasureable engagement in such relationships predicted the onset of MDD in 16 year olds over a 12 month follow-up (Joiner, Lewinsohn, & Seeley, 2002).

Research in this area is however dominated by symptom-level studies, and as mentioned earlier such findings are not necessarily directly transferrable to those with MDD. This research has demonstrated mostly cross-sectional (Braet, Van Vlierberghe, Vandevivere, Theuwis, & Bosmans, 2013; Joiner 1999), but also some prospective

associations of peer rejection with depressive symptoms (Nolan, Flynn, & Garber, 2003).

A review published in 2008 described a consistent finding of increases of depressive symptoms for adolescents in romantic relationships (Davila, J 2008). Davila theorises that this pattern may relate to such relationships taking the focus away from other important aspects of life, or inadequate resources to cope with relationship stress or particular interpersonal styles. Each of these theories has a small amount of empirical support.

A breakup of a romantic relationship could be expected to precipitate the onset of MDD, but this has had limited specific study. The OADP did find it to predict first MDD onset over a 12 month period (Monroe, Rohde, Seeley, & Lewinsohn, 1999). It may be that such an event contributes to the demonstrated prospective association of stress more generally in other studies in adolescents referred to in 4.7 below.

4.5 Macro-system

The role of socio-economic status on the onset of MDD has been explored in prospective studies in Australia (Najman et al., 2010) and the USA (Gilman, Kawachi, Fitzmaurice, & Buka, 2002). Although the Australian study was of depressive symptoms, it used a cut off of the top 10% of scores on the YASR (Achenbach 1997) to establish “caseness”.

It’s univariate analysis found an association of young adult (age 24) depression caseness with poverty at multiple time points from the time of pregnancy, with the association only persisting for poverty at age 14 in its multivariate analysis. The Gilman et al. study, which formed part of the National Collaborative Perinatal Project detected an association of low SES with onset of MDD both in adolescence and adulthood. These results are supported by a large cross-sectional population study of 14-16 year olds in Finland, which found “severe depression”, defined by a BDI (Beck, Rial, & Rickels, 1974) cutoff as being correlated with low parental education level and parental unemployment. A combination of both these factors resulted in an odds ratio of 9.9 for males and 4.9 for female for “severe depression” compared to those without these exposures.

A recent meta-analysis of community factors associated with depressive symptoms and MDD found the field dominated by symptom-level studies (Stirling, Toumbourou, & Rowland, 2015). This study found that community safety, minority ethnicity and

discrimination acted as risk factors for depressive symptoms in school-age children, across a range of countries.

It could be expected that minority ethnicity could act as a risk factor for MDD in adolescence with pre-migration experiences, high parental academic expectations and divergences in norms of adolescent behaviour between the home and adopted countries being among the potential sources of stress.

A review of studies from Canada, a country with a comparable ethnic mix and standard of living to Australia was unable to find consistent patterns of difference between migrant and non-migrant youth, but did report that females of a migrant background experienced more mental health problems than males from such a background (Guruge & Butt, 2015).

A community study of adults in the Netherlands was similarly unable to find a difference in migrants as a whole in rates of MDD (de Wit et al., 2008), but another Dutch study, of adults receiving treatment for MDD did report higher rates across 1st and 2nd generation migrant communities compared to those in ethnic-Dutch (Selten, Laan, Kupka, Smeets, & van Os, 2012).

4.6 Gender

The emergence of gender differences in rates of MDD were highlighted in 2.3 above, with prevalence rates in females diverging in mid-puberty, and this divergence continued to the mid 20s. In the late teens and early 20s, rates of MDD in females were twice those in males in the Dunedin and NCS studies.

Theorists and researchers have considered factors across the bio-psycho-social domains and proposed a range of explanatory models for this difference, with varying degrees of complexity of integration of factors in these models (Hyde, Mezulis, & Abramson, 2008). For a number of factors, gender differences exist, but although the theory for a relation to MDD is plausible the evidence linking the difference to increased rates of MDD in females is slim.

In the biological domain, a recent systematic review on serotonin transporter alleles found a differential risk of the “S” allele (or SS genotype) for depressive disorders for women, with the presence of stressful life events reinforcing the association. The authors also noted that this difference seemed to begin in adolescence, suggesting a role for hormonal factors (Gressier, Calati, & Serretti, 2015).

Hyde et al. comment that there is some evidence implicating each of DHEA, oestrogen and testosterone in the gender differences, but that the relationship is likely to be

“complex, non-linear and interactional” (Hyde et al., 2008). Early puberty in girls is associated with higher rates of MDD, and it has been suggested this could be explained by the sex hormones accentuating the adolescent “mismatch” between limbic and cortical function (Graber 2013). The implications of this finding for females in general remains unclear.

Differences in cognitive vulnerabilities have also been suggested as mediating influences in the gender divergence. As mentioned in 4.3.2 above, evidence for an impact of these on the MDD aetiology is limited. Studies have found higher rates of “depressogenic” attributional styles (Hankin & Abramson, 2002) and ruminative response styles in adolescent females (Nolen-Hoeksema, Larson, & Grayson, 1999), with differences in rumination particularly on interpersonal and body image themes (Mezulis, AH, Abramson, LY, & Hyde, JS, 2002).

These studies have also shown these styles have a role in the mediation of gender differences in depressive symptoms.

Adolescent girls have been shown to have a small increased prevalence of negative life-events and a moderate increase of negativity of appraisals of these compared to boys (Davis, Matthews, & Twamley, 1999). The degree of divergence can depend on the nature of the event, with greater relative divergence for interpersonal events (Hankin, Mermelstein, & Roesch, 2007). One study has found that higher rates of depressive disorders in adolescent girls may be explicable by greater exposure to stress (Shih, Eberhart, Hammen, & Brennan, 2006).

4.7 Life stress as a proximal aetiological agent

Adult studies in both clinical and community samples have demonstrated an association of recent major life stress with the onset of an MDE (Harkness et al., 2010; Mazure, CM 1998; Monroe, SM, Slavich, GM, & Georgiades, K, 2014; Paykel 2003; Vrshek-Schallhorn et al., 2015). The review by Mazure reported patients in clinical samples to have such events occurring at a rate of 2.5 times that of control comparisons, with the rates for people with MDEs ranging from 12% to 89%. In community samples rates of recent major life events ranged from 62-94% for those with an MDE, while controls had lower rates, between 25 and 37%.

Across such studies the time period is typically between 1-6 months, the events retrospectively reported, and assessment by interview seen to be more methodologically sound, and associated with the detection of higher rates of events (Hammen 2005).

Most of the small number of studies examining the role of stress in the aetiology of MDD in young people have been community samples focussed on its interaction with cognitive vulnerability, and have been discussed in 4.3.2. With the exception of the OADP study (Lewinsohn et al., 2001), all found stress to be an independent predictor of MDD onset (Abela & Hankin, 2011; Carter & Garber, 2011; Hammen et al., 1988). Two further prospective community studies have also demonstrated such an independent association. The European EDSP study found total life events and specifically stress related to the family to be predictive of MDD onset in their 4-5 yr study of young people 14-24 year old at baseline (Friis, Wittchen, Pfister, & Lieb, 2002). A USA-based study with an additional interest in chronic stress found the onset of MDD between ages 17 and 22 to be associated with both stressful life events and chronic interpersonal stress (Vrshek-Schallhorn et al., 2015). The interest in the interaction of stress with other risk factors in studies in young people reflects the development of the field. In their review, Monroe et al. comment on the fact that the majority of people experiencing even severe life stress do not develop MDD (Monroe, SM et al., 2014). They encourage further work on biological mediators of the influence of stress such as the hypothalamic-pituitary axis, the immune system and genetics, particularly the serotonin transporter alleles. In addition to advocating more research on chronic stress, Hammen highlights the potential role of adverse developmental experiences, personality and gender as mediators of the effect of acute stress (Hammen 2005).

4.8 Chapter summary

The purpose of this chapter is to describe the context from which MDD in young people arises. It focussed on identifying prospective associations of variables with the onset of MDD in this developmental period, using Hankin's multiple levels model to organise the variables. Estimating the true importance of the proposed aetiological factors was limited by the typically small number of studies investigating any one factor, and by analyses frequently being univariate in nature or only with a small number of competing variables in multi-variate analyses.

The single twin study assessing the heritability of MDD in young people estimated that genetic factors explain 40% of the variance in its occurrence of MDD, paralleling findings in adults and thus identifying genetic factors as highly significant. What remains unknown is what parts of the genome are involved and therefore what is encoded.

The remaining variance in MDD occurrence from this twin study was found to be due largely to environmental experiences specific to an individual, meaning this cluster of factors collectively would appear play the largest overall role in the development of MDD.

Among environmental factors in Hankin's "micro" and "meso" systems, there is evidence for an aetiological role in MDD for relationship difficulties, particularly those that are family-related. There is evidence also for an association with stressors, both distal and proximal to the onset of the disorder, with increased severity of these stressors strengthening this association.

In the domain of "individual differences", prospective associations with MDD in young people have been demonstrated with preceding common mental state disorders, cognitive vulnerabilities and personality variables, neuroticism in particular. All of these could theoretically act as mediators for stress in its relationship with MDD, with this having been shown to be the case in two projects studying rumination as a cognitive vulnerability.

Within the "individual differences" domain, Hankin also includes potential intermediate processes and endophenotypes. Among these are stress physiology, and brain structure and function. While abnormalities of these have been found in young people with MDD, the causes of these and the mechanisms of any contribution to the development of MDD remain to be elucidated. Information processing deviations are a theoretically attractive mediator of cognitive vulnerability, but even cross-sectional evidence of their association with MDD are very limited currently.

The study of "macro" system factors in young people has been focussed on depressive symptoms rather than disorder. A small number of studies have shown a prospective association of poverty, and low parental education and employment with high levels of depressive symptoms in adolescence or young adulthood.

Important questions needing further investigation are why there is such a leap in the onset of MDD in mid-adolescence, and why females are disproportionately affected. This life-period contains many complex social challenges, and difficulties negotiating these provides an understandable path to MDD, but we lack detailed evidence on such a pathway. A maturational mismatch between limbic/emotional and executive brain function development has been offered as a reason for adolescent vulnerability to MDD.

Chapter 5 The prediction of the symptomatic and functional course of Major Depressive Disorder in clinical samples of young people

5.1 Introduction

This chapter describes the findings on the predictors of the symptomatic and functional course of MDD in prospective studies of clinical samples of adolescents. As was the case with Chapter 2, the detailed information on clinical samples of adolescents is supplemented by findings from prospectively-studied samples of both adolescents in the community with MDD, and clinical samples of adults with MDD.

Supplementary evidence for the effect of predictors has been drawn from these other samples as only limited evidence for a range of predictors can be drawn from the adolescent clinical samples.

Hankin's division of groups of factors used in his model of the aetiology of MDD in young people (Hankin 2012) which was used as the template to structure Chapter 4, also provides the structure for this chapter.

The most commonly measured course parameters in the studies of predictors of MDD course are those of the duration, persistence or chronicity of an index episode, and its recurrence. The assessment of functional outcomes is becoming increasingly common. Of studies assessing functioning, most assessed cross-sectional functioning at the point of follow-up, rather than across the entire follow-up period. The outcomes measured vary between single global scores, scales with multiple domains and specific single outcomes such as employment and completion of secondary education.

The chapter begins with an overview of theoretical work on the mechanisms underlying recovery, chronicity and recurrence in MDD. This is followed by a description of the process of collecting relevant studies. Then there will be a presentation of the evidence found in these studies for the effects of possible predictors. It was observed to not be common practice for researchers to discuss the potential mechanisms of action of predictors, but where this was done, a summary of this information will also be provided.

5.2 Conceptualisation of the processes underlying the symptomatic and functional course of MDD in young people

The mechanism by which identified predictive variables exert their effect on the course of MDD is believed to be through complex inter-relationships (Birmaher et al., 2002), with each other and potentially with variables yet to be investigated. This manner of interaction is analogous to that of the multiple-level model proposed by Hankin for its aetiological factors (Hankin 2012).

An understanding of the mechanisms involved in recovery, chronicity and recurrence, as well as in functioning changes would provide a meaningful context into which one could place the empirically identified predictors.

As yet, there is no comprehensive integrative conceptual framework of such mechanisms. Rather, researchers have developed models containing small numbers of factors, often it would appear more based on cross-sectional and experimental studies in non-clinical samples, than on prospective clinically-based research. Such work has been pursued more frequently for the outcomes of recurrence and chronicity than for recovery.

5.2.1 Mechanisms of chronicity

A review on MDD persistence that explored the predictors and mechanisms of chronicity grouped these conceptually into those that are cognitive, interpersonal and stress-related (Klein, DN & Allmann, AES, 2014). A general limitation of this research is that most observations have been derived from cross-sectional differences between those with a non-chronic depressive disorder and those with a chronic depressive disorder, rather than from prospective research.

Prominent among cognitive predictors explored in the chronicity research is that of a ruminative response style (Nolen-Hoeksema, S, Wisco, BE, & Lyubomirsky, S, 2008). This style of thinking is characterised by focussing on one's distress and its possible causes and consequences rather than actively trying to make change. A ruminative response style has been found to be correlated with a number of other maladaptive cognitive styles and also with trait neuroticism (Nolen-Hoeksema, S, Wisco, BE, & Lyubomirsky, S, 2008).

Prospective findings though on the capacity of this cognitive style to predict the duration of an MDE have been inconsistent, with some positive findings (Kuehner &

Weber, 1999), but a greater number of studies not finding an effect, eg. (Arnow, Spangler, Klein, & Burns, 2004; Bagby & Parker, 2001).

In regard to interpersonal factors, low levels of support and high levels of conflict have been found to be predictive of chronic MDD (Hölzel, Härter, Reese, & Kriston, 2011). A series of “self-propagating and erosive processes” occurring at an interpersonal level have also been proposed as potentially contributing to chronicity, and have a degree of empirical support (Joiner, TE 2000).

In Joiner’s model, these processes, which are considered to induce each other, are stress generation, negative feedback seeking, excessive reassurance seeking, interpersonal conflict avoidance, and blame maintenance (Joiner, TE 2000) .

5.2.2 Mechanisms of recurrence

The observation that a history of a previous MDE prior to a presenting episode was associated with an increased risk of a recurrent MDE led to the development of the “scar” hypothesis (Burcusa & Iacono, 2007). This posits that experiencing an MDE leads to a change that makes a person more likely to have a further episode (Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013).

Scars have been proposed to be lodged in biological, psychosocial, cognitive and personality processes (Burcusa & Iacono, 2007).

An influential model in the field of scar theory is that of sensitisation, which proposes that there is a biological scar in the form of a gene-level change (Post 1992). This model and the related concept of “kindling” relates specifically to the impact of life stress on the recurrence of MDD, and stemmed from observations that there seemed to be a stronger association of psychological stressors with the onset of first episodes compared to the onset of subsequent ones (Monroe & Harkness, 2005; Post 1992). It has been commented that the evidence supporting this conceptualisation is “weak at best” (Burcusa & Iacono, 2007).

In their distillation of their findings in a recent review of risk factors for recurrence, the review authors nominated a negative self-concept as a key factor in recurrence (Buckman et al., 2018). This was considered to be the consequence of ruminative thinking patterns, information processing and cognitive biases, which the review had found to be associated with MDD recurrence. These findings were mostly drawn from the conclusions of non-systematic reviews and from experimental studies.

5.3 Search strategy and summary tables

5.3.1 Young people

The results of analyses of predictors of the course of Major Depressive Disorder and of functioning were extracted from the studies selected in the search described in 2.4.1. Eight of the thirteen studies included an analysis of predictors, and these are presented in Table 5.1 below.

Prospectively-studied samples have been selected as the source of evidence on predictors as the validity of this evidence is reliant on the accuracy of the measurements of MDD course, which would be expected to be greater in prospective studies (see 2.4.2.2).

Most of the predictors that this study will investigate are those present at or before study baseline. Prospective studies would be expected to be able to make more valid and accurate assessments than retrospective studies doing so at a greater time-distance.

The numbers in the body of Table 5-1 represent the individual studies, and a key to these is below the table. The numbers in bold indicate results from multivariate analyses, while those in plain type are from univariate analyses. Some studies only performed multi-variate analyses, and for these only the positive associations are listed, as it is unknown whether variables found to not have a significant impact would have done so in a univariate analysis.

The differing lengths of follow-up periods between the studies effects the interchangeability of results. Specifically, longer studies are able to include those with longer episodes in their analyses, as well as those taking a longer time to recover or have a recurrence, potentially affecting the profile of significant predictors. The studies measuring persistence mostly range from one to two years in duration, providing a reasonably narrow range for this variable.

It is of note that many variables have only been investigated in a small number of studies, necessitating caution regarding any conclusions on the generalisability of these findings.

This caution must be applied even more vigorously to the findings of the very few studies measuring functional outcome, which are contained in Table 5.3. All of the results from these studies are derived from multivariate analyses, with the variables tested placed in the table in either the “predictive” or “not predictive” columns.

Results from prospectively-followed community samples of adolescents with MDD have also been provided to supplement those of the clinical samples.

Table 5-1: Predictors of MDD course in longitudinally-followed clinical samples of adolescents

Variable	Duration of index MDE		Persistence		Recurrence	
	Predictive	Not Predictive	Predictive	Not Predictive	Predictive	Not Predictive
Individual differences						
<u>Genetic</u> Family history		6		6		6
Intermediate processes and endo-phenotypes						
<u>Stress physiology</u> Cortisol	6				6	2
Observable behaviours, emotions and cognitions						
<u>MDE characteristics</u> Severity Suicidality Duration untreated MDE		5 5 5	3,8	1,5,7 5,7	7 7	2,3,5,8 2 5,7
<u>MDD characteristics</u> Age of onset Previous MDE Number MDEs MDE duration	5 ¹	5	5	1,5	5 ² 8	2 5
<u>Comorbidity</u> Anxiety disorders Behaviour disorders Dysthymic disorders SUD	5	5 5 5 5	5 1 5 1	5,7,8 1,5,7,14 1,7 5,7		5 2,5,8 4,5,7,8 2,5,7 5,7
<u>Personality pathology</u> Any PD		5		5	5	
<u>Functioning</u> Global School	5		1,5,8 1	7		2,5,7,8
Micro and meso system						
<u>Relationships</u> Family environ. Social support	6		1		6	
Macro system						
Race SES				7,8 7,8	8 2	2,7 7,8
Other						
<u>Demographic</u> Female		1,5		1,5,7,8	7	2,5,8
<u>Life stress</u> Acute Chronic		6 6			6	6

1 Younger age at onset MDD predictive 2 Older age at index MDE predictive 3 Includes CD and ODD

Study Key

1 Sanford et al. 1995	2 Rao et al. 1995a, 1996	3 Birmaher et al. 2000a	4 Fombonne et al. 2001, 2001a
5 Karlsson et al. 2008	6 Rao et al. 2010	7 Curry et al. 2001	8 Vitiello et al. 2011

Table 5-2: Predictors of functioning in longitudinally-followed clinical samples of adolescents with MDD

Study	Measure	Predictive	Not predictive
Fombonne et al. 2001 20 year follow-up	Adult Personality Functioning Assessment (APFA)	Conduct disorder	Age Gender
	Marital status Educational level Social Class Housing tenure Employment Income	Conduct disorder	Age Gender
Peters et al. 2015 3.5 year follow-up	Global Functioning <19yo: CGAS >19yo: GAF	Multiple Axis I comorbidity¹ MDE recurrence	
	HoNOSCA: all factors Internalising factor Externalising factor	MDE recurrence Multiple Axis I comorbidity Multiple Axis I comorbidity Substance use disorder	No single comorbidity predictive other than SUD for externalising factor
	Developmental milestones Independent living College education Employment	Behavioural disorder	MDE recurrence Axis I comorbidity

¹ Any combination of two or more anxiety, behavioural or substance use disorders

5.3.2 Adult samples

The first step in the search for adult samples reporting predictors of MDD course was to extract any relevant results from the papers describing the six longitudinally followed cohorts listed in 2.4.5.2.

Unless otherwise stated, all the searches described below were performed in PUBMED (MEDLINE) and covered the period from 1978 to May 2017.

The next step of this search was to locate the most recently published systematic review of the predictors of the course of MDD in adults.

This was done by entering the terms “depressive disorder” AND “predict*” AND “course”, with results limited to review papers.

The most recent review at the time of the search was by Hardeveld et al. in 2010. As this review only covered the predictors of recurrence, further searches were performed to cover other MDD outcomes. Combined individually with the original search terms “depressive disorder” AND “predict*” were the terms “chronic depression”, “chronicity”, “time to recovery”, “time to remission”, “duration of episode”, “episode length”. These searches were also limited to review papers.

The Hardeveld et al. review covered studies from 1980 to August 2008. Therefore studies published since that time were sought using the search terms “depressive disorder” AND “predict*” AND “course”.

The Hardeveld et al. review set the threshold for included studies to contain at least 50 participants and be of at least 6 months duration, and for diagnoses according to RDC or DSMIII or IV or ICD 9 or 10 criteria made by a standardised instrument or checklist. These inclusion criteria were followed for other studies.

The outcome “chronicity” was generally defined as being an index MDE that continued for 2 years.

A summary of the predictors that were investigated in the selected studies is presented in Table 5-3. As for the adolescent samples, the numbers represent the studies which are identified in the key below the table. A number of the studies had assessments at multiple time points and therefore are identified by multiple numbers. In the cases of the NESDA study (2-3), and the CDS study (11-17), different subsets of the study sample were assessed at different time-points.

Any information on prediction of functioning was also extracted from the selected studies. In addition, a separate search was performed using the terms “depressive disorder” AND “functioning” AND “predict*”. Findings of studies using a global functioning measure have been represented in Table 5-4. More specific functional outcomes are presented in Table 5-5 below.

Table 5-3: Predictors of course of MDD in longitudinally-followed clinical samples of adults

Variable	Duration of index MDE		Chronicity		Recurrence	
	Predictive	Not predictive	Predictive	Not predictive	Predictive	Not predictive
Individual differences						
<u>Genetic</u> Family history					22	18,19,20
Intermediate processes and endo-phenotypes						
<u>Cortisol</u>					3	
Observable behaviours, emotions and cognitions						
<u>MDE characteristics</u>						
Severity	4,5,7,11,20	8	2,3,5,9,15	10	1,2,7,8,18,19	4,11,19
Guilt				9	7,8	
Suicidality	7	8	1		7	8
Hopelessness	7,8			5		
<u>MDD characteristics</u>						
Age of onset		7,8	2°,6°,19°		1,8	7,8,12,18,19,22
Previous MDE	12	7,8,20		11,13	8,12,14,22	7,18,19,20,21
Residual symp.s					18,20	12,22
DUD	7,8,11		2,6,11		14	7,8
<u>Comorbidity</u>						
Anxiety disorder	2	7,8	1,2	5,6	5,8	5,19
Anxiety dimension	2,5,7,12	8	2,5,12,15			7
Dysthymic disord.	8,11	7	13		22	5,7,8
SUD	5	7,8	5			7,8,21
<u>Functioning</u>						
Global	5	7,8	5,9,16	11	11	5,7,8
Employment		8				8
Education	2					
<u>Personality</u>						
Disorder	7,8,23	5	1,9,23	5	1,5,7	8
Neuroticism	2,7	8	1,2,3		7	1,8
Extroversion	2,8	7	2,3	1		1,7,8
Openness				3		
Conscientiousness	6		1			
Agreeableness				3		
Micro and meso system						
Life events	2	7,8,18	2	3,9		7,8,18
History of abuse			3		24	
Low social support	5,7,8	18	5	6		5,7,8,9,18
Macro-system						
SES						7,8,18,19
Education		20	3	2,6,9		20,22
Other						
<u>Demographic</u>						
Age	4°	7,8,11		6,9,11	8°	7,12,18,19
Female		5,7,8,11	3	5,6,9	14	7,8,17,18,19,20,22
Single		11	11	5,9	14	7,8,18,19,20,22

1 Low severity y=Younger age o=Older age

Table 5-4: Predictors of global functioning in longitudinally-followed clinical samples of adults with MDD

Variable	Functioning	
	Predictive	Not predictive
Individual differences		
<u>Genetic</u>		
Family history MDD		20
Observable behaviours, emotions and cognitions		
<u>MDE characteristics</u>		
Severity	8	2,20
<u>MDD characteristics</u>		
Age of onset MDD		6,20
DUD	6	20
<u>Comorbidity</u>		
Anxiety disorder	2	20
Dimensional Anxiety	2	6
<u>Personality</u>		
Disorder	23	
Neuroticism	23	
Extroversion	23	
Openness	23	
Conscientiousness	6,23	
Agreeableness	23	
Micro and meso-system		
Low social support	6	
Macro system		
Education		6,20
Other		
<u>Demographic</u>		
Age		6
Female		6

Study key

1 DPCRR 5yr Bukh et al. 2016	7 Vantaa 18mth Melartin et al. 2004	13 CDS 12yr Judd et al. 1998	19 Cambridge 10yr Kennedy et al. 2003
2 NESDA 2yr Spinoven et al. 2011a Rhebergen et al. 2012	8 Vantaa 5yr Holma et al. 2008	14 CDS 15yr	20 GLADS Furukawa et al. 2000 Kanai et al. 2003
3 NESDA 4yr Boschloo et al. 2014	9 KUDEP Viinamäki et al. 2006	15 CDS 17yr Coryell et al. 2012	21 Ilardi et al. 1997
4 Vantaa Primary Care 18mth Vuorilehto et al. 2009	10 Kronmuller et al. 2008	16 CDS 20yr Solomon et al. 2008	22 Maj et al. 1992
5 Vantaa Primary Care 5 yr Riihimäki et al 2014	11 CDS 2yr Keller et al. 1982, 1983, 1984	17 CDS first episode Simpson et al. 1997	23 CLPS Grilo et al. 2005 Hopwood et al. 2007
6 Kuenher & Huffziger 2013	12 CDS 5yr Keller et al. 1992	18 Cambridge 2yr Ramana et al. 1995	24. Opel et al. 2019

Table 5-5: Predictors of functioning in longitudinally-followed clinical samples of adults with MDD

	Outcome	Predictive	Not predictive
CLPS 2 year follow-up (Markowitz et al. 2007)	Subscales on LIFE Employment Relationships Spouse Parent Recreation	Baseline personality disorder persisting > Remitted personality disorder > No baseline personality disorder	No other variables in included in analysis
Vantaa 18 month follow-up (Rytsälä et al. 2007)	Receiving disability support payment	<i>Baseline</i> Age MDE severity (HAM-D) Anxiety severity Hopelessness (BHS) Suicidal ideation (SSI) No vocational education On sick leave SOFAS <i>Follow-up</i> Time in MDE	<i>Baseline</i> Marital status MDE severity Recurrent MDD Axis I comorbidity Axis II comorbidity SAS-SR
Vantaa 5 year follow-up (Holma et al. 2012)	Receiving disability support payment	<i>Baseline</i> Age>50 DUD MDE severity (BDI) Number of Axis I and II disorders Extraversion (low) No vocational education Subjective inability to work SOFAS <i>Follow-up</i> Time in MDE Number of comorbid somatic disorders	<i>Baseline</i> Gender Employment Personality disorder Anxiety disorders Substance use disorders BAI Neuroticism
Vantaa 18 month follow-up (Lekselä et al. 2009)	Objective social support (IMSR ¹) Subjective social support (PSSS-R ²)	<i>Baseline</i> Neuroticism (low) Extroversion (high)	<i>Baseline</i> Neuroticism Extroversion

1 (Brugha et al., 1987) 2 (Blumenthal et al., 1987)

5.4 Individual differences

5.4.1 Genetics

5.4.1.1 Symptomatic course

The closest to a measure of genetic influence in the longitudinal clinical studies of young people with MDD is having a family history of the disorder. The one study that investigated this variable did not find an association of parental MDD with any symptomatic outcome (Rao et al., 2010).

Three prospective community studies of adolescents however did find an association of family history and MDE recurrence (Kim-Cohen et al., 2003; Lewinsohn et al., 2000; Wilson et al., 2014).

One of four adult studies found a significant association of family history with MDD recurrence (Maj, Veltro, Pirozzi, Lobrache, & Magliano, 1992), while the sole study investigating its prediction of functional outcome did not find a significant relationship (Furukawa et al., 2001).

These findings, few as they are, suggest a possible role for family history of MDD in recurrence of MDD in young people, but indicate that the strength of this influence might be less in adults.

The mechanism of such an effect in young people could be through transmission of a genetically-mediated vulnerability or environmental effects, or of course both. It is understandable that the environmental effect of having particularly a parent with MDD could have a significant impact on a young person through an enduring impact on their development.

5.5 Intermediate processes and endophenotypes

5.5.1 Biological stress physiology

5.5.1.1 Symptomatic course

The hypothalamic pituitary adrenal (HPA) axis is believed to have a role in moderating the effect of stress on emotional, cognitive and behavioural responses, such that its dysregulation may affect the symptomatic course of MDD (Rao et al., 2010)

Nocturnal cortisol has been investigated as a marker of HPA axis dysregulation, drawing on a study which found elevated levels in depressed adolescents at this normally “quiescent” time for HPA axis activity (Dahl et al., 1991).

In a five-year study in an adolescent sample, higher nocturnal urinary cortisol was found to predict both a longer index MDE and an increased risk of recurrence (Rao et al., 2010), with a trend ($p=0.06$) towards an increased risk of recurrence found in an earlier study by the same research group (Rao et al., 1996)

In the later study, the relationship of urinary cortisol to the length of the index MDE was found to have a significant interaction with lower levels of social support, while its relationship with recurrence had a significant interaction with higher levels of acute stress over the follow-up period (Rao et al., 2010).

One of the adult studies reviewed provides support for the role of the HPA axis in influencing the symptomatic course of MDD (Hardeveld et al., 2014). Although this did not find a predictive effect of nocturnal cortisol, it did find that higher levels of the Cortisol Awakening Response (CAR) independently predicted MDD recurrence over their four year follow-up.

5.6 Observable, Accessible Behaviours, Emotions and Cognitions

5.6.1 MDD variables

5.6.1.1 Symptomatic course

It can be seen in Table 5-1 that baseline MDE illness severity is not a consistent predictor of symptomatic outcomes in adolescent clinical samples

By contrast, in the adult clinical samples selected for this review, MDE severity was generally predictive across symptomatic outcomes, as shown in Table 5-3. The relationship was particularly strong with MDE duration, severity being independently predictive in four of five studies (Keller et al., 1982a; Melartin et al., 2004; Riihimäki et al., 2014; Vuorilehto et al., 2009).

Neither of the two studies investigating an effect of duration of untreated depression (DUD) on MDD course in young people found an effect across the range of outcome variables (Curry et al., 2011; Karlsson et al., 2008).

More studied in adult samples, DUD was consistently predictive of episode duration (Holma et al., 2008; Keller, Lavori, Endicott, Coryell, & Klerman, 1983; Melartin et al., 2004) and was an independent predictor of chronicity in each of the studies in which it was investigated (Keller et al., 1984; Kuehner & Huffziger, 2013; Rhebergen et al., 2012).

5.6.1.2 Functioning

Two of the large community studies of young people investigated a proximal (as compared to a baseline) predictor of functioning, that of having a recurrence of MDD over their follow-up periods (Lewinsohn et al., 2003; Wilson et al., 2014). Both found that having a recurrence was associated with a range of functional outcomes.

An 5 year study of an adult sample analysed associations with receiving a disability support pension at follow-up. It also found the cumulative time in an MDE over the follow-up period to be independently predictive of this outcome (Holma et al., 2012).

5.6.2 Mental state disorder comorbidity

5.6.2.1 Symptomatic course

Table 5-1 demonstrates that no individual comorbid mental state disorder has thus far been shown to have a consistent impact on MDD course parameters in clinical samples of adolescents.

Two community studies of adolescents with MDD found a univariate association of comorbid anxiety disorders with symptomatic course, one with recurrence (Wilson et al., 2014) the other with persistence (Stein et al., 2001).

The most striking observation on the impact of comorbidity on MDD course to be made from adult clinical studies, as summarised in These inclusion criteria were followed for other studies.

The outcome “chronicity” was generally defined as being an index MDE that continued for 2 years.

A summary of the predictors that were investigated in the selected studies is presented in Table 5-3. As for the adolescent samples, the numbers represent the studies which are identified in the key below the table. A number of the studies had assessments at multiple time points and therefore are identified by multiple numbers. In the cases of the NESDA study (2-3), and the CDS study (11-17), different subsets of the study sample were assessed at different time-points.

Any information on prediction of functioning was also extracted from the selected studies. In addition, a separate search was performed using the terms “depressive disorder” AND “functioning” AND “predict*”. Findings of studies using a global functioning measure have been represented in Table 5-4. More specific functional outcomes are presented in Table 5-5 below.

Table 5-3 is that dimensionally-measured anxiety affects index MDE duration and chronicity. The instruments used in the different studies consistently covered Panic Disorder symptoms (Coryell et al., 2012; Gaspersz et al., 2016; Holma et al., 2008; Keller et al., 1992; Melartin et al., 2004), with Generalised Anxiety Disorder symptoms included in two studies (Coryell et al., 2012; Gaspersz et al., 2016; Keller et al., 1992) , and Obsessive-Compulsive and phobic symptoms also included in a third (Coryell et al., 2012; Keller et al., 1992) .

It would appear that the impact of dimensionally-measured anxiety is less in the longer term, with none of the three studies investigating recurrence, all focussing on Panic Disorder symptoms, reporting an association (Holma et al., 2008; Melartin et al., 2004; Riihimäki et al., 2014). Two of these three studies did however find having an anxiety disorder to be predictive of MDD recurrence (Holma et al., 2008; Riihimäki et al., 2014).

5.6.2.2 Functioning

A 20 year follow-up study of a clinical adolescent MDD sample compared adult functioning (mean age 33) in those with and without comorbid Conduct Disorder at baseline (Fombonne et al., 2001b). This comorbidity was associated with poorer functioning measured by the Adult Personality Functioning Assessment (Hill et al., 1989), both in its overall score and for each of its individual domains.

In this cohort, comorbid Conduct Disorder was also associated with poorer functioning on a range of discrete variables such as educational level and housing tenure. The study authors comment that these results are similar to those seen in those with Conduct Disorder alone, and that the presence of MDD may not be of significance. The presence of multiple comorbid mental state disorders over follow-up was predictive of functioning in another adolescent clinical MDD sample (Peters et al., 2015). These comorbidities were associated with poorer functioning measured by the CGAS (Shaffer, D et al., 1983) or GAF (American Psychiatric Association Task Force on DSM-IV 1994a), as well as by empirically developed (by factor analysis) subscales of the Health of the Nation Outcome Scales for adolescents (HoNOSCA) (Garralda, M, Yates, P, & Higginson, I, 2000). In this group with multiple comorbidities, there was in fact a decline in functioning over the course of follow-up.

Three studies of adult clinical samples investigated the impact of baseline comorbid mental state disorders on later global functioning, with two focussed on anxiety. One found an association of having an anxiety disorder or a dimensional measure of anxiety with the overall WHO DAS II (Üstün 2010) score at 2 years (Gaspersz et al., 2016), while the other study did not find a relationship of having a comorbid anxiety disorder with SOFAS (Rybarczyk 2011) score at 66 months (Kuehner & Huffziger, 2013). A third did not find an association of having any comorbidity with the SAS-SR (Weissman & Bothwell, 1976b) overall score at 6 years (Furukawa et al., 2001).

Summed comorbidity at baseline in the form of the number of mental state and personality disorders predicted receiving the disability support pension at 5 years (Holma et al., 2012).

5.7 Micro and meso-systems

5.7.1 Relationships

Two longitudinal clinical studies in young people have looked at the role of relationships in MDD symptomatic outcome (Rao et al., 2010; Sanford et al., 1995), both assessing the shorter-term course.

One of the studies found a poor response to maternal discipline and low paternal involvement assessed by the Social Adjustment Inventory (John, Gammon, Prusoff, & Warner, 1987) to be predictive of MDE persistence in their one year follow-up (Sanford et al., 1995). They found another element of family relationships, parental expressed emotion, measured with the Five Minute Speech Sample (Magaña et al., 1986) to not predict MDE persistence (McCleary & Sanford, 2002).

The other study assessed broader domains of perceived and enacted social support and found neither to be associated with MDE duration (Rao et al., 2010). These were measured on the Social Support Questionnaire (Sarason, Sarason, Shearin, & Pierce, 1987) and the Social Support Inventory (Dunkel-Schetter, Feinstein, & Call, 1986) respectively. As mentioned previously they did however find that levels of perceived support moderated the effect of high cortisol levels on MDE duration, with low support levels causing a more protracted episode in those with high cortisol. Lower levels of enacted support were shown to be predictive of recurrence.

Among three prospective community studies of samples of young people with MDD investigating relationships and MDD course, two found a significant relationship, both with young adult recurrence.

One study found that levels of conflict with parents, measured by the Issues Checklist (Robin & Weiss, 1980) predicted young adult recurrence (Lewinsohn et al., 2000).

However, in the same study, the degree of social support from family, or peers, measured by items developed by the study researchers, did not predict recurrence. In the Minnesota Twin Study, the quality of romantic relationship, as assessed by the Dyadic Adjustment Scale (Spanier 1976) predicted a recurrence of MDD between the ages of 17 and 29 (Wilson et al., 2014).

Attachment, measured by the Inventory of Parent and Peer Attachment (Armsden & Greenberg, 1987) was found to not predict MDE persistence over a 15 month study (Essau 2007).

In prospective studies of clinical adult MDD samples, baseline measures of relationships have a variable association with episode duration, and have consistently not been shown to be associated with recurrence

All of the significant associations come from two studies, in which the Perceived Social Support Scale (Zimet, GD, Dahlem, NW, Zimet, SG, & Farley, GK, 1988) was used, and which rates twelve statements of types of support, eg. "I can talk about my problems with my family".

Lower scores on this instrument were associated with longer episode duration at the 18 month (Melartin et al., 2004) and 5 year follow-ups (Holma et al., 2008; Riihimäki et al., 2014) with the latter also finding an association with chronicity (2014).

None of these findings were however retained in multi-variate analyses. At 18 month analyses severity variables were prominent among independent predictors (Melartin et al., 2004), while comorbid cluster C personality disorder and dysthymic disorder were independent predictors of episode duration at 5 years one study (Holma et al., 2008).

In contrast, a study which counted the number of a participant's satisfactory or unsatisfactory relationships (Kuehner & Huffziger, 2013) and another which counted the number of supports and the frequency of contact with them (Paykel, Cooper, Ramana, & Hayhurst, 1996), did not find an association of these variables with MDE duration.

Three of these studies investigated the relationship of baseline social support to MDD recurrence and none found a significant association (Holma et al., 2008; Kuehner & Huffziger, 2013; Riihimäki et al., 2014). Another specifically focussing on difficulties in the spousal relationship at baseline also failed to find an association with increased recurrence risk (Kronmüller et al., 2008).

In drawing any conclusions about the above findings, it is important to be mindful of the heterogeneity of the methods used to assess relationships, with each study using a different instrument, and some developed within the individual studies with unclear attention to establishing their psychometric properties.

One could tentatively speculate that family factors are more important for young people than other relationships in regard to MDD course, and that their effect can endure over the medium-term. The results from adult studies point to the potential importance of measuring the quality of relationships over their quantity, and that the impact on MDD course is shorter, rather than longer-term. These effects were not shown however to be independent, with multivariate analyses indicating that the scores on the relationship scales may be an indication of illness severity or underlying personality pathology.

5.8 Macro-system

5.8.1 Educational attainment

The level of educational attainment has not been studied as an MDD course predictor in young people, most likely as typically studies of young people typically contain those still in school, or with the possibility of return.

The specific relevance of adult studies to young people in regard to education is that they can help describe the longer-term consequences of possible educational underachievement.

In the very small number of studies in which level of education has been investigated, it has generally however not been found to be predictive of MDD symptomatic variables (Boschloo et al., 2014; Furukawa, Kitamura, & Takahashi, 2000; Kanai et al., 2003; Rhebergen et al., 2012), but not unexpectedly did predict future receipt of the disability support pension, (Holma et al., 2012; Rytsälä et al., 2006).

5.8.2 Socio-economic status

Two studies of clinical samples of adolescents found SES to be associated with neither persistence nor recurrence (Curry et al., 2011; Vitiello et al., 2011), while a third did demonstrate an association of low SES with recurrence (Rao et al., 1995).

Similarly, two adult studies finding no association of SES with recurrence risk, both at two time points (Holma et al., 2008; Kennedy et al., 2003; Melartin et al., 2004; Ramana et al., 1995). One adult study found family income, but not social class to be predictive of non-recovery of MDD at a 2 year follow-up (Keller et al., 1984).

The Hollingshead four-factor index of social class was the most common index of SES used in the adult studies. This instrument rates and sums marital status, employment status, educational attainment and occupation prestige (Hollingshead, AA n.d.).

5.8.3 Race

Non-majority racial background was found to be predictive of MDE recurrence in one clinical sample of young people (Vitiello et al., 2011), but not in two others (Curry et al., 2011; Rao et al., 1995). Nor was it predictive of episode duration or persistence in two studies (Curry et al., 2011; Vitiello et al., 2011).

Neither community studies in young people, nor the adult clinical studies reviewed had tested race as a predictor.

5.9 Gender

Among young people, female gender was generally not found to be predictive of MDD symptomatic outcome, being associated with recurrence in one study (Curry et al., 2011), but neither (Curry et al., 2011; Karlsson et al., 2008; Sanford et al., 1995; Vitiello et al., 2011) persistence or recurrence (Karlsson et al., 2008; Rao et al., 1995; Vitiello et al., 2011) in three others.

One community sample of young people found female gender to be an independent predictor of MDD recurrence between ages of 19 and 26 (Lewinsohn et al., 2000).

The pattern of results in adult samples was similar to that in adolescents with only two of fourteen studies finding any association with the symptomatic course of MDD (Boschloo et al., 2014; Mueller et al., 1999).

5.10 Life stress

The study of a clinical sample adolescents testing this variable found an association of acute stress with MDD recurrence (Rao et al., 2010). In this study, stress was not found to be associated with episode duration, nor persistence (2010). Stress was prospectively measured across the follow-up period.

One community study of adolescents found school-related events over the seven years preceding the study baseline to be associated with MDE persistence (Essau 2007). In the other community study investigating life events, the OADP, life events over the preceding twelve months prior to the age 26 assessment were not predictive of an MDE recurrence between ages 19 and 26 (Lewinsohn et al., 2000).

The adult studies assessing the impact of life events measured these events prior to baseline or during follow-up. Of two studies measuring life events prior to baseline one found an association with MDE duration (Paykel et al., 1996), and another did not (Holma et al., 2008; Melartin et al., 2004). The study measuring life-events in the 12 months prior to follow-up assessment found negative life events to be independently predictive of MDE persistence at 2 years (Spinoven et al., 2011), and with having a chronic course at 5 years for those with a chronic MDD at baseline and high neuroticism at baseline (Boschloo et al., 2014).

5.11 Global functioning

5.11.1 Prediction of symptomatic course

The findings for adolescent clinical samples are suggestive of a differential ability of baseline functioning to predict MDD course variables, consistently predicting MDE persistence with three positive findings (Karlsson et al., 2008; Sanford et al., 1995; Vitiello et al., 2011), and consistently not predicting recurrence, with four negative findings (Curry et al., 2011; Karlsson et al., 2008; Rao et al., 1995; Vitiello et al., 2011). All five studies used the single-item Children's Global Assessment Scale (Shaffer, D et al., 1983) as their predictor measure. This scale measures functioning across four social domains.

It is worth noting that the follow-up periods of two studies (Karlsson et al., 2008; Vitiello et al., 2011), at 12 and 18 months respectively were relatively short, such that those with poor baseline functioning (who in fact were found to have more persistent episodes) may not recovered, and therefore would not have had a chance to have a recurrence.

In fact, in both these shorter studies the number of people having recurrences represented approximately ten percent of the original sample, such that the result for these studies is reflective of recurrence risk for a small sub-sample.

In contrast, 69% of the Rao et al. sample had a recurrence of their seven year follow-up, while 47% of the TADS sample had a recurrence over 5 years. The non-association of baseline functioning with recurrence in these samples, and its consistent association with persistence point to the possibility it having a shorter, rather than a long-term influence on MDD course.

The findings of the few adult clinical longitudinal studies focussing on functioning are broadly similar to those in young people, with some support for a role in MDE chronicity

(Riihimäki et al., 2014; Viinamäki et al., 2006), but generally not for recurrence (Holma et al., 2008; Melartin et al., 2004; Riihimäki et al., 2014) or episode duration (Holma et al., 2008; Melartin et al., 2004).

The specific methodology a twenty year follow-up was to assess the ability of overall scores on the four domain LIFE-RIFT (Leon et al., 1999) measure to predict recovery or recurrence at the next follow-up point, at 6 months for the first five years, then yearly thereafter.

A one standard deviation elevation in the LIFE-RIFT score of the preceding assessment was associated with a 22% decreased chance of recovery from an MDE at the next assessment (Solomon et al., 2008). A 13% increased chance of recurrence was found for each point of the LIFE-RIFT. A higher score on the LIFE-RIFT indicates poorer functioning.

5.11.2 Prediction of functional outcome

As commented earlier, the evaluation of functional outcomes has been rare in the MDD literature. Rarer still has been any testing for a role of functional variables in these functional outcomes.

One study found the SOFAS (Rybarczyk 2011) to independently predictive of receiving the disability support pension at 18 months (Rytsälä et al., 2007), and to be a univariate predictor at 5 years (Holma et al., 2012). It also found the association of the SAS-SR (Weissman & Bothwell, 1976b) with this outcome approached significance as a predictor at 18 months study ($p=0.062$), but was not tested at 5 years.

5.11.3 Educational and vocational functioning

One study of a clinical sample of young people assessed the role of school functioning as a predictor of MDD course, finding that school problems assessed with the Social Adjustment Inventory (John et al., 1987) predicted persistence of an MDE over their 15 month follow-up (Sanford et al., 1995).

A community found that academic problems measured with items from the K-SADS (Kaufman, J et al., 1996) at study baseline were not predictive of young adult MDD recurrence (Lewinsohn et al., 2000).

One study of an adult sample found unemployment not to be predictive of either episode duration or recurrence at their 5 year follow-up (Holma et al., 2008).

5.12 Chapter summary

5.12.1 Prediction of symptomatic course

It is apparent from Table 5-1 that there has not been extensive study of possible predictors of the symptomatic course of MDD in prospective studies of clinical samples of adolescents with MDD.

Global functioning at baseline was the variable that has the greatest weight of evidence as a predictor, but for only for the shorter-term symptomatic course, not for recurrence.

It was predictive of either the duration of the index MDE or its persistence in three studies (Karlsson et al., 2008; Sanford et al., 1995; Vitiello et al., 2011)

There was also consistent evidence of relationship-related factors being influential.

These were associated with both the shorter-term course and recurrence across two of the studies of clinical samples (Rao et al., 2010; Sanford et al., 1995), and with recurrence in two of the studies in community samples of adolescents (Essau 2007; Lewinsohn et al., 2000).

Notable for a consistent lack of association with the symptomatic outcomes in the clinical samples of adolescents were the severity of the index MDE (particularly with recurrence), individual co-occurring mental state disorders, and female gender.

One further area in which the clinical samples of adolescents can be supplemented by those of the community samples is in regard to the effect of family history of MDD. This was predictive of recurrence in three studies (Kim-Cohen et al., 2003; Lewinsohn et al., 2000; Wilson et al., 2014).

There is a mix of consistencies and inconsistencies of the findings in young people with the evidence from studies of adult clinical MDD samples. Global functioning and the relationship factors were similarly consistently predictive of the shorter-term outcomes.

In contrast to the studies in adolescents, the severity of the index MDE had significant associations across the symptomatic outcomes. Also anxiety, rated dimensionally or as a disorder was a consistent predictor of the shorter-term symptomatic outcomes.

5.12.2 Prediction of course of functioning

One of the two studies assessing the predictors of functioning in adolescent clinical MDD samples demonstrated an enduring impact of co-occurring Conduct Disorder (Fombonne et al., 2001b). The other indicated the importance of considering the impact of disorders occurring over the follow-up period, with both a recurrence of MDD

and experiencing multiple other mental state disorders having a significant association with functioning at follow-up (Peters et al., 2015).

In the two studies of adult samples assessing predictors of global functioning the consistent predictors of the symptomatic course, MDE severity and anxiety were predictive in one study each (Holma et al., 2008; Spinhoven et al., 2011), but neither in the other (Furukawa et al., 2001).

Chapter 6 Rationale, Aims and Hypotheses

6.1 Study rationale

6.1.1 Age group

It is evident that the longitudinal follow-up of clinical samples of youth is a gap in the existing literature on the course of Major Depressive Disorder. As the period of peak onset for the disorder, the tailoring of intervention for this age group has the potential to have a large impact on the overall burden of disease for MDD, particularly should it have enduring benefit.

6.2 Key predictors of interest

The data described in the preceding chapter identify a degree of divergence between predictors of child and adolescent MDD course and that of MDD in adulthood. It may be that those factors with significant associations in children and adolescents will be more applicable to youth given the proximity of age and therefore biological maturation and developmental tasks. However there are of course differences in both these areas with increasing age.

Personality factors emerge from the above findings as an important area of investigation given the consistency of their ability to predict the range of MDD course outcomes in adult studies, albeit in a relatively small number of studies overall.

This study will take a particular interest in borderline personality disorder traits. From a theoretical point of view, borderline personality traits have the potential to be highly disruptive in key domains of adolescent development, having a number of criteria related to relationship functioning and identity formation. There is cross-sectional evidence of a relatively greater impact of borderline personality traits compared to other personality disorder traits on psychosocial functioning in a clinical population of young people (Chanen, Jovev, & Jackson, 2007).

In terms of an enduring impact, community studies have demonstrated a longitudinal effect of adolescent borderline personality disorder traits on later adolescent (Wright, Zalewski, Hallquist, Hipwell, & Stepp, 2016) and young and middle adult functioning (Winograd, Cohen, & Chen, 2008).

A small number of studies in clinical populations of young people with MDD have measured the prevalence of borderline personality disorder. In a sample of hospitalised

adolescents with MDD, 57 percent were found to have BPD (Grilo et al., 1997), while there was a prevalence of 30 percent in consecutively assessed patients with MDD in a predominantly outpatient setting (Marton, P et al., 1989). These figures do not include those with BPD traits not meeting the diagnostic cut-off of five traits, but for whom such traits may well be of clinical and functional significance.

There are yet to be clinical studies of young people with MDD in which the impact of BPD traits on course and longitudinal functioning have been evaluated. The evidence of their functional impact in community studies and the frequency of their occurrence in clinical populations of young people in MDD point to the potential significance of such an evaluation.

A short-term study (19 weeks) has demonstrated an effect of the level of BPD traits (diagnostic threshold vs. subthreshold) on depressive symptoms measured by checklists, and on global functioning (Ramleth, Groholt, Diep, Walby, & Mehlum, 2017).

There are however yet to be clinical studies of young people with MDD in which the impact of BPD traits on symptomatic course and longitudinal functioning have been evaluated beyond this short-term time-frame. The evidence of their functional impact in community studies and the frequency of their occurrence in clinical populations of young people in MDD point to the potential significance of such an evaluation.

Neuroticism was chosen as the other key personality variable of interest in this study.

As reported in 3.4.6 above, neuroticism possesses a body of evidence identifying it as a risk factor in the development of MDD in young people. One might expect that such a risk would also be present for further episodes, such that neuroticism would be a predictor of recurrence. Indeed, as described in 3.4.6, studies in adults with MDD demonstrate this can be the case, though these studies are few in number.

Chronicity has been found to be predicted by neuroticism in a larger number of studies in adults with MDD than has recurrence, with the associations in higher quality studies supplemented by those with some methodological weaknesses.

Neuroticism is however yet to be tested as a predictor of MDD course in clinical samples of young people, so the applicability of adult findings to this population remains an open question.

Two very significant findings in the last 20 years of psychiatric research have been that of the non-immutability of personality disorders over time, and the efficacy of treatments developed for those with personality disorders, particularly borderline personality disorder (Zanarini 2009). Evidence for a role of borderline personality traits in leading to a more severe course of MDD in young people would provide a rationale

for providing such treatments in this population.

There are parallels with neuroticism in that longitudinal research has shown it not to be static (Roberts et al., 2006), and also that it can change with intervention (Roberts et al., 2017). The later of these reviews describes such intervention as typically not intentionally targeting neuroticism, but mention a current of thought on the utility of doing so given the prevalence of high levels of neuroticism across psychiatric disorders (Sauer-Zavala, Wilner, & Barlow, 2017).

6.2.1 Other predictors included in the study

It was decided to also test the range of predictors investigated in previous studies in order to be inclusive of variables with a potential effect, and these are listed in Table 8-22).

6.2.2 Functioning as an outcome

Increasingly, studies are including assessment of functioning in addition to symptomatic outcomes, adding a dimension of outcome that is likely to be very important to an individual experiencing the illness.

This study seeks to add to the so far small number of studies assessing functional outcome in MDD. It would appear from the results of this review that studies in young people with MDD use multi-item measures to assess functioning more often than those in adults, which appear to have favoured single item instruments.

In this study, a multi-item cross-sectional measure will also be used, and in addition, the course of functioning will be assessed. The obvious risk of cross-sectional assessment is that it may provide a snap-shot that is not representative of how someone has generally functioned over a follow-up period. Should such non-representativeness be common across a sample, it would also diminish the probability of validly assessing the impact of baseline predictor variables

6.3 Aims

1. To chart the medium-term course of Major Depressive Disorder of a clinical cohort of youth who have experienced a Major Depressive Episode and who were treated in a specialist psychiatric setting.
2. To investigate the predictors of medium-term functional outcome of this cohort, with a specific focus on the impact of personality traits and personality disorders.

3. To investigate the predictors of the severity of the medium-term course of Major Depressive Disorder in this cohort, with a specific focus on the role of personality traits and personality disorders.

6.4 Hypotheses

1. That the dimensional measure of Borderline Personality Disorder taken at baseline will predict the medium-term functional outcome of a clinical cohort of youth who have experienced complex Major Depressive Disorder.
2. That a dimensional measure of Borderline Personality Disorder taken at baseline will predict the severity of the medium-term symptomatic course of Major Depressive Disorder in this cohort.
3. That trait neuroticism assessed at baseline will predict the medium-term functional outcome of a clinical cohort of young people who have experienced complex Major Depressive Disorder in adolescence.
4. That the degree of trait neuroticism measured at baseline will predict the severity of the medium-term symptomatic course of MDD in this cohort.

Chapter 7 Methodology

7.1 Sample

7.1.1 Clinical context

Participants in the study were drawn from members of three research cohorts established at Orygen Youth Health (known as MHSKY prior to 2004) between 1998 and 2005.

Orygen Youth Health (OYH) is a government-funded mental health service providing outpatient and inpatient psychiatric care to 15-25 year olds living in the north and north-western suburbs of Melbourne, Australia. This is an area of relative social disadvantage compared to the general Australian population, and includes a number of the most disadvantaged local government areas in the country (McKenzie, Fiona 2009).

All members of these cohorts were originally recruited from patients attending the OYH clinical program that treats non-psychotic mental disorders. The two outpatient clinics from which the participants were recruited were the Mood and Anxiety Clinic and the HYPE (Helping Young People Early) Clinic.

The Mood and Anxiety Clinic provides treatment for unipolar mood disorders and anxiety disorders. HYPE is an early intervention program for Borderline Personality Disorder, with entry determined by meeting at least three of the nine criteria for this disorder in the Diagnostic and Statistical Manual of Mental Disorders volume IV (DSM-IV). Most of the young people receiving treatment at HYPE also have a unipolar mood or anxiety disorder.

In order to access these clinical programs, young people would have a level of illness severity, safety risk or functional impairment such that the private sector was unable to meet their needs. Patients were able to receive a cumulative 2 years of care over the period they remained in the 15-25 year age-range.

All patients were offered a comprehensive bio-psychosocial treatment program. The core components of this are medical care from a psychiatrist, including pharmacotherapy where appropriate, and case-management and psychological therapy from an allied-health professional. In addition, according to need, young people are able to access family therapy, group therapy, and educational and vocational support.

For this study, the original cohorts have been designated Samples 1-3, in chronological order of commencement of these earlier studies. Details of these samples are provided below.

7.1.2 Core features of original studies

Sample 1

‘Personality Disorder Stability Study’(Chanen et al., 2004).

Consecutive consenting patients of the Older Adolescent Service, aged 15-18 years old were accepted into this naturalistic study, with data collected at baseline (between July 1998 and July 1999) and at two-year follow-up.

The psychological treatment provided for this group was Cognitive-Behavioural Therapy (CBT).

The mean number of sessions of any type (including case-management, review by doctor) attended by this study’s participants was 29, but with a wide range reflected by a standard deviation for attendances of 38, and median of 13.

Sample 2:

‘Indicated prevention and early intervention in Borderline personality disorder” (BPD) (Chanen et al., 2008, 2009)

This was a randomised-controlled trial of two forms of early intervention for BPD within the HYPE clinic.

Participants were aged 15-18 years and met at least three of the nine criteria for BPD in the Diagnostic and Statistical Manual of Mental Disorders volume IV (DSM-IV) (American Psychiatric Association Task Force on DSM-IV 1994b). The study ran from October 2000 to October 2004, with assessments at baseline as well as 6,12 and 24 months after entry to the OYH program.

The treatments provided were either Cognitive Analytic Therapy (CAT) (Ryle, A & Kerr, 2002) or manualised “Good Clinical Care”, the therapy component of which was CBT.

Sample 3:

‘Interpersonal functioning in emerging borderline personality disorder’ (Jennings, Hulbert, Jackson, & Chanen, 2012)

This was a cross-sectional study investigating social perspective co-ordination in youth being treated in either the HYPE or Mood and Anxiety Clinic. All participants met DSM-IV criteria for Major Depressive Disorder. Of these, half met at least 3 DSM-IV BPD criteria, the other half none.

In terms of psychological treatment received, the BPD group received Cognitive Analytic Therapy, and those not meeting BPD criteria received CBT. This study was conducted between November 2004 and November 2005.

The following DSM-IV exclusions were common to all three samples: Mental Retardation, Psychotic Disorder, Psychiatric Disorder due to a General Medical Condition. Participants were also required to speak sufficient English to comply with the study procedures.

7.1.3 Current study inclusion criterion

Those participants in the above three samples meeting DSM-IV criteria for Major Depressive Disorder at their original study baseline or in the 12 months prior were eligible for inclusion in the current study.

This diagnosis was made by a structured interview, the Structured Clinical Interview for DSM IV Axis I Disorders, Patient Version (SCID-I/P) (First, Spitzer, Gibbon, & Williams, 2001).

7.1.4 Current study exclusion criteria

Participants were excluded if they were found to have developed Bipolar Affective Disorder, Delusional Disorder, Schizophreniform Disorder, or Schizophrenia over the course of the follow-up period.

The reason for this exclusion is that these illnesses are likely to have independent and potentially significant effects both on occurrence of depressive symptomatology and social functioning.

7.1.5 Rationale for selection of original study cohorts

As young people who have been accepted for treatment at OYH, a specialist mental health service, all members of the original cohorts meet the key criterion necessary for this study of having mental health disorders of severity requiring specialist psychiatric care.

All participants of the selected cohorts had received a detailed assessment package at the study baselines performed by trained researchers. This included well validated structured diagnostic assessments for Axis I (SCID-I/P) and Axis II (SCID-II)(First, Spitzer, Gibbon, Williams, & Benjamin, 1994) disorders.

Data was also collected on family history of mental illness, childhood adversity, personality traits, social functioning and type and amount of treatment received at

OYH. Such a range of data enables a comprehensive assessment of outcome prediction.

7.2 Recruitment

Recruitment followed an updated version of the procedure previously used at OYH in two projects also following up former clients of the service, the EPPIC-800 (Henry et al., 2007), and PACE-400 (Lin et al., 2011).

An algorithm was developed (see section 7.2.1 below), and was worked through sequentially in order to contact participants directly, or through relatives or friends. If postal addresses were available, initial contact was made by letter in order to minimise any perceived pressure to consent to involvement. If no return contact was received by this means, phone-numbers were then used.

In order to store both the contact details of the potential participants and any relatives or friends nominated as alternative contacts, an electronic (Access) database was created. This database was also used to record all successful or unsuccessful attempts at finding participants.

In all methods of contact, efforts were made to protect the privacy of potential participants. When telephone contact was made with relatives or friends, researchers identified themselves as being from the University of Melbourne rather than OYH if it was uncertain whether that individual was aware that the potential participant had received mental health care from OYH in the past.

When contact was by letter or Facebook, privacy was protected by using only a University of Melbourne letterhead. These measures were also taken contacting potential participants themselves if there was any uncertainty whether an individual was the person we intended to contact, such as when mailing out to addresses taken from the National Electoral Roll.

In letter or Facebook contact potential participants were provided with both an email address and phone-numbers (landline and mobile) with which they could contact the research team. Those receiving letters also received a form on which they could write their current contact details and a stamped, addressed envelope in which to return this. Data on which methods of contact were successful will be provided in the Results section of this thesis.

7.2.1 Step-wise recruitment algorithm

1.Determine if individual deceased

The names and dates of birth of potential participants were provided to the National Death Index, managed by the Australian Institute of Health and Welfare. This database obtains information from the Registrars of Births, Deaths and Marriages in each Australian state and territory.

If a person were to be found to be deceased, no attempts at contacting relatives or friends were to be made. It was already known from the original studies that one person originally meeting recruitment criteria for the current study was deceased.

2.Use contact details provided in original projects.

In most cases contact details for the participants as well as relatives or friends had been recorded in the course of the original studies, and consent given for these to be used in future research.

Given that these details were from up to 14 years prior to the current study, a significant number were likely to no longer be valid.

3.Search for more recent contact details in following sources

3.1 Medical record for OYH Clinical Programs.

This contains contact information for patients and next of kin.

3.2 Victoria-wide mental health service database.

This database contains records of any service provided to an individual by the Victorian public mental health system, and contact details for that person and nominated next of kin. Potential participants may have received treatment from adult mental health services following their care at OYH, and hence have had contact details updated.

3.3 National Electoral Roll

Individuals should provide a current address at times of either state (every four years) or federal (every three years) election. Addresses are publicly available, and at the time of recruitment for this study, were able to be recorded.

3.4 White Pages telephone directory

Where no reply was received following postage to addresses found on the National Electoral Roll, telephone calls were made to matched numbers from the White Pages.

3.5 Medicare Australia

Medicare is able to match provided dates of birth and names to addresses on their records and send out letters on researchers' behalf.

3.7 Social networking website-Facebook

Individuals were searched for by name and surname on Facebook. If date of birth or geographical location indicated a reasonable likelihood that a person was from an original study cohort, and introductory message was sent.

The message asked recipients if they had taken part in a project on youth health with the University of Melbourne, and specified the year/s they would have been involved. They were asked to make contact with the researchers either via Facebook or telephone.

7.2.2 Feasibility estimates

There were a number of potential limiting factors on the rate of recruitment. Prime among these was the long time period since the individuals participated in the original studies.

Specific factors likely to mean original contact details were no longer current were that this time period for this cohort co-incided with ages that young people often leave the parental home and marriage for the young women in the cohorts.

Also it was possible that the extended time since last contact would reduce allegiance to involvement in research.

Both of the EPPIC-800 and PACE-400 studies achieved face-to-face interview rates of more than two-thirds. The recruitment rates of these projects (particularly the EPPIC-800) may however have benefited from the increased likelihood that people with psychotic illnesses, as compared to those with mood disorder continue to receive treatment within the public mental health system as adults. These studies also contained larger research teams.

If however our rates paralleled those of these studies, it would therefore be reasonable to expect that it would be possible to interview approximately 93 of the total pool of 144 potential participants for this study.

7.3 Outcomes

At follow-up, 6-15 years will have elapsed since collection of baseline data.

7.3.1 Outcomes

7.3.1.1 Functioning outcomes

- i) Social functioning at follow-up
-measured at the follow-up interview

ii) Longitudinal social functioning

-between the baseline interview in the original studies and the interview of the current study.

7.3.1.2 Symptomatic course of MDD

i) Duration of the index episode of MDD

ii) Time to recovery from index episode of MDD

iii) Recurrence of the MDD

iv) Proportion of the follow-up period not recovered from MDD

“Index” episode refers to the episode of MDD for which the young person presented to OYH for treatment. The first secondary outcome, “Duration of index episode of MDD” differs from the second in that it starts measuring from the point at which criteria are met for MDD at some point prior to presentation, while “Time to recovery” measures from presentation. The period of illness prior to presentation can be protracted and therefore its inclusion more fully characterises an episode.

Recovery was chosen in preference to remission, as by definition it defines the offset of an episode, and the study aimed to delineate the period that participants were experiencing an MDE.

The fourth outcome was chosen as a means of quantifying the illness load over the follow-up period. An alternative would have been to measure number of recurrences, but due to the variability of MDE lengths, individuals with the same number of recurrences may have markedly divergent total periods of time which were spent in an MDE (Fergusson, Boden, & Horwood, 2007). This method has been used previously in the Collaborative Depression Study (Coryell et al., 2012; Judd et al., 1998) and the two Vantaa studies (Holma et al., 2012; Riihimäki et al., 2014).

7.4 Measures

7.4.1 Assessments undertaken at previous time points

The participants in this project were interviewed at the original baselines, then at a further 1-3 time-points within the studies to which they were recruited.

7.4.1.1 DSM-IV Axis I disorders

For Samples 1 and 2, and half of Sample 3, the measure at baseline for DSM-IV Axis I disorders was the **Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Patient Edition** (SCID-I/P). The SCID-I/P is a very widely used and well-validated structured interview used for the assessment of current Axis I disorders as defined by DSM IV, with disorders rated as being present if they meet their diagnostic criteria over the preceding month.

Certain diagnostic clusters were not of interest in the baseline studies, and therefore were not assessed at that time. These were Somatoform and Adjustment Disorders. The remaining diagnostic clusters that were assessed were Mood Disorders (both unipolar and bipolar), Schizophrenia and other Psychotic Disorders, Substance Use Disorders, Anxiety Disorders and Eating Disorders.

The SCID-I/P was also used to assess for history of an MDE occurring in the twelve months prior to baseline.

In order to assess for Oppositional Defiant Disorder and Conduct Disorder, the SCID-I/P was supplemented with the Disruptive Behaviour Disorders sections of the Kiddie-Sads-Present and Lifetime Version(K-SADS-PL) (Kaufman et al., 1997) .

For Sample 1, drug and alcohol disorder diagnoses were made using the CIDI-Auto (Rubio-Stipec, Peters, & Andrews, 1999), a self-administered computerized interview. The half of Sample 3 that did not receive the entire SCID-I/P was administered only the MDD section, with other diagnostic information collected by a non-structured clinical interview.

Those participants interviewed in the current study belonging to this group had their clinical files reviewed using the OPCRIT+ checklist (Rucker et al., 2011). This instrument is designed to enable the extraction of diagnoses from case notes, and in this case was used for DSM IV Axis I diagnoses.

The severity of the baseline episode of MDD will be measured by the sum of the number of symptoms experienced in this episode. The DSM-IV specifies nine symptoms that can contribute to a diagnosis of an MDE. Summing symptoms has been found to be a valid predictor of severity(Andrews et al., 2007), specifically demonstrating a correlation with degree of impairment, as well as with length of episode and comorbidity(Kessler, Zhao, Blazer, & Swartz, 1997; Sakashita, Slade, & Andrews, 2007).

Participants in Samples 1 and 2 also had the SCID-I/P administered in the follow-up assessments of the original studies. Those in Sample 1 were assessed again at two years, those in Sample 2 at 6 months, 12 months and 2 years.

7.4.1.2 Personality Disorders

For Samples 1 and 2, Personality Disorders were assessed with the complete **Structured Clinical Interview for DSM-IV Axis II Personality Disorders** (SCID-II)(First et al., 1994).

Again, the range of measures ascertained for Sample 3 was more limited. Half of the sample was interviewed with SCID-II for Borderline, Antisocial and Schizotypal Personality Disorders, the other only for Borderline Personality Disorder.

With the SCID-II, the interviewer scores the interviewee on individual diagnostic criteria for the different Personality Disorders (PD) as one, two or three, with three representing meeting the criterion, one not, and two an intermediate score.

Interviewees are diagnosed as having a particular disorder when they meet the threshold number of criteria for that disorder.

Each of the ten PDs assessed by the instrument belongs to one of Clusters A, B or C. PDs are grouped within these clusters based on descriptive similarities (American Psychiatric Association Task Force on DSM-IV 1994a).

There are a number of categorical and dimensional methods that can be used to represent the data collected by the SCID II. At the simplest level, one can determine categorical diagnoses for an individual PD, as described above.

Dimensional scores for disorders can be calculated from the SCID-II for individual PDs by summing the scores obtained for each criterion of that PD (Chanen et al., 2004; Cyranowski et al., 2004; Levenson, Wallace, Fournier, Rucci, & Frank, 2012). Similarly, a score for each Cluster can be generated by summing the scores of all criteria relevant to a Cluster.

There are varying numbers of criteria for each DSM-IV PD. Therefore in this study, to enable more meaningful comparisons between disorders and Clusters, mean scores for each PD and Cluster were calculated by dividing the sum of scores for relevant criteria by the number of these criteria.

An overall mean score for the SCID-II was obtained by dividing the sum of all items by the total number of items of the instrument.

7.4.1.3 Personality

The **NEO-Personality Inventory-Revised** (NEO-PI-R) (Costa Jr & McCrae, 1992) was administered for all individuals in the three samples. The NEO-PI-R is a self-report instrument that produces dimensional scores on five personality factors-Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness. Within each factor are six subscales or facets, for which dimensional scores are also generated.

Costa and McCrae developed the NEO-PI instrument (1992) to measure the five-factor model. The instrument has demonstrated high levels of internal consistency of its dimensions (Cronbach's alpha 0.76-0.93), significant levels of convergent validity between self and peer report, and good test-retest reliability (0.63-0.92) (McCrae 1991; McCrae, Kurtz, Yamagata, & Terracciano, 2011).

7.4.1.4 Other

Data relating to certain other variables measured in the earlier studies were extracted from baseline interviews for participants in the current study, as it was thought these variables may have effects on the course of MDD and social functioning.

An index of socio-economic status was developed using the Victorian postcode rankings of Vinson (Vinson, Tony 1999, 2004). In his reports, Vinson ranks all Victorian postcodes sequentially from a summation of average scores on a range of indicators of disadvantage for residents of individual postcodes. These indicators are across the domains of health, education, employment and contact with the criminal justice system. For the purposes of this study Vinson's rankings were divided into tertiles in order to represent three broad social groupings.

Qualitative and quantitative data were collected on the experience of abuse, with this classified under the categories of physical, psychological, sexual and neglect.

It was also recorded whether individuals were in the care of people other than their biological parents, that is in "out of home care".

Functional level was assessed with the widely-used Social and Occupational Functioning Assessment Scale (SOFAS)(Spitzer et al., 2000). This is a single-item interviewer scored instrument that obtains a score between 0 (low functioning) and 100 (high functioning).

7.4.2 Assessment undertaken in current project

The following assessments were made at the follow-up interview:

7.4.2.1 *Social functioning at follow-up*

Functional level at follow-up was measured with the **Social Adjustment Scale-Self Report (SAS-SR)** (Weissman, Myrna 1999). The SAS-SR measures functioning in five role-areas over the preceding two weeks by means of a 54-item questionnaire, with each item scored on a five-point scale. Lower scores indicate higher functioning.

The instrument was derived from the Social Adjustment Scale interview (Weissman, MM & Paykel, ES, 1974), which its authors describe as a “modification” of the Scaled Interview to Assess Maladjustment (SSIAM) (Gurland, Yorkston, Stone, Frank, & Fleiss, 1972). The SSIAM aimed to assess aspects of functioning of interest to mental health clinicians and designed its items to measure distress, deviant behaviour, and conflict with others. Deviant is meant in the sense of diverging from normative expectations.

The Work Role assesses functioning in one of housework, study or paid work, with questions assessing attendance, performance, satisfaction and conflict. The other four scales measure aspects of interpersonal functioning, specifically Social and Leisure (items relating mostly to friends), Family, Primary relationship, and Parental role. The items of these scales explore a wide range of elements of interpersonal experience, including conflict, dependence, assertiveness, closeness, loneliness and satisfaction, including with one’s own behaviour.

In this study, mean item scores will be calculated for the instrument as a whole and the two broad sub-scales of vocational (19 items) and interpersonal functioning (35 items), as well as for the individual subscales.

High levels of internal consistency have been found for the total score of the SAS-R, with Cronbach’s α (Cronbach, LJ 1951) ranging between 0.79 to 0.90 over 18 assessment points in a study of depressed outpatients (Vittengl, Clark, & Jarrett, 2009). Concurrent validity for this instrument has been tested with the Social Adjustment Scale Interview (Weissman, MM & Paykel, ES, 1974), the interview on which the scale was based, and the LIFE-RIFT (Leon et al., 1999) (see immediately below). Correlation coefficients with the SAS of 0.40 to 0.76 were found for the sub-scales of the SAS-R, and of 0.72 for the overall scale score (Weissman & Bothwell, 1976a). A small ($r=0.11$), but statistically significant correlation was found with the overall score of the LIFE-RIFT (Vittengl et al., 2009).

It was also found to be reliable across informants, with an intra-class correlation coefficient of 0.74 between the ratings of depressed outpatients and a close associate (Weissman & Bothwell, 1976a). Test re-test reliability was performed in a non-patient sample by testing correlation over three time points, yielded a correlation coefficient (r) of 0.78 (Edwards, DW, Yarvis, RM, Mueller, DP, Zingale, HC, & Wagman, WJ, 1978).

The scale authors have calculated T scores from a non-clinical sample, which set the mean for the sample at 50 and the standard deviation at 10 (Weissman, MM and MHS staff 1999). The study manual provides mean item scores for the subscales as well as for the overall mean that correspond to T scores from 36 to 110 for both genders.

A deviation from “typical” is judged as starting at a T score 6 points above the mean, moving in 5 point grading increments through 56-60: slightly atypical (possible concern), 61-65: mildly atypical (possible significant problems), 66-70: moderately atypical (significant problem) to 71+: markedly atypical (significant problem). The threshold for “clinically significant problems” is a score over 65.

In a study of adults with DSM III R Chronic Major Depression, T scores for women ranged from 63 to 75, with a score of 73 for the overall mean, while for males, the scores ranged from 67 to 84 with a T score for the overall mean of 70 (Kornstein et al., 1995).

7.4.2.2 Course of social functioning

Functional course was assessed with the **Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool** (LIFE-RIFT) (Leon et al., 1999). This brief scale measures functioning in the four domains of vocation and education, relationships, recreation, and life satisfaction. The vocation and relationship domains have multiple sub-domains in order to capture a relevant area for every person. Specifically, the relationship domain has sub-domains of spouse, children, relatives and friends, while the vocational domain has sub-domains of employment, household and student. A score from 1-5 is given for each domain, with a scores 3 and above indicating progressively greater impairment. The vocation and education domain is rated from a level of 1, which is given for high normal functioning, then 2 for satisfactory functioning, through 3 for mild impairment, 4 for moderate and 5 for severe impairment. For the other three domains, a level of 1 denotes very good functioning, 2 good, 3 fair, 4 poor, while a 5 is rated for very poor functioning. For the vocation and relationship domains, the score for the sub-domain with the greatest impairment is used.

The instrument gives specific descriptions of the nature of impairment required for a particular score for each domain. For example, a rating of 5 (very poor) is given for the spouse sub-domain of the relationship domain if a participant “constantly argues or withdraws most of the time”, and if separated is “almost always hostile when in contact”. These descriptions act as guides for the interviewer.

Summing the scores for each domain produces an overall score, with the denotation of the levels of impairment of 4,8,12,16 and 20 following that of the individual domains (Judd et al., 2005). The scale authors do not provide specific guidance on the interpretation of scores lying between these values. As there will be a variable follow-up period, mean yearly scores for the domains will be calculated.

Given the extended follow-up period and consequent demand on participants' memories, prior to ratings being made, the researchers asked about the time-points of occurrence of significant life-events and transitions which were then recorded on the chart used for the LIFE ratings. It was anticipated that this would improve the accuracy of the ratings by better orienting the participant to the time-period under consideration. Factor analysis performed by the scale authors found substantial contributions of each of the four scale items to a one factor model, of impairment, with loadings from 0.61-1.0, and they confirmed the model with three different goodness of fit indices (Leon et al., 1999).

The concurrent validity of the LIFE-RIFT has been tested by assessing correlations with the Global Assessment of Functioning (GAF) and the SAS-SR, with significant correlations detected, with Pearson's r of -0.36 (moderate) and 0.11 (low) respectively (Vittengl et al., 2009). The study authors also tested the instrument's correlation with the Global Assessment Scale (Endicott, Spitzer, Fleiss, & Cohen, 1976) in patients with MDD (Leon et al., 1999) and BPAD (Leon et al., 2000). They found significant negative correlations in mixed-effect linear regression models, with the LIFE-RIFT accounting for 56% of the variance of the GAS in the MDD group and 38% in the BPAD group, and they suggest the strength of correlation is limited by the GAS containing information on symptoms in addition to functioning.

Reliability was also tested by the scale authors, who report the alpha coefficients for internal consistency as between 0.81 and 0.84 over four different time points. Inter-rater reliability testing for two raters of a small sample (24 MDD patients) produced an intra-class correlation coefficient for the overall score of 0.94 (1999).

The scale authors did not assess a non-clinical population with the LIFE-RIFT which one could use as a point of reference. Normative-type data is however available from

two studies. One compared bereaved adults with and without an anxiety disorder, with those without a disorder scoring a mean LIFE-RIFT total score of 6.2 (SD 1.83) (Marques et al., 2013). The other followed a cohort with OCD in childhood into adulthood, and reported a mean total LIFE-RIFT score of 6.5 in those in remission at follow-up (Palermo et al., 2011).

7.4.2.3 Severity of MDD course

The variables listed in section 7.3.1.2 above were measured using the **Longitudinal Follow-Up Evaluation** (LIFE) (Keller et al., 1987). This is a commonly used and well-validated instrument for charting the longitudinal course of mood disorders. It was used to chart the course of MDD symptoms over time the follow-up period.

The LIFE assigns periodic Psychiatric Status Ratings (PSRs) which measure a participant's degree of MDD symptomatology and functional impairment. The LIFE defines recovery from an MDE as eight weeks of a PSR of 2 or 1 (Keller et al., 1982a). A PSR at this level is defined as either being asymptomatic (PSR=1) or to have one or two symptoms of an MDE to a mild degree (PSR=2).

The use of this definition means that the time to recovery is likely, in the absence of a rapid resolution of symptoms, to include a period in which a person no longer meets threshold criteria for an MDE.

Prior to determining the recovery point, each participant was oriented to MDD symptoms by being informed of the symptoms that they had reported (and that had been recorded) at baseline. They were then asked when was the first point at which for a period of at least two months they were experiencing none of these symptoms or only one or two that were not bothering them too much. When a time period was identified, the interviewer assessed each MDD symptom with the participant to determine whether the PSR level met the recovery threshold.

There is variability in published studies regarding the duration threshold to meet for the determination of a recurrence, with durations of two (Posternak et al., 2006), four (Fombonne et al., 2001a; Keller, Shapiro, Lavori, & Wolfe, 1982b) or eight weeks applied (Gunderson et al., 2008). The Research Diagnostic Criteria for MDD (Spitzer et al., 1978) were used in the original LIFE and stipulated a four week period for the diagnosis of an MDE.

Over the time period set for a recurrence, a weekly PSR of 5 or 6 must be met. Such a PSR corresponds to meeting the symptomatic diagnostic threshold for an MDD according to DSM IV criteria, with the higher level of 6 being assigned for "extreme

impairment” (Keller MB, Warshaw MG, Dyck I, Dolan RT, Shea MT, Riley K, Shapiro R 1997).

Eight weeks was chosen as the duration threshold for this study to reduce the risk of occurrence of false-positive “recurrences” that may have been recorded using a briefer duration criterion.

The LIFE for MDD was administered as set out in the LIFE supplement of the K-SADS-PL (Kaufman, J et al., 1996). Incorporated in the instrument are probes that focus the measurement of PSRs at the time of episodes, rather than collecting these for the entire follow-up period. These probes are written to evaluate specific levels of PSR. The K-SADS-PL rates PSRs on a month to month basis, rather than weekly. Given the length of the follow-up period of this study, weekly ratings are likely to have been inaccurate, as well as placing a large time burden on the participants. Therefore this practice of the K-SADS-PL was followed.

7.4.2.4 Diagnostic measures

Both the SCID-I/P and SCID-II were performed at follow-up in order to obtain a comprehensive assessment of current mental health. The SCID-I/P was used to assess both for current disorders and for any disorders for which diagnostic criteria were met since the last SCID-I/P assessment.

The severity of any current MDE will be measured by the Centre for Epidemiological Studies Depression Scale (CES-D) (Beekman et al., 1997; Radloff 1977) , a 20-item scale that measures current MDD symptoms.

7.4.2.5 Predictor measures

Factors relating to personality are of particular interest in this study in regard to their effect on the measured outcomes. A number of other variables have been found or theorised to be predictive of adolescent MDD outcome in previous longitudinal studies. Those requiring specific assessment at follow-up will be described immediately below,

7.4.2.6 Life Stress

This was measured by the Life Events Questionnaire (LEQ). This 30 item self-report scale is based on well-established measures of life stress (Lethbridge & Allen, 2008) (Lewinsohn, Rohde, & Gau, 2003).

7.4.2.7 Other measures

The NEO-PI-R was repeated in order to explore stability of personality traits over the follow-up period.

7.4.3 Reimbursement

Participants were provided with \$50 to cover expenses involved in taking part in the project.

7.4.4 Training in measure administration

The interviews were performed either by myself or by my research assistant, a doctorate-level registered counselling psychologist. I have experience with diagnosis of Axis I and II disorders through my role as a consultant psychiatrist at OYH since 2008, and as a psychiatry trainee from 2001-2007.

Specific training was provided for the SCID-I and SCID-II interviews. This consisted initially of reading the manuals for both interviews and viewing the videos of SCID-I delivery made by the developers of the instrument, and of the SCID-II made by an experienced interviewer. Following this, an interview of a study participant using both instruments was recorded and reviewed by an experienced interviewer. Feedback was provided regarding this interview, and ongoing consultation was available over the course of the study.

My research assistant was also required to read the manuals and view the training videos mentioned above. She then observed myself performing four interviews which she also rated. Following this, she delivered four interviews that I observed and also rated.

7.5 Missing data

Among the measures of baseline data, a range of approaches were taken to missing values. The SCID-II had no missing values. Missing items in the NEO-PI were scored at the “neutral” rating of 2. For the three participants missing SOFAS ratings, this instrument was scored using information from their medical record, having obtained consent to access this at the study interview.

The method of data recording from the SCID-I/P was to list the diagnoses for which participants met criteria. This method does not indicate whether sections of the interview may have not been completed. However, such incompleteness was not

identified as being an issue by the principal investigator of the studies from which this data originated (Prof. A. Chanen, personal communication).

Five participants did not provide information on the duration of the childhood abuse that they suffered. These participants were excluded from analyses involving this particular variable, defined as “pairwise” exclusion by SPSS in its linear

The 17 participants from the original “Sample 3” for whom only incomplete data had been collected by the SCID II were also excluded from analyses in this manner.

The presence of missing data from the follow-up interview was minimised by the SCID-I/P and SCID-II, LIFE-RIFT, and MDD course data collected being visually checked by the interviewer while the participant was completing the self-report measures following the administration of the interview. Visual checking at the interview was also performed for the self-report instruments, the SAS-SR, and the NEO-PI.

Participants were contacted by telephone in a small number of instances in which data was missed despite these checks.

As with the baseline data, any missing score on the NEO-PI was recorded as a “2”. For dimensional scale scores of the SCID-II and SAS-SR, the means of completed items were calculated.

7.6 Inter-rater reliability

Inter-rater reliability of the SCID-II was assessed via independent expert ratings of a random sample of twenty five recorded interviews. All interviews were recorded if consent for this was provided.

Inter-rater reliability of the SCID-II was planned to be assessed via independent expert ratings of a random sample of twenty five recorded interviews. All interviews were recorded if consent for this was provided.

However, ultimately the independent re-rating was only performed for eight interviews, as further repeat rating was not within the resources of the project for to be performed.

In the 8 double-rated interviews, the mean percentage of items per participant that were scored identically by the two raters was 74%. Of the discrepant ratings, 82% were of one point difference. Items are rated with a nominal score of 1-3.

7.7 Analysis

Analyses were performed with SPSS statistical software (Version 22, IBM corporation 2013). The multiple predictor test used was stepwise backwards hierarchical

regression. Further details of the specific tests used are described in the following results chapter.

7.8 Power

The size of the sample is fixed by the original cohorts but will be maximized by proven tracking processes. The estimate for the number of participants that will be recruited for face to face assessments, guided by the previous studies using these tracking processes, is 93.

Sensitivity will be maximized by the use of continuous predictor variables, and the fact that all bar one of the proposed outcome variables are also continuous.

For the sole binary outcome (Recurrence vs. No recurrence) under worst-case scenarios, a sample of 80 patients will be able to detect odds and risk ratios of 3 or higher with a power of 80%.

Chapter 8 Results

8.1 Introduction

This chapter initially provides an overview of the recruitment and interview process of the study. Following this, there is a description of the sample at the time of their initial presentation, detailing the psychopathology and functional impairment that they were experiencing at this study's baseline.

The three further sections of this chapter are a description of the sample at follow-up, a review of the study's primary and secondary outcomes, with the concluding section of the chapter detailing the analyses of the predictors of these outcomes, and the results of these analyses.

8.2 Tracking and recruitment

Contact was made either directly or through relatives or friends, with 120 out of 144 (83%) possible recruits to the project. Details of the means by which study participants were recruited are contained in Table 8-1 below.

Table 8-1: Means of recruitment of study participants

Contact information source	Response to	Target	Number	Percentage of Total Sample
Research database	Letter	Participant	8	5.6
		Relative/friend	5	3.5
	Telephone	Participant	22	15.3
		Relative/friend	42	29.2
Medical record	Letter	Participant	4	2.8
		Relative/friend	2	1.4
	Telephone	Participant	11	7.6
		Relative/friend	6	4.2
Mental health service database	Letter	Participant	3	2.1
		Relative/friend	0	0
	Telephone	Participant	4	2.8
		Relative/friend	3	2.1
National Electoral Roll	Letter	Participant	1	0.7
		Relative/friend	0	0
	Telephone	Participant	2	1.4
		Relative/friend	0	0

Telephone directory	Letter	Participant	0	0
		Relative/friend	1	0.7
	Telephone	Participant	1	0.7
		Relative/friend	2	1.4
Letter sent by Medicare			0	0
Facebook			2	1.4
TOTAL			120/144	83%

The first attempt at contact with people was by letter, but this method rarely resulted in return contact being made by the individual with the research team, with only 20.2% of those who were successfully contacted replying following receiving a letter. This low percentage was a consequence of many addresses no longer being current and perhaps also the requirement for the potential participant to make an active effort to contact the research team.

With the exception of two people being contacted via Facebook, the remainder of successful contacts (77.4%) were via telephone. It was slightly more common for initial contact by telephone to be made with relatives or friends (56%), rather than with the potential participant (44%). Often this was due to the recorded landline telephone number of parents remaining current, while their children had moved residence or changed mobile phone numbers.

The highest yielding source of contact information was the contact database that was developed in the course of the earlier research projects from which those in this project were drawn. This source was responsible for the recruitment of 64.6% of the current project sample.

Medicare were able to identify eight people that were yet to be mailed out to who had addresses registered with them. Unfortunately no replies were received from this group.

Of those contacted, 21 people (17.5%), or their relatives declined participation on behalf of the potential participant at first contact. The most common reason that people gave for this was that they did not wish to revisit a difficult time of their life. Others said they did not want to take part due to the time-demands of the interview.

A further 9 people (7.5% of those contacted), though initially consenting to the study did not progress to the interview stage due to subsequently finding they could not commit the time required or the researchers having recurrent difficulties with recontacting them.

8.3 Interviews and questionnaires

Ninety interviews were conducted with study participants between January 2010 and July 2012. Eighty-two of these were conducted by the student researcher, with eight administered by the study research assistant. The interviews were usually attended by one other staff member in accordance with local occupational health and safety requirements, though no situations of concern eventuated.

Seventy seven (85%) of participants lived in metropolitan Melbourne, and most were seen at their home, with a small number preferring to come to OYH. Four interviews were performed in public locations at the request of the participants with efforts made to maximise privacy in these locations.

Six participants lived in regional Victoria and all were interviewed at their homes. A further seven lived interstate (NSW, ACT, QLD), with five people being interviewed at their homes and two via Skype. All of the interviews outside metropolitan Melbourne were performed by the student researcher.

The mean length of the interview was 133 minutes, with the range from a minimum of 68 to a maximum of 242 minutes. One interview needed to be stopped due to the participant being substance-affected.

The self-report instruments typically took a further 30 to 45 minutes. Five of the participants either did not complete these fully or at all. Most of these people had had the self-report instruments left with them after completing the interview. When the measures were not returned they were contacted and typically said they did not have the energy to contribute further to the project.

There were no adverse events related to the interview. Two participants were referred to local crisis teams, and one to the local adult community mental health service by the student researcher due to current mental health difficulties that became apparent during the course of the interview. These referrals were made with the participants' consent.

8.4 Sample characteristics at baseline

Eight of the participants that were interviewed met diagnostic criteria for Bipolar Affective Disorder (n=7) or Schizophrenia (n=1) over the follow-up period, and the data of these people were excluded from analyses. Consequently, this meant the data of 82 individuals were able to be included.

Table 8-2 shows the distribution of participants of this study among the study samples from which they were drawn. The greatest number of included participants, 36 of 82 (44%) were from the Personality Disorder Stability Study {Chanen 2004}.

Table 8-2: Distribution of study participants in relation to their original study samples

Original sample (number of potential participants)	Participants interviewed in current study			Unable to track or refusing consent
	Included	Excluded		
		BPAD	Schizophrenia	
1.Personality Disorder Stability Study (51)	36 (44% of total)	3	1	11
2.Indicated prevention and early intervention in Borderline personality disorder (52)	28 (34% of total)	1		23
3.Interpersonal functioning in emerging borderline personality disorder (41)	18 (22% of total)	3		20
TOTAL (144)	82	7	1	54

Baseline data were collected for all people in the original cohorts from which those participating in this study were drawn. Therefore, where data for variables are available, comparisons have been performed between those participating in the study and those eligible but unable to be recruited in order to assess for any biases in the obtained sample.

For categorical variables, data were compared using Pearson's chi-square test, while for continuous variables, the *t*-test for independent variables was used. For both, a *p* value of <0.05 was set for rejection of the null hypothesis of there being no difference between the groups.

All of these and subsequent analyses were performed using IBM SPSS Statistics, version 22.0.

8.4.1 Demographic characteristics and early adversity

Table 8-3 below reveals that there was a female predominance among participants with a female to male ratio of approximately 4:1. Such a gender split is higher than would be expected if a sample of young people with MDD were taken from the general community where for example the Dunedin birth cohort found an approximately 2:1 female to male ratio over the presenting ages of the current cohort (Hankin et al., 1998; McGee & Williams, 1988; Newman et al., 1996). The divergence from this value is likely to be a reflection of the higher rate of mental health treatment-seeking in young

women compared to men (Slade, T, Johnston A, Teesson M, Whiteford H, Burgess P, Pirkis J, Saw S 2009), and the fact that part of the study sample came from a clinic selecting for young people with borderline personality traits, which are more common in young women (Arens et al., 2013; Bernstein et al., 1993).

Those from the original cohorts recruited to the study were slightly younger at baseline than those not recruited with mean ages at this time point of 17.4 years as compared to 18.3 ($t=2.02, p<0.05$). The ages of participants was clustered towards the lower end of the age range of eligibility for OYH services (15-24 years)

In both groups, 80% of people were recruited from suburbs in the lower two of SES tertiles. There were no differences between the participant and non-participant groups in their gender distribution nor in membership of broad socio-economic status clusters. Levels of childhood adversity, at a prevalence of 43% were well above those reported in the general Australian population. A recent meta-analysis of general population samples reported prevalences for specific types of childhood adversity reported retrospectively ranging from 2% (neglect) to 22% (sexual abuse) (Moore et al., 2015). Those not participating in the study were significantly more likely to have suffered maltreatment in childhood on more than one occasion ($\chi^2=7.76, p<0.01$).

Table 8-3: Demographic characteristics and experiences of early adversity

	Participants (n=82)	Non-participants (n=54)	Statistic	Probability
Female (%)	65 (79.3)	42 (77.8)	$\chi^2=0.21$	0.646
Male (%)	17 (20.7)	12 (22.2)		
Age at baseline, mean	17.4 (sd=2.1)	18.3 (sd=2.66)	$t=2.02$	0.047
SES tertile, n (%)	1-34 2-32 3-16	1-20 2-23 2-11	$\chi^2=0.28$	0.871
Any history of childhood maltreatment (%)	35 (42.9)	30 (55.6)	$\chi^2=3.70$	0.055
Childhood maltreatment more than once (%)	25 (30.5)	27 (50)	$\chi^2=7.76$	0.005
Out of home care (%)	16 (19.5)	16 (29.6)	$\chi^2=2.42$	0.120

8.4.2 Characteristics of Major Depressive Disorder

The data presented in Table 8-4 are only available for the study participants as this information was collected at follow-up.

The median age at first MDE of 14 reveals that this sample contains a large proportion of young people who experienced their first episode of MDD at a young age. Given the

relatively early age of onset of MDD, it is not surprising that for the majority (61%) of participants, the index episode was a recurrence rather than a first episode.

For those participants with a recurrent disorder at baseline, the mean age of onset of their Major Depressive Disorder was 13.3 ($sd=2.4$), while it was 15.2 ($sd=2.2$) for those for whom the index MDE was their first.

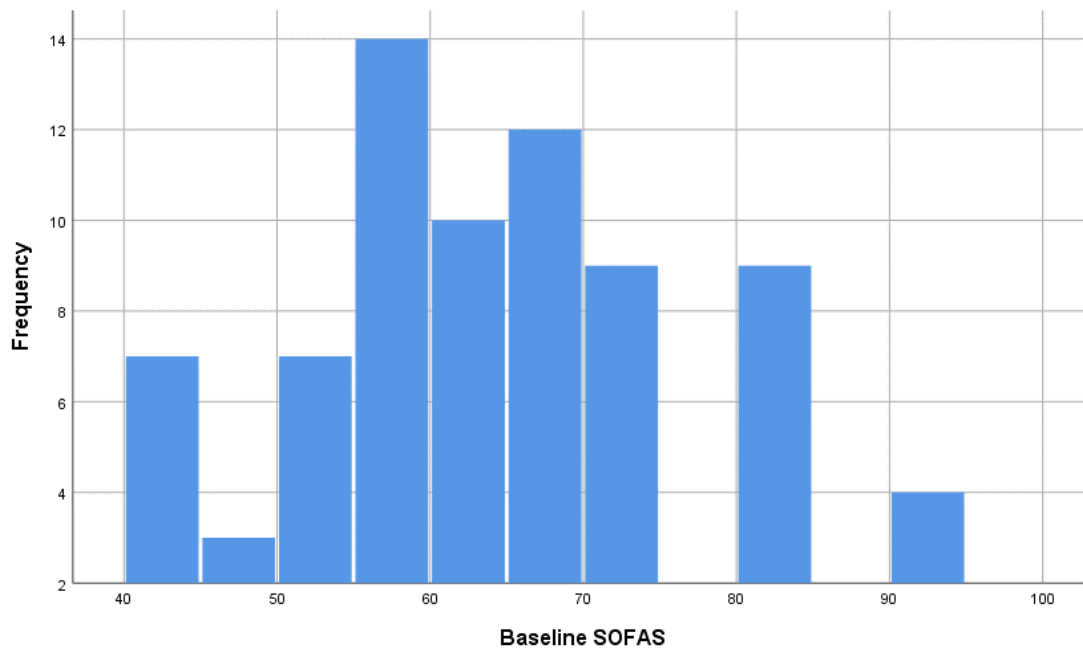
In regard to the duration of untreated MDE (ie. period above the diagnostic threshold prior to presentation), there is a wide distribution with a mean length of 7.2 months, but a standard deviation of 9 months, indicating a skewed distribution with a very long delay in receiving treatment for some individuals. A family history of MDD was very common among the study participants with 68% having a first degree relative who had also had MDD.

Table 8-4 Characteristics of MDD of study participants

	Mean (SD)	Median
Age at first MDE	14.0 (2.5)	14.0
Age at onset of index MDE	16.6 (2.4)	16.4
Duration of untreated index MDE (months)	7.2 (9.0)	4.1

Indices of severity were measured for all members of the original cohorts at baseline. Table 8-5 reveals no differences on the measures administered between participants and non-participants in baseline MDE severity nor in level of psychosocial functioning. The mean SOFAS of 63.4 is at the lower end of the 61-70 point range defined as “Some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships”. The level below this, 51-60, is defined as “Moderate difficulty in social, occupational, or school functioning (eg. few friends, conflicts with peers or co-workers)”.

Figure 8-1: Distribution of baseline SOFAS scores of study sample



As the demand for treatment at Orygen Youth Health has grown, stricter criteria around impairment have governed entry to the service. A significant negative correlation between the SOFAS score for an participant and the time since the first participant was assessed ($r=-0.376$, $p<0.001$)¹ demonstrates a temporal change that is likely to be due to this change in practice.

Table 8-5: Severity parameters

	Participant (n=82)	Non-participant (n=53)	Statistic	Probability
Index MDE severity ¹ , Mean	23.6	23.6	$t=0.002$	0.998
SOFAS, Mean (SD)	63.4 (13.5)	62.9 (12.5)	$t=0.208$	0.836
Median	62	64		

¹ Sum of scores for SCID I/P MDD criteria

8.4.3 Mental state disorder comorbidity

Most participants (57.3%) in this study were experiencing another mental state disorder in addition to an MDE at baseline, with the number of comorbid disorders that any individual had ranging from one to four. It can be seen in Table 8-6 that Anxiety

Disorders (36.6%) were the most common type of comorbid disorder, followed by Behavioural Disorders (22%), Dysthymic Disorder (19.5%) and Substance Use Disorders (15.9%).

Non-participants had higher overall rates of comorbidity ($p < 0.05$), but not for any specific mental state disorder, though there was a trend for a higher rate of substance use disorders ($p = 0.055$).

Table 8-6 Mental state disorders other than MDD

	Participant (%) (n=82)	Non-participant (%) (n=53)	Statistic	Probability
Any other mental state disorder, n (%)	47 (57.3)	41 (77.4)	4.94 ¹	0.026
Number of mental state disorders, mean (SD)	1.12 (1.17)	1.56 (1.3)	2.02 ²	0.046
Dysthymic Disorder, n (%)	16 (19.5)	14 (26.4)	0.78 ¹	0.377
Any anxiety disorder, n (%)	30 (36.6)	19 (35.2)	0.028 ¹	0.868
Panic Disorder or Agoraphobia, n (%)	12 (14.6)	7 (12.9)		
Social Phobia, n (%)	10 (12.2)	1 (1.9)		
Generalised Anxiety Disorder, n (%)	7 (8.5)	6 (11.1)		
Obsessive Compulsive Disorder, n (%)	4 (4.9)	1 (1.9)		
Post Traumatic Stress Disorder, n (%)	3 (3.7)	4 (4.9)		
Specific Phobia, n (%)	4 (4.9)	6 (11.1)		
Behavioural Disorder†, n (%)	18 (22)	15 (27.8)	0.601 ¹	0.438
Substance Use Disorder, n (%)	13 (15.9)	16 (30.2)	3.68 ¹	0.055
Eating Disorder, n (%)	3 (3.7)	5 (9.3)	1.85 ¹	0.174

¹Pearson Chi-Square, ² t-test for independent samples

† Includes Conduct Disorder and Oppositional Defiant Disorder

8.4.4 Personality variables

All of the people in the recruitment pool were administered the Borderline Personality Disorder (BPD) section of the SCID-II, but only those in the original Samples 1 and 2 completed the full SCID-II interview. Therefore there will necessarily be an underestimate of the true rate of personality disorders other than BPD in the sample. Full SCID-II results are available for 63 participants and 35 non-participants.

Table 8-7: SCID II Borderline Personality Disorder (BPD) variables

	Participant (n=82)	Non-participant (n=54)	Statistic	Probability
Borderline Personality Disorder, n (%)	25 (30.5)	21 (38.9)	1.59 ¹	0.208
BPD items, mean	1.75	1.99	2.40 ²	0.018

1 Pearson Chi-Square 2 t-test for independent samples

Table 8-7 reveals that non-participants had higher mean BPD item mean scores, but were no more likely to have a categorical diagnosis of BPD. Non-participants were also more likely to have Antisocial Personality Disorder (Table 8-9). There were no other significant differences between these groups on the other personality disorder variables measured, as seen in Table 8-8 and Table 8-9.

Table 8-8: SCID II Personality Disorder Variables

	Participant (n=63)	Non-participant (n=35)	Statistic	Probability
Cluster A Personality Disorder, n (%)	4 (6.3)	2 (5.7)	0.016 ¹	0.900
Cluster B Personality Disorder, n (%)	20 (31.7)	16 (45.7)	2.22 ¹	0.136
Cluster C Personality Disorder, n (%)	11 (17.5)	3 (8.6)	1.45 ¹	0.228
Cluster A items mean, mean	1.25	1.26	0.116 ²	0.908
Cluster B items mean, mean	1.36	1.47	1.92 ²	0.058
Cluster C items mean, mean	1.40	1.36	0.91 ²	0.366
Any Personality Disorder, n (%)	31 (49.2)	18 (33.3)	0.123 ¹	0.726
Number of Personality Disorders, n (SD)	0.63 (0.75)	0.76 (0.92)	0.75 ²	0.455
SCID II item mean, mean	1.34	1.37	0.942 ²	0.348

1 Pearson Chi-Square 2 t-test for independent samples

The rate of personality disorder in the section of the cohort assessed with the entire SCID-II was 49% (Table 8-8), which was equal to the overall rate for the sample. Two disorders accounted for almost half of all diagnosed, Borderline (31% of all participants) and Avoidant (14% of those completing the SCID-II). Table 8-9 lists disorder rates for participants completing the SCID-II.

As one of the three original samples (Sample 2) from which this study drew participants selected only those meeting at least three Borderline Personality Disorder (BPD) criteria, the rate of this disorder in the study population would be expected to be differentially elevated compared to that of other personality disorders. That said, the rate of BPD in non-psychotic patients at Orygen Youth Health is 22% (Chanen et al., 2008), pointing to a high rate of this disorder in youth receiving specialist mental health treatment.

At a Cluster level, diagnoses of Clusters B (32%) and C (18%) disorders were more common than Cluster A (6%). Borderline and Avoidant PDs accounted for most disorders in these clusters, with smaller contributions from Antisocial PD (6%) for Cluster B, and Obsessive-Compulsive Personality Disorder (5%) for Cluster C.

Table 8-9: Individual SCID II Personality Disorders

Personality Disorder	Participant (n=63)	Non-participant (n=35)
Cluster A, n (%)	4 (6.3)	-
Paranoid, n	3	2
Schizotypal, n	1	0
Schizoid, n	2	0
Cluster B, n (%)	21 (33.3)	-
Histrionic, n	1	0
Narcissistic, n	1	0
Borderline, n (%)	16 (25.4)	15 (42.9)
Antisocial*, n (%)	4 (6.3)	7 (20)
Cluster C, n (%)	11 (17.4)	-
Avoidant, n	9 (14.3)	2
Dependent, n	0	0
Obsessive-Compulsive, n (%)	3 (4.8)	1

*p<0.05, Pearson Chi-square

There were no differences between the participant and non-participant groups on the NEO Personality Inventory.

8.4.5 Summary of cohort characteristics at presentation

The participants in the study were predominantly female, with a 4:1 gender distribution and with a greater proportion in the lower end of the youth age range, with a mean age of 17.4. Eighty percent came from the lower two socio-economic status tertiles.

Childhood maltreatment was common (43% of the sample), and almost 20% of the cohort were in some form of out of home care at presentation.

A family history of MDD was very common with 68% of the sample having a first degree relative with the disorder, and over half (61%) had had a previous MDE.

Most of the study participants had a comorbid mental state disorder (57%), with anxiety disorders being the most common of these (37%). Close to half had a personality disorder (49%), with the over-sampled Borderline personality disorder being the most common at a rate of 31%, followed by Avoidant personality disorder at 11% of the

sample.

Those not able to be recruited for the study diverged from its participants on a small number of parameters related to childhood adversity and the level of psychopathology at baseline. They more frequently had had multiple experiences of maltreatment, had higher rates of mental state disorder comorbidity, had higher Borderline personality scores and were more likely to have Antisocial personality disorder.

8.5 Cohort characteristics at follow-up

8.5.1 Demographic characteristics

At follow-up, the ages of participants ranged from 20 to 30, with a mean of approximately 27, as shown in Table 8-10 below. The shortest period of follow-up since baseline was 5.3 years, with the longest 13.4 years, and the mean duration was 9.4 years.

The sample was evenly split between those in or not in a relationship, and about a third (31.5%) had children. More than half of the sample (62.2%), had completed secondary school (Year 12). In comparison, the Victorian population attainment rate for Year 12 was measured at 76% in 2001, (*Australian Social Trends March 2011* 2011) a year close to when those in the cohort would have been in Year 12.

It was less common to complete some form of further education or training, with only half of the participants having done so. This compares to a rate of 67% of the similarly-aged cohort of the Longitudinal Survey of Australian Youth in 2009 (National Centre for Vocational Education Research n.d.)

Almost 80% of people were engaged in either full or part-time employment or study, and it was rare for a government benefit to be the sole source of income (7.3%). There was also movement over the follow-up period towards living in areas of higher socio-economic status.

Table 8-10: Demographic characteristics at follow-up interview

Age, mean (SD)		26.8 (2.3)
Duration of follow-up period in years, mean (SD)		9.4 (2.1)
Relationship status, % (n)	Married/Defacto	48.8 (40)
	Single	48.8 (40)
Children, %		31.5
Highest school level, % (n)	Year 12	62.2 (51)
	Year 10 or 11	26.9 (22)
	Below Year 10	9.7 (8)
Further education, % (n)	Postgraduate degree	3.7 (3)
	Bachelor degree	22 (18)
	Diploma	12.2 (10)
	Certificate	11 (9)
	No further training or education	50 (41)
Vocational status (work/study/parenting), % (n)	Full-time work/study	69.5 (57)
	Part-time work/study	11 (9)
	Full-time parent	12.2 (10)
	Government benefit	7.3 (6)
SES tertile, % (baseline %)	I	22 (34)
	II	46.3 (32)
	III	24.4 (16)

8.5.2 Mental state disorders

At the follow-up interview, participants were assessed for both current mental state disorders and also for any disorders occurring since the preceding SCID-I/P assessment. For those participants drawn from Sample 3 the preceding assessment was the original study baseline, while those from Samples 1 and 2 had received follow-up SCID-I/P interviews since baseline. Diagnoses made at these earlier follow-up assessments are included in the rates for disorders for the total follow-up period of this study (ie. from entry to OYH).

Table 8-11: SCID I/P mental state disorders other than MDD over follow-up period

	Current diagnoses at follow-up interview (%)	Diagnoses over follow-up period[†] (%)
Any other mental state disorder	35 (43)	66 (80.5)
Dysthymic Disorder	1 (1.2)	15 (18.3)
Any anxiety disorder	28 (34.1)	44 (53.7)
Panic Disorder or Agoraphobia	14 (17.1)	20 (24.4)
Social Phobia	7 (8.5)	13 (15.9)
Generalised Anxiety Disorder	13 (15.9)	2 (2.4)
Obsessive Compulsive Disorder	3 (3.7)	7 (8.5)
Post Traumatic Stress Disorder	11 (13.4)	11 (13.4)
Behavioural Disorder[†]	NA	15 (18.3)
Substance Use Disorder	7 (8.5)	45 (54.9)
Eating Disorder	4 (4.9)	16 (19.5)

[†] Diagnoses included in this column may also be counted in the current diagnoses column if they have persisted since previous assessments.

It was very common for the study participants to experience disorders other than MDD over the follow-up period, with an overall rate of 80.5% for any other mental state disorder, and a mean number of 2.2 ($sd=2.0$) disorders per participant. Anxiety and substance use disorders were the most prevalent disorder types, with both occurring at a rate approaching 55%.

Cannabis Abuse or Dependence (32.9%) and Alcohol Abuse or Dependence (31.7%) were the most frequent substance use disorders, while Panic Disorder or Agoraphobia (24.4%) occurred most often among anxiety disorders.

Although less common, the other disorder types; behavioural, eating and dysthymic, still occurred at rates between 15 and 20%.

At the cross-sectional follow-up assessment, the rate for occurrence of a mental state disorder other than MDE was 43%, with a mean number of disorders per individual of 0.8 ($sd=1.2$) This was largely due to the presence of anxiety disorders, which were present in 34.1% of participants. At only 8.5%, the rate of substance use disorders was much less than their incidence over the entire follow-up period, and half their prevalence at baseline.

8.5.3 Personality variables

8.5.3.1 Personality disorder variables

Complete SCID II data were obtained for 80 participants at follow-up, such that detailed data were able to be collected on more people than at baseline. Overall rates of disorder at follow-up will be reported for the entire sample, but any statistical comparisons with baseline will only be made for those participants with data at both time points.

Data on Borderline Personality Disorder (BPD) variables were collected for 80 participants at both time points. There was a significant reduction in both the rate of the disorder, from 30% to 10% ($p<0.01$), and in the mean item score from 1.75 to 1.42 ($t=4.612$, $p<0.001$). The drop in the mean score is calculated from the average drop in overall sum of criteria scores by approximately 3 (2.89), which is equivalent to study participants on average meeting one and a half less full-threshold BPD criteria than they did at baseline.

Table 8-12: Borderline Personality Disorder features at follow-up interview

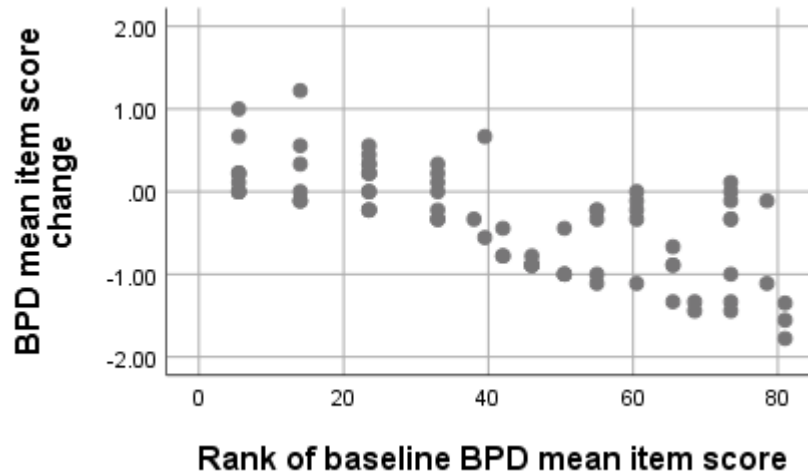
	Follow-up n=80	Baseline n=80	Statistic	Probability
Borderline Personality Disorder n (%)	8 (10)	24 (30)	-	0.001 ¹
BPD mean item score, mean (SD)	1.42 (0.46)	1.75	4.612	<0.001 ²

¹ McNemar's test ² Paired t-test

The rank-order stability of the participants for the BPD item mean was tested by calculating the Pearson's correlation coefficient (r) for baseline and follow-up scores, finding a coefficient of 0.31.

It was of interest whether there was differential effect on the change in the BPD mean item score depending on its baseline value, specifically whether those with more severe pathology were more resistant to change. In fact, as represented in Figure 8-2 below, it was found that those with greater baseline severity exhibited a greater degree of change.

Figure 8-2: Relationship of baseline ranking of BPD mean item score to its change over the follow-up period



At follow-up, Cluster C Personality Disorders were found to be the most prevalent, at a rate of 18.3%. Avoidant Personality Disorder (17.5%) was the most common of the disorders, with Borderline (10%) the only other to occur in more than 3 participants.

Table 8-13: Rates of SCID-II Personality Disorder at follow-up interview

	Number of participants (n=80)
Cluster A Personality Disorder, n (%)	3 (3.8)
Paranoid, n	3
Schizotypal, n	2
Schizoid, n	2
Cluster B Personality Disorder, n (%)	9 (11.0)
Histrionic, n	1
Narcissistic, n	1
Borderline, n (%)	8
Anti-social, n	2
Cluster C Personality Disorder, n (%)	15 (18.3)
Avoidant	14
Dependent	2
Obsessive-Compulsive	2
Any Personality Disorder, n (%)	21 (26.3)

In those with SCID-II data at both time-points, there were significant reductions in both categorical and dimensional measures of personality disorder over the follow-up period. The overall rate of personality disorder dropped from 36.6% to 24.6% ($p<0.01$),

while the mean item score from for the SCID-II fell from 1.34 to 1.26 ($t=-8.849$, $p<0.001$).

It would appear that this overall change was driven largely by significant changes occurring in Cluster B, which had a more than two-thirds reduction in prevalence from 20% to 6% ($p<0.01$) and a marked change in mean item score from 1.36 to 1.19 ($t=5.115$, $p<0.001$).

Rates of Cluster C Personality Disorders remained stable, and while proportionally the rate of Cluster A Personality Disorders fell by almost 50%, this was from a low total of four participants at baseline. In line with these results, there were not significant changes in the mean item scores for Clusters A and C.

Table 8-14: SCID-II Personality Disorder Variables for those with baseline and follow-up data

	Follow-up	Baseline	Statistic	Probability	Rank order stability
Cluster A Personality Disorder, n (%)	2 (3.3)	4 (6.3)	¹	1.000	
Cluster B Personality Disorder, n (%)	6 (9.8)	20 (31.7)	¹	0.001	
Cluster C Personality Disorder, n (%)	10 (16.4)	11 (17.5)	¹	1.000	
Cluster A mean item score, mean	1.25	1.25	-0.116 ²	0.908	0.44
Cluster B mean item score, mean	1.19	1.36	-5.115 ²	<0.001	0.41
Cluster C mean item score, mean	1.37	1.40	-1.000 ²	0.321	0.23
Any Personality Disorder, n (%)	15 (24.6)	31 (36.6)	¹	0.002	
Number of Personality Disorders, mean (SD)	0.39 (0.77)	0.63 (0.75)	-2.459 ²	0.017	
SCID-II mean item score, mean	1.26	1.34	-8.849 ²	<0.001	0.49

¹ McNemar's Test, ² t-test for paired sample

8.5.3.2 Personality Trait Variables

78 participants completed the NEO-PI at both baseline and follow-up. Table 8-15 reveals a divergence between the scales in their stability. There were significant reductions in scores on the Neuroticism scale ($t=4.342$, $p<0.001$), and significant increases on the Agreeableness ($t=4.760$, $p<0.001$), and Conscientiousness scales

($t=6.514$, $p<0.001$). In contrast, scores on the Extraversion scale and particularly on the Openness scale were stable.

The rank-order stability for Neuroticism was tested by the calculation of the Pearson's correlation coefficient (r) for baseline and follow-up scores, and was found to be 0.31.

Table 8-15: NEO Personality Inventory variables

	Follow-up	Baseline	t statistic	Probability
NEO N, mean	109.3	122.8	-4.342	<0.001
NEO E, mean	104	101.4	1.004	0.318
NEO O, mean	114.8	115.3	-0.062	0.950
NEO A, mean	120.4	110.5	4.670	<0.001
NEO C, mean	104.6	86.2	6.514	<0.001

¹ t-test for paired sample

8.6 MDD outcome

8.6.1 Description of course

The variables measured assessed both the shorter and longer-term course of the participants' MDD. Of the shorter-term variables, it may be that the time to recovery of the index MDE is more accurate, as its starting point is the diagnostic assessment performed on referral to OYH. The duration of episode relies on the participants' recall of the point prior to referral at which they met full diagnostic criteria for an MDE.

Table 8-16: MDD course parameters

<u>Course parameter</u>	Mean (SD)	Median
Duration of index episode (months)	39.1 (32.4)	30.5
Time to recovery from index episode (months)	31.9 (29.8)	22.4
Proportion of follow-up period in MDD	0.42 (0.29)	0.37
Number of recurrences	1.66 (2.47)	1.0

There was a wide range of times to recovery, with the median time to recovery 22.4 months almost 10 months less than the mean of 31.9 months, demonstrating the influence on the mean time to recovery of the protracted MDEs of a small number of participants. It should be emphasised that as mentioned earlier in 0 the episode duration is likely to include a period for which a participant did not meet threshold criteria for an MDE, but had residual symptoms, such that according to LIFE criteria they could not be classified as having recovered.

The modal time to recovery, as shown in Figure 8-3 was 6-12 months (17 participants), with the further three six-month recovery blocks up to 30 months each having around half as many people in them. Excepting the 42-48 month period, recovery rates were reasonably steady from 30 to 54 months, with 16 people recovering over this period. A further 14 people (17% of the sample) recovered over a period up to 132 months. Seven participants (8.5%) did not describe a period of recovery over their entire follow-up period

Figure 8-3: Time to recovery of index MDE

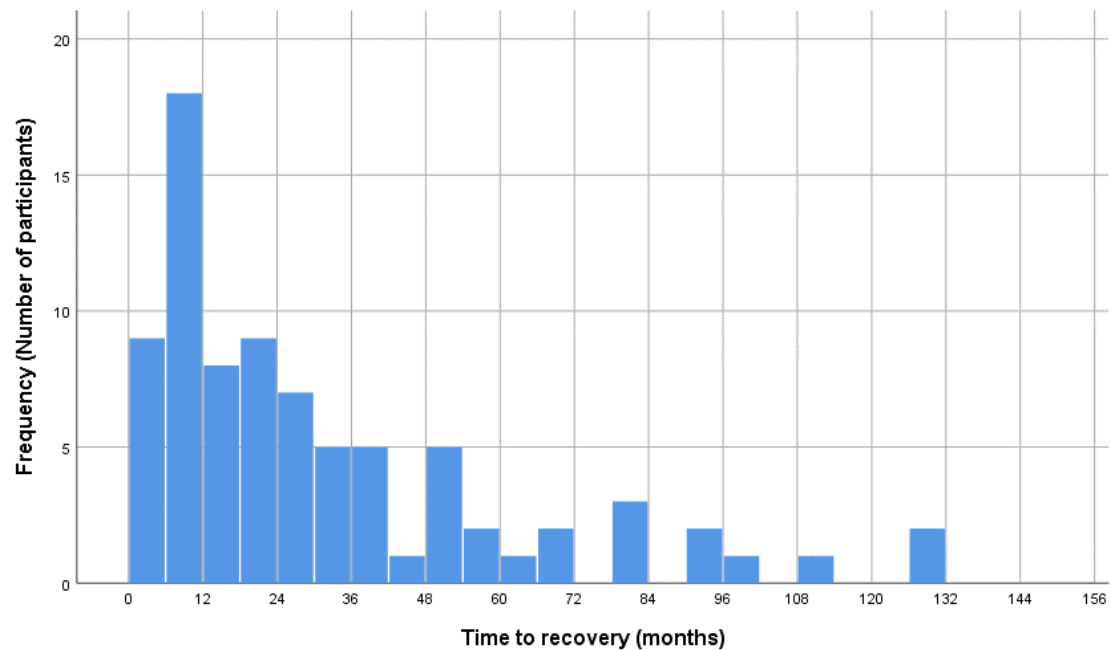
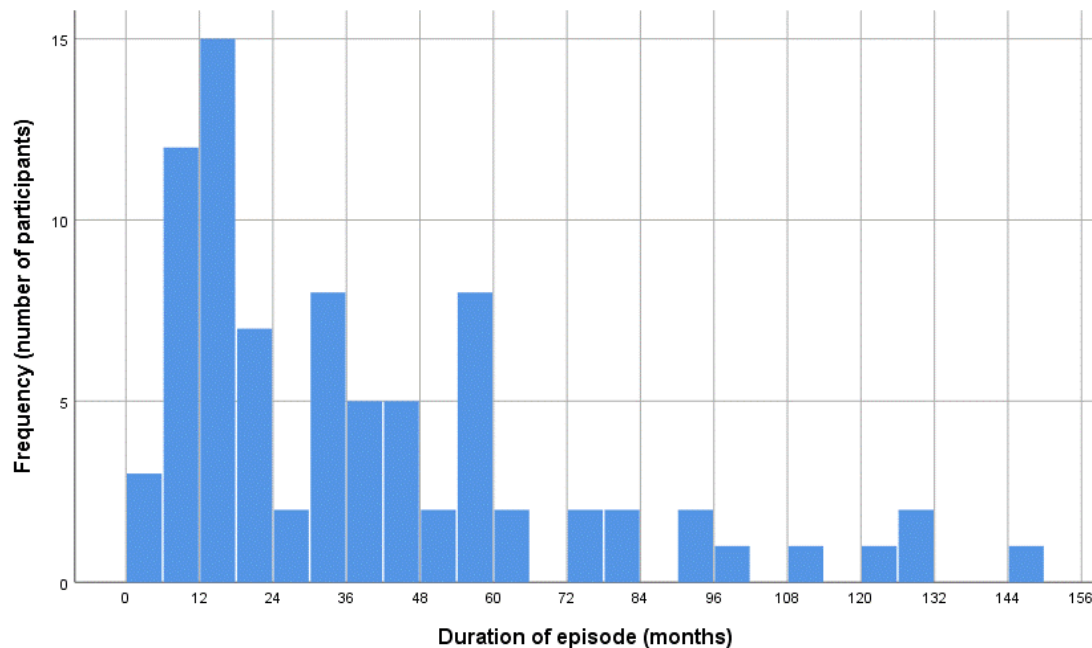


Figure 8-4 shows the distribution of the duration of the index MDE across the sample. The difference between this variable and the time to recovery is that it contains the period in which the participants reached the diagnostic threshold for MDE prior to seeking treatment, the duration of untreated depression (DUD). This distribution reveals the rate of chronicity, that is of episodes greater than two years, as being 55% (45 out of 82)

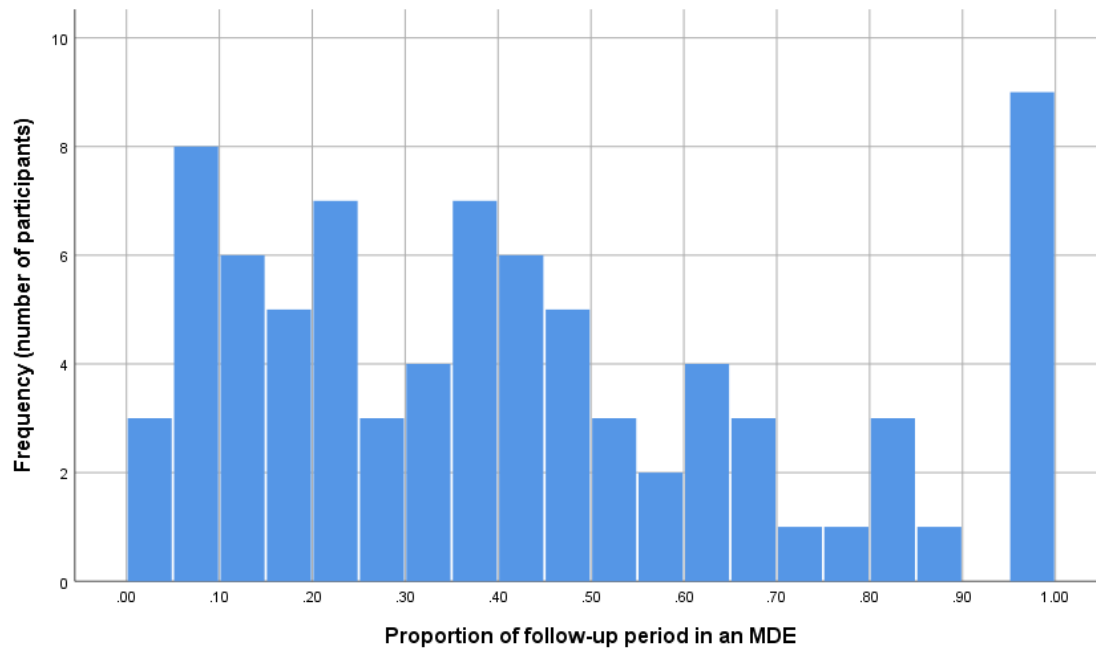
Figure 8-4: Duration of index MDE



The proportion of time spent in an MDE (ie.not meeting criteria for recovery) over the entire follow-up period also had a wide range within the sample, with a mean proportion of 0.42 and a median of 0.37. Figure 8-5 illustrates though that the mean figure is not particularly informative about what any particular individual might experience, with an overall evenness across the proportion frequency distribution, particularly up to the 0.50 point.

As there was a range of follow-up periods in the sample, the proportion of time in an MDE corresponds to a different absolute period for different individuals. The proportion lessened significantly as the length of the follow-up period lengthened ($r_s=-0.31$, $p=0.004$) implying that the period of time unwell was concentrated closer to the point of presentation. This is reflected in the finding that the mean proportion of the total period in an MDE that the index MDE represented was 0.69 ($sd=0.30$). For those followed up for at least 10 years ($n=40$), the mean proportion in an MDE fell to 0.33. Though lower than the overall figure for the entire sample, this remains a substantial period.

Figure 8-5: Proportion of follow-up period in a Major Depressive Episode



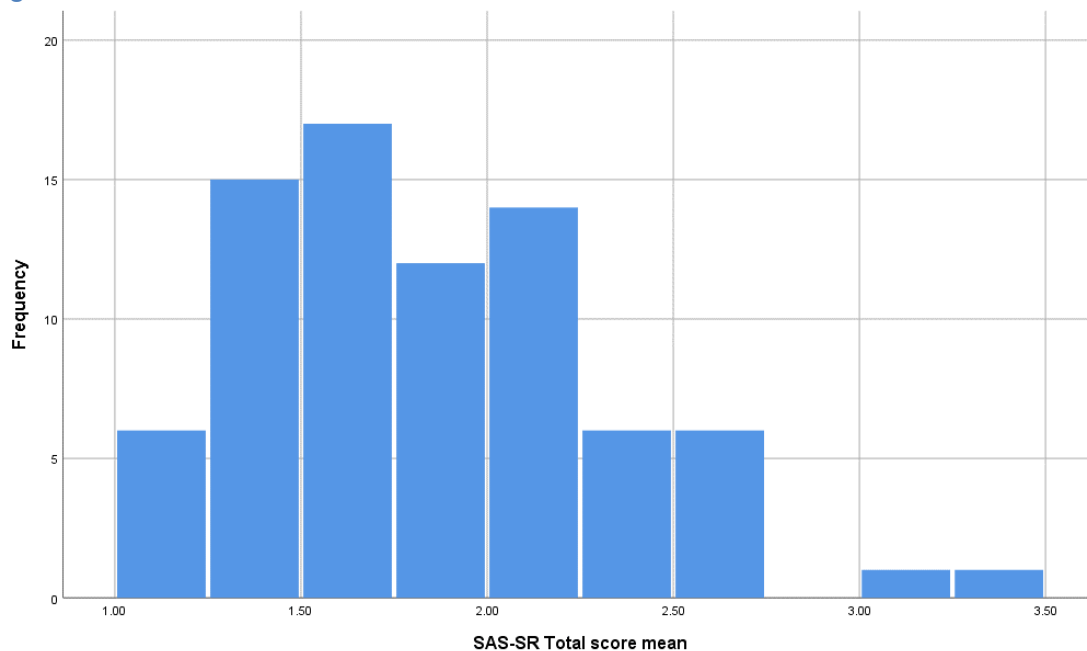
In addition to the index episode, 76% of the 91.5% of participants who recovered from the index MDE experienced a further episode over the follow-up period. Thus, 69.5% of the study cohort had a course from baseline of recovery and recurrence, while 22% had no further episodes, and the aforementioned 8.5% experienced persistent illness. Of those with recurrences, most had only one (51% of recurrence group) or two (26% of recurrence group). Two participants had a large number of recurrences, one with twelve the other seventeen. These recurrences were of relatively brief duration.

8.7 Functioning at follow-up

8.7.1 Overall score on SAS-SR

Scores at follow-up on the SAS-SR reflect a spectrum of severity at this time-point, with a mean item score of 1.85 (higher scores indicate poorer functioning).

Figure 8-6: Distribution of the SAS-SR total mean item score



The mean for this sample compares to mean item scores of 1.59 and 1.67 in two non-patient samples (Edwards, DW et al., 1978; Weissman, Myrna M et al., 1978). These samples had a standard deviations of 0.33 and 0.29, such that the mean overall score of the study sample was close to one standard deviation higher than both these non-patient means.

As described in 7.4.2, the authors of the SAS-SR provide T scores for the overall mean and subscales generated from a general population sample (Weissman, MM and MHS staff 1999) to assist with the instrument's interpretation. A deviation from "typical" is judged as starting at a T score 6 points above the mean of 50, moving in 5 point grading increments as shown in Table 8-17. The threshold set by the scale authors for "significant problems" is a score over 65.

The corresponding T-scores for the overall mean of the study sample of 58 in women and 60 for men are at the middle and high end of the "borderline/possible concern" range respectively.

Table 8-17: T score distribution for SAS-SR overall mean in study sample

T-score range	Female (n=60)		Male (n=17)	
	<i>Score</i>	<i>Proportion (n)</i>	<i>Score</i>	<i>Proportion (n)</i>
Moderately atypical (<34) <i>No concern</i>	< 1.10	.02 (1)	< 1.00	0
Mildly atypical (35-39) <i>No concern</i>	1.10-1.26	.05 (3)	1.00-1.22	.06(1)
Slightly atypical (40-44) <i>No concern</i>	1.27-1.42	.13 (8)	1.23-1.39	.06 (1)
Typical (45-55) <i>No concern</i>	1.43-1.79	.35 (21)	1.40-1.74	.24 (4)
Slightly atypical (56-60) <i>Borderline: possible concern</i>	1.80-1.99	.10 (6)	1.75-1.89	.18 (3)
Mildly atypical (61-65) <i>Possible significant problem</i>	2.00-2.16	.13 (8)	1.90-2.06	.24 (4)
Moderately atypical (66-70) <i>Significant problem</i>	2.17-2.32	.05 (3)	2.07-2.22	.12 (2)
Markedly atypical (71+) <i>Significant problem</i>	>= 2.33	.17 (10)	>= 2.23	.12 (2)

Table 8-17 reveals a gender difference in the distribution of the scores. Women were more likely to score at the extremes of functioning, with 20% of women in the sample having better than typical functioning, and 17% in the markedly atypical range. Men tended to have poorer functioning overall, with 68% of men compared to 45% of women having functioning below the typical range.

There wasn't a significant difference between the genders in the mean overall score ($t=0.374$, $p=0.709$). However, women in the normative sample tended to have higher scores than men, as reflected by their relatively higher scores for equivalent T-score ranges as shown in Table 8-17. Therefore a particular mean score has a different meaning for each gender, and a direct comparison hides what appears to be the poorer male functioning indicated by the T-score range comparison.

8.7.2 Individual role areas of the SAS-SR

Table 8-18 below contains the mean scores for men and women and

Table 8-19 the relative proportion of each gender in the functioning categories in the individual role areas of the SAS-R.

Table 8-18: Overall scores and scores for individual role areas of the SAS-SR

SAS subscale (n)	Mean (SD) <i>Female/Male</i>	Mean (SD) of community sample	T score for study sample means <i>Female/Male</i>	Median (Study sample)
Overall	1.85 1.84/1.88	1.59 (0.33)	58/60	1.76
Relationships	2.00 (0.53) 1.98/2.07	1.56 ¹		1.95
Social and Leisure (78)	2.24 (0.65)	1.83 (0.52)	58/58	2.11
Family (70)	1.75 (0.49)	Unit 1.46 (0.58) Ext. 1.34 (0.33)	53.5/58 61.5/63.5	1.73
Primary relationship (40)	1.94 (0.66)	1.75 (0.48)	54/55	1.67
Parental (22)	1.33 (0.40)	1.40 (0.42)	48/50	1.25
Work	1.78 (0.63) 1.81/1.69	1.40 (0.46)	57/64	1.67
Household (77)	1.98 (0.62)	1.53 (0.52)		1.83
Study (10)	1.58 (0.53)	-		1.50
Employment (50)	1.73 (0.61)	Male 1.27 (0.31) Female 1.30 (0.38)		1.58

¹This value derived from data in Table 3 of (Weissman, Myrna M et al., 1978)

T-scores for men are slightly higher across almost all the role areas, with the cumulative effect of these small differences reflected by the higher overall T-score for men. Although the Extended Family role area is scored as the lowest functioning, by T-score, of the sample, the two family areas were unfortunately not assessed separately in the version of the SAS-SR used in this study. Therefore this higher T-score for the Extended Family role is likely to reflect the fact that Family Unit functioning was poorer in the normative sample, as shown in Table 8-18.

The parental and primary relationship areas were those in which functioning was best, although for 21% of women in a primary relationship, which the instrument defines as co-habiting for at least six months, this area's functioning was in the significantly problematic range.

Table 8-19: Distribution of sample in T-score ranges for individual role areas of the SAS-SR

T-score range	Social & Leisure		Family Unit		Extended Family		Primary Rel.p		Parental		Work	
	F (60)	M (17)	F (56)	M (13)	F (56)	M (13)	F ¹ (34)	M (6)	F (20)	M (1)	F (60)	M (17)
Slightly atypical (40-44) <i>No concern</i>	.15		.20		.09		.18	.17	.45		.22	
Typical (45-55) <i>No concern</i>	.30	.47	.39	.46	.23	.23	.35	.48	.30		.38	.24
Slightly atypical (55-60) <i>Borderline: possible concern</i>	.23	.12	.23	.08	.16	.23	.15	.35	.15		.00	.18
Mildly atypical (61-65) <i>Possible significant problem</i>	.07	.18	.11	.31	.11	.08	.03		.05	1.0	.15	.24
Moderately atypical (66-70) <i>Significant problem</i>	.07	.06	.04	.08	.13	.15	.09		.05		.08	.18
Markedly atypical (71+) <i>Significant problem</i>	.18	.18	.04	.08	.29	.31	.12				.17	.18

¹ 3 participants in 35-39 range

At the other end of the functioning spectrum, though not dramatically different were the Social and Leisure and Work domains. Of the eleven items of the Social and Leisure role, nine relate to relationships with friends, and two specifically to recreational activities. 25% of women and 24% of men rated in the significantly problematic range for this role area.

The work role for men was the most problematic of all role areas for either gender, with 36% of the men in the sample in the significantly problematic range.

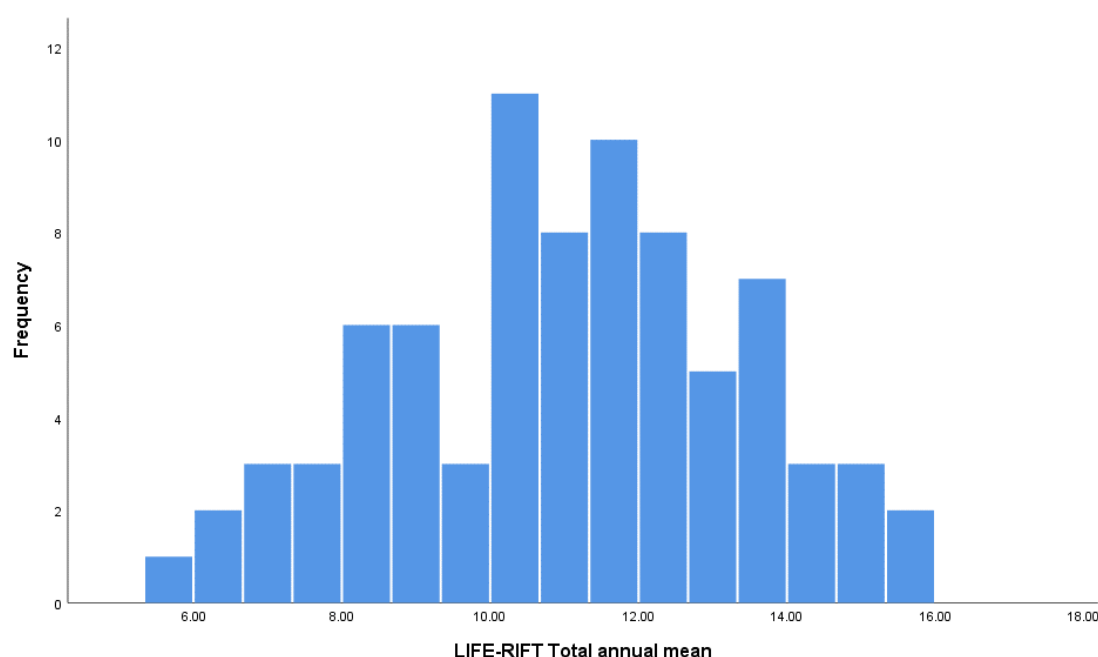
8.8 Functional course

8.8.1 LIFE-RIFT scores

The mean annual total score for the LIFE-RIFT for the study participants was 11.1. This score, as defined by the study authors, lies in the range between satisfactory normal functioning at 8 and fair functioning/mild impairment at 12 (Judd et al., 2005). Specific guidance is not provided for the interpretation of scores between these points, but the Collaborative Depression Study, for which the LIFE-RIFT was designed, found a similar mean monthly total score of 11 for its participants and described this as “suggesting mild impairment” (Judd et al., 2008).

The distribution of mean annual scores of the sample participants for the overall scale is presented in Figure 8-7, and is also presented in Table 8-20, which contains the score distributions for the four domains of the instrument. These demonstrate that a large proportion of the sample, 31.7%, had on average persistent impairment in overall functioning over the follow-up period.

Figure 8-7: Mean annual score of the LIFE-RIFT overall scale



Of the domains, interpersonal functioning was most impaired, and its mean score of 3.15 shows that there was on average consistent impairment at at least a mild level over the follow-up period. A feature of this domain, as with the vocational domain, is

that the assessor rates the sub-domain that is the most impaired. The sub-domains for interpersonal relations are spouse, children, other relatives and friends.

Table 8-20: Distribution of scoring ranges for annual mean scores of LIFE-RIFT domains

<i>LIFE-RIFT domain</i>	Mean (sd)	Median	<i>Distribution of scores % (n)</i>			
			High-normal to satisfactory 1-2	Satisfactory to mild impairment 2-3	Mild to moderate impairment 3-4	Moderate to severe impairment 4-5
Vocational	2.41 (0.80)	2.31	36.6 (30)	43.9 (36)	14.6 (12)	3.7 (3)
Interpersonal relations	3.20 (0.73)	3.15	9.8 (8)	32.9 (27)	47.6 (39)	7 (8.5)
Satisfaction	2.75 (0.65)	2.78	15.9 (13)	50 (41)	31.7 (26)	1.2 (1)
Recreation	2.65 (0.87)	2.56	25.6 (21)	46.3 (38)	18.3 (15)	8.5 (7)
Overall	11.2 (2.33)	11.2	4-8	8-12	12-16	16-20
			11 (9)	56.1 (46)	31.7 (26)	0

Table 8-21 contains the text for ratings of 2 and 3 for each domain to aid the reader's interpretation of the mean scores. For the vocational and interpersonal relations domains, it contains the ratings only for selected sub-domains. A rating of 3 for the interpersonal relations domain for family members, for family living with the participant, means that there is frequent and enduring conflict and a lack of closeness. For family members not living with the participant, contact is infrequent and rarely enjoyed. Both the satisfaction and recreation domains, with mean annual scores of 2.75 and 2.65 respectively, were closer to being persistently impaired than not. The mean score and distribution of the scores for the satisfaction domain closely follow those of the overall score. This is perhaps not surprising as the text for its rating demonstrates that the assessor tests a subject's subjective assessment of the other domains.

The vocation domain was that in which functioning was best, closer to persistent normal functioning with a mean score of 2.41, and having more than one-third (36.6%) of participants functioning in the satisfactory to high normal range.

The scale scores for these the interpersonal relations and vocational domains deviated significantly from the overall score, with impairment being greater for interpersonal relationships ($t=7.762$, $p<0.001$), and less for vocational/household ($t=-5.646$, $p<0.001$).

Table 8-21: Text for ratings of 2 and 3 for LIFE-RIFT domains

LIFE-RIFT domain	Rating of 2	Rating of 3
Vocation (<i>Employment</i>)	Worked as much as someone in his social situation would be expected to work, and worked at a satisfactory level.	Worked somewhat less than someone in his social situation would be expected to work and or had mild difficulties in carrying out work activities
Interpersonal relations (<i>Spouse, children, other relatives</i>)	Argues occasionally, but arguments usually resolve satisfactorily within a short time. May occasionally prefer not to be with them because of dissatisfaction with them or be actively working with them to improve relationship	Often argues with this family member and takes a long time to resolve arguments. Often thinks that relationship needs to be either more harmonious or closer emotionally even when no conflict is present. For those relatives not living with the subject, contacts with them by choice are less frequent than feasible or rarely enjoyed when made.
Satisfaction	Mild dissatisfaction persists, but only in one area or is intermittent in several areas. In balance is generally content and able to enjoy life most of the time, but does think there should be some improvement in either occupational role, interpersonal relations, sexual activities, or finances.	Moderate dissatisfaction in one or more areas, which is relatively persistent. Either discontent with occupational role, interpersonal relations, sexual activities, or finances.
Recreation	Participates in several activities and does not always enjoy them fully: or participates in fewer activities or less frequently than optimal, but enjoys participation.	Occasional participation in recreational activities or hobbies: or limited enjoyment when participation occurs.

8.9 Statistical methods of outcome predictor analyses

The candidate baseline predictor variables are presented in Table 8-22 and the specific outcomes that were investigated in the analyses are listed in Table 8-23.

Table 8-22: Baseline predictor variables

	Demographic	Childhood adversity	Personality	MDD variables	Comorbid mental state disorders
Binary	Gender	Out of home care <i>Abuse</i> Any abuse Multiple episodes of abuse Psychological Physical Sexual	<i>Categorical personality disorder</i> Any personality disorder (PD) Borderline PD Cluster A PD Cluster B PD Cluster C PD	History of MDD in first-degree relative Previous MDE	Anxiety disorder Behavioural disorder Dysthymic disorder Substance use disorder
Dimensional	Socio-economic status		<i>Personality traits</i> Neuroticism Extraversion Openness to experience Agreeableness Conscientiousness <i>Personality disorder</i> Borderline PD score Cluster A score Cluster B score Cluster C score Mean SCID II item score	Age of onset MDD Age of onset index MDE Severity of MDE	

Table 8-23: Outcome variables

		Instrument	Outcome
MDD symptomatic course	Short-term	LIFE	Duration of index episode Time to recovery of index episode
	Long-term		Recurrence Proportion of follow-up period in an MDE
Course of functioning	At follow-up	SAS-SR	<i>Item mean</i> Overall Work scales Relationship scales
	Longitudinal course	LIFE-RIFT	<i>Domain mean annual score</i> Overall Work Relationships Satisfaction Recreation

Selected variables measured over the follow-up period and at the follow-up interview were tested in univariate analyses for their prediction of the summary outcomes of the functioning instruments and for the proportion of time participants were in an MDE over the follow-up period. The selected predictors are presented in Table 8-24.

Table 8-24: Outcomes and follow-up period predictors

		Outcome	Predictors
MDD course	Long-term	Proportion of follow-up period in an MDE	Year 12 completed Tertiary study SCID II mean item score change Cumulative mental state disorders
Course of functioning	At follow-up	SAS-SR Overall item mean	<i>Demographic</i> Year 12 completed Tertiary study Relationship status <i>Mental state disorder</i> Proportion of follow-up period in an MDE Cumulative mental state disorders Current MDE Current anxiety disorder <i>Personality at follow-up</i> BPD mean item score Clusters A-C mean item score SCID II mean item score Personality disorder NEO-PI Five factors <i>Life events</i>
	Longitudinal functioning	LIFE-RIFT overall score annual mean	Year 12 completed Tertiary study Recurrence of MDD Proportion of follow-up period in an MDE SCID II mean item score change

8.9.1 Univariate analyses

8.9.1.1 Investigation of bias and testing of assumptions

Prior to the principal analyses, the data were explored for potential factors that could bias outcomes. Outliers were identified by means of box-plots, and if significant associations were found for a particular predictor variable, analyses were repeated with extreme outliers removed (“extreme” defined as 3 times the interquartile range).

To assess for bias in testing the association of two continuous variables, the distributions of both were plotted in histograms. Skew and kurtosis were also assessed numerically, and further graphically by the generation of P-P and Q-Q plots. If these indicated a divergence from a normal distribution for a variable, this may have indicated non-normality in the population distribution of the parameter being tested, and hence reduce the accuracy of significance tests based on a normal population distribution of this parameter. In this case non-parametric tests were used to assess for the significance of any association with this variable.

Similarly, for categorical predictors, histograms of the distributions of the outcome variables for the two categories were plotted, with non-parametric tests performed where clear divergence from normality were present.

8.9.1.2 Statistical tests

In the case of testing the association of two normally distributed continuous variables, the parameter calculated was Pearson’s correlation coefficient (r), with a two-tailed t -test used to assess significance. For non-normally distributed variables Spearman’s correlation coefficient (r_s) was calculated, with its significance also assessed with a two-tailed t -test.

T-tests were used for the comparison of the means of groups defined by the presence or absence of a categorical predictor variable. If the values of the outcome for one or both of these groups were not normally distributed, the Mann-Whitney test was used. To aid comparison of the influence of dimensional and categorical variables on the outcomes, and in order to provide an indication of effect size for all variables, Pearson’s correlation coefficient r was calculated for the associations of the categorical variables with the outcomes.

For the normally distributed variables, analysed with a t -test, the following equation was used to calculate r (Field, Andy 2000/2013) :

$$r = \sqrt{\frac{t^2}{t^2 + df}} \quad (\text{df} = \text{degrees of freedom})$$

The Mann-Whitney test statistic, used for those variables that were not normally distributed, was converted to r by means of the following equation (2000/2013) :

$$r = \frac{z}{\sqrt{N}}$$

(z = standardised test statistic, which has a distribution with a mean of zero and a standard deviation of one)

For one variable, Socio-economic status, the sample was divided into three groups. Comparison of these groups was performed by an independent ANOVA, generating an F-ratio to assess for significance of group differences.

8.9.2 Multiple predictor analysis

8.9.2.1 Statistical tests

Only significant and quasi-significant predictors identified by univariate screening were further explored in the multiple predictor models. Specifically, predictor variables were accepted for the multiple predictor analysis where the null hypothesis for their univariate association with an outcome variable had a probability of <0.10 .

Not all predictors were entered into the regression model in order to minimise the potential instability and poor replicability associated with having a large number of predictors. The larger the number of predictors, the higher the probability of correlation between the variables such that the power to detect a unique effect is reduced and the greater the risk of paradoxical suppression effects (Cohen, J, Cohen, P, West, SG, & Aiken, LS, 2003).

Therefore those variables with high levels of intercorrelation ($r > 0.80$) or theoretical overlap with another variable were not included in the regression analysis. The intercorrelations of the baseline predictor variables are presented in Table 8-25 below. Red numerals denote negative correlations.

Table 8-25: Intercorrelation of baseline predictor variables

	BPD		Cluster B		Cluster C		cA	A	S	NEO		P	Abuse		OoH	A	S
	m	PD	m	PD	m	PD	m	N	C	I	D	r	P	P	c	n	S
	e		e		e		e	Y		D		e	h	s	a	x	F
	a		a		a		a	PD		m		M	y.	y.	r	d	A
	n		n		n		n		e	a		D	c	c	e	i	S
												E	h.	h.		s.	S
BPD mean																	.45
BPD	.82																.39
cB mean	.84	.60															.47
cB PD	.74	.81	.77														.43
cC mean	.20	.16	.08	.08													.20
cC PD	.06	.07	.15	.15	.61												.05
cA mean	.13	.13	.10	.14	.20	.01											.23
ANY PD	.54	.58	.54	.72	.43	.44	.31										.41
SCID II mean	.72	.52	.77	.63	.54	.14	.58	.68									.48
NEO N	.29	.27	.22	.24	.41	.49	.15	.35	.25								.29
NEO C	.32	.16	.38	.21	.09	.07	.03	.14	.31	.42							.35
Prev. MDE	.13	.03	.11	.06	.04	.01	.13	.07	.01	.02	.17						.34
Phys. abus.	.11	.14	.01	.09	.07	.07	.08	.03	.01	.02	.06	.08					.04
Psy. abus.	.17	.25	.03	.21	.14	.01	.07	.11	.01	.11	.01	.01	.32				.18
OoH care	.27	.32	.22	.27	.20	.02	.01	.24	.26	.12	.00	.10	.18	.32			.39
Anx. dis	.15	.05	.07	.08	.50	.23	.21	.24	.34	.15	.07	.00	.03	.03	.15		.10
Behv. dis	.39	.31	.54	.49	.07	.11	.06	.26	.43	.01	.29	.06	.07	.06	.08	.08	.17

Individual predictors were then eliminated sequentially in a backwards method, that is, the predictor with the weakest association with the outcome for the model was removed and the remaining predictors re-tested in a new model. The elimination was continued to the point that the maximal number of significant predictors were present in the model.

This method was chosen to be inclusive of a range of possible predictors. It did mean however that variables were removed from the analyses on the basis of sometimes small differences in the strength of association compared to those of the remaining variables.

It was found that the inclusion of the baseline SOFAS in the model resulted in few of the other variables emerging as significant predictors in the analysis of functional course, and of the severity of the course of MDD. It is understandable particularly that the effect of variables on longitudinal functioning would be mediated by their effect on baseline functioning. Therefore, in order to overt the role of these other variables, a regression model was developed both before and after the addition of the SOFAS. Only the variables reaching a significance level of $p < 0.10$ were included in the analysis with SOFAS.

The adjusted R^2 is reported for these models. R^2 is the proportion of improvement of the regression model over a basic model (mean value of the outcome in this analysis) due to the best fit model. The adjusted R^2 is the value that would be acquired if the model were derived from the entire population from which the sample is taken. The accompanying p value is for the ANOVA (analysis of variance) testing the derived model against one using the mean value of the outcome variable as the predictor variable.

Beta values and associated t value and significance levels (p) are reported for the individual variables. Beta is the change in the outcome for a unit change in the predictor, while holding other predictor variables constant. Both standardised and unstandardised beta values are reported. For the dichotomous categorical variables where either a particular predictor was present or not, the unstandardised beta is the difference in mean scores between those participants who had this predictor and the cohort as a whole (2003).

The standardised Beta is adjusted so as to be independent of the units of measurement used. Its value is the number of standard deviations change of the outcome variable caused by a one standard deviation change of the predictor variable. Associations with the study outcomes were also tested for relevant variables collected at follow-up.

8.9.2.2 Investigation of bias and testing of assumptions

The data were analysed for the presence of outliers by the calculation of Cook's distance. This statistic assesses the influence of a single case on a model, with the general principle that values greater than 1.0 reflect undue influence (Cook, RD & Weisberg, S, 1982). If a variable was found to have a Cook's value of greater than 1, it was excluded and the analysis repeated.

The linear regression model relies upon a number of characteristics of its individual predictors and their residuals for its applicability to the observed data and for the accuracy of the significance tests applied to it. These characteristics were assessed in the analysis process.

For individual predictors, partial plots of their residuals against the residuals of the outcome variable were produced in order to test for the linearity of this relationship, as required for the linear regression model. These plots also demonstrate the homogeneity of variance for the predictors, with heterogeneity reducing the accuracy of significance tests.

High degrees of intercorrelation between one predictor variable and others in the regression equation can affect the accuracy of regression coefficients. As mentioned above generally both of a pair of highly intercorrelated variables were not included in the regression equation, so this will have reduced of any such multicollinearity. To assess for multicollinearity, the Variance Inflation Factor (VIF) was calculated for each predictor. This variable provides an index of the amount that the variance of each regression coefficient is increased relative to a situation in which all predictor variables are uncorrelated. A VIF of 10 indicates serious multicollinearity (Cohen, J et al., 2003), and an average VIF for a model substantially greater than 1 indicates that the regression may be biased (Field, Andy 2000/2013).

Significance tests for regression models were performed using the F-ratio, which relies for its accuracy on the normal distribution of residuals in a model. To assess for this normality, a histogram of standardised residuals and a P-P plot of standardised expected residuals versus standardised observed residuals were plotted for each model.

In the case of non-normality of residuals or heteroscedasticity, a bootstrap method (Wright, DB, London, K, & Field, AP, 2011) was used to re-analyse the data. This method estimates the properties of the sampling distribution from the sampling data, by creating a large number of samples from a study sample, with a default setting of 1000 created by SPSS.

The results of the tests for bias will not be specifically referred to in the following text unless there was a violation of assumptions for a particular model.

8.10 Prediction of severity of MDD course

8.10.1 Univariate baseline predictors of MDD course

The course parameters of MDD described in 8.6 above were also analysed for associations with baseline variables and the results are presented in

Table 8-26. The only significant association of a baseline variable with having a recurrence of MDD during follow-up was with baseline MDD severity ($U=338$, $p=0.034$).

The distributions for the other course parameters were all significantly positively skewed, with the Duration of episode and Time to recovery distributions also having a significant positive kurtosis. Therefore non-parametric tests were performed for the analysis of predictors of the MDD course parameters.

Table 8-26: Univariate analysis of potential baseline predictors of MDD course

	Duration of episode (mths)		Time to recovery (mths)		Proportion of follow-up in an MDE (%)	
Baseline variables	Median Predictor+ve/ Predictor-ve ¹	<i>r_s</i>	Median Predictor+ve/ Predictor-ve	<i>r_s</i>	Median Predictor+ve/ Predictor-ve	<i>r_s</i>
Personality Disorder						
Borderline score		0.19		0.25*		0.18
Cluster A score		0.00		-0.01		0.08
Cluster B score		<i>0.23</i>		<i>0.27*</i>		0.26*
Cluster C score		0.25*		0.25*		0.32*
SCID II mean score		0.25		0.27*		<i>0.32*</i>
Borderline disorder	35.0/22.5	0.15	28.6/18.6	<i>0.19</i>	0.43/0.34	<i>0.22</i>
Cluster B disorder	35.0/22.0	<i>0.24</i>	28.6/15.7	<i>0.29*</i>	0.43/0.22	<i>0.32*</i>
Cluster C disorder	25.0/30.7	-0.02	19.2/23.0	-0.02	0.36/0.35	0.12
Any disorder	0.40/0.21	0.23	23.0/12.5	0.23	0.40/0.21	0.34**
Personality						
Neuroticism		0.24*		0.23*		0.20
Extroversion		-0.15		0.09		-0.11
Openness		0.09		0.08		-0.05
Agreeableness		-0.06		0.01		-0.06
Conscientiousness		-0.35**		-0.30**		-0.28*
MDD measures						
Family history	35.0/20.0	0.16	25.0/13.4	0.17	0.38/0.34	0.17
Previous MDE	30.7/30.4	0.05	22.1/22.6	0.08	0.39/0.35	0.15
Age of onset MDD		-0.15		-0.11		-0.16
Severity index MDE		-0.04		-0.02		-0.04
Mental state disorder						
Anxiety disorder	48.7/19.2	0.37**	32.2/13.0	0.34**	0.48/0.34	0.27*
Behav. disorder	41.0/22.3	0.25*	28.6/16.9	0.26*	0.47/0.35	0.19
Dysthymic disorder	51.3/24.0	0.28*	32.9/19.2	0.24*	0.43/0.36	0.14
Subst. use disorder	32.0/27.5	0.11	23.0/22.3	0.10	0.42/0.36	0.02
Childhood adversity						
Out of home care	52.0/24.0	0.20	36.9/20.0	0.16	0.59/0.30	0.26*
Psychol.abuse	46.1/22.1	0.24*	36.2/17.2	0.24*	0.47/0.29	0.25*
Physical abuse	32.7/24.5	0.05	27.5/21.6	0.04	0.41/0.34	0.09
Sexual abuse	26.0/30.9	-0.05	16.6/22.8	-0.04	0.41/0.36	0.13
Any abuse	42.9/22.6	0.19	29.4/20.0	0.13	0.47/0.28	0.24*
Gender	31.4/22.6	0.10	22.9/20.0	0.13	0.38/0.30	0.13
SES: Tertile 1. vs 2.	20.0/41.0	-0.33**	14.9/34.1	-0.33**	0.34/0.46	-0.28*
Functioning		-0.28*		-0.28*		-0.41***

*=p<0.05, **=p<0.01, ***=p<0.001, italicised=p<0.10 Bold r scores are of those variables entered in the multiple predictor analyses

¹ Median value for participants who met criteria for this predictor/Median value for participants who did not meet criteria for this predictor

Table 8-26 reveals that significant baseline predictors of MDD course came from across the predictor groups, with the exception of the MDD-related group. There was also a consistency of variables being predictive of both the shorter and longer-term course.

Interestingly, the clusters of variables differed in whether they were more strongly predictive of the shorter or longer-term course.

8.10.1.1 Hypothesis variables

The variables highlighted in the study hypotheses, the Borderline Personality Disorder (BPD) mean item score, and trait neuroticism were found to be predictive of shorter-term outcomes, but had weaker, non-significant relationships with the proportion of time in an MDE over the follow-up period.

The BPD score and trait neuroticism had correlation coefficients of 0.25 ($p=0.025$) and 0.23 ($p=0.023$) respectively with the time to recovery of the index episode. Trait neuroticism was also associated with the duration of the index MDE ($r_s=0.24$, $p=0.033$), while the BPD score was not ($r_s=0.19$, $p=0.088$).

The BPD score and trait neuroticism had correlations with the proportion of time in an MDE, of 0.18 ($p=0.102$) and 0.20 ($p=0.076$) respectively.

8.10.1.2 Other variables

In contrast to the pattern with the BPD mean item score, reaching the diagnostic threshold for BPD had a stronger association with the longer-term course, with the median period in an MDD for those with a BPD diagnosis being 43% of the follow-up period, compared to 34% for those without ($U=509$, $z=1.95$, $p=0.051$, $r=0.22$).

Among the personality disorder variables, the effects of dimensional scores of Cluster B and C, and of a Cluster B disorder were strongest, with the strength of correlations generally greater for the longer-term outcome.

The categorical variable of having any disorder was the strongest personality disorder predictor of the proportion of follow-up period in an MDE, with a median period of 40% for those with a disorder and 21% for those without ($U=291$, $z=2.66$, $p=0.008$, $r=0.34$).

The childhood adversity variables also had relatively stronger longer-term effects, with histories of out of home care, psychological abuse and abuse of any type predicting the proportion of time in an MDE over follow-up. Out of home care was the variable associated with the greatest proportion of time spent in an MDE of any categorical predictor, with a median period of 59%, while those without this history had a median period of 30% ($U=311$, $z=2.48$, $p=0.013$, $r=0.26$).

Also exerting a stronger long-term effect, while also predictive in the short-term, was baseline functioning measured by the SOFAS. It had the highest correlation coefficient of all variables with the proportion of time spent in an MDE, at 0.41 ($p<0.001$).

Trait conscientiousness was the sole personality variable to be predictive over the short and long-term, with its strongest correlation being with the duration of the index episode ($r_s=0.35$, $p=0.014$).

Comorbid mental state disorders also seemed to exert a greater influence in the shorter-term with Anxiety, Behavioural and Dysthymic disorders all significantly correlated with the duration of the index MDE and time to recovery, but only Anxiety disorders being predictive of the proportion of follow-up in a MDE.

For time to recovery, the median period for those with an Anxiety disorder was 32.2 months, and 13 months for those without ($U=453$, $z=3.05$, $p=0.002$, $r=0.34$). Over the longer-term, participants with an Anxiety disorder spent 48% of the follow-up period in a MDE, compared to 34% for those without ($U=519$, $z=2.41$, $p=0.016$, $r=0.27$).

Unexpectedly it was found that residing in an area in the lowest socio-economic status tertile was associated with a less severe course of MDD, specifically being in Tertile One in comparison with Tertile Two. Those in Tertile One had a median time to recovery of 14.9 months, while those in Tertile Two had a median period of 34.1 months ($U=323$, $z=2.70$, $p=0.007$, $r=-0.33$). The difference between the groups though significant was less marked over the longer term, with median proportions of time in an MDE of 0.34 and 0.46 ($U=354$, $z=2.28$, $p=0.002$, $r=-0.28$).

8.10.2 Multiple predictor analysis of baseline predictors of course of MDD

Testing for violation of assumptions of the regression model revealed a degree of positive skew of the standardised residuals for all the intermediate and final models. The data were not transformed to correct for this due to the effect that a change of scaling would have on the interpretability of the study findings.

The variables that were entered in the multiple predictor analyses for each outcome are those whose correlation coefficients for the particular outcome are in bold type in Table 8-26 above. There were eleven variables initially entered for the duration of episode analysis and ten for the other two analyses.

The R^2 values for the regression models ranged from a low of 0.10 ($p=0.018$) for the intermediate model of Time to recovery, to a high of 0.20 ($p<0.001$) for the final model for the proportion of the follow-up period in an MDE. This puts all the models in or close to the medium strength range for the improvement they make on the basic model of the outcome means. In terms of the number of individual predictors, the most that any model contained was two.

8.10.2.1 Hypothesis variables

Neither of the study hypothesis variables, BPD mean item score and trait neuroticism, were found to be predictive of any of the three MDD course outcomes in the multiple predictor analyses.

To determine if the medium or strong-level correlations of the BPD item mean score with other personality disorder variables was contributing to its elimination from multiple predictor models, the regressions for Duration of Episode and Time to recovery were repeated with both the SCID II item mean, and any Personality Disorder variables no longer included in the models.

In these regressions, the BPD item mean score again accounted for little unique variance, and was eliminated after either the first or second step.

Table 8-27: Hierarchical regression of predictors of MDD course severity

Duration of episode (sd=32.4 mths)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Cluster C score	-24.4 (19.6)	-63.6, 14.7	0.20	1.51	0.136
Psychological abuse	14.4 (9.1)	-3.8, 32.6	0.17	1.62	0.110
Anxiety disorder	27.5 (9.4)	8.8, 46.2	0.32	3.07	0.003
Behavioural disorder	14.8 (9.4)	-4.1, 33.6	0.17	1.62	0.110
<i>Intermediate model</i>	<i>R</i>²		<i>p</i>		
	0.16		0.004		
SOFAS added	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Anxiety disorder	19.83 (7.09)	5.7, 34.0	0.30	2.80	0.007
SOFAS	-0.60 (0.26)	-1.11, -0.09	-0.25	-2.35	0.021
<i>Final model</i>	<i>R</i>²		<i>p</i>		
	0.14		0.001		

Time to recovery (sd=29.8 mths)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Anxiety disorder	16.35 (6.63)	3.2, 29.6	0.27	2.47	0.016
Behavioural disorder	11.33 (7.71)	-4.0, 26.7	0.16	1.47	0.146
<i>Intermediate model</i>	<i>R</i> ²		<i>p</i>		
	0.10		0.018		
SOFAS added	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Anxiety disorder	15.1 (6.67)	1.8, 28.4	0.25	2.26	0.027
SOFAS	-0.53 (0.24)	-1.00, -0.05	-0.24	-2.21	0.030
<i>Final model</i>	<i>R</i> ²		<i>p</i>		
	0.11		0.006		

Proportion of follow-up period in an MDE (sd=0.29%)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Psychological abuse	0.15 (0.07)	0.006, 0.293	0.22	2.07	0.042
Anxiety disorder	0.13 (0.07)	0.005, 0.263	0.22	2.06	0.043
Conscientiousness	-0.003 (0.002)	-0.006, 0.000	-0.21	-1.95	0.055
<i>Intermediate model</i>	<i>R</i> ²		<i>p</i>		
	0.12		0.006		
SOFAS added	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Psychological abuse	0.10 (0.07)	-0.04, 0.24	0.15	1.42	0.159
Anxiety disorder	0.13 (0.06)	0.003, 0.251	0.21	2.05	0.044
SOFAS	-0.008 (0.002)	-0.012, -0.003	-0.36	-3.44	0.001
<i>Final model</i>	<i>R</i> ²		<i>p</i>		
	0.20		<0.001		

8.10.2.2 Other variables

Having an anxiety disorder was a consistent predictor, with a significant standardised beta for both short-term variables and for the follow-up MDE proportion, including in the final models with the SOFAS added.

Its non-standardised beta for the short-term variables in the final models were 19.8 for duration of episode (95% CI 5.7 to 34.0) and 15.1 for time to recovery (95% CI 1.8 to 28.4), this value being the difference in the number of months that those with an anxiety disorder took to recover compared to the cohort as a whole. Both of these results had wide 95% confidence intervals, indicating a degree of uncertainty about

how representative these were of the hypothetical population from which the sample was drawn.

The standardised beta of -0.29 of baseline SOFAS for the regression analysis of predictors of the duration of the index MDE means that one standard deviation increase of the baseline SOFAS, which was 13.5, would reduce the duration by 0.29 of its standard deviation (32.4 months), that is by 9.4 months. Its corresponding standardised beta of -0.24 for time to recovery equates to an increase of 7.2 months for a decrease of the SOFAS by a standard deviation.

Both of the non-standardized betas for the SOFAS association with the short-term outcomes had wide confidence intervals. This was less the case with its association with the follow-up MDE proportion.

The one other significant predictor was psychological abuse in the intermediate model for the follow-up MDE proportion variable. A history of this variable resulted in an increase of 0.15 in the proportion of time in an MDE compared to that of the cohort as a whole.

SOFAS had its highest standardised beta in the final model for follow-up MDE proportion, at -0.36, meaning one standard deviation of the SOFAS would result in a 0.10 decrease in the proportion of time spent in an MDE over follow-up. The 95% confidence interval for the non-standardised beta was between -0.003 and -0.012, a narrower range than for the short-term outcomes. The SOFAS beta of the study sample of 0.008 means that for a one unit change in SOFAS, there will be a change of 0.008 change in the MDD proportion, so approaching 1% of the follow-up period.

8.10.3 Association of follow-up variables with MDD course

Variables collected at follow-up with a potential effect on MDD course were tested for an association with the follow-up MDE proportion. As seen in Table 8-28, the LIFE-RIFT annual overall mean was strongly correlated with the follow-up MDE proportion ($r_s=0.59$, $p<0.001$), while there was a medium strength correlation ($r_s=0.45$, $p<0.001$) with the number of mental state disorders experienced over the follow-up period.

Table 8-28: Association of follow-up variables with the follow-up MDE proportion

Predictor	Positive cases (n)	Negative cases (n)	<i>U</i>	<i>z</i>	<i>r / r_s</i>	<i>p</i>
Year 12 completed	0.36 (51)	0.38 (30)	688	0.753	0.08	0.451
Tertiary study	0.36 (40)	0.41 (40)	798	0.208	0.02	0.835
SCID II item mean change					-0.18	0.156
Cumulative mental state disorders					0.45	<0.001
LIFE-RIFT overall annual mean					0.59	<0.001

8.11 Prediction of functioning at follow-up

8.11.1 Univariate baseline predictors of functioning at follow-up

Baseline variables were also analysed for their association with scores on the Social Adjustment Scale-Self Report (SAS-SR)(Weissman & Bothwell, 1976a). As mentioned in 7.4 above, in addition to the overall mean item score, mean scores for items relating to work (comprising education and household management) and interpersonal roles were calculated. A higher score on the SAS-SR indicates worse functioning.

There were no extreme outliers among participants in SAS-SR scores. Both the overall mean and subdomain distributions did not diverge markedly from a normal pattern.

Three of the continuous predictors: BPD score, Cluster A mean and Extroversion had skewed distributions and therefore their relationships with the SAS-SR were analysed with non-parametric tests. Of the categorical variables, the distribution of the relationship domain for those with an anxiety disorder and of the overall mean for those with Borderline personality disorder were skewed, and therefore non-parametric tests were used for these domains.

Table 8-29: Univariate analyses of baseline predictors of SAS-R score at follow-up

	Overall		Work		Interpersonal	
Predictor	Mean or median Predictor+ve/ Predictor-ve	<i>r</i>	Mean or median Predictor+ve/ Predictor-ve	<i>r</i>	Mean or median Predictor+ve/ Predictor-ve	<i>r</i>
Personality Disorder						
Borderline score		0.03		0.04		0.14
Cluster A score		0.32*		0.16		0.23
Cluster B score		-0.04		0.06		0.06
Cluster C score		0.29*		0.20		0.22
SCID II mean score		0.23		0.16		0.23
Borderline disorder	1.85/1.73	0.12	1.75/1.67	0.11	2.12/1.94	0.16
Cluster B disorder	1.83/1.77	0.07	1.84/1.66	0.15	2.01/1.89	0.11
Cluster C disorder	1.87/1.88	0.04	1.67/1.74	0.05	1.89/1.94	0.06
Any disorder	1.84/1.73	0.13	1.79/1.65	0.11	1.99/1.87	0.12
Personality						
Neuroticism		0.10		0.02		0.07
Extroversion		-0.22		-0.02		-0.22
Openness		-0.15		-0.12		-0.10
Agreeableness		0.16		-0.02		-0.10
Conscientiousness		0.04		0.09		-0.01
MDD measures						
Family history	1.85/1.81	0.04	1.83/1.65	0.13	2.02/1.95	0.06
Previous MDE	1.91/1.74	0.18	1.83/1.70	0.11	2.10/1.83	0.26*
Age of onset MDD		-0.10		-0.03		-0.12
Severity index MDE		-0.07		-0.02		0.01
Mental state disorder						
Anxiety disorder	1.99/1.77	0.23	1.99/1.66	0.26*	2.18/1.89	0.27*
Behav. disorder	1.88/1.83	0.04	1.91/1.74	0.11	2.16/1.95	0.14
Dysthymic disorder	1.91/1.83	0.07	1.72/1.80	-0.05	2.06/1.98	0.06
Substance disorder	2.04/1.81	0.19	1.90/1.75	0.09	2.14/1.97	0.12
Childhood adversity						
Out of home care	1.98/1.81	0.14	1.91/1.75	0.10	2.28/1.93	0.26*
Psychol.abuse	1.80/1.86	-0.06	1.70/1.81	0.07	1.85/1.93	-0.08
Physical abuse	1.91/1.83	0.06	1.89/1.75	0.07	2.11/1.97	0.12
Sexual abuse	1.97/1.82	0.13	1.95/1.75	0.09	2.08/1.98	0.07
Any abuse	1.89/1.81	0.08	1.83/1.77	0.05	2.04/1.92	0.11
Gender	1.84/1.88	0.03	1.81/1.69	0.10	1.98/2.07	0.07
Socio-economic status		F =0.343		F =0.322		F =0.576
Functioning: SOFAS		-0.34**		-0.18		-0.29*

*= $p < 0.05$, **= $p < 0.01$, ***= $p < 0.001$, italicised= $p < 0.10$ Bold *r* scores are of those variables entered in the multiple predictor analysis

8.11.1.1 Hypothesis variables

Neither of the study hypothesis variables, the BPD mean item score and trait neuroticism, were associated with the overall or domain scores of the SAS-SR.

8.11.1.2 Other variables

A small number of baseline variables from a range of the predictor groups were found to be predictive of overall functioning at follow-up in the cohort, all at a medium strength of effect in terms of their *r* values.

Among the personality disorder variables, those with significant associations with the overall mean were both dimensional measures, and the Cluster A score ($r_s=0.32$, $p=0.011$), and the Cluster C score ($r=0.29$, $p=0.013$).

With the exception of the Cluster A score which had a stronger effect in the work domain, these personality disorder variables had greater correlations with the interpersonal domain scores, though not reaching statistical significance.

A co-occurring anxiety disorder was the sole variable to be predictive of the work domain ($t=2.30$, $p=0.024$, $r=0.26$), and was also predictive of interpersonal functioning ($U=465$, $z=2.34$, $p=0.019$, $r=0.27$).

The fact that a co-occurring anxiety disorder was the only predictor of the work domain is likely to be at least in part reflective of its smaller relative number of items which constrained the range of scores and hence the potential for observable differentiation by baseline variables.

Having had a previous MDE ($t=2.30$, $p=0.024$, $r=0.26$) having been in out of home care ($t=2.30$, $p=0.024$, $r=0.26$) and baseline functioning ($r=0.29$, $p=0.013$) appear to have a more specific effect on the interpersonal domain. Baseline functioning was also associated with the overall score ($r=0.34$, $p<0.01$).

8.11.2 Multiple predictor analysis of baseline predictors of functioning at follow-up

A small number adjustments were required to be made to the analysis due to the detection of outliers and the violation of assumptions of the regression analysis. Specifically, an outlier with a Cook's value of 1.26 was excluded from the analysis of the work domain. In the relationship domain analysis, the partial plot of Cluster A mean indicated possible heteroscedasticity and the plot of the residuals of both the intermediate and final models had a positive skew. Therefore the bootstrap method was used for this domain.

8.11.2.1 Hypothesis variables

As neither the BPD item score, nor trait neuroticism reached the threshold of $p<0.10$ statistical significant in their univariate associations with the SAS-SR domains, these variables were not entered into the multiple predictor analyses

Table 8-30: Regression analysis of baseline predictors of SAS-SR

Overall mean (sd=0.46)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Cluster A mean	0.48 (0.23)	0.03, 0.94	0.26	2.11	0.039
Cluster C mean	0.51 (0.25)	0.001, 1.01	0.25	2.00	0.050
<i>Intermediate model</i>	R²	<i>p</i>			
	0.12	0.009			
SOFAS added	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Cluster A mean	0.44 (0.23)	-0.02, 0.90	0.24	1.91	0.061
SOFAS	-0.10 (0.004)	-0.02,-0.001	-0.28	-2.25	0.029
<i>Final model</i>	R²	<i>p</i>			
	0.14	0.006			

Work (sd=0.58)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Anxiety disorder	0.34 (0.14)	0.05,0.62	0.26	2.34	0.022
<i>Final model</i>	R²	<i>p</i>			
	0.07	0.022			

Interpersonal. (sd=0.53)					
Predictor	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Out of home care	0.29 (0.20)	-0.10,0.68	0.18	1.48	0.062
Previous MDE	0.26 (0.13)	0.002,0.512	0.25	2.02	0.043
Cluster A mean	0.53 (-0.03)	0.05,1.01	0.27	2.22	0.011
<i>Intermediate model</i>	R²	<i>p</i>			
	0.11	0.024			
SOFAS added	B (SE)	95% CI for B	β	<i>t</i>	<i>p</i>
Out of home care	0.26 (0.22)	-0.18,0.69	0.16	1.18	0.242
Previous MDE	0.25 (0.14)	-0.03,0.53	0.24	1.76	0.084
Cluster A mean	0.52 (0.37)	-0.23,1.26	0.19	1.40	0.168
SOFAS	-0.003 (0.006)	-0.02,0.01	-0.08	-0.53	0.599
<i>Final model</i>	R²	<i>p</i>			
	0.08	0.087			

8.11.2.2 *Other variables*

In the backwards regression model, the baseline variable that emerged as predictive of the overall SAS-SR mean was the Cluster A mean score ($\beta=0.26$, $p=0.039$), while the Cluster C mean score was just below the significance threshold ($\beta=0.25$, $p=0.050$)

With the addition of baseline SOFAS, which was also predictive of the overall mean ($\beta=-0.28$, $p=0.029$), neither of the Cluster A or C scores remained as significant predictors. The standardised beta of -0.28 for SOFAS equates to an reduction of SAS-SR overall score of 0.13 for each 13.5 point increase in baseline SOFAS.

The respective R^2 of 0.12 and 0.14 of these models put them at the borderline of medium strength.

As the sole predictor in the univariate analysis, a co-occurring baseline anxiety disorder was the sole predictor in the regression model for the work domain ($\beta=0.26$, $p=0.022$).

The R^2 of 0.07 was low strength, but still an improvement on the basic model ($p=0.022$).

For the interpersonal domain, the model prior to the addition of SOFAS was in fact slightly stronger than the final model ($R^2=0.11$, vs. 0.08 with SOFAS), and contained the Cluster A mean score ($\beta=0.27$, $p=0.011$) and having had a previous MDE ($B=0.26$, $\beta=0.27$, $p=0.043$) as significant predictors, with Out of home care ($B=0.29$, $\beta=0.18$, $p=0.062$) under the significance threshold.

Within the final model, having had a previous MDE was the strongest predictor, but only at a $p<0.10$ level ($B=0.25$, $\beta=0.24$, $p=0.084$). The final model itself was not an improvement on the basic model ($R^2=0.08$, $p=0.087$).

8.11.3 **Association of follow-up variables with functioning at follow-up**

Those variables measured at follow-up potentially affecting the SAS-SR were tested for associations with the SAS overall score and the results are presented in Table 8-31 below.

All dimensional measures of personality disorder had medium to large ($r=0.43$ to $r=0.61$) and significant correlations with the SAS overall score as did the presence of any personality disorder ($t=3.43$, $p=0.001$, $r=0.43$). As the rates of categorical personality disorder were low at follow up (maximum 16% in Cluster C), associations with these were not tested.

Similarly strong correlations were found for two of the NEO-PI factors: Neuroticism ($r=0.63$), Extraversion ($r=-0.40$), with the latter having a negative relationship to the SAS score ie. higher scores associated with better functioning at follow-up.

Experiencing current mental state disorders was correlated with a medium level of strength with the SAS-SR scores, with an r of 0.36 for those participants with an anxiety disorder and 0.25 for those with an MDE.

Recent life events also affected the SAS-SR score with the score on the Life Events Questionnaire ($r=0.32$, $p=0.004$) having a medium strength association, as did the proportion of time spent in an MDD over the follow-up period ($r_s=0.37$, $p=0.004$) and the mean change in the SCID II ($r=-0.41$, $p=0.001$)

None of the three demographic variables analysed demonstrated a significant relationship with the SAS overall score.

Table 8-31: Association of variables measured over follow-up with SAS-SR overall score

a. Continuous predictors

Predictor	r/r_s	p
Personality disorder		
BPD score	0.61	<0.001
Cluster A mean	0.43	<0.001
Cluster B mean	0.47	<0.001
Cluster C mean	0.46	<0.001
SCID II item mean	0.56	<0.001
Personality		
Neuroticism	0.63	<0.001
Extraversion	-0.40	<0.001
Openness	-0.11	0.348
Agreeableness	-0.09	0.427
Conscientiousness	-0.21	0.063
Life events		
LEQ-total	0.32	0.004
MDD course		
Proportion of follow-up in an MDE	0.37	0.004
Cumulative other mental state disorders	0.41	<0.001
SCID II mean change	-0.41	0.001

b. Categorical predictors

Predictor	SAS overall mean				
	Positive cases (n)	Negative cases (n)	t	r	p
Personality disorder	2.16 (18)	1.76 (58)	3.43	0.37	0.001
Current MDE	2.19 (13)	1.78 (64)	2.22	0.25	0.043
Current Anxiety disorder	2.08 (26)	1.72 (51)	3.30	0.36	0.001
Year 12 completed	1.81 (47)	1.90 (30)	-0.77	0.09	0.446
Tertiary study	1.82 (39)	1.88 (38)	-0.54	-0.06	0.589
Relationship status	1.75 (40)	1.96 (32)	-1.86	-0.22	0.067

8.12 Prediction of functional course

8.12.1 Univariate baseline predictors of functional course

The higher the score on a LIFE-RIFT scale, the lower the functioning, such that a positive correlation with a predictor variable corresponds to a prediction of worse functioning.

Continuous variables demonstrated linearity in their associations with the LIFE-RIFT. A small number of variables violated the assumption of normality.

As can be seen in Figure 8-8 below, the mean scores for the Borderline personality disorder SCID II items were not normally distributed across the sample, with a skew to both tails, particularly towards lower scores. The distribution of scores for those meeting diagnostic criteria, shown in Figure 8-9 were also skewed, more toward higher scores. As would be expected given Borderline personality disorder accounted for 16 of the 22 Cluster B diagnoses, the distribution of LIFE-RIFT scores for participants was similar to that of those with Borderline personality disorder. Consequently, non-parametric testing was performed to assess associations with LIFE-RIFT scale annual means for these three variables.

Figure 8-8: Distribution of SCID-II baseline Borderline personality disorder scores

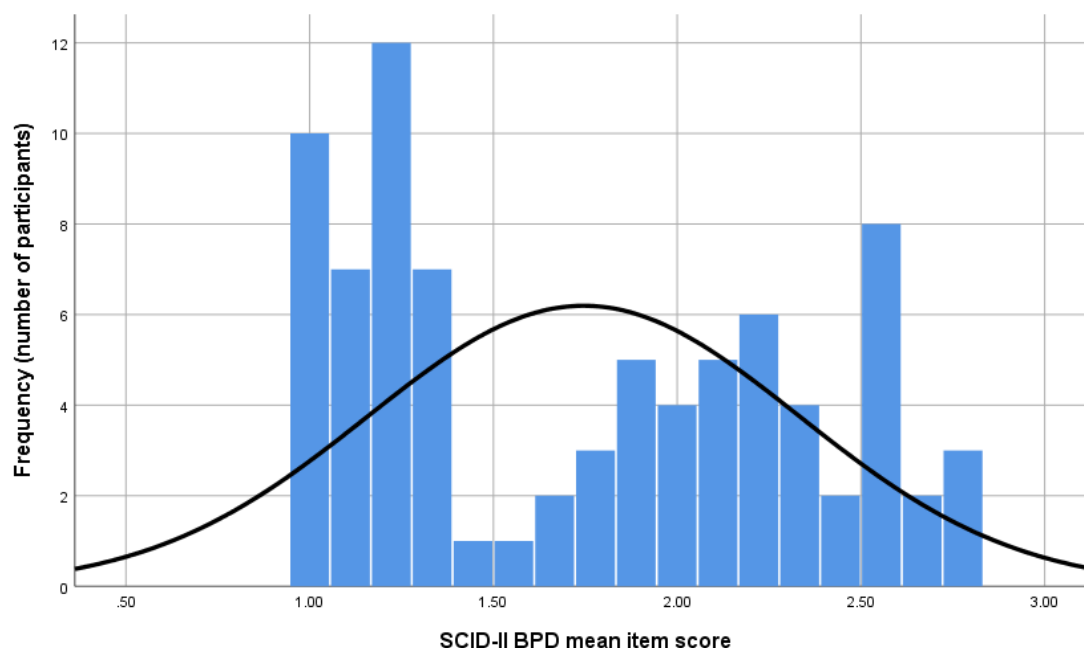


Figure 8-9: Distribution of LIFE-RIFT mean for participants with BPD diagnosis

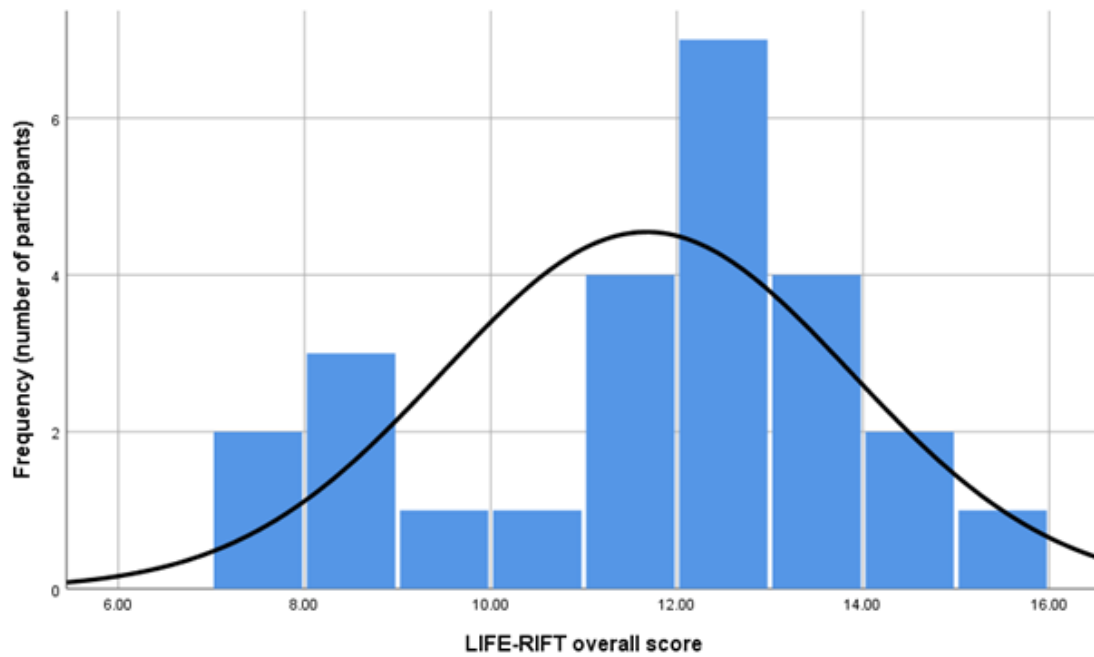


Table 8-32 contains mean LIFE-RIFT scales scores for predictors with normally distributed scores, and median scores for those that were not normally distributed. The Pearson's or Spearman's correlation coefficient is displayed for each predictor. The r or r_s values that are in bold identifies the variables entered in the multiple-predictor analysis for each domain.

Table 8-32: Univariate analysis of baseline predictors of LIFE-RIFT overall annual mean

Predictor	Mean or Median <i>Predictor +ve/ Predictor -ve</i>	<i>r/r_s</i>
Personality Disorder		
Borderline score		0.24*
Cluster A score		0.22
Cluster B score		0.25
Cluster C score		0.26*
SCID II mean score		0.34**
Borderline disorder	3.04/2.66	0.22*
Cluster B disorder	2.86/2.58	0.24
Cluster C disorder	2.85/2.63	0.14
Any disorder	2.84/2.49	0.30*
Personality		
Neuroticism		0.01
Extroversion		-0.07
Openness		-0.02
Agreeableness		-0.10
Conscientiousness		-0.19
MDD measures		
Family history	2.81/2.62	0.15
Previous MDE	2.89/2.55	0.29**
Age of onset MDD		-0.24*
Severity of index MDE		0.14
Mental state disorders		
Anxiety disorder	2.95/2.64	0.26*
Behavioural disorder	3.02/2.68	0.24*
Dysthymic disorder	2.80/2.74	0.04
Substance disorder	2.96/2.71	0.16
Childhood adversity		
Out of home care	3.00/2.69	0.30**
Psychological abuse	2.76/2.75	0.00
Physical abuse	2.88/2.72	0.11
Sexual abuse	2.79/2.75	0.03
Any abuse	2.79/2.70	0.08
Gender	2.78/2.67	0.07
Socio-economic status	I: 2.72 II: 2.83 III: 2.66	F=0.56
Functioning		-0.54***

Table 8-33: Univariate analysis of predictors of LIFE-RIFT domains

	Work		Interpersonal		Satisfaction		Recreation	
	Mean or Median Predictor +ve/-ve	<i>r/r_s</i>	Mean or Median Predictor +ve/-ve	<i>r/r_s</i>	Mean or Median Predictor +ve/-ve	<i>r/r_s</i>	Mean or Median Predictor +ve/-ve	<i>r/r_s</i>
Personality Disorder								
Borderline score		0.15		0.15		0.22		0.21
Cluster A score		0.09		0.12		0.26*		0.25
Cluster B score		0.25		0.06		<i>0.25</i>		<i>0.26</i>
Cluster C score		0.15		0.17		0.26*		0.24
SCID II mean		0.27*		0.19		0.39**		0.26*
Borderline dis..	2.62/2.26	0.17	3.42/3.10	0.11	3.00/2.70	0.14	3.00/2.48	<i>0.20</i>
Cluster B dis.	2.42/2.12	<i>0.21</i>	3.16/3.12	0.07	2.75/2.62	0.19	3.00/2.46	<i>0.28*</i>
Cluster C dis.	2.46/2.17	0.17	3.17/3.12	0.04	2.83/2.49	0.13	2.92/2.61	0.14
Any disorder	2.40/2.04	0.27*	3.19/3.07	0.07	2.49/2.22	0.28*	2.95/2.37	0.34**
Personality								
Neuroticism		0.02		-0.16		0.07		0.11
Extroversion		0.01		-0.03		-0.09		-0.03
Openness		-0.09		-0.03		0.09		-0.02
Agreeableness		-0.11		-0.08		0.02		0.10
Conscientious.		-0.17		0.02		-0.21		-0.20
MDD measures								
Family history	2.46/2.30	0.09	3.26/3.05	0.14	2.81/2.62	0.14	2.71/2.51	0.11
Previous MDE	2.54/2.20	0.21	3.32/3.01	0.20	2.92/2.50	0.31**	2.77/2.47	0.17
Age onset MDD		-0.12		-0.05		-0.24*		-0.26*
Severity MDE		-0.02		0.09		0.12		0.23*
Mental state disorders								
Anxiety disorder	2.49/2.37	0.07	3.51/3.01	0.34**	2.98/2.62	0.27*	2.81/2.56	0.14
Behav. disorder	2.70/2.34	0.19	3.47/3.13	0.19	3.02/2.68	0.21*	2.90/2.59	0.15
Dysthy.disorder	2.44/2.40	0.02	3.30/3.17	0.07	2.76/2.75	0.00	2.70/2.64	0.03
Subst. disorder	2.63/2.37	0.12	3.32/3.18	0.07	3.00/2.71	0.17	2.89/2.61	0.12
Childhood adversity								
O.o.home care	2.67/2.35	0.15	3.52/3.12	0.22*	3.12/2.67	0.28*	2.72/2.63	0.04
Psychol. abuse	2.40/2.42	0.01	3.30/3.17	0.08	2.86/2.72	0.09	2.47/2.71	-0.15
Physical abuse	2.42/2.41	0.00	3.49/3.12	0.21	2.79/2.75	0.02	2.82/2.61	0.10
Sexual abuse	2.64/2.36	0.13	3.22/3.19	0.02	2.78/2.75	0.02	2.51/2.68	0.08
Any abuse	2.49/2.31	0.10	3.29/3.10	0.13	2.82/2.70	0.09	2.58/2.70	-0.07
Gender	2.37/2.57	-0.10	3.16/3.35	-0.11	2.80/2.60	0.12	2.78/2.15	0.30**
Functioning		-		-		-		-
		0.48***		0.35**		0.49***		0.34**

*=p<0.05, **=p<0.01, ***=p<0.001, italicised=p<0.10 Bold r scores are of those variables entered in the multiple predictor analysis

8.12.2 Overall LIFE-RIFT score

8.12.2.1 Hypothesis variables

A significant association was found for the baseline Borderline personality mean item score with the LIFE-RIFT overall mean ($r_s=0.24$, $p=0.030$), supporting the first of the study hypotheses. Trait neuroticism, the other variable selected in the study hypotheses, was found to have very low correlation with the LIFE-RIFT overall mean ($r=0.01$).

8.12.2.2 *Other variables*

There were statistically significant predictors from each of the broad predictor categories that were investigated, with the exception of the personality dimensions measured by the NEO-PI.

Of the groups, the individual variables of the personality disorder category were most consistently significant, with the summary dimensional measure of the SCID-II mean score ($r=0.34$, $p=0.007$), and the general category of having any personality disorder having the strongest effect ($t=2.48$, $p=0.016$, $r=0.30$). With the exception of a Cluster C diagnosis, all of the dimensional or categorical measures, with correlations ranging from 0.22 to 0.26 were at a $p<0.05$ level of significance or at $p<0.10$.

Participants reaching the diagnostic threshold of having Borderline personality disorder ($U=506$, $z=1.98$, $p=0.047$, $r_s=0.22$) belonged to the former of these two groupings.

The strongest predictor of the overall LIFE-RIFT score was baseline functioning, measured by the SOFAS ($r=0.54$, $p<0.001$). Among the comorbid mental state disorders, anxiety disorders ($t=2.37$, $p=0.020$, $r=0.26$) and behavioural disorders ($t=2.20$, $p=0.031$, $r=0.24$) were the significant predictors. Out of home care was the sole of the childhood adversity variables to predict the overall score ($t=2.83$, $p=0.007$, $r=0.30$).

An earlier onset of MDD was also associated with the LIFE-RIFT overall score, indicated by significant associations both with having a previous MDE ($t=2.67$, $p=0.009$, $r=0.29$) and the age of onset of the disorder ($r=-0.24$, $p=0.032$). This finding raised the question of whether the earlier MDE onset may be related to experiences of childhood adversity. As shown in Table 8-25, having had a previous Major Depressive Episode was not associated with the childhood adversity factors measured in this study.

8.12.3 Individual LIFE-RIFT domains

8.12.3.1 *Hypothesis variables*

Underlying its significant association with the overall LIFE-RIFT score, the BPD mean item score had small to medium strength correlations across its individual domains.

The r_s for this variable ranged from 0.15 to 0.22, though with none of these associations reaching statistical significance.

Trait neuroticism also had no significant associations with individual LIFE-RIFT domains.

8.12.3.2 *Other variables*

As would be expected from its strong relationship with the overall LIFE-RIFT mean, the baseline SOFAS was a significant predictor across domains.

The profile of predictors of the Satisfaction domain are almost identical to those of the Overall mean. This reflects the fact that it assesses satisfaction in work, interpersonal life and activities, such that it acts as a de-facto summary scale.

Noteable for the Work domain is the dominance of personality disorder variables among its predictors, with the global variables, SCID II mean ($r=0.27$, $p=0.038$) and any personality disorder ($r=0.27$, $p=0.031$) reaching statistical significance, and the presence of Cluster B variables ($r=0.21$, $p=0.099$) approaching a significant association pointing to this as the most influential cluster in this domain.

Childhood adversity variables had their greatest effect in the Interpersonal domain, with Out of home care a significant predictor ($t=2.05$, $p=0.044$ $r=0.22$), and physical abuse at a trend level ($t=1.93$, $p=0.057$, $r=0.21$). This was also the sole of the non-summary domains for which the presence of an Anxiety disorder was a significant predictor ($t=3.17$, $p=0.002$, $r=0.34$). An unexpected result was that none of the personality disorder variables were found to have significant associations with the Interpersonal domain score.

The most distinctive of the predictors of poor functioning in the Recreation domain was female gender ($p<0.01$). Both of the global measures of personality disorder were also significant predictors of this domain, with measures of BPD and individual clusters predictive at either a $p<0.05$ or $p<0.10$ level.

8.12.4 **Multiple predictor analysis of baseline predictors of LIFE-RIFT overall score**

The results arising from the multiple predictor analysis of the associations of baseline variables with the LIFE-RIFT overall mean are presented in Table 8-34. Ten predictors were entered in the initial model. No significant outliers were detected with all Cook's values for the predictors analysed being below 1.0. Testing for bias indicated the applicability of the linear model, and the statistical tests used.

8.12.4.1 *Hypothesis variables*

One of the two study hypothesis variables, the BPD mean item score, was among the predictors entered in the multiple predictor analysis. It was eliminated prior to the intermediate model. As with the analysis of the predictors of MDD course outcome, the

regression was repeated without including the SCID II mean item score and any Personality Disorder variables in the model. The BPD mean item score was eliminated in the first step of the regression.

As it did not reach the $p < 0.10$ significance threshold for its univariate association with the LIFE-RIFT overall mean, trait neuroticism was not entered into the multiple predictor analysis.

Table 8-34: Stepwise backwards regression of baseline predictors of LIFE-RIFT overall score annual mean

LIFE-RIFT overall score (sd=0.58)					
Predictor	B(SE)	95% CI for B	β	t	p
Personality disorder	0.32 (0.14)	0.04, 0.59	0.28	2.31	0.024
Previous MDE	0.34 (0.14)	0.07, 0.62	0.29	2.48	0.016
Anxiety disorder	0.22 (0.14)	-0.06, 0.51	0.19	1.56	0.124
<i>Intermediate model</i>	R² (SE)	p			
	0.18 (0.53)	0.003			
SOFAS added	B (SE)	95% CI for B	β	t	p
Personality disorder	0.16 (0.14)	-0.13, 0.44	0.13	1.09	0.281
Previous MDE	0.17 (0.14)	-0.11, 0.46	0.15	1.21	0.230
SOFAS	-0.02 (0.01)	-0.03, -0.007	-0.43	-3.29	0.002
<i>Final model</i>	R² (SE)	p			
	0.28 (0.49)	<0.001			

8.12.4.2 Other variables

It can be seen in Table 8-34 above that for LIFE-RIFT mean, the regression model of baseline predictors prior to the addition of SOFAS contained two significant predictors, while only the SOFAS remained significant in the final model.

The significant predictors of the LIFE-RIFT overall mean in the regression analysis were having a Personality Disorder and having had a previous MDE at baseline. When the ten predictor variables were included at the start of the regression, having a previous MDE was already a significant predictor ($\beta = 0.28$, $p = 0.026$), indicating the strength of its independent role among the predictors.

When the SOFAS was added to the regression model, the β of both significant predictors fell, indicating a likely mediator role for baseline functioning on their longitudinal effect.

The β of -0.43 for SOFAS means that for each standard deviation (13.5) reduction in its value, there is 0.43 of a standard deviation of LIFE-RIFT overall mean reduction in functioning, that is an increase of 0.25 points. In a parallel with the findings for the predictors of the MDD course variables, the non-standardised beta of the SOFAS had a narrower confidence interval, at -0.03 to -0.007 than the two predictors in the intermediate model.

The BPD baseline mean was not found to be a significant predictor of the LIFE-RIFT overall mean in the multi-variate analysis. With correlations (Spearman's r_s) of 0.51 with having a Personality Disorder, and 0.42 with baseline SOFAS, it is likely that its effect on the LIFE-RIFT mean was mediated to a large degree by these associations. According to the benchmarks set by Cohen (Cohen 1992), an R^2 of 0.26 represents a large effect, while one of 0.13 is of medium strength, such that the model including the SOFAS with an R^2 of 0.28 has a large effect, while that without with its R^2 of 0.18 has of medium effect on the LIFE-RIFT overall mean.

8.12.5 Multiple predictor analyses of individual LIFE-RIFT domains

Table 8-35: Stepwise backwards regression of baseline predictors of LIFE-RIFT domains

LIFE-RIFT Work (sd=0.80)					
Predictor	B (SE)	95% CI for B	β	t	p
Personality disorder	0.45 (0.19)	0.06, 0.84	0.28	2.31	0.024
Previous MDE	0.36 (0.20)	0.04, 0.76	0.22	1.81	0.076
<i>Intermediate model</i>	R^2	p			
	0.09	0.020			
SOFAS added	B (SE)	95% CI for B	β	t	p
Personality disorder	0.18 (0.21)	-0.23, 0.59	0.11	0.86	0.392
Previous MDE	0.13 (0.21)	-0.29, 0.54	0.08	0.61	0.545
SOFAS	-0.02 (0.01)	-0.04, -0.01	-0.40	-2.92	0.005
<i>Final model</i>	R^2	p			
	0.20	0.001			

LIFE-RIFT Interpersonal (sd=0.73)					
Predictor	B (SE)	95% CI for B	β	t	p
Physical abuse	0.34 (0.18)	-0.02, 0.70	0.20	1.90	0.061
Previous MDE	0.27 (0.15)	-0.03, 0.57	0.18	1.76	0.082
Anxiety disorder	0.48 (0.15)	0.18, 0.79	0.32	3.13	0.002
<i>Intermediate model</i>	R^2	p			
	0.16	0.001			
SOFAS added	B (SE)	95% CI for B	β	t	p
Physical abuse	0.33 (0.18)	-0.02, 0.68	0.19	1.86	0.067
Previous MDE	0.13 (0.16)	-0.19, 0.44	0.09	0.80	0.424
Anxiety disorder	0.45 (0.15)	0.14, 0.75	0.30	2.94	0.004
SOFAS	-0.02 (0.01)	-0.027, -0.004	-0.29	-2.64	0.010
<i>Final model</i>	R^2	p			
	0.22	<0.001			

LIFE-RIFT Satisfaction (sd=0.65)					
Predictor	B (SE)	95% CI for B	β	t	p
Cluster A mean	0.69 (0.29)	0.11, 1.26	0.27	2.39	0.020
Out of home care	0.40 (0.18)	0.03, 0.77	0.24	2.16	0.035
Previous MDE	0.40 (0.15)	0.10, 0.70	0.30	2.65	0.010
Behavioural disorder	0.26 (0.18)	-0.09, 0.61	0.17	1.50	0.140
Anxiety disorder	0.22 (0.15)	-0.09, 0.53	0.16	1.43	0.157
<i>Intermediate model</i>	R^2	p			
	0.25	0.001			
SOFAS added	B (SE)	95% CI for B	β	t	p
Cluster A mean	0.59 (0.30)	-0.01, 1.18	0.23	1.97	0.054
Out of home care	0.23 (0.20)	-0.18, 0.64	0.14	1.12	0.266
Previous MDE	0.30 (0.16)	-0.03, 0.62	0.23	1.85	0.070
SOFAS	-0.01 (0.01)	-0.028, -0.001	-0.30	-2.19	0.033
<i>Final model</i>	R^2	p			
	0.27	<0.001			

LIFE-RIFT Recreation (sd=0.87)					
Predictor	B (SE)	95% CI for B	β	t	p
Personality disorder	0.55 (0.20)	0.16/0.95	0.32	2.80	0.007
Conscientiousness	-0.008 (0.005)	-0.017/0.002	-0.18	-1.59	0.117
Gender	0.61 (0.25)	0.11/1.11	0.29	2.42	0.019
MDE severity	0.05 (0.04)	-0.02/0.12	0.17	1.46	0.150
<i>Intermediate model</i>	R²	p			
	0.22	0.001			
SOFAS added	B (SE)	95% CI for B	β	t	p
Personality disorder	0.45 (0.22)	0.01/0.88	0.26	2.07	0.043
Gender	0.67 (0.25)	0.18/1.16	0.32	2.76	0.008
SOFAS		-0.032/-0.001	-0.24	-1.90	0.063
<i>Final model</i>	R²	p			
	0.22	0.001			

8.12.5.1 Hypothesis variables

Neither of the study hypothesis variables were found to have significant associations with individual LIFE-RIFT domains. The BPD mean item score was entered in the multiple predictor analyses for the Satisfaction and Recreation domains, but was eliminated prior to the step of the intermediate model.

As was done in the analysis of the LIFE-RIFT overall score mean, the regressions for Satisfaction and Recreation were repeated without the variables SCID II mean item score and any Personality Disorder. The BPD mean item score was eliminated in the first step in both analyses.

As it did not reach the $p < 0.10$ significance threshold for its univariate associations with any of the LIFE-RIFT domains, trait neuroticism was not entered into the multiple predictor analyses.

8.12.5.2 Other variables

As would be expected from its degree of influence on the LIFE-RIFT overall mean, the baseline SOFAS was also an independent predictor of three of its domains and approached statistical significance in the fourth, Recreation ($\beta = -0.24$, $p = 0.063$). Of the other three domains, its effect was strongest in Work ($\beta = -0.40$, $p = 0.005$).

The effect of having a previous MDE on the overall mean would appear to come from a consistent influence across domains (excepting Recreation), but only strong enough to

reach statistical significance for an individual domain in the case of Satisfaction ($B=0.30$, $\beta=0.23$, $p=0.010$) in the pre-SOFAS model.

It was uncommon for predictors that were statistically significant predictors prior to the addition of the SOFAS to maintain this status once the baseline SOFAS was added to the regression model. Those that did were anxiety disorder ($B=0.45$, $\beta=-0.30$, $p=0.004$) in the Interpersonal domain, and Personality disorder ($B=0.45$, $\beta=0.26$, $p=0.043$) and female gender ($B=0.67$, $\beta=0.32$, $p=0.008$) in the Recreation domain, indicating an effect for these variables not solely mediated by their relationship to baseline functioning.

In regard to the intermediate model for individual domains, having a Personality Disorder was the sole significant predictor ($B=0.45$, $\beta=0.28$, $p=0.024$) of the Work domain. For the Interpersonal domain, a history of physical abuse approached statistical significance as a predictor ($B=0.34$, $\beta=0.20$, $p=0.061$), maintaining a similar strength in the final model ($B=0.33$, $\beta=0.19$, $p=0.067$).

In addition to the aforementioned previous MDE, being in Out of home care ($B=0.40$, $\beta=0.24$, $p=0.035$) and the Cluster A personality disorder score ($\beta=0.27$, $p=0.020$) predicted scores in the Satisfaction domain, with the latter approaching significance in the final model ($\beta=0.23$, $p=0.054$).

The R^2 for the intermediate and final models ranged from a low of 0.09 for the Work domain intermediate model to a high of 0.27 for the final model for the Satisfaction domain. For most, the R^2 was in the low to mid 0.20s, representing an effect in the mid-range of medium strength.

8.12.6 Association of variables collected at follow-up with functional course

The variables in Table 8-36 collected at the follow-up interview were selected for this analysis due to having a potential impact on the overall functional course of the study participants during the follow-up period.

As can be seen, the strongest univariate associations with the LIFE-RIFT overall annual score were for the proportion of the follow-up period that participants were experiencing MDD ($r=0.61$, $p<0.001$) and the number of different mental state disorders that they had over this time ($r=0.40$, $p<0.001$).

The SCID-II mean change is the difference between the mean SCID-II item score at baseline and follow-up, thus a measure of stability of personality pathology. There was

a negative correlation between the degree of change of the SCID-II mean item score and the LIFE-RIFT mean ($r=0.33$, $p<0.05$), meaning that a reduction in personality pathology was associated with a better functional course.

Table 8-36: Association of follow-up variables with LIFE-RIFT Overall mean annual score

Predictor	Mean score		<i>t</i> (<i>df</i>)	<i>r</i>	<i>p</i>
	Positive cases (n)	Negative cases (n)			
Recurrence of MDD	11.0 (56)	10.0 (18)	1.44 (72)	0.17	0.164
School to Y12	10.7 (51)	11.6 (30)	-1.59 (79)	0.19	0.117
Tertiary study	10.8 (40)	11.2 (41)	-0.90 (79)	0.10	0.371
MDD proportion				0.61	<0.001
Cumulative Axis I disorders				0.40	<0.001
SCID II mean change				-0.33	0.010

8.13 Summary of the results of predictor analyses

8.13.1 Hypothesised predictors

8.13.1.1 Dimensional Borderline Personality Disorder pathology

8.13.1.1.1 Medium-term functional outcome

Dimensional Borderline Personality Disorder (BPD) pathology, measured at baseline as the SCID-II BPD mean item score was predictive ($r_s=0.24$, $p<0.05$) in the univariate analysis of overall longitudinal functioning, measured by the LIFE-RIFT overall score annual mean. The strength of its association with the Satisfaction ($r_s=0.22$) and Recreation ($r_s=0.21$) domains of the LIFE-RIFT approached statistical significance ($p<0.10$). The dimensional BPD score however was not retained as a predictor in the multiple predictor models of these outcomes.

Functioning assessed at the point of follow-up, measured by the SAS-SR was not found to be associated with baseline dimensional BPD pathology.

8.13.1.1.2 Medium-term severity of symptomatic course of MDD

The baseline SCID-II BPD mean item score predicted, in univariate analysis, the time to recovery of the index MDE for the study sample ($r_s=0.25$, $p<0.05$). It had weaker univariate relationships with the duration of the index MDE ($r_s=0.19$, $p<0.10$) and the cumulative period in an MDE ($r_s=0.18$, $p=0.10$).

In multiple predictor analyses of the time to recovery and duration of the index MDE, the baseline BPD item mean did not emerge as a significant predictor.

8.13.1.2 *Trait neuroticism*

8.13.1.2.1 *Medium-term functional outcome*

Trait neuroticism, measured at baseline with the NEO-PI was not associated with either functioning measured at follow-up by the SAS-SR, nor longitudinal functioning, measured by the LIFE-RIFT.

8.13.1.2.2 *Medium-term severity of symptomatic course of MDD*

Both the duration of ($r=0.24$) and the time to recovery ($r=0.23$) of the index MDE were associated in univariate analyses with baseline trait neuroticism at a $p<0.05$ significance level, while the strength of the relationship of baseline trait neuroticism with the cumulative time spent in an MDE over the follow-up period approached statistical significance ($r=0.20$, $p=0.08$).

Trait neuroticism was not found to be associated with these outcomes in multiple predictor analyses.

8.13.2 Other predictors

There was some specificity of predictor variables for particular outcomes in the univariate analyses. Having had a previous MDE was predictive of worse longitudinal and cross-sectional functional outcomes, but not of the MDD outcomes. Poor MDD outcomes, but not the functional outcomes, had associations with trait neuroticism (as mentioned above) and also with a history of psychological abuse and with socio-economic status.

The variable that was consistently predictive of a less favourable course across all outcomes, including when non-baseline predictors were added was baseline psychosocial functioning, measured by the SOFAS

8.13.2.1 *Baseline SOFAS*

For both longitudinal and follow-up functional outcomes, with the exception of the work domain of the SAS-SR, the baseline SOFAS had the strongest univariate correlation of all predictors for the overall scores and subdomains, with correlation coefficients ranging from -0.29 ($p=0.013$) for the relationship items of the SAS-SR to -0.54 ($p<0.001$) for the overall annual mean score of the LIFE-RIFT. It also had medium

strength correlations with the MDD outcomes, with correlations of -0.28 ($p=0.012$) with both short-term outcomes and -0.41 ($p<0.001$) with the MDD proportion.

Scores on the baseline SOFAS were predictive in the multiple predictor analyses of all the MDD course outcomes, the overall scale score for functioning at follow-up and the overall scale and all but one of the individual domains of longitudinal functioning. Due to the design of the multiple predictor analyses, with the SOFAS being introduced in a second step, its candidacy as an independent variable was not tested as thoroughly as the other predictors. The strength of its association with the outcomes though is well demonstrated by the magnitude of both its univariate and multivariate correlation coefficients.

Its effect on the MDD outcomes is most readily able to be seen to be clinically meaningful. Its standardized beta scores from the multiple predictor analysis translate to a reduction of 9.4 and 7.2 months of episode duration and time to recovery for a 13.5 point increase in its score, and a reduction in the proportion of time in follow-up in an MDD of 0.10.

The standardised beta of -0.43 for the LIFE-RIFT overall score regression equals a 0.25 point reduction in the LIFE-RIFT mean per 13.5 point increase of the baseline SOFAS, while that of -0.26 for the SAS-SR overall score translates to a 0.12 point reduction.

8.13.2.2 Comorbid anxiety disorder at baseline

After the SOFAS, the next most consistently predictive baseline variable was the presence of a co-morbid anxiety disorder. This was predictive of worse work functioning at follow-up (SAS-SR work domain) and worse short and long-term MDD outcomes. Among the LIFE-RIFT domains, it was predictive of poorer interpersonal functioning.

Across the outcomes, the betas for having an anxiety disorder had wide confidence intervals, such that it is difficult to know how clear the implications of a baseline anxiety disorder are for the clinical population of young people with MDD as a whole.

Certainly in the study sample, having an anxiety disorder at baseline was associated with clinically significant protraction of MDEs, and with changes in functioning scores that are likely to be meaningful.

8.13.2.3 Previous Major Depressive Episode

Those people who had experienced a previous Major Depressive Episode at baseline were found in the multiple predictor analyses to have poorer overall functioning, both longitudinally and at follow-up.

Having had a previous Major Depressive Episode did not remain a significant predictor on the addition of the SOFAS to the regression model for these outcomes, indicating a degree of mediation of its effect by its impact on baseline functioning.

For both functioning outcomes, the effect shown by the non-standardised betas in the regression models was not large, but neither was it negligible, being around half a standard deviation difference in the scale scores, 0.21 for the pre-SOFAS model of the SAS-SR (SD for scale of 0.46), and 0.34 for the pre-SOFAS model of the LIFE-RIFT (SD for scale of 0.58).

The presence of wide confidence intervals for the beta coefficients means that as for anxiety disorders, some caution should be applied to expectations of a similar-sized effect in the clinical population as a whole.

8.13.2.4 Personality disorder variables

Of these, the overall measures of personality pathology, the SCID II item score and having any personality disorder had the strongest univariate correlations with symptom and functional outcomes.

From these, the effects to emerge from the multiple predictor analyses were significant associations of having any personality disorder with the LIFE-RIFT work, recreation and overall means. In the overall mean analysis, the non-standardised beta for having a baseline personality disorder was 0.32 (CI 0.04-0.59), which is a little over half of the standard deviation (0.58) of the overall mean.

At a cluster level, Cluster A affected the functional course of MDD in the sample, but not the symptom course. Its mean score was a significant predictor in the multiple predictor analysis of the overall score for the SAS-SR and its interpersonal items, also in the intermediate model.

None of the Cluster B or C baseline variables were predictive of outcomes in the multiple predictor analyses, although the Cluster C score was just below the $p < 0.05$ significance threshold for an association with the SAS-SR overall score. The mean Cluster B and C scores and having a Cluster B disorder had significant univariate associations with the short and long-term symptomatic course.

The categorical measure of Borderline Personality Disorder approached statistical significance for its association with the longer-term symptomatic outcome of the proportion of time in an MDE over the follow-up period ($r=0.22$, $p=0.051$).

8.13.2.5 Other variables

Behavioural disorders were predictive of both MDD and longitudinal functional outcomes at a univariate level, but were found to have a stronger association with the MDD outcomes, being found to be independently predictive of both the short and long-term outcomes in the intermediate regression models.

Of the remaining variables, two of the childhood adversity variables were independent predictors, Out of home care was predictive of a worse functioning on the LIFE-RIFT satisfaction domain,. Female gender was predictive of worse functioning in the LIFE-RIFT recreation domain.

8.13.3 Predictors measured over the follow-up period and at follow-up

The three outcomes for which non-baseline predictors were investigated were the proportion of a follow-up time in an MDE, and the overall scales of the SAS-SR and LIFE-RIFT.

The burden of psychopathology over the follow-up period had significant associations with all of these outcomes. Specifically, the cumulative number of mental disorders other than MDD that a participant experienced over the follow-up period was associated with a greater proportion of time in an MDE and a poorer performance on both functional measures. For both functioning outcomes, the proportion of the follow-up period in an MDE and less change in personality pathology was also predictive of poorer functioning.

A higher SAS-SR overall score at follow-up, indicative of lower functioning, was also found to be associated with current psychopathology, particularly with measures of personality pathology, but also with mental state disorders, as well as with trait neuroticism.

Chapter 9 Discussion

9.1 Introduction

This chapter summarises and reviews the key findings of the current study of the symptomatic and functional course of Major Depressive Disorder in a clinical youth-aged sample.

Discussion of the predictors of the course of MDD in the sample will focus on the variables that had been hypothesised to be influential prior to the study; borderline personality features and neuroticism, and those variables that were found to be significant predictors of multiple outcomes in this sample.

These variables were the presence of a personality disorder, a comorbid anxiety disorder, having had a previous MDE, and the level of functioning measured by the SOFAS.

Thereafter follows a brief discussion of the possible mechanisms underlying the observed associations of predictors with outcomes.

Following the discussion of predictors, the potential implications of the study findings will be explored. The strength and limitations of the study will then be examined and the chapter will conclude with the identification of the future research that is indicated by this study.

9.2 Symptomatic course

The key findings in regard to the symptomatic course of the sample were the protracted length of the presenting MDE, the large proportion of the follow-up period in which participants met criteria for an MDE and the high rates of other mental state disorders that participants experienced over the follow-up period.

9.2.1 Index MDE

The mean and median times to symptomatic recovery from the presentation of the index MDE from presentation were 32 and 22 months respectively. The corresponding figures for the duration of the MDE from its onset to recovery were 39 and 31 months. These lengths are two to five times those reported in adolescent clinical samples (Table 2-1). Studies of adult clinical samples have reported a wider range of reported episode lengths (Table 2-2). Of the adult samples reviewed in 2.4.5.2, that with the longest time to recovery had a median duration of 24 months (Hoencamp et al., 2001),

while of those measuring duration of episode, the longest median duration was 20 months (Bukh, JD et al., 2016).

The differences in the findings of the study sample might be firstly because protracted episodes are characteristic of MDD experienced in late adolescence and in the transition to adulthood. Secondly, it might be that factors that have been found to predict longer episodes in other age groups are both relevant to and over-represented in the study sample. Thirdly, there might have been methodological aspects of the study that affected the measurement of this outcome. Each of these possibilities, which might have made cumulative contributions, will be considered in turn.

9.2.1.1 The developmental context of youth and protracted MDEs

As noted in 2.3, youth is the period with the highest incidence of MDD. The onset of any MDE is believed to be due to a complex interaction between vulnerabilities and stresses (Hankin 2015; Ingram, RE et al., 2014). It might be that the high incidence of MDD in youth is contributed to by a particularly significant load of vulnerabilities and stressors that are related to the social and neuro-developmental context of youth, and that this load also acts to maintain someone in an episode.

The transition from childhood to adulthood, commencing with puberty and ending around the mid to late twenties is recognised as a distinct developmental period with unique vulnerability to mental ill-health (Arnett JJ et al., 2014; Chan, Moore, Derenne, & Fuchs, 2019; Wilens & Rosenbaum, 2013). Developmental tasks include ongoing explorations of relationships and identity (Arnett JJ et al., 2014) and the furthering of independence (Wilens & Rosenbaum, 2013) which might be disrupted by an MDE.

The relationship of any developmental disruption to the persistence of the index MDE was not specifically examined in the adolescent longitudinal studies that were reviewed in this thesis. However, low levels of psychosocial functioning might be a manifestation of such difficulties and were found to predict the persistence of the index MDE in three studies (Karlsson et al., 2008; Sanford et al., 1995; Vitiello et al., 2011).

Insights into the possible cognitive mediators of this relationship come from two longitudinal studies, one a mixed child and adolescent sample (Goodyer, Herbert, Tamplin, Secher, & Pearson, 1997; Goodyer et al., 2001), the other an adult sample (Glashouwer, de Jong, & Penninx, 2012). These found, respectively, that failed expectations, and an evaluation of oneself as “useless, pessimistic, inadequate, negative or meaningless” predicted MDE persistence. Such findings indicate that negative self-perception can stall recovery from an MDE, and this could be a link

between any developmental disruption and the slow recovery observed in the study sample.

The period of transition from childhood to adulthood occurs in the neurobiological context of the mismatch between the immature regulatory cortical structures and the more developed emotion and reward centres of the subcortical region, a mismatch which does not resolve until around age 25 (Casey, Getz, & Galvan, 2008; Chung & Hudziak, 2017).

The consequent potential for excessive risk taking and difficulties with emotional regulation, which are seen as possible contributors to developing mental health disorders (Paus, Keshavan, & Giedd, 2008; Wilens & Rosenbaum, 2013), might also lead to a stress load that slows recovery from an MDE.

9.2.1.2 Established risk factors for protracted MDEs in the study sample

The second mechanism mentioned above that might have contributed to the long duration of the index MDE might be a high rate of factors that have been associated with the length of the index MDE in studies of adolescent or adult samples.

Both the current study, along with a number of the adolescent and adult clinical MDD samples reviewed in this thesis demonstrated an association of the index MDE length or persistence with the presence of a co-morbid anxiety (Bukh, Andersen, & Kessing, 2016; Sanford et al., 1995; Spinhoven et al., 2011) or dysthymic disorder (Holma et al., 2008; Karlsson et al., 2008; Keller et al., 1983) and with low global functioning (Karlsson et al., 2008; Riihimäki et al., 2014; Sanford et al., 1995; Solomon et al., 2008; Viinamäki et al., 2006; Vitiello et al., 2011).

The rates of the comorbid disorders are however not higher in the study sample than in the samples of these other age-groups. Anxiety disorders were present in 37% of the study participants, in between 23% and 71% of individuals in adolescent samples (Table 2-4) and between 16% and 59% in the earlier adult studies. In the study sample, 20% had a preceding Dysthymic Disorder at baseline, while the rate of this disorder in the adolescent samples ranged from 7 to 36%, and 25 to 46% in adults.

The current study sample did not have a mean level of functioning below that of the samples of the other age-groups. The Child-Global Assessment Scale ratings between 48 and 51 in the adolescent samples represent “moderate impairment in most areas or severe in one”. In the study sample, the Social and Occupational Functional Assessment Scale (SOFAS) mean score at baseline was 63.4. This score is at the

lower end of the 61 to 70 point range denoting “some difficulty in social, occupational or school functioning”.

Two studies measured the SOFAS at baseline in adults. These studies also found lower mean functioning than the current study sample, with scores of 56.7 (Melartin et al., 2004) and 52.4 (Riihimäki et al., 2014). Two samples used the Global Assessment of Functioning, one of which had a rating mean rating of 55 (Viinamäki et al., 2006) which is equivalent to the study sample SOFAS score, which the other had a mean score of 44 (Ramana et al., 1995), corresponding to serious impairment in one area of functioning.

Additional shared predictors of the index MDE length between the current study and studies of adult samples are the presence of a personality disorder (Bukh, JD et al., 2016; Holma et al., 2008; Melartin et al., 2004; Viinamäki et al., 2006) and trait neuroticism (Boschloo et al., 2014; Bukh, JD et al., 2016; Melartin et al., 2004; Spinhoven et al., 2011).

The rate of personality disorders in the study sample was 49% at baseline, compared to the range of 31 to 52% in the adult studies. None of the adult studies measuring trait neuroticism used the same instrument and scoring as the study sample, so a comparison of the level of severity with the study sample is not possible.

Therefore, to summarise the preceding paragraphs, the study sample does not have higher rates of, or severity of variables that have previously been found to be predictive of the symptomatic course of MDD.

9.2.1.3 Methodological factors and the protracted MDEs of the study sample
Methodological contributions to the relatively long mean and median durations of the index MDE in the current study sample might arise from the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987), the instrument used to measure episode length.

The LIFE defines the point of recovery as the time at which the individual being evaluated has had a period of at least two months in which they have been experiencing no MDE symptoms or one of two MDE symptoms to a mild degree.

In the assessments undertaken in the study, prior to trying to identify this point, each participant was asked about life events that could help orient them to the follow-up period, and these events were plotted on the LIFE assessment measure. Also, each participant was informed of the symptoms of an MDE that they had reported at study baseline.

The time since the baseline assessments were performed ranged between 5 and 13 years. Despite the attempts made to orient the study participants to the follow-up period and the symptoms that they had experienced, a precise recall at such a remote time is unlikely.

It might be expected that a point at which a participant was experiencing no symptoms would be clearer in their memory, with the nature of the recollection possibly being a general sense that life was going well at that time, which might equate with a functional recovery.

If this were the case, the assessment might not have picked up an earlier point at which there may have been one or two mild symptoms when recovery would have already been reached according to the instrument definition. A study of an adult with MDD using the LIFE described a trajectory of a progressive reduction of symptoms over time (1992).

The index MDE lengths reported in longitudinally-followed adult MDD samples support this potential association of the measured episode length with the length of the recall period of a study. Of the studies of adult samples reviewed in this thesis, those reporting the longest episode durations were those with single follow-up assessments at 3.5 to 7.5 years (Hoencamp et al., 2001) and 5 years (Bukh, JD et al., 2016). These studies reported a median time to recovery of 24 months and a median episode duration of 20 months respectively. While other studies had recall periods of up to 3.5 years, this followed earlier assessments at 6 to 12 month intervals (Kennedy et al., 2003; Penninx et al., 2011). The next closest lengths of index MDE reported of the other four studies reviewed were mean times to recovery of 12 months in these two studies. In the child and adolescent studies reviewed, the longest recall period was two years, with all others in the 3 to 12 month range.

Over the follow-up period, many participants experienced disorders other than MDD, and these might have influenced the assessment of the point of recovery by the LIFE. If indeed it were a time when the participant had general sense that life was going well or functional recovery that the assessment was classifying as the point of recovery, it might have been disorders other than MDE that would have meant that someone would not have had such a general sense, hence causing a protraction of the true MDE length.

Another means by which other mental state disorders could lead to a potentially erroneous protraction of the estimated MDE length is by having symptoms common to both disorders attributed to the MDE. Relevant symptoms of the diagnostic criteria for

an MDE are poor concentration, low energy, and sleep disturbance. These may either be among specific diagnostic criteria for other disorders or not unusual consequences of other disorders.

9.2.2 Long-term symptomatic course

The cumulative duration of time spent in an MDE by the study participants was measured in order to assess the impact of the disorder over the entire follow-up period. On average the index MDE contributed 70% of this time, such that the shorter the follow-up period, the greater proportion of time in an MDE. The mean proportion of 42% of the follow-up period in an MDE indicates a significant average burden of illness. The same potential contributors to the length of the index MDE described above might also apply to the cumulative duration. Either developmental factors might have led to a longer cumulative duration or methodological issues related to the LIFE might have had an impact.

Among the longitudinal studies reviewed in this thesis, only one study (of adults) reported the cumulative duration in an MDE, also assessing episode duration with the LIFE (Judd et al., 1998). Over a 2 to 12 year follow-up, its participants spent a mean of 15% of weeks at or above full symptomatic criteria for an MDE threshold, and a mean of 27% at the Minor Depressive Disorder threshold. These two thresholds correlate with what was defined as being in an MDE in this study, meaning at a sum of 42% the mean cumulative periods in the two studies are equal.

The median duration of index episode in this adult sample (4.4 months) is much less than that of the current study sample. Therefore the time in an MDE to reach an equivalent cumulative duration must come from recurrences. In the study sample among those who recovered from the index episode, 51% had one recurrence, 26% had two and 11% had three. This compares with rates of 64%, 36% and 20% for the adult sample (Solomon et al., 2000), indicating that more frequent recurrences might account for the equivalence of the cumulative MDE duration of this study with that of the current study sample.

Another feature of the long-term course of the study sample was the frequent co-occurrence of mental state disorders other than MDD over the follow-up period. The prevalence rates of the most common disorders, anxiety and substance use disorders, at 54% and 55% respectively, are well above rates for those of a similar age in the general Australian population.

The lifetime prevalence for anxiety disorders in 25-34 year olds is 21% (McEvoy, Grove, & Slade, 2011), while that for cannabis or alcohol use disorders, the most commonly used substances in the study sample, is 32.5% for 25-44 year olds (Butterworth, Slade, & Degenhardt, 2014; Teesson et al., 2010). Both behavioural disorders (18.3%) and eating disorders (19.5%) were also common over follow-up. The prevalence rates of other mental state disorders in the study sample parallel, though at a higher level, the rates measured in longitudinally-followed adolescent MDD samples, which had prevalence rates of anxiety disorders ranging from 19 to 38.5% (Rao et al., 1995; Weissman et al., 1999) and substance use disorders from 26 to 45% (Fombonne et al., 2001a; Hamilton & Bridge, 1999) over 5 to 21 years of follow-up. Of the three of these studies with control groups, one found a significantly higher rate of anxiety disorders among its participants with MDD (Rao et al., 1995), another a significantly higher rate of marijuana use disorders in its patient group (Hamilton & Bridge, 1999).

The study findings demonstrate a potentially elevated risk compared to the general population for experiencing other mental state disorders in youth with MDD over the medium term. The presence of an association between these disorders is suggested by the rates of comorbidity at baseline. The follow-up findings show that those without a baseline comorbidity might also go on to develop other mental state disorders.

The trajectory of personality pathology is also an important part of the context of the MDD course of the current study participants. Comparing baseline and follow-up assessments revealed a differentiation between the disorder clusters. While the Cluster B item mean, incorporating a significant change in the Borderline personality disorder score, significantly fell, the mean item scores for Clusters A and C were stable.

This Borderline personality disorder score trajectory extends the findings of an earlier 2-year follow-up study with which this sample shares some participants (Chanen et al., 2004). In this shorter-time frame there had not been significant change in the Borderline personality disorder score.

9.3 Course of functioning

In summary, a key finding at follow-up was that overall functioning was impaired, with a wide range of functioning, particularly for women, underlying this overall result.

Average yearly ratings of functioning over the follow-up period were indicative of persistent impairment, and this impairment was most marked in the domain of interpersonal relationships.

9.3.1 Functioning at follow-up

The current study sample's functioning at follow-up was assessed by general indices of functioning including educational attainment and socio-economic status, and by the self-report scale, the Social Adjustment Scale Self-Report (SAS-SR) (Weissman & Bothwell, 1976a). Both of these methods indicated a lower average level of functioning of the study participants compared with the general population.

Secondary school completion rates of 62% for the study sample compare to a population rate of 76% (*Australian Social Trends March 2011* 2011) and post-secondary education rates of 50% in the study sample compare to 67% in the general population (National Centre for Vocational Education Research n.d.).

Overall scores on the SAS-SR (higher scores indicate poorer functioning) were close to one standard deviation above population norms (Weissman, Myrna M et al., 1978). The scale authors define the scoring range in which the mean for the sample fell as "slightly atypical" and as indicating "possible concern" (Weissman, MM and MHS staff 1999).

It is important to note that while female participants rated across the scoring range, the scores of male participants were more sharply skewed towards lower functioning.

The finding of worse functioning than the general population at a medium-term follow-up point mirrors the results of two follow-up studies of adolescents at a mean of 7 (Rao et al., 1995) and 11 years (Weissman et al., 1999).

These studies collectively (both had non-psychiatric controls) reported findings of worse overall and vocational functioning and poorer functioning in friendship, parental and family roles. Global and friendship functioning were the two areas that were rated as poorer than the controls in both studies, raising the possibility of a specificity for difficulties in friendships for young people with MDD.

Such a possibility is supported by the findings of this study. Although the SAS-SR Family role functioning was the relationship domain that was most divergent from that of a non-clinical sample (Weissman, Myrna M et al., 1978), the significance of this is uncertain due to the method of scoring used in the study sample (see 8.7.2). The Social and leisure role which assesses functioning in friendships, was the next most impaired, equally so for both genders.

9.3.2 Longitudinal functioning

The average functioning for the sample as a whole over the follow-up period was at a mild impairment level, as defined by the authors of the assessment scale, the LIFE-RIFT (Judd et al., 2008). Almost one third (32%) of the sample was assessed as having average functioning at a mild to moderate impairment level.

The use of the LIFE-RIFT in a range of psychiatric and non-psychiatric populations provides a context for the scores of the study sample. The mean overall rating of 11.1, with higher scores indicating higher impairment, compares with ratings of 6.2 in a sample experiencing bereavement without a psychiatric disorder (Marques et al., 2013), and 6.5 in a sample of children with remitted Obsessive-Compulsive Disorder followed into adulthood (Palermo et al., 2011). In studies assessing adults experiencing an acute MDE, overall scores were between 13.6 and 13.9 (Berk et al., 2014; Judd et al., 2008).

An argument could be made that the threshold set for “mild” impairment by the LIFE-RIFT, particularly in the Interpersonal Relations and Recreation domains is too high. The text for the mild impairment rating for family relationships includes the description “often argues with this family member and takes a long time to resolve arguments”. This is representative of the level of impairment described for this rating. Therefore, it might be that the rating level of the instrument understates the degree of impairment that its text describes.

It was, in fact, the Interpersonal Relations domain that was the most impaired in the study sample. A methodological issue needs consideration. This domain is one of two (the other Vocational) that contains multiple sub-domains, of spouse, children, other relatives and friends, with the assessor instructed to score the sub-domain that is most impaired. Consequently, there is the possibility that the sub-domain that is selected for the score of the domain is an isolated area of poor functioning that is not representative of the domain as a whole.

Difficulties with interpersonal functioning are consistent with the findings of the SAS-SR at follow-up, and again raise the question of whether this is a specific area of persistent dysfunction for youth with MDD.

Unfortunately, the studies in adults with MDD that used the LIFE-RIFT did not report their findings for the Interpersonal Relations domain (Berk et al., 2014; Judd et al., 2008; Solomon et al., 2008, 2004). Of two studies in non-MDD samples that did report scores for this domain, one, the previously mentioned study of Obsessive-Compulsive

Disorder found it to be the most impaired (Palermo et al., 2011), the other of a sample with post-partum psychosis, found it to be the least impaired (Burgerhout et al., 2017).

9.4 Predictors

The following discussion of predictors concerns their association with the symptomatic outcomes of duration of episode and time to recovery of the index MDE and of the cumulative proportion of time spent in an MDE over the follow-up period. Only one variable was shown to be associated MDE recurrence.

Functioning at follow-up, (measured by the SAS-SR) and of longitudinal functioning, assessed with the LIFE-RIFT are also explored.

9.4.1 Hypothesised predictors

9.4.1.1 Dimensional Borderline Personality Disorder pathology

9.4.1.1.1 Medium-term severity of symptomatic course of MDD

The dimensional measure of Borderline personality disorder (BPD) features assessed at baseline, the SCID-II (First, MB et al., 1997) BPD mean item score was associated with a longer time to recovery of the index Major Depressive Episode in univariate analysis. The cumulative period in an MDE over the follow-up period was not found to be associated with the baseline BPD mean item score.

In the multiple predictor analysis for predictors of time to recovery for the index MDE, the baseline BPD mean item score was the first variable eliminated. This is likely to reflect the relatively low strength of its correlation with the outcome and its intercorrelation with the other variables entered into the model.

It is as yet uncommon for studies of clinical samples of people with MDD to investigate the longitudinal influence BPD as a dimensional construct. One small, short-term study has though demonstrated such an influence. In this small treatment sample (n=15) of 12-18 year olds with MDD, meeting the diagnostic threshold for BPD was shown to be associated with less reduction in depressive symptoms at 19 weeks compared to those with sub-threshold BPD pathology (Ramleth, Groholt, Diep, Walby, & Mehlum, 2017).

Two community-based studies of young people have found an association of BPD traits (Lewinsohn et al., 2000) and the related variables, the Cluster B score (Hart et al., 2001) and construct of Interpersonal hypersensitivity (Craighead et al., 2011; Sheets et al., 2014) with the course of MDD. The outcome of interest in these studies was recurrence.

In the current study, dimensional BPD pathology was not associated with recurrence. However, It is likely the high 76% rate of recurrence of the current study, contributed to by its length, mitigated against a similar finding in this sample.

This possibility is underlined by the fact that, in contrast to the other outcomes of the study, there was only one variable, the severity of the baseline MDE, that had a significant univariate association with recurrence.

As reported in 3.4.6, clinically-based longitudinal studies of adults with MDD have not investigated dimensional BPD pathology. Most often, they have considered personality pathology in terms of a categorical diagnosis of any personality disorder, less commonly in DSM-classified clusters, and rarely as individual disorders.

The two studies that did analyse the effect of Borderline PD as an individual disorder did find an effect on MDD course. One found an association with a longer duration of the index MDE and shorter time to recurrence (Grilo et al., 2005, 2010), the other a greater risk of relapse (Alnaes & Torgersen, 1997).

The lack of association of the baseline BPD item mean with the longer-term outcome of the cumulative period in an MDE over follow-up might have been contributed to by its significant attenuation over the follow-up period.

9.4.1.1.2 Medium-term functional outcome

In univariate analyses, the baseline BPD mean item score was associated with poorer overall functioning over the course of the follow-up period for the study sample.

The baseline BPD mean item score was not however associated with functioning assessed at the point of follow-up by the SAS-SR (Weissman & Bothwell, 1976a).

The baseline BPD mean item score was not retained as a significant predictor in the multiple predictor models of any outcomes. It was in fact the first or second variable eliminated in the stepwise regressions in which it was entered.

The absence of associations of the baseline BPD item mean with the more distal functional outcome of the SAS-SR at follow-up might have been contributed to by its significant attenuation over the period of follow-up.

A study in adults with MDD and co-morbid full-threshold BPD found a remission in PD-status to be associated with improvement in some, but not all functional domains at a 2-year follow-up (Markowitz et al., 2007). This indicates that the functional impacts of a personality disorder are not necessarily enduring should people experience a reduction in their quantum of personality pathology.

The study data also showed a greater impact of BPD as a categorical disorder. A diagnosis of BPD had stronger (but also not statistically significant) associations with these more distal outcomes compared to the BPD item mean. The SAS-SR overall mean had a small correlation of 0.12 with a diagnosis of BPD, while its correlation was only 0.3 for the BPD item mean.

It might be that the enduring effect of BPD does not rise evenly with its severity, but rather there is a more pronounced effect at the higher level of severity represented by the disorder diagnostic threshold.

9.4.1.2 Neuroticism

9.4.1.2.1 Medium-term severity of symptomatic course of MDD

It was found that baseline neuroticism, measured by the NEO-PI-R was predictive of the time to recovery and duration of the index Major Depressive Episode. However, it was not retained as a significant predictor in the multiple predictor models of these outcomes. Neuroticism was neither predictive of the cumulative time spent in an MDE over the follow-up period

Previous studies in adult MDD samples have similarly demonstrated an association of neuroticism with the duration of an index MDE or MDE chronicity that is not retained in a multiple predictor analysis (Boschloo et al., 2014; Melartin et al., 2004; Spinhoven et al., 2011). Each of these studies found that the severity of the MDE was a significant predictor in their multiple predictor models, while one of the studies also found anxiety severity to be predictive of the duration of index MDE (Melartin et al., 2004).

However, it does not seem that a relationship between baseline neuroticism and either MDE severity or anxiety explains the lack of an independent association of neuroticism with the index MDE length in this study. MDE severity did not reach the $p < 0.10$ significance threshold for univariate correlation, and therefore did not enter the multiple predictor analysis for this outcome. It had only a small ($r = 0.15$) correlation with having an anxiety disorder at baseline, and it is unlikely that an association of such a strength was solely responsible for its elimination from the regression model.

Neuroticism did have significant correlations ($r = 0.29$ to 0.4) with four other variables that did enter the multivariate analysis: the BPD mean item score, any personality disorder, conscientiousness, and the Cluster C mean. It might be that a relationship with a broad range of other predictors meant that neuroticism accounted for little unique variance of the outcome.

It might be that a lack of stability of the baseline neuroticism score contributed to lack of significant relationships with the longer-term outcome of cumulative time in an MDE. As mentioned in 8.4.3, there was a significant attenuation of the mean neuroticism score over the follow-up period, and a low rank-order stability of ($r=0.31$). This rank-order stability is less than has been observed in general population samples of youth, though followed up over somewhat shorter periods. These results include a rank-order stability of 0.65 in youth between ages 19 to 22 (Deventer et al., 2019), and 0.59 for the related construct of negative emotionality between ages 18 and 26 (Robins et al., 2002). A contributor to the the instability of the neuroticism score might be the “mood-state distortion” (Naragon-Gainey et al. 2013), by which the measured level is elevated during an acute MDE. It is possible that a stronger effect of neuroticism would be seen by testing the effect of its more stable trait-like components (Clarke, LA 1993; Vittengl, Clark, Thase, & Jarrett, 2014).

9.4.1.2.2 Medium-term functional outcome

Trait neuroticism, measured at baseline was not predictive of either of the functional outcomes of the study. Given that these outcomes, particularly the SAS-SR score, measured time periods quite distal from baseline, the comments in 9.4.1.1.1 above regarding the potential influence of the instability of the neuroticism score also apply here.

There are parallels of the findings of this study with those from the small pool of studies of adult MDD samples investigating personality and functioning.

The finding of non-association with SAS-SR replicates that of an 18 year follow-up study using an earlier version of this instrument (Duggan et al., 1990)

The strongest observed association of baseline neuroticism in this study was a negative (not statistically significant) relationship with the Interpersonal domain of the LIFE-RIFT ($r=-0.16$, $p=0.15$). An 18 month study in adults with MDD found a negative association of trait neuroticism with social support (Melartin et al., 2004).

It might therefore be that the neuroticism measured in an MDE has a somewhat enduring effect on relationship functioning.

9.4.1.3 Functioning

The baseline functioning of the sample, measured by the SOFAS tended to have the strongest univariate associations of any predictor variable with all the study outcomes. Because SOFAS might mediate the effect of the other variables it was introduced in a

second step of the multiple predictor analyses in order to not obscure which were the most influential of the other predictor variables.

This meant, however that the SOFAS was not exposed to the potential risk of being eliminated in the first stage of the backwards elimination. In the multiple predictor analyses, it was a significant predictor of all of the symptomatic outcomes, of the overall SAS-SR score at follow-up, and of the overall score of the LIFE-RIFT and all of its domains except Recreation.

In Chapter 8, the effect of SOFAS on the outcomes was quantified. This could be summarised as follows: a large difference in functioning at baseline was associated with a moderate change in symptomatic course, and with a small effect on functioning, both measured at follow-up and longitudinally. The effect on functioning is more significant in regard to longitudinal functioning as it is a yearly average.

This effect of functioning on symptomatic course aligns with the findings of the studies of adolescent and adult clinical MDD samples reviewed in this thesis. These found global functioning to be consistently predictive of index MDE persistence (Karlsson et al., 2008; Riihimäki et al., 2014; Sanford et al., 1995; Solomon et al., 2008; Viinamäki et al., 2006; Vitiello et al., 2011), and predictive in most studies of index MDE duration (Karlsson et al., 2008; Riihimäki et al., 2014).

One mechanism by which the functioning, indexed by the SOFAS, might act on the symptomatic course of MDD is through a lack of social support. A lack of social support was shown to be associated with the duration of an index MDE and with persistence in a number of studies of adult MDD samples reviewed in this thesis (Holma et al., 2008; Melartin et al., 2004; Riihimäki et al., 2014).

The level of baseline functioning might also be marker of illness severity. Although the measure of severity used in this study was not predictive of symptomatic course other than for recurrence (as detailed in Chapter 8) severity has been consistently found to be predictive of MDE duration and persistence in adult MDD samples.

A further explanation of the mechanism of the effect of functioning on the symptomatic course of MDD in the sample is mutual reinforcement. As mentioned earlier in this discussion, such re-inforcement could be cognitively mediated, with negative self-evaluation due to poor functioning contributing to such depressive symptoms as feelings of hopelessness and low mood.

Further evidence for the relationship between functional impairment and depressive symptom burden comes from the strong correlation ($r=0.61$, $p<0.001$) between the

proportion of time in an MDE in the follow-up period and the LIFE-RIFT overall score annual mean.

9.4.1.4 Anxiety disorder

The presence of a comorbid anxiety disorder was a significant predictor in the multiple predictor analyses for both the symptomatic and the functioning outcomes of this study. For the symptomatic outcomes, it was predictive of both measures of the index episode length and of the cumulative time in an MDE over the follow-up period.

These effects on symptomatic outcome can be argued to have reached the threshold of clinical significance, with for example the presence of an anxiety disorder adding 15 months the time to recovery from the index MDE.

Effects of an anxiety disorder on the index MDE length and its persistence were found in the adult MDD samples reviewed in this thesis, though with a more consistent effect seen for dimensionally-measured anxiety (Coryell et al., 2012; Keller et al., 1992; Melartin et al., 2004; Riihimäki et al., 2014; Spinhoven et al., 2011) than for categorical disorders (Bukh, JD et al., 2016; Spinhoven et al., 2011).

However, the effect of anxiety disorders observed in this study was not seen with three of the four adolescent MDD samples (Curry et al., 2011; Karlsson et al., 2008; Vitiello et al., 2011) that investigated the predictive role of anxiety disorders on the index MDE length. A potential explanation for this difference for two of these studies was that they were of short (12 and 18 months) duration and had high rates of persistence of the index MDE, 59% (Karlsson et al., 2008) and 39% (Vitiello et al., 2011) such that a limited number of participants could be included in the predictor analyses. Another possibility is that anxiety disorders have a more significant impact in the youth (and adult) age group.

In regard to the mechanism of the potential relationship between a baseline anxiety disorder and the more severe symptomatic course, one issue to consider is whether a history of an anxiety disorder might cause someone to recall a longer MDE than actually occurred. This might be due to the assessed length of the index MDE being erroneously extended to some degree by the length of the recall period, and anxiety disorders were associated with the length of the index MDE.

There are other potential mechanisms worthy of consideration. One such mechanism would be that the presence of a comorbid anxiety disorder is an indication of a high susceptibility to internalising disorders, a susceptibility that also results in more enduring depressive symptoms.

The presence of both anxiety and depressive symptoms can also be readily understood as mutually re-inforcing. For example the behavioural avoidance characteristic of anxiety disorders might reduce opportunities for the positive emotional experiences that might assist with the recovery from an MDE.

It has been remarked on above that the mean and median lengths of the index MDE in the study sample were two to five times those of adolescent samples, and the possibility was considered that this might be an overestimation contributed to by the length of the recall period.

If there is an overestimation, this would mean that any predictor of the length of the index MDE would be a predictor of this overestimation. One possible mechanism of an overestimation that was proposed above was that a participant might identify a point at which they were minimally affected by any disorder as being the time at which they recovered from their index MDE.

It could be therefore that the apparent prediction of the length of the index MDE by a comorbid anxiety disorder reflects anxiety disorders being more enduring than the MDE. In a study in an adult population with MDD where the lengths of episodes of both disorders were measured, anxiety disorders were in fact longer than MDEs (Penninx et al., 2011).

In the multiple predictor analyses of the functioning outcomes, a baseline anxiety disorder had a specific domain association with the Interpersonal Relations domain of the LIFE-RIFT. It's unstandardised beta of 0.45 in the final multiple predictor model indicates that an anxiety disorder at baseline independently added 0.45 to the annual mean of the Interpersonal Relations score. It is of course challenging to quantify the clinical significance of this effect, but it does represent 14% of the annual mean of this domain of 3.15, so one could propose that it is at least mildly influential.

The score of the Interpersonal Relations domain measures the degree of conflict or distance in relationships, and it might be that an anxiety disorder is more likely to cause distance.

9.4.1.5 Personality pathology other than BPD

Any personality disorder at baseline and the baseline Cluster A mean score had small but significant effects detected in the first step of the multiple predictor analyses of longitudinal functioning (LIFE-RIFT overall score, Recreation and Work domains) and of functioning at follow-up (SAS-SR overall and interpersonal means) respectively, with

the Cluster C mean score falling just short of a significant effect on the SAS-SR overall mean ($\beta=0.25$, $p=0.050$).

This intermediate model (not including SOFAS) of the multiple predictor analysis showed participants with a personality disorder diagnosis had a mean annual overall score on the LIFE-RIFT that was 1.2 points higher than the sample as a whole, while a one standard deviation increase of the Cluster A mean was associated with an SAS-SR overall score 0.12 points higher and an interpersonal score 0.14 points higher. Such results indicate the small but enduring influence of these personality pathology variables. These effects were no longer statistically significant after the addition of the baseline SOFAS to the models, with the exception of a baseline personality disorder remaining a significant predictor of poorer functioning on the Recreation domain of the LIFE-RIFT ($\beta =0.26$, $p=0.043$). The regression coefficients of all the variables were reduced on the addition of the baseline SOFAS, indicating a degree of mediation of their effects by baseline functioning.

None of the adolescent longitudinal MDD studies reviewed investigated the relationship of personality disorder variables to outcomes other than MDD recurrence, so comparison with the above results is not possible.

Of the adult studies reviewed, similar to the current study, one study found a univariate association of a baseline personality disorder with work and recreational functioning, as well as with relationship functioning, all measured on the LIFE-RIFT (Markowitz et al., 2007).

Given that interpersonal difficulties are common to many personality disorders, it was surprising that an association of a baseline personality disorder with the Interpersonal Relations domain of the LIFE-RIFT was not found in the study sample. A possible contributor to this might have been the LIFE-RIFT's method of selecting the worst functioning of the Interpersonal Relations subdomains as that domain's score. This might have had the effect of levelling the field if many participants had a problematic subdomain that was not representative of their overall relationship functioning. It was still possible however for a baseline anxiety disorder to emerge as a predictor of this domain.

The use of functioning outcomes different to those of the study sample make comparison with most adult MDD samples difficult. Two other studies generally did not find personality disorders predictive of their functioning outcomes in multivariate analyses (Table 3-4) (Holma et al., 2012; Riihimäki, Vuorilehto, & Isometsä, 2015) . An exception, which parallels the finding of an association with poor work functioning in

the study sample was a baseline Cluster B personality disorder predicting unemployment at 5 years (2015).

9.4.1.6 Previous MDE

Having had a previous MDE at baseline was associated with a range of functional outcomes in the multiple predictor analyses, with all of these associations no longer significant after the addition of the baseline SOFAS to the model, indicating at least a degree of mediation of its effect by its association with baseline functioning.

The effect of having had a previous MDE was found across multiple domains of the functioning outcomes of this study, it being associated with the SAS-SR interpersonal item mean and the LIFE-RIFT overall and Satisfaction domain annual means.

Analysis of predictors of functioning in the adolescent MDD samples reviewed was rare, with none investigating the role of a previous MDE. Comparison with adult studies might be of little relevance as it is possible that the effect of having a previous MDE in the study sample is specific to the fact that it occurred at an early age.

In the study sample, the mean age at which those with a previous MDE at baseline had their first episode was 13.3, while those without a previous MDE had a mean age of 15.2 for their onset.

It might be that the effect on baseline functioning of having a previous MDE is a “scar” from the earlier episode, and it may also be contributed to by other factors that were involved in the aetiology of the first episode.

There is evidence from two prospectively-followed community samples of factors that differentiate adolescents with an onset of MDD before the age of 15 to those with onset after 15 (Jaffee et al., 2002; Rice et al., 2018). Common to these studies were associations of the earlier onset of MDD with neurodevelopmental difficulties such as Attention Deficit Hyperactivity Disorder and impairments in language and social communication.

It is understandable that such disorders, which were not assessed in this study, might lead to enduring functional problems.

9.4.2 Predictors measured over the follow-up period

The three outcomes for which non-baseline predictors were investigated were the proportion of a follow-up time in an MDE, the mean overall item score of the SAS-SR and the LIFE-RIFT overall score annual mean. Univariate analyses demonstrated a

consistent effect of the burden of psychopathology experienced over the follow-up period on these outcomes.

This burden was measured in three ways; the cumulative number of mental state disorders, the degree of change in the SCID II mean item score, and of relevance to the functional outcomes, the proportion of the follow-up period in an MDE.

The effect of psychopathology experienced over a follow-up period on outcomes has not been commonly assessed in previous studies, though when it has, consistent negative effects have been shown on functional outcomes.

One adolescent clinical longitudinal study demonstrated an association of the occurrence of multiple co-morbid mental state disorders over its 3.5 year follow-up with scores on functional scales at follow-up (Peters et al., 2015). The OADP community sample, including participants with and without MDD at baseline found an association of disorders experienced between its baseline at age 14 to 18 and age 30 with a range of poor functional outcomes, including higher scores on the SAS-SR (Farmer, Kosty, Seeley, Olino, & Lewinsohn, 2013).

The OADP study authors identify the effect of the cumulative number of “unique” diagnosed disorders, defined as “disorder aggregation” (Angold, Costello, & Erkanli, 1999), as being an understudied phenomenon, of importance to treatment program development.

Relatively better functioning at follow-up associated with a decrease in personality pathology from baseline was also shown in one adult sample (Markowitz et al., 2007). A feature of the analysis of the variables measured at follow-up with the SAS-SR was a range of medium to strong correlations of the overall SAS-SR score with personality disorder and personality variables in particular, but also with current mental state disorders.

While one would expect some association with these variables given a purpose of the instrument is to measure functional impairment associated with psychopathology, it might be that the apparent high sensitivity to current psychopathology and personality made it difficult for baseline predictors to have an identifiable effect.

More broadly, the intercorrelations reflect the challenge of integrating personality traits and personality pathology in a conceptualisation of functioning (Ro & Clark, 2013), an issue that will be addressed further below.

9.5 Theoretical implications

A key contribution of this study is to provide information on the medium-term course of MDD in a clinical sample of youth, an age cohort that to this point had not had such longitudinal investigation. More broadly, the study adds to the currently small pool of knowledge on the predictors of outcome of MDD in young people.

Particular contributions that it makes to this pool are detailed assessments of the role of personality and personality pathology, and of the predictors of functioning both at follow-up and longitudinally. The predictors referred to in this section and those following, with the exception of the variables of the study hypotheses, are those found to be predictive in the multiple predictor analyses of this study.

As detailed above, the participants had, on average, protracted index MDEs, functional impairment at a mild level across the follow-up period and slightly atypical functioning at follow-up. Among the functioning domains measured over the follow-up period, relationship functioning was the most impaired.

Given that comparison data on other youth-age clinical cohorts with MDD are not available it is not possible to know how representative these outcomes are. They are of course subject to the methodological limitations described below.

A wide range of severity of the outcomes underlay the average scores, meaning that the predictor analyses were important to describe the sample more fully, and identify potential priorities for intervention.

The study found that both a dimensional measure of Borderline Personality Disorder (BPD) and trait neuroticism were associated with the length of the presenting MDE in this clinical sample of youth, but not independently of their relationships with other measures of psychopathology, personality and childhood adversity.

The dimensional measure of BPD was also associated with longitudinal functioning, but again not independently of other predictors.

Such findings regarding the effect of BPD measured dimensionally on the course of MDD have not been made previously in studies of either young people or adults. The finding for neuroticism, though new for samples of young people, extends those in adults demonstrating an association of trait neuroticism with MDE length and chronicity.

A number of the findings regarding the variables that emerged as significant predictors from the multiple predictor analyses parallel those consistently made in longitudinal studies of clinical samples of adults with MDD. These were the effects of a baseline

anxiety disorder and low baseline functioning on making the symptomatic course of MDD more severe.

Other findings paralleled those from the small evidence base of the predictors of functioning in clinical adult MDD samples. These were the effect of a baseline anxiety or personality disorder on longitudinal functioning, each of these found to be predictive of functioning at follow-up in one adult MDD sample.

The investigation of a wide range of predictors of functioning led to some findings not previously reported in the research literature that might be specific to the youth age group. These were the association of having had a previous MDE with both worse functioning longitudinally and at follow-up, and of baseline Cluster A personality disorder traits with worse functioning at follow-up.

In addition to the findings on baseline predictors of outcome, this study found a number of associations of longitudinally measured variables with the study outcomes. It demonstrated the inter-relationship of the longitudinal symptomatic and functional course of MDD, as there was a strong correlation ($r_s=0.59$) between the LIFE-RIFT overall mean and the cumulative proportion of time in an MDE.

The study also indicated the significant contribution made by the longitudinal occurrence of other mental state disorders to the longitudinal symptomatic and functional course of MDD, as the number of mental state disorders occurring over the follow-up period had medium strength correlations with the cumulative proportion of time in an MDE ($r_s=0.45$) and the LIFE-RIFT overall mean ($r=0.40$).

A final contribution to highlight is that the study demonstrated that persistent personality pathology affects functioning, as the amount of change in the mean SCID II item score had medium-strength correlations with both the LIFE-RIFT overall mean ($r=-0.33$), and with SAS-SR overall score ($r=-0.41$).

9.6 Practical implications

The information obtained from this study on the course of MDD, together with corroborating data from samples of other age groups can inform practices in the assessment and treatment of MDD in youth presenting to clinical services. These areas will be considered in turn.

9.6.1 Assessment

The study sample and previously studied adolescent samples demonstrate that young people who present to clinical services for treatment of an MDE are a population with a wide range of both psychopathology and functional difficulties.

These wide ranges presents the challenge of a wide potential scope of assessment.

Though providing important information to guide treatment, assessment processes run the risk of impairing engagement if they are too burdensome.

The question of how to optimise these assessment processes in youth with MDD is therefore worthy of detailed consideration, but such an exploration is beyond the scope of this thesis. Some further discussion of this broad topic will be in the Future Research section below, while in this section, the discussion will be narrowed to the assessment of those variables identified as being significant predictors of the course of MDD in the multiple predictor analyses of this study.

This study indicates an impact of anxiety and personality disorders, a previous MDE and baseline functioning on MDD course in youth. These variables are therefore nominated as priorities for assessment, though the practice of their assessment is not without challenge.

Most straightforward are anxiety disorders and a previous MDE, which can be assessed with the appropriate subsections of an instrument such as the SCID-5 (First, MB, Williams, JBW, Karg, RS, & Spitzer, RL, 2016). the updated version of the SCID I (First et al., 2001) that was used in this study.

A significant constraint on the assessment of personality pathology in clinical practice is the complexity of the diagnostic assessment dictated by the categorical system (Tyrer et al., 2015). A further issue is the application of the information collected, as there is a paucity of evidence for treatment of disorders other than borderline personality disorder (BPD) (Newton-Howes et al., 2015).

Therefore, an argument can be made to prioritise the assessment of borderline personality traits. The availability of validated screening instruments (Chanen et al., 2008; Henze et al., 2013) for BPD reduces assessment burden.

9.6.2 Treatment

It is as yet an assumption that addressing the predictors of poor outcome would improve the course of MDD, so this proposition should be evaluated. However, an argument could be made for intervention targeted at those predictors for which there is an established evidence base for treatment.

This would at least be expected to reduce the distress and impairment associated with these predictors. If there is not an evidence base for interventions for a particular predictor, this represents a potential path for future research.

The two predictors of a worse course of MDD identified in the multiple predictor analysis of this study for which an evidence base for treatment exists are anxiety and personality disorders. However, for both disorder types, the evidence for treatment that is designed to be specifically integrated with that for MDD is currently limited.

A transdiagnostic treatment protocol ("Unified Protocol"), designed to treat both anxiety and MDD has been tested against a wait-list control in an adolescent sample, with the finding of a significantly greater reduction of symptoms in the treatment group (Ehrenreich-May et al., 2016). However, a study of this treatment in an adult sample in which the comparison group received treatment targeted at a single disorder failed to show an advantage for the transdiagnostic protocol (Steele et al., 2018).

It might therefore be that the best model of treatment is to provide the evidence-based treatment for both disorders, whether in a sequential or parallel manner.

As yet, there are no completed trials of treatments designed to specifically treat both MDD and personality disorders. There is a trial in process in an adult sample (Kool et al., 2018) that has the aim to treat both disorder types concurrently with Schema Therapy (Young, JF, Klosko, JS, & Weishaar, ME, 2003) or Short-term Psychodynamic Supportive Psychotherapy.

It is not uncommon for studies of treatments for personality disorder to evaluate changes in depressive symptoms, or the less specific internalising symptoms. As with treatment studies of personality disorder in general, these are dominated by samples of individuals with borderline personality disorder.

In samples of adolescents with borderline personality traits or disorder, mentalization-based treatment {Rossouw 2012} and dialectical-behaviour therapy {Mehlum 2014}{Ramleth 2017} have reduced depressive symptoms. Two further studies of mentalization in this population demonstrated an improvement in internalising symptoms (Bo et al., 2017; Laurensen et al., 2018), as did a trial of cognitive-analytic therapy (Chanen et al., 2009).

A three-armed study of adults with borderline personality disorder demonstrated a reduction in depressive symptoms with treatment with dialectical behavioural, transference-focussed or dynamic supportive therapies (Clarkin, Levy, Lenzenweger, & Kernberg, 2007). Two studies of mentalisation therapy for adults with borderline

personality disorder found this treatment reduced depressive symptoms more than standard treatment (Bateman & Fonagy, 1999, 2009).

It would therefore be reasonable to offer one of these treatments to a youth with both an MDE and borderline personality disorder, with the caveat that information is lacking on whether one could expect symptomatic improvement equating to remission or recovery from the MDE.

The study findings of a consistent association of poorer baseline functioning with worse outcomes indicates a likely role for interventions directed at functioning in improving outcomes. Such interventions could include family therapy, school liaison, and vocational support.

Intervention should also take a longitudinal perspective for this group, given that episodes of MDE appear to be protracted, and frequently recurrent, and because other mental state disorders continue to occur over the transition to adulthood.

Components of such longitudinal consideration would be a young person having an understanding of the factors leading to the development of their MDE and its recovery. Knowledge of these might be able protect them from future episodes and also inform their response to any future episode. It is also important that young people be able to identify potential warning signs of a recurrence, and know where to seek appropriate professional support.

9.7 Strengths

Strength of this study can be found in the success of the recruitment processes, the comprehensive nature of its assessments, and the inclusivity of its analyses.

63% of eligible participants for the study were interviewed, and all but two of the ninety interviews were face to face. This 63% rate is in the mid-range of the 44% to 93% retention rate of longitudinal studies of clinical samples of adolescents with MDD

The study assessments included the performance of semi-structured interviews for mental state disorders (SCID-I) and personality disorders (SCID-II) at baseline and follow-up, with a comprehensive self-report measure of personality (NEO-PI) also administered at both these time-points. This ensured that diagnoses were made with a high degree of rigour.

A particular benefit of the detailed assessment of personality and personality pathology at the follow-up assessment was the demonstration of age-related normative changes. This revealed the attenuation of mean neuroticism and borderline personality trait

scores, which is likely to explain to some degree the lack of strength of the association of the baseline scores of these variables with the study outcomes.

The multiple predictor analyses in this study included a broad range of potential predictors of the outcomes. Therefore, it should be possible to have a high degree of confidence that those predictors found to have significant associations with the study outcomes did have genuine associations.

Included in the study analysis was the testing of associations of psychopathology occurring over the follow-up period with the study outcomes. It was the case that the regression models of the baseline variables explained a small amount of the variance of the outcomes, with R^2 for these models ranging from 0.9 to 0.28. The significant univariate associations of psychopathology occurring over the follow-up period with the study outcomes reveal a likely role in explaining a proportion of the remaining variance.

9.8 Limitations

A factor that might limit the generalisability of the outcomes of this sample to other clinical samples of youth with MDD is the level of borderline personality pathology, and the overall rate of personality disorder in the sample.

The rate of borderline personality disorder (BPD) at 31% is higher than that reported in samples of adolescent outpatients with MDD, in which the highest rate was 20% (Marton, P et al., 1989). However, the overall rate of personality disorder in the study sample of 49% does not exceed that of the other samples. Rather, it is towards the upper end of the rates of the adolescent samples, which ranged from 30% to 65% (Karlsson et al., 2006; Marton, P et al., 1989; Ramirez et al., 2015).

The size of the univariate correlations that the mean borderline personality item score had with time to recovery of the index MDE ($r_s=0.25$), and longitudinal functioning ($r_s=0.24$) indicate only a small impact on the study outcomes.

The participants in the study had lower levels of psychopathology than the eligible members of the samples from which they were drawn who did not participate.

Specifically, they had lower rates of comorbid mental state disorders (57% vs. 77%), and a lower mean BPD item score (1.75 vs. 1.99), differences that were statistically significant at a $p<0.05$ level.

Such differences are consistent with those found at an earlier stage of a follow-up study that included members of this study's sample (Allott, Chanen, & Yuen, 2006). As higher levels of psychopathology were associated with worse outcomes in the study, it

is likely therefore that the results represent an underestimate of the severity of MDD course of the entire potential sample.

In regard to methodological limitations of the study, comment has already been made in 9.2 above regarding the long recall period of the study, its possible impact on the estimation of index MDE lengths and the potential mechanisms behind any overestimation.

Reference has also been made to the scores of the LIFE-RIFT Interpersonal Relations and Vocational domains potentially not reflecting overall functioning in these domains, due to the instruction to assessors to choose the worst functioning of sub-sections of these domains.

A more general limitation of this study is that consumers were not involved in its design. Specifically, consumers would have insights into how to most accurately explore the trajectory of symptoms over a long recall period. It would also have been helpful to hear consumers' opinions on what constitutes a reasonable burden of assessment.

9.9 Future research

9.9.1 Direct extension

The findings of this study of a protracted index MDE, and of a high symptomatic burden of MDE over the medium-term in a clinical sample of youth with MDD should be investigated again with a protocol that addresses the possible methodological shortcoming of this project of a prolonged recall period.

This would mean multiple assessments at shorter intervals. It would also be possible to assess the effect of a longer recall period on participants' description of their symptomatic course by repeating the assessment of earlier, previously assessed periods at later assessments.

The study has shown an influence of both mental state disorders and personality pathology on the course of MDD. An extension of these findings would be to assess the predictive capacity of the structure of psychopathology that has been defined in the recently-developed classificatory frameworks.

Of particular relevance, given the study findings, would be an assessment of the internalising dimension (that includes both depressive and anxiety disorders), and the dimensional representation of personality pathology described in Section III of the DSM-V (American Psychiatric Association 2013). As substance use disorders were

common over the follow-up period, it would be appropriate to also assess for the externalising dimension.

It was evident from this study that baseline functioning had an important influence on the course of MDD. Unfortunately the measure used, the SOFAS is a single item measure. The use of more detailed instrument would have the capacity to provide information on which domains are particularly important which could guide future intervention. A comprehensive empirically-developed conceptualisation of functioning has been proposed (Ro & Clark, 2009, 2013), but as yet there is no clinically-applicable method of assessing this.

9.9.2 Broader research

An area of broader research indicated by this study would be the development of clinically-viable yet comprehensive assessment processes for young people with complex presentations. It is apparent that a wide range of psychopathology and functional impairment has an impact on the course of MDD in youth. However it would be a challenge to assess every element of these areas in detail, particularly while attempting to engage a young person in treatment.

Therefore the aim of such research would be to determine the most efficient method of assessment. Particular focus would be on method of collecting information, finding the optimal combination of interview of the young person or informant, and self-report and structured measures.

As mentioned in 5.2, the understanding of the process of recovery from an MDE remains limited. This study did not attempt to explore this processes, though the implicit assumption is that the predictors of MDD course play a role in it. A further assumption is that it is change in the nominated targets of treatment that mediate the process. However, evidence at least for cognitive-behavioural therapy, the psychotherapy with the strongest evidence base, is limited and not compelling (Cuijpers, Reijnders, & Huibers, 2019; Weersing, Jeffreys, Do, Schwartz, & Bolano, 2017). It would therefore be of potential benefit for the development of more effective treatment to gain a more detailed understanding of the steps that lead to recovery. Related to the complexity of the assessment of clinical samples of youth with MDD is the complexity of any treatment that aims to address the many psychopathological and functional components of its presentation. The development of treatments that are able to integrate coverage of these many facets that impact on a young person's outcome should also be the focus of the broad research agenda.

9.9.3 Conclusion

This study has recorded, from its clinical sample of youth with MDD, a medium-term course characterised by a protracted index episode and a high rate of recurrence, amounting to a significant symptomatic burden. It has demonstrated persisting functional impairment for this sample, particular in interpersonal relationships.

Underlying these results for the sample as a whole is a heterogeneity of outcomes, and this study has found that anxiety disorders, pathological personality features, and poor functioning at the time of presentation are more common in those with less favourable outcomes.

The longitudinal evaluation of the sample showed that MDD symptoms and functioning continue to have a negative influence on each other over the medium-term. It also recorded the frequent longitudinal occurrence of other mental state disorders that were associated with the symptomatic and functional burden of MDD.

As this is the first longitudinal study in a clinical sample of youth with MDD, it is important for the findings to be replicated in order to evaluate their generalisability. Such a replication would be enhanced by more frequent assessments over the follow-up period, and by using instruments to assess psychopathology that are informed by recent developments in classification.

It would be hoped that the study findings can inform the development of more systematic assessment processes and more integrated treatment programs that will lead to improved outcomes for young people with MDD.

Appendix A: Supplementary Tables

Prospective studies of community samples of adolescents with MDD

	Sample population	Number in sample with MDD	Age at baseline	Assessment points	Outcomes	Predictors of outcomes
<u>Birth cohort</u>						
Christchurch Health and Development Study (Fergusson & Woodward 2002, 2007)	All births in geographical area of New Zealand over 4 months in 1977 n=1265	14-16yo, incidence n=124 16-21yo incidence n=346	0	23 occasions until 35 yo	1.Adult MDD recurrence 2.Functional outcome	
Dunedin Multidisciplinary Health and Development Study (Milne et al. 2009)	All births in geographical area of New Zealand from 1972-1973 n=1037	18-32yo incidence n=351	0	11 occasions from 3 to 32yo	1.Adult MDD recurrence 2.Functional impairment	1. Family history of MDD (males) 2. Family history of MDD (trend, p=0.10)
<u>Adolescent cohort</u>						
OADP (Lewinsohn et al. 2000)	High school students (randomly selected) n=1709	T1.Baseline n=24 with current MDE, 261 with past. T1-2 (12 mths) 59 new onset cases	14-18 (mean 16.6)	12 months Age 24 Age 30	1.MDD recurrence age 19-23 2.Functioning	1. Family history of recurrent MDD Borderline personality disorder (dimensional measure) Conflict with parents Female gender 2.MDD recurrence
University of Colorado (Hart et al. 01, Craighead et al. 2011, Sheets et al. 2014)	University undergraduates	Study 1 (s1) n=65, all with lifetime history of MDD Study 2 (s2) n=150 all with lifetime history of MDD	s1. Mean age =19 s2. Age 18-21	Both 18 months	MDD recurrence	s1. Overall score on IPDE Cluster B score of IPDE s2. Interpersonal hypersensitivity Antisocial conduct Social anxiety
EDSP (Stein et al. 2001, Friis et al. 2002)	Community sample (n=3021)	Baseline n=282 with lifetime hx. n=623 by 33yo	14-24	3 follow-up points over 10yrs	MDD recurrence	Social phobia
Bremen (Essau et al. 2007)	High-school students n=1035 (522 at follow-up)	90 with current MDE at baseline	12-17	15 months	MDD persistence	Life events
AADS (Rohde et al. 2009)	High school n=496 females	Baseline, n=37 with history of MDE, 88 had MDE during study	12-20		MDE duration	
<u>Family studies</u>						

Minnesota Twin (Wilson et al. 2014b)	Same-sex twins born between 1971 and 1985 in geographical area of USA Total n=2764	MDD onset prior to age 17, n=332 MDD onset after age 17, n=499	11 or 17	6 occasions between 11 and 29yo	1.MDD recurrence 2.Functioning	1. Family history of MDD Comorbid anxiety disorder Positive Emotionality (low) Quality of romantic relationship 2. MDD recurrence

Prospective studies of clinical samples of adults with MDD

		Sample population	Sample size at baseline (final follow-up)	Age at baseline (mean)	Assessment points	Outcomes	Predictor variables of key interest
1	Danish Psychiatric Central Research Register (DPCRR)	Denmark Inpatient and outpatient First episode	301	18-70	5yrs	Chronicity -Non-remission in 5 years Recurrence	Personality Personality Disorder
2,3	Netherlands Study of Depression and Anxiety (NESDA)	Netherlands Community, Primary care and specialist	1115 (767) (*current defined as MDD in past 6 months)	18-65 (40.8)	2yrs, 4yrs	Time to remission Chronicity -2 yr: Categories developed by LGCA -4 yr: >24months in MDE Recurrence Functioning -WHO DAS II at 2yrs	Personality Anxious distress Life events
4,5	Vantaa Primary Care	Finland Primary care	137 (102)	20-69 (45.6)	18mths, 5yrs	Time to remission Chronicity -Time in MDE Recurrence	Personality Disorder Medical illness
6	Kuenher & Huffziger	Germany Inpatients	68	18-70 (45.2)	6, 42, 66mths	Duration of episode Time to relapse/recurrence Functioning: SOFAS	Cognitive traits -Action vs. state orientation Social support
7,8	Vantaa	Finland Inpatient and outpatient	269 (198)	20-59 (39.3)	18mths, 5yrs	Time to remission Chronicity -Time spent in MDE in 5 yrs Recurrence Functioning -SOFAS, SAS-R -DSP at 5yrs	Personality Personality Disorder Social support
9.	KUDEP	Finland Outpatients	137 (109)		6,12,18 mths, 2 yrs	Chronicity -Persistence at 2yr Life satisfaction	Personality Disorder Alexithymia
10.	Kronmuller et al.	Germany Inpatient	50	25-63 (44.7)	1,2,10yrs	Recurrence	Family relationships
11-17	Collaborative Depression Study	USA	476 (215)	>18 (39.5)	2,5,10,12,15,20 yrs	Time to recovery Chronicity -2 yr non-recovery	Comorbid Dysthymic Disorder

		Inpatient and outpatient				-12yr weekly symptom ratings -Time in MDD over 16.7yrs Recurrence Functioning -LIFE-RIFT	Anxiety dimensions
18, 19	Cambridge	England Inpatient and outpatient	70 (65)	18-65 (40.9)	3 mthly to 15-30mths, 8-11yrs	Time to recovery Relapse	Social support Life events
20.	GLADS	Japan Inpatient and outpatient First treated MDE	95 (91)	44.6	6 mthly to 2 yrs, then annually to 6 yrs	Time to recovery Relapse Functioning -SAS-SR	
21.	Ilardi, Craighead & Evans	USA Inpatients	50	18-65 (38.3)	33-84 mths	Relapse	Personality disorder Cognitive style
22.	Maj et al.	Italy Inpatient and outpatient	72	27-55 (42.3)	66 mths	Recurrence	Dysthymic disorder
23.	Collaborative Longitudinal Personality Study	USA Inpatient and Outpatient	MDD group 104 PD group 421	18-45	2,4yrs	Time to remission Chronicity -Non-recovery at 2yrs Functioning (GAF)	Personality Personality Disorder

Appendix B: Assessment materials

Outcome assessment instruments

1. Scoring document for Longitudinal Interval Follow-Up Evaluation (LIFE), and Longitudinal Interval Follow-Up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) (developed by student researcher)
2. Longitudinal Interval Follow-Up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 1999)
3. Social Adjustment Scale-Self Report (SAS-SR) (Weissman, Myrna 1999)

Selected baseline assessment measures

1. Social and Occupational Functioning Assessment Scale (Spitzer et al., 2000)

LIFE time-line for MDD

[illegible][illegible]

LONGITUDINAL INTERVAL FOLLOW-UP EVALUATION-RANGE OF IMPAIRED FUNCTIONING TOOL (LIFE-RIFT)

THE LIFE-RIFT

Work

(1 a) Employment: _____

Which of the following categories best characterizes the degree to which the patient's current (past week) work activities have been impaired as a result of psychopathology?

- 0 = Not applicable. Did not work during the past week, for reasons other than psychopathology.
- 1 = No impairment - high level. Worked as much as someone in his social situation would be expected to work, and worked at a high level.
- 2 = No impairment - satisfactory level. Worked as much as someone in his social situation would be expected to work, and worked at a satisfactory level.
- 3 = Mild impairment. Worked somewhat less than someone in his social situation would be expected to work and/or had mild difficulties in carrying out work activities.
- 4 = Moderate impairment. Has missed a lot of work and/or has had considerable difficulties in carrying out work activities.
- 5 = Severe impairment. Has missed a great deal of work when someone in his social situation would have been expected to work and/or has been virtually unable to carry out his work activities when he did work.
- 6 = No information.

(1 b) Household: _____

Which of the following categories best characterizes the degree to which the patient's current (past week) household work has been impaired as a result of psychopathology?

- 0 = Not applicable. Did not carry out household duties during the past week for reasons other than psychopathology.
- 1 = No impairment - high level. Has carried out housework most of the time that would be expected, and worked at a high level.
- 2 = No impairment - satisfactory level. Has carried out housework most of the time that would be expected, and worked at a satisfactory level.
- 3 = Mild impairment. Worked somewhat less than expected and/or had mild difficulties in carrying out housework.
- 4 = Moderate impairment. Has missed a lot of housework when expected and/or has had considerable difficulties in carrying out house work.
- 5 = Severe impairment. Has missed a great deal of housework when expected to work and/or has been virtually unable to carry out housework when he attempts it.
- 6 = No information.

(1 c) Student: _____

Which of the following categories best characterizes the degree to which the patient's current school work has been impaired as a result of psychopathology?

- 0 = Not applicable. Because not currently enrolled in a student program for reasons other than psychopathology.
- 1 = No impairment - high level. Worked as much as would be expected if not symptomatic and got high grades.
- 2 = No impairment - satisfactory level. Worked as much as would be expected if not symptomatic and got satisfactory grades.
- 3 = Mild impairment. Worked somewhat less and/or got grades somewhat below expected if not symptomatic.
- 4 = Moderate impairment. Missed a lot of school work and/or got grades consistently below expected.
- 5 = Severe impairment. Missed most of school work and/or dropped out of school or got grades far below those expected.
- 6 = No information.

(1) Work (maximum of 1 a, 1 b and 1 c): _____

Interpersonal relations

Which of the following best characterizes the patient's level of interpersonal relationships with his family currently (past month)? [Provide separate ratings for spouse (2a), children (2b) and other relatives (2c).]

(2a) Interpersonal relations with spouse: _____

(2b) Interpersonal relations with children: _____

(2c) Interpersonal relations with other relatives: _____

- 0 = Not applicable because does not have relatives in this category.
- 1 = Very good. Experiences very good relationships with this/these family member(s), with only transient friction which is rapidly resolved. Feels only very minor or occasional need to improve quality of relationship, which is usually close and satisfying.
- 2 = Good. Argues occasionally, but arguments usually resolve satisfactorily within a short time. May occasionally prefer not to be with them because of dissatisfaction with them or be actively working with them to improve relationship.
- 3 = Fair. Often argues with this (these) family member(s) and takes a long time to resolve arguments. May withdraw from this person (these people) due to dissatisfaction. Often thinks that relationship needs to be either more harmonious or closer emotionally even when no conflict is present. For those relatives not living with the subject, contacts with them by choice are less frequent than feasible or rarely enjoyed very much when made.
- 4 = Poor. Regularly argues with this (these) family member(s) and such arguments are rarely ever resolved satisfactorily. Regularly prefers to avoid contact with them and/or feels great deficit in emotional closeness. For those family members out of the household, subject avoids seeing them as much as possible and derives no pleasure from contact when made.
- 5 = Very poor. Either constantly argues with this (these) family member(s) or withdraws from them most of the time. Separated or divorced from spouse or children moved out of household or almost always hostile to them when in contact.
- 6 = Variable. Different levels for various members of this group, and would warrant a rating of good or better (2, 1) with at least 1 member of this group. (Rate as 2.)
- 7 = Variable. Different levels for various members of this group, and would not warrant a rating of good or better (2, 1) with any member of this group. (Rate as 4.)
- 8 = No information.

(2d) Interpersonal relations with friends:

Which of the following best characterizes the patient's interpersonal relationships with friends currently (past month)?

- 1 = Very good. Had several special friends that he saw regularly and frequently and was close to.
- 2 = Good. Had at least two special friends that he saw from time to time and was fairly close to.
- 3 = Fair. Had only one special friend that he saw from time to time and was fairly close to; or contacts limited to several friends that he was not very close to emotionally.
- 4 = Poor. Had no special friends he saw from time to time and was fairly close to; or contacts limited to one or two friends that he was not very close to.
- 5 = Very poor. Had no special friends and practically no social contacts.
- 6 = No information.

(2) Interpersonal relations (maximum of 2a, 2b 2c and 2d): _____

Satisfaction

(3) Satisfaction : _____

Which of the following best characterizes the patient's overall level of satisfaction (contentment, degree to which he feels fulfilled, gratification derived from activities) for the past week.

- 1 = Very good. Transient problems may occur, but generally satisfied with all aspects of his life. Occasional minor dissatisfaction in one area, but overall is quite content with himself, job, family, friends, activities, and finances.
- 2 = Good. Mild dissatisfaction persists, but only in one area or is intermittent in several areas. In balance, is generally content and able to enjoy life most of the time, but does think there should be some improvement in either occupational role, interpersonal relations, sexual activities, or finances.
- 3 = Fair. Moderate dissatisfaction in one or more areas, which is relatively persistent. Either discontent with occupational role, interpersonal relations, sexual activities, or finances.
- 4 = Poor. Very dissatisfied in most areas and derives little pleasure from life. Rarely able to derive any satisfaction from activities or relationships.
- 5 = Very poor. Derives no satisfaction from anything. May feel no desire to carry out the smallest task or to be with other people.
- 6 = No information.

Recreation

(4) Recreation: _____

At what level has the patient been involved in and able to enjoy recreational activities and hobbies (reading, spectator or participant sports, gardening, music, sewing, attending parties or gatherings, church or community organizations) in the past week

- 1 = Very good. Has at least two activities which he enjoys fully and frequently.
- 2 = Good. Participates in several activities and does not always enjoy them fully; or participates in fewer activities or less frequently than optimal, but enjoys participation.
- 3 = Fair. Occasional participation in recreational activities or hobbies; or limited enjoyment when participation occurs.
- 4 = Poor. Some participation in recreational activities or hobbies, and derives very little enjoyment from such activities.
- 5 = Very poor. No involvement in recreational activities or hobbies.
- 6 = No information.

THE LIFE-RIFT SUMMARY

(1) Work (maximum of 1a, 1 b and 1c): _____

(2) Interpersonal relations (maximum of 2 a, 2 b, 2c and 2d): _____

(3) Satisfaction: _____

(4) Recreation : _____

Total score (sum of 1, 2, 3 and 4): _____

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SAS

Section A: The following questions relate to work inside the home. Please circle the appropriate answer below.

1. How many days did you do some housework during the last two weeks? This includes cooking, cleaning, laundry, grocery, shopping, errands, picking up, and chore responsibilities in shared living settings (i.e., group home, hospital)

1 = Every day

2 = Almost every day

3 = About half the time

4 = I usually did not do housework

5 = I was completely unable to do housework

-3 = I was away from home or did not need to do housework

2. During the last two weeks, have you kept up with your work around the house? This includes cooking, cleaning, laundry, grocery shopping, errands, and picking up.

1 = I did my work very well

2 = I did my work well but had some minor problems

3 = I needed help with my work and did not do it well about half of the time

4 = I did my work poorly most of the time

5 = I did my work poorly all of the time

3. Have you been ashamed of how you did your work around the house during the last two weeks?

1 = I never felt ashamed

2 = Once or twice I felt ashamed

3 = About half of the time I felt ashamed

4 = I felt ashamed most of the time

5 = I felt ashamed all the time

4. Have you had any arguments with salespeople, tradesmen, or neighbours in the last two weeks?

1 = I had no arguments and got along well

2 = I usually got along well, but had minor arguments

3 = I had more than one argument

4 = I had many arguments

5 = I was constantly in arguments

5. Have you felt upset while doing your work around the house during the last two weeks?

1 = I never felt upset

2 = Once or twice I felt upset

3 = Half the time I felt upset

4 = I felt upset most of the time

5 = I felt upset all of the time

6. Have you found your work around the house interesting these last two weeks?

1 = My work was almost always interesting

2 = Once or twice my work was not interesting

3 = Half the time my work was uninteresting

4 = Most of the time my work was uninteresting

5 = My work was always uninteresting

Section B: The following questions relate to friends. Please circle the appropriate answer below.

7. How many friends have you seen or spoken to on the telephone in the last two weeks?

1 = Nine or more friends

2 = Five to eight friends

3 = Two to four friends

4 = One friend

-3 = No friends

8. Have you been able to talk about your feelings and problems with at least one friend during the last two weeks?

1 = I can always talk about my innermost feelings

2 = I usually can talk about my feelings

3 = About half the time I felt able to talk about my feelings

4 = I usually was not able to talk about my feelings

5 = I was never able to talk about my feelings

-3 = Not applicable; I have no friends

9. How many times in the last two weeks have you gone out socially with other people? For example, visiting friends, gone to movies, bowling, church, restaurants, invited friends to your home?

1 = More than three times

2 = Three times

3 = Twice

4 = Once

5 = None

10. How much time have you spent on hobbies or spare time interests during the last two weeks? For example, bowling, sewing, gardening, sports, reading?

1 = I spent most of my spare time on hobbies almost every day

2 = I spent some spare time on hobbies some of the days

3 = I spent a little spare time on hobbies

4 = I usually did not spend any time on hobbies but did watch TV

5 = I did not spend any spare time on hobbies or watching TV

11. Have you had open arguments with your friends in the last two weeks?

1 = I had no arguments and got along very well

2 = I usually got along well but had minor arguments

3 = I had more than one argument

4 = I had many arguments

5 = I was constantly in arguments

-3 = Not applicable; I have no friends

12. If your feelings were hurt or offended by a friend during the last two weeks, how badly did you take it?

1 = It did not affect me or it did not happen

2 = I got over it in a few hours

3 = I got over it in a few days

4 = I got over it in a week

5 = It will take me months to recover

-3 = Not applicable; I have no friends

13. Have you felt shy or uncomfortable with people in the last two weeks?

1 = I always felt comfortable

2 = Sometimes I felt uncomfortable but could relax after awhile

3 = About half the time I felt uncomfortable

4 = I usually felt uncomfortable

5 = I always felt uncomfortable

-3 = Not applicable; I was never with people

14. Have you felt lonely and wished for more friends during the last two weeks?

- 1 = I have not felt lonely
- 2 = I have felt lonely a few times
- 3 = About half the time I felt lonely
- 4 = I usually felt lonely
- 5 = I always felt lonely and wished for more friends

15. Have you felt bored in your spare time during the last two weeks?

- 1 = I never felt bored
- 2 = I usually did not feel bored
- 3 = About half the time I felt bored
- 4 = Most of the time I felt bored
- 5 = I was constantly bored

Section C: The following questions relate to interpersonal relationships with parents, brothers, sisters, guardians, children or in-laws. Please circle the appropriate answer below.

16. Are you currently living with a parent, brother, sister, guardian, in-law or child(ren)?

- 1 = Yes
- 2 = No

17. Have you been in contact with any of them in the last two weeks?

- 1 = Yes
- 0 = No (Please go to question 29)

18. Have you had open arguments with your relatives in the last two weeks?

- 1 = We always got along very well
- 2 = We usually got along well but had some minor arguments
- 3 = I had more than one argument with at least one relative
- 4 = I had many arguments
- 5 = I was constantly in arguments

19. Have you been able to talk about your feelings and problems with at least one of your relatives in the last two weeks?

- 1 = I can always talk about my feelings with at least one relative
- 2 = I usually can talk about my feelings
- 3 = About half the time I felt able to talk about my feelings
- 4 = I usually was not able to talk about my feelings
- 5 = I was never able to talk about my feelings

20. Have you avoided contact with your relatives in these last two weeks?

- 1 = I have contacted relatives regularly
- 2 = I have contacted a relative at least once
- 3 = I have waited for my relatives to contact me
- 4 = I avoided my relatives, but they contacted me
- 5 = I have not had contacts with any relatives

21. Did you depend on your relatives for help, advice, money, or friendship during the last two weeks?

- 1 = I never needed to depend on them
- 2 = I usually did not need to depend on them
- 3 = About half the time I needed to depend on them
- 4 = Most of the time I depended on them
- 5 = I depend completely on them

22. Have you wanted to do the opposite of what your relatives wanted in order to make them angry during the last two weeks?

- 1 = I never wanted to oppose them
- 2 = Once or twice I wanted to oppose them
- 3 = About half the time I wanted to oppose them
- 4 = Most of the time I wanted to oppose them
- 5 = I always opposed them

23. Have you been worried about things happening to your relatives without good reason in the past two weeks?

- 1 = I have not worried without reason
- 2 = Once or twice I worried
- 3 = About half the time I worried
- 4 = Most of the time I worried
- 5 = I have worried the entire time
- 3 = Not applicable; my relatives are no longer living

24. During the last two weeks, have you been thinking you have let any of your relatives down or have been unfair to them at any time?

- 1 = I did not feel that I let them down at all
- 2 = I usually did not feel that I let them down
- 3 = About half the time I felt that I let them down
- 4 = Most of the time I have felt that I let them down
- 5 = I always felt that I let them down

25. During the last two weeks, have you been thinking that any of your relatives have let you down or have been unfair to you at any time?

- 1 = I never felt that they let me down
- 2 = I felt that they usually did not let me down
- 3 = About half the time I felt they let me down
- 4 = I usually have felt that they let me down
- 5 = I am very bitter that they let me down

Answer these questions about family who you do not live with (e.g. parents, brothers, sisters, guardians, children)

26. Have you worried about your family without any reason during the last two weeks, even if you are not living together now?

- 1 = I never worried
- 3 = About half the time I worried
- 2 = Once or twice I worried
- 4 = Most of the time I worried
- 5 = I always worried
- 3 = Not applicable; partner and children not living

27. During the last two weeks, have you been thinking that you have let down your family?

- 1 = I did not feel I let them down at all
- 2 = I usually did not feel that I let them down
- 3 = About half the time I felt I let them down
- 4 = Most of the time I have felt that I let them down
- 5 = I let them down completely

28. During the last two weeks, have you been thinking that your family have let you down at any time?

- 1 = I never felt that they let me down
- 2 = I felt they usually did not let me down
- 3 = About half the time I felt they let me down
- 4 = I usually felt they let me down
- 5 = I feel bitter that they have let me down

THE FOLLOWING QUESTIONS RELATE TO SCHOOL. ONLY ANSWER THESE QUESTIONS IF YOU ARE CURRENTLY ENROLLED IN SCHOOL, TAFE, UNIVERSITY OR ANY OTHER COURSE.

Section D: the following questions relate to school work. Please circle the appropriate answer below.

Definition of Student: A subject is enrolled in a student program as long as she is in a course of study being carried out at a recognized educational institution (e.g., university, high school, technical or trade school, extension courses). Do not include activities that are better classified as hobbies (e.g., night courses in photography or art where you don't get a certificate upon completion).

29. What best describes your school program?

- 1 = Full time
- 2 = 3/4 time
- 3 = Half time
- 4 = Less than half-time
- 3 = I would not classify myself as a student. (Please go to section D)

30. How many days of classes did you miss in the last two weeks?

- 1 = No days missed
- 2 = A few days missed
- 3 = I missed about half the time
- 4 = Missed more than half time but did make at least one day
- 5 = I did not go to classes at all
- 6 = I was on vacation all of the last two weeks

31. Have you been able to keep up with your class work in the last two weeks?

- 1 = I did my work very well
- 2 = I did my work well but had minor problems
- 3 = I needed help with my work and did not do well about half the time
- 4 = I did my work poorly most of the time
- 5 = I did my work poorly all the time

32. During the last two weeks, have you been ashamed of how you do your school work?

- 1 = I never felt ashamed
- 2 = Once or twice I felt ashamed
- 3 = About half the time I felt ashamed
- 4 = I felt ashamed most of the time
- 5 = I felt ashamed almost all of the time

33. Have you had any arguments with people at school in the last two weeks?

- 1 = I had no arguments and got along well
- 2 = I usually go along well but had minor arguments
- 3 = I had more than one argument
- 4 = I had many arguments
- 5 = I was constantly in arguments
- 3 = Not applicable; I did not attend school

34. Have you felt upset at school during the last two weeks?

- 1 = I never felt upset
- 2 = Once or twice I felt upset
- 3 = Half the time I felt upset
- 4 = I felt upset most of the time
- 5 = I felt upset all of the time
- 3 = Not applicable; I did not attend school

35. Have you found your school work interesting these last two weeks?

- 1 = My work was almost always interesting
- 2 = Once or twice my work was not interesting
- 3 = Half the time my work was uninteresting
- 4 = Most of the time my work was uninteresting
- 5 = My work was always uninteresting

THE FOLLOWING QUESTIONS RELATE TO WORK. ONLY ANSWER THESE QUESTIONS IF YOU ARE CURRENTLY WORKING (FULL-TIME, PART-TIME, OR CASUAL)

Section E: The following questions relate to employment/work outside the home. Please circle the appropriate answer below.

36. In the past two weeks, have you participated in employment or work outside the home?

1 = Yes

0 = No - DO NOT COMPLETE THIS SECTION

37. How many work days did you miss from work in the past two weeks?

1 = No days missed

2 = One day missed

3 = Missed approximately half the time

4 = Missed more than half the time but did make at least one day up

5 = Did not work any days

6 = On vacation all of the past two weeks

38. Have you been able to do your work in the last two weeks?

1 = Very well

2 = Well, but with minor problems

3 = Needed help with work, and did not do well about half the time

4 = Did poorly most of the time

5 = Did my work poorly all the time

39. Have you been ashamed of how you do your work in the last two weeks?

1 = Never once felt ashamed

2 = Once or twice felt a little ashamed

3 = About half the time felt ashamed

4 = Most of the time felt ashamed

5 = Felt ashamed all the time

40. Have you had any arguments with people at work in the last two weeks?

1 = No arguments and got along very well

2 = Usually got along well but had minor arguments

3 = Had more than one arguments

4 = Had many arguments

5 = Was constantly in arguments

41. Have you felt upset, worried, or uncomfortable while doing your work during the last two weeks?

1 = Never felt upset

2 = Once or twice felt upset

3 = Half the time felt upset

4 = Most of the time felt upset

5 = All of the time felt upset

42. Have you found your work interesting in the past two weeks?

1 = Work was almost always interesting

2 = Once or twice work was not interesting

3 = Half the time work was uninteresting

4 = Most of the time work was not interesting

5 = Work was always uninteresting

Section F:

THE FOLLOWING QUESTIONS RELATE TO YOUR LIVING ARRANGEMENTS. ONLY ANSWER THESE QUESTIONS IF YOU ARE CURRENTLY LIVING WITH A PERSON OF THE OPPOSITE/SAME SEX IN A PERMANENT RELATIONSHIP.

43. ARE YOU LIVING with your spouse or have you been living with a person of the opposite sex/same sex in a permanent relationship (six months or longer)?

1 = YES

0 = NO - DO NOT COMPLETE THIS SECTION

44. Have you had open arguments with your partner in the last two weeks?

1 = We had no arguments and we got along well

2 = We usually got along well but had minor arguments

3 = We had more than one arguments

4 = We had many arguments

5 = We were constantly in arguments

45. Have you been able to talk about your feelings and problems with your partner during the last two weeks?

1 = I could always talk freely about my feelings

2 = I usually could talk about my feelings

3 = About half the time I felt able to talk about my feelings

4 = I usually was not able to talk about my feelings

5 = I was never able to talk about my feelings

46. Have you been demanding to have your own way at home during the last two weeks?

1 = I have not insisted on always having my own way

2 = I usually have not insisted on having my own way

3 = About half the time I insisted on having my own way

4 = I usually insisted on having my own way

5 = I always insisted on having my own way

47. Have you been bossed around by your partner during the last two weeks?

1 = Almost never

2 = Once in a while

3 = About half the time

4 = Most of the time

5 = Always

48. How much have you felt dependent on your partner these last two weeks?

1 = I was independent

2 = I was usually independent

3 = I was somewhat dependent

4 = I was usually dependent

5 = I depended on my partner for everything

49. How have you felt about your partner during the last two weeks?

1 = I always felt affection

2 = I usually felt affection

3 = About half the time I felt dislike and half the time affection

4 = I usually felt dislike

5 = I always felt dislike

50. How many times have you and your partner had sex?

1 = More than twice a week

2 = Once or twice a week

3 = Once every two weeks

4 = Less than once every two weeks, but at least once in the last month

5 = Not at all in the last month or longer

51. Have you had any problems during sex, such as pain, these past two weeks?

1 = None

2 = Once or twice

3 = About half the time

4 = Most of the time

5 = Always

-3 = Not applicable; no intercourse during the last two weeks

52. How have you felt about sex during the last two weeks?

1 = I always enjoyed it

2 = I usually enjoyed it

3 = About half the time I did and half the time I did not enjoy it

4 = I usually did not enjoy it

5 = I never enjoyed it

SECTION G:

THE FOLLOWING QUESTION RELATES TO CHILDREN. ONLY ANSWER THESE QUESTIONS IF YOU ARE A PARENT AND CURRENTLY LIVING WITH YOUR CHILD/REN.

53. CHILDREN. Have you had children, stepchildren, or foster children living at home with you during the last two weeks?

1 = YES

0 = NO DO NOT COMPLETE THIS SECTION

54. Have you been interested in what your children are doing: school, play, or hobbies during the last two weeks?

1 = I was always interested and actively involved

2 = I usually was interested and involved

3 = About half the time interested and half the time not interested

4 = I was usually disinterested

5 = I was always disinterested

55. Have you been able to talk and listen to your children during the last two weeks? Include only children over the age of two.

1 = I always was able to communicate with them

2 = I usually was able to communicate with them

3 = About half the time I could communicate

4 = I usually was not able to communicate

5 = I was completely unable to communicate

-3 = Not applicable; no children over the age of two

56. How have you been getting along with the children during the last two weeks?

1 = I had no arguments and got along well

2 = I usually got along well but had minor arguments

3 = I had more than one argument

4 = I had many arguments

5 = I was constantly in arguments

57. How have you felt toward your children these last two weeks?

1 = I always felt affection

2 = I mostly felt affection

3 = About half the time I felt affection

4 = Most of the time I felt affection

5 = I never felt affection toward them

Social and Occupational Functioning Assessment Scale (SOFAS)

Consider social and occupational functioning on a continuum from excellent functioning to grossly impaired functioning. Include impairments in functioning due to physical limitations, as well as due to mental impairments. To be counted, impairment must be a direct consequence of mental and physical health problems: the effects of lack of opportunity and other environmental limitations are not to be considered.

Code	Note: Use intermediate codes when appropriate e.g., 45, 68, 72.
100 91	Superior functioning in a wide range of activities
90 81	Good functioning in all areas, occupational and socially effective
80 71	No more than a slight impairment in social, occupational, or school functioning (e.g. infrequent interpersonal conflict, temporarily falling behind in schoolwork)
70 61	Some difficulty in social, occupational or school functioning, but generally functioning well, has some meaningful interpersonal relationships
60 51	Moderate difficulty in social, occupational or school functioning (e.g. few friends, conflicts with peers, coworkers).
50 41	Serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job)
40 31	Major impairment in several areas such as work or school, family relations (e.g. depressed man avoids friends, neglects family and is unable to work: child frequently beats up younger children, is defiant at home, and is failing school)
30 21	Inability to function in almost all areas (e.g. stays in bed all day, no job, home or friends)
20 	Occasionally fails to maintain minimal personal hygiene. Unable to function independently.

11	
10 1	Persistent inability to maintain minimal personal hygiene. Unable to function without harming self or others without considerable external support (e.g. nursing care and supervision)
0	Inadequate information

Appendix C: Research and Ethics Approval

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Mental Health Research and Ethics Committee Approval Certificate

The MHREC operates in accordance with the *NHMRC National Statement on Ethical Conduct in Human Research 2007*

This is to certify that

MHREC Project No: 2009.642

Approval date: 21/12/2009

Expiry date: 20/12/2012

Project Title: Evaluation of medium-term course, outcome, and treatment of adolescents with Major Depressive Disorder (MDD)

Principal Investigator: Dr Andrew Chanen
ORYGEN Youth Health Research Centre
Locked Bag 10
PARKVILLE 3052

Protocol No: Amended application dated 18 December 2009

Participant Information and Consent Form: Version 1 dated 12 October 2009

Other: Letter of Invitation

Conducted at: ORYGEN Youth Health **has been approved.**

This proposal meets the requirements of the *NHMRC National Statement on Ethical Conduct in Human Research 2007*.

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Manager of the Mental Health Research and Ethics Committee of:

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study;
- Serious adverse effects on subjects and the action taken to manage them, including an amended Patient Information and Consent Form where appropriate;
- Any unforeseen events;
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study;
- A delay of more than 12 months in the commencement of the project; and
- The actual date of commencement of the study.

You are required to submit the following reports to the Mental Health Research and Ethics Committee:

- An Annual Report every twelve months for the duration of the project; and
- A detailed Final Report at the conclusion of the project.

The Mental Health Research and Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Mental Health Research and Ethics Committee.

Signed:

Michelle Clemson
Manager, Mental Health Research and Ethics Committee

Appendix D: Plain language statement and consent form

Participant Information and Consent Form

Site: Orygen Youth Health – Research Centre

Full Project Title: **Evaluation of medium-term course, outcome, and treatment of adolescents with complex Major Depressive Disorder (MDD)**

Principal Researcher: Dr Andrew Chanen

Associate Researchers: Professor Andrew MacKinnon, Professor Nicholas Allen, Dr Mark Phelan, Ms Emma McDougall, Dr Jennifer Betts, Ms Khai-Ying Lau, Ms Yian-Kim Ko.

Research Interviewer: Dr Mark Phelan

1. Introduction

You are being invited to participate in this project because you have previously participated in one of three research projects conducted by Dr Andrew Chanen and his colleagues at Orygen Youth Health (OYH) or at Mental Health Services for Kids and Youth (MHSKY). These projects have produced valuable findings that have influenced the care of patients with mental health problems. We are now seeking to build upon this work by studying the longer-term course of mental health problems.

We have made contact with you by using the details you provided when you took part in earlier research projects at Orygen Youth Health (OYH) for MHSKY.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask any questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in the research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

We are particularly interested in the outcome of depression in young people and how this compares with other mental health problems. Previous research has shown that young people who have had depression (also known as Major Depression) often have further episodes of depression as they move into young adulthood and that they can have difficulties reaching their goals with work, relationships and friendships. We also want to interview people who have had mental health problems other than depression to document their experiences and because little is known about the outcome for some mental health problems. In total, there will be a possible 237 people taking part in this study.

In this project, we will be charting the course of depression that young people have had since finishing their treatment at Orygen or MHSKY. We will also be asking about the type of treatment that you have received and how well this has met your needs. We will also ask about other factors, particularly aspects of your social circumstances and personality, that might influence the course of the depression.

The information that we collect will inform our understanding of young people's mental health needs in the longer-term, and whether these are being met in our current system. It is likely that some of the factors we study will promote positive outcomes or protect people from having a more severe illness, and others will do the opposite. Our aim is to use the information from this project to design better treatments that strengthen the protective factors and work to change those factors that make it harder to recover.

The results of this research will also be used by the researchers to gain research degrees, a Doctor of Medical Science in the case of Dr Mark Phelan, and Bachelor of Medical Science Degrees for Ms Lau and Ms Ko.

The research has been funded by the National Health and Medical Research Council through its Centre for Clinical Research Excellence at OYH. It has also received a grant from the Royal Melbourne Hospital Lottery Research Fund.

3. What does participation in this research project involve?

A. Questionnaires

We will be asking you to fill in some questionnaires which should take about 1 hour. These ask about aspects of your personality, general questions about your current mental health, how you feel about your work situation, friendships and relationships, as well as about stigma and mental illness.

B. Interview

We are inviting you to participate in an interview that lasts from 1 to 2 hours. In the interview, you will be asked questions about your current mental health. If you have experienced depression, we will also ask about how this has affected you since your treatment at Orygen or MHSKY. The final section of the interview will ask about your experiences of treatment after finishing at Orygen or MHSKY.

The interview will be completed with a member of the research team and can be

done at a location convenient to you (e.g. at Orygen Youth Health or in your own home).

C. Permission to access information held in State and Federal government health department databases

We would also like to collect information that is held by state and federal government health departments about the types of treatment that you have received. The Victorian Department of Human Services (DHS) maintains a record of the contacts that people have with the public mental health service on its CMI system. The federal government, through the Medicare Benefits Scheme, records contacts with health professionals. It also collects data on medication use via the Pharmaceutical Benefits Scheme.

The purpose of collecting this information is to understand the treatment that you have received.

D. Permission to access information in your Orygen or MHSKY medical record

We would also like to gather information from your medical record about any treatment that you received while in this service.

E. Permission to audio-tape interview

We will audio-tape a small number of randomly-selected interviews performed by Dr Phelan to be reviewed by Dr Chanen as a means of checking the accuracy of the interview findings. This material will be stored in the locked archives of Orygen Youth Health Research Centre and will only be accessed by Dr Phelan and Dr Chanen's research team.

F. Permission for future contact

Should the opportunity arise, we would like to be able to contact you in the future to build upon this research.

G. Re-imbursement

In order to cover you for any costs involved in participating in the research, e.g. travel costs, we can reimburse you \$50

4. What are the possible benefits?

We cannot guarantee or promise that you will receive any benefits from this project. However, we anticipate that the information gathered from you will help to improve our understanding of the longer-term mental health of young people and to improve mental health treatments and the mental health system.

5. What are the possible risks?

There are no physical risks involved in this project.

The types of questions asked in this study have been used in previous projects and no one has reported any adverse effects. As you might remember from taking part in the earlier research, most of the questionnaires and interviews involve asking questions about different aspects of your mental health. Although the questions do not ask for a lot of detail, it is possible that they could be upsetting. You can choose not to answer any questions or participate in any part of the project if it makes you feel uncomfortable.

If you do become upset, you are free to stop the interview for a break or withdraw from the interview at any stage. Also, the researcher is able to arrange for counselling or other appropriate support.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at a later stage.

If you decide to leave the project, the researchers would like to keep the personal and/or health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you withdraw from the research project.

Your decision to take part or not, or to take part and then withdraw will not affect your relationship with the researchers.

7. How will I be informed of the final results of this research project?

If you would like, a summary of the results of this project can be sent to you when it finishes. This is likely to be in mid-2013.

8. What will happen to information about me?

Only the principal investigator, Dr Andrew Chanen, and members of the research team, Dr Phelan, Ms Yian-Kim Ko and Ms Khai-Ying Lau will have direct access to the information gathered.

Any information gathered by this project that can identify you will remain confidential. The information would only be passed on with your permission, except as required by law. Any information that we collect will be kept for a minimum of five years.

Your name and any other information which may identify you will be removed from the information. These details will be replaced by a coded number, known only to the research team. The coded information gathered will be kept in a locked filing cabinet in the locked archives of Orygen Youth Health Research Centre.

A. Permission to store your data in a databank

We would like permission to store;

1. The contact details that you have provided AND;
2. The results that we have collected in past studies, and will collect in this study

in two separate computer databanks for an indefinite period. This information will only be accessible to researchers from Dr Phelan and Dr Chanen's research group and only by means of password. This information will also be de-identified, with the code to link the two databanks kept in a locked filing cabinet in the locked archives of Orygen Youth Health Research Centre.

B. Permission to use data for research not described here

We would like your permission to use the data that we collect in this study for projects that are not described here that will be related to this research. This future research would involve de-identified data (you cannot be individually identified from this data). Any future project would be reviewed by a properly constituted research and ethics committee. By agreeing to this, you will help us to maximize the outcome of our research effort and avoid the need to re-approach you to obtain your consent.

The information gathered from the interviews and questionnaires will be summarised in research reports that might be published in professional journals and read by other health professionals. We might also give talks about the project at conferences and meetings. In all cases, there will be no information given which would identify you or any other individual participant in the study.

9. Can I access research information kept about me?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws you have the right to access the information collected and stored by researchers about you. Please contact one of the researchers named at the end of this document if you would like to access your information

10. Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research and Ethics Committee of Melbourne Health.

11. Consent

CONSENT OF PARTICIPANT

The purpose of the above project has been fully explained to me and I have read and understood the attached Participant Information Form.

I understand the aim and procedures and risks of the study and any risks to myself which are involved.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public forum.

I understand that I will be given a signed copy of this document to keep.

I request to participate in the following parts of the study on condition that I can withdraw my consent at any time.

	Consent of participant
A. Questionnaires & Interview	Yes / No
B. Permission to access medical records	Yes / No
C. Permission to access information held by Department of Human Services Victoria, Medicare and Pharmaceutical Benefits Scheme	Yes/No
D. Permission to audio-tape interview	Yes/No
E. Permission to store your contact details in a databank	Yes / No
F. Permission to store the results from the interview and questionnaires in a databank	Yes / No
G. Permission to contact you for potential future research	Yes / No
H. Permission to use acquired data for research not described in this project	Yes / No

Participant's Name (printed)

Participant's Signature.....

Date:.....

WITNESS OF SUBJECT'S SIGNATURE

I,.....

of.....

as an independent witness confirm that the aims and procedures of the study and any risks to the subject has been adequately explained to the subject whose signature I witness. In my opinion he/she appears to understand and wishes to participate.

Witness' Signature:.....

Date:.....

RESEARCHER

I, _____, certify that I have fully explained the aims, risks and procedures of the research to the subject named herein and have

handed to the subject a copy of this consent, together with a plain English statement of the aims and procedures of the study and any risks to the subject.

In my opinion the subject appears to understand and wishes to participate.

Researcher's Signature:.....

Date:.....

12. Who can I contact?

For further information:

If you would like more information about the study or if there is anything about it that concerns you, either now or in the future, please do not hesitate to contact the members of research team listed below who are available on phone number 03 9342-2800.

Dr Andrew Chanen

Dr Mark Phelan

Professor Andrew Mackinnon

Professor Nicholas Allen

For complaints:

If you have any complains about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, you may contact Ms Michelle Clemson.

Name: ***Ms Michelle Clemson***

Position: ***Manager, Mental Health Research and Ethics Committee***

Telephone: ***(03) 9342 7215***

You will need to tell her the name of the researchers and the title of the project (both listed on the front of this document).

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