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Adulthood Outcomes of Child and Adolescent Depression

From Mental Health to Social Functioning

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Abstract
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Depression is a common mental disorder affecting people across the lifespan, with first onset frequently occurring in the teenage years. The disorder is costly to society and constitutes one of the leading causes of disability in youths and adults worldwide. Research demonstrates that depression in childhood or adolescence is linked to adverse adult consequences, including mental health problems, physical health issues, various social difficulties, and economic hardships. While the specific factors and mechanisms associated with these long-term adversities are not well understood, previous studies point to the relevance of considering the heterogeneity in early-life depression.

The overarching aim of this doctoral thesis was to shed more light on long-term outcomes of childhood and adolescent depression across multiple life domains. This work made use of extensive follow-up data gathered in Sweden and USA, as part of two community-based longitudinal cohort studies of depressed and nondepressed youths prospectively followed into adulthood. In the Uppsala Longitudinal Adolescent Depression Study, participants were interviewed around age 16 (n=631) and age 31 (n=409). Using linkage to nationwide population-based registries, participants were followed up around age 40 (n=576). In the Great Smoky Mountains Study, participants were interviewed at repeated occasions in childhood and adolescence (n=1,420), and at further follow-ups in adulthood extending up to age 30 (n=1,336).

Findings from this work suggest that childhood/adolescent depression can have long-lasting associations with a broad spectrum of adverse outcomes. First, the risk of adult depression is known to be elevated among those exposed to depression in early life; however, depressed youths experiencing major conflicts with parents may be at an additionally increased risk of subsequent depression recurrence. Second, early-life depression was found to be associated with higher levels of adult psychiatric disorders, and also with worse health, criminal, and social functioning, even when accounting for a multitude of potential confounders. Third, early-life depression was predictive of poor labor market outcomes, especially for those with persistent depression. This link was partially mediated by the course of depression. Fourth, the welfare burden associated with early depression amounted to considerable public expenditures in adulthood, particularly for those with persistent depression or comorbid psychiatric conditions such as anxiety and disruptive behavior disorders.

The adverse long-term consequences in the wake of early-life depression underscore the importance of prevention and treatment approaches that are both efficacious and cost-effective. Such targeted efforts may have the potential to avert later ill-health, impairment, and possibly also economic disadvantage.

Keywords: Depression, Childhood, Adolescence, Psychiatric diagnoses, Social functioning, Long-term outcome, Follow-up study, Longitudinal design

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Sedan kom miljonprojekten, människorna,
allt det trasiga
som samtidigt också var mer *helt*:
ungarna som dånade ut i trappuppgångarna
som svarthåriga åskväder, skrek
klockslag på spanska eller persiska
genom halvstängda ytterdörrar
och försvann bort från sina fäder
ut över den nya kontinenten.

Johannes Anyuru

In memoriam
Hamid Alaie
1955–2005

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Alaie, I., Philipson, A., Ssegonja, R., Hagberg, L., Feldman, I., Sampaio, F., Möller, M., Arinell, H., Ramklint, M., Päären, A., von Knorring, L., Olsson, G., von Knorring, A., Bohman, H., Jonsson, U. Uppsala Longitudinal Adolescent Depression Study (ULADS). *BMJ Open*. 2019; 9: e024939.

II Alaie, I., Låftman, S. B., Jonsson, U., Bohman, H. Parent–Youth Conflict as a Predictor of Depression in Adulthood: A 15-Year Follow-up of a Community-Based Cohort. *European Child & Adolescent Psychiatry*. 2020; 29(4): 527-536.

III Copeland, W., Alaie, I., Jonsson, U., Shanahan, L. Associations of Childhood and Adolescent Depression with Adult Psychiatric and Functional Outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2021; 60(5): 604-611.

IV Alaie, I., Philipson, A., Ssegonja, R., Copeland, W., Ramklint, M., Bohman, H., Jonsson, U. Adolescent Depression and Adult Labor Market Marginalization: A Longitudinal Cohort Study. *European Child & Adolescent Psychiatry*. 2021 June 25 [Epub ahead of print].

V Alaie, I., Ssegonja, R., Philipson, A., von Knorring, A., Möller, M., von Knorring, L., Ramklint, M., Bohman, H., Feldman, I., Hagberg, L., Jonsson, U. Adolescent Depression, Early Psychiatric Comorbidities, and Adulthood Welfare Burden: A 25-Year Longitudinal Cohort Study. *Social Psychiatry and Psychiatric Epidemiology*. 2021 March 14 [Epub ahead of print].

Contents

Abbreviations

AD	Anxiety Disorder
ADHD	Attention Deficit/Hyperactivity Disorder
BDI-C	Beck Depression Inventory–Child
CBT	Cognitive Behavioral Therapy
CAPA	Child and Adolescent Psychiatric Assessment
CD	Conduct Disorder
CES-DC	Centre for Epidemiological Studies–Depression Scale for Children
CI	Confidence Interval
CLEI	Children's Life Events Inventory
DBD	Disruptive Behavior Disorder
DICA-R-A	Diagnostic Interview for Children and Adolescents in the Revised form according to DSM-III for Adolescents
DSM	Diagnostic and Statistical Manual of Mental Disorders
GEE	Generalized Estimating Equations
GPA	Grade Point Average
GSMS	Great Smoky Mountains Study
IRR	Incidence Rate Ratio
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
LMM	Labor Market Marginalization
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
PDD	Persistent Depressive Disorder
PIN	Personal Identity Number
STBs	Suicidal Thoughts and Behaviors
ULADS	Uppsala Longitudinal Adolescent Depression Study
USD	US Dollar
WMH	World Mental Health
YAPA	Young Adult Psychiatric Assessment

Introduction

Depression is a common mental disorder with varying degrees of symptom severity, duration, and related functional impairment (Otte et al., 2016). The disorder affects people at all ages and often recurs across the lifespan (Kessler & Bromet, 2013). The first onset of depression is frequently occurring in early-to-mid adolescence (Thapar et al., 2012), and the cumulative probability increases considerably towards young adulthood (Merikangas, He, Burstein, et al., 2010). Viewed in a life-course perspective, depression in early life is widely reported to forecast poor general health (Thapar et al., 2012), mental ill-health (Johnson et al., 2018), and numerous social difficulties (Clayborne et al., 2019) in adulthood. However, less is known about who is being at risk of adverse longer-term consequences among children and adolescents with depressive disorder, especially when individual and contextual factors are taken into account. Such an understanding is central to improving targeted prevention and treatment, but is also highly relevant from a broader societal perspective inasmuch as depression represents one of the leading causes of the burden of disease in both youths (Kyu et al., 2016; Reiner et al., 2019) and adults (James et al., 2018; Vos et al., 2016) worldwide. The full context and extent of early-life depression must therefore be considered with regard to its longer-term burden, in order to inform judicious policymaking and healthcare planning. This raises questions about the illness course of early-life depressive disorders and the configuration of risk factors linked to future health problems, functional impairments, and related overall societal costs. Longitudinal cohort studies, based on well-characterized and population-representative samples of depressed youths, are well suited to address such key questions. To date, only few such studies have been carried out (Clayborne et al., 2019; Johnson et al., 2018), and most of these have followed up only into young adulthood.

The present doctoral thesis builds on prospective data gathered as part of the Uppsala Longitudinal Adolescent Depression Study (ULADS) and the Great Smoky Mountains Study (GSMS), respectively. The overarching aim of this work was to increase the knowledge about the longer-term outcomes of childhood and adolescent depression across multiple life domains, including mental health status, psychosocial functioning, and socioeconomic circumstances in adulthood, while also accounting for key sources of heterogeneity.

Nosology of depression

The modern concept of clinical depression is characterized by multiple and continual cognitive, emotional, behavioral, and physiological symptoms, which significantly impair one's capacity to function in daily life (Akiskal & McKinney, 1973). While 'depression' is frequently used as a generic term, the current psychiatric nomenclature distinguishes between the various depressive disorders based on clinical assessment of symptomatology, timing, duration, and presumed etiology. The overlapping feature of all depressive disorders is the symptoms of sadness, emptiness, hopelessness, or irritability. Moreover, thoughts about death or suicide are not uncommon among individuals suffering from any kind of depression (American Psychiatric Association, 2013).

Diagnostic classification

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is a widely used classification system for diagnostic assessment of mental disorders in children, adolescents, and adults (American Psychiatric Association, 2013). The DSM system, now in its fifth edition (i.e., DSM-5), defines mental and behavioral disorders according to explicit criteria based on symptoms and signs that are characteristic of these conditions. As such, the American Psychiatric Association (2013) proclaims that clinical expertise is required for determining a diagnosis, and that the DSM-5 can aid in directing attention towards the most prominent symptoms and signs, along with empirically based information about developmental history, risk factors, correlates, and typical course of illness. While there has been a long-standing debate over nosologic issues in psychiatry, the past decade has witnessed an increasing academic interest in the basic operationalizations of the DSM disorders (Kendler, 2017), including empirical tests of both DSM and non-DSM symptoms of depression (Fried, 2017; Kendler, Aggen, et al., 2018).

Major depressive disorder (MDD) is the most well-documented condition among the depressive disorders, manifesting as a lowered mood, diminished interest or pleasure in activities normally enjoyed, and other typical symptoms including changes in sleep pattern, general appetite, activity level, energy, and cognitive functioning. The depressive episode must have been present for at least two weeks to qualify for a formal MDD diagnosis, although an untreated episode typically lasts much longer and the condition is recurring in the vast majority of cases. The current criteria for MDD have virtually not changed from previous DSM-III and DSM-IV definitions, with the exception that the former bereavement exclusion criterion has been omitted in the DSM-5.

Persistent depressive disorder (PDD) is a new diagnosis in the DSM-5 and subsumes previous DSM-III and DSM-IV definitions of chronic MDD and dysthymic disorder, featuring symptoms occurring for at least two years in adults, or at least one year in children and adolescents. The reason for the

combination of these previous DSM diagnoses into PDD was the absence of scientifically meaningful differences between chronic MDD and dysthymic disorder. Further, the DSM-5 includes specifiers so as to identify pathways to the PDD diagnosis, given that a condition such as MDD may precede PDD, or occur after the onset of PDD. Aside from the longer duration of this disorder, the most salient difference between PDD and MDD is that the minimum number of symptoms required for PDD is less than for MDD.

The DSM-5 also contains descriptions of other depressive disorders, such as substance/medication-induced depressive disorder, but there is currently no evidence to substantiate that these emerge during childhood or adolescence. However, an important exception is disruptive mood dysregulation disorder (DMDD), which is a new diagnosis intended for children manifesting frequent episodes of extreme behavioral dysfunction, including severe temper outbursts and also persistently irritable or angry mood in-between the outbursts (American Psychiatric Association, 2013).

Measurement

In research and clinical practice, the diagnostic assessment of mental disorders (e.g., depression) is often based on standardized interview techniques. These range from semi-structured interviews to highly structured interview protocols (Brugha et al., 1999). In semi-structured interviews, standardized questions are asked to the interviewee in a systematic order, but the interviewer may reword any questions as well as insert additional queries when appropriate to determine whether diagnostic criteria are fulfilled. On the other hand, the highly structured interviews also include standardized questions, but these are asked verbatim in accordance with a fully scripted manual, without additional queries. Moreover, there are also some interview protocols that combine these two approaches, including both closed- and open-ended questions. Overall, the aim of the standardized approach to diagnostic assessment is to increase the reliability of psychiatric diagnoses. Additionally, there are several self-report questionnaires designed to measure depressive symptomatology, and such self-ratings are used both in research and clinical contexts.

Differential diagnoses

According to the DSM-5 (American Psychiatric Association, 2013), a formal diagnosis of MDD needs to be distinguished from bipolar disorders, attention-deficit/hyperactivity disorder (ADHD), adjustment disorder, and also other depressive disorders. The DSM enterprise clearly states that sadness should not be classified as MDD, unless diagnostic criteria for MDD are met. The differential diagnoses of PDD include MDD, psychotic disorders, and other depressive or bipolar disorders. Moreover, careful evaluation of personality disorders should be considered, as personality disturbances are not uncommon

in PDD. The diagnosis of DMDD requires differentiation from bipolar disorders, but also MDD, ADHD, oppositional defiant disorder (ODD), anxiety disorder, autism spectrum disorder, and intermittent explosive disorder.

Epidemiology of depression

The basis for scientific inquiry into depression, or any other mental disorder, ties in with fundamental ontologic approaches to mental illness in general. According to Kessler (2007), there is no other branch in the long history of medicine that has a situation comparable to that of psychiatry, in terms of disagreements concerning the validity and the operationalization of psychiatric diagnoses. It has been argued that these theoretical issues have impacted on the field of psychiatric epidemiology, such that much research has focused on descriptive investigations whereas less analytical and clinical research has been undertaken. Historically, this debate has not only arisen within the field of adult psychiatry, but also within child and adolescent psychiatry. Donohue et al. (2019) have described that, less than two decades ago, the very idea that depression could occur in early childhood run counter to prevailing theories about child development and developmental psychopathology. Yet, psychoanalyst Rene Spitz had documented depressive symptoms in institutionalized infants already in the mid-1940s, a clinical phenomenon that he described as 'anaclitic depression' (Spitz & Wolf, 1946). As the idea of depression in early life began to gain ground, an increasing number of case studies reporting on childhood and adolescent depression were published in the decades to come (Kashani et al., 1981; Poznanski & Zrull, 1970; Toolan, 1962). These landmark studies spurred the emergence of psychometric measures of depression targeting youngsters (Kazdin & Petti, 1982), which in turn prompted an increased research output. An important lesson learned over the past decades is that mental disorders by no means are confined to adulthood only, but rather that these disorders typically have their first onset in childhood and adolescence (Kessler, Berglund, et al., 2005).

Prevalence

Childhood

A growing body of research has documented the overall prevalence rates of depressive disorders in children and adolescents, as reported in meta-analyses of epidemiologic investigations carried out worldwide. Costello et al. (2006) found that the prevalence of any depressive disorder was 2.8% in children under 13 years of age, whereas Polanczyk et al. (2015) estimated the overall prevalence to be 2.6% in children and adolescents, including individuals up to 18 years of age. Although both Costello et al. (2006) and Polanczyk et al.

(2015) did select studies that used diagnostic assessments to derive formal diagnoses of depression, there is still considerable methodological variability across studies included in these meta-analyses. This applies to, for example, key features of sample characteristics (e.g., representativeness), assessment procedure (e.g., time frame of current or past disorder), case definition (e.g., measure of depression), and also the source of information (e.g., parent, child, or both).

Adolescence

Costello et al. (2006) estimated that the overall prevalence of depressive disorders was 5.6% in adolescents aged 13 to 18, when adjusting for the effect of the time frame of the diagnostic interviews used in previous studies. For the same age group of a population-representative sample of U.S. adolescents, Merikangas, He, Burstein, et al. (2010) estimated that the overall lifetime prevalence of MDD and dysthymia was 11.7%, with females being twice as likely as males to be experiencing these conditions. In a Swedish study by Olsson and von Knorring (1999), the lifetime prevalence of MDD at age 16 to 17 was found to be 11.4%, with a fourfold higher rate in females than in males.

While overall rates are low and quite similar in females and males in the pre-pubertal period (Costello et al., 2006; Maughan et al., 2013), the gender differences emerge during adolescence, or possibly already in childhood (Breslau et al., 2017), with a clearly higher risk of depression consistently observed in females (Hankin et al., 1998; Salk et al., 2017). The cumulative probability of depression increases from around 5% in early teenage years to almost 20% in late adolescence (Hankin et al., 1998; Lewinsohn et al., 1999; Merikangas, He, Burstein, et al., 2010). The strong female preponderance (about 2:1) observed by adolescence is quite similar to what has been reported throughout adulthood (Bromet et al., 2011; J. S. Hyde et al., 2008; Seedat et al., 2009). Further, evidence from community-representative samples suggests that long episodes of depression – of about one year's duration – are highly prevalent in adolescence (Essau et al., 2010; Olsson & von Knorring, 1999; Sund et al., 2011).

Adulthood

Recent meta-research demonstrates that most meta-analyses reporting on prevalence rates of depression have primarily included studies that used screening tools or self-report questionnaires to classify depression, thereby making interpretations of reported rates rather difficult (Levis, Yan, et al., 2019). This methodological variability across studies was also noticed in a recent meta-analysis by Lim et al. (2018), who reported on the prevalence of depression in the community across 30 countries and estimated that the point prevalence appeared to be much higher when measured with self-ratings as compared with diagnostic interviews (17.3% vs. 8.5%).

To date, the largest cross-national investigation of depression prevalence was carried out as part of the World Mental Health (WMH) surveys, involving a series of community-based studies conducted around the world (Bromet et al., 2011). The key feature of the WMH surveys is that a common protocol and a diagnostic interview were used to assess a range of mental disorders. The average 12-month prevalence of MDD was reported to be 5.5% in high-income countries, and 5.9% in low- to middle-income countries. The average lifetime prevalence of MDD was found to be 14.6% in high-income countries, and 11.1% in low- to middle-income countries. However, the true cumulative prevalence of depression may have been seriously underestimated in the WMH surveys, as prospective-longitudinal evidence from Germany (Beesdo-Baum et al., 2015), Switzerland (Angst et al., 2016), New Zeeland (Moffitt et al., 2010), and USA (Hamdi & Iacono, 2014; Tanner et al., 2007) suggest lifetime prevalence rates between 25% and 41% at various ages in mid-adulthood.

Comorbidity

Psychiatric comorbidity has long been observed to be the rule rather than the exception in epidemiologic samples (Kessler, Chiu, et al., 2005), and there is extensive evidence that co-occurrence of mental disorders is even more common in clinical samples (Fava et al., 2000; Kovacs et al., 1989; Parker et al., 1999). The co-occurrence of disorders can be described in terms of concurrent comorbidity, meaning that the disorders have been present during the same time, albeit not necessarily with coterminous times of onset and offset, or alternatively, in terms of successive comorbidity, such that the disorders may not have been overlapping in time but instead occurred during a lifetime (Angold, Costello, et al., 1999). It is well documented that depressive disorders co-occur with other diagnoses more frequently than would be expected by chance alone both in early life (Angold, Costello, et al., 1999; Kessler et al., 2012) and later across the lifespan (Caspi & Moffitt, 2018; Plana-Ripoll et al., 2019). As for comorbid psychiatric conditions in early depression, the most common diagnoses include anxiety disorders, conduct disorder (CD), and ADHD (Angold, Costello, et al., 1999). However, the pattern of depression comorbidity may vary depending on age and gender (Rao & Chen, 2009).

Suicidal thoughts and behaviors

Suicide is estimated to be the leading cause of death among adolescents worldwide, with higher suicide rates observed among those aged 15 to 19 compared with those aged 10 to 14, and overall higher rates among males compared with females (Glenn et al., 2020). Adolescents manifesting suicidal thoughts and behaviors (STBs), defined as suicidal ideation, suicide attempt, and suicide death, are therefore of particular clinical concern (Cha et al., 2018). Although STBs are rare in the pre-pubertal period, the prevalence rapidly increases in

early-to-mid adolescence, and the vast majority of youths reporting suicidal behavior also present with pre-existing mental disorders (Nock et al., 2013).

While individual factors, such as depression and other mental disorders, are considered to have the strongest effect on suicide rates (Chesney et al., 2014), there is evidence of several other predisposing risk factors for suicide, such as genetics, familiality of suicidal behavior, exposure to early adversity, lack of social support, major life events, economic circumstances, access to lethal means, and contagion by media (Fazel & Runeson, 2020).

There are several longitudinal studies reporting on associations between childhood/adolescent STBs and adult health and functioning, including mental health outcomes (Briere et al., 2015; Copeland et al., 2017; Dhossche et al., 2002; Fergusson et al., 2005; Goldman-Mellor et al., 2014; Herba et al., 2007; Reinherz et al., 2006) and psychosocial outcomes across various life domains (Briere et al., 2015; Copeland et al., 2017; Goldman-Mellor et al., 2014; Reinherz et al., 2006). While research suggests that the association between early-life STBs and adverse adult outcomes may be explained by other factors than the effect of STBs, such as childhood adversities, disruptive behaviors, and depression (Copeland et al., 2017), there is strong evidence demonstrating that early STBs are predictive of adult STBs (Briere et al., 2015; Copeland et al., 2017; Fergusson et al., 2005; Goldman-Mellor et al., 2014; Herba et al., 2007; Reinherz et al., 2006).

Etiology

There has been increasing research devoted toward understanding the factors contributing to the onset and persistence of depression. Several possibilities have been explored, including broad societal mechanisms and person-specific factors, examined at different levels of analysis (Otte et al., 2016). Current evidence is suggestive of multiple etiological pathways leading to depression, as many individual, familial, and social risks interact with one another and, in addition, also relate to continuing as well as later adversities, thereby increasing the risk of depression in a probabilistic way (Thapar et al., 2012).

Gender

The gender disparity in depression is one of the most consistent findings in both cross-sectional and longitudinal research, given that females are about twice as likely as males to become depressed in adolescence and across adulthood (Salk et al., 2017). Several psychological, social, and physiological mechanisms have been proposed to account for the overall gender difference in prevalence rates (Girgus & Yang, 2015). Prospective research suggests that early pubertal timing and higher testosterone levels are linked to higher levels of adolescent depression in females (Copeland et al., 2019). There is also other research indicating that early pubertal timing is predictive of recurrent depressive episodes not only in females but also in males (Hamlat et al., 2020).

Heritability

The heritable nature of depressive disorder has been reported to be moderate, with somewhat higher heritability estimates observed in females (about 40%) than in males (about 30%) (Kendler et al., 2001; Kendler et al., 2006b). These seminal studies by Kendler and colleagues have been done using the twin methodology, which assesses sibling resemblance for the condition of interest. However, a recent cross-generational study based on an extended adoption design found that genetic factors and rearing experiences contributed equally to the parent–offspring resemblance in depression (Kendler, Ohlsson, et al., 2018). Moreover, a growing body of genome-wide association studies have been undertaken in recent years to identify genetic variants contributing to liability to depression, and several risk loci have been discovered in various populations (Amare et al., 2019; Cai et al., 2015; Direk et al., 2017; Howard et al., 2019; Howard et al., 2018; C. L. Hyde et al., 2016; Okbay et al., 2016; Schwabe et al., 2019; Wray et al., 2018). Nonetheless, less is known about which genetic variants are causally involved in the onset and recurrence of depression (Ormel et al., 2019).

Stress

Stressful interpersonal contexts and life events have long been recognized as key risk factors increasing vulnerability to depression (Hammen, 2018; Monroe et al., 2019). Much research in recent decades has been predominated by a diathesis–stress perspective (Bebbington, 1987; Monroe & Simons, 1991; Robins & Block, 1989), in which stressors are conceptualized to predict depression as moderated by key vulnerability factors including cognitive and emotional components (Gotlib & Joormann, 2010; LeMoult & Gotlib, 2019), interpersonal characteristics (Hammen, 2018), and biological vulnerability (Arnau-Soler et al., 2019; Colodro-Conde et al., 2018). Importantly, the link between stress and depression is increasingly recognized to be bidirectional and not unidirectional (Hammen, 2015). Most people experiencing stressful events do not get depressed, but those who do tend to generate various stressors themselves, thereby portending subsequent experiences of depression as well as a continuity of stress (Hammen, 2018).

Gene–environment interaction

Candidate genes for depression, and in particular gene-by-environment interaction hypotheses, have garnered a great deal of attention (Border et al., 2019; Caspi et al., 2010; Caspi & Moffitt, 2006; Caspi et al., 2003; Flint & Kendler, 2014; Karg et al., 2011; McIntosh et al., 2019; Munafo et al., 2009; Risch et al., 2009; Sharpley et al., 2014; Uher et al., 2011), and controversy (Ancelin & Ryan, 2018; Fergusson et al., 2011; Flint & Munafo, 2013; Kaufman et al., 2010; McGuffin et al., 2011; Moffitt & Caspi, 2014), in the past two decades. In a pioneering study by Caspi et al. (2003), it was found that the 5-HTTLPR

repeat polymorphism in the serotonin transporter gene (SLC6A4) was linked to an increased risk of depression, but only in individuals exposed to early-life stress. Later, a great number of large-scale studies have attempted to replicate this finding, but confirmatory evidence of such an interaction is still lacking (Culverhouse et al., 2018), possibly due to systematic publication bias (Border et al., 2019; Duncan & Keller, 2011; Van der Auwera et al., 2018).

Personality

The link between personality and mental health has a long-standing history in psychological and psychiatric sciences (Kotov et al., 2010), with emerging ideas tracing back to the time of the ancient Greeks (Maher & Maher, 1994). Perhaps the most robustly established relationship between personality traits and mental disorders is the now well-documented association of neuroticism with depression (Hakulinen et al., 2015; Klein et al., 2011). High levels of neuroticism have been shown to be predictive of considerable economic costs to society (Cuijpers et al., 2010), other psychiatric disorders (Kotov et al., 2010), and also higher suicide rates (Batty et al., 2018). Nonetheless, the question has arisen as to whether the construct of neuroticism only may be a non-specific risk factor, without any direct etiological relevance to depression (Ormel et al., 2013). Etiologically, research suggests that neuroticism and depression share a proportion of their genetic variance (Kendler et al., 2019; Kendler et al., 2006a; Kendler & Myers, 2010), and genome-wide association studies have identified some genetic variants associated with both neuroticism and depression (de Moor et al., 2015; Lo et al., 2017; Luciano et al., 2018). Furthermore, several longitudinal studies demonstrate that personality traits assessed in early life predict the later development of adult mental health problems (Allebeck et al., 1988; Caspi, 2000; Fergusson et al., 2003; Fergusson et al., 2000; Hayes et al., 2017; Junker et al., 2019; Samek et al., 2018; Slutske et al., 2012), including depression (Aldinger et al., 2014; Caspi et al., 1996; Kendall et al., 2015; van Os et al., 1997; Wilson et al., 2014), and a range of adverse psychosocial outcomes (Caspi, 2000; Daly et al., 2015; Fergusson et al., 2013; Moffitt et al., 2011). While the mechanisms in the linkage between early personality (including neuroticism) and later adversities remain unclear, it is possible that people manifesting high levels of neuroticism are more vulnerable to depression when exposed to stressful life events as compared to those with lower levels (Kendler et al., 2004).

Socioeconomic background

Socioeconomic disadvantage is widely reported to be a risk factor of psychopathology, including depression, such that those in the lower social strata are at higher risk of reporting depressive symptoms than those in the higher social strata (Lorant et al., 2003). Most studies investigating this question have so far been based on cross-sectional data and adult populations, which preclude conclusions about the directionality of findings and overall generalizability.

Yet, recent research on youths indicates that socioeconomic disadvantage, alongside family and neighborhood characteristics, may be a risk factor for negative adolescent development (Devenish et al., 2017; Straatmann et al., 2019), including depression (Denny et al., 2016). This association between socioeconomic disadvantage and depression may possibly be even stronger when coupled with racial discrimination (Cheng et al., 2015; Hou et al., 2015), although prior research has not found a consistent inverse relationship between socioeconomic status and depression among minority groups (Anderson & Mayes, 2010). Moreover, the comparatively limited longitudinal research on children and adolescents has yet produced inconsistent results, as some studies suggest that those growing up socioeconomically disadvantaged are particularly prone to depression in adulthood (Gilman et al., 2002; Korhonen et al., 2017; Park et al., 2013; Ritsher et al., 2001; Stansfeld et al., 2011; Wu et al., 2018), whereas no such long-term association has been found in other studies (Gibb et al., 2012; Melchior et al., 2007; Miech et al., 1999; Quesnel-Vallee & Taylor, 2012). Importantly, recent large-scale research by Sariaslan et al. (2021) demonstrates that the linkages between family income in early life and later psychiatric disorders, substance misuse, and criminal arrests are accounted for by unmeasured familial confounders, suggesting that there is no evidence for a causal association. However, it should be borne in mind that this finding pertained to psychiatric diagnoses recorded in hospital-based settings, as no information from primary care was included. Although informative, the study by Sariaslan et al. (2021) may therefore have limitations in terms of generalizability, given that most people with common mental disorders tend to seek treatment within primary care only (Sundquist et al., 2017).

Neurobiology

Despite decades of research into the pathogenesis of depression, there is still only limited knowledge about the etiologic mechanisms at play, and, more specifically, the complex interplay between genetic, biological, and environmental factors contributing to the onset and persistence of the disorder. As such, there is no established mechanism that can fully explain the etiology underlying depressive disorder. Several theories have been proposed, which have been paralleled by the development of animal models and clinical studies to put various hypotheses to the test. Here, one important example is the long-standing hypothesis of monoamine deficiency, suggesting that serotonin, noradrenaline, and dopamine are implicated in depression. Although this line of research stimulated the development of pharmacological treatment of mental disorders, including depression, the exact mechanisms of action are still not fully understood, and far from all individuals with depression respond to antidepressant medications (see Otte et al., 2016).

Research has suggested that two interrelated neural circuits and associated modulatory systems may be linked to increased risk of depression. The first circuit involves the amygdala, hippocampus, and the prefrontal cortex, which

in turn is linked to activity in the hypothalamic-pituitary-adrenal axis, while the second circuit involves the striatum and the prefrontal cortex. Both these circuits mature over time, with sex differences emerging during adolescence, and both heritable and nonheritable factors seem to be at play in these circuits (Thapar et al., 2012). Further, a recent systematic review on neuroimaging markers associated with childhood and adolescent depression found a reduced response to reward in the ventral striatum and prefrontal cortex, but no consistent evidence for other functional or structural brain abnormalities, possibly due to confounding factors (Toenders et al., 2019).

Course of illness

An increasing number of longitudinal studies have been conducted worldwide to examine the course of depression and other affective disorders, and the key determinants influencing their incidence, recurrence, and overall prognosis over the life course. The vast majority of studies have typically relied on screening tools or self-report questionnaires to classify cases of depression, whereas only a few studies have used standardized interview techniques for diagnostic ascertainment of depression and other mental health problems (Beard et al., 2008). In addition, there has in recent years been a growing research output based on nationwide registry data, primarily in the Nordic countries, where clinical diagnoses of depression and other diseases are routinely recorded both in inpatient care and specialized outpatient care (Fazel et al., 2015; Korhonen et al., 2017; Wirback et al., 2018). Importantly, however, it is widely reported that a substantial proportion of youths and adults suffering from depression go undiagnosed or untreated (Costello et al., 2014; Merikangas, He, Brody, et al., 2010; Merikangas et al., 2011; Thornicroft et al., 2017), thereby implying that the information gathered in national registries most likely underestimates the true levels of depressive disorders in the general population (Schaefer et al., 2017). As already noted, recent research from Sweden demonstrates that the vast majority of people with a common mental disorder, such as depression, tend to seek treatment within primary care only, from which no data are transferred to the national registries (Sundquist et al., 2017), with the exception of dispensed medication (Wallerstedt et al., 2016; Wettermark et al., 2007). Therefore, the longitudinal course of early-life depression and other common mental disorders can only be duly investigated using either population- or community-representative samples prospectively followed from childhood or adolescence onwards, and ideally with repeated measurements of the outcome of interest. Otherwise, there is the obvious risk that studies may underestimate or overestimate the magnitude of differences between those with and without the condition.

Typically in epidemiology, the frequency of a particular outcome is compared in two or more groups that differ in some characteristic or exposure of interest (Aschengrau & Seage, 2019). For example, this could be depressed

youths (i.e., the exposed) being compared to nondepressed youths (i.e., the nonexposed). The measures of association when calculating the relationship between an exposure and an outcome may differ across studies; however, the odds ratio (OR) is often used to describe the strength of the association.

Adult health outcomes of early-life depression

In recent meta-analytic work, Johnson et al. (2018) reported that adolescent depression was associated with increased odds of adult depression (OR = 2.78) and anxiety disorder (ORs ranging from 1.40 to 8.14), yet there were mixed findings on whether adolescent depression was predictive of adult suicidality. While previous research has typically focused on adolescent depression more generally, recent studies point to a particularly poor long-term prognosis for those presenting with chronic/persistent depression (Colman et al., 2007; Jonsson, Bohman, von Knorring, et al., 2011; Ssegonja, Alaie, et al., 2019). Further, longitudinal research suggests that early depression is linked to poor general health in adulthood, such as higher rates of smoking (Bardone et al., 1998), obesity (Hasler et al., 2005), sexually transmitted disease (Jonsson, Bohman, Hjern, et al., 2011), and physical health problems (Bardone et al., 1998; Keenan-Miller et al., 2007).

Adult psychosocial outcomes of early-life depression

Depression is widely reported to be detrimental to overall social functioning, including role impairments across, for example, academic, occupational, and interpersonal domains (Hirschfeld et al., 2000). In recent meta-analytic work by Clayborne et al. (2019), adolescent depression was found to be associated with decreased odds for entry into tertiary education (OR = 0.75) and being currently employed or in tertiary training (OR = 0.70), and with increased odds for current or recent unemployment (OR = 1.66) and long-term or repeated spells of unemployment (OR = 1.56). Further, there was also an indication that adolescent depression may be linked to, for example, welfare dependency, loneliness, and problems in intimate relationships; however, some findings were based on a limited number of studies, and some studies had relatively few cases, suggesting that the estimates should be interpreted with caution.

In the literature, there are only a few studies in which participants have been followed up after age 25 years (Jonsson et al., 2010; McLeod et al., 2016; Naicker et al., 2013; Weissman et al., 1999; Wickrama et al., 2012). While the overall impression from previous research is that early depression is predictive of adverse long-term outcomes, some studies suggest that this link is mainly attributable to adolescent functioning and early adverse experiences (McLeod et al., 2016), or subsequent depression recurrence (Lewinsohn et al., 2003). This may imply that the associations with adulthood adversities are not due to independent linkages with childhood/adolescent depression.

Societal burden

Globally, the depressive disorders are estimated to be among the top leading causes of disability and disease burden, both among adults (James et al., 2018) and adolescents (Reiner et al., 2019). The regional variation in the burden seems to be greater for MDD than for PDD, with an overall higher burden in females than in males, and the largest proportion of years lived with disability from depression occurring among adults of working age (Ferrari et al., 2013). The most burdensome domains of psychosocial functioning associated with depression include domestic life, work, and interpersonal activities (Kamenov et al., 2016). Further, meta-analytic findings imply a substantial cost burden of depression at all ages (Konig et al., 2019). Yet, most studies on the costs of depression have primarily reported on healthcare expenditures among adults, and only to a lesser extent on the societal burden among youths (Bodden et al., 2018; Ssegonja, Alaie, et al., 2019).

Clinical management

Effective depression management is available (Clark et al., 2018; Ludlow et al., 2020), but remains inaccessible for most depressed people throughout the world (Thornicroft et al., 2017). The management of depressive disorder is recommended to be followed according to a stepped-care model (National Institute for Health and Care Excellence, 2009, 2019). Generally speaking, psychological treatments (e.g., cognitive behavioral therapy, CBT) and anti-depressant medications (e.g., selective serotonin reuptake inhibitors, SSRIs) are considered to be treatments of choice. Other treatments are available for severe and complex depression, such as electroconvulsive therapy (National Institute for Health and Care Excellence, 2009).

Recent treatment innovations include Internet-delivered psychotherapies, smartphone apps, and blended approaches combining traditional face-to-face therapy, such as CBT, with modern technology (Andersson et al., 2019). Other emerging treatment options are repetitive transcranial magnetic stimulation (Baeken et al., 2019; McClintock et al., 2018), intranasal administration of esketamine (Kim et al., 2019; Mahase, 2019), and intravenous ketamine (Krystal et al., 2019) for those manifesting treatment-resistant depression. Moreover, indicated preventive interventions based on group-delivered CBT may have favorable effects for children and adolescents presenting with sub-threshold depression (Ssegonja, Nystrand, et al., 2019).

The motivation behind the thesis

While an increasing number of observational cohort studies have looked at a vast range of adult outcomes following childhood and adolescent depression, the generalizability of past research efforts is still quite limited, and a number of questions remain unanswered. First, most previous studies have followed up into young adulthood only (e.g., age < 30), thereby leaving the question of longer-term outcomes unanswered (Clayborne et al., 2019; Johnson et al., 2018). This points to the need of using repeated outcome measurements over extended periods of time. Second, several studies in the past have classified cases and controls solely on the basis of self-report questionnaires. Such an approach may provide a rough approximation at a given point in time, but is generally prone to exposure misclassification or measurement error (Joffres et al., 2013; Levis, Benedetti, et al., 2019), which is the main reason why standardized diagnostic interviews are needed to ascertain the validity of the depression measurement. Third, the outcomes in prior research have typically been assessed using self-reports only, which is subject to recall failure and other potential biases (Moffitt et al., 2010; Patten et al., 2012; Takayanagi et al., 2014). Linkage with population-based registries could partly resolve such issues. Fourth, a substantial proportion of previous studies have not accounted for important potential confounders, such as gender and socioeconomic status, while studies controlling for a range of covariates have often reported mixed results (Clayborne et al., 2019). More research is thus needed to clarify which effects of early-life depression on adult outcomes are independent of other childhood experiences, including comorbid psychiatric conditions and social adversities. Fifth, the duration and course of early-life depression are still not well understood, as surprisingly little research has distinguished between chronic and nonchronic (i.e., episodic) forms of depression in youths, and there is also limited knowledge about the role of later depression recurrence in determining longer-term health and functioning. Given that early PDD is known to have a particularly poor prognosis (Johnson et al., 2018), additional research is much needed to gain deeper insights into the future prospects of those afflicted by this disorder in childhood or adolescence.

The empirical work presented herein contributes to the literature on the long-term consequences of early-life depression by an attempt to address the aforementioned limitations of past research. The advantage of using extensive data gathered from two community-representative samples – one based in Sweden and one based in the U.S. – made it possible to study a number of social, economic, and health-related outcomes at a time in the life cycle when a substantial proportion of the general population has achieved educational milestones, entered the workforce, and taken on adulthood responsibilities in terms of forming a family and establishing financial independence.

Aim and objective

The overarching aim of this thesis was to shed more light on the long-term outcomes of childhood and adolescent depression. The overall objective was to increase the knowledge about some major sources of heterogeneity related to the course of early-life depression across multiple life domains, including adult mental health, psychosocial functioning, and economic circumstances.

Principal research questions

Four general research questions, one each for Study II–V, were addressed herein. A cohort profile was included to enhance clarity and transparency (I).

II Do depressed adolescents with a history of parent–child conflicts have a higher risk of depression in adulthood than their nondepressed peers with a similar history?

III Are children and adolescents with depression at higher risk of adverse adult outcomes in life domains related to mental health, wealth, social functioning, and criminality, as compared with their nondepressed peers, and are these effects independent of other adversities and comorbid psychiatric conditions?

IV Are adolescents with depression at higher risk of marginalization from the labor market in adulthood, as compared with their nondepressed peers, and what role is played by educational milestones and the course of illness of depression?

V Do adolescents with depression have a higher recipiency of social transfer payments in adulthood than their nondepressed peers, and are early psychiatric comorbidities related to any potential differences in the magnitude of recipiency?

Methodology

Study population and procedure

This thesis is based on follow-up data from two longitudinal cohort studies: the Uppsala Longitudinal Adolescent Depression Study (ULADS) and the Great Smoky Mountains Study (GSMS). First, both studies are presented herein with respect to key methodological features. Next, an overview of the empirical work included in the thesis is provided.

Uppsala Longitudinal Adolescent Depression Study

The initial aim of this community-based epidemiologic investigation was to examine the prevalence, clinical characteristics, and psychosocial correlates of adolescent depression. The project has subsequently evolved into a series of long-term follow-up studies, with a broad focus on social, economic, and health-related outcomes. An overview of each study phase and the data sources relevant to the thesis are described below, alongside Figure 1 outlining the overall procedure. Detailed information about the data collection waves, including a complete list of measures, has previously been reported by Alaie et al. (2019) (i.e., study I).

Baseline measurement

Screening

The original investigation comprised a total population of first-year students aged 16–17 years in all upper-secondary schools of Uppsala in 1991–1992 (Olsson & von Knorring, 1999). First, 2,300 (93% participation rate) underwent a screening procedure by means of two self-report questionnaires: the Beck Depression Inventory–Child (BDI-C; Beck et al., 1961) and the Center for Epidemiological Studies–Depression Scale for Children (CES-DC; Schoenbach et al., 1982). Next, adolescents with positive screening, defined as BDI-C $\geq$ 16 (Larsson & Melin, 1990), CES-DC $\geq$ 30 + BDI-C $\geq$ 11 (Roberts et al., 1991), or a self-reported suicide attempt, were invited to a comprehensive face-to-face assessment. An equal number of adolescents with negative screening, matched for sex, age, and school class, were also invited. Out of 710 selected, 631 (89%) agreed to take part in the face-to-face assessment.

Clinical interview

Mental health problems were assessed using the Diagnostic Interview for Children and Adolescents in the Revised form according to DSM-III-R for Adolescents (DICA-R-A; Boyle et al., 1993; Ezpeleta et al., 1997; Herjanic & Reich, 1982; Reich et al., 1982; Welner et al., 1987). The DICA-R-A was originally developed as a structured clinical interview, covering a broad range of childhood and adolescent psychiatric disorders, such as depression, anxiety disorders, substance abuse, and behavioral disorders. Later on, it was proposed that the interview could be administered in a semi-structured format (Reich, 2000). The interview also contains a module with specific questions about overall social situation and adverse family-related circumstances. As the DICA-R-A is designed to assess life-time diagnoses, additional questions were included in order to determine the timing of the relevant diagnoses (e.g., the most recent bout of MDD).

Self-report questionnaire

The significance of life events was self-evaluated using the Children's Life Events Inventory (CLEI; Coddington, 1972). The CLEI was developed to capture various life experiences relevant to childhood emotional distress and overall psychosocial situation, with several items focusing on family-related factors. These include, for example, conflict with parents, parental separation or divorce, and financial hardships.

15-year follow-up

In 2006–2008, about 15 years after baseline, eligible participants were invited to take part in a comprehensive face-to-face reassessment focusing on mental health, general health, and psychosocial functioning. Written information about the follow-up assessment was sent to the participants by mail, whereupon a research group member contacted the participants by phone to provide an opportunity for questions and additional information. Out of 609 eligible participants, 409 completed the reassessment. However, those with mania or hypomania in adolescence ($n = 27$) were excluded from the present work. This is because bipolar disorders are classified separately from depressive disorders in DSM-5, due to key differences in symptomology and presumed etiology. Thus, this left a total of 382 participants, including cases with any adolescent depression ($n = 227$) and controls without adolescent depression ($n = 155$).

Clinical interview

Mental health problems were reassessed using the Mini International Neuropsychiatric Interview Plus (MINI; Lecrubier et al., 1997; Sheehan et al., 1998). The MINI is a structured clinical interview covering a vast range of psychiatric disorders as defined in the DSM. The interview was supplemented with

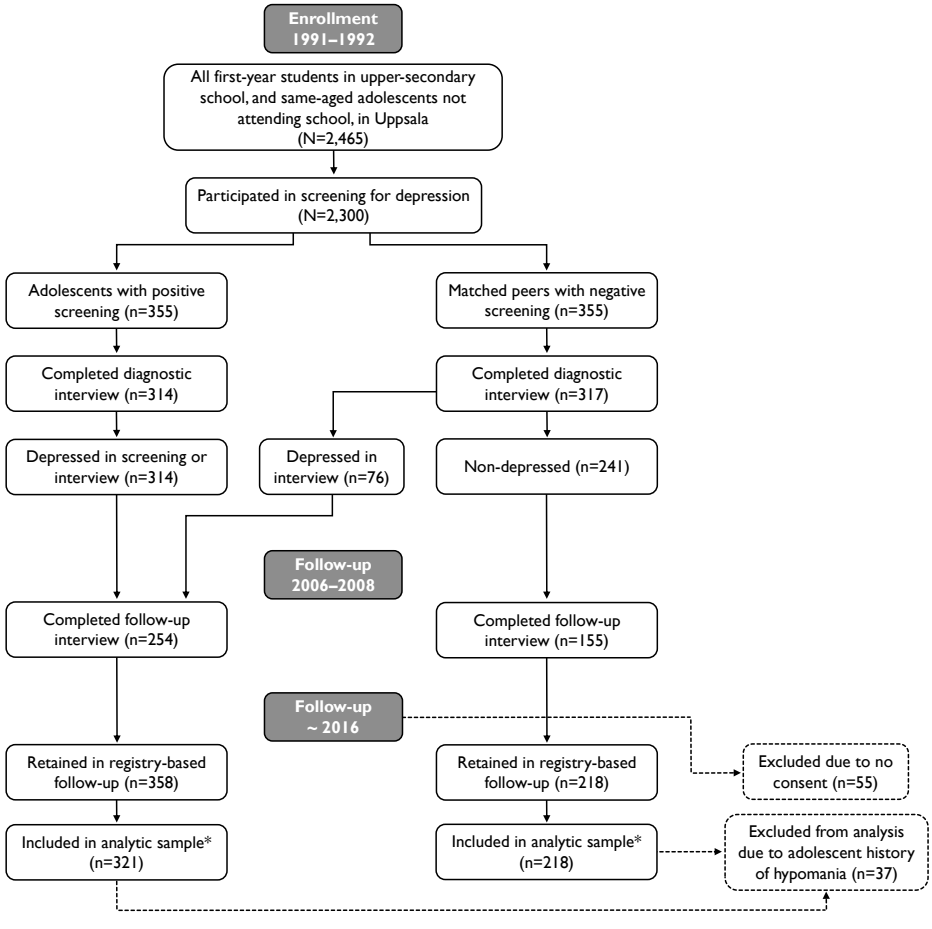
additional questions and a life-chart spanning late adolescence onwards, to facilitate recollection of previous episodes of depression and mania/hypomania. Past and present social situation, major life events, healthcare usage, and family history of mental illness were probed using pre-defined questions.

25-year follow-up

In 2017–2018, a 25-year follow-up was carried out through record linkage to various nationwide population-based registries kept by various government agencies. Extensive pseudonymized data on all retained participants were linked at the individual level using the unique personal identity number (PIN), which is assigned to all Swedish citizens and foreign residents planning to live in Sweden for at least one year (Ludvigsson et al., 2009). The registry-based data comprised detailed information about social insurance benefits, healthcare utilization, social services, education, income, migration, and convictions. Corresponding data on a reference population ($N > 200{,}000$), comprising all individuals who were born in 1975–1976 and who resided in the country in 1992, were also retrieved. In addition, registry data on parents of all subjects, both from the ULADS cohort and the reference population, were also retrieved to provide details about sociodemographic background. In all, 576 of the original participants were retained in the 25-year follow-up; however, the present work excluded those with mania/hypomania in adolescence ($n = 37$), given the rationale provided earlier. Consequently, this left a total of 539 participants, including cases with any adolescent depression ($n = 321$) and controls without adolescent depression ($n = 218$).

Nationwide population-based registries

The registry data used for the present doctoral thesis were mainly retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), kept by Statistics Sweden (Ludvigsson et al., 2019). The LISA registry was launched in 1990 and is updated every year by the transmission of annual data on the labor market, educational systems, and social sectors from various source registries. The registry includes all individuals (aged ≥ 16) who were registered as residents of Sweden as of December 31 each year. Overall, the source registries incorporated in LISA have been reported to have good quality, with limited attrition (Ludvigsson et al., 2019). For the present work, several variables were used to examine long-term outcomes associated with adolescent depression, in terms of educational milestones, workforce participation, and recipiency of social transfer payments. Further, data on grade point average (GPA) from year 9 of compulsory school were retrieved from the Pupil Registry, while parental data on education and income were retrieved from the Education Register and the Register of Income and Taxation, respectively.



* Note: In the retained cohort included in the analysis, 351 (65%) participants were interviewed in the follow-up in 2006–2008.

Figure 1. Flowchart illustrating the inclusion and subsequent follow-ups of study participants in the Uppsala Longitudinal Adolescent Depression Study.

Great Smoky Mountains Study

The initial aim of this community-based epidemiologic investigation was to examine the need for and use of mental health services among children and adolescents in an area of the southeastern United States. The project started out with addressing the prevalence and incidence of early psychiatric and substance abuse problems, along with their predictors and correlates, and it has subsequently expanded to focus on overall adult outcomes of early adverse experiences and various markers of risk, including childhood and adolescent psychopathology. An overview of the study and the data relevant to this thesis are described below, along with Figure 2 illustrating the procedure. Detailed information about the data collection waves of the GSMS has been reported elsewhere (Costello et al., 1996; Costello et al., 2016).

Baseline measurement

Screening

At the outset of the GSMS in 1993, three cohorts of children aged 9, 11, and 13 years were recruited from eleven predominantly rural counties of western North Carolina (Costello et al., 1996; Costello et al., 2016). Out of some 12,000 children in these age groups of the population, potential participants were randomly selected on the basis of a two-stage sampling design (Schaie, 1965). Next, potential participants were screened for risk of psychopathology using a brief questionnaire for parents. The questionnaire was mainly composed of the externalizing items from the Child Behavior Checklist (Achenbach & Edelbrock, 1981), including an expansion of the substance abuse question covering a list of various substances (e.g., tobacco, cannabis, etc). Then, all children with screen scores above a pre-determined cutoff (top 25% of total scores), plus a 1-in-10 random sample of the rest, were invited to take part in comprehensive face-to-face assessments. Additionally, children of American Indian heritage were oversampled to constitute 25% of the study sample, irrespective of initial screen score. The total screening sample comprised 4,517 children, whose parents were approached for screening by telephone or in person. Of those selected on the basis of the aforementioned criteria, 1,420 children (80% participation rate) agreed to take part in at least one face-to-face assessment with interviewers. Annual assessments with the participant and a parent were carried out through age 16 years.

Clinical interview

Mental health problems and associated functional impairments were assessed using the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 1995; Angold et al., 1995). The CAPA is a highly structured clinical interview intended for use in the general population, covering a broad range of childhood psychiatric disorders based on the DSM. In the CAPA, the time

frame for determining the presence of most psychiatric symptoms is the past three months preceding the interview, and a symptom is counted as present if it is reported by either parent or participant. The CAPA interview also includes questions about various family hardships and early life adversities, including low socioeconomic status, unstable family structure, family dysfunction, child maltreatment, and peer victimization. In addition, information on mental health services use within childhood and adolescence was collected using the Child and Services Assessment (Ascher et al., 1996; Farmer et al., 1994), which is an interview about the use of specialty mental health providers, other medical care providers, and social services.

Multiple follow-ups

Starting in 1999 and extending up to 2016, participants were followed up with repeated assessments at ages 19, 21, 25, and 30 years, as shown in Table 1. Unlike previous assessments in childhood and adolescence, participants were interviewed without any parents being present. Of the total sample, 1,336 (94%) were reassessed at least once during adulthood (Costello et al., 2016).

Clinical interview

A vast range of adult outcomes, covering psychiatric disorders, physical health, wealth, social functioning, and risky/criminal behaviors, were assessed using the Young Adult Psychiatric Assessment (YAPA), an upward extension of the CAPA interview (Angold, Cox, et al., 1999). In addition, official criminal records were retrieved from the North Carolina Administrative Offices of the Courts Database to assess if participants had been convicted with any form of serious criminal activity (i.e., felony charges).

The YAPA is a highly structured clinical interview, which is designed to be used with adults aged 18 years and older. As such, there are no questions directed toward parents in the interview. While the YAPA was developed for the diagnostic assessment of a broad range of common mental disorders, the interview aims at mapping not only adult psychiatric diagnoses but also the full range of living situations, interpersonal relationships, and various domains of social functioning.

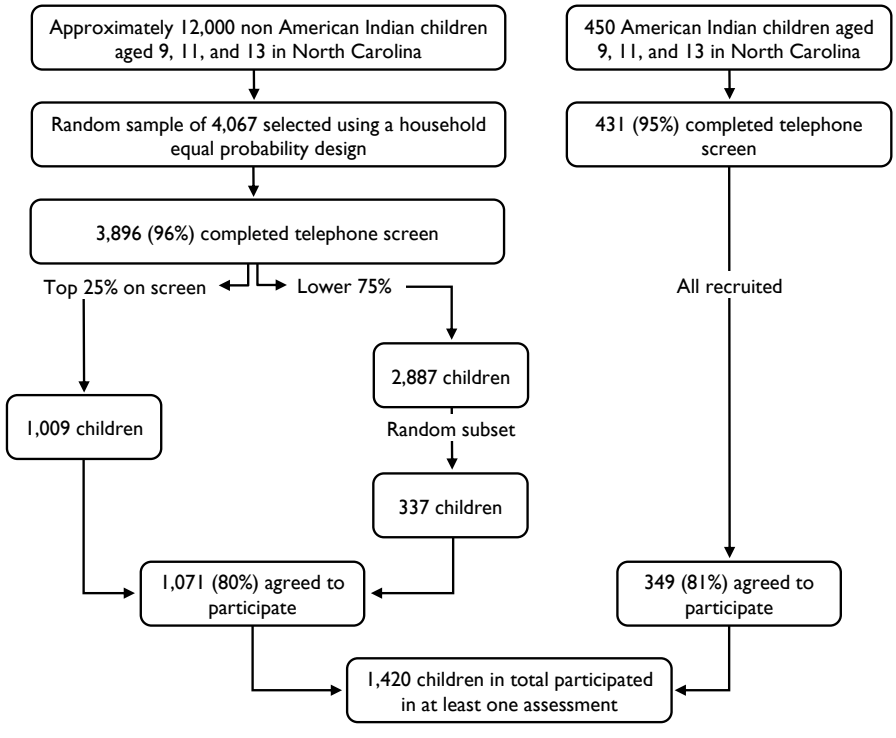


Figure 2. Chart of the procedure for inclusion in the Great Smoky Mountains Study.

Table 1. *Data collection by cohort and year in the Great Smoky Mountains Study.*

Cohort	Age	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
A n=508	9	A1																						
	10		A2																					
B n=497	11	B1		A3																				
	12		B2		A4																			
C n=415	13	C1		B3																				
	14		C1		B4		A5																	
	15			C3		B5		A6																
	16				C4		B6		A7															
	19							C5		B7		A8												
	21									C6		B8		A9										
	24-26														C7		B9		A10					
	30																		C8		B10		A11	
% completed		**94**	**91**	**87**	**78**	**80**	**81**	**74**	**81**	**81**		**80**		**76**	**80**		**84**		**82**		**82**		**83**	

Note: 93–15 denote the years 1993 to 2015, respectively. None in the youngest cohort (i.e., A) was interviewed at age 13, and only half were interviewed at age 14.

Ethical aspects

Uppsala Longitudinal Adolescent Depression Study

The first wave of data collection was approved by the Ethical Committee of Uppsala University, and all follow-ups over the course of the study were subsequently approved by the Regional Ethical Review Board in Uppsala.

Of those completing the first wave of data collection ($N = 631$), nearly 97% consented to future contact ($n = 609$). This procedure involved that participants provided their PIN to the members of the research group. In terms of the most recent follow-up – about 25 years after the first wave – individualized registry data were obtained from various government agencies, as has been described. The registry data were linked to the original dataset by Statistics Sweden using PINs of the retained cohort. All data were returned to the research group in a pseudonymized form. The data were harvested only for those considered as eligible ($n = 576$), excluding those who at the first wave of data collection did not consent to future contact ($n = 22$), and those who later refused extraction of individualized registry data as part of the preceding 15-year follow-up around age 30 ($n = 33$). As such, none of the participants in the retained cohort were directly contacted in person for the 25-year follow-up. However, information about the follow-up was posted on a website hosted by Uppsala University. Contact details to the principal investigator were also posted on the website should any of the eligible participants request to be removed, or in case there were any questions related to the project.

This procedure was ethically approved, and the unanimous judgement of the research group was that the potential benefits clearly exceed the potential risks. However, it could be argued that this question is pertinent to the broader issue of research studies involving large-scale population-based registries. As pointed out by Ludvigsson et al. (2015), registry-based research at the present time is seldom carried out with informed consent collected from individual participants, and the most central reason for this is that such a requirement would most likely give rise to systematic errors in the results (e.g., selection bias). Thus, it could be argued that the advantages of well-reasoned research may outweigh the disadvantages, insofar as the study serves a constructive purpose. Still, what may constitute a 'constructive' purpose is certainly not an easy matter to determine, and this has of course long been a topic of concern and conversation in academia as well as in society at large.

In the face of these key questions, longitudinal cohort studies of adolescent depression are much needed and quite rare, which arguably makes it even more important to utilize the data in the best possible way, as already noted by Alaie et al. (2019). Ultimately, the present approach to addressing long-term consequences of early-life depression may potentially generate new

knowledge relevant to the prevention and treatment of future generations of youths impacted by the disorder. It may also prove helpful in identifying subgroups at particular risk of later adversity.

Great Smoky Mountains Study

The study protocol was approved by the Institutional Review Board (IRB) of Duke University Medical Center. Participants and their parents or guardians provided written consent/assent forms prior to enrollment in the investigation. All follow-up assessments in adulthood were also approved by the IRB.

As described earlier, participants with American Indian heritage were oversampled in the GSMS, to enable the study of health and social outcomes for this particular subgroup in relation to their Anglo American and African American peers residing in the same community. Such an approach may prove to be key to a better understanding of the overall life prospects of this group and, potentially, to the development of targeted interventions for youths with, or at risk of, mental health problems in the context of adversity. This seems especially important in view of the limited information about American Indian youths available at the time of the launch of the GSMS (Costello et al., 1997; Costello et al., 1999), and, in particular, with respect to the alarming notion that these youths may be exceedingly exposed to mental ill-health and stressful interpersonal contexts (US Congress, 1990). Hypothetically, however, even the well-motivated study of an identified population, be it depressed youths or American Indians or depressed American Indian youths, could give rise to the potential for stigmatization among vulnerable groups, perhaps as an unintended consequence of study findings. This could be the case if it turns out that certain groups may fare worse than others. As such, people may feel pointed at after the study has been published and made its way into public awareness, which in turn could aggravate their health and personal well-being. In such a scenario, the study runs the risk of doing more harm than good. However, while the option not to conduct any research on socially sensitive issues might be equally problematic when balancing the risks against the presumptive benefits, it seems more reasonable to carry out the study after all, albeit with the aforementioned caveats in mind. Another relevant question that arises from this issue concerns how professionally responsible communication of study findings is best conveyed to the scientific community, news media, patient organizations, and the public at large. Clearly, this matter highlights the importance of established standards to ensure the integrity of individuals and groups of people, such as the widely used reporting guidelines published by the American Psychological Association (2020).

Study I

Uppsala Longitudinal Adolescent Depression Study

A cohort profile in the context of similar longitudinal studies

Research has shown that depressed children and adolescents are more likely than their nondepressed peers to become adults with mental health problems, general health issues, economic difficulties, and other social impairments. Nonetheless, current evidence points to a considerable methodological and statistical heterogeneity across previous follow-up studies (Clayborne et al., 2019; Johnson et al., 2018), further underscoring the urgent need to obtain a comprehensive prospective picture of the overall long-term burden following early-life depressive disorders and subthreshold depressive symptoms.

For this reason, a cohort profile of the ULADS was undertaken to place the key characteristics of this cohort into the broader research context of other diagnostically well-characterized and community-representative longitudinal studies of early depression. As such, study I contains no original empirical research other than some descriptive statistics. Instead, it serves the purpose of a narrative review portraying the general learning objectives as well as the specific methodological features of the ULADS over the course of the study. Additionally, an overview of key findings up to year 2018 is presented, of which a few are cited herein to highlight what has been learnt so far.

Key elements of study design

As detailed above, the ULADS is a longitudinal cohort study of individuals who originally were recruited in 1991–1992, and the majority took part in a subsequent 15-year follow-up conducted in 2006–2008. At both occasions, extensive information was collected on a broad range of psychiatric disorders, personality traits, and psychosocial circumstances. Later on, in 2017–2018, detailed data were retrieved from the Swedish nationwide population-based registries covering information on, for example, school achievement, income, employment, sickness absenteeism, and welfare benefit receipts.

Selected findings from previous reports

In previous research based on the ULADS, the 1-year and lifetime prevalence rates of major depression were estimated to be 5.8% and 11.4%, respectively, among adolescents in the community. Depressive disorder with a duration of at least 1 year (i.e., PDD according to DSM-5) was found to be the most common type of depression (Olsson & von Knorring, 1999). Comorbid psychiatric conditions, especially anxiety and conduct disorder, were common among depressed adolescents (Olsson, 1998).

In the 15-year follow-up study, the majority of cases reported depression recurrence or continued depression lasting into young adulthood, whereas about a third of the matched peers reported an adult onset of major depression (Jonsson, Bohman, von Knorring, et al., 2011). Further, adolescent depression was found to be associated with increased odds of other adverse outcomes in young adulthood, including additional mental health problems (Jonsson, Bohman, von Knorring, et al., 2011), lower educational attainment (Jonsson et al., 2010), and difficulties related to intimate relationships (Jonsson, Bohman, Hjern, et al., 2011). Multiple somatic symptoms in adolescence were observed to predict depression recurrence as well as other adult mental health problems (Bohman et al., 2012; Bohman et al., 2018).

New knowledge, new recommendations?

As the present 25-year follow-up of the ULADS was made possible through linkage between the national registries and the wealth of information gathered from previous in-person assessments, it may offer a unique opportunity to gain deeper insights into the future prospects of adolescents with depression. Such an understanding may have the potential to better inform public health policy and clinical decision-making.

Study II

Parent–youth conflict as a predictor of depression in adulthood

Background and aim

Social difficulties across various interpersonal contexts, including the family and the relationships with parents, are common among depressed adolescents (Hammen, 2018). While minor conflict in the parent–youth relationship is generally considered to be rather normative during adolescence (Smetana et al., 2006), prior research suggests that major conflict with parents is predictive of onset, recurrence, and worse treatment outcome of adolescent depression (Restifo & Bögels, 2009). However, it is not clear whether the adverse effects of parent–youth conflict may extend into adulthood. The aim of this study was therefore to test if minor and major conflict with one's parents while growing up are predictive of depression in adulthood.

Methods in brief

The data were drawn from the 15-year follow-up assessment of the ULADS. Participants with adolescent depressive disorders or symptoms (n = 227) and their nondepressed peers (n = 155) were included in the analysis.

Parent–youth conflict was operationalized using items of the CLEI (Coddington, 1972), as self-reported at baseline, comprising dichotomous questions (i.e., yes/no) asking whether a particular event had occurred in the past year and/or earlier in life. The categorization of parent–youth conflict was based on two items asking if one had experienced minor and major conflict with parents, respectively. Three strata were created based on participants' responses to these particular items: no conflict with parents (n = 144); minor conflict with parents (n = 168); major conflict with parents (n = 70).

Main outcome

The main outcome was depression in adulthood, as assessed retrospectively at the 15-year follow-up. Depression in adulthood was defined as experiencing either one long (≥ 6 months) or recurrent (≥ 2) major depressive episodes occurring between 19 and 31 years of age, in line with previous work (Jonsson, Bohman, von Knorring, et al., 2011).

Statistical analysis

A series of logistic regression models were fitted to the data. Each estimate was reported as an OR with a 95% CI. Several factors of potential relevance for the risk of adulthood depression were controlled for in adjusted analyses, including gender, ADHD, CD, ODD, financial strain in the family, parental separation, and parental history of depression. All analyses were run using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Key findings

In the total sample at follow-up, 37.7% of participants fulfilled criteria for adult depression. This was more common among those who were depressed as adolescents (48.5%) than among their nondepressed peers (21.9%), as shown in Table 2. Among those who reported no conflict with parents, 28.5% suffered from depression in adulthood. The corresponding share for those who reported minor conflict was 36.3%, and for those reporting major conflict the share was 60.0% (results not shown in table).

Table 2. *Descriptives of participants in study II.*

	All (*n* = 382)		**Depressed adolescents** (*n* = 227)		**Nondepressed controls** (*n* = 155)	
	n	***%***	***n***	***%***	***n***	***%***
Baseline characteristics						
Conflict with parents						
No	144	37.7	72	31.7	72	46.5
Minor	168	44.0	93	41.0	75	48.4
Major	70	18.3	62	27.3	8	5.2
Gender						
Males	79	20.7	47	20.7	32	20.7
Females	303	79.3	180	79.3	123	79.3
ADHD	26	6.8	25	11.0	1	0.7
CD/ODD	62	16.2	54	23.8	8	5.2
Family income reduced	64	16.8	49	21.6	15	9.7
Parental separation	136	35.6	94	41.4	42	27.1
Parental depression[a]	124	32.7	84	37.5	40	25.8
Follow-up						
Depression in adulthood	144	37.7	110	48.5	34	21.9

Note: [a] All *n*=379; depressed *n*=224

ADHD=attention deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder

The covariate-adjusted model demonstrated that the only predictors associated with increased odds of adulthood depression were major conflict with parents (aOR = 2.26, 95% CI = 1.16–4.39) and adolescent depression (aOR = 2.70, 95% CI = 1.65–4.42), as shown in Figure 3.

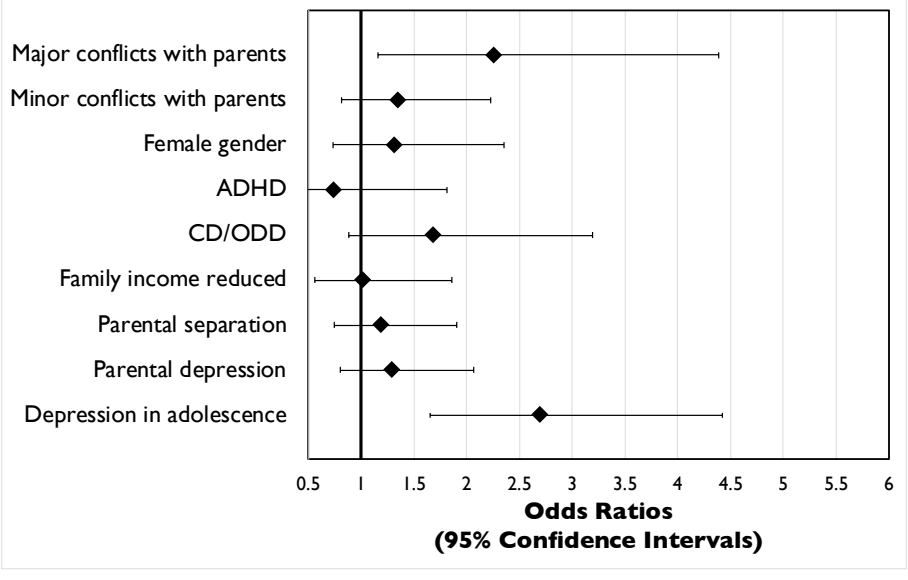


Figure 3. Forest plot illustrating the association between parent–youth conflict and depression in early adulthood, with adolescents reporting no conflict with parents as the reference category and with simultaneous adjustment for potential confounders.

After stratifying the analysis by adolescent depression status, major conflict was associated with increased odds of adulthood depression among those with adolescent depression (aOR = 2.28, 95% CI = 1.07–4.87). A nonsignificant association of a similar magnitude was also observed among the nondepressed peers (aOR = 2.47, 95% CI = 0.49–12.48).

Further analyses of parent–youth conflict as the predictor variables and a range of mental health outcomes suggested no evidence of associations with adult anxiety, somatoform disorders, psychotic disorders, suicidal behavior, or substance use; however, major conflict with parents was strongly associated with bipolar disorder in adulthood (aOR = 6.38, 95% CI = 1.70–24.00).

It was found that the timing of conflict mattered: adolescents who reported major conflict with parents both in the past year and earlier in life (n = 14) were more likely to have depression in adulthood than those who reported having had no major conflict with parents (aOR = 4.54, 95% CI = 1.18–17.44). In contrast, the adolescents who reported major conflict with parents only in the past year (n = 29), or only earlier in life (n = 27), did not differ significantly from those who reported no major conflict.

Conclusion

This study found that highly conflictual relationships with parents while growing up may have more enduring mental health consequences than previously known. As available longitudinal research shows that adolescent depression is predictive of subsequent depression recurrence in adulthood, this study showed that depressed adolescents experiencing major conflict with parents were at an additionally increased risk of depression recurrence. While major conflict with parents was infrequently reported by the nondepressed controls, a similar tendency of depression onset in adulthood was nonetheless observed in this group. Perhaps more importantly, the severity of conflict emerged as decisive for the long-term mental health outcome, as major (but not minor) parent–youth conflict was found to be predictive of adulthood depression. The highest risk of adulthood depression was observed in adolescents reporting experiences of major conflict with parents in the past year *and* earlier in life, suggesting that both severity and duration of conflict may be crucial for the long-term mental health outcome. Overall, findings from this study add to the literature by pointing to a long-lasting link between early family conflict and later mental ill-health. The study also replicates some key findings of other long-term follow-up studies in diverse populations (Green et al., 2013; McLeod et al., 2016).

Although the direction of causality in the well-documented link between early depression and parent–child conflict remains unclear, it might be the case that early exposure to conflictual relationships may increase individual vulnerability to depression by lowering the threshold for affective problems, potentially due to a mechanism conceptualized as stress sensitization (Hammen, 2018). However, additional research is needed to better understand the role of early stress and its long-term effects on health and functioning across the life course. Another mechanism of potential relevance to the long-term effects of highly conflictual parent–child relationships may be 'expressed emotion', which has been described as a form of toxic family stress (Peris & Miklowitz, 2015). Given that major conflict with parents was predictive of adult depression as well as bipolar disorder among those with a prior history of adolescent depression, there may be certain overlapping symptoms in the mood spectrum disorders (e.g., irritability) that are particularly relevant to the family dynamics and interactional patterns in the parent–child relationship.

In the face of previous longitudinal research showing that the quality of parent–child relationships and family bonding in adolescence is only modestly protective against adult depression (Raudino et al., 2013), more research is needed to disentangle how stressful interpersonal contexts, family dynamics, and individual susceptibility to mood disorder are related to one another, to further inform the clinical management of early depression.

Study III

Associations of childhood and adolescent depression with adult psychiatric and functional outcomes

Background and aim

Recent research suggests that the links between adolescent depression and adult mental health and psychosocial functioning are largely attributable to other factors than depression, such as early adverse experiences and other mental health problems in childhood and adolescence (McLeod et al., 2016). Additional work is therefore needed to clarify which longer-term effects of early depression are independent of other early risk factors. The overall aim of this study was to examine associations of childhood/adolescent depression with a broad range of adult psychiatric and functional outcomes.

Methods in brief

The data were drawn from multi-wave follow-ups of the GSMS (Costello et al., 2016), with reassessments extending up to age 30 years. Participants with depressive disorder or symptoms (n = 140) and with no depressive disorder or symptoms (n = 1,280) in childhood/adolescence were included in the analysis.

As for psychiatric outcomes, an indicator was coded positive if diagnostic criteria were met at any adulthood observation. As regards physical health and functional outcomes, an indicator was coded positive if reported at any point in adulthood; however, in some cases the most recent observation was used to determine status.

Main outcomes

Psychiatric disorders included any disorder, anxiety disorder, depressive disorder, nicotine use disorder, alcohol use disorder, cannabis use disorder, illicit drug use disorder, and antisocial personality disorder.

Physical health included being diagnosed with a serious illness, being in a serious accident, or having a sexually transmitted disease at any time during adulthood. Other health problems, regular smoking, obesity, and markers of elevated C-reactive protein were also included.

Wealth comprised both financial and educational accomplishments. In terms of financial situation, being impoverished was defined on the basis of

thresholds issued by the U.S. Census Bureau. Moreover, being dismissed or fired from a job, quitting a job without financial preparations, failing to honor debts or financial obligations, and being a poor manager of one's finances were also included. As for educational accomplishment, high school dropout and completion of any college/university education were included.

Social functioning referred to interpersonal relationships, including marital, parenthood, and divorce status. The quality of the participant's relationships with parents, spouse or significant other, and friends was repeatedly assessed in adulthood. Further, there were variables to indicate violence in a primary relationship, poor relationship with one's parents, no best friend or confidante, and problems with making or keeping friends.

Risky/criminal behaviors included official felony charges harvested from the North Carolina administrative Offices of the Courts records. Moreover, self-reported information about police contact, lying, physical fighting, and burglary was also included. Ascertainment of frequent drunkenness was made if the participant reported drinking excessively at least once weekly for the past three months. Recent use of marijuana or other illegal substances was also included, as were one-time sexual encounters with strangers.

Statistical analysis

A series of regression models were fitted to the repeated measures data using a generalized estimating equations (GEE) modeling approach (Liang & Zeger, 1986). Weighted models were used to examine differences in adult outcomes by childhood/adolescent depression status. These included logistic (for binary outcomes such as adult psychiatric status) and linear (for continuous outcomes such as *z*-scores for adult health and functioning) regression models.

A broad range of early adverse experiences were accounted for in adjusted analyses, including low socioeconomic status, unstable family structure, dysfunctional family functioning, maltreatment, and peer victimization. Further, adjustment was also made to account for the effects of gender, race, and comorbid psychiatric conditions in childhood/adolescence.

Analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

Key findings

As shown in Table 3, participants with childhood/adolescent depression had much higher levels of various psychiatric problems in early life, and they were also more exposed to a broad range of social adversities, including adverse family-related circumstances and peer victimization, as compared with the nondepressed controls. At follow-up, it was found that childhood/adolescent depression was associated with higher levels of adult psychiatric problems as well as substantial role impairments across all functional domains.

Table 3. *Descriptives of participants in study III.*

	No childhood/adolescent depression		Childhood/adolescent depression	
	n	***%***	***n***	***%***
Total	1,280	92.3	140	7.7
% Female	556	48.2	74	56.9
White	878	89.1	105	93.4
African-American	81	7.3	7	2.8
American-Indian	321	3.7	28	3.8
Early psychiatric disorders				
Any anxiety disorder	129	7.5	65	46.0
ADHD	58	2.7	20	10.9
ODD	163	6.7	75	46.3
CD	158	6.9	45	28.5
Substance disorder	78	4.7	30	25.5
Early adverse experiences				
Low socioeconomic status	584	33.7	65	38.1
Family instability	405	25.2	65	38.2
Family dysfunction	383	24.7	93	53.4
Maltreatment	343	18.0	86	51.0
Peer victimization	357	24.9	64	41.0
Follow-up				
Adulthood psychiatric disorders				
Any disorder	505	43.4	87	76.1
Any anxiety disorder	170	14.3	47	48.7
Any depressive disorder	128	8.9	29	26.7
Any substance disorder	370	32.3	63	45.2
Adulthood functional outcomes	***M***	***SD***	***M***	***SD***
Physical health	0.07	0.97	-0.83	0.95
Wealth	0.05	0.99	-0.58	0.94
Social functioning	0.06	0.99	-0.61	0.94
Risky/criminal behavior	0.04	0.99	-0.52	0.92

Note: All percentages are weighted, all *n*s are unweighted. *M*s and *SD*s for adulthood functional outcomes are *z*-transformed scores on continuous scales.

ADHD=attention deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder

As presented in Figure 4, children and adolescents with depression were found to be at increased odds of any psychiatric disorder, anxiety, depression, and substance disorder in adulthood, as compared with the nondepressed controls. In the fully adjusted model, the associations with depression and substance disorder became nonsignificant; however, childhood/adolescent depression remained predictive of any adult psychiatric disorder (aOR = 2.5, 95% CI = 1.2–5.4) and anxiety disorder (aOR = 3.3, 95% CI = 1.6–6.8).

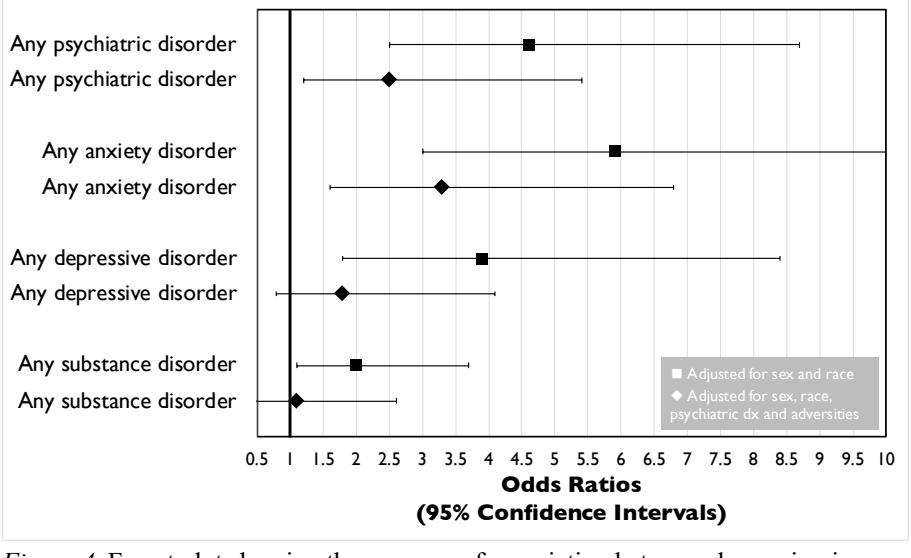


Figure 4. Forest plot showing the measure of association between depression in childhood/adolescence and psychiatric disorders in adulthood, as compared with nondepressed controls as the reference category.

Childhood/adolescent depression was found to be predictive of worse physical health (β = 0.89, 95% CI = 0.55–1.22), wealth (β = 0.68, 95% CI = 0.38–0.99), social functioning (β = 0.69, 95% CI = 0.37–1.01), and also risky or criminal behavior (β = 0.65, 95% CI = 0.40–0.90) in adulthood. After adjustment for covariates, these associations attenuated but persisted for physical health (adjusted β = 0.48, 95% CI = 0.13–0.84), social functioning (adjusted β = 0.38, 95% CI = 0.05–0.71), and risky/criminal behavior (adjusted β = 0.29, 95% CI = 0.02–0.56).

Further, there was no clear evidence that associations between childhood/adolescent depression and adult outcomes varied by gender.

It was observed that those who became depressed as adolescents did fare worse in adulthood than those who had depression onset in childhood.

The results suggested a cumulative effect of exposure to depression, such that persistence of elevated levels of early depression was associated with more adverse adult psychiatric and functional outcomes.

Among participants with childhood/adolescent depression, 63.1% reported receiving some type of care service, and 34.5% reported receiving specialty mental health services. Use of specialty mental health services within childhood and adolescence was found to be associated with lower risk for any adult psychiatric disorder; however, there was no indication that any services use moderated the effect of early depression on adult functioning.

Conclusion

This study found that childhood and adolescent depression was predictive of a vast range of mental health problems and functional impairments in early adulthood, which is a finding that generally resonates well with the literature on long-term outcomes of early-life depression (Clayborne et al., 2019; Johnson et al., 2018). The study also adds to the literature by suggesting that early depression is associated with many psychiatric and functional outcomes even when accounting for a multitude of potential confounders. Notably, the long-term effects of childhood/adolescent depression may be independent of other adversities, though the magnitude of these effects was rather moderate. Overall, the study supplements a recent report from the Christchurch Health and Development Study (McLeod et al., 2016), in which it was suggested that the long-term functional impairments observed in those exposed to adolescent depression are largely attributable to other key factors than depression per se (e.g., comorbid conditions, cognitive ability, and social adversity). While it seems likely that differences in individual characteristics and circumstances play a key role in determining overall life outcomes, there is now reason to challenge the notion that depression in itself may have no substantial impact on adult health and functioning. Equally important, the present study found a cumulative effect of exposure to early depression, thereby suggesting that it is not only a time-limited, single-episode depression that is predictive of adverse outcomes, but also the persistence of depressive symptomatology across childhood and adolescence. As such, it is not merely a diagnosis of depression that is predictive of adverse long-term outcomes.

There is the need to better understand if other markers of early risk may interact with the timing of the depression exposure, and if targeted interventions may have the potential to mitigate the longitudinal course of the illness. While use of specialty mental health services may be protective against adult mental health problems, more research is needed to better understand how to best implement timely and targeted treatment, and if support services during the transition to adulthood may have the potential to help improve the future life chances of depressed youths.

Study IV

Adolescent depression and adult labor market marginalization

Background and aim

Depression in adolescence is associated with lower educational attainment and workforce participation in adulthood (Clayborne et al., 2019), although the key factors and mechanisms linking adolescent depression to adult functional impairments are not well understood. Today, the spread of unemployment and work incapacity – often called labor market marginalization (LMM) – has been recognized as especially harmful to the life prospects of youths with common mental disorders. Therefore, there is the need to better understand what role the clinical heterogeneity in depression plays for the adult labor market outcome, and if the long-term functional impairment may differ by the specific type of depression. The main aim of this study was thus to examine the associations between adolescent depression and adulthood LMM outcome, including a DSM-based differentiation between depressive disorders. Further, the study aimed to test the extent to which depressive episodes in early adulthood may mediate the subsequent LMM outcome, and also to explore if higher education may mediate or moderate the LMM outcome.

Methods in brief

The data were drawn from the 15- and the 25-year follow-ups of the ULADS. Participants with adolescent depression (n = 321) and their nondepressed peers (n = 218) were included in the analysis. As the baseline assessments were based on DSM-III-R criteria, the original classifications were converted to current DSM-5 taxonomy. The following subgroups were identified:

Persistent depressive disorder (PDD, n = 175);
Major depressive disorder (MDD, n = 82);
Subthreshold depression (SUB DEP, n = 64);
No adolescent depression (n = 218).

Main outcomes

All LMM outcomes were dichotomized and based on consecutive annual data from Statistics Sweden (Ludvigsson et al., 2019), with each indicator coded positive conditional on its occurrence in each year between ages 21 and 40.

Long-term unemployment was defined as ≥ 180 annual net days of being registered as full- or part-time unemployed or included in labor market policy programs (Niederkrotenthaler et al., 2014; Niederkrotenthaler et al., 2016).

Work disability was defined as granted disability pension or ≥ 60 annual net days of being registered as sickness absent due to disease or injury (Helgesson et al., 2018; Swedish Social Insurance Agency, 2016).

Social welfare assistance was defined as a welfare receipt in the form of income support, regardless of the monetary amount of the support received.

Overall marginalization was defined as an occurrence of any labor market outcome, including long-term unemployment, work disability, and/or social welfare assistance.

Mechanisms under study

Depression in adulthood, assessed at the 15-year follow-up interview, was tested as a potential mediator for the overall marginalization outcome. Here, as in study II, depression in adulthood was defined as experiencing either one long (≥ 6 months) or recurrent (≥ 2) major depressive episodes between 19 and 31 years of age, in keeping with previous work based on the ULADS (Jonsson, Bohman, von Knorring, et al., 2011; Philipson et al., 2020; Ssegonja, Alaie, et al., 2019).

Two registry-based variables, both retrieved from Statistics Sweden (Ludvigsson et al., 2019), were used to capture educational milestones achieved in adulthood. *Educational attainment* was defined as ≥ 3 years of completed tertiary/higher education by age 30/31, and this was also explored as a mediator for the overall marginalization outcome. Furthermore, *tertiary education entry* was defined as all post-secondary education that participants had enrolled by age 25/26, including vocational training, college, or university studies, and this variable was explored as a moderator (or effect modifier) for the overall marginalization outcome.

Statistical analysis

A series of binary logistic regression models were fitted to the repeated measures data using a GEE modeling approach (Liang & Zeger, 1986). Each estimate was reported as an OR with a 95% CI. All models were used to look at differences in adult LMM outcomes by adolescent depression status, with the nondepressed controls entered as the reference category.

The indirect effect of depression in adulthood (ages 19–30) on the overall marginalization outcome (ages 31–40) was tested in mediation analysis based on the counterfactual framework for causal inference (VanderWeele, 2016).

The mediation analyses were conducted using a logistic regression model for the hypothesized mediator (i.e., adult depression; binary variable, yes/no) and a quasi-Poisson regression model for the outcome (i.e., subsequent overall marginalization; count outcome, frequency of years in any marginalization), with robust standard errors. Likewise, educational attainment was explored as a putative mediator using the same analytic approach.

Moderation by entry into tertiary education was explored using interaction terms (depression status × tertiary education entry), alongside tests of main effects. In terms of the temporal ordering of events, the effect of entry into tertiary education on the risk of marginalization was explored for the latter 15 years of the follow-up period.

Several factors of potential relevance for the future labor market outcome were accounted for in adjusted analyses, including gender, anxiety, disruptive behaviors, tobacco use/misuse, GPA, parental income, and parental education.

Data management and analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) and R version 4.0.3 (R Core Team, 2021). The mediation analyses were run using the package 'mediation' (Tingley et al., 2014).

Key findings

Descriptive characteristics of the participants are presented in Table 4. Among those with adolescent depression, the majority of cases presented with PDD.

Of those retained from the 15-year follow-up, some 21% of the formerly nondepressed controls and 51% of the depressed cases fulfilled the criteria for depression in adulthood.

It was observed that 40% of those with adolescent depression had entered tertiary education by their mid-twenties, as compared to 49% among the non-depressed controls. Regarding educational attainment by the early thirties, 36% of those with adolescent depression had completed at least 3 years of tertiary education, compared with 43% among the nondepressed controls.

The mean frequency of years meeting the pre-defined cutoff for the overall marginalization outcome was 4.0 years (SD = 4.7) and 2.2 years (SD = 3.7) among the depressed and the nondepressed groups, respectively.

Table 4. *Descriptives of participants in study IV.*

	No adolescent depression (*n* = 218)		**Adolescent depression** (*n* = 321)							
					Type of adolescent depression					
					SUB DEP (*n* = 64)		**MDD** (*n* = 82)		**PDD** (*n* = 175)	
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	***n***	***%***
Early-life characteristics										
Females	171	78	254	79	46	72	68	83	140	80
ADs	32	15	145	45	6	9	34	41	105	60
DBDs	16	7	96	30	16	25	20	24	60	34
Tobacco use/misuse	57	26	170	53	37	58	42	52	91	52
GPA, *M (SD)*	3.5	0.6	3.3	0.7	3.3	0.7	3.2	0.8	3.3	0.6
Low parental education	102	47	152	50	30	51	45	58	77	45
Low parental income	68	32	109	35	20	33	27	35	62	36
Interview-based follow-up										
Diagnostic reassessment	147	67	204	64	30	47	59	72	115	66
Depression in adulthood										
Yes	31	21	103	51	11	37	21	36	71	62
No	116	79	101	49	19	63	38	64	44	38
Registry-based follow-up										
Tertiary education entry										
Yes	107	49	128	40	25	39	33	41	70	40
No	111	51	192	60	39	61	48	59	105	60
Educational attainment										
≥ 3 years	93	43	115	36	23	36	29	36	63	36
No or < 3 years	125	57	205	64	41	64	52	64	112	64
Labor market outcome	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
Long unemployment	1.3	2.3	2.1	3.0	1.6	2.5	1.9	2.4	2.4	3.5
Work disability	0.8	2.5	1.4	3.0	0.8	1.6	1.3	2.8	1.7	3.4
Social welfare recipiency	0.4	1.3	1.2	2.7	1.3	2.7	0.9	2.5	1.3	2.8
Overall marginalization	2.2	3.7	4.0	4.7	3.0	3.8	3.5	4.3	4.6	5.2

Note: Tertiary education entry refers to enrollment in higher education by age 25.
Educational attainment is the level of tertiary education achieved by age 30.
Labor market outcome refers to the number of years meeting cut-off across ages 21 to 40.
SUB DEP=subthreshold depression; MDD=major depressive disorder; PDD=persistent depressive disorder; ADs=anxiety disorders; DBDs=disruptive behavior disorders; GPA=grade point average

In the unadjusted analyses, adolescent depression was associated with higher levels of all LMM outcomes, as shown in Figure 5. After covariate adjustment, the association with long-term unemployment and work disability were no longer significant; however, the association with social welfare assistance (aOR = 2.1, 95% CI = 1.3–3.5) and the overall marginalization outcome (aOR = 1.5, 95% CI = 1.1–2.0) attenuated but persisted.

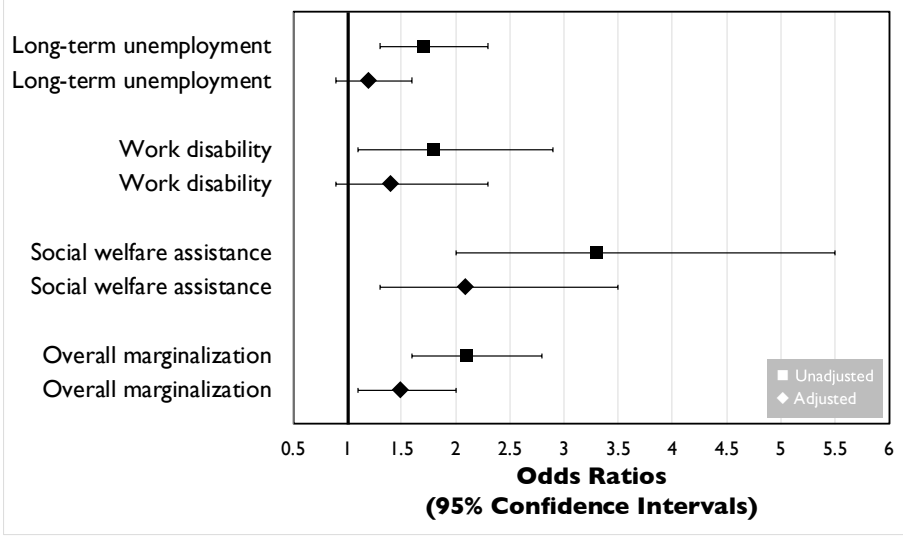


Figure 5. Forest plot illustrating the associations of adolescent depression with adult labor market marginalization outcomes, as compared with nondepressed controls.

In terms of differences by the clinical form of depression, those with PDD had higher odds of all LMM outcomes compared with the nondepressed controls, including long-term unemployment (aOR = 1.5, 95% CI = 1.0–2.1), work disability (aOR = 1.8, 95% CI = 1.1–3.1), social welfare assistance (aOR = 3.0, 95% CI = 1.7–5.3), and the overall marginalization outcome (aOR = 2.0, 95% CI = 1.4–2.7). Those with MDD and SUB DEP had also higher odds of some LMM outcomes, but these associations attenuated and became nonsignificant after covariate adjustment.

Depression in adulthood was significantly associated with the subsequent marginalization outcome, both in unadjusted (IRR = 2.4, 95% CI = 1.8–3.2) and adjusted analysis (IRR = 2.3, 95% CI=1.7–3.3), where the latter included prior adolescent depression along with all aforementioned covariates. Unadjusted analysis revealed a significant indirect effect of adulthood depression (β = 0.25, 95% CI = 0.09–0.46) and a significant direct effect of adolescent depression (β = 0.56, 95% CI = 0.11–1.00) with respect to the subsequent marginalization outcome. After adjustment for covariates, the direct effect of adolescent depression attenuated and became nonsignificant, whereas the

indirect effect remained significant. The average proportion mediated by adult depression was 35%.

Furthermore, for those with PDD in adolescence, the unadjusted analysis demonstrated an indirect effect of adulthood depression (β = 0.36, 95% CI = 0.11–0.68) and a direct effect of adolescent PDD (β = 0.92, 95% CI = 0.34–1.56). These estimates remained roughly unchanged in the adjusted analysis, and the average proportion mediated by adult depression was 31%. Regarding the MDD and SUBDEP subgroups, there was no significant indirect effect of adult depression on the overall marginalization outcome.

There was no evidence to suggest any indirect effect of educational attainment with regard to subsequent marginalization, not for the broader group of depressed cases and nor for the specific subgroups. However, exploratory analyses indicated moderation, or effect modification, by entry into tertiary education, such that the effect of episodic MDD on the subsequent risk for LMM was found to be mitigated for those enrolling in tertiary education in early adulthood. However, entry into tertiary education was not differentially associated with subsequent LMM for the other depressed subgroups.

Finally, there was a somewhat differential outcome by gender; compared to their nondepressed counterparts, the males with adolescent depression had higher odds of long-term unemployment (OR = 3.5, 95% CI = 1.7–7.1) while the females with adolescent depression had higher odds of work disability (OR = 2.0, 95% CI = 1.2–3.2). Yet, these associations attenuated and became non-significant in adjusted analyses, most prominently for the depressed males.

Conclusion

This study found that depression in adolescence was predictive of worse labor market outcomes across early-to-middle adulthood. Consistent with recent longitudinal research (McLeod et al., 2016), the associations were attenuated once potential confounders were accounted for. However, further subgroup analysis showed that adolescents with PDD had around two-fold higher odds of overall marginalization than the nondepressed peers, even after covariate adjustment. Evidence suggests that this elevated risk may to some extent be attributed to the longitudinal course of depression. While the overall pattern of results was less clear for adolescents with MDD and subthreshold depression, a similar direction of findings was partly observed in these subgroups. Further, findings from this study imply that entry into tertiary education can be protective against adverse effects in the labor market, at least for those with MDD. In conclusion, this study supports the notion that exposure to chronic depression in early life is a crucial risk factor for a vast range of long-term functional impairments (Johnson et al., 2018). The findings also emphasize that diagnostic differentiation between episodic and chronic forms of early-life depression seems important both from a clinical and societal perspective.

Study V

Adolescent depression, early psychiatric comorbidities, and adulthood welfare burden

Background and aim

Evidence shows that depressive disorders at all ages are costly to society, yet prior research has primarily reported on healthcare expenditures among adults and only to a lesser extent on the cost burden among those with depression onset in early life. The aim of this study was therefore to examine associations between adolescent depression and social transfer payments in various welfare sectors across early-to-middle adulthood. The study also addressed the impact of psychiatric comorbidities on the associations with social transfer payments.

Methods in brief

The data were drawn from the 25-year follow-up of the ULADS. Participants with adolescent depression (n = 321) and their nondepressed peers (n = 218) were included in the analysis. As noted earlier in the summary of study IV, the original diagnostic assessments were reclassified in accordance with the current DSM-5 taxonomy, whereby the following subgroups were identified: PDD (n = 175); MDD (n = 82); SUB DEP (n = 64); and no adolescent depression (n = 218). In addition, this study also differentiated between the various configurations of comorbid psychopathologies, irrespective of which type of adolescent depression that was met. The comorbid psychiatric conditions comprised separation anxiety disorder, overanxious disorder, and avoidant disorder (i.e., anxiety disorders, ADs) as well as ADHD, ODD, and CD (i.e., disruptive behavior disorders, DBDs). These subgroups were identified:

Noncomorbid depression (n = 132);
Depression + ADs (n = 93);
Depression + DBDs (n = 44);
Depression + DBDs + ADs (n = 52).

Main outcomes

Four types of social transfer payments were used as main outcome measures. All social transfer payments were based on consecutive annual data, harvested from Statistics Sweden (Ludvigsson et al., 2019), spanning from age 18 to 40.

Unemployment benefits were defined as payments for those registered as full- or part-time unemployed or as included in labor market policy programs.

Work disability benefits were defined as payments due to disability pension or sickness absence.

Public assistance was defined as social welfare assistance, housing supplement, housing allowance, and maintenance support.

Overall benefits in aggregate were defined as a summed measure of all types of cash benefits and financial support previously described.

Statistical analysis

The associations of adolescent depression and psychiatric comorbidities with subsequent social transfer payments were analyzed using the GEE modeling approach (Liang & Zeger, 1986). All associations were modeled by fitting a Tweedie distribution with an identity link function to the repeated measures data on social transfer payments, in order to account for the excess of zeros in each outcome (Kurz, 2017).

The annual payments were converted to the value of January 2019 using Consumer Price Index (Statistics Sweden, 2019), after which all payments were converted from Swedish krona (SEK) to US dollar (USD) by using an approximated exchange rate of 1 SEK = 0.1113 USD, as valid in January 2019. Each estimate was calculated as the average of payments per year exceeding the nondepressed controls, with a 95% CI. Gender and educational level of parents were included as covariates in adjusted analyses.

Data management and analysis were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) and Stata version 16 (StataCorp LLC, College Station, TX, USA).

Key findings

In the total sample at follow-up (N = 539), co-occurring ADs and DBDs of childhood/adolescence were observed among 10% of participants (n = 55), DBDs without ADs were observed among 11% (n = 57), and ADs without DBDs were observed among 23% (n = 122). These conditions were primarily concentrated in those with depressive disorders or subthreshold depressive symptoms in adolescence, but, as noted earlier, 41% (n = 132) of the depressed cases presented with no psychiatric comorbidity.

Descriptive data of the expenditures of social transfer payments, expressed in USD per year (with 95% CI), are shown in Figures 6 and 7.

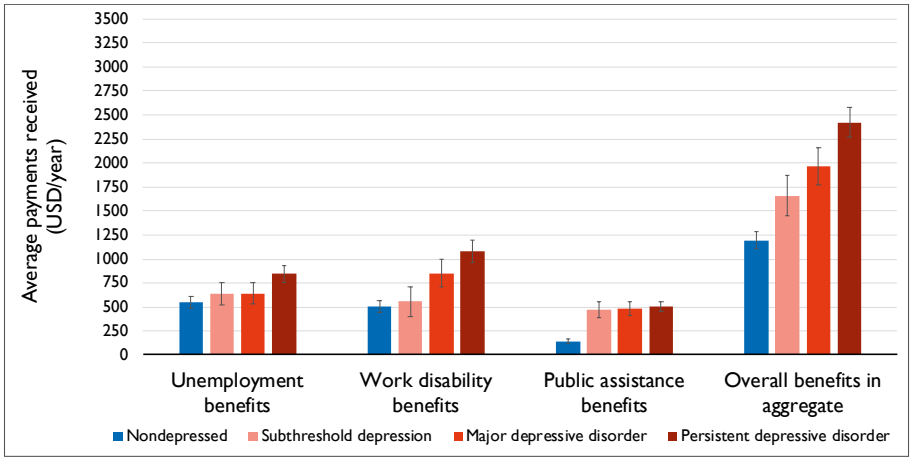


Figure 6. Average payments received in USD per year during a time frame spanning from age 18 to 40. Descriptive data are shown for those with adolescent depressive disorders or symptoms and their nondepressed peers.

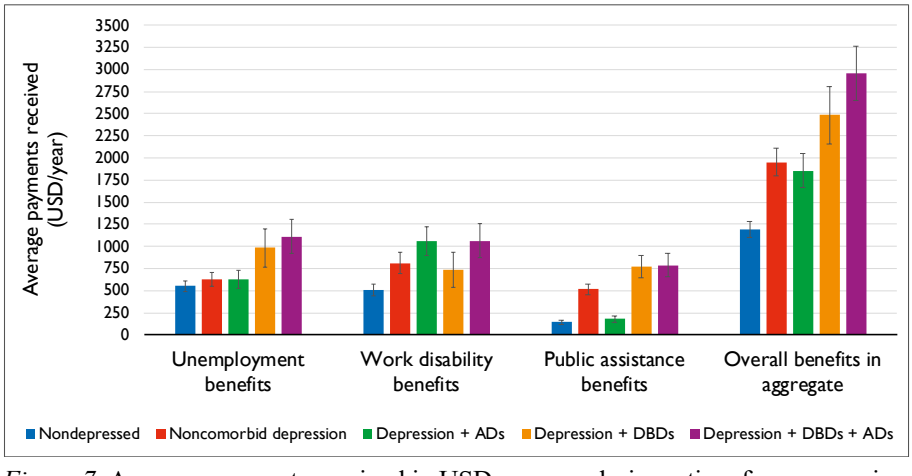


Figure 7. Average payments received in USD per year during a time frame spanning from age 18 to 40. Descriptive data are shown for those with comorbid/noncomorbid adolescent depression and their nondepressed peers.

The results showed that adolescent depression was associated with all forms of social transfer payments, including overall benefits, estimated as 938 USD (95% CI = 551–1326) more per year than the nondepressed controls. Those with PDD had a markedly higher recipiency across all outcomes, with overall benefits estimated as 1172 USD (95% CI = 673–1670) more per year compared with the nondepressed controls. There were less pronounced differences between the other depressed subgroups and the nondepressed; however, those

with MDD evidenced higher overall benefits, estimated as 793 USD (95% CI = 176–1410) more per year.

Adolescents with comorbid DBDs and ADs demonstrated a markedly higher recipiency across all outcomes, including unemployment benefits (566 USD, 95% CI = 60–1071), work disability benefits (545 USD, 95% CI = 9–1081), public assistance (634 USD, 95% CI = 237–1031), and overall benefits (1753 USD, 95% CI = 887–2620). Aside from overall payments, the depressed adolescents with only comorbid DBDs also had higher recipiency of public assistance (582 USD, 95% CI = 230–935), while those with only comorbid ADs had higher recipiency of work disability benefits (495 USD, 95% CI = 67–924). The noncomorbid subgroup of depressed adolescents were found to show higher recipiency of public assistance (390 USD, 95% CI = 186–594). In a multivariable model accounting for the separate sources of exposure (i.e., depressive disorders, ADs, and DBDs), alongside gender and educational level of parents, it was found that PDD (1006 USD, 95% CI = 515–1497), MDD (660 USD, 95% CI = 8–1311), and DBDs (961 USD, 95% CI = 362–1559) were all associated with higher recipiency of overall benefits.

Conclusion

This study found that depression in adolescence was associated with higher social transfer payments across early-to-middle adulthood, with the average payments associated with adolescent depression amounting to a total of around 1,000 USD per year for each affected individual. The study also found evidence to suggest a clinical patterning of findings. Adolescents with PDD had a particularly high recipiency across all outcomes, suggesting that this subgroup may have driven a substantial part of the differences between those with and without adolescent depression. Further, there was also evidence that comorbid psychopathology in adolescent depression may play a key role in determining the magnitude of adulthood welfare sector costs, especially the combination of depression, DBDs, and ADs.

These results may imply that the poor socioeconomic outcomes following adolescent depression and its psychiatric comorbidities can be rooted in the stagnating effects of early psychopathology on human capital development (Johar & Truong, 2014). Early exposure to depression, particularly when co-occurring with other forms of major psychopathology, may exert a profound influence on the acquisition of important skills and abilities required for adult functioning. As a consequence, this stagnation may increase the risk of future marginalization from the labor market and, in effect, lead to increased costs to society. Altogether, this suggests that the clinical heterogeneity of adolescent depression should be considered from a longer-term societal perspective.

General discussion

The empirical studies presented in this doctoral thesis sought to advance the knowledge about long-term outcomes of childhood and adolescent depression. Overall, the studies clearly suggest that depression with early onset is a major risk factor for mental ill-health, functional impairment, and socioeconomic disadvantage in the long run. This general conclusion is thus in keeping with previous longitudinal studies reporting on adult outcomes following early-life depression (Clayborne et al., 2019; Johnson et al., 2018).

Evidently, the heterogeneous long-term outcome arises as the most striking finding of the present work, and this may to quite a large extent be attributable to the clinical heterogeneity in depression. In particular, this work points to the unfavorable life prospects of children and adolescents exposed to chronic/persistent depression, but also those manifesting depression combined with other psychiatric conditions, and those who are faced with subsequent depression recurrence in early adulthood. Here, the following discussion starts with an overview of the main findings, continues with some methodological considerations, and ends with a reflection on overall implications along with a few suggestions for the direction of future research in this field.

Main findings

Could conflict in the parent–child relationship be a risk factor for depression in early adulthood?

Adolescents with depression are widely known to be at increased risk of subsequent depressive episodes and other mental health problems in adulthood when compared with nondepressed controls (Johnson et al., 2018; Jonsson, Bohman, von Knorring, et al., 2011). In study II, depressed adolescents were found to be at an additionally increased risk of adult depression if they also had experienced major conflicts with their parents while growing up. This finding is in line with other prospective evidence (Green et al., 2013; McLeod et al., 2016), implying that maladaptive family dynamics emerges as a risk factor for recurrence or persistence of depression extending into adulthood. However, given that the nondepressed peers with a similar history of major parent–child conflicts also were observed to have elevated levels of adulthood depression, this seems to tentatively signal that maladaptive family dynamics

may be a nonspecific risk factor for the emergence of affective problems. Nonetheless, more research is needed to gain deeper insights into the causative mechanisms and pathways involved in heightening vulnerability to onset and recurrence of depression. This seems particularly important in view of some previous notions supporting a bidirectional relation between family conflict and youth depression (Hale et al., 2020; Restifo & Bögels, 2009).

Is early-life depression linked to longer-term adverse consequences independently of childhood adversities and psychiatric comorbidities?

While meta-analytic work has established strong linkages between adolescent depression and adverse adulthood outcomes, there has also been some concern about the impact of potentially confounding factors, such as gender, comorbid psychiatric conditions, family hardships, and genetic vulnerability (Clayborne et al., 2019). In study III, depression with early onset was found to have robust, lasting associations with worse adult health and functioning, as the depressed children and adolescents had elevated levels of subsequent anxiety disorders as well as diminished physical health, social functioning, and risky/criminal behavior. Importantly, these links persisted even when a very broad range of potential confounders were taken into account, further confirming the poor long-term prognosis of early-life depression. In addition, the study found that the persistence of depressive symptoms across childhood and adolescence was predictive of more adverse adult outcomes, which is an important finding that replicates and supports the notion that chronic or multiple exposures to the disorder may be especially harmful to normal development (Johnson et al., 2018). However, it remains for future research to establish to what extent these linkages may be influenced by genetic vulnerability, to better understand the etiological mechanisms at play.

Are depressed adolescents at increased risk of marginalization from the labor market in early-to-middle adulthood?

Previous research estimating the risk of adulthood unemployment and welfare dependency among those exposed to adolescent depression has been rather inconclusive, and only a small number of longitudinal studies have yet looked into this matter (Clayborne et al., 2019). In study IV, adolescent depression was found to be associated with elevated levels of long-term unemployment, work disability, and welfare dependency across early-to-middle adulthood. While these associations attenuated after a range of potential confounders were taken into account, there was clearly a different pattern of findings when looking at these outcomes by the clinical form of depression. Adolescents with PDD (i.e., chronic/persistent depression) had higher risks of all labor market outcomes, and this was partially explained by depression recurrence during early adulthood. The inconclusive pattern of findings regarding adolescents with MDD and subthreshold depression revives the question as to whether episodic depression is more of a transitory developmental phenomenon for

some of those early affected, or perhaps may have a long-lasting impact on only some life domains (Steinhausen et al., 2006). However, findings from this study suggest that entry into tertiary education may be protective against marginalization from the labor market, at least for adolescents with episodic depression. Further, while the vast majority of previous long-term follow-up studies have looked at adolescent depression in a more general sense, or only differentiated between MDD and subthreshold depression (Johnson et al., 2018), this study expanded on prior research by showing that the distinction between episodic and chronic/persistent forms of depression may be crucial from a life-course perspective. As such, the study adds to current literature on the unfavorable course of PDD, including its adverse effects on overall social functioning (Evans et al., 1996; Hellerstein et al., 2010; Leader & Klein, 1996). As noted earlier, however, it remains to be seen to what extent these poor long-term outcomes are influenced by genetic and nongenetic factors.

What are the longer-term welfare sector costs associated with adolescent depression and its major combinations of psychiatric comorbidities?

Depression is costly to society, but less is known about the long-term cost burden of depressive disorders with early onset (Konig et al., 2019). Study V estimated the welfare burden associated with adolescent depression and its comorbidities. Three important findings were obtained. First, adolescents with PDD had a particularly high recipiency of welfare benefits as adults. Second, early psychiatric comorbidities were found to play a key role in determining various welfare sector costs, in particular for those manifesting with both comorbid DBDs and ADs early in life. Third, it was found that depressive disorders and DBDs were independently associated with higher recipiency of welfare benefits. These results add to the literature on the long-term burden following early depression (Clayborne et al., 2019) and DBDs (Bevilacqua et al., 2018; Erskine et al., 2016), further underscoring the societal challenges posed by these conditions in the long run. These findings should be viewed in light of recent reports published by the OECD regarding the life prospects of economically inactive youths and young people struggling with mental illness, as there has been increasing concern that granting benefits to vulnerable groups over the long term may, in effect, trap them in subsequent poverty and welfare dependency (OECD, 2010, 2012, 2013, 2015).

Methodological considerations

A few issues of importance to the overall evaluation of these findings deserve particular mention: bias, confounding, random error, and generalizability. These issues are often covered in depth in various textbooks on epidemiology and scientific research methods, in the context of key threats to internal and external validity (Aschengrau & Seage, 2019; Celentano & Szklo, 2019;

Rothman, 2012), as they are relevant to the assessment of experimental as well as nonexperimental studies, such as longitudinal cohort studies.

Selection bias

In the ULADS, the enrollment of participants was accomplished using a total population of first-year students aged 16–17, with 2,300 (93% response rate) completing the initial screening. While several attempts were made to include the 183 adolescents who had dropped out of school, only 97 (53%) school dropouts accepted to undergo screening (Alaie et al., 2019; Olsson & von Knorring, 1999). Therefore, it cannot be ruled out that some of the eligible nonparticipants might have been probable cases with diagnosable depression or subthreshold depressive symptoms. In fact, this seems rather plausible in view of the findings from the baseline study, as a substantial proportion of the included school dropouts did present with positive screening results. This may, in effect, imply that the adolescent lifetime prevalence of depression was somewhat underestimated in the baseline study, as noted previously (Olsson & von Knorring, 1999). This notion is further strengthened by prospective evidence from the U.S. showing that prior depressive symptoms increased the probability of dropping out of high school, even after adjustment for familial confounding (Fletcher, 2010). Consequently, in view of the potential for such underascertainment of cases in the ULADS, this may have impacted on the estimated magnitude of the association between adolescent depression and subsequent outcome, such that estimates may be somewhat biased toward the null. Although speculative, some of the adolescents most severely affected by depression may have been among the school dropouts, due to the health issues, anhedonia, and social impairments associated with having depression and other mental health problems. Further, this potential for underestimations should also be reckoned in light of recent population-based data from Norway, showing that high school dropouts were more likely to have poorer health, psychosocial difficulties, and socioeconomic disadvantage than same-aged high school completers, and also a much higher risk of marginalization from the labor market in young adulthood (De Ridder, Pape, Cuypers, et al., 2013; De Ridder, Pape, Johnsen, et al., 2013). Further, it should be noted that 79 (11%) of the 710 adolescents who were selected after the screening procedure actually declined further participation, such that they never took part in the baseline diagnostic assessment. This is also a source of potential selection bias, though it is more difficult to evaluate how the loss of these selected non-participants may have impacted on the results presented herein.

Important aspects pertaining to selection bias concern not only enrollment of participants, but also retention rates over the course of the study and, in particular, differential losses to follow-up. As for the 15-year follow-up study, about one third of the original ULADS cohort did not take part in the in-person diagnostic reassessment. This could, of course, be an important limitation in

case dropout was somehow related to either the exposure status or the later outcome under investigation. While there was virtually no difference in the attrition rates between depressed adolescents and their nondepressed peers, those with subthreshold depressive symptoms in adolescence were more likely to drop out than other subgroups (Alaie et al., 2019). Regarding the 25-year follow-up studies based on linkage to population-based registries, slightly more than 90% of the original participants were retained. The main source of complete or intermittent missingness was migration, though the vast majority of participants resided in Sweden during the entire follow-up period. Further, the overall pattern of missingness was quite similar in the various subgroups.

In the GSMS, the enrollment of participants was based on parental responses to a brief screening questionnaire with the externalizing items derived from the Child Behavior Checklist. In addition, the question about substance abuse was elaborated to cover a broad range of substances. According to Costello et al. (1996), this particular approach was taken to achieve a reasonable trade-off for optimizing case identification while keeping the screening procedure as short as possible. This means that participants were not specifically screened for other childhood psychiatric problems, such as depression and anxiety, which arguably could be considered a drawback of the study design insofar as this approach may have relevance to the research presented herein. Consequently, it seems likely that there was an underascertainment of children and adolescents with nonexternalizing problems in the GSMS. This may have impacted on the overall results, as it cannot be ruled out that the observed associations between early depression and long-term outcomes could be somewhat biased toward the null. All participants in the GSMS were interviewed at least once in childhood or adolescence, and 94% of the total sample were followed up at least once at ages 19, 21, 25, or 30. There was no evidence for differential losses to follow-up, as early depression was not found to be associated with lower levels of participation in the adulthood interviews.

Information bias

In the baseline study of the ULADS, adolescents with positive screening and matched peers with negative screening were invited to an in-person diagnostic assessment with an interviewer blind to the initial screen scores. As diagnostic ascertainments were made for all of those included in the final cohort, this procedure most likely reduced the risk of incorrect classification of cases and controls. The accuracy of the exposure assessment was ensured using the DICA-R-A, a reasonably sound measure available at the time. In fact, about one-fifth of the adolescents with negative screening did meet the diagnostic criteria for a lifetime depressive disorder, while a roughly similar proportion of adolescents with positive screening did not meet the criteria. Further, all interviewers were individually trained by an experienced psychiatrist with a

specialty training in child and adolescent psychiatry. Overall, the inter-rater agreement between interviewers was considered high, but no kappa statistics was calculated as part of the baseline study. As noted earlier, this instrument was designed to make lifetime diagnoses, even though additional questions were included at baseline to determine, for example, the first bout of MDD. While the risk of poor recall cannot be ruled out, given the lengthy period assessed spanning from childhood to mid-adolescence, the observed lifetime prevalence of depression in this community sample of Swedish adolescents was found to be quite similar to estimates reported in other epidemiologic studies (Costello et al., 2006; Merikangas, He, Burstein, et al., 2010).

Similarly, the 15-year follow-up assessment was executed by interviewers who were blind to the diagnostic outcome of the baseline study. The interviews with the MINI were all supplemented with a life-chart procedure, to facilitate recollection of previous episodes of depression and mania/hypomania. This meant that retrospective assessment was used for tracking affective problems over a period spanning from age 19 to about 31 years of age. While there is clear evidence that adult mental disorders are underreported in retrospective studies, due to recall failure (Moffitt et al., 2010; Patten et al., 2012; Takayanagi et al., 2014; Wells & Horwood, 2004), this may in fact imply that the true levels of adult depression and other disorders were underestimated among those participants completing the reassessment (Caspi et al., 2020).

As regards the 25-year follow-up, which was solely based on data retrieved from nationwide population-based registries, the risk of potential biases may arguably be considered to be less of an issue. The overall coverage and quality of the annual data on educational milestones, welfare sector costs, and labor market conditions have generally been reported to be good (Ludvigsson et al., 2019). It can be argued that complete and accurate registry-based information may contain more objective and precise data than self-reported information collected from interviews. This applies particularly to situations where there is a high likelihood of poor recall or if there are queries regarding socially sensitive issues. In terms of the risk of differential outcome misclassification, however, it is difficult to appreciate the full scope of this potential problem, and to what extent the use of registry-based data may remedy such an issue.

In the GSMS, a distinct feature of the design of the GSMS concerns how the exposure assessment was accomplished. As already noted, participants were invited to take part in annual assessments across childhood and adolescence up to age 16, and thereafter at multiple follow-ups in adulthood up to age 30. The assessment of various exposures was made using the CAPA interview, which takes a quite different approach to diagnostic ascertainment than many other instruments used in research or clinical practice. To minimize forgetting, participants and their parents were queried about psychiatric symptoms during the past three months immediately preceding the interview, and a symptom was counted as being present if reported by either participant or parent. As

such, this means that cases with childhood/adolescent depression may have been undetected in the study if participants in fact met criteria for a depression diagnosis either before the study was launched, between the assessments, or after their last adolescent interview at age 16 years. This approach to ascertain caseness, with the potential risk of an underestimation of the true lifetime prevalence of early-onset depression, may have resulted in biased estimates. Thus, it cannot be ruled out that there may be an even stronger relationship between childhood/adolescent depression and adverse longer-term outcomes.

As for the assessment of outcome, the adult follow-up interviews were based on the YAPA, an upward extension of the CAPA with a similar focus on a primary period of three months applicable for most psychiatric diagnoses. However, for most functional outcomes, the participants were queried about problems or experiences occurring at any time point during adulthood, and a particular outcome was counted as being present if reported at any assessment. While the risk of forgetting or recall bias cannot be entirely ruled out, there is the possibility that this approach might be more advantageous in assessing certain outcomes, such as risky behaviors and interpersonal difficulties, as the alternative strategy to focus on a time-limited window runs the risk of omitting key information relevant to the core aim of the follow-up.

Confounding

While most studies herein adjusted for several potential confounders, there is still the possibility that key factors associated with the exposure as well as the outcomes of interest were omitted. These may include measured, unmeasured, and unknown confounders, including (mis)measured variables that in fact were included as covariates in the outcome regression models (D'Onofrio et al., 2020). Thus, the overall findings should be interpreted with some degree of caution as alternative explanations cannot be entirely ruled out and, therefore, no causal inferences can be made regarding the effects of childhood and adolescent depression per se.

Generally, the findings are in keeping with what has been reported in other longitudinal cohort studies (Clayborne et al., 2019; Johnson et al., 2018), yet the present studies contribute with a few novel insights into some key sources of clinical heterogeneity related to the adult outcome of early-life depression. It might be argued that these observations have a certain signal value, but that further replication is needed to strengthen the validity of findings. To this end, it would arguably be of particular interest to account for measured as well as unmeasured confounders using advanced analytic approaches, such as family-based designs (D'Onofrio et al., 2020). Such approaches have the advantage of accounting for the influence of genetic factors, thereby unfolding etiologic mechanisms of potential relevance to the management of depressed youths.

Random error

Statistical significance (or alpha) was set at the conventional level of $p < 0.05$ throughout all studies. When evaluating the results of each study, it is difficult to determine the presence of any type I or type II error, respectively. This is due to the commonly occurring sources of unsystematic error in epidemiologic research, including measurement error and sampling variability. The former comprises any inaccuracies in how exposure to depression and later outcomes were measured, while the latter refers to a scenario in which the selection of participants has led to an unrepresentative sample of the population of interest (Aschengrau & Seage, 2019). As already noted, the ULADS and the GSMS had quite different approaches to exposure assessment, and more specifically to the measurement of childhood/adolescent depression, and this applies to some apparent differences in the assessment of longer-term outcomes as well. Likewise, there were also different methodological approaches to the selection of study participants, as described previously.

The concern of random error is highly intertwined with statistical inference in general, which indeed extends beyond the reliance on p-values obtained from hypothesis testing. Here, the use of confidence intervals may be of help in quantifying the extent of any random error, as the confidence intervals provide a measure of the precision of the observed point estimates (Aschengrau & Seage, 2019). For this reason, the statistically nonsignificant associations observed for the various groups and subgroups of depressed youths should be interpreted with caution, as some null findings may be attributable to a lack of statistical power to detect potential differences due to reduced sample size. Conversely, there is also the possibility that chance may explain some or all of the observed associations, although this seems less likely for a number of reasons: the growing body of evidence suggesting that early-life depression is associated with adverse long-term outcomes, the various a priori hypotheses underlying the present studies, and the strength of the estimated associations along with the observed p-values.

Generalizability

The matter of generalizability of findings is closely related to the important question of representativeness. While clinical or referred samples are unlikely to be fully representative of the broader population of youths with diagnosable depression, the sample of study participants should ideally be drawn from the general population. This was the case both in the ULADS and in the GSMS, even though there may have been some underascertainment of depressed cases in both studies, as previously mentioned. Moreover, the historical context is also relevant to the question of representativeness. While none of the studies may be considered nationally representative, it seems reasonable to assume

that both are community-representative in their specific historical and social context with reference to how the sampling of participants was accomplished.

It might be asked whether depressed youths of today's society are different in any fundamental way from their counterparts growing up in the early 1990s, given the societal changes occurring over the past decades. This question seems particularly relevant with the advent of electronic communication and social media in recent years, and the serious concerns about media effects (Niederkrotenthaler et al., 2019). This also emerges as an important question in light of recent large-scale research suggesting lowered thresholds for seeking mental health care services among young people (Forslund et al., 2020; Kosidou et al., 2017; Olfson et al., 2014; Olfson et al., 2015; Potrebny et al., 2021), which could be related to an increased accessibility to care services, and perhaps also to a heightened awareness and diminished stigma linked to mental ill-health (Mansfield et al., 2020). Importantly, however, there is no clear evidence of any sharp increase in the prevalence of early-life depression in population or community samples (Sawyer et al., 2018; Wiens et al., 2017), although there is the risk that methodological differences across studies make it difficult to draw firm conclusions regarding time trends (Merikangas, 2018). This calls for further surveys and more studies using advanced designs aiming to help improve public policy (e.g., Bauducco et al., 2020).

Implications and future directions

This work adds to the growing literature on adult outcomes of childhood and adolescent depression. It emphasizes the relevancy of conducting longitudinal research on community-based samples of youths prospectively followed over the transitional period spanning from adolescence to middle adulthood (Clayborne et al., 2019; Johnson et al., 2018). Such a life-course perspective may prove helpful to generate deeper insights into the long-term consequences of early exposure to depression, and it may also be key to judicious policy-making for future generations to come. Herein, a few potentially important clues towards an improved understanding of the overall life prospects of depressed children and adolescents have been uncovered, albeit on an aggregate level, further pointing to the need of additional work in this area.

In light of the well-documented poor longer-term prognosis of childhood and adolescent depression, it seems highly important to intervene early on through prevention and treatment approaches that are both efficacious and cost-effective. Such targeted efforts may have the potential to avert later ill-health, impairments, and possibly also social and economic disadvantages. Preventive measures, such as interventions based on CBT, have previously shown some favorable effects (Ssegonja, Nystrand, et al., 2019), and this is also the case for early treatment and timely contact with healthcare services (Neufeld et al., 2017).

The impact of any interventional strategies should ideally be addressed in future research using prospective pragmatic cohort studies. While such studies targeting childhood/adolescent depression have been lacking to date, there have been some recent research initiatives to develop programs and services for psychologically distressed youths and young people who are at risk of long-term economic disadvantage and marginalization from the labor market (McDaid et al., 2019). These programs and services have so far shown quite promising results in terms of returns on investment, and this may hold promise as a starting point for the design of future research efforts focusing on how to best provide clinical management and support to depressed youths as well.

Concluding remarks

Depression in early life can cast a long and dark shadow extending into middle adulthood, with several negative consequences in the form of mental health problems, physical health issues, psychosocial difficulties, and socioeconomic disadvantage. This dissertation expands upon previous longitudinal research pointing to the importance of accounting for key sources of heterogeneity when addressing the long-term outcome of childhood/adolescent depression. To sum up, these are the main conclusions of the work presented herein:

- The risk for mood disorder in early adulthood is elevated among depressed adolescents experiencing major conflicts with parents while growing up. The severity and duration of parent–child conflict seem to be decisive for the mental health outcome. Interventions targeting adverse family climate could possibly be a useful supplement to existing prevention and treatment strategies in specific cases; however, future research should clarify if, how, and when such an add-on may help optimize current best practice.
- Childhood/adolescent depression is associated with increased risks of adult psychiatric disorders, and also with worse physical health, social functioning, and criminality. The persistence of depressive symptoms across development emerges as particularly predictive of adverse adult outcomes. Those who become depressed as adolescents may fare worse in the long term than those who have their first bout of depression already in childhood. Mental health services use in childhood/adolescence may be protective against later mental ill-health, for example, adult anxiety.
- Adolescent depression is associated with increased risk of marginalization from the labor market across early-to-middle adulthood, especially for those exposed to chronic/persistent depression. This link may, in part, be attributed to the continuity of depression extending from adolescence to early adulthood. Furthermore, there is preliminary evidence implying that entry into tertiary education may be protective against adverse effects in the labor market, at least for those with episodic adolescent depression.
- The welfare sector costs associated with adolescent depression amount to considerable public expenditures in adulthood, most notably for those with chronic/persistent depression or early psychiatric comorbidities such as childhood anxiety and disruptive behaviors. Altogether, this suggests that the clinical heterogeneity of early depression needs to be considered from a broad long-term societal perspective.

Sammandrag på svenska/Summary in Swedish

Bakgrund och syfte

Depression är ett psykiskt sjukdomstillstånd som utgör ett tydligt folkhälsoproblem över hela världen. Tillståndet kan drabba människor i alla åldrar, men debuterar ofta runt puberteten, en period i livscykeln som präglas av tillväxt, inlärning och utveckling av olika sociala, emotionella och kognitiva förmågor. Alltmer forskning tyder på att depression i unga år kan störa denna utveckling och försvåra övergången till vuxenlivet. Barn och ungdomar med depression löper generellt sett en ökad risk för varaktiga psykiska besvär, kroppsliga åkommor, skolmisslyckanden, arbetslöshet, ekonomiska bekymmer och andra sociala svårigheter. Samtidigt finns det fortfarande begränsat med kunskap om vilka specifika riskfaktorer och mekanismer som är bidragande till negativa konsekvenser på lång sikt. Därför är det viktigt med representativa långtidsuppföljningar av deprimerade barn och ungdomar, för att klargöra hur tidigt debuterande depression inverkar på framtida hälsa, generell funktionsförmåga och etablering i vuxenlivet. Sådan forskning torde ge ett förbättrat kunskapsunderlag för prognostisk bedömning och planering av riktade preventions- och behandlingsinsatser för barn och ungdomar med depression, för att därmed söka förebygga en ogynnsam utveckling på längre sikt.

Det övergripande syftet med denna avhandling är att närmare undersöka kopplingen mellan tidigt debuterande depression och flera långsiktiga utfall i vuxenlivet, såsom psykiatrisk sjuklighet och etablering på arbetsmarknaden. Avhandlingen syftar till att öka kunskapen om vilka specifika riskfaktorer och mekanismer som är avgörande för långtidsutfallet, även när hänsyn tas till olika stör- eller förväxlingsfaktorer som är förknippade med såväl depression som det långsiktiga sociala, ekonomiska och hälsorelaterade utfallet.

Metod

Avhandlingen är baserad på omfattande långtidsuppföljningar av deprimerade barn och ungdomar som med upprepade mätningar följts in i vuxenlivet. Långtidsuppföljningarna är genomförda inom ramen för två longitudinella kohortstudier, dels Uppsala Longitudinal Adolescent Depression Study (ULADS), dels Great Smoky Mountains Study (GSMS), från Sverige respektive USA.

ULADS inleddes under åren 1991–1993, initialt i form av en screening på gymnasieskolorna i Uppsala kommun. Samtliga förstaårselever tillfrågades om att fylla i ett par självskattningsformulär med frågor om depression. Även

jämnåriga ungdomar som av olika skäl inte gick på gymnasiet blev tillfrågade. Sammanlagt 2300 (93 % svarsfrekvens) ungdomar genomgick screeningen. De ungdomar som screenat positivt för depressionssymtom bjöds sedan in att delta i en strukturerad diagnostisk intervju kring psykisk ohälsa, samt besvara ytterligare självskattningsformulär. För varje ungdom med positiv screening inbjöds även en klasskamrat av samma kön med negativ screening. Av 710 utvalda ungdomar intervjuades 631, varav 78 % var flickor. Av dessa samtyckte 609 deltagare till att kontaktas i framtiden. Efter ca 15 år, under åren 2006–2008, kontaktades kohorten och deltagarna följdes upp för första gången, både med förnyade diagnostiska intervjuer och personliga uppgifter uttagna från flera nationella register. Ungefär ett decennium senare, under åren 2017–2018, genomfördes den senaste uppföljningen av kohorten, denna gång helt baserad på registerdata, för de deltagare där detta var möjligt. I denna registerbaserade 25-årsuppföljning inhämtades personliga uppgifter om en rad sociala, ekonomiska och hälsorelaterade omständigheter, såsom utbildning, inkomst, arbetslöshet, sjukskrivning och försörjningsstöd, både för deltagarna med tidigt debuterande depression och för de icke-deprimerade kontrollerna.

GSMS inleddes år 1993 genom att ett slumpmässigt urval av barn och ungdomar – 9, 11 och 13 år gamla – valdes ut från allmänbefolkningen i den västra delen av delstaten North Carolina. I det initiala skedet tillfrågades föräldrarna till de utvalda barnen att besvara ett kort formulär med frågor om framför allt utåtagerande beteenden och bruk av substanser, såsom tobak och cannabis. Alla barn som bedömts uppvisa tydliga symtom på beteendestörning bjöds in att en gång om året delta i strukturerade diagnostiska intervjuer kring psykisk ohälsa, psykosociala faktorer och socioekonomiska omständigheter. Likaså inbjöds en andel jämnåriga barn utan tydliga symtom på beteendestörning, samt barn med bakgrund i ursprungsbefolkningen (tidigare kallade indianer), att också delta i studien. Både studiedeltagarna och föräldrarna medverkade i årliga uppföljningsintervjuer fram till dess att deltagarna fyllt 16 år. Sammanlagt 1420 deltagare samtyckte till att låta sig intervjuas vid åtminstone ett tillfälle under barn- och ungdomsåren, motsvarande ca 80 % av alla tillfrågade. Vidare inbjöds alla deltagare till fortsatta uppföljningar i vuxenlivet mellan år 1999 och 2016, med intervjuer genomförda vid 19, 21, 25 och 30 års ålder. Fokus för dessa uppföljningar kretsade kring att undersöka olika centrala aspekter avseende hälsa, funktionsförmåga och social etablering i vuxenlivet.

Resultat

Studie I beskriver ULADS genom projektets olika faser. Förutom en utförlig beskrivning av projektets metodologi ingår även en kortare sammanfattning av tidigare fynd. Därtill ingår en översikt av jämförbara långtidsuppföljningar världen över, givet det fåtal longitudinella kohortstudier som hittills gjorts med fokus på konsekvenser av depression hos barn och unga. Studien kan sägas komplettera den metodbeskrivning som givits i respektive artikel som bygger på ULADS (studie II, IV och V).

Studie II är baserad på ULADS och undersöker huruvida konflikter mellan barn och föräldrar har ett samband med depression och annan psykiatrisk sjuklighet i vuxenlivet. Självrapporterade uppgifter om föräldra–barn-konflikter under uppväxten användes för att kategorisera nivåerna i prediktorvariabeln, vilket resulterade i följande kategorier: inga konflikter; små konflikter; stora konflikter med föräldrarna. Vidare definierades depression i vuxenlivet som återkommande episoder (två eller fler) av egentlig depression, alternativt en mer långdragen episod (sex månader eller längre). I korthet visade studien att stora konflikter var förenade med en ökad risk för depression i vuxenlivet. Detta samband kunde också påvisas hos de som tidigare haft tonårsdepression, även efter att hänsyn tagits till viktiga störfaktorer. Dock var sambandet desto mer osäkert för de som inte varit deprimerade i tonåren.

Studie III bygger på GSMS och undersöker sambandet mellan depression i barndomen/tonåren och ett brett spektrum av utfall inom olika livsområden. Studien visade att tidigt debuterande depression har varaktiga samband med flera problem i vuxenlivet, såsom ångesttillstånd, drogmissbruk, kriminalitet och psykosocial belastning. Barn och ungdomar med ihållande depressionssymtom visade sig ha ett särskilt ogynnsamt utfall. Vidare noterades det att tidiga insatser inom specialistsjukvård (liknande barn- och ungdomspsykiatri) föreföll ha en modererande effekt på sambandet med vuxenpsykiatriska sjukdomstillstånd. Detta innebär att deprimerade barn som behandlats inom barnpsykiatriska inrättningar hade en lägre risk för vuxenpsykiatriska tillstånd jämfört med deprimerade barn som inte fått någon vård.

Studie IV är baserad på ULADS och undersöker sambandet mellan tonårsdepression och risken för marginalisering från arbetsmarknaden, inklusive möjliga mekanismer för utfallet. Studien visade att tonårsdepression generellt var förknippad med en ökad risk för senare marginalisering, såsom långtidsarbetslöshet och långvarig arbetsoförmåga. Dock försvagades flera samband efter att hänsyn tagits till viktiga störfaktorer. I subgruppsanalyser framkom det att de med ihållande depression i tonåren hade klart förhöjda risker för samtliga former av marginalisering, men detta kunde inte påvisas hos de med subklinisk eller episodisk egentlig depression efter att man tagit hänsyn till störfaktorer. Vad gäller överriskerna för marginalisering hos de med ihållande depression indikerade medieringsanalyser att sambanden i viss mån kunde förklaras av att deltagarna i många fall haft återkommande depression i tidigt vuxenliv. Vidare visade explorativa analyser att påbörjad högre utbildning, exempelvis universitetsstudier, hade en viss skyddande effekt mot risken för marginalisering, åtminstone för de som haft episodisk egentlig depression. Samtidigt framkom det att de med ihållande depression hade en fortsatt ökad risk för senare marginalisering, oavsett utbildningsstatus i tidigt vuxenliv.

Studie V är baserad på ULADS och undersöker sambanden mellan tonårsdepression och transfereringar i socialförsäkringssystemet, vilket innefattar kostnaderna inom exempelvis sjukförsäkringen, arbetslöshetsersättningen och andra solidariskt finansierade utgifter, såsom ekonomiskt bistånd. Utöver att

estimera magnituden i transfereringarna kopplade till tonårsdepression så klassificerades alla deprimerade deltagare avseende olika kombinationer av tidigt debuterande psykiatrisk problematik. I korthet visade studien att tonårsdepression generellt var förenad med betydande transfereringar i vuxenlivet; totalt 938 USD genomsnittligen i årliga merkostnader för varje deprimerad ungdom. Dessa kostnader drevs huvudsakligen av subgruppen med ihållande tonårsdepression. Vidare visade studien att även psykiatrisk samsjuklighet hade stor betydelse för magnituden i skillnaderna; deprimerade tonåringar med utåtagerande beteenden och ångestproblematik stod för särskilt höga transfereringar i vuxenlivet, motsvarande 1753 USD genomsnittligen i årliga merkostnader för varje drabbad ungdom.

Slutsats

Generellt kan sägas att avhandlingen visar att depression i barndomen/tonåren hänger samman med en förhöjd risk för långtgående negativa konsekvenser inom flera olika livsområden. Detta visar sig i att barn och ungdomar med depression har ökade förekomster av såväl psykiska sjukdomar som fysiska hälsoproblem, men även svårigheter med att etablera sig på arbetsmarknaden, ekonomisk utsatthet och andra sociala bekymmer i vuxenlivet. Flera av dessa longitudinella samband förefaller vara robusta även när hänsyn tas till en rad viktiga störfaktorer, såsom annan psykiatrisk problematik, familjesituation och olika negativa upplevelser under uppväxten. Emellertid är det viktigt att notera att de ogynnsamma utfallen är särskilt uttalade hos de ungdomar som varit drabbade av ihållande depression, medan det generella utfallsmönstret tycks vara spretigare för de med subklinisk eller episodisk egentlig depression. Vidare visar avhandlingen att tidigt debuterande depression har varaktiga samband med omfattande samhällskostnader över levnadsloppet, vilket främst gäller de som haft ihållande depression eller psykiatrisk samsjuklighet i form av utåtagerande beteenden och ångesttillstånd (i tillägg till tonårsdepression).

Sammantaget signalerar avhandlingens resultat att förebyggande åtgärder och utökade behandlingsinsatser, exempelvis inom skolväsendet, primärvården och inte minst barn- och ungdomspsykiatrin, skulle kunna ha potential att reducera de långsiktiga samhällskostnader som visats vara förknippade med depression hos barn och unga. Förhoppningsvis skulle en sådan strategisk satsning medföra att fler individer erbjuds adekvat hjälp och vård i ett tidigt skede av sjukdomsförloppet, vilket torde förbättra den långsiktiga prognosen. Och möjligen även lönsamheten för samhället som helhet.

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