Life Stress and Risk for Major Depression: A Latent Profile Analysis

By

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Abstract

Major Depressive Disorder (MDD) affects over 280 million individuals and accounts for more years of 'healthy' life lost than any other medical condition. Half of all individuals with an initial onset of MDD will experience recurrences, whereas half will have only one or very few lifetime episodes. The Dual Pathway Model (DPM) proposes that major life stress may be able to distinguish risk for recurrent versus non-recurrent depression at first episode onset. Objectives were to use Latent Profile Analysis (LPA) to uncover profiles of risk in currently depressed individuals and determine whether major life stress prior to episode onset is associated with likelihood of profile membership. We hypothesized that those in a recurrent episode and those in a first-onset episode *not* preceded by major life stress will be more likely to belong to high-risk profiles. In contrast, those in a first-onset episode preceded by major life stress will be more likely to belong to low-risk profiles. The sample included 853 currently depressed individuals from six completed projects. Four latent profiles were identified: "Low Overall Risk", "High Childhood Maltreatment, Low Symptom Severity", "Moderate Overall Risk", and "High Overall Risk". Consistent with hypotheses, those in a recurrent episode were significantly more likely to belong to the moderate and high overall risk profiles than the low overall risk profile. Females were also significantly more likely to belong to the moderate and high overall risk profiles than the low risk profile. Contrary to hypotheses, those in a first episode without a preceding stressor were significantly more likely to belong to the low overall risk profile than the moderate and high overall risk profiles. Prospective studies are needed to make predictive claims about life stress and risk for recurrent depression. Nonetheless, the present findings have implications for the development of tailored intervention strategies with the highest chances of success based on a patient's etiological profile.

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List of Abbreviations

AIC……. Akaike Information Criterion

ARP…… Adolescent Risk Project

BDI……...Beck Depression Inventory

BIC…….……. Bayesian Information Criterion

BSP ……..…… Blue Sky Project

CBN01 ……...…….…… CAN-BIND-1

CBN04 ……...…….…… CAN-BIND-4

CECA…… The Childhood Experience of Care and Abuse Interview

CM……...…… Childhood Maltreatment

DARS……... Dimensional Anhedonia Rating Scale

DPM…….…….…… Dual Pathway Model

DSM……..…Diagnostic and Statistical Manual of Mental Disorders

GAD-7…….…… Generalized Anxiety Disorder 7-item

HRSD……..……. Hamilton Rating Scale for Depression

ICD-10…….……International Classification of Diseases, Tenth Revision

KSADS……Kiddie Schedule for Affective Disorders and Schizophrenia

LEDS …….…… Life Events and Difficulties Schedule

LPA…….Latent Profile Analysis

MADRS……Montgomery-Ashberg Depression Rating Scale

MASQ……. Mood and Anxiety Symptom Questionnaire

MASQ-AA…… Mood and Anxiety Symptom Questionnaire, Anxious Arousal

MASQ-AD…… Mood and Anxiety Symptom Questionnaire, Anhedonic Depression

MASQ-GDA…… Mood and Anxiety Symptom Questionnaire, General Distress Anxiety

MDD…….…… Major Depressive Disorder

MINI……..……. MINI Psychiatric Interview

NEO-FFI…….…… NEO Five Factor Inventory

NEO-PI-R…….…… NEO Personality Inventory-Revised

OMHF…… Ontario Mental Health Foundation

PAD …… Psychobiology of Adolescent Depression Project

PBLRT…….…..……...… Parametric Bootstrapped Likelihood Ratio Test

SCID…….Structured Clinical Interview for the DSM

SHAPS-C…… Snaith-Hamilton Pleasure Scale, Clinician Administered

SSA-BIC……Sample-Size Adjusted Bayesian Information Criterion

SSH……..…… Stress Sensitization Hypothesis

Sx……...…….…… Symptom

VLMR-LRT…….…..…… Vuong-Lo-Mendell-Rubin Likelihood Ratio Test

Chapter 1: Introduction

Major Depressive Disorder (MDD) affects over 280 million individuals (World Health Organization, 2023) and accounts for more years of 'healthy' life lost than any other medical condition (Lopez et al., 2006; Moussavi et al., 2007; Stonebridge & Sutherland, 2016; Whiteford et al., 2013). In Canada alone, MDD has a staggering economic impact of $32.3 billion per year in productivity losses (Eaton et al., 2008) and has been identified as a major contributor to the global burden of disease (World Health Organization, 2023). Approximately 40-50% of individuals who become clinically depressed initially will have at least one recurrent episode throughout their lifetime (Nöbbelin et al., 2018). With each recurrence, the risk rises for another, resulting in individuals who experience many, many depressive episodes throughout their lifetime (Monroe & Harkness, 2011). Those who experience repeated episodes of depression throughout their lifetime drive the bulk of MDD's personal and economic burden, accruing significantly higher healthcare costs, experiencing higher rates of comorbid conditions, and having an increased risk for suicidality (Gauthier et al., 2019). Thus, prevention of recurrent depression is a pressing priority. A significant obstacle to this goal, however, is our current inability to predict, at the time of initial depression onset, who is and is not prone to multiple lifetime recurrences. Early detection of recurrence prone individuals would inform the dissemination of tailored treatment and maintenance resources to those most in need and prevent overtreatment of those who may never experience another episode in their lifetime.

Life Stress and Depression

Life stress and its relationship to depression may harbour important clues as to who among the initially depressed will become recurrent. Robust evidence has documented that stressful life events are potent causes of MDD (e.g., Hammen, 2005; Mazure, 1998; Monroe et

al., 2014). Highly threatening or major life events are especially potent for provoking onset (e.g., job loss, divorce, developing a life-threatening illness (Brown & Harris, 1978; Kendler et al., 1998). Even controlling for other risk factors, major stressful life events remain among the strongest predictors of depression onset (e.g., Kendler et al., 2002, 2004; Rudolph et al., 2000). Indeed, life stress has shaped the development of many, if not most, theories of depression to date. Intriguingly, however, the etiological role of life stress in depression appears to change across recurrences. Further, research indicates that the association of major stressful life events with depression onset is moderated by number of prior depressive episodes (e.g., Hammen, 2018; Lamers et al., 2012; Post, 1992; Stroud et al., 2008, 2011). Specifically, major life events occur most frequently before first episodes and are progressively less likely to occur before successive recurrences.

Competing Theories of Recurrence

The current reigning theory of MDD recurrence, the Stress Sensitization Hypothesis (SSH) (Monroe & Harkness, 2005; Post, 1992) was designed to explain the changing association of life stress over successive recurrences. It proposes that major stressful life events are required to trigger the very first episode of depression. However, over time, people become increasingly sensitized to the life events they encounter, and to the depressive episodes themselves, such that increasingly more minor events acquire the capability to trigger subsequent recurrent episodes. That is, less severe life events are needed to trigger depression as people become sensitized over time.

While the observation of a decreasing relation between major life events prior to a first onset through successive recurrences is well-documented (see meta-analysis by Stroud, 2018; see also Stroud et al., 2008) and the SSH is intuitively appealing, concerns have been raised about

potential limitations (Monroe & Harkness, 2022). For instance, findings that support this observation are based on between-person effects, whereas stress sensitization is based upon a within-person effect; very limited evidence exists for a decline in the presence of major events over successive episodes within individuals themselves (e.g., Kendler et al., 2000). Moreover, evidence for the unique premise of stress sensitization— that progressively lower degrees of life stress within individuals become increasingly more capable of triggering recurrences—does not yet appear to exist (Monroe et al., 2019). The theory also fails to account for a sizable proportion of depressed individuals; namely, the 50% or more individuals in a first episode who will never have any recurrences, and the 40% or more individuals whose first episodes are not preceded by major life events (Monroe et al., 2019; Post, 1992).

To address these issues, an alternative framework has been proposed to guide the discovery of those who will go on to have recurrent episodes: the Dual Pathway Models (DPM) (Monroe et al., 2019; Monroe & Harkness, 2022). In brief, the DPMs propose that there are two subgroups of depressed individuals: (1) 'depression capable' individuals (i.e., those who develop depression only in the context of a major stressful life event and are thus not likely to have many recurrences) and (2) 'recurrence prone' individuals (i.e., those who develop depression in the context of either minor stressors or in the absence of stressors, and thus, are susceptible to repeated episodes). If these two subgroups could be reliably distinguished at initial onset, then precious clinical resources and considerable economic costs could be spared and directed toward the more vulnerable recurrent subgroup (Monroe & Harkness, 2022).

According to the DPMs, these two subgroups may be distinguished by the presence or absence of a major stressful life event prior to episodes (see Figure 1). Because, according to the theory, depression capable (low risk, in green) individuals require all episodes to be provoked by

major life events, their proportionate representation within each successive recurrence drops progressively, as reflected in the decreasing presence of the mandatory major life events. In contrast, recurrence prone (high risk, in blue) individuals do not require major events to provoke onset of any episodes. Thus, their proportionate representation within each subsequent recurrence rises progressively, mirrored by a corresponding drop in the presence of unnecessary major life events. What the SSH posits as a decreasing association of major life events over successive recurrences, the DPMs posit as the changing representation of the nonrecurrent and recurrent subgroups over repeated recurrences (see Figure 1). The DPMs further propose that recurrence prone individuals may be vulnerable to the development of recurrence due to underlying risk indicators. However, this proposal has yet to be systematically investigated.

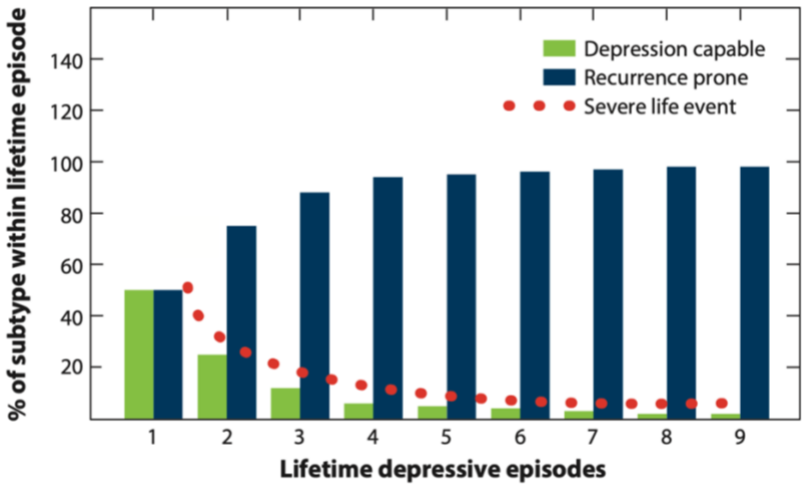

Figure 1. The changing representation of the depression capable (low risk, in green) and recurrence prone (high risk, in blue) subgroups with lifetime depressive episode number as explained by the DPMs. The red dotted line represents the decreasing percentage of cases preceded by a major life event as the depression-capable subtype becomes less common (Monroe & Harkness, 2022).

In sum, the SSH specifies that people who become depressed for the first time after a major stressful life event are most vulnerable to develop recurrent depression. The DPMs specify the opposite: people who become depressed for the first time due to major life stress are the least

likely to have many recurrences, whereas those who become depressed in the absence of stress are more prone to recurrent depression due to other underlying risk indicators. The DPMs provide an alternative framework for identifying individuals at risk of the greatest burdens of depression and greatest need for treatment and prevention; however, given the recency of this model's introduction, its predictions have not yet been systematically tested.

The DPMs theorize that there are two subgroups of depressed individuals: depression-capable (low-risk) and recurrence-prone (high-risk). Recurrence-prone individuals may be at greater risk for recurrence due to their high levels of underlying risk indicators for depression, which may include, for example, symptoms, early stress history, personality, and so on. In contrast, in line with the DPMs, depression-capable individuals may have lower levels of these indicators, and this may be why they 'require' major life stress to trigger an episode of depression. As such, the DPMs posit that the presence or absence of a major stressor prior to episode onset may be used to predict which group an individual will fall into if they are on their very first episode of depression. Individuals in a first episode with a preceding stressor may look like the depression-capable individuals in terms of underlying risk indicators (low-risk), whereas those in a first episode with no preceding stressor may look like the recurrence-prone individuals (high-risk). The present study, therefore, seeks preliminary evidence for the DPMs by examining whether low and high-risk profiles of risk indeed exist in depression, and whether individuals in specific episode groups (i.e., first episode with a preceding stressor, first episode without a preceding stressor, and recurrent episode) are differentially distributed across profiles.

LPA and Depression

Specifically, the current study will use Latent Profile Analysis (LPA), which is a statistical technique used to uncover hidden subgroups within large samples of data. It is widely

known that depression is a highly heterogeneous disorder; diagnostic criteria can be met using more than 1,400 possible combinations of symptoms, and two individuals diagnosed with MDD may not share any symptoms with one another (Østergaard et al., 2011). This gives rise to substantial patient-level variability in risk factors, severity, and illness course (Rush, 2007) as well as suboptimal treatment outcomes (Volkmann et al., 2020). One review attributed this heterogeneity to various causes including symptomatology, trajectories, and biological factors (Lynch et al., 2020). Future directions included using data-driven strategies to discover novel subtypes of depression. LPA is an example of one such strategy; designed to uncover hidden subpopulations in data, it is well-suited to the purpose of parsing heterogeneity, and has become increasingly popular among researchers for this reason.

Previous studies have used latent class models to examine heterogeneity in depression related to the COVID-19 pandemic (Landi et al., 2022; Lu et al., 2024; Wu et al., 2021), and in various subpopulations including children (Petersen et al., 2019), emerging adults (Barton et al., 2017), and older adults (Hou & Zhang, 2023). In terms of risk indicators, LPA studies tend to focus on individual 'categories' of risk, such as childhood maltreatment (Xiao et al., 2023) or personality indicators (Ortelbach et al., 2022). A childhood maltreatment study by Xiao et al. (2023), for example, found that the 'High-Maltreated' profile in their study was associated with higher levels of depression whereas the 'Low-Maltreated' profile was associated with low levels of depression. However, more general studies examining large groups of individuals of various ages on multiple, varied risk indicators are lacking. One meta-analysis examined 24 articles that used Latent Class Analysis (LCA), a version of LPA that uses categorical rather than continuous indicators, to describe similarities and differences in the studies' methods and conclusions (Ulbricht et al., 2018). Researchers found no consistent subtypes among studies and concluded

that this is likely due to variability in terms of model construction, selection, and interpretation, as well as the different subpopulations being studied. Recommendations included following established guidelines for reporting LCA models, using large, diverse samples of depressed individuals, and incorporating dimensional indicators for depression other than symptoms to characterize heterogeneity more fully.

Consistent with the DPMs, I hypothesize that we will find at least one 'high risk' profile, characterized by high scores on the underlying risk indicators (presumably the recurrence-prone group), and one 'low risk' profile, characterized by low scores on the underlying risk indicators (the depression-capable group). Further, I hypothesize that individuals in a recurrent episode and individuals in a first-onset episode that was *not* preceded by major life stress will be significantly more likely to belong to high-risk profiles compared to low-risk profiles. In contrast, I hypothesize that individuals in a first-onset episode that was preceded by major life stress will be significantly more likely to belong to low-risk profiles compared to high-risk profiles.

The present study aims to address several limitations of current research examining the correlates of recurrent depression. First, while previous studies have examined one or few risk indicators for recurrent depression in isolation, none have attempted to identify latent subgroups of depressed individuals based on a wide range of indicators simultaneously. Therefore, the use of LPA in the current study will allow for the identification of complex patterns among risk indicators and provide a more nuanced understanding of how these factors cluster together. In addition, studies examining risk for recurrence generally include greater proportions of recurrent individuals than single lifetime episode individuals. Examining predictors of recurrence among highly recurrent individuals is not productive, as they are likely to have similar underlying liabilities and are all likely to have recurrences. Very few studies examine risk factors that

influence the shift from zero recurrences to one, which are of greater theoretical interest (Monroe & Harkness, 2022). Thus, the current study includes a large sample of individuals in a current episode of depression, approximately 23% of whom are on their very first episode. Finally, studies are often conducted cross-sectionally, comparing those in a first episode to those in a recurrent episode at an arbitrary timepoint. The problem here is that approximately 50% of these first episode cases will become recurrent, thus they will be single lifetime cases only temporarily, and likely share similar liabilities to depression as individuals who have already had recurrences. These study designs conflate first episode cases with single lifetime episode cases and prevent the identification individuals who will never have recurrences (Monroe & Harkness, 2022). The present study is also cross-sectional. However, it leverages the predictions of the DPMs to stratify those in a first episode by the presence or absence of major life stress prior to onset as a proxy for recurrence-proneness.

Risk Indicators for Recurrent Depression

The following variables have been identified as negative prognostic indicators in individual studies and, thus, will serve as the targets for integrative analysis with LPA in the current study. It should be noted, however, that many of these studies are cross-sectional. Thus, while they can provide evidence for associations between variables at a single point in time, they have limited ability to make predictive claims. Longitudinal, prospective studies are needed to clarify the associations between these indicators and risk for recurrent depression.

Clinical Indicators.

Age at First Onset. Several studies have examined age at first-episode onset as a predictor of depression trajectories. Many have reported that an earlier onset is related to greater risk (e.g., (Zisook et al., 2007; O'Leary & Lee, 1996; Jeuring et al., 2018). For example, one study

recruited 3,896 outpatients with MDD ages 18–75- from primary and psychiatric care practices (Zisook et al., 2007). The researchers found that earlier age at first episode onset was associated with multiple indicators of greater disease burden (i.e., poorer social and occupational functioning and quality of life, greater symptom severity, increased suicide attempts), including more lifetime episodes of depression, compared to those with later ages at first episode onset. Likewise, one prospective study examined seven-year mortality and recurrence risk in 234 patients ages 22-85 in a trial of electroconvulsive therapy for MDD and found that earlier age at onset was associated with greater risk for recurrence and hospital readmission over the seven-year period (O'Leary & Lee, 1996). Another prospective study followed 378 individuals ages 60+ with MDD, dysthymia, and minor depression, as well as healthy controls, for six years to examine predictors of depression onset and course (Jeuring et al., 2018). They found that among the depressed participants, an earlier age at onset was associated with an 'unfavourable' (i.e., chronic or recurrent) course of depression.

Depression Symptom Severity. Evidence suggests that more severe symptoms during the index episode of MDD may be related to increased risk for recurrences. For example, a study of 201 depressed hospital patients ages 18-65 found that those with a severe symptom profile in their most recent episode of MDD (defined as several marked and distressing ICD-10 depressive symptoms accompanied by severe functional impairment) were at five times higher likelihood of developing recurrent depression compared to those with mild to moderate symptom profiles (Lye et al., 2020). In a study of 100 depressed inpatients over age 18, O'Leary et al. (2000) found that a Hamilton Depression Rating Scale (HRSD) score of ≥ 20 on admission into the study predicted recurrence leading to re-hospitalization during an 18-month follow-up period. In a study of 7,199

depressed inpatients, Kessing (2004) further demonstrated that greater ICD-10 depression severity is associated with higher risk for recurrence during a six-year follow-up period.

Anhedonia Symptom Severity. Anhedonia, defined as reduced pleasure and deficits in motivation and reward processing (American Psychiatric Association, 2013), has been suggested as a marker of a more severe depression and, as such, has also been linked to risk of depression recurrence. In a cross-sectional study of 90 adolescents with MDD, greater severity of anhedonia was associated with more severe clinical correlates including a greater number of lifetime depressive episodes (Gabbay et al., 2015). Another study included 1,887 depressed individuals, some of whom were on their first onset episode of depression and some in a recurrent episode (Ren et al., 2023). The researchers found that individuals in a recurrent episode displayed greater severity of anhedonia than individuals in a first-onset episode of depression.

Anxiety Symptom Severity. Anxiety symptoms are highly prevalent and frequently co-occur in individuals with depression (Kessler et al., 1996). Evidence suggests that those with higher levels of anxiety may be at increased risk for adverse clinical outcomes as well as recurrent depression as opposed to a single episode of depression. For example, Andreescu et al. (2007) included 181 participants ages 70+ in a late-life depression treatment study and found that high pre-treatment levels of anxiety increased both risk of treatment non-response and risk for recurrence in the two years following treatment. In addition, a retrospective study compared 101 individuals with recurrent depression to 99 individuals who had experienced only one episode (Nuggerud-Galeas et al., 2020). Findings indicated that those in the recurrent group were significantly more likely to have a history of anxiety disorders compared to the nonrecurrent group. Furthermore, a meta-analysis of 13 studies of adults who had completed a course of CBT for depression investigated factors associated with an increased risk of relapse and/or recurrence

after treatment (Wojnarowski et al., 2019). They found that high pre-treatment scores on the Beck Anxiety Inventory (BAI) were associated with shorter time to relapse or recurrence after treatment.

Childhood Maltreatment Indicators.

Maltreatment in childhood, including exposure to physical, sexual, or emotional abuse or neglect, raises the risk for the onset of MDD three-fold (Gilbert et al., 2009). A meta-analysis of 16 epidemiological studies including 23,500 participants found that individuals with a history of childhood maltreatment were at elevated risk of developing recurrent and persistent depression compared to those without a history of childhood maltreatment (Nanni et al., 2012). Similarly, a study by Opel et al. (2019) assessed 275 depressed individuals at baseline and a two-year follow-up and found that history of childhood maltreatment was significantly associated with depression recurrence.

Childhood emotional abuse has been identified as a core component of child maltreatment that has severe developmental consequences (Schulz et al., 2017). One form of emotional abuse is antipathy, defined as 'criticism, hostility, coldness, or rejection shown by parent figures towards the child (Bifulco et al., 1994). Another form is neglect, which can involve disinterest in material care (e.g., feeding and clothing), health, schoolwork, and friendships (Bifulco et al., 2005) as well as the absence of emotional support or failure to facilitate a child's emotional or cognitive development (Hart & Brassard, 1991). One meta-analysis examined 184 studies that reported an association between childhood maltreatment and depression outcomes in adult populations. Findings indicated that maltreated individuals were significantly more likely to develop depression in adulthood, had an earlier depression onset, and were twice as likely to develop recurrent or treatment-resistant depression. This was particularly salient for childhood

emotional abuse (Nelson et al., 2017). In addition, a prospective study that followed 165 individuals for 2.5 years found that childhood emotional maltreatment predicts a shorter time from onset to recurrence (Liu et al., 2009). Numerous studies have shown that emotional abuse is a particularly salient predictor of adult depression, over and above the effects of other forms of childhood maltreatment (e.g., Neumann, 2017; Martins et al., 2014).

Childhood physical abuse and sexual abuse were also considered as indicators of depression onset and recurrence. In the present study, physical abuse is defined as hitting or other attacks (e.g., with implements such as belts and sticks, punching, kicking) by caregivers or other older household members (Bifulco et al., 2005). Sexual abuse is defined as physical contact or approach of a sexual nature by any adult to the child but excludes willing sexual contact with peers (Bifulco et al., 2005). Various meta-analyses have demonstrated that physical and sexual abuse in childhood are associated with depression over the life course. For example, Lindert et al. (2014) included 19 studies of 115,579 participants comparing history of abuse vs. no abuse before age 16 to depression after age 16. They concluded that adults who had been exposed to childhood sexual and physical abuse reported higher levels of depression after age 16 compared to those not exposed. Likewise, a longitudinal study of 1,167 non-depressed adults found that physical and sexual abuse in childhood were associated with increased risk of first onset and recurrence of depressive disorders over a two-year period (Hovens et al., 2015). Some studies have found that victims of both physical and sexual abuse are at a particularly high risk for depression (e.g., Roth et al., 1997) while others have suggested that sexual abuse is a stronger predictor of depression than physical abuse (e.g., Brown et al., 1999).

Personality Indicators.

Neuroticism. Evidence suggests that higher levels of the personality trait neuroticism, or one's tendency to experience negative affect, predict increased risk for MDD (e.g., Kendler et al., 2004; Ormel et al., 2001). Indeed, one such study identified neuroticism as "the primary personality variable that serves as a vulnerability factor for depression" (Butcher et al., 2004). Hakulinen et al. (2015) looked at data from 10 prospective community cohort studies of 117,899 participants in an individual participant data meta-analysis and found that high neuroticism was associated with an increased risk of depressive symptoms at follow-up (mean follow-up period across studies was five years). A study by Berlanga et al. (1999) included 42 patients who participated in a pharmacological treatment study for depression and examined rates of recurrence at one-year post-treatment. They found that patients who experienced a recurrence throughout this period had significantly higher neuroticism scores than patients who did not. Furthermore, a prospective study of 91 subjects from the Longitudinal Aging Study Amsterdam, who were depressed at baseline but had recovered over the course of three years, was conducted to determine whether personality predicts recurrence of late-life depression (i.e., 55+ years of age) (Steunenberg et al., 2010). Participants were followed over six-years and results indicated that neuroticism scores were significantly associated with depression recurrence at follow-up.

Extraversion. Extraversion, or the tendency to focus on gratification obtained from outside the self, may also be a relevant personality trait in the onset and recurrence of depression. In addition to associations with neuroticism, the aforementioned Hakulinen et al. (2015) study found a significant negative association between extraversion scores and depressive symptoms at follow-up. A review by Kotov et al. (2010) including 175 studies also found significant associations between low extraversion and the presence of depressive symptoms in participants. However, other studies did not find significant associations between extraversion and depression

outcomes. For example, Kendler et al. (2006) conducted a longitudinal study of 20,692 members of same-sex twin pairs from the Swedish Twin Registry and found that extraversion is only weakly associated with risk for MDD. Another study examining baseline and two-year follow-up data from 2,981 respondents found that neuroticism, and not extraversion, predicted recurrence at two-year follow-up (Noteboom et al., 2016).

Objectives

The objectives of the present study are to 1) identify latent profiles of risk in currently depressed individuals using Latent Profile Analysis (LPA); and 2) compare the likelihood of membership in each profile for individuals who are a) in a first episode preceded by a major stressful life event, b) in a first episode not preceded by a major stressful life event, or c) in a recurrent episode. I hypothesize that 1) individuals in a recurrent episode and 2) individuals in a first-onset episode that was *not* preceded by a major stressful life event will be more likely to belong to high-risk profiles (i.e., profiles characterized by an early age at onset, high severity of depression, anhedonia, and anxiety symptoms, high severity of childhood maltreatment, high neuroticism, and low extraversion). In contrast, I hypothesize that individuals in a first-onset episode that was preceded by a major stressful life event will be more likely to belong to profiles characterized by low levels of these risk indicators.

The overall objective is to lay the groundwork for reliably forecasting at the time of initial depression onset who is and is not prone to recurrent depression. Results have the potential to inform the dissemination of tailored treatment and maintenance resources to those who need them most, ultimately alleviating the individual and global burdens of major depression.

Chapter 2: Methods

Participants

Participants included 853 individuals drawn from six larger projects assessing psychological and/or biological risk factors for depression in adults (Study 1: CAN-BIND-1 [CBN01; Lam et al., 2016]; Study 2: CAN-BIND-4 [CBN04; Cunningham et al., 2021]; Study 3: Ontario Mental Health Foundation [OMHF, Bulmash et al., 2009]) or in adolescents and young adults (Study 4: Psychobiology of Adolescent Depression Project [PAD; Harkness et al., 2011]; Study 5: Blue Sky Project [BSP; Harkness et al., 2015]; Study 6: Adolescent Risk Project [ARP; Harkness et al., 2006]). To be included in the current project, participants had to meet DSM-IV-TR criteria (American Psychiatric Association, 2000) for a current episode of MDD, as assessed with a structured diagnostic interview (see below). Exclusion criteria for all studies included a history of psychotic disorders, bipolar disorder, substance dependence, or acute suicidality. For the current analyses, participants in the healthy comparison groups of the above studies, and participants who did not meet current MDD criteria but may have met criteria for a different psychiatric disorder, were also excluded.

Participants were recruited from the Kingston and/or Greater Toronto Area communities by way of advertisements or clinician referrals (Studies 2-6). Participants from Study 1 were recruited from six outpatient centres across Canada. The combined full sample size from these six larger projects was 1,447 individuals (Study 1: n = 323; Study 2: n = 222; Study 3: n = 214; Study 4: n = 209; Study 5: n = 300; Study 6: n = 179). Of these, 583 participants were excluded for diagnostic reasons, as outlined above (Study 1: n = 112; Study 2: n = 117; Study 3: n= 0; Studies 4 and 5: n = 267; Study 6: n = 87). An additional 11 were excluded as they had missing data on all variables of interest (Study 3: n = 7; Study 5: n = 4). Thus, final analyses for objective

1 included a total of 853 participants. Study 3 did not collect data on four variables of interest: anxiety symptoms, anhedonia, neuroticism, and extraversion. For the remaining variables, data were missing at-random. Table 1 presents descriptive data for the final included sample.

Table 1. *Demographic Characteristics Stratified by Study and in the Overall Sample.*

Study	*N*	*Sex: Female (%)*	*Ethnicity: White (%)*	*Age range*	*Age M (SD)*	*Years of Education M (SD)*
Study 1 (CBN01)	211	133 (63)	142 (67)	18-61	35.30 (12.65)	15.89 (2.14)
Study 2 (CBN04)	105	77 (73)	78 (74)	18-66	31.54 (13.97)	15.50 (2.28)
Study 3 (OMHF)	207	132 (64)	NR	20-66	41.37 (12.28)	16.02 (2.83)
Study 4 (PAD)	85	66 (78)	70 (82)	12-21	16.41 (1.86)	11.14 (1.85)
Study 5 (BSP)	153	114 (75)	109 (71)	15-33	21.15 (3.42)	13.88 (1.38)
Study 6 (ARP)	92	66 (72)	89 (97)	13-21	15.99 (1.73)	10.66 (1.82)
Overall sample	853	588 (69)	488 (75.5)[1]	12-66	29.81 (13.97)	14.51 (3.04)

Note. NR= not reported.

[1] Calculated using only studies that reported ethnicity data (n=646).

For objective 2, life event data could not be analyzed for approximately 50% of the full sample. Of these individuals, 242 were missing life event data. A further 177 had life event data but were excluded from the present analyses because they had chronic depression (i.e., an onset date of at least two years prior to the interview date). Thus, the interviewer could not assess for life events that occurred prior to the index episode onset. An additional 13 individuals were excluded at this stage due to missing data on the 'number of previous episodes of depression' variable. Distal outcome analyses for episode groups were therefore performed on a reduced sample of 421. Demographic characteristics of this sample are presented in Table 2, stratified by episode group. There were no significant differences among episode groups on sex or ethnicity. However, there were significant differences based on age and education level. As expected,

Table 2. *Demographic Variables Stratified by Episode Group (n = 421).*

	First episode with stressor (*n* = 63; 7.4%)	First episode no stressor (*n* = 129; 15.1%)	Recurrent episode (*n* = 229; 26.8%)	Omnibus Test Statistic ($\chi 2$ or F)	*p-value*
Sex[1] *n* (%)					
Female	48 (76.2)	86 (66.7)	167 (72.9)	2.39	.303
Male	15 (23.8)	43 (33.3)	62 (27.1)		
Age *M*(*SD*)					
Range = 12-66	21.8 (8.6)	23.1 (10.43)	30.37 (14.19)	20.18	<.001
Ethnicity[2] *n* (%)					
White	41 (65.1)	83 (64.3)	138 (60.3)	1.73	.422
Black	1 (1.6)	2 (1.6)	2 (0.9)		
Asian	6 (9.5)	11 (8.5)	13 (5.7)		
Indigenous	2 (3.2)	1 (0.8)	1 (0.4)		
Hispanic	2 (3.2)	3 (2.3)	5 (2.2)		
Other	3 (4.8)	13 (10.1)	14 (6.1)		
Years of Education *M(SD)*	13.18 (3.34)	12.94 (3.28)	14.93 (2.73)	17.81	<.001

[1] Data on gender identity was not collected. Thus, the binary sex variable is reported here.
[2] While all ethnicity categories are presented here for descriptive purposes, due to low cell counts, all analyses were conducted on a dichotomous ethnicity variable (1=White, 2=BIPOC). Study 3 did not collect ethnicity data, thus data for this variable are provided for *n* = 331.

average age and years of education in the recurrent group were significantly higher than those in the first episode with a stressor group and the first episode no stressor group.

Measures

Depression and Comorbid Diagnoses

For adult participants, either the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First, 2015) or the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to determine diagnoses of MDD and comorbid conditions. For adolescent participants, the child and adolescent version of the Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) was used. The SCID, MINI, and K-SADS are semi-structured interviews that include stem questions and follow-up probes querying the symptoms of Axis I psychiatric disorders. Interviews were conducted by trained clinicians or by senior graduate students in clinical psychology trained and supervised by a registered clinical psychologist. All interviews demonstrate excellent reliability and clinical validity and are widely used in research and clinical practice (Osório et al., 2019, Pettersson et al., 2018, Lauth et al., 2010). Psychometric properties of each interview within the present sample can be found in the original publications (Study 1: Lam et al., 2016; Study 2: Cunningham et al., 2021; Study 3: Bulmash et al., 2009; Study 4: Harkness et al., 2011; Study 5: Harkness et al., 2015; Study 6: Harkness et al., 2006). Demographic variables, medication history, and depressive episode history were also assessed at this time.

Depression Severity

Severity of depression was assessed with either the self-report Beck Depression Inventory (BDI-II; Beck et al., 1996; Studies 3, 4, 5, and 6) or the clinician Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979; Studies 1 and 2). Scores were

standardized prior to analyses to permit the use of an omnibus depression severity score. While these tools vary somewhat in the specific depressive symptoms measured, evidence suggests that they have strong concurrent validity for assessing overall depression severity (Svanborg & Åsberg, 2001), which is of primary importance for the current project. In addition, evidence suggests a strong correlation between BDI and MADRS total scores (Lahlou-Laforêt et al., 2015).

The BDI-II is a 21-item self-report questionnaire that assesses severity of depressive symptoms over the past two weeks. Items represent a range of depressive symptoms, including sadness, pessimism, change in appetite, and change in sleep patterns, all of which are rated on a 4-point scale from 0 to 3. Total BDI-II scores can range from 0 – 63, with higher scores indicating more severe depressive symptoms. The BDI-II has good psychometric properties and is one of the most widely used measures of depression severity in research and clinical practice (Beck et al., 1996)For all questionnaires, McDonald's omega (ω) was calculated to assess internal consistency within the current sample. Values above 0.70 are considered acceptable, and values above 0.80 indicate good reliability. McDonald's omega was used rather than Cronbach's alpha because evidence suggests that it provides a more accurate and flexible estimate of internal consistency by accommodating differences in item loadings, accounting for potential measurement error, and appropriately handling multidimensional scales (Hayes & Coutts, 2020). In the present sample, McDonald's omega (ω) for the BDI was 0.95, indicating good reliability.

The MADRS is a clinician-rated interview designed to assess depression severity in individuals with mood disorders. It includes 10 items that measure sadness, inner tension, reduced sleep and appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Overall scores range from 0-60, with higher scores indicating

more severe depression. The MADRS demonstrates good psychometric properties (Vestin et al., 2023). McDonald's omega (ω) for the MADRS in the present sample was 0.96.

Anhedonia

Anhedonia was assessed using either the self-report Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015; Study 1), the clinician administered version of the Snaith-Hamilton Pleasure Scale (SHAPS-C; Snaith et al., 1995; Study 2), or the Anhedonic Depression subscale of the MASQ (MASQ-AD; Watson et al., 1988; Studies 4, 5, and 6). Study 3 did not collect data on anhedonia. Scores were standardized prior to analyses for ease of comparison. Studies have shown that total scores on DARS are strongly correlated with total scores on the SHAPS-C (Gorostowicz et al., 2023). No studies have directly compared the MASQ-AD to the SHAPS-C or the DARS. However, it was the only source of anhedonia data collected for these studies.

The DARS is a 17-item self-report questionnaire that measures loss of interest and pleasure in four areas: hobbies, food/drinks, social activities, and sensory experiences. Participants are asked to generate examples of enjoyable activities or stimuli in each domain and rate whether they elicit pleasure on a 5-point Likert scale: 0= Not at all, 1= Slightly, 2= Moderately, 3= Mostly, 4= Very much. The total score is a sum of all items, and ranges from 0-68, with lower scores indicating more severe anhedonia. The DARS has demonstrated good reliability and validity in diverse samples (Rajeh et al., 2022). In the current sample, McDonald's omega (ω) was 0.98.

The SHAPS-C is a 14-item, clinician-rated measure of anhedonia. Participants are asked to rate the extent to which they agree with certain statements, e.g., "I would enjoy being with my family or close friends" on a 4-point Likert scale: 0 = strongly disagree, 1 = disagree, 2 = agree, 3 = strongly agree. The items cover similar areas to the DARS: social interaction, food and drink,

sensory experience, and interests/pastimes. Total scores can range from 0 to 42, with higher scores indicating higher levels of anhedonia. Evidence suggests that the SHAPS-C is a valid and reliable measure of anhedonia in both clinical and non-clinical samples regardless of differences in demographic features (Gürcan et al., 2022). McDonald's omega (ω) in the present sample was 0.94.

The 21-item MASQ–Anhedonic Depression subscale (MASQ-AD; Watson et al., 1988) is similar in format to the MASQ-GDA but asks about anhedonia (e.g., "felt really happy," reverse scored). Individuals are asked to rate, on a Likert scale from 1 ("Not at all") to 5 ("Extremely") the presence and severity of a series of anhedonic symptoms. Scores can range from 0-110, with higher scores indicating more severe anhedonia. While McDonald's omega (ω) could not be calculated for the present sample, the MASQ-AD has shown excellent internal consistency in previous psychometric studies (e.g., Buckby et al., 2007).

Anxiety Symptoms

Anxiety symptoms were assessed using the Generalized Anxiety Disorder 7-item (GAD-7; Spitzer et al., 2006; Study 1) or the General Distress-Anxiety subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-GDA; Watson et al., 1988 ; Studies 2, 4, 5, and 6). Study 3 did not collect data on anxiety symptoms. Scores were standardized prior to analyses to permit the use of a single anxiety score for each participant. No studies have directly examined correlations between the GAD-7 and the MASQ-GDA. However, the scales are similar in terms of content. Both the MASQ-GDA and the GAD-7 measure general levels of anxiety, whereas other scales, like the Anxious Arousal subscale of the MASQ (MASQ-AA), focus on somatic symptoms.

The GAD-7 is a seven-item self-report scale that is used to assess the severity of symptoms of generalized anxiety disorder. Individuals are asked about the severity of their symptoms over

the past two weeks. GAD-7 total scores range from 0-21, with higher scores indicating more severe levels of anxiety. The GAD-7 has demonstrated good psychometric properties in various samples, including adolescents and adults (Tiirikainen et al., 2019). McDonald's omega (ω) for the GAD-7 in the present sample was 0.93.

The MASQ-GDA includes a specific subset of 11 items from the full MASQ questionnaire specifically measuring general anxiety symptoms. Individuals are asked to rate, on a Likert scale from 1 ("Not at all") to 5 ("Extremely"), the presence and severity of a series of anxiety symptoms. GDA total scores range from 0-55, with higher scores reflecting greater levels of anxiety. The MASQ has excellent reliability for assessing symptoms of anxiety (Hackert, 2020). McDonald's omega (ω) for the MASQ-GDA in the present sample was 0.72.

Childhood Maltreatment

In all studies, childhood maltreatment was assessed using the Childhood Experience of Care and Abuse scale (CECA; Brown & Harris, 1994). The CECA is a semi-structured interview that assesses the quality of parental care and abuse up to age 18. Interviews are audiotaped and subsequently rated by independent judges using the standardized exemplars present in the CECA rating manuals. Ratings of 1 (little/none) to 4 (marked) are provided for parental antipathy (i.e., hostility and criticism), parental neglect, parental discord/violence, parental physical abuse, sexual abuse by any perpetrator, and bullying from peers or similarly aged siblings. For the current project, only ratings for antipathy, neglect, physical abuse, and sexual abuse were included. These indicators were treated separately rather than combined as research shows that emotional maltreatment variables (i.e., antipathy and neglect) are more salient predictors of depression outcomes than other forms of childhood maltreatment (Khan et al., 2015). The CECA has advantages over more widely used self-report measures, including addressing issues with

retrospective bias and using raters blind to psychiatric status (Brown & Harris, 1994). The CECA further shows satisfactory psychometric properties (Bifulco et al., 2005).

Neuroticism and Extraversion

Trait neuroticism and extraversion were measured using either the 240-item self-report NEO Personality Inventory-Revised (NEO PI-R; Costa & McCrae, 1992; Studies 3, 4, 5, and 6) or the 60-item NEO Five Factor Inventory (NEO-FFI; Costa & McCrae, 1992; Studies 1 and 2). The NEO-FFI consists of a subset of NEO-PI-R questions. Thus, for consistency, data for studies that used the NEO-PI-R (i.e., Studies 3, 4, 5, and 6) were re-scored to produce NEO-FFI scores. Study 3 participants received the NEO-PI-R, but item-level scores were missing, so they could not be transformed into NEO-FFI scores. Thus, participants from this study received 'missing' scores on NEO variables.

Both scales assess the personality domains of the Five Factor Model of personality (FFM), specifically Neuroticism, Extraversion, Openness to Experience, Conscientiousness, and Agreeableness. Participants are asked to read each item carefully and fill in the answer that best corresponds to their level of agreement or disagreement. Items are rated on a 5-point Likert scale: Strongly Disagree (0), Disagree (1), Neutral (2), Agree (3), Strongly Agree (4). Items are grouped into 5 personality domains, and total scores range from 0-192 points on each domain. Higher scores indicate greater evidence of the domain. For the current analysis, only scores on Neuroticism and Extraversion were examined. The NEO-FFI has demonstrated sound reliability and validity in several psychometric studies (e.g., Anisi, 2012; Dwan et al., 2017).

Stressful Life Events

In all studies, stressful life events were assessed using the Life Events and Difficulties Schedule (LEDS; Bifulco et al., 1989). The LEDS is a semi-structured contextual interview and

rating system that assesses life stress across various domains: health, housing, employment, education, money, criminal or legal issues, accidents, and personal relationships (with romantic partners and family and friends). Trained graduate student interviewers administered the LEDS to participants. Following the interview, trained research assistants listened to digital recordings of interview content and created written summaries of each stressful life event. These written vignettes were then read aloud to a panel of 2-3 research assistant raters who were "blind" to any other participant characteristics (e.g., depression status). Events were rated in terms of severity on a 5-point scale: 5-marked, 4-high moderate, 3-low moderate, 2-some, 1-little/none. Ratings were based on a manual that contains over 5,000 examples that are used to standardize the ratings. The raters received extensive training in contextual stress assessment by Dr. Kate Harkness, an international expert in these methods. The LEDS has sound psychometric properties including reliability (i.e., levels of inter-rater agreement of 80% or more) and validity (i.e., high levels of agreement between different informants) (Beards et al., 2020).

Studies have demonstrated that highly threatening stressful life events are especially potent for provoking depression onset (Brown & Harris, 1978; Kendler et al., 1998). In addition, evidence suggests that stressful life events that occur within 3-6 months prior to a depressive episode are most etiologically relevant to episode onset (Monroe et al., 2019). Thus, for the current project, the presence versus absence of a 'very undesirable' stressful life event (i.e., an event that received a severity rating of either 3-low moderate, 4-high moderate, or 5-marked) within six months prior to the start of the participant's current depressive episode was used to define groups for analysis.

Procedure

Ethical approval for each study was obtained by each institution's research ethics board. All participants and a parent or guardian for those under 18 provided written informed consent. Full details regarding each study procedure are provided in previous reports. The procedures of each study differed somewhat. However, across all studies, participants received a diagnostic interview, clinical scales, and psychological scales (i.e., NEO-FFI, if relevant) at an initial baseline session.

In all studies, the CECA interview was conducted at a second session 1-2 weeks after baseline to reduce participant burden. In Studies 2, 3, 4, and 5, the LEDS interview was also conducted at this second baseline session. However, in Study 1, participants completed the LEDS following 16 weeks of anti-depressant medication treatment. In Study 6, participants completed the LEDS following randomization to 16 weeks of cognitive-behavioural therapy, interpersonal psychotherapy, or anti-depressant medication treatment. In all studies, the LEDS covered the period from 6 months prior to onset of the index episode to the date of the interview. All projects also included additional measures not of relevance to the current project.

Data Analysis

Preliminary Analyses

Data cleaning and preliminary analyses were conducted using version 28.0 of SPSS (IBM Corp., 2021). Data cleaning involved combining variables of interest from the six completed studies and ensuring that they were coded the same way throughout. Each individual dataset was also checked for formatting errors, outliers, and impossible values. A preliminary analysis examining any differences in sex, ethnicity, and education level between groups (i.e., first episode preceded by a stressful life event, first episode not preceded by a stressful life event, recurrent episode) was conducted using either chi-squared tests or one-way analyses of variance

(ANOVA) followed by Tukey's HSD. Further, following selection of the optimal profile solution, differences between demographic variables across profiles were assessed using Wald chi-square tests in a distal outcome analysis.

Primary Analyses

Objective 1: Identify latent profiles of risk in individuals in a current episode of depression using latent profile analysis (LPA). The DPMs suggest that there are distinct groups of depressed individuals characterized by differences in underlying risk indicators for recurrent depression. Latent Profile Analysis (LPA) is a technique used for recovering hidden groups in data by obtaining the probability that individuals belong to different groups defined using continuous observed variables (Ferguson et al., 2019). In alignment with my first objective, I used MPlus software system version 8.3 to detect underlying subgroups in depression risk variables (i.e., age at first episode onset; anxiety symptom severity; depression symptom severity; anhedonia; severity of childhood antipathy, neglect, physical abuse and sexual abuse; neuroticism; and extraversion) following the steps outlined by Ferguson et al. (2019). Any risk indicator variables that had not already been standardized (i.e., all variables except for anxiety symptoms, depression severity, and anhedonia) were z-transformed prior to inclusion in analyses so they could all be displayed on the same scale. Maximum likelihood estimation was used to account for data missing at-random. As LPA is a relatively new statistical technique, there are currently no established methods of estimating required sample size (Dziak et al., 2014; Tein et al., 2013). However, simulation studies have suggested minimum overall samples of 300 to 500 (Nylund-Gibson & Choi, 2018; Tein et al., 2013). Thus, the present sample size of 853 participants across six completed studies is satisfactory.

In terms of model selection, LPA lacks a gold standard for model fit indicators. Therefore, multiple fit indices in conjunction with model parsimony and meaningful theoretical interpretation were used to determine the best-fitting model (Nylund et al., 2007). Given that LPA is an iterative process, two to seven models were compared, as is often done in published LPA studies (Masyn, 2013; Tein et al., 2013). The following indices were evaluated for each model: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample-size adjusted Bayesian Information Criterion (SSA-BIC), entropy, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR-LRT; Lo et al., 2001), Parametric Bootstrapped Likelihood Ratio Test (PBLRT; Peel & McLachlan, 2000), and whether the minimum profile size consisted of 8% or less of the total sample, as these profiles may be spurious (Nylund-Gibson & Choi, 2018). All LPAs were initially performed with the default number of random starts (50, 5). The selected profile was re-run with increased random starts (i.e., 100, 25; 500, 50) to ensure replication of the global maxima and protect against misidentification errors. There was no change in the profiles from increasing random starts. Following selection of the optimal latent profile solution, parameter comparisons using Wald chi-square tests were performed to examine significant differences between risk indicators across profiles. Statistical significance was set at $\alpha = 0.008$ to control for Type-I errors (i.e., Bonferroni Correction).

Objective 2: Compare the likelihood of membership in each profile for individuals who are a) in a first episode preceded by a major stressful life event, b) in a first episode not preceded by a major stressful life event, or c) in a recurrent episode. In line with the DPMs, I hypothesized that recurrent individuals, and individuals in a first episode that is not precipitated by a stressful life event, will be more likely to belong to profiles characterized by high scores on the 10 risk indicators. In contrast, individuals in a first episode that is precipitated

by a stressful life event will be more likely to belong to low-risk profiles. For my second objective, I tested these hypotheses by performing distal outcome analyses. Following selection of the optimal latent profile solution, this involved conducting Wald chi-square tests to examine significant differences in likelihood of membership in each profile within each group of interest: first episode preceded by a stressful life event, first episode not preceded by a stressful life event, and recurrent episode. Since outcome variables were categorical (i.e., presence or absence of a stressful life event, presence or absence of recurrent episodes), a three-step DCAT command was used for the test of equality of probabilities (Lanza et al., 2013). This method was selected over one-step methods or three-step modal methods to reduce classification error and increase estimation accuracy (Nylund-Gibson & Choi, 2018).

To simplify LPA interpretation, researchers used to assign each individual to one profile only: the one for which they have the highest classification probability. This method is known as 'hard classification'. However, recent studies advise against this as it often leads to information loss (i.e., due to the 'latent' structure of the analysis, individuals may not fit neatly into one profile). For example, if an individual has membership probabilities of 0.51 for Profile 1 and 0.49 for Profile 2, assigning them solely to Profile 1 ignores the significant probability of them belonging to Profile 2 (Nylund-Gibson & Choi, 2018). Thus, the present analyses were interpreted using membership probabilities rather than hard classification.

Chapter 3: Results

Objective 1: Identify latent profiles of depression risk.

Descriptive statistics for risk indicator variables can be found in Table 3. Pearson correlations between risk indicator variables can be found in Table 4. Two to seven latent profile models were tested. The log likelihood value quantifies how well a model fits the observed data. It is the natural logarithm of the likelihood function, which represents the probability of the observed data given the model parameters (Nylund et al., 2007). Thus, higher log likelihood values indicate better model fit. The best log likelihood value must be replicated across multiple simulations to ensure the stability and reliability of the model. To replicate the best log likelihood value, the five through seven latent profile models required increased random starts (i.e., 5,000, 10,000). This indicates that these models attempted to form more profiles than fit the data, and a more parsimonious model is needed (Ferguson et al., 2019).

To compare models with different numbers of profiles, AIC, BIC, and SSA-BIC indices were considered, with lower values suggesting better-fitting solutions. As seen in Table 5, each of these indices successively decreased with an increasing number of latent profiles. As such, they failed to converge on an optimal solution, and likely overestimate the goodness of fit of higher profile models (see Nylund et al., 2007). This result is not uncommon in LPA practice (Nylund-Gibson et al., 2018).

The LMR-LRT statistic compares goodness-of-fit between two models: one more complex (i.e., more parameters, more profiles) and one more parsimonious. A significant LMR-LRT value ($p < .05$) indicates that the more complex model provides a significantly better fit to the data than the model with one fewer profile. In the present analysis, the LMR-LRT suggested that each successive model was a better fit than the one before it, up until the five-profile solution,

Table 3. *Descriptive Statistics for Risk Indicator Variables for the Full Sample (N = 853)*

Variable	*M (SD)*
Clinical Characteristics	
Age at Onset	20.88 (10.65)
Depression Severity	
MADRS[1]	29.00 (6.34)
BDI-II[2]	29.40 (9.90)
Anxiety Symptoms	
GAD-7[3]	11.79 (5.02)
MASQ-GDA[4]	28.71 (7.79)
Anhedonia	
DARS[5]	33.80 (14.19)
SHAPS-C[6]	34.12 (6.70)
MASQ-AD[7]	81.93 (12.50)
Childhood Maltreatment Severity	
Antipathy	1.98 (1.03)
Neglect	1.66 (0.86)
Physical Abuse	0.92 (1.35)
Sexual Abuse	0.71 (1.31)
Personality	
Neuroticism	36.56 (10.10)
Extraversion	28.56 (7.51)

Note. Study 3 did not collect data on anxiety symptoms or anhedonia.

[1] Study 1, Study 2
[2] Study 3, Study 4, Study 5, Study 6
[3] Study 1
[4] Study 2, Study 4, Study 5, Study 6
[5] Study 1
[6] Study 2
[7] Study 4, Study 5, Study 6

Table 4.

Pearson Correlations Between all Risk Indicator Variables (n = 853)

Variable	1	2	3	4	5	6	7	8	9	10
1. Age at Onset	1.0									
2. Depression Severity	-.03	1.0								
3. Anxiety Symptoms	.04	.44**	1.0							
4. Anhedonia	.10*	.19**	.10*	1.0						
5. Antipathy	.12**	.15**	.14**	.03	1.0					
6. Neglect	.02	.15**	.06	.07	.62**	1.0				
7. Physical Abuse	-.04	.08*	.03	.06	.54**	.47**	1.0			
8. Sexual Abuse	-.10**	.14**	.18**	.09*	.30**	.23**	.24**	1.0		
9. Neuroticism	.11*	.19**	.24**	.01	.16**	.08	.10*	.10*	1.0	
10. Extraversion	.13**	-.13**	-.06	-.04	.06	.03	.04	.06	.20**	1.0

Note. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 5. *LPA Comparative Fit Indices and Model Characteristics (n = 853).*

No. of profiles	AIC	BIC	SSA-BIC	LMR-LRT	BLRT	Final log-likelihood	Entropy	Smallest profile (% of total sample)
2	18451.621	18598.833	18500.386	$p < .001$	$p < .001$	-9194.81	.86	29.23
3	18044.721	18244.169	18110.789	$p < .001$	$p < .001$	-8980.36	.91	8.40
4[a]	17642.986	17894.670	17726.357	$p = .007$	$p < .001$	-8768.49	.82	8.70
5	17408.005	17711.925	17508.680	$p = .002$	$p < .001$	-8640.00	.87	8.84
6	17278.696	17634.853	17396.675	$p = .30$	$p < .001$	-8564.35	.85	4.50
7	17094.112	17502.505	17229.394	$p = .41$	*p= 1.00*	-8461.06	.84	6.70

[a] Chosen as optimal profile solution.

Note: LPA = Latent Profile Analysis; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; SSA-BIC = Sample-Size Adjusted Bayesian Information Criterion; LMR-LRT = Lo-Mendell-Rubin Likelihood Ratio Test; BLRT = Bootstrap Likelihood Ratio Test.

which was optimal. However, as previously mentioned, the five-profile solution required increased random starts to replicate the best log likelihood value. Thus, it is likely over-extracted and unstable (Nylund-Gibson et al., 2018). This suggests that the next best-fitting model, the four-profile solution, may be optimal.

Entropy was roughly equivalent for all reported models, with the two through seven latent profile models having values > .80. As such, these models all had highly discriminating latent profiles (Weller et al., 2020). The three-profile model had the highest entropy value (.91). However, a vast majority of the total sample was assigned to one profile (77%), suggesting that information may be lost compared to models with more profiles. In addition, theoretical interpretation is an important consideration in selection of an optimal profile solution (Ferguson et al., 2019), and the four-profile model yielded more theoretically interesting differences between profiles than the three-profile model. The six and seven-profile models both had at least one profile that represented < 8% of the sample, indicating potential over-extraction.

Therefore, the four-profile model was selected as the optimal solution based on comparison indices (i.e., lower AIC, BIC, SSA-BIC, and LMR-LRT), satisfactory entropy, model parsimony, signs of possible data over-fitting with increasing latent profiles, and meaningful theoretical interpretation. This model grouped participants primarily based on high or low childhood maltreatment variables, symptom risk variables, and overall risk (see Figure 2). As such, profiles were labelled as follows: Profile 1: “Low Overall Risk”, Profile 2: “High Childhood Maltreatment, Low Symptom Risk”, Profile 3: “Moderate Overall Risk”, Profile 4: “High Overall Risk”. Final profile counts based on the most likely profile membership for each individual are presented in Table 6.

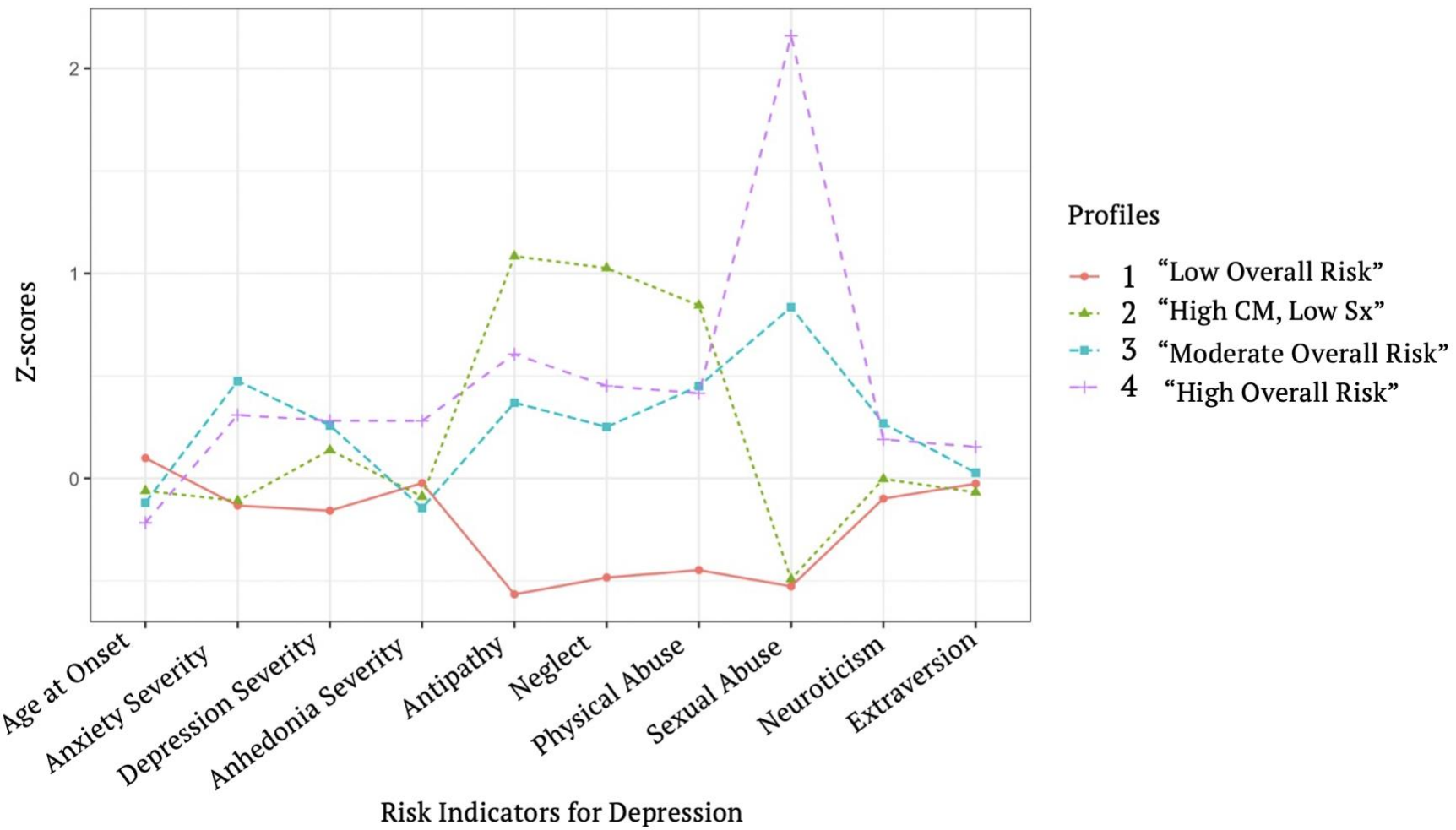

Figure 2. Plot of the four-profile solution of risk indicators for depression.
Note. Data summarized in Z-scores. CM= Childhood Maltreatment, Sx= Symptom.

Table 6. *Four-Profile Model: Final Profile Counts and Proportions for Most Likely Profile Membership (n = 853)*

Profiles	*n*	Proportion of total sample (%)
Profile 1:	531	62.25
Profile 2:	133	15.60
Profile 3:	74	8.70
Profile 4:	115	13.50

Risk indicator differences across profiles are displayed in Table 7. Omnibus chi-square tests demonstrated significant differences among profiles on every risk indicator except for anhedonia, neuroticism, and extraversion. Differences in age at onset were significant at the $p < .05$ but not the $p < .008$ level. Profile 1 ("Low Overall Risk") had significantly lower depression severity, antipathy, neglect, and physical abuse than all other profiles. It also had significantly lower anxiety symptoms and sexual abuse than profiles 3 and 4.

Profile 2 ("High Childhood Maltreatment, Low Symptom Risk") had significantly higher antipathy and neglect than all other profiles, and significantly higher physical abuse than profiles 1 and 4. While this profile evidenced significantly higher depression severity than profile 1, it did not differ significantly from the low risk profile on the other psychological indicators and evidenced significantly *lower* anxiety symptoms and sexual abuse severity than profiles 3 and 4.

Profile 3 ("Moderate Overall Risk") had significantly higher anxiety and depression symptoms, higher severity of antipathy, neglect, physical abuse, and sexual abuse than profile 1, and significantly higher level of anxiety symptoms and sexual abuse severity than profile 2. However, this moderate profile evidenced significantly *lower* antipathy and neglect than profile 2 and lower sexual abuse severity than profile 4.

Table 7.

Risk Indicator Differences Across Latent Profiles (n = 853)

Variable	Profile 1 *"Low Overall Risk"*	Profile 2 *"High CM, Low Sx Risk"*	Profile 3 *"Moderate Overall Risk"*	Profile 4 *"High Overall Risk"*	Omnibus $\chi 2$	*p-value*
Clinical Variables						
Age at Onset	0.10 (0.05)[a]	-0.06 (0.10)[a,b]	-0.12 (0.12)[a,b]	-0.22 (0.09)[b]	10.61	.014*
Depression Severity	-0.16 (0.05)[a]	0.14 (0.13)[b,c,d]	0.26 (0.14)[b,c,d]	0.28 (0.10)[b,c,d]	21.90	<.001**
Anxiety Symptoms	-0.13 (0.06)[a]	-0.11 (0.14)[a]	0.48 (0.15)[b,c]	0.31 (0.12)[b,c]	23.57	<.001**
Anhedonia	-0.02 (0.06)[a]	-0.09 (0.11)[a]	-0.15 (0.17)[a]	0.28 (0.10)[a]	7.75	.051
Childhood Maltreatment						
Antipathy	-0.60 (0.04)[a]	1.08 (0.09)[b]	0.37 (0.16)[c,d]	0.61 (0.10)[c,d]	458.53	<.001**
Neglect	-0.48 (0.04)[a]	1.03 (0.13)[b]	0.25 (0.14)[c,d]	0.45 (0.11)[c,d]	203.47	<.001**
Physical Abuse	-0.45 (0.05)[a]	0.84 (0.16)[b]	0.45 (0.14)[b,c]	0.42 (0.11)[c,d]	111.62	<.001**
Sexual Abuse	-0.53 (0.01)[a]	-0.49 (0.05)[a]	0.84 (0.14)[b]	2.16 (0.04)[c]	5931.89	<.001**
Personality						
Neuroticism	-0.10 (0.06)[a]	0.00 (0.15)[a]	0.27 (0.20)[a]	0.19 (0.11)[a]	7.70	.052
Extraversion	-0.30 (0.06)[a]	-0.07 (0.13)[a]	0.03 (0.18)[a]	0.15 (0.13)[a]	1.90	.592

Note. Data summarized as mean (SE) in Z-scores. Alphabetized superscripts denote profiles that differ significantly by Wald $\chi 2$ test parameter constraints. (*) indicates significance at the $p < .05$ level. (**) indicates significance at the $p<.008$ level. CM= Childhood Maltreatment, Sx= Symptom.

Profile 4 ("High Overall Risk") was distinguished by significantly higher sexual abuse severity than all other profiles, and relatively elevated levels of all other risk variables. In terms of statistical significance, severity of anxiety symptoms, depression, antipathy, neglect, and physical abuse were significantly higher than profile 1, and anxiety was also higher than profile 2. Further, this profile evidenced the earliest age of onset, which was lower than profile 1 at the $p<.05$ level. However, antipathy and neglect severity were significantly lower than profile 2.

Objective 2: Compare the likelihood of membership in each profile for individuals within episode groups.

Distal Outcomes: Demographic Variables

Distal outcome analyses were performed on a reduced sample of 421. Preliminary analyses revealed that those included in the reduced sample were significantly younger than those excluded ($M_{included}$= 27.19, $SD_{included}$= 13.15; $M_{excluded}$= 32.48, $SD_{excluded}$=14.26, $p<.001$). Those included also had lower scores on neglect ($M_{included}$= -.062, $SD_{included}$= 0.94; $M_{excluded}$= .089, $SD_{excluded}$= 1.07, p= .013) and neuroticism ($M_{included}$= -.21, $SD_{included}$= 1.02; $M_{excluded}$= .24, $SD_{excluded}$=0.91, p= .008). There were no significant differences between those included and excluded on any other demographic or indicator variables. As displayed in Table 8, there were no age, ethnicity, or education level differences across profiles. There was a significant difference in sex across profiles. Specifically, those in the "High Overall Risk" profile, $\chi 2$ = 40.82, and those in the "Moderate Overall Risk" profile, $\chi 2$ = 10.56, were significantly more likely to be Female than those in the "Low Overall Risk" profile (*ps* <.008). Individuals in the "High Overall Risk" profile were also more likely to be Female than those in the "High Childhood Maltreatment, Low Symptom Risk" profile, $\chi 2$ = 9.40, $p<.008$.

Distal Outcomes: Episode Groups

See Tables 9 and 10 for a full breakdown of episode group differences between profiles. As detailed above, data are presented in terms of probability of profile membership. Therefore, rather than assigning each individual to only one latent profile, each individual is given a probability of belonging to each profile. Thus, these probabilities change depending on the episode groups being compared. First, a test was conducted to determine if there were any significant differences within episode groups (i.e., first episode with a stressor, first episode no

Table 8.

Distal Outcomes: Demographic Differences Across Latent Profiles (n = 853)

Variable	Profile 1 *"Low Overall Risk"*	Profile 2 *"High CM, Low Sx Risk"*	Profile 3 *"Moderate Overall Risk"*	Profile 4 *"High Overall Risk"*	Omnibus $\chi 2$	*p-value*
Age	29.21 (0.69)	30.70 (1.50)	30.28 (1.90)	30.50 (1.40)	1.17	0.76
Sex[1]	0.62 (0.02)[a]	0.70 (0.05)[a,b]	0.80 (0.05)[b,c]	0.90 (0.03)[c]	44.76	<.001
Ethnicity[2]	0.80 (0.02)	0.70 (0.05)	0.72 (0.06)	0.77 (0.05)	3.64	0.30
Education level	14.61 (0.17)	14.50 (0.31)	14.17 (0.34)	14.27 (0.29)	1.86	0.60

Note. Data summarized as probability of profile membership (categorical variables) or mean (SE) (continuous variables). CM= Childhood Maltreatment, Sx= Symptom.

Alphabetized superscripts denote profiles that differ significantly by equality tests of probabilities (categorical variables: Sex and Ethnicity) or by bch-weighted equality of means tests (continuous variables: Age and Education Level) at the $p < .008$ level.

[1] Sex reported as probability of being Female.
[2] Ethnicity reported as probability of being White (total for ethnicity analyses $n = 646$).

Table 9.

Distal Outcomes: Overall Test of Episode Group Differences Between Latent Profiles (n = 421).

Comparison	Omnibus $\chi 2$	*p-value*
Overall Test	16.03	0.001**
Profile 1 vs. 2	1.73	0.19
Profile 1 vs. 3	9.37	0.002**
Profile 1 vs. 4	9.71	0.002**
Profile 2 vs. 3	2.26	0.13
Profile 2 vs. 4	1.50	0.22
Profile 3 vs. 4	0.22	0.64

Note. (**) indicates significance at the $p<.008$ level.

Table 10.

Distal Outcomes: Follow-Up Tests of Episode Group Differences Between Profile 1 and Profiles 3 and 4 (n = 421).

Comparison	Profile 1 *"Low Overall Risk"*	Profile 3 *"Moderate Overall Risk"*	Profile 4 *"High Overall Risk"*	Omnibus $\chi 2$	*p-value*
Recurrent vs. Stressor				5.62	.13
Recurrent	0.75 (0.03)	0.74 (0.08)	0.84 (0.05)		
First episode (stressor)	0.25 (0.03)	0.27 (0.08)	0.16 (0.05)		
Recurrent vs. No Stressor				16.03	.001
Recurrent	0.57 (0.03)[a]	0.83 (0.08)[b]	0.78 (0.06)[b]		
First episode (no stressor)	0.43 (0.03)[a]	0.17 (0.08)[b]	0.22 (0.06)[b]		
Stressor vs. No Stressor				3.83	.28
First episode (stressor)	0.30 (0.03)	0.58 (0.15)	0.40 (0.11)		
First episode (no stressor)	0.71 (0.03)	0.42 (0.15)	0.60 (0.11)		

Note. Data summarized as probability of profile membership. Alphabetized superscripts denote profiles that differ significantly by equality tests of probabilities at the $p < .008$ level. CM= Childhood Maltreatment, Sx= Symptom.

stressor, and recurrent episode) in membership likelihood between profiles (Table 9). The omnibus test was significant, and pairwise comparisons revealed significant differences between profiles 1 vs. 3, and profiles 1 vs. 4. Next, follow-up tests were conducted to determine where exactly these differences were within episode groups. Dummy Coding was used to facilitate three separate comparisons: 1) recurrent episode vs. first episode with a stressor; 2) recurrent episode vs. first episode no stressor; 3) first episode with a stressor vs. first episode no stressor (Table 10).

For comparison 1 and comparison 3, neither omnibus test reached significance at the $p < .008$ level. For comparison 2, the omnibus test was significant, and pairwise comparisons indicated that those in the recurrent episode group were more likely to be in the "Moderate Overall Risk" profile, $\chi 2 = 9.37$, and the "High Overall Risk" profile, $\chi 2 = 9.71$, compared to the "Low Overall Risk" profile (*ps* <.008). They also indicated that those in the first episode no stressor group were more likely to be in the "Low Overall Risk" profile compared to the "Moderate Overall Risk" profile and the "High Overall Risk" profile. An additional test was conducted to determine if there were any significant differences within parent studies (i.e., Studies 1-6) in membership likelihood between profiles. The omnibus chi-squared test did not reach significance at the $p < .008$ level, indicating that parent study was not significantly associated with profile membership.

Chapter 4: Discussion

In a large sample of currently depressed individuals, we identified four latent profiles of risk. Profiles were differentiated most dramatically by history of childhood maltreatment, and, to a lesser extent, by depression and anxiety symptom severity. We found that being in a recurrent episode and being female were significantly associated with higher likelihood of membership in the moderate and high overall risk profiles compared to the low overall risk profile. In contrast, being in a first episode not preceded by a major stressor was significantly associated with higher likelihood of membership in the low overall risk profile compared to the moderate and high overall risk profiles.

Latent Profiles of Depression Risk

The identified four-profile solution adds to the existing literature on poor prognostic indicators for depression by examining how indicators cluster together rather than examining one or few in isolation. Findings demonstrate that certain indicators were able to significantly differentiate between profiles, namely the childhood maltreatment and symptom severity variables. Whereas, other indicators did not significantly differentiate between profiles, despite studies showing that they are salient risk factors when considered alone, including anhedonia symptom severity, neuroticism, and extraversion.

Specifically, the low overall risk profile was characterized by the lowest levels of depression and anxiety symptom severity and childhood maltreatment severity. In contrast, the high overall risk profile was characterized by high severity of these indicators across the board, with particularly high severity of sexual abuse. This was also the only profile that had a significantly earlier age of onset than the low overall risk profile. The two remaining profiles were mixed, with one (High CM, low symptom severity) showing relatively low depression and

anxiety symptom severity, but the highest severity of antipathy, neglect, and physical abuse. The other (Moderate Overall Risk) showed relatively high depression and anxiety symptom severity, but lower childhood maltreatment severity than the previous two profiles.

The present study complements previous literature on LPA and depression. First, results support the contention that depression is, indeed, heterogenous (Lynch et al., 2020; Østergaard et al., 2011), and that this heterogeneity can be parsed particularly in terms of early environmental etiology and symptom presentation, at least in the current sample. This is consistent with studies included in the Lynch et al. (2020) review, which found that symptomatology is a strong area of heterogeneity in depression. It is also consistent with Xiao et al. (2023), which found that profiles characterized by higher levels of childhood maltreatment were associated with higher risk for depression. However, more research in this area is needed to converge on a set of widely replicable depression subtypes. Our study addresses shortcomings of other LPA in depression studies by using dimensional indicators, following established LPA reporting guidelines, and using a large, general sample of depressed individuals at various stages of life.

In terms of the specific indicators, results were generally consistent with the wider literature examining them separately as markers of risk. First, anxiety and depression symptom severity were lowest in the low overall risk profile and highest in the high and moderate overall risk profiles. This is consistent with previous studies demonstrating that higher anxiety and depression symptom severity are associated with higher risk (e.g., Kessing, 2004; Lye et al., 2020; Nuggerud-Galeas et al., 2020). Interestingly, we found a dissociation in childhood maltreatment across profiles, which anxiety symptom severity seems to mirror. The low CM, high symptom severity profile had particularly high antipathy, neglect, and physical abuse as well as low levels of anxiety. The high overall risk profile had particularly high sexual abuse as

well as high levels of anxiety. In contrast, depression symptom severity did not align with childhood maltreatment indicators in the same way, as symptom levels were simply lowest in the low overall risk profile, highest in the high overall risk profile, and moderate in the two other profiles. This raises the intriguing possibility that anxiety clusters together more strongly with sexual abuse compared to other forms of childhood maltreatment. To test this, future work could separate those who have experienced sexual abuse from those who have experienced other forms of childhood maltreatment but no sexual abuse and compare their levels of anxiety. If this idea were supported, it may also be worth testing whether anxiety moderates the relationship between sexual abuse and poor prognostic outcomes in depression.

In direct contrast, we did not find any significant differences among profiles in terms of anhedonia severity. This is surprising, as previous studies have found associations between higher anhedonia symptom severity and increased depression risk (Gabbay et al., 2015; Ren et al., 2023). It suggests that, while anhedonia may emerge as a salient risk indicator when considered alone, it may not be as important when considered amongst other risk indicators. Alternatively, it may be that the way we measured anhedonia in the present study did not properly capture the construct. The completed projects that made up our dataset included three different measures of anhedonia: the MASQ-AD, SHAPS-C, and DARS. While the measures all purport to measure one construct, each has a specific focus and structure, catering to different aspects of anhedonia for use in different settings. For example, the MASQ-AD was designed for the purpose of distinguishing between general distress and anhedonia in depressed individuals and is often used in research settings (Watson et al., 1988). Whereas, the SHAPS-C asks about more general experiences of pleasure and is not primarily intended for use with depressed patients (Snaith et al., 1995). The DARS was designed to capture multiple facets of anhedonia,

including social, recreational, and sensory, as and is commonly used in both clinical and research settings (Gorostowicz et al., 2023). Considering these differences, anhedonia scores may not be entirely consistent across individuals. In our study, we conceptualized anhedonia as an indicator that is separate from general symptoms of depression. Thus, perhaps the definition used in the MASQ-AD suits our purposes, and those of similar studies, best. Further research is needed to understand the role of anhedonia in depression risk and clarify the best definition of anhedonia to use for this purpose.

Domains of childhood maltreatment were the indicators that most strongly differentiated profiles in the current sample. This is consistent with a robust body of literature that has examined childhood maltreatment on its own as a predictor of multiple negative outcomes (e.g., Gilbert et al., 2009; Nanni et al., 2012; Schulz et al., 2017) and adds to this literature by showing that childhood maltreatment significantly and strongly differentiates among profiles even when considered amongst other risk indicators. Sexual abuse was particularly high in the high overall risk profile compared to all other profiles, suggesting that it may be particularly important to consider when exploring risk. In contrast, severity of childhood antipathy, neglect, and physical abuse clustered together, and were highest, in the high CM, low Sx profile, which had very *low* levels of sexual abuse severity. These findings suggest that childhood physical and emotional abuse may be associated with a particular subtype of depression that is distinct from either high or low overall risk subtypes. It would be interesting to explore whether this subtype has different etiological mechanisms than the profile with high levels of sexual abuse due to its unique syndromal manifestation. Results are consistent with previous studies demonstrating that childhood sexual abuse is a stronger predictor of adverse outcomes in depression than other forms of childhood maltreatment (Brown et al., 1999) and is associated with more complex

clinical profiles, including higher risk of comorbid conditions such as substance abuse (Rossi et al., 2023) but inconsistent with studies claiming that emotional maltreatment (i.e., antipathy and neglect) is a more salient predictor of depression risk than other forms of childhood maltreatment (e.g., Khan et al., 2015). Further research is needed for consensus. Regardless, findings highlight the importance of considering childhood maltreatment indicators separately when exploring risk. Due to its unique use of LPA, our study is the first to demonstrate differential patterns of risk in childhood maltreatment types through distinct etiological profiles incorporating multiple risk indicators within one large sample.

Age at first depressive episode onset was significantly lower in the high overall risk profile compared to the low overall risk profile. This finding is consistent with studies reporting that an earlier age at onset is a salient risk factor (Kovacs et al., 1984; O'Leary & Lee, 1996). However, age at onset did not significantly differ among any other profiles. This suggests that, while age at onset may be useful in differentiating between 'extreme' risk profiles, it may not be as strong a discriminator of depression heterogeneity as symptom severity or childhood maltreatment. Alternatively, sample characteristics may have limited our ability to test age at onset as an indicator. It could be that the higher age at onset, low risk group is made up of older people who have only ever had one or few episodes, or relatively young people whose first episode was recent. The lower age at onset, high risk group may be older people who have struggled with depression throughout their lifetime, or very young people who are already recurrent. The best design in which to examine age of first episode onset as a risk indicator would be a study of individuals who have all passed through the period of greatest depression risk.

Finally, contrary to studies demonstrating that neuroticism and extraversion are associated with poor depression prognosis (e.g., Hakulinen et al., 2015; Kotov et al., 2010; Steunenberg et

al., 2010) we did not find any significant differences across profiles based on these indicators. Like anhedonia, while neuroticism and extraversion have emerged as strong risk factors in studies that consider them in isolation, they were not as salient when considered amongst the other risk factors. Perhaps, then, childhood maltreatment and symptom severity are stronger prognostic indicators than these. However, it may be that we did not properly capture the personality constructs of interest. Of our included studies, some used the NEO-PI-R and some the NEO-FFI. The former is a more in-depth examination of the Five-Factor model of personality, where each factor is divided into six facets (e.g., for neuroticism: anxiety, angry hostility, self-consciousness, depression, impulsiveness, and vulnerability). For consistency, we re-scored all participants' questionnaires to produce NEO-FFI scores. This meant losing information about specific facets of neuroticism and extraversion that could potentially be salient risk indicators on their own. Research examining the role of personality in depression outcomes should incorporate facets to thoroughly examine each construct of interest.

Distal Outcomes: Episode Group and Sex

The second phase of the current study provided evidence that the profiles identified in the LPA had prognostic validity. Prognostically meaningful profiles would have significant implications for research and clinical purposes. Research-wise, profiles could provide insights into the etiology and maintenance of depression; by identifying which profiles are associated with poor outcomes, researchers can investigate the specific factors contributing to these differences. Clinicians can then use these insights to develop targeted prevention and treatment approaches for each patient and allocate resources more efficiently by focusing on individuals likely to belong to high-risk profiles.

Consistent with hypotheses, individuals in a recurrent episode of depression were significantly more likely to belong to the moderate and high overall risk profiles compared to the low overall risk profile, with no significant within-group differences emerging for the high childhood maltreatment, low symptom severity profile. This finding is consistent with the Dual Pathway Models (DPMs; Monroe et al., 2019; Monroe & Harkness, 2022) which propose that the reason why some individuals with depression proceed to recurrence is that they have underlying risk indicators for depression. It suggests that it is necessary to consider an individual's levels of risk on multiple indicators simultaneously, rather than their levels of risk on one or few indicators in isolation, and that an individual's history of childhood maltreatment (especially sexual abuse), in combination with symptom severity scores, are of particular importance. Findings also demonstrate that the profiles are indeed prognostically meaningful. Specifically, profiles associated with high levels of sexual abuse and anxiety (i.e., the high and moderate overall risk profiles) were associated with being recurrent, whereas the profile associated with high antipathy, neglect, and physical abuse, and low anxiety (i.e., the high CM, low symptom severity) was not. As such, if an individual on a first episode has no history of sexual abuse or high symptom severity, their risk of becoming recurrent may be relatively low, even if they have a very strong history of other forms of childhood maltreatment. Likewise, if an individual on a first episode has a history of sexual abuse and high symptom severity, they may be at particularly high risk of becoming recurrent even in the absence of other risk indicators.

Findings also have important implications for the treatment of depression. Specifically, if an individual in a first episode of depression has a strong history of sexual abuse as well as elevated symptom severity scores, clinicians may want to consider long-term maintenance treatment in addition to acute phase treatments. If, on the other hand, an individual on their first

episode does not present with these specific risk factors, then perhaps acute treatment is all they need, and precious clinical and economic resources can be spared and redirected towards the more vulnerable subgroup. This contrasts with studies that view depression as recurrent by nature and recommend long-term recurrence prevention efforts in every case (e.g., Andrews, 2001; Frank et al., 1991). Future studies should examine whether an individual's likelihood of profile membership is associated with treatment outcomes such as time to recovery, response to psychological and pharmacological interventions, and treatment efficacy. For example, it remains unknown whether those with a high likelihood of belonging to the high overall risk profile are more treatment resistant or respond differently to certain interventions compared to those likely to belong to other profiles.

Based on the DPMs, we hypothesized that individuals in a first episode *with* a preceding stressor would be more strongly represented in the low overall risk profile because, in the absence of underlying risk indicators, these individuals would theoretically require a major life event to precipitate the onset of their illness. Further, we hypothesized that individuals *without* a preceding stressor would be more strongly represented in the high overall risk profile because these individuals would theoretically not require a major life event to precipitate the onset of their illness. In direct contrast to the predictions emanating from the DPMs, we found no evidence for significant differences in profile membership among individuals in a first episode with a preceding stressor, and we found that the first episode group *without* a preceding stressor was significantly more likely to belong to the *low* overall risk profile compared to the moderate and high overall risk profiles.

These unexpected results have important implications for tests of the DPM in the future, and for informing our understanding of depression recurrence. The DPM is a novel theory that

has, until now, not been tested in any way. The current study proposed a potential cross-sectional approach to testing the tenets of the DPM that leveraged the role of life stress in precipitating the first onset. The current findings did not support the claim that those who become depressed for the first time following major life stress have lower levels of underlying risk indicators, whereas those who become depressed in the absence of stress have higher levels. On the one hand, it may be that the DPM fails to explain the association between life stress and recurrent depression as intended. On the other hand, it is possible that the DPM is a valid theory of depression recurrence and that features of the current design played an explanatory role in the unexpected findings. For example, it is important to note that the subset of individuals who were in a first episode preceded by a major stressor was small (n = 63; 7.4%), thus potentially explaining the null findings for this group. Therefore, studies including a greater number of individuals in a first episode of depression are warranted and may be necessary to detect true effects involving this subgroup. It is also worth noting that many of the included indicators were measured by self-report. Evidence suggests that life stress can influence the interpretation and reporting of personal information such as depressive symptoms. For example, one study found that attentional biases towards negative information were more pronounced in depressed individuals with high levels of life stress (Kircanski et al., 2012). Thus, it may be that individuals in a first episode without a stressor were underreporting their experiences on the self-report measures compared to the first episode with a stressor and recurrent episode groups. This underreporting on risk indicator measures could explain why the first episode without a stressor group was more likely to belong to the low-risk profile. To address this issue, future work should incorporate standardized, clinician-administered measures instead of (or in addition to) self-report measures.

It is also possible that the present cross-sectional study design is not a valid way to test the DPM's central claims. The theory proposes a within-person effect: that the presence or absence of a major stressor prior to the very first episode onset may be used to *predict* recurrent vs. non-recurrent lifetime trajectories of depression. Our study, however, is cross-sectional. Thus, it is subject to the pitfalls of using a between-study design to investigate within-person effects, as are many studies of the relationship between life stress and depression recurrence (Monroe & Harkness, 2022). We intended to use the presence or absence of major life stress prior to episode onset as a proxy for recurrence-proneness, but perhaps prospective designs are needed to truly test the model's validity. It may also be that we did not include all the most appropriate risk indicators in our LPA, and that life stress would become more relevant with the inclusion of additional indicators. Future work is therefore needed to incorporate other strong prognostic indicators for depression, such as genetic (Binder et al., 2004), family history (Gotlib et al., 2014), and neurobiological indicators (Videbech & Ravnkilde, 2004), as well as cognitive schemas (Bishop et al., 2022), as these may differentiate between profiles. For example, a study by Rowe et al. (2024) that is currently in progress seeks to examine latent profiles of environmental and neural indicators of stress sensitivity among those in a current episode of depression.

Another possibility is that the competing theory of recurrence, the Stress Sensitization Hypothesis (SSH), is correct. The SSH proposes that recurrence is a developmental phenomenon that emerges within individuals with depression due to sensitization to the major life events that precipitate early episodes. However, our findings do not appear to be consistent with the SSH either and, instead, support the criticisms of the SSH proposed by Monroe and Harkness (2022). For example, the SSH takes as its starting point that individuals with a first episode of depression

become sensitized to the major life events that precipitate this first episode and, thus, require lower levels of stress to precipitate further recurrences. This basic tenet of the SSH suggests that all first episodes are precipitated by major life stress. In the present sample, however, we found that most first episodes (129/192, 67%) were *not* preceded by major life stress. For these individuals, the question of why they experienced an episode remains. It may be that, as previously mentioned, other indicators are more relevant in this group but were not accounted for by the present LPA. The SSH also specifies that those who become depressed for the first time following major life stress are most vulnerable to develop recurrent depression. Based on this, we would expect that the first episode with a stressor group would be more likely to belong to high-risk profiles, which was not the case. In summary, neither the DPM nor the SSH was fully corroborated by our findings. Further research, particularly prospective studies following large groups of individuals across the lifespan, is necessary to elucidate the relationship between life stress and risk for recurrent depression.

Nevertheless, our findings did reveal that individuals in a recurrent episode of depression were distinct from those in a first episode based on the derived profiles, and that the recurrent group had a more high-risk profile than the first episode groups, taken together. Clearly all participants in the recurrent group were at one time in a first episode. What we could not determine from the current analyses, however, is how to stratify the first episode group in a prognostically predictive way. As noted above, future studies examining other risk indicators may be useful in this regard.

Finally, although not part of our primary research question, secondary analyses revealed that females had a significantly higher likelihood of belonging to the moderate and high overall risk profiles compared to the low overall risk profile, even though there were no significant

differences in the proportion of males and females in each episode group (see Table 2). This is consistent with robust meta-analytic evidence indicating that depression is 2-3x more prevalent in females than males (Salk et al., 2017). It may be that the reason why females are at higher risk for depression is that they have higher levels of the underlying risk indicators that characterize the high and moderate overall risk profiles (i.e., childhood maltreatment and symptom severity). This highlights the importance of early maltreatment prevention and mental health support interventions for girls specifically.

Some studies suggest that, while females are more likely than males to become depressed initially, they may not be more likely to be recurrent (Kessler et al., 1993). In our study, both females and those in a recurrent episode of depression were more likely to belong to high and moderate overall risk profiles compared to the low risk profile. One possible interpretation of this finding is that, while females were not more likely to be in the recurrent episode group, their risk profiles tended to look like those who were recurrent, suggesting that they may be more likely to become recurrent in the future. In the present analyses, comparisons focused on differences between profiles rather than between sexes. Future work aiming to explore sex differences in risk for recurrent depression should compare profiles in males and females directly. For example, studies might stratify first episode individuals by sex rather than the presence or absence of life stress. One hypothesis could be that first episode females will look more like recurrent individuals (i.e., be more likely to belong to high-risk profiles), whereas first episode males are more likely to belong to low risk profiles. If supported, sex could be a valuable indicator for stratifying the first episode group and identifying those most vulnerable to recurrences.

Limitations

Findings should be considered in light of the following limitations. First, although our sample size was satisfactory in terms of LPA guidelines (Nylund-Gibson & Choi, 2018; Tein et al., 2013), replication in a larger sample may be useful to identify rarer profiles of depression. In keeping with best practice, identified profiles also require validation in multiple datasets (Ferguson et al., 2019) to confirm their accuracy across different samples and test their predictive utility in clinical contexts. Second, the current sample is ethnically homogenous, with over 75% of the sample identifying as White. Considering the large body of evidence on the unique stressors faced by minoritized individuals (Carter, 2007) and how these stressors increase risk for depression (Mereish et al., 2022), investigations of the identified profiles in more diverse samples are necessary. Despite being ethnically homogenous, the sample is heterogeneous in terms of age (range= 12-66), recruitment strategy (outpatient centre or community), and type of study (treatment vs. non-treatment). Distal outcome analyses revealed that there were no significant differences in age across profiles. However, it would be worth conducting these analyses in different subgroups of depressed individuals (e.g., in children vs. adults, outpatients vs. community participants, treatment-seeking vs. non-treatment-seeking individuals) to see if the same profiles emerge and yield similar findings across episode groups. Moreover, exclusion criteria from the six parent studies may limit the generalizability of our findings. For example, individuals with co-occurring psychosis, substance dependence, and acute suicidality were excluded. Third, as previously mentioned, the present study was cross-sectional, and thus, only captures a 'snapshot' of individuals' risk for depression and episode group at a single point in time. Prospective studies are needed to model profiles and profile membership within individuals across the life course. In addition, the reduced sample size used for distal outcome analyses may not be representative of the larger LPA sample.

Fourth, certain risk indicators (i.e., depression, anhedonia, and anxiety symptom severity) were measured differently across the studies that made up the present sample. While evidence suggests that the depression symptom severity (BDI and MADRS) and anxiety symptom severity (GAD-7 and MASQ-GDA) measures are either similar in content or highly correlated, no such evidence exists for the anhedonia symptom severity measures (MASQ-AD, SHAPS-C, and DARS). As such, anhedonia scores within the sample may not be consistent. Furthermore, in terms of childhood maltreatment indicators and precipitating stressful life events, we relied on retrospective reports, which could have been biased by current symptoms. To address this, we utilized a contextual interview with independent ratings of maltreatment and life events. This method is based on a manual of standardized exemplars and rating rules and is known as the 'gold standard' in the assessment of stress exposure in adults (Bifulco et al., 1994; Harkness & Monroe, 2020). In terms of childhood maltreatment, meta-analytic evidence indicates that, compared to self-report checklists, this method yields conclusions that are more highly correlated with official documents of maltreatment (Baldwin et al., 2019). Still, prospective studies following cohorts of children into adulthood are needed to draw predictive conclusions about maltreatment and depression.

Conclusions

In summary, this study presented one way of testing the Dual Pathway Model of depression, which aims to predict an individual's recurrent or non-recurrent trajectory based on underlying risk factors and history of life stress at first episode onset. Results offer preliminary evidence for four latent profiles of risk, characterized by differences in childhood maltreatment history and symptom characteristics. Profiles included a low overall risk profile, a high childhood maltreatment and low symptom severity profile, a moderate overall risk profile, and a

high overall risk profile. Those in a recurrent episode of depression and females were more likely to belong to the moderate and high overall risk profiles compared to the low overall risk profile. In contrast, those in a first episode not preceded by major life stress were more likely to be in the low risk profile. Profiles evidenced different syndromal manifestations, particularly regarding sexual abuse versus other form of childhood maltreatment and anxiety. Specifically, the high overall risk profile had high levels of sexual abuse and anxiety and low levels of other childhood maltreatment, whereas the high CM, low symptom severity profile had high levels of other forms of childhood maltreatment but low levels of sexual abuse and anxiety. Considering the risk patterns associated with each profile, clinicians and policymakers can develop more effective, personalized intervention strategies for first-episode individuals, ultimately improving depression outcomes and reducing risk for recurrences. Future directions include developing prospective studies that follow groups of individuals from first episode onset, measuring risk and depression outcomes across the lifespan. Further research is needed to replicate the four-profile solution in different, more diverse datasets, accurately test the DPM model, and draw predictive conclusions. Nevertheless, the present findings mark a significant advance in our understanding of how risk indicators for depression cluster together and underscore the utility of latent profiles for identifying those most vulnerable to recurrence.

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