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# Risk Factors for Recurrent Major Depressive Disorder in a Nationally Representative Sample

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Risk Factors for Recurrent Major Depressive Disorder  
in a Nationally Representative Sample

by

Graig C. DeFeo

A thesis submitted in partial fulfillment  
of the requirements for the degree of  
Master of Science in Public Health  
with a concentration in Behavioral Health  
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College of Public Health  
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## Abstract

The public use version of the National Comorbidity Survey – Replication (NCS-R) dataset was used (N = 995) to investigate risk factors for recurrent major depressive disorder (MDD) that are evident before recovery from the first major depressive episode (MDE) by comparing persons diagnosed with MDD who experienced a single MDE to persons with recurrent MDD.

Multiple logistic regression analyses assessed the independent risk of recurrent MDD for each of the following risk factors: an early age of onset (<30 years old), absence of a life stress trigger, chronic first episode, childhood parental loss, parental maltreatment, parental depression, comorbid anxiety disorder, and comorbid substance disorder. The relative excess risk due to interaction (RERI) assessed the risk of recurrent MDD associated with the interaction of an early onset with three childhood-based vulnerabilities: a) parental depression, b) parental loss, and c) parental maltreatment.

There was a statistically significant risk of recurrent MDD found for the following risk factors: early onset, stress trigger absent, childhood parental loss, parental maltreatment, parental depression, and anxiety disorder; marginally significant results suggested an increased risk of recurrent MDD for substance disorder. There was a significant increased risk found for the interaction of an early onset with parental depression and similar non-significant trends were found for the interactions of early onset with parental loss and early onset with parental maltreatment.

An early onset, the absence of a life stress trigger, and the presence of parental loss, parental maltreatment, parental depression, a comorbid anxiety disorder, and a comorbid substance disorder each confer greater risk of recurrent MDD among persons that have not yet recovered from their first lifetime MDE. The presence of an early onset combined with a childhood-based vulnerability such as parental depression, parental loss, or parental maltreatment, indicate an especially high risk of recurrent MDD. These findings may inform the development of a screening tool to assess risk for recurrent MDD and early intervention to prevent recurrent MDD. Future research should employ a longitudinal research design to replicate and expand upon these findings.



## **Chapter One: Introduction**

Major depressive disorder (MDD) is one of the most common (Kessler et al., 2003; Kessler & Wang, 2009) and costly (Greenberg et al., 2003) forms of psychopathology. According to the World Health Organization (WHO), MDD is the second greatest cause of years lived with a disability (YLD) and fifth greatest cause of disability-adjusted life-years (DALYs) in the United States (Murray & Lopez, 2013). MDD is also the most important risk factor for suicide as two thirds of all patients who commit suicide have a depressive disorder and 21% of patients with recurrent depressive disorders will attempt suicide (Sartorius, 2001).

MDD also has a large impact on the U.S. economy, as patients with depression have significantly higher annual health care costs than do patients without depression (Simon, VonKorff, & Barlow, 1995; Welch, Czerwinski, Ghimire, & Bertsimas, 2009). The impact of MDD on the U.S. economy for the year 2000 was estimated at \$83.1 billion (Greenberg et al., 2003), and the annual cost of MDD on absenteeism and lost productivity in the workplace was greater than \$36 billion for the year 2006 (Kessler et al., 2006). These burdens underscore the need to improve and expand the reach and effectiveness of preventive and treatment services for persons with depression.

The negative impacts of MDD are spurred by a lifetime prevalence rate that has been estimated at over 23% for adults in the U.S. (Kessler & Wang, 2009), according to the most recent nationally representative survey of the non-institutionalized U.S. adult population (Kessler, Berglund, et al., 2004). Over 30 million U.S. adults have met criteria for MDD at some

point during their lifetime (Kessler et al., 2003). The high prevalence of MDD is exacerbated by the frequently recurrent nature of the condition, as at least 90% of all episodes that occur in a given year are recurrences, rather than first onsets (Kessler & Wang, 2009).

## Key Terms

Several key change points in the course of MDD are important to define before discussing the prior research on risk factors of MDD: *episode*, *remission*, *response*, *recovery*, *relapse*, *recurrence*, and *recurrent* (see Figure 1). An *episode* represents the presence of a certain number of symptoms that persist for a specific duration of time (Boland & Keller, 2009). *Remission* represents a period of time during which the individual no longer satisfies criteria for an episode and can be either partial or full. According to *the Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-V*; American Psychiatric Association [APA], 2013), a *partial remission* indicates that either symptoms of the immediately previous major depressive episode (MDE) are present but full criteria for a MDE are not met, or that there has been a period lasting less than two months without any significant symptoms of a MDE following the end of such an episode (APA, 2013). *DSM-V* defines *full remission* as the absence of any significant signs or symptoms of the immediately previous MDE during the past 2 months (APA, 2013). *Response* is a remission that is believed to be the result of a treatment intervention. *Recovery* is defined as a full remission that lasts for a period of at least two consecutive months. Recovery indicates the end of an episode, rather than the end of the illness. A *relapse* is a return of symptoms satisfying full criteria for a MDE that occurs during a period of remission, before achieving recovery. A relapse represents a change from either a partial or a full remission to a condition satisfying the full criteria for a MDE (Frank et al., 1991). A *recurrence* refers to an onset of a new major

depressive episode (MDE) that occurs subsequent to achieving recovery from a previous MDE (Boland & Keller, 2009). *Recurrent MDD* is a course specifier for persons with MDD that distinguishes persons with two or more lifetime MDEs from persons with a single lifetime MDE. Further, in order for a return of symptoms of sufficient severity to satisfy criteria for a MDE to represent a recurrence of depression there must be an interval of at least two consecutive months during which the individual does not meet criteria for a MDE (APA, 2013).

Recurrent MDD is very common, as greater than 80% of people with at least one lifetime MDE will have at least one recurrence (Kessler et al., 2003). Longitudinal studies of youth find the cumulative probability of recurrence is 40% by 2 years, 60% by 5 years, 75% by 10 years, and 87% by 15 years (Boland & Keller, 2009). The risk for a future recurrence also increases with the onset of each new MDE, as evidenced by a longitudinal study of patients with depression that found the risk of recurrence to increase by 16% with the onset of each new episode (Solomon et al., 2000). In addition, each recurrence becomes more difficult to treat, and the intervals between episodes become progressively shorter (Eaton et al., 1997). Thus, there is a potential to alleviate significant burden by identifying effective strategies to prevent people with a single lifetime MDE from experiencing a recurrent course.

### **Study Goals**

The goal of the present investigation is to utilize a large nationally representative dataset to identify reliable indicators of an increased risk for recurrent MDD versus a single lifetime MDE, focusing on risk factors that could be identified prior to or during a first episode. This information could help to improve treatment and preventive efforts by helping service providers identify persons with the greatest need for services. Further, this could enhance the degree to

which persons with one or more MDE receive services most appropriate for their unique risk factor profile. Individuals suffering their first MDE at low risk of a recurrent course may require less intensive treatment, whereas those at high risk of recurrent MDD may require services that are more intensive in order to prevent recurrences of depression. Thus, the long-term goal of the current study is to inform service delivery in order to provide the most effective and efficient treatment and preventive resources.

## Literature Review

A number of risk factors have been examined as predictors of recurrence of depression. These risk factors include demographic characteristics such as sex and marital status; characteristics of the first depressive episode such as age of onset, life stress trigger, and episode duration; childhood adversities such as parental loss and parental maltreatment; and clinical conditions such as parental depression, comorbid anxiety disorder, and comorbid substance disorder.

**Demographic characteristics. Sex.** MDD is more common in women than men, as roughly twice as many women meet the criteria for a depressive disorder at some time in their lives (Kessler et al., 2003). Females may have an increased risk of relapse or non-remission (Kuehner, 2003); however, the majority of research indicates that there is no significant difference between males and females in their risk of recurrence (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Specifically, gender did not have a significant relationship with later recurrence of depression in a 2 ½ year follow-up study of 159 college students with MDD (Iacoviello, Alloy, Abramson, Whitehouse, & Hogan, 2006). Sex did not predict a recurrent course of depression versus having a single lifetime MDE in seven-year follow-up study of 28

adolescents with depression (Rao et al., 1995) or in a ten-year follow-up study of 87 children and adolescents with MDD (Kovacs, Obrosky, & Sherrill, 2003). A fifteen-year follow-up study on the long-term outcome of depression in 197 adults after their first lifetime MDE also found no significant difference between males and females in number of recurrences or time to a first recurrence (Simpson, Nee, & Endicott, 1997).

Two exceptions are worthy of note, however. First, female sex was predictive of recurrence in a five-year follow-up study of 68 children and adolescents with MDD (Birmaher et al., 2004); however, this study did not distinguish persons with a history of multiple prior episodes from persons with only one prior MDE. Thus, the findings of this study do not indicate a greater risk of recurrent MDD for females with a single lifetime MDE than for males with a single lifetime MDE. Second, a retrospective assessment of more than 2,000 adults found a greater risk of recurrence for females (Lewinsohn, Zeiss, & Duncan, 1989). The definition of recurrence in this study, however, represented persons with at least two episodes of major depression (MD), minor depression (mD), or intermittent depression. Thus, these results do not reflect a sex difference in risk of recurrent MDD among persons with a single lifetime MDE.

***Marital status.*** The findings of a systematic review of the literature suggest that marital status may relate to risk of a first onset of depression, but that it does not appear to have a relationship with recurrence of depression (Hardeveld et al., 2010). There are two studies that did find a significant relationship between marital status and recurrence of depression that are worthy of note (Kessing, Andersen, & Mortensen, 1998; Solomon et al., 2000). First, having never been married was a significant predictor of recurrence in a 15-year follow-up study of 318 patients with major depression (Solomon et al., 2000). However, this study examined risk factors associated with recurrence of depression without regard for individual histories of depression.

Thus, this study does not provide information regarding the degree to which marital status confers risk for recurrent MDD, relative to a single lifetime MDE. This distinction is significant since the factors that confer risk of a first lifetime recurrence are not necessarily the same as those that confer risk for subsequent recurrences (Monroe & Harkness, 2011).

The importance of this distinction is evident in the results of a retrospective assessment of greater than 20,000 first admission hospital patients, which was the second study that found marital status to be predictive of recurrence of depression (Kessing et al., 1998). Specifically, persons who were divorced or separated were more likely to suffer a recurrence following a first lifetime MDE than persons who were not divorced or separated; however, marital status did not associate with risk of recurrence following a 2nd, 3rd, 4th, or 5th MDE (Kessing et al., 1998). These findings do not reflect risk of recurrent MDD however; as the measure of recurrence in this study was the number of hospital re-admissions for depression. Thus, interpretation of these results warrants caution as this study did not assess recurrences that may have taken place without a corresponding hospital re-admission. Therefore, these findings reflect the risk of hospital re-admission for depression rather than the risk of recurrence of depression. Thus, the research altogether suggests that marital status is not a significant indicator of risk for recurrent MDD.

**First episode characteristics. Age of onset.** Research on the relationship between age at first onset of depression and risk of recurrence has thus far been inconsistent according to a systematic review of the literature (Hardeveld et al., 2010). Several studies have not found a significant relationship between age at onset and risk of recurrence (Birmaher et al., 2004; Kovacs, Obrosky, & Sherrill, 2003; Lewinsohn, Zeiss, & Duncan, 1989; Lewinsohn, Clarke, Seeley, & Rohde, 1994), whereas several studies have found an earlier age of onset to confer a

greater risk of recurrence (Eaton et al., 2008; Giles, Jarrett, Biggs, Guzick, & Rush, 1989; Gilman, Kawachi, Fitzmaurice, & Buka, 2003; Klein et al., 1999; Zisook, et al., 2007). Interestingly, three of the four studies that did not find a significant relationship included samples of only children and/or adolescents (Birmaher et al., 2004; Kovacs et al., 2003; Lewinsohn et al., 1994). Thus, the range of ages of onset in these studies may have been too narrow for significant differences to emerge.

There are several studies suggesting an early onset associates with greater risk of recurrence (Eaton et al., 2008; Giles, Jarrett, Biggs, Guzick, & Rush, 1989; Gilman, Kawachi, Fitzmaurice, & Buka, 2003; Klein et al., 1999; Zisook, et al., 2007). The most methodologically sound investigation of this this relationship is a 23-year follow-up study of 92 persons with a single lifetime MDE (Eaton et al., 2008) with a wide range of age of onsets (10 to  $\geq 60$ ). This study reported a 4% reduction in the risk of recurrence for each additional year of age of onset. This corresponds with a 40% relative risk reduction with every ten additional years of age of onset. Thus, the best available evidence suggests an early onset confers risk of recurrent MDD and points to the importance of employing samples that represent a wide rather than narrow range of age of onset values in order to investigate age of onset as a risk factor for recurrent MDD.

***Life stress trigger.*** There has not yet been an investigation of whether presence versus absence of life stress before the first MDE may confer risk of recurrent MDD; however, the most relevant research suggests that the absence of life stress during this time is more likely to confer risk of recurrent MDD. The most consistent finding from the most relevant research studies is the finding that persons suffering a first MDE are more likely than persons suffering a recurrence to report the presence of significant life stress prior to the onset of their most recent episode

(Monroe & Harkness, 2005). Although this finding does not directly pertain to the risk of recurrent MDD due to the presence of life stress before the first MDE this finding does link persons with recurrent MDD to the absence of a precipitating life stress. A second consistent finding throughout the most relevant research depicts a diminishing association between life stress and the onset of new depressive episodes over the life course of MDD, such that each successive episode is less likely to associate with a life stress trigger (Kendler, Thornton, & Gardner, 2000). Although this finding is also an indirect depiction of the relationship between the presence of life stress before the first MDE and risk of recurrent MDD, this consistent finding links the absence of life stress with more frequent recurrences of depression.

Lastly, the results of a meta-analysis (Stroud, Davila, & Moyer, 2008) found stressful life events were more likely to precipitate first onsets than recurrences and that this trend was particularly strong among studies of older adults. Furthermore, a study of patients experiencing their first MDE (Bukh, Bock, Vinberg, Gether, & Kessing, 2011), found persons with an early onset (age  $\leq 30$ ) were less likely than persons with a later onset (age  $> 30$ ) to report a stressful life event prior to the onset of their first MDE. Thus, this third line of indirectly relevant research links the absence of a life stress trigger with an early onset and links the presence of a life stress trigger with a later onset. This final line of indirectly relevant research also supports the notion that an absence of life stress before the first MDE is more likely to confer risk of recurrent MDD on the basis of prior research indicating that an early onset is more likely to confer risk of recurrent MDD than a later onset.

***Episode duration.*** The evidence to date indicates that a lengthier first MDE does not confer greater risk of recurrent MDD. In a seven-year follow-up study of 185 6<sup>th</sup> grade students, the duration of the first MDE was not significantly different between students with a single



lifetime MDE and those with recurrent MDD (Kaminski & Garber, 2002). In addition to several additional studies that report similar findings (Kovacs et al., 1984; O'Leary, Costello, Gormley, & Webb, 2000), the research altogether suggests that the duration of the first MDE is not a risk factor for recurrent MDD.

**Childhood adversities. Parental loss.** Research indicates that experiences of parental loss during childhood, such as parental death or parental divorce, may leave a child more vulnerable to a recurrent course of MDD. The experience of parental divorce by age 16 was significantly associated with an increased risk of recurrence in a one-year follow-up of 3,617 adults (Kessler & Magee, 1993) and a large-scale population study of 3,491 adults found a significant relationship between the childhood experience of parental divorce and risk of recurrence (Wainwright & Surtees, 2002).

There are some contradictory findings in the literature; however, these differences may reflect methodological inconsistencies between studies. A longitudinal study of over one thousand adults (N=1,089) found the experience of parental divorce by age seven did increase lifetime risk of depression, but did not relate to risk of recurrence (Gilman et al., 2003). These findings may altogether indicate that the vulnerability for recurrence is greatest when the childhood experience of parental divorce occurs after age seven.

Experiencing the death of a parent during childhood appears to increase the risk for a first onset of depression but the degree to which it confers risk for recurrence of depression is unclear. A study of 3,481 men and women followed over 13 years did not find a relationship between experiencing the death of a mother before age 17 and later psychopathology; however, experiencing the death of a father before age 17 did confer greater risk of MDD in adulthood (Jacobs & Bovasso, 2009). Experiencing the death of a parent by age 16 was associated with a

greater risk of a first onset of depression by age 20 but not with risk of a first onset after age 20 or risk of a recurrence over the past year in a retrospective assessment of 331 adults with MDD (Kessler & Magee, 1993). Thus, the research suggests that experiencing the death of a parent during childhood increases the likelihood of a first onset of depression, especially a first onset before age 20; however, the experience of parental death during childhood may not confer risk of recurrence of depression.

***Parental maltreatment.*** Parental maltreatment appears to be associated with an increased risk of recurrence according to a meta-analysis of studies investigating the association of childhood maltreatment with treatment outcome and course of depression that found childhood maltreatment to confer a significantly increased risk of recurrent depression (Nanni, Uher, & Danese, 2012). In addition, two studies that were included in this meta-analysis hold particular relevance to the aims of the present investigation.

The first study of particular relevance to this investigation is a study of 865 adults that found the risk of recurrence was greater for persons with a history of childhood adversity (Danese et al., 2008). The significance of this finding is that risk of recurrence in this study reflects the odds of having two or more lifetime episodes relative to the odds of having fewer than two lifetime episodes. Thus, the risk of recurrence in this study reflects the risk of recurrent MDD associated with childhood adversity, versus having single episode MDD or not having MDD. The assessment and incorporation of individual histories of depression was necessary in order to be able to distinguish between the presence and absence of two or more lifetime MDEs. This distinction is necessary in order to conduct a valid investigation of risk for recurrent MDD and is a distinction that the majority of prior risk factor research has overlooked.

The second study of relevance to the present one is a study of 942 older adults that found having exposure to at least one adverse childhood event increased the odds of having two or more lifetime MDEs (odds ratio=2.89, 95% CI=1.83-4.57) compared to that of having zero lifetime episodes (Ritchie et al., 2009). Thus, the odds ratio in this study indicates that the odds of developing two or more lifetime MDEs compared to having zero lifetime MDEs is much greater for persons with a history of exposure to any adverse events during childhood. Thus, the available evidence suggests childhood maltreatment confers greater risk of recurrent MDD.

**Clinical conditions. Parental depression.** Research consistently indicates that children of parents with MDD have an increased risk of recurrence of depression (Birmaher et al., 2004; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013; Rohde, Lewinsohn, Klein, & Seeley, 2005). In fact, a 12-year follow-up study of risk factors for recurrent MDD in a sample of 59 adolescents with a single lifetime MDE determined that a family history of depression was a significant predictor of risk of recurrent MDD that was evident prior to the first onset of depression (Pettit et al., 2013). Further, several studies comparing persons with a family history of depression to those without a family history of depression have found a significantly increased risk of recurrence amongst those with a family history of depression (Gershon, Weissman, Guroff, Prusoff, & Leckman, 1986; Kendler, Gardner, & Prescott, 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1994).

**Comorbid anxiety disorder.** MDD is often comorbid with at least one anxiety disorder, and research indicates that anxiety disorder comorbidity confers an elevated risk of recurrence. Presence of a comorbid anxiety disorder was found to predict risk of recurrence in a sample of 244 young adults with a history of depression before age 19 (Rohde et al., 2005). A five-year

follow-up study of 163 patients with MDD found the presence of comorbid social phobia was predictive of a shorter time to recurrence and an increased risk for having a recurrence (Holma, Holma, Melartin, Rytala, & Isometsa, 2008). A study of 915 adult females with MDD also found the presence of a comorbid anxiety disorder to associate with a significantly increased risk of recurrent MDD (Cyranowski et al., 2012). The available research altogether indicates the presence of an anxiety disorder confers a significantly greater risk of recurrent MDD.

***Comorbid substance disorder.*** Substance disorders also appear to confer an increased risk of recurrent MDD. For instance, comorbid substance disorders and comorbid anxiety disorders were each independently associated with an increased risk of recurrent MDD in an 8-year follow-up of 274 young adults that had their first onset of MDD during adolescence (Lewinsohn et al., 2000). The presence of a comorbid substance disorder by age 18 was associated with a recurrent course of MDD in a retrospective assessment of 116 outpatients with depression (Alpert, Maddocks, Rosenbaum, & Fava, 1994). The available evidence suggests substance disorder comorbidity increases the risk of recurrence for persons with MDD.

**Literature summary.** The available research literature strongly suggests an increased risk of recurrent MDD associated with parental maltreatment, parental depression, anxiety disorder comorbidity, and substance disorder comorbidity. The available evidence is mildly suggestive of an increased risk of recurrent MDD associated with parental loss, especially for the parental loss experience of parental divorce. Prior research strongly suggests that sex, marital status, and duration of the first MDE are not significant indicators of risk for recurrent MDD.

Research on the relationship between age of onset and risk of recurrence is largely inconsistent; however, an early age of onset seems most likely to confer risk of recurrent MDD when the sample includes a large range of age of onset values. In contrast, an early onset appears

much less likely to confer risk of recurrence when the investigation includes a sample that possesses a limited range of age of onset values.

The degree to which risk of recurrent MDD has an association with the presence of life stress before the first MDE has not yet been the subject of investigation; however, the most relevant research indirectly links the absence of a life stress trigger before the first MDE with greater risk of recurrent MDD.

**Gaps in existing research.** There has been a considerable amount of research conducted with the aim of identifying risk factors for recurrence of depression; however, there are three limitations likely responsible for many of the inconsistent findings that currently exist along this line of research. These limitations include the following; a) recurrence (i.e., new episode onset after having at least one prior episode) and recurrent (i.e., at least two lifetime episodes) distinction; b) importance of focusing on risk factors that are evident before a first episode recovery; and c) oversight of investigating interactions between age of onset with childhood vulnerabilities.

***Recurrence and recurrent distinction.*** The overlap between a *recurrence* of depression and *recurrent* depression has led to a frequent conflation of the terms in the literature. Recurrence is an indefinite episode-specifier that represents the presence of a new MDE that occurs subsequent to the recovery from at least one prior MDE. Recurrent depression is synonymous with major depressive disorder, recurrent sub-type, thus, the term recurrent is a course specifier that distinguishes persons with single episode MDD from persons with two or more lifetime MDEs. This is an important distinction because the risk factors for a recurrent course are not necessarily the same as those that confer risk for a 3rd, 4th, or nth lifetime recurrence (Monroe & Harkness, 2011). As such, future research must ascertain the number of

lifetime episodes of depression to allow for the distinction of persons with single episode MDD from persons with recurrent MDD in order to investigate risk factors of recurrent MDD.

***Significance of first episode recovery.*** Studies frequently overlook the importance of investigating risk factors that are evident prior to the recovery from a first lifetime MDE. This is important because a risk factor for a particular condition that becomes evident only after the onset of the condition has limited value. Consider a study of risk factors related to mortality amongst persons with cancer that concludes the most significant risk factor is an autopsy report. Such a finding holds little value because the risk factor (autopsy report) for the condition (mortality) becomes evident only after the outcome of interest has taken place (death). This same logic applies to the identification of risk factors of recurrent MDD that are not possible to detect prior to the onset of at least one recurrence. In such a scenario, the individual would receive a diagnosis of recurrent MDD and no longer be at risk of recurrent MDD. Thus, in order to identify risk factors for recurrent MDD that possess clinical predictive utility, the risk factor must be evident before the onset of recurrent MDD.

To date, only two studies have accounted for these first two limitations (Eaton et al., 2008; Pettit et al., 2013). Eaton et al. (2008) found that an early age of onset was the only significant predictor of recurrent MDD; however, this study did not investigate many risk factors for recurrent MDD because this was not the primary goal of the study (Eaton et al., 2008). Pettit et al. (2013) found only parental history of recurrent MDD and the presence of minor depression before the first onset were predictive of recurrent MDD. The study by Pettit et al. (2013) may have lacked sufficient power to detect additional significant predictors of risk, as the size of the overall sample (N=59) and the single episode MDD sub-sample (N=16) were relatively small.

*Age of onset interactions.* The third limitation concerns the absence of investigations into the possibility that age of onset (for example, an early first onset versus a later first onset) may function as a meaningful interaction term for investigating risk of recurrent MDD. The concept of a time-window of risk will help to illustrate the rationale for considering the absence of interactions involving age of onset as an oversight of prior research. A time-window of risk refers to a finite length of time that likely begins in childhood and ends some time during early adulthood. This time-window of risk is initially triggered open by experiencing a particular risk factor during childhood and causes the young person to be especially vulnerable to depression in response to increasingly less severe risk factors throughout the duration of time during which his or her time-window of risk remains open.

The time-window of risk concept then relates to the belief that age of onset may prove valuable as an interaction term through the consideration of an early onset as a mechanism that prolongs the duration of time the time-window of risk remains open. This means that rather than the increased vulnerability ceasing to exist during early adulthood, the early experience of depression while the window is open extends the period of vulnerability into early adulthood and possibly beyond. Thus, the combination of a childhood-based vulnerability for depression with an early onset could create an extended period of time during which the individual is especially vulnerable to additional episodes of depression.

Consider two hypothetical examples, such as a child or adolescent that experiences maltreatment that triggers a time-window of risk. If this individual has an MDE while this window is open then the duration of time that the time-window of risk would remain open and may increase and extend, possibly into early adulthood or later. The depressive episode may intensify the emotional impact of the maltreatment, or perhaps this interaction negatively affects

the child's development in other ways (e.g., neurobiological imprint, negativistic worldview, perception of limited coping skills) that leave this person more vulnerable to future depressive episodes than persons without early childhood vulnerability and an early onset of depression. In contrast, consider a child or adolescent who experiences child maltreatment, thus triggering open the time-window of risk, but somehow manages to exit adolescence without experiencing an episode of depression, thus allowing for the time-window of risk to close. Perhaps this person developed certain coping skills, a more positive worldview, or a more resilient attitude during stressful situations after having overcome the maltreatment. In continuing through life, even if this person experiences one MDE, this person will be more likely than the first person to be able to "bounce back" and not experience future episodes.

### **Study Aims and Hypotheses**

The present study seeks to attain a greater understanding of the etiology of recurrent MDD and overcome limitations of prior research to identify valid risk factors for recurrent MDD that are evident prior to the recovery from a first lifetime episode. This study addresses these goals by using a large nationally representative sample of the non-institutionalized U.S. adult population to investigate risk factors for recurrent MDD by comparing persons with a single lifetime episode to those with recurrent MDD. In addition, this study focuses on risk factors evident prior to recovery from a first lifetime episode and investigates the degree to which age of onset may function as a valuable interaction term for assessing risk factors for recurrent MDD.

The motivation for attempting to identify valid indicators of an increased risk for recurrent MDD is that the identification of these risk factors could facilitate the development of strategies and methods for more successfully identifying, targeting, and treating persons most



likely to suffer recurrent MDD. Then, those individuals at higher risk for a recurrent course could receive services that both treat their current MDE as well as improve their chances for preventing future recurrences of depression. Thus, the purpose of this study is to investigate the research question: What risk factors for recurrent MDD (versus a single episode) can be identified prior to the recovery from a first lifetime episode? To investigate this research question, two study aims were developed, with four associated hypotheses:

**Aim 1.** The first aim of this study was to identify risk factors for recurrent course versus a single MDE course that are evident before recovery from the first MDE using a large, nationally representative dataset.

**Hypothesis 1.** To address the first study aim the first study hypothesis expects significantly greater odds of a recurrent course if age of onset is early, life stress trigger is absent, parental loss is present (parental death or parental divorce), maltreatment is present (parental abuse or parental neglect), parent depression is present, anxiety disorder is present, and substance disorder is present.

**Aim 2.** The second study aim was to investigate the degree to which age of onset and childhood-based vulnerabilities interact to produce an excess risk of recurrent MDD.

**Hypothesis 2.** The second hypothesis expects the interaction of an age of onset that is early to interact with the presence of parental depression to produce a greater risk of recurrent MDD than would be expected on the basis of their independent risk estimates.

**Hypothesis 3.** The third study hypothesis anticipates an interaction effect between an age of onset that is early and the presence of childhood parental loss that associates with an increased risk of recurrent MDD that is greater than the amount of risk expected based on their independent risk estimates.

***Hypothesis 4.*** The fourth hypothesis expects the combination of an age of onset that is early and a childhood experience of parental maltreatment to produce an excess risk of recurrent MDD compared to the expected amount of risk associated with their independent risk estimates.

## Chapter Two: Method

### Dataset

The data for the present study comes from the public-use version of the National Comorbidity Survey Replication (NCS-R) dataset (Kessler & Merikangas, 2004). The NCS-R is a face-to-face survey of English speaking adults performed between February 2001, and April 2003, in a multistage-clustered probability sample of the U.S. household population. The primary goal of the NCS-R is to provide accurate nationally representative descriptive data on the prevalence and correlates of mental disorders. An additional function of the NCS-R is to create a valuable resource for conducting provisional tests of hypotheses concerning psychosocial risk factors and the onset and course of mental disorders (Kessler & Merikangas, 2004). The dataset was downloaded from <http://www.icpsr.umich.edu/icpsrweb/CPES/studies/20240> on January 16, 2014.

Sample recruitment for the NCS-R began with a letter and a study fact brochure, followed by in-person interviewer visits where the purpose and goals of the study were explained and verbal informed content was secured. Respondents were paid \$50 for participation and the overall response rate was 70.9%. Part 1 of the interview included a core diagnostic assessment administered to all respondents (N=9,282), and part 2 included additional questions about correlates and additional disorders. Part 2 was administered to all part 1 respondents that met lifetime criteria for at least one of the disorders assessed in part 1, plus a probability subsample of additional part 1 respondents (n=5692). The part 2 sample was then weighted to adjust for the

lower selection probabilities of part 1 respondents without any mental disorders and to match the 2000 census population in the cross-classification of multiple socio-demographic and geographic characteristics. More detailed information on NCS-R sampling, design, weighting, and socio-demographic distribution is reported elsewhere (Kessler, Berglund, et al., 2004).

## **Materials**

Diagnoses of mental disorders in the NCS-R were ascertained with a modified version of the World Health Organization's (WHO) Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). The CIDI is a fully structured interview designed to allow for trained interviewers without clinical experience to estimate the general population prevalence of mental disorders according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994). An NCS clinical reappraisal study (Kessler, Abelson, et al., 2004) found generally good concordance between diagnoses based on the CIDI and those based on blinded clinical re-interviews using the Structured Clinical Interview for *DSM-IV* (First, Spitzer, Gibbon, & Williams, 2002).

The CIDI assessed the age of onset of each disorder using a question sequence designed to improve the accuracy of reporting, as evidence suggests retrospective age of onset reports are often erroneous (Simon & VonKorff, 1995). The sequence of questions began with questions that emphasized the importance of accurate responses: "Can you remember your exact age the very first time when you had [the symptom/the syndrome]?" Respondents that answered "no" provided a bound of uncertainty by indicating the earliest age at which they clearly remember having the disorder. The age of onset was then set at the upper end of this bound, as research indicates that this approach yields more plausible age of onset values than those obtained through

standard age of onset questions (Knäuper, Cannell, Schwarz, Bruce, & Kessler, 1999).

## **Sample**

There was a need to implement six inclusion and exclusion criteria to secure an appropriate sample for conducting the present investigation. The criteria for inclusion in the present study included: a) lifetime diagnosis of MDD; b) completion of both parts of the NCS-R interview; c) Age 12 or older at first onset of MDD; d) valid data for duration of first MDE; e) one or more lifetime MDEs; and f) at risk of recurrent MDD for two years or more.

Regarding the first criterion (see Figure 2), persons with a lifetime diagnosis of MDD were identified by the survey item ‘DSM-IV Major Depressive Disorder) w/ hierarchy (LifeT).’ This item identifies persons with a lifetime diagnosis of MDD according to DSM-IV criteria and excludes persons with a lifetime diagnosis of bipolar I disorder, bipolar II disorder, or sub-threshold bipolar disorder. The application of this first criterion identified 1,579 NCS-R participants with a lifetime diagnosis of MDD.

The second criterion reduced the sample to 1,548 after excluding 31 persons who did not complete both parts of the NCS-R interview. This criterion was necessary to ensure that the entire sample had the same opportunity to answer all of the survey questions because many of the risk factors under investigation are based on responses to survey items administered only in the second part of the interview. Persons were identified as having participated in both parts of the interview by the survey weight variable “NCSRWTLG”. A value greater than zero indicated the person had taken part in both parts of the interview and a value less than or equal to zero indicated the person did not take part in the second part of the interview.

Based on the third criterion, 1,417 persons remained in the sample after excluding 131 persons with a MDE before age 12. The exclusion of these persons was necessary to increase

confidence in the degree to which the maltreatment risk factor would reflect experiences and/or events that were present before the recovery from the first MDE because the maltreatment risk factor does not have a corresponding age of onset item. Thus, the application of this third criterion renders the maltreatment risk factor valid for all persons in this study except for persons with an age of first MDE onset greater than 12 that have a history of maltreatment that did not begin until after age 12 and before the first onset of depression. Thus, although there may be persons in the final sample that meet these criteria, the exclusion of persons with an onset before age 12 will significantly reduce the impact of such persons on the final study results.

The fourth criterion excluded 73 persons with missing data for the first episode duration item and reduced the number of persons in the sample to 1,344. Valid data for the first episode duration was necessary in order to calculate the age of each individual at the time of their recovery from their first MDE. The age of each individual at the time of their recovery from their first MDE was necessary in order to calculate the number of years at risk of recurrent MDD for each person in the sample. The number of years at risk of recurrent MDD reflects the difference between age at the time of the survey interview and age at the time of recovery from the first MDE and defines the sixth study criterion that restricts the sample to only persons with at least two years at risk of recurrent MDD.

Applying the fifth criterion reduced the sample to 1,150 persons by excluding 194 persons with less than one lifetime MDE. This exclusion criterion was necessary in order to create a valid sample for conducting an investigation of risk for recurrent MDD because none of these persons could have spent any time at risk for recurrent MDD. Most likely, this group was comprised of individuals that had not yet recovered from their first lifetime MDE.

Based on the sixth criterion, the size of the sample decreased to 995 after excluding 155

persons who were less than two years removed from the recovery from their first MDE. The purpose of this criterion was to improve the degree to which the characteristics of the sub-sample of persons with single episode MDD would reflect the characteristics of the population of persons with single episode MDD that will not develop recurrent MDD. Thus, the exclusion of these persons was necessary because the majority of persons less than two years removed from the recovery from their first MDE will eventually develop recurrent MDD. Thus, including these persons would have distorted the characteristics of the sub-sample of persons with single episode MDD because there was no way to distinguish the persons with single episode MDD who will suffer recurrent MDD from those who will not suffer recurrent MDD.

Further, the exclusion of persons less than two years removed from the recovery from their first MDE that reported experiencing multiple episodes during that time was necessary to support the integrity of the sub-sample of persons with recurrent MDD. The basis for this rationale stems from the close proximity of the reported recurrences with the first MDE suggests the possibility that the individual experienced one or more relapses of their first MDE and thus, did not achieve a full recovery from their first MDE and was never yet at risk of recurrent MDD.

## **Variables**

This study utilizes 18 variables including the outcome variable, course; the demographic variables of age, sex, race, marital status, and education; first episode characteristics of age of onset, life stress trigger, and episode duration; the childhood adversities of parental loss, parental divorce, parental death, parental maltreatment, parental neglect, and parental abuse; and the clinical conditions of parental depression, comorbid anxiety disorder, and comorbid substance disorder.

**Course.** The dichotomous outcome variable, *course*, indicates whether the individual has recurrent MDD or single episode MDD, and is the product of two survey items. The first item represents the number of depressive episodes for each person in their lifetime but does not include any episodes that may have occurred during the twelve months prior to the survey interview. The second item indicates whether the individual had a MDE during the twelve months prior to the date of the survey interview. If the number of lifetime episodes was two or more or if the number of lifetime episodes was one and the individual had a MDE during the twelve months prior to the date of the survey interview then course was *recurrent*, otherwise course was *single episode*.

**Demographic characteristics.** The age at the time of the survey interview was represented by *age* and was coded with the following values: *18-29*, *30-44*, *45-59*, and  $\geq 60$  years, as these are the values employed in prior research with this dataset (Kessler, Berglund, et al., 2003). *Race* was coded *White*, *Black*, *Hispanic*, and “*other*,” a category that includes Asian, Pacific Islander, American Indian, Alaska Native, and those of unknown or unspecified race. *Marital status* was coded *married*, *divorced/separated/widowed*, and *never married*. Lastly, *Education* was coded *less than high school*, *high school*, *some college*, and *college degree*.

**First episode characteristics. Age of onset.** *Age of onset* values were determined by the survey item representing the age of the individual at the time of the onset of their first lifetime MDE, *DSM-IV Major Depressive Disorder w/ hierarchy Onset*. Age of onset was *early onset* for individuals younger than 30 at the time of the onset of their first MDE and was otherwise *later onset*. Preliminary analyses were conducted (See Table 1) to determine an optimal cut point for defining an early versus later onset and different patterns arose for the age groups under 30



(overall >80% recurrent) compared to those 30 and older (overall <60% recurrent). Thus, these descriptive analyses are consistent with prior research suggesting a meaningful difference between persons with a first onset by early adulthood. There was not a third category created to represent persons with a very late onset (e.g., 40 or later). Although such an investigation would provide a valuable contribution to the literature, the sample for this study was comprised of too few persons with a first onset during midlife or later for meaningful findings to emerge for persons with a very late onset.

***Life stress trigger.*** The risk factor, *life stress trigger*, indicates whether some stressful experience brought on the first MDE and reflects two survey items. The first item asked the following question about their first episode of depression: “Was that episode brought on by some stressful experience or did it happen out of the blue?” Life stress trigger was coded *stress trigger present* for persons indicating that some stressful experience had brought on their first episode and otherwise coded *stress trigger absent* for persons with non-missing data for this item. For persons missing data for the first item, a second survey item asked the following question about the episodes of depression they had experienced over their lifetime: “How many of these episodes were brought on by some stressful experience?” Life stress trigger was coded *stress trigger present* if the number of lifetime episodes brought on by some stressful experience was equal to the number of overall lifetime episodes for the individual. The logic here is that if some stressful experience brought on all of their episodes that a stressful experience must have been present before the first episode. Life stress trigger was coded *stress trigger absent* if the number of lifetime episodes brought on by some stressful experience was equal to zero. The logic here is that some stressful experience could not have brought on the first episode if the person has never had an episode that brought on by some stressful experience. Life stress trigger was otherwise

*missing* for persons missing data for both items.

**Episode duration.** *Episode duration* was defined by the duration of first episode items and was coded *duration chronic* if the duration was twelve months or greater and otherwise coded *duration not chronic*. The DSM-IV (APA, 1994) defines a chronic MDE for adults as the presence of a MDE where the person has continuously met the criteria for a MDE for at least the past two years; however, children and adolescents have a lower threshold of twelve continuous months. Thus, this study utilizes the twelve-month threshold to define the presence of a chronic first lifetime MDE in order to employ a uniform definition for the entire sample.

**Childhood adversities. Parental loss.** *Parental loss* indicates whether the individual had experienced the loss of a parent through either parental divorce or parental death and was coded according to two constructed variables. The first constructed variable represented the childhood experience of parental divorce and the second represented the childhood experience of parental death. Parental loss was coded *parent loss present* if either parental divorce and/or parental death were present, coded *missing* if both parental divorce and parental death were missing, and otherwise coded *parent loss absent*.

*Parental divorce.* Four survey items were used to construct the item, *parental divorce*, to indicating the presence of a childhood experience of parental divorce. The first item determined whether both biological parents raised the respondent until age 16. Persons reporting no to this first item received two follow-up questions that identified the reason or reasons why both of their biological parents did not raise them until age 16. Persons who indicated the reason for reporting no to the first item was because their parents separated, divorced, or never lived together were then given a final follow-up question to ascertain the age of the individual at the time of the divorce or separation of his or her parents. Parental divorce was coded *parent divorce present* for

persons reporting no to the first item because their parents separated, divorced, or never lived together and reported that their age at the time of the divorce or separation of their parents was less than or equal to their age at the time of the onset of their first MDE. Parental divorce was *missing* if persons were missing data for all four items and otherwise coded *parent divorce absent*.

This study did not investigate the risk of recurrent MDD associated with a personal experience of divorce that occurs subsequent to the onset of a first MDE because the purpose of this study is to focus on risk factors of recurrent MDD that are evident the recovery from a first MDE. For the purposes of this study, life stress trigger reflects the type of risk associated with the personal experience of divorce for persons that deem their personal experience of divorce as a stressful experience that brought on their first MDE.

*Parental death.* The item, *parental death*, represented the childhood experience of parental loss due to the death of a parent. Parental death was constructed with the same four items used for constructing parental divorce. The first item determined whether both biological parents had raised the respondent until the age of 16. Persons reporting no to the first item that indicated in either of the first two follow-up questions that the reason was the death of his or her mother and/or father then indicated their age at the time of the death of his or her parent in the final follow-up question. Parental death was coded *parent death present* if the age of the individual at the time of the death of his or her mother and/or father was less than or equal to the age of his or her first MDE onset. Parental death was *missing* if the person was missing data for all four items and was otherwise coded *parent death absent*.

Life stress trigger also indirectly represents risk of recurrent MDD that would associate with an experience of parental death during adulthood. As the death of a parent after childhood is

an example of one type of potentially stressful experience but not a form of childhood adversity.

**Parental maltreatment.** *Parental maltreatment* indicates whether the individual had any childhood experience of parental neglect or abuse. Maltreatment was formulated on the basis of two constructed items. The first represented the childhood experience of parental neglect and the second indicated the presence of any parental abuse during childhood. Parental maltreatment was coded *maltreatment present* if parental neglect and/or parental abuse was present, coded *missing* if both parental neglect and parental abuse were missing, and otherwise coded *maltreatment absent*.

**Parental neglect.** *Parental neglect* indicates the presence of any parental neglect during childhood and represents the combination of four items that indicated the frequency with which the respondent experienced each of four different forms of parental neglect. Each of the four items was prefaced with the following statement: “How often did you have each of the following experiences during your childhood...” The first item then asked, “How often were you left alone or unsupervised when you were too young to be alone-often, sometimes, rarely, or never?” The second item asked “How often did you go without things you needed like clothes, shoes, or school supplies because your parents or caregivers spent the money on themselves-often, sometimes, rarely, or never?” The third item asked, “How often did your parents or caregivers make you go hungry or not prepare regular meals-often, sometimes, rarely, or never?” The fourth item asked, “How often did your parents or caregivers ignore or fail to get you medical treatment when you were sick or hurt-often, sometimes, rarely, or never?” Parental neglect was coded *neglect present* for persons who reported a frequency greater than never (rarely, sometimes, or often) for any of the parental neglect items. Parental neglect was *missing* for persons missing data for all four items and otherwise coded *neglect absent*.

*Parental abuse.* *Parental abuse* reflects the presence of any form of physical abuse from a parent during childhood. There were five items used to construct this item. The first item asked, “When you were growing up, how often did someone in your household do any of the things (on List A) to you - often, sometimes, rarely, or never?” List A was comprised of the following: “pushing, grabbing or shoving”, “slapping, hitting or spanking”, and “throwing something.” The second through fifth items asked who was responsible for the acts of physical abuse. Parental abuse was coded *abuse present* if the individual reported experiencing physical abuse at a frequency greater than never (rarely, sometimes, or often) and indicated that the person responsible for the physical abuse experience was a mother or father. Parental abuse was *missing* if the individual was missing data for all five items and was otherwise *abuse absent*. Although the risk associated with more severe forms of physical abuse may be different from the risk associated with less physically threatening experiences of parental abuse, this study does not investigate the risk associated with the more severe experiences of abuse because the public use version of the NCS-R dataset does not provide the data for these items.

**Clinical conditions. Parental depression.** The risk factor *parental depression* reflects seven survey items and indicates whether the individual has at least one parent with depression. The first survey item asked “During the years you were growing up, did [(woman who raised respondent)] ever have periods lasting two weeks or more where she was sad or depressed most of the time?” The second survey item asked “During the years you were growing up, did [(man who raised respondent)] ever have periods lasting two weeks or more where he was sad or depressed most of the time?” The third item asked whether the individual had a close relative with depression and this item was linked to the fourth through seventh survey items where the

individual identified which of their close relatives have had depression. Parental depression was coded *parent depression present* if the person answered yes to at least one of the first two items or answered yes to the third item and indicated one of their close relatives with depression was a mother or father. Parental depression was coded *missing* if the individual was missing data for all seven items and was otherwise coded *parent depression absent*.

***Comorbid anxiety disorder.*** *Comorbid anxiety disorder* indicates whether any anxiety disorders were present before the recovery from the first MDE and was defined according to 20 survey items based on the CIDI (Kessler & Üstün, 2004). The first ten survey items indicate whether the individual has had any of the following anxiety disorders in their lifetime; agoraphobia with panic disorder, agoraphobia without panic disorder, anorexia nervosa, binge-eating disorder, bulimia nervosa, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, social phobia, and specific phobia. The remaining ten items were indicators of the age of first onset for each of the ten corresponding lifetime diagnostic items. Comorbid anxiety disorder was coded *anxiety disorder present* for persons that had at least one anxiety disorder with an age of onset that was less than or equal to the age of the individual at the time of the onset of their first MDE. Comorbid anxiety disorder was *missing* for persons missing data for all of the anxiety disorder items and otherwise coded *anxiety disorder absent*.

***Comorbid substance disorder.*** *Comorbid substance disorder* indicates the presence of any substance disorder before recovery from the first MDE and was developed using eight survey items based on the CIDI (Kessler & Üstün, 2004). Four of the items were lifetime diagnosis indicators for the following substance use disorders; alcohol abuse, alcohol dependence, drug abuse, and drug dependence. The fifth through eighth items reflected the corresponding age of onset values for the four diagnostic items. Comorbid substance disorder

was coded *substance disorder present* for persons that had at least one substance disorder with an age of onset that was less than or equal to the age of the individual at the time of the onset of their first MDE. Comorbid substance disorder was *missing* for persons missing data for all eight items and was otherwise coded *substance disorder absent*.

## **Analysis**

Comparisons of all variables by course were assessed using chi-square tests and a series of logistic regression analyses were conducted to test each of the study hypotheses.

**Hypothesis 1.** To test the first hypothesis, separate multivariable logistic regression analyses were performed for each of the twelve risk factors (see detailed descriptions of variables and values in Figure 3). Each analysis included the same outcome variable, course, and the same demographic control variables of age, sex, and race. Marital status and education were not included as control variables because these variables reflect the status of the individual at the time of the survey interview, rather than the time of their first MDE. Age was included as a covariate in these models even though it reflects the status of each individual at the time of the survey interview because it is a valid indicator of birth year and subsequently, provides a valid method for limiting the risk of possible cohort effects confounding the study results.

Separate multiple logistic regression analyses were then performed to assess the risk of recurrent MDD associated with each of the twelve following risk factors; age of onset, life stress trigger, episode duration, parental loss, parental divorce, parental death, parental maltreatment, parental neglect, parental abuse, parental depression, comorbid anxiety disorder, and comorbid substance disorder. Age, sex, race, and one risk factor variable were entered simultaneously into each of the twelve logistic regression models and adjusted odds ratio estimates with 95%

confidence intervals assessed the independent risk of recurrent MDD for each twelve risk factors. A risk factor was defined as significant if the adjusted odds ratio was greater than one and the corresponding 95% confidence interval did not include one.

Alternate logistic regression analyses were conducted to compare the findings of the test of Hypothesis 1 with the results of logistic regression models conducting the same analyses with the absence of any control variables (uncontrolled model) and with the presence of every variable (fully controlled model). For the uncontrolled analyses, separate bivariate logistic regression analyses were conducted to estimate the individual risk of recurrent MDD for each of the control variables and risk factor variables. Except for parental divorce, parental death, parental neglect, and parental abuse, all variables were entered simultaneously into one logistic regression model. This model did not include parental divorce and parental death because these risk factors were represented by parental loss; likewise, parental neglect and parental abuse were represented by parental maltreatment.

**Hypothesis 2.** A multivariable logistic regression model was developed and relative excess risk due to interaction (RERI; Rothman, 1986) assessed the second hypothesis regarding the interaction of parental depression with age of onset. The logistic regression model was set up with the same outcome variable (course) and the same covariates (age, sex, race) as the models developed to test the first hypothesis. The risk factor for this hypothesis test was the interaction of parental depression with age of onset and this interaction was represented by a categorical variable with the absence of risk representing the reference level for the interaction variable (see Figure 3). This categorical interaction variable was represented in a multiple logistic regression model by three indicator variables such that the reference level represented the interaction of parental depression absent with later onset. These indicator variables were simultaneously



entered into the logistic regression model along with age, sex, and race.

To determine the significance of the interaction between parental depression and age of onset the maximum likelihood estimates and covariation matrix results from the multivariable logistic regression analysis were then used to compute RERI and the corresponding 95% confidence intervals (Hosmer & Lemeshow, 1992). The calculation of RERI was necessary because the logistic model operates on a multiplicative scale and an interaction effect is a departure from additivity. Thus, RERI offers a method for estimating the amount of excess additive risk associated with the interaction of two variables operating on a multiplicative scale (Andersson et al., 2005). Therefore, RERI and 95% confidence intervals were calculated to estimate the additive risk associated with the interactions assessed by the remaining study hypotheses. The RERI for the interaction of parent depression with age of onset was calculated with the equation described by Rothman (1986):

$$RERI_{pd\_X\_eo} = e^{\beta^{pd\_only} + \beta^{eo\_only} + \beta^{pd\_X\_eo}} - e^{\beta^{pd\_only}} - e^{\beta^{eo\_only}} + 1.$$

The delta method described by Hosmer & Lemeshow (1992) and further outlined for implementation with Statistical Analysis Software (SAS) by Lundberg et al. (1996) was used to calculate the 95% confidence interval for RERI. A RERI greater than zero indicates excess risk associated with the interaction and RERI equal to zero indicates a complete absence of any interaction effect. The interaction of parental depression and age of onset was defined as significant if RERI is greater than zero and the 95% confidence interval does not include zero.

**Hypothesis 3.** A multivariable logistic regression model was then developed to test the third hypothesis regarding the interaction of parental loss with age of onset. The logistic regression model was set up in the same fashion as the model for testing the interaction of parental depression and age of onset except the interaction term was defined by the appropriate

interaction variables (see Figure 3). The categorical variable was then simultaneously entered into a logistic regression model along with age, sex, and race, and was represented by three indicator variables such that with the reference level represented the interaction of parental loss absent with later onset. RERI for the interaction of parental loss with age of onset was calculated as:

$$RERI_{pl\_X\_eo} = e^{\beta^{pl\_only} + \beta^{eo\_only} + \beta^{pl\_X\_eo}} - e^{\beta^{pl\_only}} - e^{\beta^{eo\_only}} + 1 .$$

The 95% confidence interval was calculated using the same method as was done for the interaction of parental depression and age of onset. The interaction of parental loss and age of onset was defined as significant if RERI is greater than zero and the corresponding 95% confidence interval does not include zero.

**Hypothesis 4.** A multivariable logistic regression model tested the hypothesis that the interaction of parental maltreatment and age of onset would confer excess risk for recurrent MDD. The model for this interaction was the same as the models from the first two interaction analyses except for the categorical interaction term (see Figure 3). Age, sex, and race were simultaneously entered into the regression model along with the three indicator variables for the categorical interaction term and RERI was calculated as:

$$RERI_{pm\_X\_eo} = e^{\beta^{pm\_only} + \beta^{eo\_only} + \beta^{pm\_X\_eo}} - e^{\beta^{pm\_only}} - e^{\beta^{eo\_only}} + 1 .$$

The 95% confidence intervals and significance of RERI was the same for this interaction as in the first two interaction analyses. All analyses were performed using SAS version 9.3.

Table 1. Distribution of age of onset values by course.

Age of Onset	Course			
	Recurrent		Single Episode	
	N	Row%	N	Row%
12-15	166	96.0%	7	4.0%
16-19	140	84.3%	26	15.7%
20-24	114	74.5%	39	25.5%
25-29	84	73.7%	30	26.3%
30-34	70	63.1%	41	36.9%
35-39	54	54.5%	45	45.5%
40-44	36	45.0%	44	55.0%
45-49	29	53.7%	25	46.3%
50-54	10	52.6%	9	47.4%
55-59	7	70.0%	3	30.0%
60-64	5	55.6%	4	44.4%
65-69	3	75.0%	1	25.0%
70-74	0	0.0%	0	100.0%
75-79	0	0.0%	1	100.0%
80-84	0	0.0%	2	100.0%
All	718	72.2%	277	27.8%

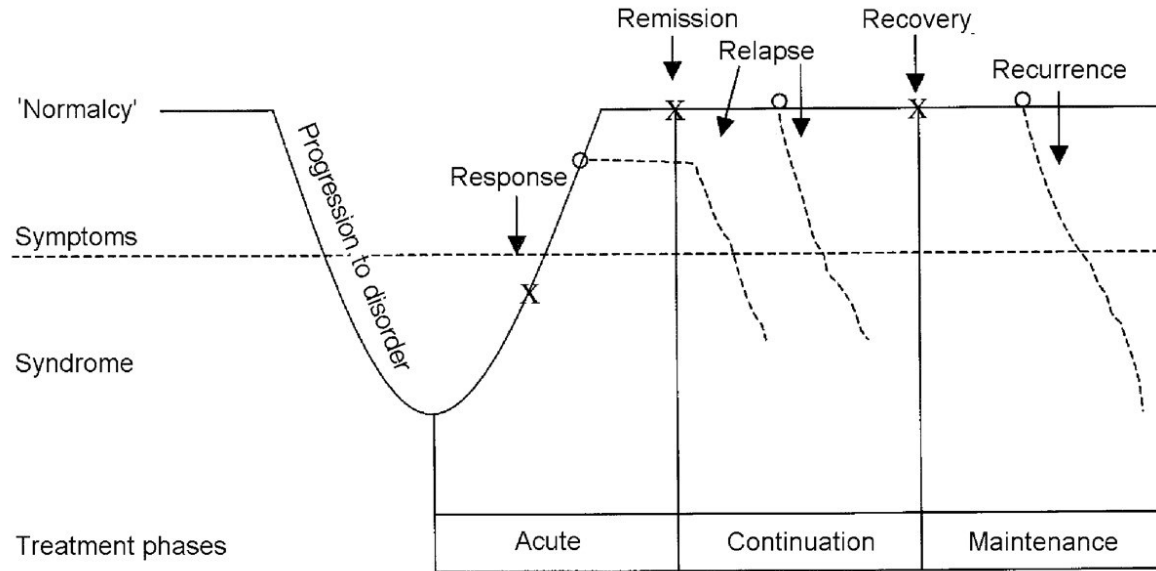


Figure 1. Episode (“Syndrome”), remission, recovery, relapse and recurrence of depression. From Kupfer, D. J. (1991). Long-term treatment of depression. *Journal of Clinical Psychiatry*, 52 Suppl, 28-34.

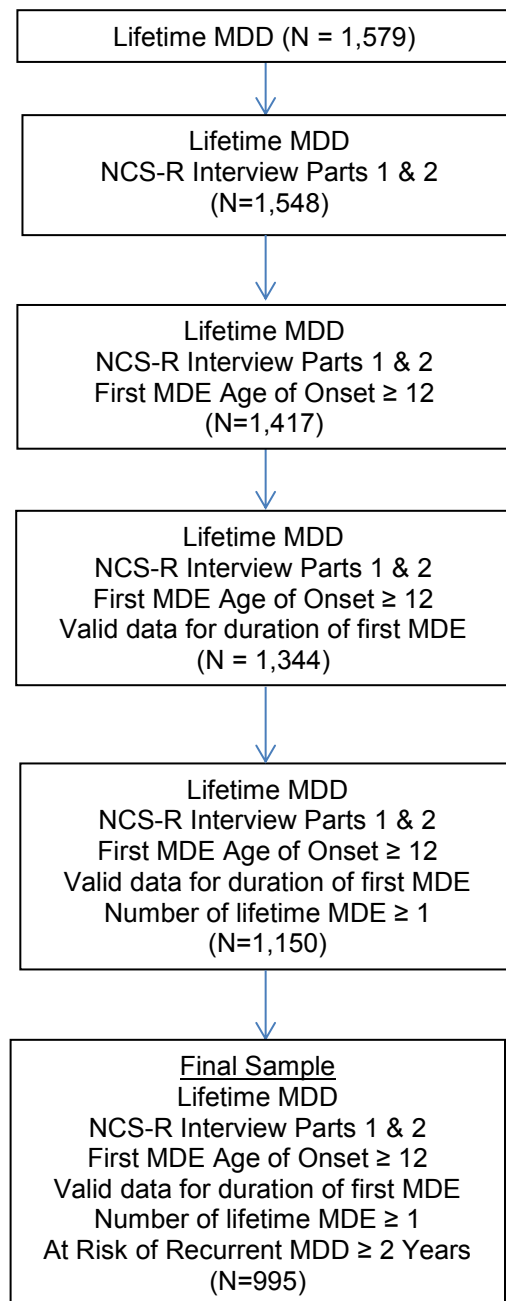


Figure 2. Flow-chart demonstrating impact of study exclusion criteria on final sample.

- Outcome
  - Course [0 = Single Episode, 1 = Recurrent]
- Control variables
  - Age
    - Agevar1 [0 = Otherwise, 1 = 18-29]
    - Agevar2 [0 = Otherwise, 1 = 30-44]
    - Agevar3 [0 = Otherwise, 1 = 45-59]
  - Sex
    - Sex [0 = Male, 1 = Female]
  - Race
    - Racevar1 [0 = Otherwise, 1 = Black]
    - Racevar2 [0 = Otherwise, 1 = Hispanic]
    - Racevar3 [0 = Otherwise, 1 = Other]
- Hypothesis 1
  - Regression model for testing each of the twelve risk factors
    - Course = Risk factor \* Age \* Sex \* Race
  - Risk Factors
    - Age-of-Onset [0 = Later, 1 = Early]
    - Life Stress Trigger [0 = Stress trigger present, 1 = Stress trigger absent]
    - Episode Duration [0 = Duration not chronic, 1 = Duration chronic]
    - Parental Loss [0 = Parent loss absent, 1 = Parent loss present]
    - Parental Divorce [0 = Parent divorce absent, 1 = Parent divorce present]
    - Parental Death [0 = Parent death absent, 1 = Parent death present]
    - Parental Maltreatment [0 = Maltreatment absent, 1 = Maltreatment present]
    - Parental Neglect [0 = Neglect absent, 1 = Neglect present]
    - Parental Abuse [0 = Abuse absent, 1 = Abuse present]
    - Parental Depression [0 = Parent depression absent, 1 = Parent depression present]
    - Comorbid Anxiety Disorder [0 = Anxiety disorder absent, 1 = Anxiety disorder present]
    - Comorbid Substance Disorder [0 = Substance disorder absent, 1 = Substance disorder present]
- Hypothesis 2
  - Interaction Terms
    - PD\_only [0 = Otherwise, 1 = Parent depression present & Later]
    - EO\_only [0 = Otherwise, 1 = Parent depression absent & Early]
    - PD\_X\_EO [0 = Otherwise, 1 = Parent depression present & Early]
  - Regression Model
    - Course = PD\_only \* EO\_only \* PD\_X\_EO \* Age \* Sex \* Race
- Hypothesis 3
  - Interaction Terms
    - PL\_only [0 = Otherwise, 1 = Parent loss present & Later]
    - EO\_only [0 = Otherwise, 1 = Parent loss absent & Early]
    - PL\_X\_EO [0 = Otherwise, 1 = Parent loss present & Early]
  - Regression Model
    - Course = PL\_only \* EO\_only \* PL\_X\_EO \* Age \* Sex \* Race
- Hypothesis 4
  - Interaction Terms
    - PM\_only [0 = Otherwise, 1 = Maltreatment present & Later]
    - EO\_only [0 = Otherwise, 1 = Maltreatment absent & Early]
    - PM\_X\_EO [0 = Otherwise, 1 = Maltreatment present & Early]
  - Regression Model
    - Course = PM\_only \* EO\_only \* PM\_X\_EO \* Age \* Sex \* Race

Figure 3. Components of the logistic regression models developed to test each of the four study hypotheses.

## Chapter Three: Results

### Sample Characteristics

The final sample (N = 995) had a mean age of  $43.6 \pm 0.59$ , was mostly female (63.5%), White (79.5%), married (55.1%), and had some college experience without a college degree (31%). Sample characteristics stratified by course are presented in Table 2. Descriptively, a greater prevalence of recurrent MDD was found for the youngest age group (79.7%), other race (81.7%), never married (84.7%), and those with less than a high school education (82.3%). The risk factors that were most prevalent amongst those with a recurrent course were early onset (84.8%), parent divorce present (81.5%), stress trigger absent (81%), and anxiety disorder present (79.5%).

### Hypothesis 1

Results of the age, sex, and race adjusted logistic regression analyses tests of hypothesis 1 are presented in Table 3. The results support hypothesis 1 for early onset (OR=5.88; 95% CI=3.89, 8.88), stress trigger absent (OR=1.68; 95% CI=1.15, 2.46), parent loss present (OR=1.70; 95% CI=1.04, 2.78), maltreatment present (OR=1.72; 95% CI=1.36, 2.16), parent depression present (OR=1.76; 95% CI=1.26, 2.47), and anxiety disorder present (OR=1.96; 95% CI=1.51, 2.55). The only hypothesized risk factor that was not statistically significant at  $p < 0.05$  was comorbid substance disorder, for which the results approached significance (OR=1.47; 95% CI=0.98, 2.22).

For purposes of comparison, the pattern of results from the unadjusted and the fully adjusted models were mostly similar to the results of the age, sex, and race adjusted models. The first discrepancy between the models was the finding that a younger age at the time of the survey interview was associated with a greater risk of recurrent MDD in the unadjusted model; however, the oldest age at the time of the survey interview was associated with the greatest risk of recurrent MDD according to the fully adjusted model. This is likely a spurious byproduct of the fully adjusted model including two age variables for each person. The second and final discrepancy between models was the finding that parental depression was only marginally significant for the fully adjusted model but was statistically significant in the unadjusted model.

## **Hypothesis 2**

Table 4 presents the results of the assessment of the interaction of parental depression with age of onset. The RERI estimate for the interaction of parent depression with age of onset was 5.81 (95% CI= 0.41 to 11.2) and these results are statistically significant because the confidence interval does not include zero. This means that the interaction of parent depression that is present with an age of onset that is early confers 5.81 higher odds for recurrent MDD than the odds of recurrent MDD for persons with an early onset and parent depression absent combined with the odds of recurrent MDD for persons with a later onset and parent depression present.

The odds ratios and corresponding 95% confidence intervals for the four levels of interaction between parent depression and age of onset reflect the odds of recurrent MDD for each level in comparison with the reference group of having a later onset and no parent depression. The results for each level of interaction between age of onset and parental depression



were as follows: early onset without parent depression (4.83; 3.12-7.47), later onset with parent depression (1.38; 0.87-2.20), and early onset with parent depression (11.0; 6.31-19.3). This indicates that the odds of recurrent MDD for an early onset without parent depression are 4.83 times the odds of recurrent MDD for a later onset without parent depression. Likewise, the odds of recurrent MDD for a later onset with parent depression are 1.38 times the odds for those with a later onset without parent depression, and the odds of recurrent MDD for those with an early onset and parent depression is 11 times the odds of recurrent MDD for those with a later onset without parent depression.

The measure of interaction on the multiplicative scale, the ratio of odds ratios, was 1.65 (95% CI=0.83-3.3). This indicates that the joint effect on the odds ratio scale of parental depression and an early onset is greater than the product of the effects of a later onset with parent depression and an early onset without parent depression. Thus, there was a positive interaction on the multiplicative scale found for the presence of an early onset with parental depression.

### **Hypothesis 3**

Table 5 presents the results of the analyses assessing the interaction of parental loss with age of onset. The RERI estimate for the interaction of parental loss with age of onset was 6.22 (95% CI= -3.3 to 15.7). This indicates that the interaction of a childhood experience of parental loss with an early age of onset confers 6.22 higher odds of a recurrent course than the combined odds of a recurrent course for persons with an early onset but no parental loss and persons with a later onset and parental loss. Interpretation of these results warrants caution however, as the confidence interval includes zero, meaning that the RERI for this interaction is not statistically significant.

The odds ratios and corresponding 95% confidence intervals for the four levels of interaction between parental loss and age of onset reflect the odds of a recurrent course in comparison with the odds of a recurrent course for the reference group of having a later onset without parental loss. The findings and 95% confidence intervals were: early onset without parental loss (5.54; 3.70-8.30), later onset with parental loss (1.43; 0.65-3.19), and early onset with parental loss (12.2; 5.08-29.3). These findings indicate the odds of recurrent MDD for persons with an early onset without parental loss are 5.54 times the odds of recurrent MDD for those with a later onset without parental loss. The odds of recurrent MDD for those with a later onset and parental loss are 1.43 times the odds of recurrent MDD for those with a later onset but no parental loss. The interaction of an early onset with parental loss confers odds of recurrent MDD that are 11 times the odds of recurrent MDD for those with a later onset and no parental loss.

The assessment of the interaction of age of onset with parental loss on the multiplicative scale was 1.54 (95% CI=0.52 to 4.5). This indicates that the combined effect of an early onset with parental loss on the odds ratio scale is greater than the product of the effects for having parental loss with a later onset and an early onset without parental loss. Thus, these findings indicate a positive interaction between an early age of onset and the presence of parental loss.

#### **Hypothesis 4**

Table 6 presents the results of the assessment of the interaction of maltreatment with age of onset. RERI estimate for the interaction of maltreatment with age of onset was 3.63 (95% CI=-0.83 to 8.1). This indicates that this interaction confers odds of recurrent MDD that are 3.63 greater than the combined odds for having recurrent MDD for an early onset without

maltreatment and a later onset with maltreatment. The RERI estimate for this interaction was not statistically significant; however, the confidence interval did not fall far below zero indicating that the RERI was nearly statistically significant.

The odds ratios and corresponding 95% confidence intervals for the interaction of maltreatment with age of onset are in comparison to the reference group of having a later onset without maltreatment. These findings for the interaction of age of onset with maltreatment were as follows: early onset without maltreatment (5.65; 3.59-8.90), later onset with maltreatment (1.66; 1.18-2.34), and early onset with maltreatment (9.94; 5.69-17.3). These results indicate that the odds of recurrent MDD for an early onset without maltreatment are 5.65 times the odds of recurrent MDD for a later onset without maltreatment. The odds of recurrent MDD for a later onset with maltreatment are 1.66 times the odds of recurrent MDD for a later onset without maltreatment. The odds of recurrent MDD for an early onset with maltreatment are 10 times the odds of recurrent MDD for a later onset without maltreatment.

The interaction of age of onset with maltreatment on the multiplicative scale was 1.06 (95% CI=0.57 to 2.0), indicating that the combined effect of an early onset with maltreatment on the multiplicative scale is not significantly different from the product of the effects of maltreatment with a later onset and an early onset without maltreatment. Thus, these findings indicate the absence of an interaction effect between an early age of onset and the presence of maltreatment on the multiplicative scale.

Table 2. Demographic and risk factor characteristics presented by course.

		Recurrent (N=718)			Single Episode (N=277)			P-value
		Freq	Weight	Row %	Freq	Weight	Row %	
Age	18 to 29	154	94	79.7%	42	24	20.3%	0.06
	30 to 44	261	158	74.4%	99	54	25.6%	
	45 to 59	218	147	71.3%	86	59	28.7%	
	60+	85	51	61.9%	50	31	38.1%	
Sex	Female	488	290	73.9%	182	103	26.1%	0.45
	Male	230	159	70.7%	95	66	29.3%	
Race	White	555	359	73.1%	214	132	26.9%	0.47
	Black	55	27	70.7%	21	11	29.3%	
	Hispanic	63	38	66.4%	29	19	33.6%	
	Other	45	25	81.7%	13	6	18.3%	
Marital Status	Married	381	232	68.2%	172	108	31.8%	<.01
	Never Married	153	105	84.7%	31	19	15.3%	
	Divorce/Separate/Widow	184	113	73.1%	74	41	26.9%	
Education	Less than High School	86	59	82.3%	16	13	17.7%	0.34
	High School	190	129	70.3%	93	55	29.7%	
	Some College	238	142	74.1%	78	49	25.9%	
	College Degree	204	120	69.7%	90	52	30.3%	
First Episode Characteristics	Early Onset	504	312	84.8%	102	56	15.2%	<.01
	Stress Trigger Absent	143	84	81.0%	33	20	19.0%	
	Duration Chronic	172	104	75.2%	61	34	24.8%	
Childhood Adversities	Parental Loss <sup>a</sup>	169	107	81.0%	45	25	19.0%	<.05
	Parental Divorce	132	84	81.5%	33	19	18.5%	
	Parental Death	37	23	79.0%	12	6	21.0%	
	Maltreatment <sup>b</sup>	380	241	78.2%	105	67	21.8%	
	Parental Neglect	208	134	79.2%	54	35	20.8%	
	Parental Abuse	291	186	79.2%	76	49	20.8%	
Clinical Conditions	Parental Depression	325	203	79.0%	82	54	21.0%	<.01
	Anxiety Disorder	407	255	79.5%	105	66	20.5%	
	Substance Disorder	121	84	78.6%	35	23	21.4%	
Total Sample		718	449	72.7%	277	169	27.3%	

<sup>a</sup> Parent loss represents presence of parent divorce and/or parent death.

<sup>b</sup> Maltreatment represents presence of parent neglect and/or parent abuse.

Table 3. Risk of recurrent course for twelve possible risk factors.

		<u>Unadjusted Model</u>		<u>Age, Sex, &amp; Race Adjusted Model</u>		<u>Complete Adjusted Model</u>	
		<u>OR</u>	<u>(95% CI)</u>	<u>OR</u>	<u>(95% CI)</u>	<u>OR</u>	<u>(95% CI)</u>
Age	18 to 29	2.41	(1.28; 4.55)*	N/A	N/A	0.35	(0.14; 0.88)*
	30 to 44	1.79	(0.90; 3.53)	N/A	N/A	0.81	(0.35; 1.87)
	45 to 59	1.53	(0.72; 3.22)	N/A	N/A	1.17	(0.53; 2.56)
	60+	1.00	(Ref ; Ref)	N/A	N/A	1.00	(Ref ; Ref)
Sex	Female	1.17	(0.77; 1.78)	N/A	N/A	1.17	(0.75; 1.84)
	Male	1.00	(Ref ; Ref)	N/A	N/A	1.00	(Ref ; Ref)
Race	White	1.00	(Ref ; Ref)	N/A	N/A	1.00	(Ref ; Ref)
	Black	0.89	(0.54; 1.47)	N/A	N/A	0.73	(0.39; 1.36)
	Hispanic	0.73	(0.31; 1.70)	N/A	N/A	0.65	(0.27; 1.55)
	Other	1.64	(0.92; 2.94)	N/A	N/A	1.31	(0.62; 2.80)
Marital Status	Married	1.00	(Ref ; Ref)	1.00	(Ref ; Ref)	1.00	(Ref ; Ref)
	Never Married	2.58	(1.70; 3.92)*	2.55	(1.57; 4.14)*	2.62	(1.53; 4.50)*
	Divorce/Separate/Widow	1.27	(0.91; 1.76)	1.32	(0.92; 1.90)	1.40	(0.98; 2.00)
Education	Less than High School	2.02	(0.99; 4.10)	2.48	(1.37; 4.47)*	2.15	(1.21; 3.83)*
	High School	1.03	(0.64; 1.67)	1.13	(0.69; 1.83)	1.33	(0.94; 1.88)
	Some College	1.25	(0.68; 2.29)	1.29	(0.73; 2.28)	1.45	(0.93; 2.26)
	College Degree	1.00	(Ref ; Ref)	1.00	(Ref ; Ref)	1.00	(Ref ; Ref)
First Episode Characteristics	Early Onset	4.57	(3.46; 6.04)*	5.88	(3.89; 8.88)*	5.59	(3.72; 8.40)*
	Stress Trigger Absent	1.71	(1.17; 2.50)*	1.68	(1.15; 2.46)*	1.74	(1.09; 2.78)*
	Duration Chronic	1.18	(0.80; 1.75)	1.24	(0.84; 1.84)	1.18	(0.76; 1.84)
Childhood Adversities	Parental Loss <sup>a</sup>	1.78	(1.08; 2.95)*	1.70	(1.04; 2.78)*	1.67	(1.07; 2.62)*
	Parental Divorce	1.81	(1.00; 3.26)*	1.70	(0.95; 3.05)	N/A	N/A
	Parental Death	1.43	(0.68; 3.03)	1.43	(0.67; 3.02)	N/A	N/A
	Maltreatment <sup>b</sup>	1.73	(1.38; 2.17)*	1.72	(1.36; 2.16)*	1.52	(1.14; 2.02)*
	Parental Neglect	1.60	(1.20; 2.13)*	1.62	(1.23; 2.14)*	N/A	N/A
	Parental Abuse	1.75	(1.33; 2.31)*	1.75	(1.33; 2.30)*	N/A	N/A
Clinical Conditions	Parental Depression	1.78	(1.27; 2.50)*	1.76	(1.26; 2.47)*	1.43	(0.96; 2.14)
	Anxiety Disorder	2.06	(1.61; 2.62)*	1.96	(1.51; 2.55)*	1.81	(1.38; 2.38)*
	Substance Disorder	1.46	(0.91; 2.37)	1.47	(0.98; 2.22)	1.22	(0.82; 1.83)

<sup>a</sup> Parent loss represents presence of parent divorce and/or parent death.

<sup>b</sup> Maltreatment represents presence of parent neglect and/or parent abuse.

\* p < .05.

Table 4. Risk of recurrent course for the interaction of age of onset with parental depression.

		Age of Onset				Odds Ratio (95%CI) for Early Onset within strata of Parental Depression
		Later Onset		Early Onset		
		N Single MDE/ Recurrent	Odds Ratio (95%CI)	N Single MDE/ Recurrent	Odds Ratio (95%CI)	
Parental Depression	Absent	73 / 78	1.0	41 / 163	4.83 (3.12-7.47)	5.69 (3.76-8.61)
	Present	39 / 57	1.38 (0.87-2.20)	15 / 146	11.0 (6.31-19.3)	8.74 (2.31-33.1)
Odds Ratio (95%CI) for Parent Depression within strata of Age of Onset			1.41 (0.89-2.25)		2.29 (1.37-3.83)	
Measure of interaction on additive scale: Relative Excess Risk due to Interaction (95%CI)					5.81 (0.41-11.2)	
Measure of interaction on multiplicative scale: Ratio of Odds Ratios (95%CI)					1.65 (0.83-3.30)	
ORs are adjusted for age, sex, and race						

Table 5. Risk of recurrent course for the interaction of age of onset with parental loss.

		Age of Onset				Odds Ratio (95%CI) for Early Onset within strata of Parental Loss
		Later Onset		Early Onset		
		N Single MDE/ Recurrent	Odds Ratio (95%CI)	N Single MDE/ Recurrent	Odds Ratio (95%CI)	
Parental Loss <sup>a</sup>	Absent	96 / 111	1.0	48 / 231	5.54 (3.70-8.30)	5.69 (3.76-8.61)
	Present	17 / 26	1.43 (0.65-3.19)	8 / 81	12.2 (5.08-29.3)	8.74 (2.31-33.1)
Odds Ratio (95% CI) for Parent Loss within strata of Age of Onset			1.40 (0.64-3.08)	2.44 (1.20-4.94)		
Measure of interaction on additive scale: Relative Excess Risk due to Interaction (95%CI)					6.22 (-3.30-15.7)	
Measure of interaction on multiplicative scale: Ratio of Odds Ratios (95%CI)					1.54 (0.52-4.50)	
Odds Ratios are adjusted for age, sex, and race						

<sup>a</sup> Parental loss represents presence of parental divorce and/or parental death.

Table 6. Risk of recurrent course for the interaction of age of onset with maltreatment.

		Age of Onset				Odds Ratio (95%CI) for Early Onset within strata of Maltreatment
		Later Onset		Early Onset		
		N Single MDE/ Recurrent	Odds Ratio (95%CI)	N Single MDE/ Recurrent	Odds Ratio (95%CI)	
Maltreatment <sup>a</sup>	Absent	66 / 64	1.0	35 / 144	5.65 (3.59-8.90)	6.71 (3.98-11.3)
	Present	46 / 73	1.66 (1.18-2.34)	21 / 168	9.94 (5.69-17.3)	5.17 (2.60-10.3)
Odds Ratio (95% CI) for Maltreatment within strata of Age of Onset			1.67 (1.16-2.39)	1.78 (1.12-2.83)		
Measure of interaction on additive scale: Relative Excess Risk due to Interaction (95%CI)					3.63 (-0.83-8.10)	
Measure of interaction on multiplicative scale: Ratio of Odds Ratios (95%CI)					1.06 (0.57-2.00)	
Odds Ratios are adjusted for age, sex, and race						

<sup>a</sup> Maltreatment represents presence of parental neglect and/or parental abuse.



## Chapter Four: Discussion

This study has two main sets of findings. This study was successful in achieving the first study aim of utilizing a large nationally representative dataset to identify risk factors for recurrent MDD that are present before the recovery from a first lifetime episode. Consistent with the first hypothesis, a greater risk of recurrent MDD was found for the presence of a MDE before age 30, absence of a life stress trigger before the first episode onset, having a childhood experience of parental loss or maltreatment, having a parent with depression, and having a comorbid anxiety disorder. The results indicated that having a comorbid substance disorder did associate with an increased risk for recurrent MDD; however, this finding only approached a statistically significant level.

This study was also successful in achieving the second study aim of investigating risk for recurrent MDD associated with the interaction of an early onset of depression with a childhood-based vulnerability for depression. The second set of results was generally supportive of the remaining study hypotheses, as the findings for all of the interaction analyses indicated an excess risk for recurrent MDD due to the interaction of having an early onset and childhood vulnerability (See Figure 4). There is an excess risk of recurrent MDD that results from an interaction between having a parent with depression and having an onset of depression before age 21. Similar interaction patterns for parental loss and childhood maltreatment were observed, although the results for these interactions were not statistically significant.

Results for the first hypothesis are largely consistent with the findings of prior research. For instance, the finding that an early age of onset confers an increased risk of recurrence is in agreement with the findings of earlier studies that assessed this relationship (Eaton et al., 2008; Giles, Jarrett, Biggs, Guzick, & Rush, 1989; Gilman, Kawachi, Fitzmaurice, & Buka, 2003; Klein et al., 1999; Zisook, et al., 2007). The presence of childhood parental loss was associated with an increased risk of recurrent MDD, and this corroborates the findings from a study of the relationships among parental loss, recurrence of depression, and severity of life stress prior to the onset of the most recent MDE (Slavich, Monroe, & Gotlib, 2011). This finding is also consistent with prior research that found an increased risk of recurrent MDD associated with the experience of parental divorce before age 16 (Kessler & Magee, 1993; Wainwright & Surtees, 2002).

Childhood maltreatment was significantly associated with an increased risk of a recurrent course of depression in this study, and this is consistent with the findings of a meta-analysis of earlier studies of this relationship (Nanni, Uher, & Danese, 2012). The increased risk of recurrent MDD for persons with one or more parents with a history of depression replicates the findings of numerous studies of this relationship (Birmaher et al., 2004; Gershon, Weissman, Guroff, Prusoff, & Leckman, 1986; Kendler, Gardner, & Prescott, 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1994; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013; Rohde, Lewinsohn, Klein, & Seeley, 2005; Sullivan, Neale, & Kendler, 2000). The increased risk of recurrent MDD associated with anxiety disorder comorbidity also is consistent with prior research (Cyranowski et al., 2012; Holma, Holma, Melartin, Rytsala, & Isometsa, 2008; Lewinsohn et al., 2000). The nearly significant findings for the relationship between having a substance use disorder and

recurrent MDD risk are also consistent with the findings of prior research (Alpert, Maddocks, Rosenbaum, & Fava, 1994; Davis et al., 2010; Lewinsohn et al., 2000).

The findings for an early age of onset confirm the earlier speculation and extend the research literature in two ways. The first is that an early onset appears to be a significant predictor of recurrent MDD risk when the sample represents a sufficient range of ages of onset. The second is that the threshold for defining an early onset should exclude persons with a first onset during middle adulthood. The findings for the absence of a life stress trigger also add new information to the body of research on risk factors for recurrent MDD, as the absence of a life stress trigger was found to confer an increased risk of recurrent MDD.

The interaction of having at least one parent with depression and an early age of onset appears especially toxic, as the results found the combination of an early onset with parental depression to confer an excess risk for recurrent MDD that was statistically significant. The magnitude of this relationship was large in the current study; individuals with both risk factors (early onset, parent depression) had 11 times the odds of recurrent MDD compared to those with neither risk factor (later onset, no parent depression). Although the interaction of parental loss and early onset was not statistically significant, the results suggest that persons who suffer the loss of a parent through death or divorce during childhood and have an onset of depression before age 21 are especially prone to having a recurrent course. The marginally significant findings for the interaction of childhood maltreatment with an early age of onset also suggest that the combination of an onset of depression before age 21 with the experience of parental abuse or neglect during childhood confers an excess risk for recurrent MDD. These findings should be viewed as preliminary, given the lack of statistical significance for parental loss or maltreatment. Nonetheless, the consistency of the pattern of findings across all three childhood vulnerabilities

supports the time-window of risk concept. Thus, it appears plausible that experiencing childhood vulnerabilities and then experiencing a first episode of MDD while still young may lead to a recurrent MDD course. As discussed in the section on implications for behavioral health, these findings suggest that it may be possible to prevent recurrences if these high-risk individuals can be identified earlier in the course of depression and receive appropriate interventions.

### **Limitations and Strengths**

This study has several limitations and strengths to keep in mind while interpreting the findings and considering implications. The first study limitation concerns the use of cross-sectional data for investigating issues that involve changes over time. This is a limitation because cross-sectional data reflects measurements from a single point in time and, thus, necessitate the use of retrospective assessments for investigating issues pertaining to different points in time. The optimal research design for investigating issues involving changes over time is a longitudinal design. A longitudinal design is preferable because this design permits the use of prospective assessments of issues that change over time. In addition, prospective assessments are much less vulnerable than retrospective assessments to the effects of measurement error issues such as participant recall bias.

The use of secondary data to conduct the present investigation is another limitation to the findings of this study. This is because the data collection process did not occur with the primary intent of achieving the goals of this study. Thus, the measurement of some of the risk factors was not as precise as they it would have been if the data were collected specifically for achieving the goals of the present investigation. For instance, to compensate for the lack of any age of onset variables for the childhood maltreatment risk factor the study had to exclude persons with an age

of onset before age 12 to ensure the experiences of maltreatment would reflect incidents that happened prior to the first onset. This information would have most likely been attainable had the data been collected specifically for this study.

Another limitation is the use of data collected in 2001-2003. The findings may have been different had the investigation been conducted with more recent data. Thus, the generalizability of the findings to the present population may have been compromised; however, the NCS-R possesses the largest and most recent nationally representative data available.

The physical abuse component of the childhood maltreatment variable also represents a limitation to this study. This is because the physical abuse item reflects relatively less severe examples of physical abuse as the more severe examples of physical abuse were not made available for the public-use version of the NCS-R dataset. Thus, the results for parental maltreatment may have been different had the analyses included the more severe physical abuse items. Despite the absence of more severe physical abuse items, the persons with those experiences were likely represented by the maltreatment variable nonetheless as the individuals with more severe abuse experiences probably had physical abuse experiences of lower severity as well.

An additional study limitation is the likely insufficient number of persons in the sample with a childhood experience of parental loss. Thus, this sample may have lacked sufficient power to detect a statistically significant interaction between parental loss during childhood and an early age of first onset of depression. Future research should attempt to expand upon the findings of this study for the interaction of parental loss and an early onset by recruiting a sample that consists of a greater number of persons with a childhood history of parental loss to include in the study sample.

The absence of physical conditions from the analyses of risk factors for recurrent MDD represents another limitation of this study. Although the influence of physical comorbid conditions on risk for recurrent MDD is an issue that warrants additional research, this study was unable to conduct an appropriate investigation of this topic for two reasons. The first reason is that the average age of first onset is during mid-life or later for most physical comorbid conditions, whereas the first onset of depression typically occurs during adolescence or early adulthood. Thus, there were too few persons with a physical comorbid condition prior to their first episode recovery to conduct statistical analyses with sufficient power to detect any possible statistically significant relationships. A fruitful avenue for future research would be to recruit a sample of persons with MDD that includes more persons that have a later age of first onset of depression so that an appropriate investigation of the risk of recurrent MDD associated with physical comorbid conditions could take place.

The exclusion of persons with an onset before age 12 is also a study limitation because the findings of this study may not generalize to persons with an onset of depression before age 12 because of their exclusion. The restriction of the sample to persons with an onset at age twelve or later was necessary, however, to ensure that the experience of childhood maltreatment was reflective of a risk for a first onset that occurred prior to the recovery from a first episode.

Despite these limitations, this study possesses several strengths that contribute new information to the existing literature. A primary strength was the use of a large nationally representative dataset, which enhances the external validity of the study findings and allowed for the investigation of relatively uncommon risk factors. Another important strength of this study was the identification of persons with a single lifetime MDE and persons with multiple lifetime episodes in order to investigate risk factors for recurrent MDD. This is an important distinction

because much of the prior research has investigated risk factors for depression recurrence by assessing differences between persons followed over time according to whether there was an experience of a recurrence during the follow-up time period, irrespective of each individual's history of depressive episodes prior to the study onset. Thus, this study contributes new knowledge to the limited body of research literature on risk factors for recurrent MDD that are evident prior to the recovery from a first episode.

## **Implications**

**Behavioral health practice.** The findings of this study have implications for behavioral health practice, policy, and future research. Although many persons with MDD could benefit from treatment, less than one-half of persons with depression actually seek treatment (Rupp, Gause, & Regier, 1998) and only 37.5% of persons with depression make contact with a treatment provider within one year of their first onset. Thus, reducing the prevalence and burdens of depression require increasing the rate of persons with depression who receive evidence-based treatment during their first depressive episode.

The identification of risk factors of recurrent MDD may help to ensure persons at risk of recurrent MDD receive the services and supports they need to prevent the onset of recurrent MDD through supporting the development of a screening tool. The development of a screening instrument for assessing risk of recurrent MDD could increase the rates of treatment and decrease the rates of recurrence for persons at risk of recurrent MDD and holds implications for behavioral health practice, policy, and research.

The identification of risk factors for recurrent MDD demonstrates the feasibility of developing and implementing a screening tool able to briefly assess risk for recurrent MDD. The

screening tool should consist of several self-report items that assess lifetime history of depression, aspects of the first experience of depression, and the presence of several risk factors for recurrent MDD. According to this study's findings, the screening tool should assess age of first onset of depression, presence of life stress before the first episode, parental loss, parental maltreatment, parental depression, comorbid anxiety disorders, and comorbid substance disorders. The presence of any of these conditions would indicate a greater risk of recurrent MDD, especially the combination of early onset with a childhood-based vulnerability.

Based on the current findings, it may be valuable for the screening tool to begin with an assessment of whether the individual has any lifetime experiences of depression. For persons with any lifetime experience of depression, the screening tool should ascertain the age of the individual at the time of the onset of their first experience of depression and the duration of this experience. The screen should then assess the number of experiences of depression the individual has had during their lifetime and whether the individual was free from significant depression symptoms for a period of at least two consecutive months at any point in time since the onset of their first experience of depression. At this point the screen could assess risk factors for recurrent MDD such as, whether the individual believes their first experience of depression was the result of some stressful life experience, whether the individual has a childhood experience of parental divorce, parental death, parental abuse, and parental neglect. Lastly, the screen should determine whether the individual has any parent with a history of depression, whether the individual has had an anxiety disorder during their lifetime, the age of their earliest anxiety disorder experience, whether the individual has had a problematic substance use experience in their lifetime, and the age of their earliest problematic substance use experience. The presence of any of these



conditions would indicate greater risk of recurrent MDD and the combination of an early onset with a childhood-based vulnerability would confer an especially high risk of recurrent MDD.

Service settings in which such a screening tool might identify significant numbers of people at high risk of recurrent MDD include primary care, urgent care, emergency departments, and schools. Universal depression screening including this recurrent risk tool would require staff training and procedures for notifying providers (e.g., physician, nurse, school counselor) who could then initiate a discussion with the patient about possible treatment options and offer the patient an opportunity to ask any questions they may have regarding inhibitions, fears, or concerns that may prohibit or facilitate his or her initiation of a program of treatment. The files of persons with a high risk of recurrent MDD could then receive a physical or digital flag that alerts staff personnel of the need for initiating a schedule with more frequent follow-up appointments. This would provide greater vigilance of any changes in depressive symptomatology so that the identification of persons in need of treatment services can occur as early as possible. The goal is to initiate a course of treatment or at least introduce and address treatment options and concerns of the patient at the earliest possible time in order to maximize their chances of receiving the information and/or services that would enable the successful prevention or at least postponement of any recurrences of depression.

Limited research has examined interventions that specifically prevent recurrent MDD, although certain forms of psychotherapy have shown promise. The treatment preferences of the patient may also be important for mental health service providers to consider because there is evidence indicating patients with depression experience greater treatment benefit when they receive their preferred treatment. For example, a study by Kocsis et al. (2009) found psychotherapy to be most effective for patients with a preference for psychotherapy and

antidepressant medication to be most effective for patients with a preference for antidepressant medication. In one study, although most patients experiencing their first depressive episode preferred psychotherapy to antidepressant medication, the majority received antidepressant medication (Houle, Villaggi, Beaulieu, Lespérance, Rondeau, & Lambert, 2013). This pattern is especially concerning as it relates to persons during their first episode and thus, at a critical juncture regarding their long-term course of MDD.

A therapy that integrates interpersonal therapy (IPT) and cognitive behavioral therapy (CBT) may reduce the risk of recurrence according to a study of young adults (N=74) that had a first onset of depression during adolescence (Sheets et al., 2013). The recurrence rate for the control condition was 51%, as 21 of the 40 persons who did not receive the IPT/CBT intervention had a recurrence during the eighteen-month follow-up period; whereas only 11 of the 33 persons in the IPT/CBT intervention group had a recurrence (33%) over the eighteen-month follow-up period.

The results of a two-year follow-up study of patients with recurrent MDD found that, for patients with recurrent MDD with fluctuating patterns of residual symptomatology during an acute-phase remission, the continued receipt of antidepressant medication or being switched from antidepressant medication to mindfulness-based cognitive therapy (MBCT) significantly lowered the risk of recurrence (Segal et al., 2010). A meta-analysis of randomized controlled trials found MBCT significantly reduces the risk of relapse or recurrence compared to treatment as usual or placebo controls (Piet & Hougaard, 2011), especially for individuals with a greater number of recurrences. The risk ratio was 0.66 for MBCT compared to treatment as usual or placebo controls, indicating a 34% relative risk reduction overall; however, for persons with three or more prior episodes the relative risk reduction was 43%, whereas there was no risk

reduction for persons with two episodes. This means that MBCT was more effective at reducing risk for relapse or recurrence for persons with three or more episodes rather than only two lifetime episodes. Lastly, electroconvulsive therapy (ECT) is a fairly effective form of continuation or maintenance treatment for preventing recurrences of depression according to a systematic review of ECT studies of adults with major depression (Brown, Lee, Scot, & Cummings, 2014).

In summary, the treatment research suggests that combination CBT/IPT program, MBCT, continuation antidepressant treatment, and ECT are viable treatment options for preventing recurrences of depression. Nonetheless, sizeable numbers of individuals in these treatment studies who received the active treatment still suffered recurrences. As such, there is a great need to improve the effectiveness of treatments to prevent recurrences of depression and recurrent MDD. Given that childhood-based vulnerabilities in combination with early onset appear to confer excess risk of recurrence, treatment may be improved for these individuals if it specifically targets these vulnerabilities. For example, IPT strategies might be beneficial to target interpersonal issues related to growing up with a depressed parent or grief related to loss or separation from a parent. Similarly, CBT could be used to explore core schema that developed as a result of having a depressed parent or loss or separation from a parent. A mindfulness-based intervention could be used to target acceptance of past adversities, and trauma-informed strategies (Williams, Teasdale, Segal, & Soulsby, 2000) could be integrated for those individuals who experienced childhood abuse or neglect. Given the link of comorbid anxiety and possibly substance use disorders with MDD recurrence, incorporating evidence-based treatment strategies for anxiety or substance misuse also is indicated, if individuals show signs of these conditions.

Thus, reducing the prevalence and burdens of depression requires increasing the rate of persons with depression who receive treatment within one year of the onset of their first depressive episode, improving the effectiveness of treatments for depression, and placing a greater emphasis on the treatment preferences of the patient in order to minimize their risk of prematurely discontinuing with treatment. The current findings suggest that treatments could potentially be improved by targeting specific vulnerabilities, such as childhood vulnerabilities and comorbid conditions.

**Behavioral health policy.** The findings of this study also have implications for policy development. There exists a great deal of potential for reducing the annual burdens of depression by reducing the prevalence of recurrent MDD, and effective screening methods provide one of the most promising avenues for pursuing this goal.

The implications of these findings for behavioral health policy concern the facilitation of the means necessary to develop and implement a screening tool for quickly assessing risk of recurrent MDD. Behavioral health policies could support the research efforts necessary to develop and validate a brief screening tool for assessing risk of recurrent MDD through ensuring the availability of the financial resources necessary to conduct this research. The availability of necessary financial resources for conducting this research would support an earlier development and institution of a valid screening instrument for assessing risk of recurrent MDD. This is an important element of the screening tool development because the risk for future recurrences increases with the onset of each successive episode, thus the burdens of depression would decrease with each first-recurrence of depression effectively prevented or postponed. Thus, the earlier implementation of a screening tool could facilitate a reduction in the annual burdens of MDD in a manner that would be evident immediately and would remain evident throughout the

duration of the life course of every person for whom the screening tool was responsible for preventing or postponing a first recurrence. Thus, over time, the economic savings likely to accrue would recompense the initial cost of increasing the financial support of the research necessary to implement a valid screening tool for assessing risk of recurrent MDD.

In order to implement a valid screening tool behavioral health policy would be necessary to develop and disseminate training resources to ensure that staff members are able to administer, score, troubleshoot, and communicate effectively with patients taking the screen. For example, the risk factors of parental abuse during childhood and parental neglect during childhood reflect relatively sensitive concepts, and appropriate training for the staff members would ensure that they are able to communicate with patients completing the screen in a manner that is appropriate for discussing such sensitive topics. This would protect against any occurrences involving an inadvertent violation of the privacy of a patient and safeguard against situations arising wherein the screen causes the patient to incur any form of psychological or physical insult or injury.

In addition to screening, behavioral health policy could support access to evidence-based interventions that may prevent recurrent MDD. For example, a great deal of health care reform is focused on broadening the scope of primary care and better integrating primary and specialty services, including policies and financial incentives created by the Affordable Care Act to create patient-centered medical homes and accountable care organizations (Bao, Casalino, & Pincus, 2013). At the same time, behavioral health care services are being integrated into primary care and other health settings at an increasing pace (Katon & Unützer, 2013). These policy and service system changes create potential opportunities for conducting universal screening and delivering effective mental health services to prevent or treat recurrent depression.

**Behavioral health research.** These findings also have implications for future research, as there is a need for research that focuses on increasing the proportion of persons with depression who engage in treatment during their first episode. Future research must work towards increasing the prevalence of persons receiving treatment services for depression during the first year of the onset of their first episode. This is important because the period of time immediately following recovery from the first episode is a critical juncture in determining the future life course of MDD.

Research is necessary in order to develop and evaluate a reliable and valid screening tool for conducting brief assessments of risk for recurrent MDD. Perhaps the implementation of a screening tool could lead to the creation of a risk factor profile database that stores the data from the patient screens and tracks patient outcomes according to the risk factor profile of the patient and the type and duration of the treatments or preventive services the patient receives. A database possessing this quality of information would help reduce the burden of depression by providing depression researchers with a resource that would allow them to ascertain the efficacy of particular treatments for patients with particular risk factor profiles. Over time, this research would produce new knowledge that would inform behavioral health practice of which treatment services are most likely to prevent or postpone recurrent MDD for each patient according to their unique risk factor profile. As mentioned previously, although certain treatments are promising, treatment outcomes leave room for improvement; thus research also is needed regarding the most effective interventions to prevent recurrent MDD. It is possible that different high-risk individuals need personalized interventions that target their specific risk factors, such as early onset, childhood vulnerabilities, or comorbid anxiety disorders. This research not only ensures

that patients receive the most efficacious treatment services but also ensures that the patients receive these services at the earliest point in time.

The implications of the present study also include a need to investigate the degree to which the findings from this study may or may not pertain to persons with an age of onset before age 12. Future research should also attempt to replicate and expand upon the findings of this study by employing a longitudinal research design to investigate the same risk factors for recurrent MDD that were a part of the present investigation. Specifically, the ideal replication of this study would include a random sample of several thousand individuals and conduct follow-up assessments with these individuals every one to two years. The individuals in the ideal sample would not be younger than age three nor older than age five at the beginning of the study and the study would conclude at the time of the death of every individual in the sample. Indeed, such an endeavor would consume a substantial amount of financial and personnel resources; however, this ideal study design is useful as a model for future research attempts to replicate the findings of the present investigation.

## **Conclusions**

In conclusion, these findings demonstrate the existence of risk factors for recurrent MDD that are measurable prior to recovery from the first episode. Thus, future research of recurrent MDD risk should distinguish persons with a single lifetime episode from those with more than one lifetime MDE. The most important contribution of this study to the existing research literature may be calling attention to the use of age of onset as an interaction term to help further the understanding of the factors ultimately responsible for causing recurrent MDD. This information may be especially useful in efforts seeking to implement universal screening

processes as this study identifies several risk factors of recurrent MDD that could inform the development of a brief yet valid screening instrument for assessing risk of recurrent MDD. The goal of this research is to reduce the burdens of MDD by engaging a greater percentage of persons at risk of recurrent MDD into treatment services as early as possible in order to maximize their chances of preventing the onset of recurrent MDD and sustaining a long-term recovery from depression.



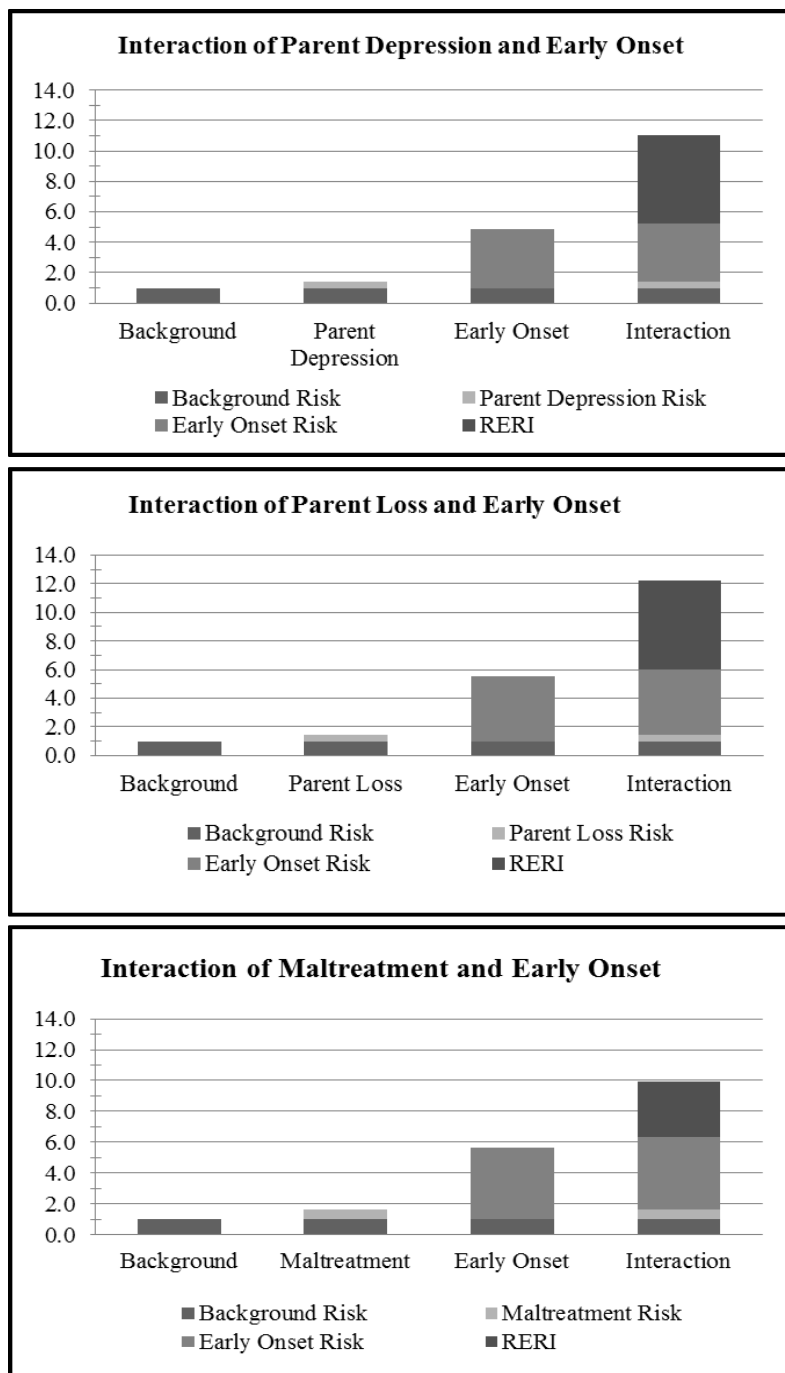


Figure 4. Risk of recurrent course for the interaction of early onset with parental depression, parental loss, and maltreatment for each level of interaction.

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## Appendix A: IRB Letter



RESEARCH INTEGRITY AND COMPLIANCE  
Institutional Review Boards, FWA No. 00001669  
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799  
(813) 974-5638 • FAX (813) 974-7091

7/24/2014

Graig DeFeo  
Community and Family Health  
13201 Bruce B Downs Blvd, MDC 56  
Tampa, FL 33612

RE: **NOT Human Research Activities Determination**

IRB#: Pro00018411

Title: Risk Factors for Recurrent Major Depressive Disorder in a Nationally Representative Sample

Dear Mr. DeFeo:

The Institutional Review Board (IRB) has reviewed the information you provided regarding the above referenced project and has determined the activities do not meet the definition of human subjects research. Therefore, IRB approval is not required. If, in the future, you change this activity such that it becomes human subjects research, IRB approval will be required. If you wish to obtain a determination about whether the activity, with the proposed changes, will be human subjects research, please contact the IRB for further guidance.

All research activities, regardless of the level of IRB oversight, must be conducted in a manner that is consistent with the ethical principles of your profession and the ethical guidelines for the protection of human subjects. As principal investigator, it is your responsibility to ensure subjects' rights and welfare are protected during the execution of this project.

Also, please note that there may be requirements under the HIPAA Privacy Rule that apply to the information/data you will use in your activities. For further information about any existing HIPAA requirements for this project, please contact a HIPAA Program administrator at 813-974-5638.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

A handwritten signature in blue ink that reads "Vjorgensen MD".

E. Verena Jorgensen, MD., Chairperson  
USF Institutional Review Board