

4-25-2011

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A Retrospective and Prospective Comparison of Hungarian Children Who Have One or
Two Episodes of Depression

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Arts
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Date of Approval:
April 25, 2011

Keywords: major depression, depression recurrence, early onset MDD, childhood
depression, first MDD episode

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ABSTRACT

Early onset depression is associated with high recurrence rates later in life. Recurrent depressive episodes during childhood may be particularly problematic, if additional episodes have a scarring effect that hinders healthy development. Distinguishing between first onsets and recurrences has been useful in understanding adult depression. This distinction has seldom been examined in pediatric depression, in part because it is difficult to enroll adequate samples of children with recurrent depression. We conducted archival analyses of carefully-diagnosed pediatric probands with depression first onset between ages of 4 and 12. Probands who reported one depressive episode (N = 435) were compared with probands who reported two depression episodes (N = 115) on clinical (treatment, comorbidities), psychosocial (negative life events (NLEs), parental psychopathology) and emotion regulation measures. Based on previous findings in older adolescents and adults, we hypothesized that probands with two MDEs will have higher comorbidity, parental psychopathology, more NLEs, and higher maladaptive emotion regulation scale scores than probands with one MDE. Surprisingly, probands with one and two MDEs were indistinguishable on psychological and pharmacological treatment variables. As expected, probands with two MDEs had lower age of first onset, higher maladaptive emotion regulation scores, higher rates of comorbid anxiety and reported more NLEs than probands with one MDE. Probands with two MDEs also spent a longer total time in episode; group differences remained after controlling for time spent

depressed. Distinguishing between first onsets and recurrences is meaningful in pediatric depression.

A retrospective and prospective comparison of Hungarian children who have one or two episodes of depression

Major depressive disorder (MDD) in children and adolescents sets the ground for unfavorable developmental outcomes throughout life. Childhood depression often results in stable cognitive vulnerability to depression (Clark, Beck & Alford, 1999; Timbremont & Braet, 2004), interpersonal difficulties with siblings (Puig-Antich et al., 1985) and peers (Altmann & Gotlib, 1988) and high rates of co-occurring psychiatric problems (Kovacs, 1996). In adolescents, MDD is a significant contributor to social impairment, academic difficulties and even early death (Fleming & Offord, 1990). Early onset depression is also highly recurrent, with the cumulative probability of recurrence estimated as high as 70% within 5 years of first onset (Emslie et al., 1997) and high recurrence rates continuing into adulthood (Kovacs, 1996); (Weissman, Wolk, Goldstein, et al., 1999). Longer term, MDD is associated with high vulnerability to developing other mental disorders (e.g. antisocial and borderline personality disorder traits; Lewinsohn, Rohde, Klein, & Seeley, 1999). While some research has focused on the future consequences of early onset of depression, other research has examined the antecedent risk factors that contribute to depression onset and recurrence.

Early onset of depression is an established risk factor for depression recurrence (Dunn & Goodyer, 2006; Geller, Zimmerman, Williams, Bolhofner, & Craney, 2001; Kovacs, 1996). Extant data are consistent with the possibility that those with juvenile-onset depression have one or more risk factors that put them at an especially high risk for depression over their life span: relative to adult-onset depression, early onset depression

may be associated with an increased number of stressors, qualitatively more severe stressors, a stronger genetic predisposition through familial history of depression (Dempster et al., 2007), and higher severity compared to the severity of depression that onsets later in life (Gollan, Raffety, Gortner, & Dobson, 2005), severity being a risk factor for recurrence (see Burcusa & Iacono, 2007).

Depression in childhood up through the first 12 years occurs infrequently (i.e. .03 - 3%, (Costello, Foley, & Angold, 2006) and, while recurrence rates are constant throughout the life span (Kovacs, 1996), pre-adolescent children with recurrent depression have rarely been studied, in part because of the difficulties of obtaining pediatric samples of repeatedly depressed children. Consequently, adult samples provide most what we know about the differences between persons who have one MDE versus those that have experienced multiple MDEs. To the extent that has been any study of recurrent depression in the young it has focused on adolescence.

The current study used a retrospective and prospective design to assess differences among children with one and two MDEs and potential precursors to future recurrences in children. To set the stage for addressing risks for recurrence in a child sample, we reviewed clinical, demographic, emotion and cognitive regulation factors associated with recurrence in adults with early onset depression. The limited literature on first and recurrent MDEs in youth was also reviewed, with attention to key unanswered questions.

Early Onset Depression

Depression in childhood up through age 12 is relatively uncommon, with rates found to be anywhere from .03 to 3% in a recent meta-analysis (Costello, et al., 2006). While prevalence is low, outcomes are often devastating. MDEs, on average, last 9 months (Kovacs, 1996) with most children recovering within 2 years after onset (Birmaher, Arbelaez, & Brent, 2002). Childhood depression is highly recurrent over the life span, with risk for recurrence escalating with additional MDEs (Emslie, et al., 1997). Thus depression appears to breed depression. It is unknown whether the harms associated with recurrence in childhood are associated more with the effects of having multiple MDEs or with a greater total time spent being depressed.

Long Term Outcomes of Childhood Onset Depression

Early onset depression has unfavorable outcomes later in life. These include: recurrence of depression in adulthood (Kovacs, 1996; Weissman, Wolk, Wickramaratne, et al., 1999; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000), impaired functioning (i.e. high treatment utilization) and behavioral problems (Harrington, Fudge, Rutter, Pickles, & Hill, 1990); (Weissman, Wolk, Wickramaratne, et al., 1999), impaired social functioning (Gotlib, Lewinsohn, & Seeley, 1998), vulnerability to other psychopathology (e.g. antisocial and borderline personality disorder traits; (Lewinsohn, Rohde, et al., 1999) and impaired emotion regulation (Kovacs, Rottenberg, & George, 2009). Fergusson, Boden, and Horwood (2007) looked at a cohort of youth with one or more MDEs between the ages of 16 and 21 and found that more episodes were predictive of later lower educational attainment, higher rates of major depression, anxiety disorders, suicidal ideation and attempts. Recurrence also impacted employment, income and

welfare use; those with recurrent MDD in adolescence had higher likelihood of having a lower income, being unemployed and/or being dependent on the welfare system in adulthood. The risk that early onset depression has on adult development underscores the importance of understanding its developmental impact in children.

Clinical and demographic Factors Associated with Multiple Episodes in Childhood

Comorbidities

Children who suffer from depression often have other co-occurring psychiatric disorders. Comorbidity rates have been found to average anywhere from 30% to 95% (Kovacs, 1996; Sorensen, Nissen, Mors, & Thomsen, 2005). One highly comorbid disorder is dysthymia. Rates of comorbid dysthymia differ depending on whether MDD is the primary diagnosis (30%) or subsequent to dysthymia onset (70%; Kovacs, Akiskal, Gatsonis, & Parrone, 1994). Children with double depression (dysthymia superimposed on MDD) have a more severe course of the depressive disorder. Goodman, Schwab-Stone, Lahey, Shaffer, and Jensen (2000) found that children with double depression had protracted MDEs, additional comorbid disorders, and more suicidality, all indicative of higher overall clinical severity.

Anxiety disorders are also highly comorbid with MDD, with rates ranging from 16% to 75% (Angold, Costello, & Erkanli, 1999; Seligman & Ollendick, 1998).

Interestingly, several studies of children with MDD have found that comorbidity with anxiety does not impact recurrence of depression (Kovacs, Gatsonis, Paulauskas, & Richards, 1989; McCauley et al., 1993; Rao et al., 1995). However, children suffering

from depression and anxiety often suffer from multiple psychiatric disorders both externalizing and internalizing (Bernstein & Borchardt, 1991), which in turn may put children at risk for a more severe outcome of MDD: recurrent episodes, length of episodes and suicidality (Ezpeleta, Domenech, & Angold, 2006).

Gender

Gender has historically been a preeminent variable in depression research. It is also an important variable developmentally. During adolescence, girls become twice as likely to become depressed as boys (Nolen-Hoeksema, 2001). However, once a person has had an episode of depression, findings conflict as to whether females have higher recurrence rates than males (Kessler, 1993), or whether there are no gender differences in course (Simpson, Nee, & Endicott, 1997). In children and adolescents, the relationship between gender and multiple MDEs has not been strongly established, with some studies finding that the gender differences in observed depression emerges primarily from more girls having a first onset than boys of same age (Hankin, 2001; Kovacs, 2001). However, gender can be conceived as a potential moderator, strengthening, for example, the path between stressors and future depression: starting in childhood, girls report increasing negative life events compared to boys (Garber, 2007). For example, Lewinsohn, Rohde, Seeley, et al (2000) specifically found that only among girls, increased conflict with parents predicted future recurrence, while boys were more likely to develop other nonmood disorders later in life.

Parental psychopathology

Parental psychopathology has also been identified as a risk factor for early onset depression and recurrence. Compared to children of nondepressed parents, offspring of depressed parents have a two to three fold increase in their chances to develop depression in childhood and early adolescence (Hammen & Brennan, 2001; Williamson, Birmaher, Axelson, Ryan, & Dahl, 2004; Halligan, Murray, Martins, & Cooper, 2007). Hammen and Brennan (2003) reported severity of parental depression to be associated with a worse outcome among offspring. Consistent with the idea that parental psychopathology is associated with negative outcomes in offspring, depressed children with depressed parents were also found to have a lower age of onset, higher severity of symptoms and higher comorbidity rates than depressed children who had no family history of depression (Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Rohde, Lewinsohn, Klein, & Seeley, 2005).

Early adversities and negative life events

In considering the onset and course of major depression scholars have distinguished between the quantity versus the severity of negative life events. Post's (1992) theory was the first to underscore the importance of stressful life events in first onsets, but not subsequent onset of MDEs. Literature shows that severe life events are more often associated with first rather than recurrent episodes (Mitchell, Parker, Gladstone, Wilhelm, & Austin, 2003). However, severe life events continue to be a strong risk for later depressive episodes, but less severe events also become potent in triggering subsequent episodes (see Monroe & Harkness (2005) for a review). This suggests that in predicting the recurrence of MDEs the absolute number of negative life

events may become as or more important than the severity of life events. Indeed, adults suffering from recurrent MDD experience significantly higher numbers of stressful life events than those with one episode (Harkness, Monroe, Simons, & Thase, 1999).

The literature looking at the difference between severity and number of life events among children is scarce. However, studies (Cole, Nolen-Hoeksema, Girgus, & Paul, 2006; Gibb & Alloy, 2006) have demonstrated the importance of stress exposure in the development and maintenance of depression in children. Stress exposure has been shown to be particularly problematic if the stressor is chronic, severe and starting at an age when development is particularly open to environmental effects such as in childhood (see Gotlib, Joormann, Minor, & Hallmayer, 2008).

Important considerations when interpreting and drawing conclusions from the literature on negative life events are those of conceptualization and measurement of life events and stress. The concept of stress is broad and has been described from different perspectives, thus a variety of measurement options are available. One manner in which life stress has been operationalized has been as discrete life events and there are different measures that document negative events. Many of these measures, however, use a self-report methodology, that has subsequently been critiqued for limitations, such as overly broad categories of included events (e.g. natural disasters) (Dohrenwend, 2006). While other, investigator based measures (narrative-rating approaches) (e.g., Life Events and Difficulties Interview (LEDS), Brown & Harris, 1978) have been developed to remedy the limitations in self report methodology in that they tend to capture more acute life events (e.g. fight with a friend) and life difficulties, comparative literature so far has only

been able to conclude that the different measures seem to capture different aspects of life stress and events (e.g. Lewinsohn et al, 2003).

Negative cognition

Negative cognitive styles has been proposed to be implicated in the onset of depression (e.g. hopelessness, Abramson et al, 1989; Beck et al, 1979) and individuals reporting negative cognition have also been found to be more vulnerable to recurrent MDEs (Mongrain & Blackburn, 2005; Alloy et al., 2006; Iacoviello, Alloy, Abramson, Whitehouse, & Hogan, 2006). Researchers have related changes in information and emotion processing (e.g. identifying and evaluating emotional stimuli) to the development of subsequent MDEs in youth. For example, Lewinsohn, Allen, Seeley, and Gotlib (1999) found that adolescents with more MDEs were more likely to exhibit dysfunctional thinking styles (negatively biased interpretations of experiences; e.g. “My life is wasted unless I am a success”: Cane, Olinger, Gotlib, & Kuiper, 1986), which in turn was a stronger predictor of recurrent episodes than of first episodes, indicating that subsequent MDEs may be triggered by different cognitive processes than first episodes.

Emotional dysregulation

Emotion regulation is broadly defined as a set of processes, both internal and external that aid in changing the emotional response to stimuli both in intensity and duration (Thompson, 1991). Emotion dysregulation is another broad term, usually one that refers to one or more problems in emotion regulation that might contribute to bad outcomes such as psychopathology. One aspect of emotion dysregulation that may be

particularly important in the context of depression, is difficulty in down regulating sadness, a central symptom of depression (Kovacs, Joorman & Gotlib, 2008). There is some evidence that people who are prone to depression engage in maladaptive emotion regulatory strategies with respect to sadness. High scores on scales measuring maladaptive cognitive regulation (e.g. rumination) increase the probability of a recurrent depressive episode among young adults with early onset MDD (Kovacs, Rottenberg & George, 2009).

Previous Studies Contrasting One MDE Versus Subsequent MDEs in Youth

While there is ample work among adults showing the importance of distinguishing first onsets versus subsequent MDEs (e.g. Nandrino, Dodin, Martin, & Henniaux, 2004; Harkness, et al., 1999; Daley, Hammen, & Rao, 2000; Mitchell, et al., 2003), this distinction has been little studied in children. Pettit, Lewinsohn, and Joiner (2006) have found that adolescents experiencing depressed mood and increased appetite in the first episode were more likely to experience a recurrence than adolescents that did not report these symptoms. Secondary analyses of Williamson and colleagues (1998) compared adolescents with one versus recurrent episodes of depression on both chronic and acute stressors that took place in the year prior to the onset of the last documented MDE. Interestingly, in contrast to Post's (1992) theory that stress is a strong predictor of first onsets but not subsequent episodes, Williamson et al. found that adolescents with one versus recurrent MDEs were indistinguishable on rates of refined severe events (specific, focused events that can pose long term threat; e.g. SAT test). However, adolescents with recurrent MDEs reported higher rates of major life difficulties (chronic

life difficulty defined by marked to moderate severity, about 2 years long, and that involved more than health problems; e.g. losing home). These results imply that adolescents experiencing chronic stressors are at higher risk for recurrence. In contrast, Lewinsohn and colleagues (1999) found that major life stress was a stronger predictor of first episodes than recurrent episodes in community adolescents. This idea was further supported by Monroe, Rohde, Seeley, and Lewinsohn (1999) who looked at how relationship loss plays an important role in first onsets, but not in subsequent episodes.

The Current Study

MDD in children is often recurrent and followed by a disrupted development across the life span (Kovacs, 1996). Unfortunately, few studies have looked at preadolescent children, and most have been limited by modest sample sizes. Most studies to date that have looked into first and subsequent episodes of depression have used adolescent samples, in part because the prevalence of depression increases dramatically in adolescence. This is the first study to look at younger children with a first onset and first recurrent episode. Recurrent depressive episodes during childhood may be particularly problematic, if additional episodes have a scarring effect that hinders healthy development.

Key features of the current study were designed to overcome the limitations of previous studies. First, sample size limitations were addressed by using a current large clinical sample of children with at least one major depressive episode between the ages of 4 and 12 (Kovacs, 1996). Second, the study afforded an in-depth comparison of children

with one MDE and children with two MDEs; the groups were compared on stressful events, maladaptive emotion regulation styles as well as clinical and demographic factors. We also were able to examine risk for additional MDEs through a longitudinal design that followed the children clinically over 1 year. Lifetime MDEs at intake and at follow up were carefully assessed by trained clinicians using multiple informants.

Hypotheses

Hypothesis 1 - Clinical and demographic factors associated with multiple episodes in childhood

(1a) Comorbidities are highly prevalent in children with depression and some investigations suggest that comorbidities are indicative of a more severe outcome (Ezpeleta, et al., 2006). Most of the studies looking at the impact of comorbidities on depression outlook have reported mixed results depending on the nature of the disorders (dysthymia: Goodman, et al., 2000 vs. anxiety: Rao, et al., 1995). We predict that probands with two MDEs will be more likely to report comorbid diagnoses. Since multiple MDEs and comorbidities are generally indicative of more severe depression, it is also expected that these children with two MDEs will exhibit higher rates of treatment for depression than do children who report one MDE.

(1b) While parental psychopathology and exposure to stress are two of the strongest risk factors associated with depression, we have little knowledge about these factors in children with multiple episodes. However, in adults, for example, recurrent MDD is related to higher numbers of stressful life events (Harkness et al., 1999). We

predict that probands with two MDEs will be more likely to report parental psychopathology and multiple past negative life events than probands with one MDE.

Hypothesis 2 – Emotional and cognitive dysregulation associated with multiple episodes in childhood

In adults with early onset depression, indices of emotion dysregulation are associated with recurrent depression (Lewinsohn et al, 1999). More specifically, one study has shown that one metric of emotion dysregulation – endorsement of maladaptive strategies for down regulating sadness – predicts MDE recurrence (Kovacs, Rottenberg & George, 2009). Based on these findings, we expect that children with two MDEs will report higher levels of maladaptive emotion regulation (that can exacerbate sadness by not effectively coping, e.g. rumination, eating) and hopelessness and lower levels of adaptive emotion regulation (that can attenuate sadness, e.g. refocusing attention, working on a task) than children with a single MDE.

Hypothesis 3 – Independent predictors of multiple MDEs in children

If consistent with Hypotheses 1 and 2, we find that several factors discriminate children with one MDE from children with two MDEs, it will be important to determine which factors are *the best at discriminating the two groups*. Negative life events, comorbidities and maladaptive emotion regulation (ER) are expected to be independent predictors of children with two MDEs.

Hypothesis 4 – Does recurrent depression predict future depression in childhood?

Studies have repeatedly shown that rate of recurrence increases over time and that recurrent MDD episodes increase the likelihood of development of future depressive episodes in adults (Lavori, Keller, Mueller, & Scheftner, 1994; Solomon et al., 1997; Keller & Bollard, 1998). Relative to children who have a single MDE at intake, we predict that children with two MDEs at intake will be more likely to develop an additional MDE at a 12 month follow-up.

Methods

Participants

The original impetus for the data collection was to uncover genetic and psychosocial risk factors for childhood-onset depression. Participants were recruited through 23 mental health facilities throughout Hungary. The clinical sample consisted of 550 proband children between the ages of 7 and 12, meeting DSM-IV criteria for a mood disorder. This sample was formed of 225 females (mean age 11.5 years) and 325 males (mean age 10.9 years) and the mean age of MDD onset was 10.8 years ($SD = 2.2$). The probands had to have at least one biological parent and sibling of comparable age (age 7 to 17.9). Subjects with mental retardation or any major systemic medical disorders were excluded.

Diagnostic Procedure

Children were invited to the diagnostic procedure if their parent signed an informed consent (65.6% of the contacted families), if the child scored > 5 on the short Children's Depression Inventory (CDI; Kovacs, 2003) and if the parent completed the second section of the Child Behavior Checklist (CBCL; Achenbach, 1991) concerning child's behavior and emotional problems during the past 6 months. The diagnostic procedure took place on two occasions 6 weeks apart, and was conducted by different highly trained clinicians using two different semi structured interviews. The first part of the evaluation

was done using the “Mood Disorder Module” of the DSM IV and the Intake General Information Sheet (IGIS), which is an event focused structured interview done with the parent as informant about the child. To facilitate proper recall, which is crucial for child diagnosis purposes and relies on parent child report agreement, the researchers performed a semi-structured interview designed to set a “time line” for the proband from birth to intake. The time line used both public (e.g. major holidays) and personal events (e.g. birthdays) to facilitate recall of the information and dates of events needed about the child’s symptoms and for the disorder onset and offset dates.

The second part of the evaluation was done using a full diagnostic interview and it was administered only to children that had met the DSM criteria for a mood disorder at the initial evaluation. The diagnosis of MDD and potential comorbid disorders was done using the Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D), an extension of the Interview Schedule for Children and Adolescents (ISCA; Sherrill & Kovacs, 2000). The interview includes relevant Axis I DSM-IV and DSM-III disorders. This second part of the evaluation was conducted with the parent and the child separately about the child, using the previously created timeline for the child’s life. This interview yielded symptom ratings and diagnoses for current and lifetime disorders.

All documentation that resulted from the first and second interviews and all other materials, as well as psychiatric records, were used for a consensus diagnostic procedure (Maziade et al, 1992). The final diagnostic decision was taken by pairs of senior child psychiatrists who had been trained in Best Estimate Diagnosticians and who separately reviewed all materials to derive a consensus diagnosis together. Operational rules were

used to define disorder onset and recovery and in instances where dating was not exact a midpoint rule was used for onset and offset dates. Only children that passed this consensus diagnostic procedure for a diagnosis of mood disorder were included in the proband sample. Thus, the current study only used data from children with a confirmed diagnosis of MDD at intake.

As described in previous work (Kapornai et al, 2007), the interviews were administered by child psychiatrists and psychologists who completed 3 months of didactic and practical training in the semi-structured interview technique. They were required to reach an average of 85% symptom-agreement on 5 consecutive videotaped interviews against “gold standard” interview ratings provided by the trainers. Routine monitoring and follow-up training sessions served to minimize rater drift. All interviews were audiotaped. Interrater reliability on ISCA-D symptoms was satisfactory (using audiotapes of interviews for n=46 pairs of raters). For MDD symptoms, kappas ranged from .64 to .88, with 80% of the coefficients at or above .70. Similar inter-rater reliability coefficients were obtained for other diagnoses.

Follow-up Diagnostic Procedure

At the one year anniversary from intake, packets containing the CDI, a follow-up version of the IGIS and Feelings and Me were mailed out to participants. Of the children contacted through the mail, 92% returned completed questionnaires. Thirty three percent of the respondents scored > 5 on the CDI and were invited for a diagnostic follow-up procedure, similar to the one at intake, using the ISCA-D. A score of 5 on the CDI-Short Form is comparable to the cutoff point of 12 on the 27 item version of the CDI, which

has been proposed as an adequate cut-off point in clinical contexts, where the base rate of depression is generally higher than the general population (Sitarenios & Kovacs, 1999). Although a low cut-off point may increase false positives, when used as a screener such as in this case, the goal of decreasing false negatives is more important.

Measures

Current and lifetime MDD episodes, severity of current MDD episode and comorbidities. Interview Schedule for Children and Adolescents — Diagnostic Version (ISCA-D) is a semistructured diagnostic interview used to assess current and lifetime major depressive disorder (MDD) in children. This is an extended version of the Interview Schedule for Children and Adolescents (ISCA; Sherrill & Kovacs, 2000), which organises symptoms into disorders, including most DSM-IV Axis I diagnoses as well as some DSM III disorders. The interview is done with the parent and child separately and diagnostic decisions are ultimately made by consensus of both sets of ratings. Child Depression Inventory (CDI) – Short Form is a self administered scale used to assess depression severity in children and adolescents ages 7-17 at intake and follow-up. The CDI has extensive supportive reliability and validity data (reliability = .80) (Kovacs, 1992). The short form scale is composed of 10 items inquiring about key symptoms of depression in the previous 2 weeks. The items are scored on a three point scale (0 to 2) with a total score ranging from 0 to 20. The CDI short form correlates highly with the full CDI ($r = .89$; Kovacs, 1992)

Child's stressful life events. Intake General Information Sheet (IGIS; see (Kapornai et al., 2007) is a questionnaire that was used to collect demographic

information on the participating children, such as age, gender, ethnic and social background, and family background. An important section of the IGIS inquires about major life events the child has experienced (e.g. “Death of a sibling.”, “Significant financial family problems/financial hardship/poverty.”), including items rated in most life event scales (e.g., Coddington for children (Coddington, 1972), Holmes-Rahe for young adults (Holmes & Rahe, 1967): the item list distinguishes depressed youths from school-based controls (Mayer et al., in press). The IGIS items are structured, precoded multiple choice and are parent administered.. The negative life events section was structured to differentiate between events that took place the year prior to intake and lifetime events that occurred more than a year prior to intake.

Severe parental psychopathology. The IGIS has four questions: two that inquire about maternal and two about paternal psychiatric hospitalization during the year prior to intake and lifetime (e.g. “Did Biological mother have a psychiatric/mental health/drug alcohol related hospitalization More Than 1 Year ago?”). Studies have shown good agreement between self report and medical records for psychiatric and substance abuse inpatient admissions (i.e., Killeen, Brady, Gold, Tyson, & Simpson, 2004). Moreover, research showed that severity of symptoms is related to treatment setting, more severe psychopathology being related to inpatient treatment (McDermott, McKelvey, Roberts, & Davies, 2002). Consequently, the four questions inquiring about parental hospitalization for psychiatric and substance related hospitalization served as a proxy for severe parental psychopathology in the current study.

Emotional dysregulation: Feelings and Me (Kovacs, 1998) is a measure of strategies children use to regulate dysphoria. The self-report instrument queries the child

about his or her typical responses to feeling sad in order to yield 3 subscores: an adaptive emotion regulation score, a maladaptive emotion regulation score and the proportion of adaptive responses. The two scales have 54 items divided into 32 "adaptive" items (e.g., "When I feel sad or upset, I listen to fun music") and 32 "maladaptive" items (e.g., When I feel sad or upset, I take pills, or drugs, or drink alcohol). The scale has good initial psychometric properties, including internal consistency and predictive validity (Tamas et al., 2007). The scale showed high internal consistency in the current sample (Cronbach's alpha = .89).

Probands also reported on their emotion regulation through the Responses to Depression Questionnaire for Youngsters (RDQY) (Kovacs, 1998). This is a modified version of the Responses to Depression Questionnaire (RDQ) (Nolen-Hoeksema, Morrow, & Fredrickson, 1993). Studies have shown RDQ to be a valid and reliable measure of rumination and distraction in particular (e.g. Nolen-Hoeksema & Morrow, 1991) The items have been restructured to be appropriate and relevant to children. The RDQY includes 18 items on rumination, 11 items on distraction and 3 items on problem-solving responses. In the current sample, internal consistency of the full RDQY was high with Cronbach's alpha of .84.

A self report scale about feelings of hopelessness that are related to depression, Hopelessness Scale for Children (R-SKALA) (Kazdin, Rodgers, & Colbus, 1986), was also administered. The scale is composed of 17 true/false items (e.g. "I might as well give up because I can't make things better for myself."). Higher scores reflect higher levels of hopelessness and negative expectations about the future (Kazdin, 1986). In previous psychometric analysis, the scale showed acceptable internal consistency (alpha of .97 and

Spearman-Brown split-half reliability of .96) and good concurrent validity (positively correlated with the depression, $r = .58$, and negatively correlated with self-esteem, $r = -.61$) (Kazdin et al., 1986). In the present sample, the scale showed acceptable internal consistency, with Cronbach's alpha reaching .69.

Hypothesis Testing

Hypothesis 1 - Clinical and demographic factors associated with MDEs in children

(1a) We predict that probands with two MDEs will report higher rates of comorbid diagnoses and treatment for depression than probands with one MDE. This hypothesis was tested with the chi-square test.

(1b) We predict that probands who report two MDEs will be higher on additional conventional risk factors for depression and will be more likely to report parental psychopathology and multiple past negative life events than children who report one MDE. Chi-square tests will test whether children with two MDEs report higher rates of parental psychopathology than children with one MDE; and independent sample t-tests will test whether children with two MDEs endorse higher numbers of negative life events than children with one MDE.

Hypothesis 2 – Emotional dysregulation associated with MDEs in children

We predict that relative to children with a single MDE, children with two MDEs will report higher levels of maladaptive emotion regulation and higher levels of hopelessness. Two t-tests will be employed to test whether children with two episodes have overall higher scores on the Feelings and Me and Hopelessness scales. For

descriptive purposes, chi-squares will be used to test whether specific items of Feelings and Me are more often endorsed by children with two MDEs versus those with one MDE.

Hypothesis 3 – Independent predictors of MDEs in children.

A third goal will be to identify three independent predictors of having multiple episodes. Negative life events, comorbidities and maladaptive emotion regulation (ER) are expected to be independent predictors of a recurrent episode. This will be determined by executing a logistic regression with number of episodes as the outcome variable and number of negative life events, comorbidities and maladaptive emotion regulation as individual predictors. For these three predictors to remain independent predictors they have to remain significant in the result of the logistic regression and have ORs with confidence intervals that do not include 1.

Exploratory Analyses

It is likely that children with two MDEs are different from children who have one MDE not only in the number of episodes experienced, but also in the total time spent depressed. If we find that children with one and two episodes differ significantly in the amount of time spent depressed, a series of ANCOVAs will be performed, in which number of episodes is the independent variable, each of the risks factors found statistically differentiate the one versus two episode groups as the dependent variables and time depressed as the covariate. These analyses will help tease whether longer time depressed fully accounts the effects of recurrent depression.. If controlling for time depressed annuls the initial differences, then this suggests that it is length of time and not number of episodes that effectively accounts for detrimental effects. In other words,

experiencing one long MDE can be equally or more detrimental than having two short MDEs.

Hypothesis 4 – Does recurrent depression predict future MDEs in children?

A fourth hypothesis is that children with two MDEs at intake will be more likely to have a recurrence at a 1 year follow-up than children with one MDE. Rate of recurrence among children with one versus two MDEs at intake will be assessed with a chi-square.

Power Analysis

Testing Mean Differences

In order to detect a medium effect size (0.50) for alpha of 0.05 and power of 0.80 with the planned analyses looking at mean differences, an adequate sample size per group would be 64. All the planned analyses for this project compare two groups for a total sample size of 128. If we consider a 20% attrition rate to follow-up, then a sample of 154 probands would be an adequate sample size. Our sample size of 550 probands is clearly adequate for the analyses planned, even considering that it will be divided into the two groups of probands with one MDEs (N = 435) and two MDEs (N = 115).

Testing Proportions or ORs

To detect a medium difference in sample proportions ($h = .50$) (Cohen, 1992) for alpha of 0.05 and power of 0.80, an adequate sample size per group would be 63. All the planned analyses for this project compare two groups for a total sample size of 126. If

we consider a 20% attrition rate to follow-up, then a sample of 152 probands would be an adequate sample size. Our sample size of 550 probands is clearly adequate for the analyses planned.

Results

Sample Characteristics

Participants were recruited through 23 mental health facilities throughout Hungary. The clinical sample consisted of 550 proband children between the ages of 7 and 17 at intake, meeting DSM-IV criteria for lifetime MDD. The mean age of MDD onset was 9.9 years (SD = 1.9), with an age range of 3.8 to 12.9 years old. This sample was formed of 225 females (mean age 11.5 years) and 325 males (mean age 10.9 years). Most children (N=435) had experienced one MDE at intake and 21% of the sample had experienced two MDEs (n = 115). It should be noted that less than 3% of the sample experienced more than two MDEs (range = 3 - 6) at intake (N= 16); these children were not considered further because of inadequate statistical power to test hypotheses about this group. At study intake, 29% of the sample had a history of inpatient psychiatric treatment, 5% day/residential treatment, 75% outpatient psychotherapy and 46% reported taking some type of antidepressant. Common lifetime comorbidities in the current sample were: dysthymic disorder (11.5 %), overanxious disorder (DSMIII) (10%) and generalized anxiety disorder (8.7%). This data is displayed more fully in Table 1. Of the entire sample, 25% reported having at least one parent that had been hospitalized for mental health purposes at least once over their lifetime.

Preliminary Analyses

Table 1 shows that the probands with two MDEs were similar to those with one MDE in gender breakdown ($X^2 = .001$). Consequently, gender was not considered further for the current study¹. The two groups also differed in severity of depression at intake; children with two MDEs scored about 2 points higher on the CDI-short form than those with one MDE ($t = 3.32, p = .001$).

Factors Associated with MDEs in Children

Table 1 shows that the two groups of probands did not differ in rates of outpatient psychological treatment ($X^2 = 2.45$) and pharmacological treatment ($X^2 = .13$), all p -values $> .05$, which was counter what was initially hypothesized. Interestingly, probands with one MDE showed a trend of higher rates of inpatient treatment than probands with two MDEs ($X^2 = 3.63, p = .057$). Number of episodes did however relate to age of onset of MDD ($t = 5.85, p < .001$); probands with two MDEs were about a year younger at first onset than probands with one MDE (mean ages: 9 versus 10 years old respectively).

Table 2 presents rates of comorbidities and negative life events and scores on hopelessness and emotion regulation scales for probands with one and two MDEs. Probands with two MDEs were more likely to be diagnosed with a comorbid anxiety disorder ($X^2 = 5.16, p < .05$) than those with one MDE. Interestingly, those with one MDE showed a trend for higher diagnosed rates of comorbid dysthymia than those with

¹ Gender was further investigated in an exploratory analysis in relation to the risk factors found to differentiate the one and two MDE groups as a mediation moderator candidate in future studies, however these results are not reported given that this analysis was not initially proposed. Girls scored significantly higher on the CDI, the Hopelessness scale, on the maladaptive ER subscale and had an older age at first onset. Boys and girls did not differ in treatment rates, parental psychopathology rates, or number of negative life events.

two MDEs ($X^2 = 2.90$, $p = .089$). Hence the results only partly support our hypothesized positive relationship between comorbidity rates and MDEs. The two groups showed similar high rates of parental psychiatric hospitalization, with about 1 in 4 children having a parent that had experienced at least one hospitalization ($X^2 = .25$, $p > .05$), which is inconsistent with our hypothesis. The two groups experienced similar numbers of negative life events in the year prior to intake ($t = 1.02$, $p > .05$). However, in line with expectations, those with two MDEs experienced more lifetime negative events than children with one MDE ($t = 2.32$, $p < .05$; the groups differed by about one life event on average). Relative to probands with one MDE, those with two MDEs also reported higher levels of hopelessness on the Hopelessness scales ($t = 2.49$, $p < .05$), on the Maladaptive emotion regulation subscale of Feelings and Me ($t = 2.17$, $p < .05$), and endorsed more negative cognitive ER on the same scale ($t = 2.13$, $p < .05$), all consistent with predictions. The two groups reported similar use of adaptive emotion regulation strategies according to the scores on the Adaptive subscale of Feelings and Me ($t = 1.04$, $p > .05$) (see Table 1)². Interestingly, scores on both the adaptive and maladaptive emotion regulation subscales were comparable to scores observed in a sample of depressed adults with early onset depression (Kovacs, Rottenberg & George, 2009).

Independent Predictors of 2 MDEs in Children

A logistic regression was performed that included simultaneous entry of all variables proposed in hypotheses 1 and 2 that differentiated the one and two MDE groups. This allowed us to determine which (if any) of these variables independently

² Results of the total FAM scores and subscale scores alone are reported; for differences of the two groups on individual items see Appendix G.

predicted membership in the two MDE group when accounting for the other risks. Prior to performing the regression, bi-variate correlations between the predictor variables were examined and no evidence of multicollinearity was present (see Table 3). Overall classification was good with 79% correct classification.

Table 4 shows regression coefficients, Wald statistics, odds ratios (OR), and 95% confidence coefficients for odds ratios for the predictors. According to the Wald statistics and p values, rates of negative life events, comorbid anxiety disorder, maladaptive emotion regulation and age of onset were all significant predictors of group membership. By contrast, Hopelessness was *not* an independent predictor of two MDEs once the other predictors were taken into account ($X^2 = 2.91, p = .088$). According to the OR, each negative life event was associated with a 10% greater likelihood of a two MDE group classification. Likewise, each additional point on the Maladaptive emotion regulation subscale of Feelings and Me covaried with a 3% greater chance of a two MDE group classification. The most powerful predictors were comorbidity of overanxiety disorder and MDD age of onset. Having a comorbid anxiety disorder covaried with a doubled likelihood of a two MDE classification with an increase by 131%. Increased MDD age of onset covaried with 24% decreased likelihood of a two MDE classification.

Exploratory Analysis

Not unexpectedly, children with two MDEs in their lifetime had spent about two more months in episode, on average, than children with one episode (9.5 vs. 11.8 months respectively) ($t = -2.53, p = .012$). Consequently, total time spent depressed was entered

as a covariate in a series of ANCOVAs with number of episodes as the independent variable and number of past life events, maladaptive emotion regulation, hopelessness, age of first onset, and comorbidity of overanxious disorder, each separately entered as dependent variables. Children with two MDEs remained different on these key variables even after the model controlled for total time spent depressed, indicating that these differences are not explained as a simple function of time in episode.

Does Recurrent Depression Predict Future MDEs in Children?

Finally, inconsistent with our prediction, children with recurrent MDEs did not differ in the depression course from children with one MDE, Table 1 shows the two groups were equally likely to have an additional MDE one year after intake, with about 5% of children with 1 or 2 MDD episodes at intake experiencing another depression episode by the one year follow-up.

Discussion

MDD is an impairing disorder and empirical evidence in adults and children indicates that early onset of a first episode can be indicative of a more severe course of depression long term. Childhood-onset depression is clinically more severe compared to depression that onsets later in life (Gollan, et al., 2005) and it is an established risk factor for depression recurrence (Dunn & Goodyer, 2006; Geller, et al., 2001; Kovacs, 1996). In an attempt to better understand early onset depression, a considerable body of research has looked into risks and outcomes of depression in youth. While many studies have investigated depression in adolescents, few have looked into depression that onsets in childhood. This is in part due to difficulties collecting child samples, with depression being a rare phenomenon before puberty. Consequently, many studies that have looked at first versus recurrent MDEs did so retrospectively, or in samples that have suffered from depression for a considerable amount of time, making it ever more complicated to detect factors that may put people at further risk for future depression early in the development of depression. Thus, the current study sample afforded a great opportunity to test a set of hypotheses about younger children who had recurrent depression, and whether such children were higher on a number of conventional depression risk factors than children who had suffered only one episode of depression.

A major strength of the current study comes from the sample itself. The hypotheses were tested using data from a large sample of children with carefully diagnosed juvenile-onset depression (onset before age 12) that have been recruited from a significant number of mental health clinics in Hungary. Indicative of the clinical status of the sample is that about a third of them had experienced inpatient treatment, about three fourths reported outpatient treatment and about half reported some type of psychotropic treatment. Interestingly, the overall gender distribution of the sample showed that more boys than girls experienced juvenile onset depression in this sample. However, important aspects of the sample that may explain this gender distribution, are that: one, children were relatively young at intake, and the gender gap in depression is not generally observed until later in adolescence, and two, these were children for whom parents sought treatment, and consequently, more disruptive symptoms (e.g. higher irritability) that boys more often exhibit compared to girls, may trigger earlier treatment. Importantly, gender did not predict more recurrent depression, a finding consistent with previous conclusions that gender is not a covariate of depression course (Rao et al, 1995; Kovacs, Obrosky, & Sherrill, 2003). In addition to gender breakdown similarities, our MDE groups were remarkably similar in their clinical characteristics; children with one and two MDEs were indistinguishable with similar rates of outpatient treatment, antidepressant medication and severe parental psychopathology. However, against expectations, children with two episodes showed a trend of lower rates of inpatient treatment rates, although this may fit with a trend of higher rates of double depression among these children. Prolonged depression episodes could potentially trigger caregiver concern and propensity to seek treatment for the child. Although it is difficult to know why inpatient

treatment rates were slightly higher among children with one MDE (although not reaching statistical significance) there was no clear evidence that either group had more severe or impairing depression. In fact, CDI (another index of severity) was higher in children reporting two MDEs.

Early Onset as a Risk Factor for Depression Recurrence in Childhood

Early onset depression has been identified as a risk for recurrence in adults (Kovacs, 1996; Weissman, Wolk, Wickramaratne, et al., 1999; Lewinsohn, et al., 2000). Few studies have looked at recurrence patterns early in the developmental stages of depression. Because of low rates of depression in children under age 12 (Costello et al, 2006), much of the research that has looked at early depression has been on adolescents and often community samples. Results from the current considerably younger sample indicated that children with two MDEs reported a lower age of first onset, on average, compared to children with one MDE at intake. While this is a first study comparing children experiencing their first episode to children that have experienced their first recurrence, the results reinforce the relationship between younger age of first MDD onset and recurrent episodes. One possible explanation for the observed relationship between age of onset and recurrence can be that depression that onsets earlier in life is more severe compared to adult onset depression (Gollan et al, 2005) and in a systematic review Burcusa and Iacono (2007) concluded that severity of depression is a risk for recurrence. Surprisingly, this pattern was not fully supported in the current study: while children with two MDEs reported higher scores on the CDI, treatment rates for depression were similar among children with one and two MDEs.

Comorbidities

One potential indicator of depression severity is presence of comorbidity, or co-occurring disorders. Hence, we predicted that comorbidities would be more likely among children with two MDEs than among children with one MDE. Current results show that overall comorbidity was not related to number of episodes, however a different pattern was observed when looking at specific comorbidities. Among comorbid disorders, dysthymia and anxiety disorders are most often seen to co-occur with MDD in children. Current results show a trend for double depression to be more frequent among those children with one episode. A more in-depth analysis revealed that children with double depression experienced slightly longer episodes, thus potentially never having remitted from their first episode like the children with two episodes, although, double depression was not a significant covariate with number of episodes. It is possible that with an increased age range children with double depression would show increased recurrence rates, similarly to previous studies such as the one by Keller, Lavori, Endicott, Coryell, and Klerman, (1983) who found that double depression may predict worse course and higher recurrence rates. One idea for why dysthymia and MDD co-morbid individuals experience longer episodes, yet high chances of recurrence may be that they tend to remain symptomatic even after the major depression subsides (Keller, 1988).

Anxiety disorders are commonly comorbid with depression in childhood and throughout the life span. In the current study we hypothesized that anxiety comorbidity in a clinical sample is also a risk for recurrence of depression. Unlike previous null findings in children (Kovacs, 2001; Birmaher et al, 2004), children with two MDEs were more

likely to report an anxiety disorder than children with one MDE. One possible explanation of the current results is that comorbidity is often associated with severity and complexity of depression in children (Angold, Costello, & Erkanli, 1999) and consequently increased chances of recurrence of depression.

Severe Parental Psychopathology

We hypothesized, consistently with the logic of previous studies (Lewinsohn et al, 2000; Birmaher et al, 2004), that parental psychopathology would be a predictor of recurrence in children. Inconsistent with this prediction, children with one MDE episode were just as likely to have a parent who had experienced psychiatric hospitalization as those with two MDEs. The measure used to identify parental psychopathology was limited to questions concerning parental psychiatric hospitalization. The current results, in this light, may be even more striking, given that this may be a more conservative way of measuring parental psychopathology as it only identifies more severe psychopathology (i.e. that requires hospitalization) which, intuitively, would be associated with children with more MDEs (that we hypothesized would be associated with a more severe depression) and favoring our hypothesis.

Negative Life Events

Adults with recurrent depression consistently report more negative life events in contrast to those that have experienced one episode (Harkness, Monroe, Simons, & Thase, 1999). Current results showed a similar pattern among children: those with two MDEs reported a higher number of lifetime negative life events than children with one

episode. These results are indicative of a more negative psychosocial history compared to children that experienced one episode of depression. Given that the two groups did not differ in the number of events in the year prior to intake, those children with two MDEs also show a pattern of significant events happening earlier in life, which is consistent with the idea that aversive life events happening earlier in life can have a detrimental effect on development (i.e. more MDEs). Although, we did not examine the exact timing of the events with respect to prior depression episodes, so we cannot make strong statements about life stress being an antecedent.

Maladaptive Emotion Regulation

The current study also investigated maladaptive emotion regulation in depressed children with one and two MDEs. Maladaptive emotion regulation scores were found to be significantly higher, on average, among children with two MDEs than those children with one MDE. These results converge with previous findings in adult samples with early onset depression that high scores on scales measuring maladaptive cognitive regulation (e.g. rumination) increase the probability of a recurrent depressive episode among young adults with early onset MDD (Kovacs, Rottenberg & George, 2009), however, this is the first study to show such a difference in children and early in the developmental stages of depression. One intriguing finding of the current study was that, while children with two MDEs showed significantly higher rates of maladaptive emotion regulation skills, rates on the adaptive scale were equally high among children with one and two MDEs. This suggests that while children with two MDEs have a similar armamentarium of adaptive regulation skills as children with one MDE, they also have a richer set of maladaptive

skills; this may potentially decrease the beneficial effects of the protective skills. It is also possible that in the face of a negative event, engaging in adaptive strategies to cope entails more effort; indeed, looking at the individual items of the emotion regulation scale (see appendix G), it seems that, on average, children with two MDEs engage maladaptive emotion regulation skills more often than the children with one MDE. Another explanation could be that, as noted earlier, children with two MDEs also have a younger age of onset of depression and, since emotion regulation skills are perfected over the life span, intuitively, early onset depression can have a profound impact on long term development and perhaps interfere with spontaneous engagement of protective skills.

Independent Predictors of Membership in the One and Two MDE Groups

Given the novelty of the study, a first step is identifying independent factors that may explain *why* some children are vulnerable to repeated depression (Kramer, Stice, Kazdin, Offord, & Kupfer, 2001). Of the variables that were identified to differentiate the children with one and two MDEs, four independently predicted risk for having two MDEs: increased negative life events, higher rates of comorbid diagnosis of overanxiety disorder, higher scores on maladaptive emotion regulation, and a lower age of first onset. Hopelessness did not remain significant in this model due to its overlap with the emotion regulation scale that accounted for some hopelessness in these children. While, intuitively, these risks can be interconnected in their impact on the course of depression, it is the independent risk they contribute to this important problem that was the endeavor of the current study. Although as a first study we examined these factors in a simpler

additive model, it would be reasonable in future work to ask whether interactions among risk factors are more predictive (Kramer et al, 2001) of recurrence.

Since most of our findings are cross-sectional, it is difficult to interpret the current results in a cause effect relationship; predictors of number of episodes identified statistically in cross-sectional data will have to be followed by mediation analysis to determine whether these risks further mediate the relationship between number of episodes at intake and a recurrence at follow-up, however this is the topic of a future study. Despite this limitation, being able to detect cross-sectional differences between young children with one and two MDEs can have multiple interpretations. Children with two MDEs potentially exhibited vulnerabilities prior to developing the first episode of depression that then further exacerbated this risk. Another possibility is that these children all started off equally, however due to the development of additional vulnerabilities concurrent with their depression further risk was generated. Last but not least, it is possible that the differences that we identified are overall resulting from an additional episode of depression that some of the children developed.

Does Recurrent Depression Predict Future Depression in Childhood?

A second major strength of the current study is the design: data were collected both retrospectively, for a rich cross-sectional look at this sample of children, and prospectively, for in vivo observation of the development of depression over time. Contrary to expectations, the relationship between multiple MDEs and future depression was not supported by the results of the one year follow-up, children with one and two

MDEs showing similarly low rates of recurrence within one year post intake, making power to detect differences a potential problem. Additionally, depression in children is often protracted and we believe that it is possible that a follow-up period longer than one year is necessary to see such differences surface; Birmaher, Arbelaez, and Brent (2002) have reported that the majority of depressed children recover from an MDE by 1.5 to 2 years. Longer follow-up periods may be especially important given that some children reported double depression, which according to some can take a remarkably long time to reach full recovery (4 years: Kovacs et al, 1984). Consequently, research on children and adolescents often benefited from prolonged follow-up periods (5 years: Emslie et al, 1997; 9 years: Kovacs, 1996).

Profiles of Children With One and Two MDEs

Taken together, the results provide new data on the profiles of children with one and two MDEs. Despite the remarkable similarities in the overall clinical presentation of the children with one and two MDEs and that no differences were found in course, differences were also observed. In line with expectations, children with two MDEs had younger ages at first onset, higher rates of anxiety comorbidity, more negative life events and more maladaptive emotion regulation skills, despite similar rates of adaptive emotion regulation skills as children with one MDE. In these respects, those with two MDEs seem to be children coming from more aversive environments and suffering from more complex psychopathology profiles. While the children with two MDEs endorsed just as many adaptive emotion regulation skills as those with one episode, it is possible that they more readily engage in the maladaptive emotion regulation given the higher rates of

maladaptive skills in both the cognitive and non cognitive realms. Overall, the children with two MDEs have more severe social histories and, while well equipped with adaptive skills, are more likely to engage in maladaptive ways of regulating emotions; both are aspects that blend well with more severe (higher CDI scores among those with two MDEs) and more protracted depression among children with two MDEs.

Limitations, Conclusions and Future Directions

This is the first study to compare younger children with one and two MDEs and had several strengths. Depression episodes were carefully diagnosed by two clinicians and only the children whose diagnosis reached by the two clinicians agreed were accepted into the study. Children were recruited from 23 mental health facilities throughout Hungary enabling the employment of a considerable sample size, which afforded good statistical power for the primary analyses.

One limitation of the current study is the parent administered life events scale that records negative events in the child's life. One problem of this method is that some items inquire about physical, sexual and psychological abuse experienced by the child. Given the young age of many of the participants in the current study, it is often the case that in abuse instances, parental figures are the perpetrators. Consequently, it is likely that our measure of negative life events undercounts these types of events and research has shown that children tend to report more life events than parents (Bailey & Garralda, 1990; Johnston, Steele, Herrera, & Phipps, 2003). However, regardless of the raw numbers, similar discrepancies would be found in both groups employed in the current study, and

overall, the majority of the studies looking at negative life events in children have used parental reports (Bailey & Garralda, 1990), child self reports coming with their own limitations (e.g. not remembering major life events that took place earlier in life).

Another potential limitation is the homogeneous cultural context in which the current study was conducted. The current sample was collected from 23 mental health facilities throughout Hungary which provide services to at least 80% of the newly registered juvenile psychiatric cases (Kapornai et al, 2007). This offered access to a large clinical sample, still generalizability limitations come into question. One potential limitation could be outlook and bias towards mental health services in lower socioeconomic countries (Saxena, Thornicroft, Knapp, & Whiteford, 2007), possibly resulting in more severe cases alone accessing these services. This could have implications for some of our findings that both one and two MDE groups showed high treatment rates and high parental mental health hospitalization rates. While we take caution in generalizing the current results to other populations, previous studies have shown that in terms of clinical characteristics and course of MDD, Hungarian youths are comparable to USA samples (Kovacs et al, 1997).

Despite some of the limitations of the current study, this is a first step towards understanding children with one and two episodes of depression and marking important differences between the two groups. Markers of experiencing two episodes were, in addition to younger age of first onset, utilization of maladaptive emotion regulation strategies, multiple negative life events experienced early in life and comorbid anxiety, all of which correspond to characteristics observed in adults with recurrent episodes of

depression, suggesting that vulnerabilities and differences in children with one episode and those with a recurrence are present early in the development of depression. These findings are an indication that early stages of depression may replicate patterns of data seen later in the lifecourse; for example young children in this sample reported similar levels of maladaptive emotion regulation skills as adults with early onset depression. An important next step is to temporally position these events and changes. While it is likely that children with two episodes have a more negative past history and engaged in maladaptive ER prior to MDD onset, it is equally likely that their maladaptive emotion regulation style exacerbated following a second episode. This issue can only be reconciled by prospective studies following healthy and at risk children over time. Nonetheless, the findings of the study show that a mere additional episode of depression is related to a more severe clinical characterization of children marked by higher rates of maladaptive emotion regulation and higher rates of comorbid anxiety.

Tables

Table 1. Demographics and treatment rates in children with one and two MDEs

Variable	One MDE (N = 435)	Two MDEs (N = 115)
Gender (%Female)	40.9%	40.9%
* Age of 1 st MDE onset (Mean, SD)	10.07 (1.75)	9.17 (2.06)
*Age at Intake (Mean, SD)	11.05 (1.74)	11.78 (2.02)
*Intake CDI	6.57 (3.90)	8.04 (4.39)
**Inpatient Treatment	30.8%	21.7%
Outpatient Treatment	73.8%	80.9%
Antidepressant Medication	46.0%	47.8%
Severe Parental Psychopathology	24.4%	28.7%
Recurrence by 1 year FU	4.4%	5.2%

*p<.05; **p = .057; MDD = Major depressive disorder; FU = Follow-up

Table 2. Comorbidity rates, emotion regulation and hopelessness scores in children with one and two MDEs.

Variable	One MDE (N = 435)	Two MDEs (N = 115)
Any comorbidity	59.0%	58.3%
**Dysthymia	12.6%	7.0%
*Overanxious Disorder (DSM III)	8.5%	15.7%
*NLE (> 1 year) (Mean, SD)	4.62 (2.86)	5.32 (2.97)
*Hopelessness (Mean, SD)	6.26 (3.34)	7.21 (3.60)
*Maladaptive ER (Mean, SD)	15.60 (8.84)	17.63 (8.64)
Adaptive ER (Mean, SD)	24.81 (11.01)	23.61 (9.84)
*Negative Cognitive ER (Mean, SD)	6.97 (4.35)	7.95 (4.50)

*p<.05; **p = .089; NLE = Negative life events; ER = Emotion regulation

Table 3. Correlation matrix of number of episodes in children with MDD.

	Age of 1 st MDE Onset	Maladaptive ER	Anxiety Comorbidity	Hopelessness	NLE
Age of 1 st MDE Onset		-.184	.003	-.050	-.043
Maladaptive ER	-.184		-.016	-.367	.004
Anxiety Comorbidity	.003	-.016		.054	.016
Hopelessness	-.050	-.367	.054		-.004
NLE	-.043	.004	.016	-.004	

Table 4. Independent predictors of number of episodes in children with MDD.

Variable	B	SE	Wald	Sig	OR	95% CI- Low	95% CI – High
Negative life events	.09	.04	5.58	.018	1.10	1.016	1.186
Maladaptive ER	.03	.01	5.54	.019	1.04	1.006	1.064
Anxiety Comorbidity	.84	.34	5.94	.015	2.31	1.178	4.532
Hopelessness	.06	.04	2.91	.088	1.07	.991	1.145
Age of 1 st onset	-.27	.06	17.86	.000	0.76	.672	.865

References

- Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness depression: A theory based subtype of depression. *Psychological Review*, *96*, 358-372.
- Achenbach, T. (1991). *Manual for the Child Behavior Checklist 4-18 and 1991 Profile*. Burlington: University of Vermont, Department of Psychiatry.
- Alloy, L. B., Abramson, L. Y., Walshaw, P. D., & Neeren, A. M. (2006). Cognitive vulnerability to unipolar and bipolar mood disorders. *Journal of Social and Clinical Psychology*, *25*, 726-754.
- Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Panzarella, C., & Rose, D. T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *J Abnorm Psychol*, *115*(1), 145-156. doi: 2006-02317-016 [pii] 10.1037/0021-843X.115.1.145
- Altmann, E. O., & Gotlib, I. H. (1988). The social behavior of depressed children: an observational study. *J Abnorm Child Psychol*, *16*(1), 29-44.
- Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *J Child Psychol Psychiatry*, *40*(1), 57-87.
- Bailey, D., & Garralda, M. E. (1990). Life Events - Childrens Reports. *Social Psychiatry and Psychiatric Epidemiology*, *25*(6), 283-288.

- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. Guilford Press, New York.
- Bernstein, G. A., & Borchardt, C. M. (1991). Anxiety disorders of childhood and adolescence: a critical review. *J Am Acad Child Adolesc Psychiatry*, *30*(4), 519-532. doi: S0890-8567(09)64316-1 [pii] 10.1097/00004583-199107000-00001
- Birmaher, B., Arbelaez, C., & Brent D. (2002). Course and outcome of child and adolescent major depressive disorder. *Child and Adolescent Psychiatric Clinics of North America*, *11*, 619-637.
- Birmaher, B., Williamson, D., Dahl, R. E., Axelson, D. A., Kaufman, J., Dorn, L. D., et al, (2004). Clinical presentation and course of depression in youth: Does onset in childhood differ from onset in adolescence? *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 63-70.
- Brown GW, Harris TO. (1978). *Social origins of depression: A study of psychiatric disorder in women*. New York: Free Press.
- Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. *Clin Psychol Rev*, *27*(8), 959-985. doi: S0272-7358(07)00058-X [pii] 10.1016/j.cpr.2007.02.005
- Cane, D. B., Olinger, L. J., Gotlib, I. H., & Kuiper, N. A. (1986). Factor structure of the dysfunctional attitude scale in a student population. *Journal of Clinical Psychology*, *42*, 307-309.
- Clark, D. A., Beck, A. T., & Alford, B. A. (1999). *Scientific foundations of cognitive theory and therapy of depression*. John Wiley & Sons, Inc.

- Coddington, R. D. (1972). The significance of life events as etiologic factors in the diseases of children—II: A study of a normal population. *Journal of Psychosomatic Research, 16*, 205-213.
- Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*, 155-159.
- Cole, D. A., Nolen-Hoeksema, S., Girgus, J., & Paul, G. (2006). Stress exposure and stress generation in child and adolescent depression: a latent trait-state-error approach to longitudinal analyses. *J Abnorm Psychol, 115*(1), 40-51. doi: 2006-02317-005 [pii] 10.1037/0021-843X.115.1.40
- Costello, E. J., Foley, D. L., & Angold, A. (2006). 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: II. Developmental epidemiology. *J Am Acad Child Adolesc Psychiatry, 45*(1), 8-25. doi: S0890-8567(09)62256-5 [pii] 10.1097/01.chi.0000184929.41423.c0
- Daley, S. E., Hammen, C., & Rao, U. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *J Abnorm Psychol, 109*(3), 525-533.
- Dempster, E. L., Burcescu, I., Wigg, K., Kiss, E., Baji, I., Gadoros, J., . . . Barr, C. L. (2007). Evidence of an association between the vasopressin V1b receptor gene (AVPR1B) and childhood-onset mood disorders. *Arch Gen Psychiatry, 64*(10), 1189-1195. doi: 64/10/1189 [pii] 10.1001/archpsyc.64.10.1189
- Dohrenwend, B. P. (2006). Inventorying Stressful Life Events as Risk Factors for Psychopathology: Toward Resolution of the Problem of Intracategory Variability. *Psychological Bulletin, 132*, 477-495.

- Dunn, V., & Goodyer, I. M. (2006). Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. *Br J Psychiatry, 188*, 216-222. doi: 188/3/216 [pii] 10.1192/bjp.188.3.216
- Emslie, G. J., Rush, A. J., Weinberg, W. A., Gullion, C. M., Rintelmann, J., & Hughes, C. W. (1997). Recurrence of major depressive disorder in hospitalized children and adolescents. *J Am Acad Child Adolesc Psychiatry, 36*(6), 785-792. doi: S0890-8567(09)66504-7 [pii]10.1097/00004583-199706000-00015
- Ezpeleta, L., Domenech, J. M., & Angold, A. (2006). A comparison of pure and comorbid CD/ODD and depression. *J Child Psychol Psychiatry, 47*(7), 704-712. doi: JCPP1558 [pii] 10.1111/j.1469-7610.2005.01558.x
- Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2007). Recurrence of major depression in adolescence and early adulthood, and later mental health, educational and economic outcomes. *Br J Psychiatry, 191*, 335-342. doi: 191/4/335 [pii] 0.1192/bjp.bp.107.036079
- Fleming, J. E., & Offord, D. R. (1990). Epidemiology of childhood depressive disorders: a critical review. *J Am Acad Child Adolesc Psychiatry, 29*(4), 571-580. doi: S0890-8567(09)64642-6 [pii] 10.1097/00004583-199007000-00010
- Garber, J. (2007). Depression in youth: A developmental psychopathology perspective. In A. Masten & A. Sroufe (Eds.), *Multilevel dynamics in developmental psychopathology: Pathways to the future* (Vol. 34, pp. 181-242). New York: Erlbaum.
- Geller, B., Zimmerman, B., Williams, M., Bolhofner, K., & Craney, J. L. (2001). Adult psychosocial outcome of prepubertal major depressive disorder. *J Am Acad Child*

- Adolesc Psychiatry*, 40(6), 673-677. doi: S0890-8567(09)60471-8 [pii]
0.1097/00004583-200106000-00012
- Gibb, B. E., & Alloy, L. B. (2006). A prospective test of the hopelessness theory of depression in children. *J Clin Child Adolesc Psychol*, 35(2), 264-274. doi: 10.1207/s15374424jccp3502_10
- Gollan, J., Raffety, B., Gortner, E., & Dobson, K. (2005). Course profiles of early- and adult-onset depression. *J Affect Disord*, 86(1), 81-86. doi: S0165-0327(04)00445-8 [pii]10.1016/j.jad.2004.12.009
- Goodman, S. H., Schwab-Stone, M., Lahey, B. B., Shaffer, D., & Jensen, P. S. (2000). Major depression and dysthymia in children and adolescents: discriminant validity and differential consequences in a community sample. *J Am Acad Child Adolesc Psychiatry*, 39(6), 761-770. doi: S0890-8567(09)66246-8 [pii]
10.1097/00004583-200006000-00015
- Gotlib, I. H., Joormann, J., Minor, K. L., & Hallmayer, J. (2008). HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biol Psychiatry*, 63(9), 847-851. doi: S0006-3223(07)00991-2 [pii]
10.1016/j.biopsych.2007.10.008
- Gotlib, I. H., Lewinsohn, P. M., & Seeley, J. R. (1998). Consequences of depression during adolescence: marital status and marital functioning in early adulthood. *J Abnorm Psychol*, 107(4), 686-690.
- Grant, D. M., & Beck, J. G. (2006). Attentional biases in social anxiety and dysphoria: does comorbidity make a difference? *J Anxiety Disord*, 20(4), 520-529. doi: S0887-6185(05)00065-4 [pii] 10.1016/j.janxdis.2005.05.003

- Halligan, S. L., Murray, L., Martins, C., & Cooper, P. J. (2007). Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. *J Affect Disord*, *97*(1-3), 145-154. doi: S0165-0327(06)00277-1 [pii] 10.1016/j.jad.2006.06.010
- Hammen, C., & Brennan, P. A. (2001). Depressed adolescents of depressed and nondepressed mothers: tests of an interpersonal impairment hypothesis. *J Consult Clin Psychol*, *69*(2), 284-294.
- Hammen, C., & Brennan, P. A. (2003). Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Arch Gen Psychiatry*, *60*(3), 253-258. doi: yoa10230 [pii]
- Hammen, C., Burge, D., & Adrian, C. (1991). Timing of mother and child depression in a longitudinal study of children at risk. *J Consult Clin Psychol*, *59*(2), 341-345.
- Hankin, B. L. & Abramson, L. (2001). Development of gender differences in depression: An elaborated cognitive vulnerability-transactional stress theory. *Psychological Bulletin*, *127*, 773-796.
- Harkness, K. L., Monroe, S. M., Simons, A. D., & Thase, M. (1999). The generation of life events in recurrent and non-recurrent depression. *Psychol Med*, *29*(1), 135-144.
- Harrington, R., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1990). Adult outcomes of childhood and adolescent depression. I. Psychiatric status. *Arch Gen Psychiatry*, *47*(5), 465-473.
- Holmes, T. & Rahe, R. (1967). Holmes-Rahe Social Readjustment Rating Scale. *Journal of Psychosomatic Research*, vol. II.

- Iacoviello, B. M., Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., & Hogan, M. E. (2006). The course of depression in individuals at high and low cognitive risk for depression: a prospective study. *J Affect Disord*, *93*(1-3), 61-69. doi: S0165-0327(06)00089-9 [pii]10.1016/j.jad.2006.02.012
- Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Arch Gen Psychiatry*, *59*(3), 215-222. doi: yoa10107 [pii]
- Johnston, C. A., Steele, R. G., Herrera, E. A., & Phipps, S. (2003). Parent and child reporting of negative life events: Discrepancy and agreement across pediatric samples. *Journal of Pediatric Psychology*, *28*, 579–588.
- Kapornai, K., Gentzler, A. L., Tepper, P., Kiss, E., Mayer, L., Tamas, Z., . . . Vetro, A. (2007). Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary. *J Affect Disord*, *100*(1-3), 91-101. doi: S0165-0327(06)00441-1 [pii] 10.1016/j.jad.2006.10.002
- Kazdin, A. E., Rodgers, A., & Colbus, D. (1986). The hopelessness scale for children: psychometric characteristics and concurrent validity. *J Consult Clin Psychol*, *54*(2), 241-245.
- Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol Psychiatry*. 1998;44:348-360.
- Keller, M. B., Lavori, P.W., Endicott, J., Coryell, W., & Klerman, G. L. (1983). ‘Double depression’: Two-year follow-up. *American Journal of Psychiatry*, *140*, 689–694.

- Kessler, R.C., McGonagle, K.A., Swartz, M., Blazer, D.G., & Nelson, C.B. (1993). Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity, and recurrence. *Journal of Affective Disorders, 29*, 85–96
- Killeen, T. K., Brady, K.T., Gold, P., Simpson, K., & Tyson, C. (2004). Comparison of self-report and archival data abstraction of service utilization in a community sample of treatment seeking alcohol abusing individuals. *Drug and Alcohol Dependence, 73*, 141-147.
- Kovacs, M. (1996). Presentation and course of major depressive disorder during childhood and later years of the life span. *J Am Acad Child Adolesc Psychiatry, 35*(6), 705-715. doi: S0890-8567(09)63905-8 [pii] 10.1097/00004583-199606000-00010
- Kovacs, M. (2001). Gender and the course of major depressive disorder through adolescence in clinically referred youngsters. *J Am Acad Child Adolesc Psych, 40* (9), 1079– 1085.
- Kovacs, M., Akiskal, H. S., Gatsonis, C., & Parrone, P. L. (1994). Childhood-onset dysthymic disorder. Clinical features and prospective naturalistic outcome. *Arch Gen Psychiatry, 51*(5), 365-374.
- Kovacs, M., Devlin, B., Pollock, M., Richards, C., & Mukerji, P. (1997). A controlled family history study of childhood-onset depressive disorder. *Archives of General Psychiatry, 54*, 613-623.
- Kovacs, M., Feinberg, T. L., Crouse-Novak, M. A., Paulauskas, P., Finkelstein, R. (1984a). Depressive disorders in childhood: I. A longitudinal prospective study of characteristics and recovery. *Arch Gen Psychiatry, 41*, 229–237.

- Kovacs, M., Feinberg, T. L., Crouse-Novak, M. A., Paulauskas, P., Pollock, M., Finkelstein, R. (1984b). Depressive disorders in childhood: II. A longitudinal study of the risk for a subsequent major depression. *Arch Gen Psychiatry*, *41*, 643–649.
- Kovacs, M., Gatsonis, C., Paulauskas, S. L., & Richards, C. (1989). Depressive disorders in childhood. IV. A longitudinal study of comorbidity with and risk for anxiety disorders. *Arch Gen Psychiatry*, *46*(9), 776-782.
- Kovacs, M., Obrosky, D. S., Sherrill, J. (2003). Developmental changes in the phenomenology of depression in girls compared to boys from childhood onward. *J Affect Disord*, *74* (1), 33– 48.
- Kovacs, M., Rottenberg, J., & George, C. (2009). Maladaptive mood repair responses distinguish young adults with early-onset depressive disorders and predict future depression outcomes. *Psychol Med*, *39*(11), 1841-1854. doi: S0033291709005789 [pii]
10.1017/S0033291709005789
- Kraemer, H. C., Stice, E., Kazdin, A., Offord, D., & Kupfer, D. (2001). How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. *American Journal of Psychiatry*, *158*, 848-856.
- Lavori, P. W., Keller, M. B., Mueller, T. I., Scheftner, W., Fawcett, J., Coryell, W. (1994). Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. *Int J Methods Psychiatr Res*, *4*, 211-229.

- Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression: differential processes of psychosocial risk. *J Abnorm Psychol*, *108*(3), 483-489.
- Lewinsohn, P. M., Pettit, J. W., Joiner Jr., T. E., Seeley, J. R. (2003). The symptomatic expression of major depressive disorder in adolescents and young adults. *J Abnorm Psychology*, *112* (2), 244–252.
- Lewinsohn, P. M., Rohde, P., Klein, D. N., & Seeley, J. R. (1999). Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. *J Am Acad Child Adolesc Psychiatry*, *38*(1), 56-63. doi: S0890-8567(09)62866-5 [pii] 10.1097/00004583-199901000-00020
- Lewinsohn, P. M., Rohde, P., Seeley, J. R., Klein, D. N., & Gotlib, I. H. (2000). Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. *Am J Psychiatry*, *157*(10), 1584-1591.
- Lieb, R., Isensee, B., Hofler, M., Pfister, H., & Wittchen, H. U. (2002). Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*, *59*(4), 365-374. doi: yoa01030 [pii]
- Mayer, L., Lopez-Duran, N. L., George, C., Baji, I., Kapornai, K., Kiss, E., Kovacs, M., Vetró, A., & The International Consortium for Childhood-Onset Mood Disorders (in press).
 Characteristics of stressful life events in a clinical sample of depressed children in Hungary.
- Maziade, M., Roy, M. A., Fournier, J. P., Cliché, D., Merette, C., Caron, C., Garneau, Y.,

- Montgrain, N., Shriqui, C., Dion, C. (1992). Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies. *Am J Psychiatry*, *149*, 1674–1686.
- McCauley, E., Myers, K., Mitchell, J., Calderon, R., Schloredt, K., & Treder, R. (1993). Depression in young people: initial presentation and clinical course. *J Am Acad Child Adolesc Psychiatry*, *32*(4), 714-722. doi: S0890-8567(09)64859-0 [pii] 0.1097/00004583-199307000-00003
- McDermott, B. M., McKelvey, R., Roberts, L., Davies, L. (2002). Severity of children's psychopathology and impairment and its relationship to treatment setting. *Psychiatric Services*, *53*(1), 57-62.
- Mitchell, P. B., Parker, G. B., Gladstone, G. L., Wilhelm, K., & Austin, M. P. (2003). Severity of stressful life events in first and subsequent episodes of depression: the relevance of depressive subtype. *J Affect Disord*, *73*(3), 245-252. doi: S0165032701004797 [pii]
- Mongrain, M., & Blackburn, S. (2005). Cognitive vulnerability, lifetime risk, and the recurrence of major depression in graduate students. *Cognitive Therapy and Research*, *29*, 747-768.
- Monroe, S. M., & Harkness, K. L. (2005). Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychol Rev*, *112*(2), 417-445. doi: 2005-02750-005 [pii] 10.1037/0033-295X.112.2.417

- Monroe, S. M., Rohde, P., Seeley, J. R., & Lewinsohn, P. M. (1999). Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J Abnorm Psychol*, *108*(4), 606-614.
- Nandrino, J. L., Dodin, V., Martin, P., & Henniaux, M. (2004). Emotional information processing in first and recurrent major depressive episodes. *J Psychiatr Res*, *38*(5), 475-484. doi: 10.1016/j.jpsychires.2004.03.002 S0022395604000408 [pii]
- Nolen-Hoeksema, S. (2001). Gender differences in depression. *Current Directions in Psychological Science*, *10*, 173-176.
- Nolen-Hoeksema, S., & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: the 1989 Loma Prieta earthquake. *Journal of Personality and Social Psychology*, *61*, 115-121.
- Nolen-Hoeksema, S., Morrow, J., & Fredrickson, B. L. (1993). Response styles and the duration of episodes of depressed mood. *J Abnorm Psychol*, *102*(1), 20-28.
- Pettit, J. W., Lewinsohn, P. M., & Joiner, T. E., Jr. (2006). Propagation of major depressive disorder: relationship between first episode symptoms and recurrence. *Psychiatry Res*, *141*(3), 271-278. doi: S0165-1781(05)00229-5 [pii] 10.1016/j.psychres.2005.07.022
- Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*, *149*(8), 999-1010.
- Puig-Antich, J., Lukens, E., Davies, M., Goetz, D., Brennan-Quattrock, J., & Todak, G. (1985). Psychosocial functioning in prepubertal major depressive disorders. II. Interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry*, *42*(5), 511-517.

- Rao, U., Ryan, N. D., Birmaher, B., Dahl, R. E., Williamson, D. E., Kaufman, J., . . . Nelson, B. (1995). Unipolar depression in adolescents: clinical outcome in adulthood. *J Am Acad Child Adolesc Psychiatry, 34*(5), 566-578. doi: S0890-8567(09)63541-3 [pii] 10.1097/00004583-199505000-00009
- Rohde, P., Lewinsohn, P. M., Klein, D. N., & Seeley, J. R. (2005). Association of parental depression with psychiatric course from adolescence to young adulthood among formerly depressed individuals. *J Abnorm Psychol, 114*(3), 409-420. doi: 2005-09257-008 [pii] 10.1037/0021-843X.114.3.409
- Saxena, S., Thornicroft, G., Knapp, M., & Whiteford, H. (2007). Resources for mental health: scarcity, inequity, and inefficiency. *Lancet, 370*, 878-889.
- Sherrill, J. T., Kovacs, M. (2000). Interview Schedule for Children and Adolescents (ISCA). *J Am Acad Child Adolesc Psych, 39*, 67-75.
- Seligman, L. D., & Ollendick, T. H. (1998). Comorbidity of anxiety and depression in children and adolescents: an integrative review. *Clin Child Fam Psychol Rev, 1*(2), 125-144.
- Simpson, B.H., Nee, J.C., & Endicott, J. (1997). First-episode major depression: Few sex differences in course. *Archives of General Psychiatry, 54*, 633-639.
- Sitarenios, G. & Kovacs, M. (1999). Use of the Children's Depression Inventory. In M.E. Maruish (Ed.), *The use of psychological testing for treatment planning and outcome assessment* (pp. 267-299). Mahwah, NJ: Erlbaum.
- Sorensen, M. J., Nissen, J. B., Mors, O., & Thomsen, P. H. (2005). Age and gender differences in depressive symptomatology and comorbidity: an incident sample of

- psychiatrically admitted children. *J Affect Disord*, 84(1), 85-91. doi: S0165-0327(04)00304-0 [pii] 10.1016/j.jad.2004.09.003
- Stroud, C. B., Davila, J., & Moyer, A. (2008). The relationship between stress and depression in first onsets versus recurrences: a meta-analytic review. *J Abnorm Psychol*, 117(1), 206-213. doi: 2008-01363-017 [pii] 10.1037/0021-843X.117.1.206
- Tamás, Z., Kovacs, M., Gentsler, A. L., Tepper, P., Gádoros, J., Kiss, E., Kapornai, K., Vetró, Á. & The International Consortium for Childhood-Onset Mood Disorder (2007). The relations of temperament and emotion self-regulation with suicidal behaviors in a clinical sample of depressed children in Hungary. *Journal of Abnormal Child Psychology*, 35, 640-652.
- Thompson, R. A. (1991). Emotional regulation and emotional development. *Educational Psychology Review*, 3, 269-307. 640-652.
- Timbremont, B., & Braet, C. (2004). Cognitive vulnerability in remitted depressed children and adolescents. *Behav Res Ther*, 42(4), 423-437. doi: 10.1016/S0005-7967(03)00151-7 S0005796703001517 [pii]
- Weissman, M. M., Warner, V., Wickramaratne, P., Moreau, D., & Olfson, M. (1997). Offspring of depressed parents. 10 Years later. *Arch Gen Psychiatry*, 54(10), 932-940.
- Weissman, M. M., Wolk, S., Goldstein, R. B., Moreau, D., Adams, P., Greenwald, S., . . . Wickramaratne, P. (1999). Depressed adolescents grown up. *JAMA*, 281(18), 1707-1713. doi: joc81650 [pii]

- Weissman, M. M., Wolk, S., Wickramaratne, P., Goldstein, R. B., Adams, P., Greenwald, S., . . . Steinberg, D. (1999). Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry*, *56*(9), 794-801.
- Williamson, D. E., Birmaher, B., Axelson, D. A., Ryan, N. D., & Dahl, R. E. (2004). First episode of depression in children at low and high familial risk for depression. *J Am Acad Child Adolesc Psychiatry*, *43*(3), 291-297. doi: S0890-8567(09)66047-0 [pii]10.1097/00004583-200403000-00010
- Williamson, D. E., Birmaher, B., Frank, E., Anderson, B. P., Matty, M. K., & Kupfer, D. J. (1998). Nature of life events and difficulties in depressed adolescents. *J Am Acad Child Adolesc Psychiatry*, *37*(10), 1049-1057. doi: S0890-8567(09)63313-X [pii]10.1097/00004583-199810000-00015

