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Risk for Recurrence in Depression

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Abstract

Depression is a highly recurrent disorder with significant personal and public health consequences. Prevention of recurrence would be extremely desirable, and thus researchers have begun to identify risk factors that are specific to recurrence, which may be different from risk factors for first-onset of depression. Methodological issues in this area of research are briefly reviewed (e.g., the various definitions of "recurrence" and "depression"), followed by a review of studies on specific risk factors, including demographic variables (gender, socio-economic status, marital status), clinical variables (age at first onset, number of prior episodes, severity of first/index episode, comorbid psychopathology), family history of psychopathology, and psychosocial and psychological variables (level of psychosocial functioning, cognitions, personality, social support, and stressful life events). In addition, scar theories are evaluated for their potential to explain how these variables and recurrent depression are linked. Our review suggests that recurrent depression reflects an underlying vulnerability that is largely genetic in nature and that may predispose those high in the vulnerability not only to recurrent depressive episodes, but also to the significant psychosocial risk factors that often accompany recurrent depression.

Major depressive disorder is one of the most common forms of psychopathology, one that will affect approximately one in six men and one in four women in their lifetimes (Kessler et al., 1994). It is also usually highly recurrent, with at least 50% of those who recover from a first episode of depression having one or more additional episodes in their lifetime, and approximately 80% of those with a history of two episodes having another recurrence (American Psychiatric Association, 2000; Kupfer, Frank, & Wamhoff, 1996; Post, 1992). Once a first episode has occurred, recurrent episodes will usually begin within five years of the initial episode (Belsher & Costello, 1988; Lewinsohn, Clarke, Seeley, & Rohde, 1994), and, on average, individuals with a history of depression will have five (Kessler & Walters, 1998) to nine (Kessler, Zhao, Blazer, & Swartz, 1997) separate depressive episodes in their lifetime.

Due to the fact that depression can be so recurrent, it can have significant personal and public health consequences. For example, one meta-analysis found that the suicide rate among those with depression is approximately twenty times higher than the rate for the general population (Harris & Barraclough, 1997). In addition, a study of over 3000 adolescents and young adults found that 90% of those with recurrent depression reported "very much" impairment, limiting work productivity and social interactions, and 40% sought professional help as a result (Wittchen, Nelson, & Lachner, 1998). Depression can also have a significant economic impact due to decreased productivity in affected individuals (Klerman & Weissman, 1992); in 1996 the annual direct (e.g., visits to doctors, pharmaceutical costs) and indirect (e.g., time/

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productivity decreased due to illness) costs of depression were estimated to be $16.3 billion (Kupfer et al., 1996).

As a result of the often recurrent course of depression, as well as the significant impact it has in many areas, there has been considerable effort to determine the causes of depression so prevention efforts can be implemented. However, rather than focusing on identifying the causes of first episodes of depression, several researchers have narrowed their search to identify the causes of recurrence in particular, which may be different from the causes of first episodes (Lewinsohn, Allen, Seeley, & Gotlib, 1999). For example, onset of depression is associated with being female, having a low socio-economic status, presence of comorbid psychiatric disorders (particularly anxiety disorders), family history of depression, and exposure to stressful life events (Birmaher et al., 2004); as will be shown in this review, not all of these risk factors for onset also convey risk for recurrence. In addition, this line of research is significant for applied settings because the individuals at risk for the more adverse side effects and long-term consequences from depression are those with the recurrent subtype, therefore it is important to identify the risk factors for recurrence so these at-risk individuals can be identified and prevention efforts can be implemented.

Studies considered in this review were identified through literature searches of combinations of key words (e.g., “recurrence,” “recurrent,” “depression,” “risk,” “correlate”) in PsycINFO and the Science Citation Index Expanded. In addition, reference sections of located studies were inspected for relevant reports that were missed in the initial search. Given the focus on clinical and psychosocial risk factors, studies examining biological measures (such as physiological reactivity to stress) were not considered in this review.

We begin by examining important definitions and methodological issues, followed by a review of specific risk factors for recurrence. We then evaluate scar theories for their potential to explain recurrence risk. Based on our findings, we offer suggestions on how to best identify those at greatest risk for recurrent depression and suggest future areas worthy of research attention. Our review points to the conclusion that recurrent depression is due to a stronger underlying vulnerability to depression than is found in non-recurrent depression, that this underlying vulnerability is largely genetic in nature, and that this underlying genetic vulnerability to recurrence also affects whether the risk factors are also present.

Definitions and Methodological Issues

Due to the fact that several different approaches have been taken to define both “depression” and “recurrence,” it is important to understand how these terms have been defined and what the methodological implications are of the different approaches adopted by investigators when studying recurrent depression.

Depression

Much research on recurrence of depression has relied on the criteria for major depressive disorder (MDD) in the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 1980, 1987, 1994, 2000), or on similar diagnostic approaches that served as the precursor for DSM-III (e.g., Feighner et al., 1972; Spitzer, Williams, & Gibbon, 1987). The most recent edition of the DSM defines a major depressive episode as a period of two weeks or more in which at least five symptoms are expressed most of the day nearly every day, including either depressed mood or the loss of interest in nearly all activities, weight/appetite disturbance, sleep disturbance, psychomotor agitation/retardation, fatigue, feelings of worthlessness/guilt, decreased concentration/decision-making, and suicidal ideation. Other researchers have employed the diagnostic criteria of the International Classification of Diseases (ICD, World Health Organization, 1978), which are highly similar to those found in the DSM.

Researchers employing either DSM or ICD criteria either utilize symptom counts in their analyses, or they utilize the present/absent diagnostic threshold.

Rather than relying on one of these formal classification systems to operationalize depression, other researchers have used symptom checklists and rating scales such as the Beck Depression Inventory (BDI, Beck, 1996), a self-report measure of depressive symptomatology, or the Hamilton Rating Scale (Hamilton, 1960), a clinician-rated measure. The BDI comprises 21 items such as "Sadness: 0=I do not feel sad, 1=I feed sad, 2=I am sad all the time and I can't snap out of it, 3=I am so sad or unhappy that I can't stand it." Scores are derived by summing the responses to each of the 21 items, with scores of 14-19 generally indicating mild depression, 20-28 suggesting moderate depression, and 29-63 indicating severe depression. The Hamilton Rating Scale is a similar measure of severity of seventeen depressive symptoms (Hamilton, 1960; Ramana et al., 1995), and, despite the different reporting method, scores on this scale correlate quite highly with those on other depression inventories such as the BDI (Dozois, 2003).

Another issue in defining "depression" regards whether other forms of psychopathology are excluded. This is clearly important regarding bipolar disorder. Many studies did not exclude those with a history of mania, which may be problematic because bipolar and unipolar depression may have disparate etiologies. However, given the 10- (Kessler et al., 1994) to 20- (American Psychiatric Association, 2000) times greater prevalence of major depression compared to bipolar disorder in the population, this is likely less of a concern in large, epidemiological studies than it would be in studies with clinic-referred patients where bipolar patients are likely to be represented in large numbers. Another important consideration is the presence of comorbid dysthymia. It may be easier for those who recovered from depression to dysthymia (but who did not recover fully to an absence of depressive symptoms) to slip back into depression again. Researchers also have differed in how they handle the presence of other comorbidities such as anxiety disorders or substance use disorders. Some researchers only select individuals with a history of depression and no other forms of psychopathology, while others allow any form of comorbid psychopathology in their participants with depression. These different approaches toward the treatment of comorbid psychopathology are also echoed in control groups, with some researchers requiring their controls to be completely clean of psychopathology, while others only require that the controls do not have a history of depression. The inclusion and exclusion criteria used for comparison groups is as likely to be as important as those used for the depressive target groups because choice of controls has been shown to influence the outcome of research on mood (Depue & Iacono, 1989) and other disorders (Iacono, 1991).

Recurrence

The approaches taken to identify "recurrence" have been at least as varied as those used to operationalize "depression." Early studies equated relapse and recurrence, and it was not clear how relapse, recurrence, and remission were differentiated. In 1988, however, the MacArthur Foundation Research Network on the Psychobiology of Depression formed a task force to propose standard definitions for the terms used in research on depression (Frank et al., 1991). First, they defined "partial remission" as a period in which the individual is no longer fully symptomatic but displays more than minimal symptoms, and "full remission" as a brief period where the individual is asymptomatic. "Recovery" was conceptualized as a period of full remission lasting at least a certain number of days, usually at least eight weeks. They defined "relapse" as a return of symptoms to the full syndrome criteria for an episode during remission but before recovery (i.e., within eight weeks), whereas "recurrence" was defined as the appearance of a new episode after a period of recovery (Frank et al., 1991). No specific term was assigned to capture those with only minimal symptoms of depression. Other groups have

made slight revisions to this model (e.g., Kupfer & Frank, 2001), but the basic definitions outlined by Frank and colleagues (1991) have become standard in the recent literature.

In addition, confusion can result even when an accepted definition of "recurrence" is studied. That is, recurrence can refer to either a subtype of depression marked by multiple recurrent episodes, or it can refer to the next depressive episode after a prior episode. Thus, researchers sometimes identify risk factors for depressive subtypes characterized by either multiple or single episodes, or they may identify risk factors for a specific future episode, given a history of one (or, in many studies, more than one) previous episode of depression.

Finally, it is important to note that there are considerable differences in how treatment is handled. Some studies are epidemiological or community-based and make no mention of treatment (e.g., Barkow et al., 2003), while other studies are clinic-referred or treatment-outcome samples which clearly outline the interventions used in the sample (e.g., Gonzales et al., 1985). How treatment is handled may be important in the latter type of sample because the risk factors for recurrence in these studies could be confused with the risk factors for treatment non-compliance and the differential effectiveness of various interventions.

In the literature on recurrence of depression, much has been made of these differences in definitions and methodologies. As will be shown in this review, it appears that these differences in "depression" are not very meaningful in that they appear not to account for important differences among findings from various studies. Thus, "depression" in this paper can either refer to diagnosable DSM or ICD major depressive disorder, or to scores above a specific cut-off on a rating scale such as the BDI or Hamilton. On the other hand, confusion between relapse and recurrence has been shown to be important in accounting for discrepancies in early research on this topic, and thus Frank and colleagues' (1991) descriptions are intended in this paper whenever "recurrence" or "relapse" are used to refer to a specific episode. When identifying "risk factors for recurrence," however, this will refer to the identification of risk factors for the recurrent subtype of depression (as opposed to single-episode depression), unless "risk for a recurrent episode" (whether it is a second episode or a later recurrence) is specified instead. Due to the fact that sample exclusions, statistical approaches, and treatment interventions vary so widely among studies, these will be specified as necessary in the text on a per-case basis. In addition, important methodological details of reviewed studies can be found in Table 1.

Demographics

Considerable research on risk factors for recurrent depression has focused on demographic variables. These include gender, socioeconomic status, and marital status. Generally, these variables have been considered risk factors for recurrence when they are more likely to be present in those with multiple episodes of depression, as opposed to those with only one episode or those with no history of depression.

Gender

The influence of gender on depression has been a major topic of study. There is considerable evidence to suggest that women are at increased risk for a lifetime history of depression, due to their higher prevalence (Kessler, 2000) and increased risk of relapse (Kuehner, 2003). However, despite women being at increased risk for developing depression and for depression relapse, female gender does *not* appear to be a significant risk factor for recurrence.

The effect of gender on the recurrence of depression has been evaluated in several ways. For example, Gonzales and colleagues (1985) followed 113 participants in a treatment-outcome study for one year. In a multiple linear regression used to predict having a recurrent episode, gender was a non-significant variable. However, their participants varied in the number of

episodes of depression they had already experienced prior to entry in the study, and thus they could not determine if gender differentiated between a recurrent and non-recurrent course specifically after the first episode. In order to address this possibility, Rao and colleagues (1995) studied the course of depression in 28 depressed adolescents. They found that gender did not predict having a recurrent course of depression, as compared to having only one episode of depression, during their seven-year follow-up. Kovacs and colleagues (2003) also found no differential risk for recurrence following a first episode of depression in boys versus girls over a ten-year follow-up period. Simpson et al. (1997) similarly found no difference in risk for recurrence over a five-year follow-up in their sample of 195 adults in their first episode of depression. In addition, the men and women in their sample did not differ in the *number* of recurrent episodes they had during the follow-up period. The non-significant role of gender in the recurrence of depression has also been replicated in other studies (Coryell, Endicott, & Keller, 1991; Kovacs, 2001; Kovacs et al., 1984; Lewinsohn, Zeiss, & Duncan, 1989).

The failure of gender to be associated with the depression recurrence has also been replicated in larger, epidemiological samples. Wainwright and Surtees (2002), for example, studied 3491 adults (aged 48-79) in the European Prospective Investigation into Cancer and Nutrition (EPIC) study and found that men and women with a history of depression did not significantly differ in risk of recurrent depression (60.4% of women and 60.1% of men had had more than one episode). Kessler and colleagues (1993), using data from over 8000 participants in the National Comorbidity Survey, also found that the higher lifetime prevalence of depression among women is likely due to their increased risk of first onset, because men and women did not significantly differ in their risk for recurrence.

Thus, there is considerable evidence that men and women do not differ in their risk for recurrence of depression. One notable exception to this is the studies published by Kessing and colleagues (Kessing, 1998, 2004; Kessing, Andersen, & Andersen, 2000), who consistently find that women are at higher risk of “recurrence.” However, there are several unique aspects to their sample that might account for this finding. First, theirs is a psychiatric hospital sample, and their findings are based on increased hospital *readmission* rates for women as compared to men. Thus, they may be missing recurrent episodes that are less severe and thus do not lead to re-hospitalization, which could influence this gender ratio. They also may simply be detecting relapses rather than recurrences, which previous research has been shown to be more common among women. Second, they used ICD-10 diagnoses, while all of the other studies cited here used either DSM criteria or Research Diagnostic Criteria. While highly similar, it is possible that there are subtle differences in these systems that could affect the gender ratio in recurrent episodes. Third, it may be the case that the threshold for hospital admission for men is higher than that for women, and this may be driving the lower rates of readmission for men, despite possibly similar symptom pictures of recurrence in men and women. This is likely, particularly given the fact that women are significantly more likely to receive treatment for depression than are men, despite similar symptom presentation and illness course between the sexes (Hasin, Goodwin, Stinson, & Grant, 2005). Last, their sample is Danish, while other studies are predominantly American. It is unclear precisely how this last point might influence the relative risk of recurrence for men versus women, but it bears mentioning. Again, these studies by Kessing and colleagues are virtually the only exceptions to overwhelming findings that suggest men and women are at equal risk for recurrence of depression.

Socio-Economic Status and Marital Status

Socio-economic status (SES) and marital status have also been studied to determine if they play a role in the risk for recurrence in depression. Just like gender, however, it appears that although low SES and being single are associated with increased likelihood of developing

depression, these factors are unrelated to risk for recurrence (Belsher & Costello, 1988; Birmaher, Arbelaez, & Brent, 2002).

For example, Birmaher and colleagues (2004) followed 68 children and adolescents, and found that SES, as measured by the Hollingshead four-factor index, was not associated with risk for future recurrences during the five-year follow-up. Gonzales and colleagues (1985) found similar results with a five-category Hollingshead rating scale in their sample of 113 adults, and also found that marital status was non-significant in their multiple linear regression to predict recurrent episodes. Kessing, Andersen, and Mortensen (1998) found that marital status was related to first recurrence following hospitalization for depression, but not to any later risk for recurrence; controlling for age may have minimized this effect. One study that did find a significant effect of SES may be an anomaly because it only measured parental SES at the time of the participants' birth, rather than participants' SES at the time of depression recurrence (Gilman, Kawachi, Fitzmaurice, & Buka, 2003). Thus, the common findings appear to be that demographic variables such as gender, marital status, or SES may be important for first onset of depression, but they appear not to be significantly related to risk for a recurrent course of depression.

Clinical Picture and Family History

Several clinical features of depression have been investigated to see if they explain risk for recurrence. These factors include age at onset of the first episode, lifetime number of depressive episodes, severity of first episode, presence of comorbid psychopathology, and family history of depression and other mental illness. Research in this area has not investigated the impact of DSM- or ICD-defined depressive subtypes, such as the melancholic subtype, on risk for recurrence, although this may be a fruitful area to examine. As described further below, age at onset and number of depressive episodes, although confounded, may be risk factors for recurrence. In addition, number of symptoms in the first episode (but not episode duration), comorbid psychopathology, and a family history of psychopathology (particularly mood disorders) are also related to recurrence.

Age at Onset of First Episode and Number of Depressive Episodes

There have been several studies that have examined the role of age at onset of the first episode as it relates to later recurrence of depression. These studies have yielded conflicting results. Some studies have reported that an earlier onset of depression is related to greater risk for recurrence (Gilman et al., 2003; Klein et al., 1999; Kovacs et al., 1984; O'Leary & Lee, 1996), while others studies have found no relationship between age at onset and risk of subsequent recurrent episodes (Birmaher et al., 2004; Kovacs et al., 2003). Surprisingly, one study found that a *later* age at first onset was related to faster recurrence (Lewinsohn et al., 1994), although this study only examined time to recurrence and not whether age was related to a recurrent course of depression. Interestingly, the studies that did *not* find a significant relationship between age at onset and risk of recurrence are all similar to each other, and different from the studies that did find such a relationship, in three ways: they are all prospective, include relatively small sample sizes, and include only children and/or adolescents. Thus, it is possible that there is a recall bias or a power issue that is accounting for the different findings across these two groups of studies. These possibilities deserve further attention in future research. It should also be noted that none of these studies control for number of prior episodes; instead, these studies have looked at risk for recurrence in those with a history of any number of depressive episodes. This is an important question because, while age at onset and number of depressive episodes are moderately correlated, they are not completely synonymous. Thus, while number of depressive episodes has consistently been shown to predict risk for recurrence (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999;

Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000; O'Leary & Lee, 1996), this does not mean that age at first onset could not also provide independently meaningful information about risk for recurrence. In fact, some researchers have begun to look at both variables, age at first onset and number of lifetime episodes, at the same time in an attempt to untangle their correlated influences.

Gonzales and colleagues (1985) completed a classic study on the relationship between risk for a recurrent episode and age at onset of first episode or number of depressive episodes. They followed 113 adults for one year after recovery from the index episode and found that number of prior episodes was the variable in their multiple linear regression equation that accounted for the greatest increase in explanatory variance, while age at onset of depression was not included as a significant predictor. However, they still believed that age at onset may be an important variable, and explained that the high intercorrelation between these variables ($r = -.41$) may have caused age at onset to not be included in the equation after number of episodes was already entered.

Since this classic study, a few other investigations have examined this issue, but none have gotten any further at disentangling the interrelationship between age at onset and number of lifetime depressive episodes as they relate to relative risk for recurrence. For example, Giles and colleagues' (1989) univariate analyses showed that only age at onset, but not number of lifetime episodes, was significant in predicting a recurrent episode. However, Lewinsohn and colleagues (1989) found the opposite pattern of results in their univariate comparisons of survival curves from a first to a second episode of depression, whereas Kessing and colleagues (2000) found that both variables significantly predicted recurrence (i.e., re-hospitalization) when examined separately, in a sample of first-admission hospitalized patients.

An interesting study that used path analytic techniques to predict "persisting alterations" of depression (in either bipolar or unipolar affective disorder) found that age at onset only indirectly (via number of episodes), and not directly, predicted number of recurrent depressive episodes (Deister & Marneros, 1993). However, this path was also influenced by the presence of mania such that those with bipolar disorder tended to have more total episodes and thus more depressive recurrences. Of additional concern is the tendency of bipolar disorder to onset earlier, and the researchers did not specify the relative numbers of individuals with unipolar versus bipolar disorder in the sample. Thus, mania could be the driving force in this relationship, leaving recurrent unipolar depressive episodes unexplained in their model.

Another promising approach for untangling the relative contribution of these two variables is to examine the risk for recurrence, based on age, for individuals who have had only one prior episode of depression. Kessing, Andersen, and Andersen's (2000) previously mentioned study comes the closest to this methodology because they found effects for each variable in a sample of first-admission patients. However, their study included several important deviations from the ideal. First, they did not look at first-episode patients; rather, they examined individuals after their first hospitalization, which may have yielded a more severely affected sample. Second, they did not distinguish between different mood disorders. They looked at recurrence of any affective episode (i.e., depressive, manic, or hypomanic) during the follow-up period, even though the risk for recurrence of these different types of affective episodes may vary greatly. Although this study comes closest to parsing out the relative contribution of age at onset vs. number of prior episodes, their results are not conclusive.

Given the conflicting results from this body of research, it is clear that additional work will be required to delineate the relative importance of these confounded variables when predicting recurrence of depression. Path analysis can be employed to test whether age at onset and number of lifetime episodes *both* have a direct effect on risk for recurrence, or whether one of

these variables is a mediator through which the other variable exerts an indirect influence. In addition, amply powered longitudinal research could be used to advantage to disentangle the relationship between age at onset and number of depressive episodes in predicting recurrence. Furthermore, a genetically informative sample could yield important information about the nature of the correlation between these two variables. It is possible that they are genetically correlated, suggesting that those with a large genetic risk for recurrence are experiencing the effects of genes influencing both earlier onsets and greater numbers of episodes.

Severity of First/Index Episode

Severity of depression has been operationalized by examining the duration of the first or index episode, and by the number or type of symptoms present. While episode duration has not been consistently related to risk for recurrence, a more severe symptom picture during the first/index episode may be.

Several studies have examined episode duration, each using a different type of sample. Gonzales and colleagues (1985) examined a sample of 113 adults and found that duration in weeks of the index episode did not predict a recurrent episode; however, the index episode was not the first episode for the majority of the participants, and their results may simply be reflecting treatment response. Similarly, a study of 100 adult psychiatric inpatients found that length in weeks of the index episode, which represented a first episode in 74% of the sample, did not predict a recurrent episode (O'Leary, Costello, Gormley, & Webb, 2000). Equivalent results have also been found in younger samples. For example, Kaminski and Garber (2002) followed 185 high-risk children annually from 6^{th} grade through 12^{th} grade. They found that, compared to those with only one lifetime episode of depression, those with recurrent depression did not experience significantly longer first episodes of depression. Kovacs and colleagues (1984) also found that first episode duration did not affect risk for a recurrent episode in another sample of high-risk children and adolescents.

While duration of the first depressive episode has not been shown to significantly predict risk for recurrence of the disorder, there is evidence that the symptom picture during the first episode may be related to recurrence. The severity of the symptom picture has been conceptualized using clinical severity subtypes or specifiers inherent to the classification system adopted by a study, the nature of the specific symptoms that are present, or the number of items endorsed on a self-report measure of depression. A more severe first-episode symptom picture has fairly consistently been shown to be related to recurrence.

Barkow and colleagues (2003) examined data from the World Health Organization's "Psychological Problems in General Health Care study," a cross-cultural investigation of over 25,000 individuals in 15 locations throughout the world. They found that those who met ICD-10 criteria for depression at time one were significantly more likely to also meet criteria for depression at time two, 12 months later, if they had a more severe ICD-10 depression subtype (i.e., mild vs. moderate vs. severe) at intake. However time-two depression could reflect a sustained episode rather than a recurrence. O'Leary and colleagues (2000), in a study of 100 depressed inpatients, also found that the ICD-10 severity subtype predicted recurrence or relapse leading to re-hospitalization during an 18-month follow-up period. Kessing (2004) found similar results in his sample of over 7000 depressed inpatients over a five-year follow-up period.

Specific symptoms have also been shown to predict risk for recurrence of depression. For example, in Barkow and colleagues' (2003) WHO study, the presence of suicidal thoughts during the index episode predicted presence of depression at time two. In a study of 1508 adolescents, Lewinsohn and colleagues (1994) found that a suicide attempt or suicidal ideation during the index episode, often the first episode for individuals in the sample, predicted time

to recurrence (although not recurrence itself) during the follow-up period. In addition to finding an effect for suicidality, O'Leary and Lee (1996) uncovered a nonsignificant trend indicating that presence of psychomotor agitation, but not presence of delusions, during the index episode of depression was associated with greater risk for having a recurrent episode. Furthermore, studies have shown that primary sleep disturbance or disruptions of the sleep-wake cycle increase the risk not only for depression onset (Butcher, Mineka, & Hooley, 2004) but also for recurrence of depression (Alpert, 2006). Finally, relying on symptom counts, Coryell and colleagues (1991) found that the number of depressive symptoms present during the worst episode the participants could remember also predicted having a recurrent episode during their six-year follow-up period.

Rating scales, such as the Hamilton, have also been utilized as predictors of recurrence. Several researchers have found that an increased Hamilton score, reflecting the presence of a large number of symptoms and/or several severe symptoms, predicts recurrent episodes in adult inpatient samples (e.g., Belsher & Costello, 1988; O'Leary et al., 2000; Ramana et al., 1995). However, there have been a few exceptions, including two studies of children and adolescents which found that severity of depression, as indicated by an extracted Hamilton score, does not predict later recurrent episodes (Birmaher et al., 2004; Rao et al., 1995). There are several differences between these sets of studies that could account for these discrepant findings. First, the age of the samples is very different (i.e., children/adolescents vs. adults). Second, the age at first onset of depression in these samples is also different (i.e., onset in childhood vs. in adulthood). Third, the former studies tend to be of hospitalized individuals, while the latter tend to be outpatients. Fourth, the latter studies used a proxy for the true Hamilton Rating scores, an estimated Hamilton score extracted from the K-SADS-P diagnostic interview for depression (see Williamson, Ryan, Dahl, & Jeannette, 1992). All of these differences could contribute to the discrepant findings between these sets of studies. However, given the high correlations between extracted Hamilton scores and true Hamilton Rating scores (Williamson et al., 1992), and given the high correlation between Hamilton scores and other scores on other depression rating scales (Dozois, 2003), it is unlikely that there is something unique about how the Hamilton score is working in these two types of samples. Instead, it is more likely that depression severity is not a predictor of recurrence in children, whereas it is in adults. Further studies of depression severity predicting recurrence in non-hospitalized adults would also be beneficial.

In sum, these findings point to severity as a marker of recurrence risk, whether severity is operationalized as ICD/DSM severity, presence of certain symptoms such as suicidality, presence of greater numbers of symptoms, or higher BDI or Hamilton scores. The apparent exception to this conclusion is duration of the first or index episode, which appears to be unrelated. However, it is important to note that the examination of this variable is confounded by the issue of treatment response in clinical samples, and in differences between first and index episodes in non-clinical samples.

Comorbid Psychopathology

Many researchers have examined the impact of comorbid psychopathology on risk for recurrence of depression. Interestingly, studies of adults have shown that comorbid Axis I disorders, particularly dysthymia, are related to increased risk for recurrence. Studies of children and adolescents, however, have had more mixed results but often find that comorbid anxiety and/or behavior disorders are *not* related to later recurrence of depression.

Studies in adult samples have found that the presence of any of a large assortment of comorbid disorders is related to risk for recurrence (Segal, Pearson, & Thase, 2003). For example, Rao, Hammen, and Daley (1999) found that presence of any comorbid non-affective Axis I disorder led to increased risk for recurrence in a sample 155 women over a five-year follow-up period.

More specifically, Wilhelm and colleagues (1999) followed 164 teachers for fifteen years and found that those with a lifetime anxiety disorder diagnosis (i.e., panic disorder, generalized anxiety disorder, agoraphobia, and/or simple phobia) were at increased risk for recurrent depression as opposed to a single episode of depression over the course of the study. In addition to phobic disorder diagnoses increasing the risk for recurrence of depression, Coryell and colleagues (1991) also found that alcohol and/or drug disorders were associated with recurrence. Other researchers have also replicated this association between substance use disorders and recurrent depression (e.g., Alpert, Maddocks, Rosenbaum, & Fava, 1994; Barkow et al., 2003).

In addition to anxiety disorders and substance use disorders increasing the risk of recurrence for depression, other affective disorders have also been related to subsequent episodes. For example, in a sample of 30 unipolar depressed patients, Giles and colleagues (1989) found that those with a lifetime diagnosis of other affective disorders (e.g., dysthymia, bipolar disorder) were at significantly increased risk of recurrent episodes during the 36-month follow-up. Other researchers have also shown that the presence of dysthymia in particular is related to recurrence (e.g., Barkow et al., 2003; Warner, Weissman, Fendrich, Wickramaratne, & Moreau, 1992). Similarly, researchers have found that “minor depression” (i.e., the presence of 2-4 symptoms of major depression, rather than the five or more required for a diagnosis), is associated with an increased risk for recurrence in major depression (Coryell et al., 1991). These latter findings that “lesser” forms of depression are related to recurrence is perhaps not surprising, given the continuous distribution of depression symptomatology in the general population (Kessler et al., 1997). That is, if less severe forms of depression are present even when the full-blown depressive disorder is not, it is not surprising that these individuals would have a greater risk of slipping back into a depressive episode more easily than would individuals who have no depressive symptoms between major depressive episodes.

In contrast to studies of adult samples which have found a large variety of comorbid psychopathology to be related to recurrence of depression, studies of children have predominately found no relationship between recurrence and comorbidity, with the exception of dysthymia. Lewinsohn and colleagues (2000) found that presence of any form of Axis I comorbid psychopathology was unrelated to recurrence in their sample of 274 adolescents followed for approximately eight years. Similarly, Birmaher and colleagues (2004), in a sample of 68 children and adolescents, found that neither comorbid anxiety disorders nor comorbid disruptive behavioral disorders was related to recurrence over the five-year follow-up period. Kovacs (2001) found the same null relationship in her study of 92 children over six years. More specifically, Fombonne and colleagues (2001a; 2001b) found that those with both conduct disorder and major depression were not at increased risk for recurrence over a 20-year follow-up, as compared to those with depression but without comorbid conduct disorder.

An exception to these findings that comorbid psychopathology in children is not related to risk for recurrence involves the presence of dysthymia. In a study of 65 children, Kovacs and colleagues (1984) found that those who also had a lifetime diagnosis of double depression (i.e., major depression superimposed on dysthymia) were more likely to have a recurrent major depressive episode over the 48-month follow-up. Specifically, approximately 55% of those with double depression had a second episode, whereas only 30% of those with no history of dysthymic disorder had a recurrence. In addition, those with dysthymia had recurrences sooner than those without. While this finding has not yet been replicated, it is reasonable to consider that, after an episode of depression, it would be easier for those with dysthymia to “slip” back into a depressive episode than it would be for those who recover more fully and do not show significant depressive symptomatology.

The finding that comorbid psychopathology, other than dysthymia, is largely unrelated to recurrence in children, but highly related to recurrence in adults, should be examined further in future studies. In addition, understanding the contribution of morbidity would be enhanced if these studies controlled for level of functioning (occupationally, socially, etc.) when comparing risk for recurrence in those with only depression versus in those with depression plus at least one other disorder. It is conceivable that the very presence of additional psychopathology makes recurrent episodes of depression more likely by compromising the individual's overall level of functioning. It is also possible that this mechanism is manifest more strongly in adults than children due to the increased role obligations adults have.

Family History of Psychopathology

Recurrence of depression has been linked to a family history of various types of psychopathology, including any mental illness, affective disorders in general, and major depression in particular. Most studies that examine the relationship between recurrence of depression and family history of psychopathology have focused on family history of depression in particular (Rice, Harold, & Thapar, 2002). Bland, Newman, and Orn (1986) examined the risk for depression in 763 first-degree relatives of 75 adult probands with unipolar depression who had been followed for 12 to 18 years. They found "significant independent differences … according to the proband's age at onset and whether the proband had had a single episode or recurrent depression." Specifically, they found a morbidity risk of 3.4% in relatives of those with late-onset single episodes, 7.5% in relatives of those with early-onset single episodes, 8.2% in relatives of those with late-onset recurrent episodes, and 17.4% in relatives of those with early-onset recurrent episodes. Zubenko and colleagues (2001) examined 1242 relatives (407 first-degree and 835 extended) of 81 probands with recurrent, early-onset depression. They found that prevalence rates of depression were approximately 7.7 times higher in first-degree relatives and 3.8 times higher in extended relatives than would be expected based on epidemiological prevalence rates reported in the Epidemiological Catchment Area study.

Other researchers have focused on parent-offspring effects. Birmaher and colleagues (2004), in a study of 68 children and adolescents, found that father's lifetime diagnosis of major depression significantly predicted recurrence in the children; they noted that they could not investigate the effect of mother's depression status because the vast majority of mothers had a history of depression. In another sample of children and adolescents, Lewinsohn and colleagues (2000) examined 274 individuals with or without recurrent depressive episodes between their adolescent-onset of depression and their 24th birthday. They found that a family history of either major depressive disorder or recurrent major depressive disorder significantly predicted recurrence in the adolescents.

One study that did not find a significant relationship between family history of depression and recurrence of depression was conducted by Wilhelm and colleagues (1999); however, it should be noted that their findings were in the expected direction and fell just short of statistical significance. These researchers followed 164 teachers for 15 years and divided the sample into those with no lifetime episodes of depression, one lifetime episode, and two+ lifetime episodes. They found that the percentage of those with a family history of depression increased as the number of lifetime episodes in the probands increased, from 38% to 44% to 63%. Thus, their results are consistent with those of others showing that recurrence is related to a family history of depression.

A few studies have examined the relationship between psychopathology other than depression in family members and risk for recurrence. Lewinsohn and colleagues (2000) found that family history of a non-mood disorder was *not* a significant predictor of recurrence in those with adolescent-onset depression. However, other studies have shown that a family history of any mental illness (Kessler & Magee, 1993), and of affective disorders in general (Gonzales et al.,

1985), is related to recurrence of depression. Future research is required to determine if there are specific non-mood disorders in family members that are related to recurrence. For example, it could be that the affective disorders alone are responsible for the connection between family history of psychopathology and recurrence of depression; alternatively it could be that anxiety disorders or substance use disorders, for example, are also related to recurrence. In addition, studies of this type must be performed on genetically informative samples in order to account for the high comorbidity and familial liability between depression and other forms of psychopathology (Burcusa, Iacono, & McGue, 2003; Kendler et al., 1995; Kessler et al., 1996; Krueger, 1999).

There are different mechanisms through which a family history of psychopathology could be related to recurrence of depression. The results of family studies suggest that the familial transmission of recurrent depression is even stronger than the familial transmission of depression in general (Klein, Lewinsohn, Rohde, Seeley, & Durbin, 2002; Zubenko et al., 2001), particularly if it is early-onset recurrent depression (Moldin, Reich, & Rice, 1991). Increased recurrence risk in offspring could reflect environmental contributions stemming from a disorganized home life that includes being reared by a parent who is repeatedly compromised by episodic depression during the child's upbringing. However, the extant evidence more clearly points to a role for genetic influences. Twin studies of depression indicate that depression in general is transmitted through genetic and non-shared environmental influences (Sullivan, Neale, & Kendler, 2000), and studies of the transmission of recurrent depression in particular also indicate that recurrent depression is transmitted through a combination of genetic and non-shared environmental influences, with little evidence of shared environmental influence (Kendler, Neale, Kessler, Heath, & Eaves, 1992). However, there has been some evidence that, once a recurrent course of depression is established, shared environmental factors may influence the number of episodes one has (Kendler et al., 1992). Thus, studies that have investigated the etiology of recurrent depression using genetically informative designs find little evidence of a role for shared family environment in the development of recurrent versus non-recurrent depression. Instead, this line of research supports the importance of genes and non-shared environmental factors.

As a result of these findings regarding the transmission of recurrent depression, some researchers have begun the search for genes for recurrent depression. Zubenko and colleagues (2002) identified a susceptibility locus for recurrent, early-onset major depression in women. They had three groups: 100 depressed participants (50 of each sex); 100 age-, sex-, race-, and ethnicity-matched controls; and 407 first-degree and 835 extended relatives of the probands. They found that women with the D2S2944 124-bp allele were significantly more likely to have a diagnosis of recurrent major depression compared to males and to female controls. In addition, family data provided evidence of linkage and linkage disequilibrium among female probands in this sample. While this tetranucleotide repeat marker on 2q35 does not itself have functional significance, the researchers have suggested that "sequence variation conveying increased susceptibility to MDD [major depressive disorder]…is in close proximity to D2S2944" (p. 39). This finding has been replicated in women in the Iowa Adoption Studies (Philibert et al., 2003). Thus, there appears to be promising evidence for at least one genetic locus influencing the genetic transmission of recurrent depression in families.

In sum, many "clinical picture" variables have been investigated to determine if they are risk factors for recurrence of depression. Age at first onset of depression and lifetime number of depressive episodes appear to be related to increased risk for recurrence, although further research disentangling these variables is necessary. Severity of the first episode, as indicated by a severe symptom picture (measured in any one of several ways) and not by initial duration, is also implicated as a risk factor for recurrence. Comorbid psychopathology has also been associated with recurrence, although this may only hold true for adults and not for children, a

finding that could be due to the greater numbers of disorders and functional impairment present in adults with recurrent depression. In addition, certain forms of psychopathology in family members have also been implicated as a risk factor for recurrence, most likely due to the transmission of genetic risk from parents to children, although it is also important to note the significant influence of nonshared environmental influences on psychopathology as well.

It is likely that all of these clinical picture variables represent markers of the severity inherent in recurrent depression, as opposed to non-recurrent depression. That is, individuals with more than one episode of depression may also have earlier ages at onset, more severe episodes, more comorbid disorders, and a stronger family history of psychopathology. It is also conceivable that all of these clinical picture variables reflect an underlying genetic vulnerability to the recurrent type of depression, particularly given the likely genetic transmission of recurrent depression (Kendler et al., 1992; Sullivan et al., 2000; Zubenko et al., 2002). Earlier age at onset, more severe early episodes of depression, greater comorbidity, and greater family history of psychopathology may all reflect an underlying genetic predisposition to the more severe recurrent type of depression. Future studies with genetically informative samples are needed to resolve the degree to which the relationship between these many variables and depression recurrence reflect heritable and shared environmental influences.

Psychological and Psychosocial Risk Factors for Recurrence

Cognitions

Negative cognitive styles have long been implicated as a risk factor for the onset of depression. For example, it has been posited that individuals who attribute global, stable, and internal causes to stressful life events are more likely to become depressed than are those that attribute the causes to temporary, stable, and external influences (Abramson, Seligman, & Teasdale, 1978). Similarly, Beck hypothesized that those with dysfunctional beliefs and resulting negative cognitive biases would be prone to develop depression (e.g., Beck, Rush, Shaw, & Emery, 1979). Recent research has supported negative cognitions as a risk factor for the onset of depression. For example, Lewinsohn and colleagues (Lewinsohn, Joiner, & Rohde, 2001) found that adolescents with the most dysfunctional attitudes at time 1, as well as more stressful life events in the interim, were most likely to experience a depressive episode by time 2.

Research has also supported the existence of a relationship between cognitions and recurrence of depression. In a study of initially non-depressed participants, Iacoviello and colleagues (2006) found that those with high cognitive vulnerabilities to depression experienced significantly more episodes of depression (M= 2.9) during the 2.5-year follow up than did individuals at low risk cognitively (M=2.0). Similarly, Mongrain and Blackburn (2006) found that negative attributions predicted depression recurrence over a 16-month follow-up in a sample of previously depressed participants, even when controlling for the number of past episodes. Other studies have shown that treatment with cognitive therapy significantly lessens the risk for future recurrences of depression (Bockting et al., 2005), and that cognitive style similarly predicts both first onset and recurrence of depression (Alloy et al., 2006). Thus, there appears to rather consistent evidence supporting negative cognitive styles as a risk factor for not only depression in general, but for recurrence in particular.

Personality

Many studies have documented the relationship between high levels of neuroticism and risk for depression (e.g., Duggan, Sham, Lee, Minne, & Murray, 1995; Enns & Cox, 1997; Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Ormel, Oldehinkel, & Brilman, 2001). Indeed, Butcher and colleagues (2004) have identified

neuroticism as “the primary personality variable that serves as a vulnerability factor for depression” (p. 230).

High levels of neuroticism have been associated with a worse long-term outcome from depression, which has sometimes been operationalized to include greater numbers of recurrent episodes. For example, Duggan and colleagues (1995) examined neuroticism scores on the Eysenck Personality Inventory in 34 individuals with a history of depression, as indicated by high scores on the BDI, compared with 45 controls without such a history. They found significantly higher neuroticism scores in the former group. Furthermore, when this group was split into those with a history of recurrent episodes versus those with only one past episode, they found significantly higher neuroticism scores in those with a history of recurrent depression. Similarly, Berlanga et al. (1999) also found that higher neuroticism scores predicted a future recurrence of depression, following pharmacological treatment. While one study (Bos et al., 2005) did not find different neuroticism scores between the recurrent and single-episode participants, this appears counter to rather overwhelming evidence supporting the relationship between risk for recurrent depression and for negative emotionality, particularly when considered in concert with the research (below) on personality scarring.

Stressful Life Events (SLEs)

Many studies have examined the relationship between SLEs and the first onset of major depression (e.g., Kendler, Karkowski, & Prescott, 1999; Lewinsohn et al., 1999), and some studies have begun to examine the association between SLEs, either in childhood or adulthood, and the risk for recurrence of depression in particular. In a sample of 3491 individuals, Wainwright and Surtees (2002) examined the relationship between retrospective reports of childhood SLEs and risk for a history of depression in adulthood. They found that three of their SLEs were associated with a lifetime history of depression (parental divorce, experiencing a frightening event in childhood, and physical abuse), while the other SLEs were unrelated to depression (separation from mother, hospital stay, parental unemployment, parental drinking or dug abuse). However, further analysis of these three significant SLEs showed that only parental divorce was associated with an increased risk for recurrence, while the other two were associated with increased risk for a first onset of depression. Kessler and Magee (1993) similarly found that parental divorce and family violence were associated with risk for recurrence during a one-year follow-up of 3617 adults, although parental drinking, parental marital problems, death of mother, and death of father were associated with first-onset of depression, particularly an early first-onset, and not associated with recurrence. However, Gilman and colleagues (2003), found that childhood adversity (e.g., parental separation/divorce, residential instability) was not associated with recurrence of depression in their sample of 1089 individuals who were part of the National Collaborative Perinatal Project and who were assessed again between ages 18 and 39.

A problem with these studies of the relationship between childhood SLEs and risk for recurrence of depression is that it seems unlikely that childhood SLEs are exerting a direct influence on individuals that leads to recurrence, because the recurrences are occurring decades after exposure to the childhood SLE. Instead it would appear more likely that the relationship between childhood SLEs and adult recurrence is mediated by other variables, such as changing genetic influences, or exposure to new stresses in adulthood. Kessler and Magee (1994) examined this latter possibility in their previously mentioned sample of 3617 adults. They found that chronic interpersonal stress in adulthood (including demands and conflicts with friends and relatives, demands and conflicts with children, and negative interactions with spouses) mediated the effect of childhood SLEs on recurrence of depression. Furthermore, they found that there was no association between childhood SLEs and recurrence of depression, if chronic interpersonal stress in adulthood was absent. They did not investigate, however,

whether chronic interpersonal stress in adulthood was sufficient to increase liability to recurrence of depression, in the absence of childhood stressful life events.

The importance of adult SLEs has been highlighted in many other studies (Belsher & Costello, 1988). For example, one study followed 67 individuals with recurrent depression following successful treatment for depression (i.e., psychotherapy and/or medication). The researchers found that higher scores on a stressful life events scale after recovery was significantly associated with higher rates of recurrence during the three-year follow-up period (Monroe, Roberts, Kupfer, & Frank, 1996). Similarly, Gonzales and colleagues (1985) found a nonsignificant trend supporting the relationship between SLEs and recurrence during a three-year follow-up of 113 recovered patients with a history of recurrent depression. However, a different study found that recurrence is associated only with one-month prevalence of SLEs, and that this association dissipates with lengthier periods in which SLEs are tabulated (Paykel & Tanner, 1976). A broader, dimensional approach to this topic was undertaken by Lewinsohn, Hoberman, and Rosenbaum (1988). They found that major life events predicted significantly increased depression scores eight months later, even when controlling for depression scores at intake.

Thus, in sum, it appears there is considerable evidence that stressful life events, both in childhood and especially in adulthood, are associated with recurrence of depression, and there is evidence to support that SLEs are risk factors for recurrent depression.

Social Support

Presence of adequate social support has been implicated as a protective factor for depression (e.g., Sheeber, Hops, Alperty, Davis, & Andrews, 1997; Stice, Ragan, & Randall, 2004), and it has been associated with a better long-term outcome after an episode of depression (Brugha, Bebbington, Stretch, MacCarthy, & Wykes, 1997; Lara, Leader, & Klein, 1997). Some studies have shown that social support may protect not only against first episodes of major depression, but also against recurrent episodes. However, other studies have suggested that there is overlapping genetic vulnerability to both recurrent depression and to low social support, and thus there is not a directly causal relationship between these two variables.

Wilhelm and colleagues (1999), in a retrospective study of 164 individuals, found that those with two or more past episodes of depression reported less satisfactory social support in their lives, compared to those with only one episode of depression or to those with no past episodes. In a prospective study, Lewinsohn and colleagues (1988) also found that having few or no social supports at intake prospectively predicted having an episode of depression (a recurrent episode in 90% of the subjects) during the eight-month follow-up period, but only for female and not male participants. These studies seem to indicate that social support is protective against recurrent episodes of depression.

Alternatively, other studies have found opposite results, although they have some significant methodological differences that could account for their divergent findings. Staner and colleagues (1997) investigated social support as a predictor of recurrence across a one-year follow-up in a sample of 24 recovered depressed patients, 27 bipolar patients, and 26 controls. They found that a lack of social support did not significantly predict new affective episodes. However, the inclusion of both bipolar and unipolar cases to predict either depression or mania may have confounded their results. Kessler and Magee (1993) found that lack of a close relationship to an adult while still a child was predictive of depression recurrence; however, this does not mean that social support in adulthood is not protective, since this was not investigated. Meanwhile Paykel and colleagues (1996) also did not find that social support was protective against relapse, although their sample was restricted to those with severe episodes of depression; it may be the case that social support is less able to protect against more severe

episodes of depression. Finally, research reviewed earlier on the effects of marital status indicate that it is related only to onset of depression and not recurrence (Belsher & Costello, 1988; Birmaher et al., 2002); however, this is but one specific facet of social support (Spotts et al., 2004).

Finally, twin studies of depression and social support have yielded conflicting results. Some studies have found that some forms of social support exert a direct influence on risk for recurrence, while other forms of social support are influenced themselves by recurrence (e.g., Wade & Kendler, 2000); other research has shown that there is common genetic vulnerability to both recurrence and social support, and that this is the factor driving their relationship (Bergeman, Plomin, Pederson, & McClearn, 1991; Wade & Kendler, 2000).

Thus, while further research is certainly warranted in this area, the research to date indicates that, particularly for women, social support may be a protective factor against recurrent episodes of depression. However, it is still unclear whether those who are prone to recurrent depression simply have less social support due to common underlying genetic vulnerabilities to both, or whether social support could be manufactured (such as through therapy) in order to directly prevent recurrences in those otherwise identified to be at risk.

Scar Theories: An Explanatory Mechanism for Elevated Recurrence Risk

Due to the greater rates of depression in those who have a history of depression compared to those who have no such history, it must be the case that either the depression itself somehow increases the vulnerability to becoming depressed again, or that individuals at high risk for multiple episodes already possessed the necessary characteristics to make them prone to depression even before their first episode. Scar theories focus on the former of these suppositions and are all similar in that they surmise that something, presumably encoded at the biological level, changes during an episode of depression, that this change is long-lasting, and that the change makes future episodes more likely. Thus, for a scar to be present, research must support all of the following: (1) individuals who subsequently have a first episode of depression and those who do not should not initially differ on the variable of interest. (2) Once the depressive episode occurs, however, the scar should manifest, and those with a history of depression should significantly differ from those without such a history on that variable. (3) Finally, the scar variable should also independently predict future recurrences. That is, it is not enough to simply show that a variable changes following depression, as it could be the case that the threshold for depression was already met, and thus the changed variable does not lead to any additionally conferred risk for recurrent depression. Thus, all three of the aforementioned points must be present, albeit not necessarily in a single study, in order for the presence of a scar to be supported. In cases where the first requirement is not met (i.e., when a variable appears to index risk for first onset of depression), then it is even more crucial that both the second and third criteria be satisfied. In other words, change alone is not sufficient to document presence of a scarred variable.

Psychosocial Scar

Zeiss and Lewinsohn (1988) investigated the possibility that depression leaves a psychosocial scar. They compared three groups of participants on several social/interpersonal variables, including self-report, peer-ratings, and experimenter-ratings. None of the variables they examined fit the expected scar pattern. Instead, they found that self-report variables appeared to be concomitants of depression that remit when depression improves, whereas most other-rated variables fit a pattern premorbidly differentiating improvers from nonimprovers. Thus, they concluded that psychosocial scarring is unlikely to account for the increased risk of recurrent episodes compared to first episodes of depression.

One methodological issue that Zeiss and Lewinsohn (1988) did not address was that their depressed participants all varied in the number and severity of depressive episodes they had already experienced, which may have influenced their ability to detect scarring. Rohde, Lewinsohn and Seeley (1990) sought to control this by comparing 49 individuals before (T1) and after (T2) their *first* episode of depression, and also comparing them to a group of 351 never-depressed controls at the same two time points, approximately two years apart. They first identified variables that significantly differentiated those with new cases of depression from the never-depressed controls at T2, and then examined these variables at T1. Only one variable, self-perceived social skills, fit the theorized scar pattern such that this variable did not differentiate the new cases from the controls at T1, did differentiate the groups at T2, and represented a significant change within the new-case individuals from T1 to T2. This finding may represent a scar because social skills were equivalent prior to the depressive episode, but were significantly lower after a depressive episode, suggesting that social skills were scarred by the depressive episode. However, to show that this is truly a scar, there would also have to be evidence that poor social skills also predict future recurrences of depression; without this, this change may simply reflect a consequence of depression that is unrelated to future risk. Furthermore, since these were self-ratings of perceived social skills, it is also possible that the researchers were actually measuring cognitive style. A drawback of this study is that all of the participants were at least 50 years old; due to the previously documented evidence that a younger age at first onset may be more highly related to recurrence, studying only those with a first onset of depression after age 50 may be eliminating a considerably more informative segment of the population, those at highest risk for recurrence given their young age at first onset of depression. Nevertheless, although Rohde et al. (1990) did not assess other-rated perceptions of the new depressives' social skills, their findings, other than those for self-rated social skills, are comparable to those of Zeiss and Lewinsohn (1988) in indicating an absence of psychosocial scarring.

Cognition Scar

Given the strong relationship between cognition and depression (e.g., Beck et al., 1979), other researchers have investigated whether there might be cognitive scars of depression that lead to increased likelihood of recurrence. Teasdale's differential activation hypothesis states that dysphoric mood states tend to activate negatively biased interpretations of experience, and, in those with a history of depression, these negative cognitive processes more easily exacerbate the dysphoric mood state and lead to another episode of clinical depression (e.g., Teasdale & Dent, 1987). This creates a vicious cycle where people predisposed to negative affect then have negative cognitions, which lead to depressed mood and depressive episode, which in turn cause low levels of negative affect in general, and so on. Similarly, as cited in Lewisohn and colleagues (1999), Williams et al. (1988) proposed that "negative self-referential material is extensively rehearsed and elaborated during depressive episodes, strengthening the likelihood that this material might contribute to a recurrence of depression, even though it may not have been implicated in the onset of the initial depressive episode" (p. 483). Thus, several researchers have attempted to show that there is a scar on cognition that results from a first episode of depression, such that the link between a depressogenic information-processing style and dysphoric affect is stronger in those with a history of depression than in those without. Support for this notion derives particularly from those who were children or adolescents during their first episode of depression.

Nolen-Hoeksema, Girgus, and Seligman (1992) followed a sample of 508 children in the third grade every six months for five years, investigating depressive symptoms, negative life events, explanatory style, and helplessness behaviors. They compared a subset of children with high levels of depressive symptoms (although not technically diagnosed major depression) to a subset of children with low levels of depression. Their regression analyses showed that

depression scores (controlling for initial explanatory style scores) predicted change toward a more negative explanatory style, in the sample overall and when compared between the two subsets of the sample. Their analyses also showed that continued depression was not simply accounting for the increasingly negative explanatory style, because individuals with high depression scores at one time were actually more likely to show a decrease in depression over time. The fact that the depressed children's explanatory styles deteriorated over time, and that they remained pessimistic even after the depression subsided, presumably left them at greater risk for future episodes of depression. However, the researchers did not formally test whether this hypothesis about risk for future depression was borne out, and thus their results suggest the possibility of a cognitive scar in children but do not fully support its presence.

In contrast to the evidence of a cognitive scar found by Nolen-Hoeksema and colleagues (1992), Lewinsohn, Steinmetz, Larson, and Franklin (1981) did not find evidence of a depression-related scar on cognitions in their community sample of adults. They followed 998 adults for one year, and compared scores on several cognitive measures (locus of control, expectancies of positive and negative outcomes, irrational beliefs, perception of control, and self-esteem) among eight subgroups in their sample, classified according to their history of depression at each time point. Based on their visual inspection (but not statistical testing), the means for each cognitive measure were highly similar across groups; the overall multivariate test was nonsignificant when tested. Furthermore, the specific contrast between those with or without a history of depression was also nonsignificant, indicating that depression does not leave a lasting effect on individuals. Thus, there was clearly no evidence of a cognitive scar effect of depression, although the researchers did not investigate individual-level change over time. Surprisingly, however, there was also little evidence of dysfunctional cognitions even being a concomitant of depression, which was highly unexpected given previous research.

Given this unexpected result, it is possible that Lewinsohn and colleagues' non-scar findings are also suspect. Alternatively, another possibility to account for the discrepancy between Lewinsohn and colleague's (1981) findings and those by Nolen-Hoeksema and colleagues (1992) is that children are more susceptible to the cognitively scarring effects of depression because their cognitive styles are still developing whereas adults' cognitive interpretations are more solidly formed by the time they encounter a depressive episode and thus their cognitions are not as impacted. This is certainly a reasonable consideration, as other studies in children and adolescents have also shown evidence of cognitive scarring from depression. For example, Lewinsohn, Allen, Seeley, and Gotlib (1999) studied 1709 adolescents, of whom 286 had a history of major depression. In their one-year follow-up period, 43 adolescents had a recurrent episode and 70 had a first onset of depression. They hypothesized, based on the theories of Teasdale (1987) and Post (1992) reviewed earlier in this section, that, even when not currently depressed (i.e., without mood priming), measures of "dysphoric mood or symptoms and dysfunctional thinking would be a stronger predictor of onset of recurrent episodes than of first onsets" (p. 483). This is precisely what they found. Those adolescents who scored highly on the Dysfunctional Attitudes Scale (DAS) and on the Beck Depression Inventory (BDI) did not differ significantly in rate of first-episode onset compared those whose scores were lower. However, this group with high scores on the DAS and the BDI did have significantly greater rates of recurrence after a first episode, compared to those whose scores were not elevated on these measures. The recurrence odds ratio was also significantly greater than the first onset odds ratio. In sum, there appears to be support to the theory that, at least in children and adolescents, perhaps due to their currently developing cognitive schemas, depression may leave a lasting cognitive scar which could possibly increase the likelihood of recurrent episodes.

Personality Scar

Another area in which a scar from depression has been hypothesized to occur has been in personality, particularly neuroticism. Specifically, researchers have begun to investigate whether a depressive episode changes one's personality in such a way that future recurrent episodes become more likely.

Duggan and colleagues (1995) found significantly higher neuroticism scores in those with a history of recurrent depression, compared to those with only one past episode. It is possible that there was a scarring effect in their sample, however, because this study was unable to investigate premorbid personality levels, they couldn't examine whether recurrence actually led to a change in neuroticism scores. Thus, the presence of a personality scar is thrown into question. These results may simply reflect higher levels of neuroticism predisposing individuals to greater numbers of depressive episodes, as other researchers have found.

Different researchers have attempted to address this methodological issue by obtaining pre- and post-depression neuroticism scores. For example, Oldehinkel, van den Berg, Bouhuys, and Ormel (2003) examined neuroticism scores on the revised Eysenck Personality Questionnaire (EPQ) in 26 elderly adults before and after they experienced an episode of depression. They also had personality data on 96 controls across the same time period. They found that individuals who would go on to experience an episode of depression had significantly higher neuroticism scores at baseline than did the controls, suggesting that neuroticism is involved in vulnerability to onset of depression. However, neuroticism scores of those who experienced their first episode of depression did not significantly differ from those who experienced a recurrent episode, either at baseline or at follow-up. Thus, Oldehinkel and colleagues found no evidence of a personality scar. Similarly, Shea and colleagues (1996) examined Maudsley Personality Inventory neuroticism scores in four groups of participants: those with no prior psychopathology who had a major depressive episode during the six-year follow-up (N=28), those with no prior psychopathology who remained as such (N=526), those with no prior major affective disorder who had a major depressive episode during the six-year follow-up (N=94), and those with no prior major affective disorder who remained as such (N=708). In both the comparison of those with no prior mental disorder and of those with no prior major affective disorder, there was a significant main effect such that neuroticism scores were higher at T1 and T2 in those who experienced a first episode of depression. However, there was no significant interaction between group (presence vs. absence of depression) and time on neuroticism, and there was no effect such that T2 neuroticism scores were higher than T1 neuroticism scores in either group. Thus there was no personality scar following an episode of depression, although it is important to note the relatively small recurrent group may have hindered the authors' ability to detect such an interaction.

At the same time, one study has found preliminary evidence of a scar on personality resulting from depression. In an elegant genetically-informative study, Kendler, Neale, Kessler, Heath, and Eaves (1993) gathered data from 707 complete female-female twin pairs in the population-based Virginia Twin Registry. They obtained depression-history data (DSM-III-R diagnosis) and personality data (neuroticism from the EPQ) at two time points approximately 15 months apart. Those with one or more episodes of depression between the two time points, and no history of depression prior to it, showed small but significant increases in neuroticism by follow-up, controlling for their neuroticism scores at intake (regression $b=.07$, $p<.007$), suggesting that there a small scarring effect of depression on neuroticism. In addition, the best-fitting longitudinal structural equation model for the data indicated that, of the total correlation between neuroticism and liability to depression, 70% was due to shared genetic factors, 20% to common environmental risk factors, and 10% to a direct causal effect of depression on neuroticism scores. However, the authors did not test whether this small but significant change in neuroticism also led to an increased risk for recurrence, on top of the risk for depression

recurrence already conferred by high neuroticism. It would be necessary to demonstrate this before elevated neuroticism could more definitively be considered a scar, and not just a change resulting from prior depression. Otherwise, elevated neuroticism may not add any meaningful information in and of itself about risk for recurrence in depression because the threshold for risk for recurrence has already been surpassed.

Thus, the jury is still out on whether neuroticism scores are "scarred" by depression. Largely, this is because most studies on this topic are missing the critical last piece of data on whether a change in neuroticism also leads to an increased risk for future episodes of depression, beyond the risk already conferred by high levels of neuroticism. Until this effect can be demonstrated, the relationship between neuroticism and depression, as understood at this time, can best be characterized such that high levels of neuroticism to begin with are simply related to risk for more episodes of depression.

Stressful Life Events (SLEs)

There are two types of scar models that are related to the occurrence of SLEs: sensitization and stress generation. The first model, sensitization, posits that both sensitization to stressors (i.e., less stress is required to elicit the same depressogenic response) and episode sensitization (i.e., it takes less dysphoric mood to produce a major depressive episode) occur after each episode of depression; this change is believed to be encoded at the level of gene expression (Post, 1992). Thus, SLEs are hypothesized to be most important in causing early recurrences of depression, but they become less associated with depression as episode sensitization and sensitization to stressors increases with each new episode of depression. In other words, the "scar" in this model is that some sort of biological change after an episode of depression leads to SLEs mattering *less* with increasing numbers of recurrences because the later episodes eventually will occur independently of environmental stressors. The second model, stress generation, predicts the opposite, This model posits that depressed individuals actually generate more stressful conditions for themselves as their number of depressive episodes increases, which in turn leads to additional recurrences (Hammen, 1991). Here, the scar is that SLEs become *more* important in predicting recurrent episodes of depression. These models could ideally be tested against one another by determining if the number of stressful life events an individual experiences increases (stress generation) or decreases (sensitization) as they have increasing numbers of depressive episodes. However, this comparison has not been carried out and thus we review the models separately below.

Sensitization—Sensitization has been investigated in several samples, with mixed results. Swann and colleagues (1990) divided their sample of 85 unipolar depressed participants into two groups: environment-sensitive (those with a high perceived role of SLEs in the onset of their current episode) and autonomous (those with a minimal perceived role between SLEs and their current depressive episode); perceived role of SLEs was averaged between ratings by the researchers and by the participants themselves. They found that those in the environment-sensitive group had experienced significantly fewer prior episodes of depression (M=3.7) than those in the autonomous group (M=13.4). Thus, although they did not use a longitudinal design to test the hypothesis, it is possible that their findings can be explained by increased sensitization over time. Similarly, Mitchell and colleagues (2003) found that severe SLEs, both as rated by the patients and as rated by the clinicians, were more likely to occur prior to first-onset cases of depression rather than recurrent episodes, in their sample of 270 depressed inpatients. Likewise, in an eight-month longitudinal study of 1709 adolescents, Lewinsohn et al. (1999) found that SLEs more strongly predicted first onsets (n=70) than recurrences (N=43) during the follow-up, and found that dysfunctional thinking was a stronger predictor of recurrence than of first onset.

The above studies indicate evidence that sensitization may occur as an effect of depression. However, results from other studies have not supported the existence of such an effect. For example, Joffe and colleagues (1999) examined antidepressant response in 135 depressed outpatients. They surmised that, since sensitization is hypothesized to occur via biological changes on the level of gene expression (Post, 1992), effectiveness of antidepressants would decrease as sensitization increases. However, they did not find a significant difference in antidepressant response based on the number of prior episodes their participants had experienced. Kessing and colleagues (2000; 1998) also did not find evidence of sensitization. In their first study, they examined over 20,000 first-admission hospital patients with affective disorders. They found that divorce/separation significantly increased risk for recurrence after a first episode, but not after a 2nd, 3rd, 4th, or 5th episode, while death of a spouse was not significantly related to recurrence after any episode. Furthermore, since the hazard ratio for each of the SLEs did not significantly decrease across successive episodes, this does not support the existence of sensitization (Kessing et al., 1998). They found similar results in their second study, when controlling for age, gender, calendar time between episodes, and individual heterogeneity (Kessing et al., 2000).

There are a few significant methodological differences that might account for the discrepant findings regarding sensitization in these groups of studies. First, the latter set of studies which did not find evidence of sensitization all relied solely on inpatient hospitalization data whereas the former set of studies finding support of sensitization all included outpatient samples. It is possible that, by the time of first hospitalization, the individuals in the latter set had already experienced several depressive episodes which already led to sensitization, which is why it could not be detected by the time of hospitalization. Second, the latter set includes both unipolar depressed individuals as well as participants with bipolar disorder who are currently in a depressive episode. It is possible that depression in bipolar disorder is less influenced by SLEs in general, and thus the bipolar depressed patients wash out any effects that could be found in just the unipolar patients. Clearly more research is necessary in this area, but there is some support for the presence of sensitization, particularly earlier in the course of depression.

Stress Generation—Hammen (1991) proposed the hypothesis of stress generation; she examined SLEs over the course of one year in 14 women with unipolar depression, 11 with bipolar disorder, 13 with chronic medical illnesses, and 22 with no illness (physical or psychological). She found that, over the course of one year, the depressed women experienced more SLEs than did women in any of the other comparison groups. In addition, the depressed women experienced significantly more dependent life events (i.e., SLEs to which they had contributed), particularly in the area of dependent negative interpersonal events. She hypothesized that women with depression may be somehow generating these dependent SLEs, which contributes to the cycle of recurrence of depression.

Hammen (2003) also expanded these findings in a larger sample (N=816) of women, of whom 358 had a history of major depression. Here she found that individuals with a history of depression had higher rates of current interviewer-rated SLEs than did never-depressed controls. In addition, a logistic regression analysis was performed to predict recurrence in those with any history of depression. The significant variables included SLEs, as well as spouse's psychopathology, early onset of depression, quality of relationship with spouse, and quality of relationship with child(ren). Finally, she found that chronic marital stress was the strongest predictor of depressive outcome. She concluded that stress generation, a type of scar through which increasing numbers of SLEs result after depressive episodes, is likely be the mechanism through which women are at risk for recurrence.

It is certainly possible that stress generation is the causal mechanism for Hammen's findings that show a relationship between SLEs and recurrence, although there were a few limitations

to these studies that make such a conclusion far from definitive. First, she was unable to examine SLE levels prior to depression versus after one or more depressive episodes. Thus, it is unclear whether the high levels of stressful life events are related to recurrence in particular, or just to first-onset, because she could not examine individual-level change. Second, she did not control for whether current depressive state might have influenced ratings of SLEs, particularly in the interpersonal domain. It is possible that there are higher perceived levels of interpersonal stress during a depressive episode that are solely driven by the dysfunctional thinking that is often present during depression. Finally, she did not look at individual-level change in SLEs as the number of recurrences increases. It is possible that those who are at risk for multiple recurrences are the same individuals who have always experienced high levels of SLEs, but not that their numbers of SLEs increased as their number of recurrences increased.

Harkness, Monroe, Simons, and Thase (1999) addressed one of these concerns. They compared SLEs, both dependent and independent, in three currently-depressed groups: those with no prior depressive episodes (N=28), those with one prior episode (N=10), and those with two or more episodes (N=21). Thus, while this study did not address the concern of whether current depressive thinking influences the rating of SLEs, and this research is not a longitudinal study that allows for analysis of changes within person across time (in order to rule out the perhaps more parsimonious explanation of SLEs simply being a risk factor for recurrence rather than a scar), this study does address the concern of whether SLEs increase as number of episodes increases. Harkness and colleagues found that number of dependent life events significantly correlated with number of prior depressive episodes in the whole sample. Furthermore, in the 12 months prior to current episode, the multiple-prior-episode group had significantly more dependent SLEs than the no-prior-episode group, while the one-prior episode group did not significantly differ from either of the two extremes; there were no differences in the number of total independent SLEs between these groups.

However, other researchers have found evidence to support SLEs being considered risk factors for recurrence but not scars. A study by Caspi and colleagues (2003) showed that individuals with at least one copy of the short allele of the 5-HTT promoter polymorphism evidenced significantly higher rates of depression by age 26, in relation to increasing numbers of SLEs between 21 and 26, than did individuals homozygous for the long allele. More importantly regarding the stress generation hypothesis, they also showed that there was no interaction between the 5-HTTPLR alleles and SLEs between 21 and 26, when trying to postdict depression between ages 18 and 21. Thus, their analyses showed that those with a history of depression did not generate more SLEs for themselves prior to their recurrent episodes.

In sum, results of studies on the stress generation hypothesis have been somewhat mixed but largely suggest that, while stressful life events are clearly supported as a risk factor for recurrence, stress generation does not necessarily occur with recurrent depression. In future research, a longitudinal study (which includes individuals with a range of prior depressive episodes) in which the stress generation hypothesis and the sensitization hypothesis could be directly compared to one another would be particularly interesting. At present, there appears to be more evidence for the existence of sensitization, although it is far from definitive. Alternatively, the possibility remains that there is no change in SLEs following depression and thus no scar, which would account for the null findings in several of these studies.

This section reviewed the evidence for the various types of scar theories that have been implicated in recurrent depression. There is considerable evidence that psychosocial scarring does not occur, while the research on cognitive scarring suggests that it may occur in children but not in adults. Results of studies on a potential personality scar have largely been negative, although many are lacking follow-up data to determine if the putative scar truly leads to recurrence. Finally, stressful life events have been clearly implicated as risk factors for

depression recurrence, and current research suggests that the relationship may fit the sensitization model of scarring better than the stress generation model, although evidence of SLE scarring is still weak at best.

It is interesting to note that the very premise of scarring supposes that, due to the greater rates of depression in those who have a history of depression compared to those who have no such history, it must be the case that depression itself somehow increases the vulnerability to becoming depressed again. However, no research in this area has yet addressed why, if scarring in any of these realms does occur, *all* individuals with a history of depression would not then go on to have recurrent episodes, if it is the experience of depression itself that is the risk factor making recurrence more likely. It still remains that perhaps 50% of depressed people have only one episode of depression. Thus, a more parsimonious explanation of the findings reviewed above regarding the possibility of scarring might be that individuals at high risk for multiple episodes possessed the necessary characteristics to make them prone to recurrent depression even before their first episode. Rather than continuing to investigate the possible existence of these various types of scarring, which has not yielded compelling findings, perhaps it would be more advantageous to further clarify the contribution of characteristics conferring elevated risk for recurrent depression, rather than continuing to examine whether depression itself causes recurrences through scarring.

Summary and Conclusions

Depression is a very common mental illness that is highly recurrent in individuals. In addition, it is a disorder with substantial personal and public health consequences. Thus, there is great interest in the development of strategies that might reduce the recurrence of depression. Important to the development of preventive interventions is a basic understanding of the factors that predict and contribute to recurrence. However, research in this area is rife with methodological variability. First, there are different definitions for “depression” in use in the literature, from diagnosed DSM or ICD Major Depressive Disorder, to high scores on depression inventories such as the BDI or Hamilton Rating Scale. However, these differences do not seem to have an impact on study findings because study results do not appear to vary according to the method used to identify depressed people. Second, there have been differing definitions of recurrence, although this is less of a problem since the publication of proposed consensus terms by Frank and colleagues (1991), and now most recent research employs these standard definitions. In addition, there has also been confusion about whether recurrence refers to a recurrent episode or whether it refers to a recurrent subtype of depression. Third, studies have varied in whether they include only individuals with unipolar depression, or whether they also include those with bipolar disorder who have experienced recurrent depressive episodes; this difference may account for some of the divergent findings reviewed in this paper, especially in studies using clinical samples where rates of bipolar disorder are often higher. Fourth, studies have varied in whether they include individuals with only unipolar depression and no comorbid psychopathology, which represent unusually “clean” cases of depression that are not representative of the general population of individuals with depression (Kessler et al., 1996). Alternatively, some studies only examine hospital readmission rates, which may represent only unusually severe cases of depression and may be missing the presence of less severe recurrent episodes which do not lead to re-hospitalization. Both of these factors may play a role in some of the divergent findings across studies. Fifth, investigations have varied in the extent to which they address the potential influence of maintenance therapy, psychotherapy or antidepressants, on recurrence. Finally, many studies note the high attrition rates that occur in research on depression, which might be influencing all of the reviewed research.

Despite these methodological differences, some variables *have* consistently been found to relate to recurrence of depression, while for other variables the evidence is more mixed. There

is considerable evidence that demographic variables are related to first-onset of depression. However, this is not the case for recurrence. Instead, from the studies reviewed, it appears that sex, SES, and marital status are not risk factors for depression recurrence.

Several clinical and family history variables do appear to be related to increased risk for recurrence, however. For example, there is evidence that both age at onset and number of prior episodes are related to recurrence, although their importance relative to one another has been difficult to determine due to their moderate intercorrelation. In addition, the severity of the first or index episode (as measured by number of symptoms or presence of suicidal thinking, but not duration) has been linked to increased risk for recurrence in adults but not in children. The presence of comorbid psychopathology, especially other affective disorders, also is related to recurrence risk in adults but not children. However, more research is necessary to determine which specific non-affective disorders confer increased risk for depression recurrence. Family history of psychopathology, particularly depression or other affective disorders, is also associated with increased risk for recurrence in those of all ages, although again more research is necessary regarding the role of non-affective disorders in increasing risk for recurrence of depression.

In addition, several psychological and psychosocial variables have been proposed as risk factors for recurrent depression, including negative cognitions, high neuroticism, poor social support, and stressful life events. There appears to be ample evidence from the studies reviewed that each of these variables is related not only to risk for first onset of depression, but also for recurrent depression. However, it is important to note that there is recent evidence supporting common genetic vulnerability to both recurrent depression and neuroticism or social support, and thus this might not be a directly causal relationship.

Thus, many variables appear to be related to risk for recurrence of depression. Many researchers, it seems, interpret these findings to mean that these risk factors are causally related to depression recurrence, and that if they could be somehow ameliorated, then recurrent episodes could potentially be avoided. A problem with this assumption is that it does not consider the possibility that these “risk factors” could actually be manifestations of the underlying liability to depression in general. Research on liability to depression has shown that it is due to genetic influences (h^2=40%) as well as to nonshared environmental factors. Research has also shown that depression liability may be better conceptualized as an underlying liability to internalizing disorders in general (e.g., Krueger, 1999). It is possible that those individuals who have inherited a greater risk for depression are at risk not only for an early age at first onset and for comorbid psychopathology, particularly other internalizing disorders, but also for a family history of depression, increased neuroticism, more stressful life events, and for greater numbers of episodes in their lifetime. On the other hand, individuals with a small inherited risk for depression would have later ages at first onset, fewer numbers of lifetime episodes, less neuroticism, fewer stressful life events, and less comorbid psychopathology in themselves and in their family members. Analyses on genetically informative samples will be necessary to determine if these clinical variables are indeed good candidate targets for preventative interventions, or if they might be better conceptualized as markers of the severity of the underlying liability to depression in general.

Finally, several scar theories were also reviewed. They are all similar in that they propose that something, presumably encoded at the biological level, changes during an episode of depression, which then makes future episodes more likely. There was virtually no evidence to support the existence of a psychosocial scar, but there was slight evidence in favor of the occurrence of a scar on cognitions, although only in children and adolescents, but not adults. Research on a personality scar suggested a very subtle impact of depression on later neuroticism, although it was not clear that the slight change in neuroticism scores could truly

be considered a scar and that this finding did not more simply reflect neuroticism's status as a risk factor for depression in general. Regarding stressful life events, there was considerable research to support SLEs as a risk factor for recurrent depression. In addition, there was some evidence to support the idea that sensitization to SLEs occurs, although it was not definitive. There was also some evidence of stress generation occurring. A direct comparison of these two hypotheses regarding SLEs would make an interesting future study.

One problem with the scar theories in general, however, is that they do not address the concern that the "cut-off" for depression risk may have already been met even before the first episode. For example, individuals with high levels of neuroticism are already at increased risk for a first-onset of depression. Just because one episode of depression increases their neuroticism scores, on average, this does not mean that their subsequent risk for depression is automatically increased; instead, it could be that they are at the same risk for recurrence because they already had sufficient levels of neuroticism in order to lead to depression in the first place. This is relevant for the other scar theories as well. Furthermore, it is important to note that the scar theories suppose that due to the greater rates of depression in those who have a history of depression compared to those who have no such history, it must be the case that depression itself somehow increases the vulnerability to becoming depressed again. However, a more parsimonious explanation may instead be that individuals at high risk for multiple episodes already possessed the necessary characteristics to make them prone to recurrent depression, and that these necessary characteristics existed even before their first episode. For example, individuals at high risk for a recurrent subtype of depression may already have higher levels of neuroticism or SLEs, even before their first episode; any changes in these domains that occur after a depressive episode may simply be reflecting a sequela of depression rather than a scar per se. Given the largely null findings in the area of scar theories, this is a highly plausible alternative. More specifically, the mechanism conferring premorbid risk for recurrent depression could involve an underlying genetic liability.

In conclusion, the prevention of recurrence is a daunting but important task. To date, several variables have been identified as risk factors for recurrence in adults deriving from the clinical picture (age at onset/number of episodes, severity, comorbidity), family history, cognitions, personality (neuroticism), poor social support, and stressful life events. Research to date, however, has *not* supported demographic variables (gender, SES, marital status) or duration of first/index episode as risk factors for recurrence. Finally, it should be noted that there is little evidence to support the idea that any of these risk factors operate through scarring.

It is also important to note that the literature has yielded somewhat different results for children and adolescents. While age at onset, family history of psychopathology, personality, and SLEs appear to act as risk factors for recurrence in both children and adults, severity of the first episode and comorbidity of other forms of psychopathology do *not* appear to be related to increased risk for recurrence in children and adolescents. Furthermore, there is some evidence to suggest that there *is* scarring on cognitions in children and adolescents with depression, whereas in adults cognitions are more likely risk factors rather than scars. Thus, these different findings regarding risk for recurrence of depression in children versus adults certainly deserves further exploration from researchers.

Another important issue, however, is the question of *why* this pattern of risk factors has emerged. The putative risk factors for recurrence may simply be reflecting an underlying vulnerability to a recurrent subtype of depression. That is, those at underlying risk for recurrent depression may also, even before their first episode onset, be at risk for the risk factors reviewed herein. More specifically, it is hypothesized that individuals inherit a level of risk for recurrent depression. If they are high in this underlying genetic vulnerability, they are also likely to have an earlier age at onset, greater numbers of depressive episodes, more severe episodes, greater

comorbidity, a stronger family history of depression, higher neuroticism scores, more SLEs, a depressogenic cognitive style, and less social support. While this is not to say that there is genetic predeterminism and that this genetic risk for recurrence and its associated risk factors cannot be modified through environmental mechanisms in order to alter the course of recurrences, it is likely that genetic factors may be strongly at play in the recurrent subtype of depression. It is this hypothesis regarding the underlying genetic vulnerability for recurrence and the putative risk factors reviewed herein that is most in need of further testing. There is a dearth of research on recurrence of depression using genetically informative samples, but it is with such samples that the most information can be obtained. Further research on the genetic underpinnings of recurrent depression, as well as how this relates to the putative risk factors reviewed earlier, is the most promising line of research for us to learn more about the etiology of recurrent depression.

References

Abramson LY, Seligman ME, Teasdale JD. Learned helplessness in humans: Critiques and reformulation. Journal of Abnormal Psychology 1978;87:49–74. [PubMed: 649856]

Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Panzarella C, Rose DT. Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. Journal of Abnormal Psychology 2006;115(1):145–156. [PubMed: 16492105]

Alpert JE. Improving depression outcome: New concepts, strategies and technologies. Journal of Psychopharmacology 2006;20(3 Suppl):3–4. [PubMed: 16644765]

Alpert JE, Maddocks A, Rosenbaum JF, Fava M. Childhood psychopathology retrospectively assessed among adults with early onset major depression. Journal of Affective Disorders 1994;31:165–171. [PubMed: 7963068]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington, DC: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd - revised. Washington, DC: American Psychiatric Association; 1987.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 1994.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Text Revision - Fourth. Washington, D.C.: American Psychiatric Association; 2000.

Barkow K, Maier W, Ustun TB, Gansicke M, Wittchen HU, Heun R. Risk factors for depression at 12-month follow-up in adult primary health care patients with major depression: an international prospective study. Journal of Affective Disorders 2003;76:157–169. [PubMed: 12943946]

Beck, A.; Rush, AJ.; Shaw, BF.; Emery, G. Cognitive Therapy of Depression. New York: The Guilford Press; 1979.

Beck, AT. Beck Depression Inventory - II. San Antonio, TX: The Psychological Corporation; 1996.

Belsher G, Costello CG. Relapse after recovery from unipolar depression: A critical review. Psychological Bulletin 1988;104(1):84–96. [PubMed: 3043528]

Bergeman CS, Plomin R, Pederson NL, McClearn GE. Genetic mediation of the relationship between social support and psychological well-being. Psychology and Aging 1991;6(4):640–646. [PubMed: 1777153]

Berlanga C, Heinze G, Torres M, Apiquian R, Caballero A. Personality and clinical predictors of recurrence of depression. Psychiatric Services 1999;50(3):376–380. [PubMed: 10096642]

Birmaher B, Arbelaez c, Brent D. Course and outcome of child and adolescent major depressive disorder. Child Adolesc Psychiatric Clin N Am 2002;11:619–627.

Birmaher B, Williamson DA, Dahl RE, Axelson DA, Kaufman J, Dorn LD, Ryan ND. Clinical presentation and course of depression in youth: Does onset in childhood differ from onset in adolescence? Journal of the American Academy of Child & Adolescent Psychiatry 2004;43(1):63–70. [PubMed: 14691361]

Bland RC, Newman SC, Orn H. Recurrent and nonrecurrent depression. Archives of General Psychiatry 1986;43:1085–1089. [PubMed: 3767598]

Bockting CL, Schene AH, Spinhoven P, Koeter MWJ, Wouters LF, Huyser J, Kamphuis JH. Preventing relapse/recurrence in recurrent depression with cognitive therapy: A randomized controlled trial. Journal of Consulting and Clinical Psychology 2005;73(4):647–657. [PubMed: 16173852]

Bos EH, Bouhuys AL, Geerts E, Van Os TWDP, Van der Spoel ID, Brouwer WH, Ormel J. Cognitive, physiological, and personality correlates of recurrence of depression. Journal of Affective Disorders 2005;87:221–229. [PubMed: 15979155]

Brugha TS, Bebbington PE, Stretch DD, MacCarthy B, Wykes T. Predicting the short-term outcome of first episodes and recurrences of clinical depression: A prospective study of life events, difficulties, and social support networks. Journal of Clinical Psychiatry 1997;58(7):298–306. [PubMed: 9269250]

Burcusa SL, Iacono WG, McGue M. Adolescent twins discordant for major depressive disorder: Shared familial liability to externalizing and other internalizing disorders. Journal of Child Psychology and Psychiatry 2003;44(7):997–1005. [PubMed: 14531582]

Butcher, JN.; Mineka, S.; Hooley, JM. Abnormal Psychology. 12. Boston: Pearson; 2004.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386–389. [PubMed: 12869766]

Coryell W, Endicott J, Keller M. Predictors of relapse into major depressive disorder in a nonclinical population. American Journal of Psychiatry 1991;148(10):1353–1358. [PubMed: 1897616]

Deister A, Marneros A. Predicting the long-term outcome of affective disorders. Acta Psychiatrica Scandinavica 1993;88:174–177. [PubMed: 8249648]

Depue RA, Iacono WG. Neurobehavioral aspects of affective disorders. Annual Review of Psychology 1989;40:457–492.

Dozois DJA. The psychometric characteristics of the Hamilton Depression Inventory. Journal of Personality Assessment 2003;80(1):31–40. [PubMed: 12584065]

Duggan CF, Sham P, Lee A, Minne C, Murray R. Neuroticism: A vulnerability marker for depression evidence from a family study. Journal of Affective Disorders 1995;35:139–143. [PubMed: 8749842]

Enns MW, Cox BJ. Personality dimensions and depression: Review and commentary. Canadian Journal of Psychiatry 1997;42:274–284.

Fanous A, Gardner CO, Prescott CA, Cancro R, Kendler KS. Neuroticism, major depression and gender: a population-based twin study. Psychological Medicine 2002;32:719–728. [PubMed: 12102386]

Feighner JP, Robins E, Guze SB, Woodruff RA, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Archives of General Psychiatry 1972;26:57–63. [PubMed: 5009428]

Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression: I. Psychiatric outcomes in adulthood. British Journal of Psychiatry 2001a; 179:210–217. [PubMed: 11532797]

Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression: II. Suicidality, criminality, and social dysfunction in adulthood. British Journal of Psychiatry 2001b;179:218–223. [PubMed: 11532798]

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Archives of General Psychiatry 1991;48:851–855. [PubMed: 1929776]

Giles DE, Jarrett RB, Biggs MM, Guzick DS, Rush AJ. Clinical predictors of recurrence in depression. American Journal of Psychiatry 1989;146(6):764–767. [PubMed: 2729427]

Gilman SE, Kawachi K, Fitzmaurice GM, Buka SL. Socio-economic status, family disruption and residential stability in childhood: Relation to onset, recurrent, and remission of major depression. Psychological Medicine 2003;33:1341–1355. [PubMed: 14672243]

Gonzales LR, Lewinsohn PM, Clarke GN. Longitudinal follow-up of unipolar depressives: An investigation of predictors to relapse. Journal of Consulting and Clinical Psychology 1985;53(4): 461–469. [PubMed: 4031201]

Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 1960;23:56–62.

Hammen C. Generation of stress in the course of unipolar depression. Journal of Abnormal Psychology 1991;100(4):555–561. [PubMed: 1757669]

Hammen C. Social stress and women's risk for recurrent depression. Arch Womens Ment Health 2003;6:9–13. [PubMed: 12715260]

Harkness KL, Monroe SM, Simons AD, Thase M. The generation of life events in recurrent and non-recurrent depression. Psychological Medicine 1999;29:135–144. [PubMed: 10077302]

Harris EC, Barraclough B. Suicide as an outcome for mental disorders: A meta-analysis. British Journal of Psychiatry 1997;170:205–228. [PubMed: 9229027]

Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder. Archives of General Psychiatry 2005;62:1097–1105. [PubMed: 16203955]

Iacono, WG. Control groups in schizophrenia research: A neglected source of variability. In: Cicchetti, D.; Grove, WM., editors. Thinking clearly about psychology: Essays in honor of Paul E Meehl. Minneapolis: University of Minnesota Press; 1991. p. 430-450.

Iacoviello BM, Alloy LB, Abramson LY, Whitehouse WG, Hogan ME. The course of depression in individuals at high and low cognitive risk for depression: A prospective study. Journal of Affective Disorders 2006;93:61–69. [PubMed: 16545464]

Joffe RT, Young T, Levitt AJ, MacQueen G, Marriott MJ, Robb J. Number of episodes and antidepressant response in major depression. International Journal of Neuropsychopharmacology 1999;2:111–113. [PubMed: 11281978]

Kaminski KM, Garber J. Depressive spectrum disorders in high-risk adolescents: Episode duration and predictors of time to recovery. Journal of the American Academy of Child and Adolescent Psychiatry 2002;41(4):410–418. [PubMed: 11931597]

Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. American Journal of Psychiatry 1999;156(6):837–841. [PubMed: 10360120]

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Familial influences on the clinical characteristics of major depression: a twin study. Acta Psychiatrica Scandinavica 1992;86(5):371–378. [PubMed: 1485527]

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A longitudinal twin study of personality and major depression in women. Archives of General Psychiatry 1993;50:853–862. [PubMed: 8215811]

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. Archives of General Psychiatry 1995;52(5):374–383. [PubMed: 7726718]

Kessing LV. Recurrence in affective disorder: II. Effect of age and gender. British Journal of Psychiatry 1998;172:29–34. [PubMed: 9534828]

Kessing LV. Severity of depressive episodes according to ICD-10: Prediction of risk of relapse and suicide. British Journal of Psychiatry 2004;184:153–156. [PubMed: 14754828]

Kessing LV, Andersen EW, Andersen PK. Predictors of recurrence in affective disorder - Analyses accounting for individual heterogeneity. Journal of Affective Disorders 2000;57:139–145. [PubMed: 10708825]

Kessing LV, Andersen PK, Mortensen PB, Bolwig TG. Recurrence in affective disorder: I. Case register study. British Journal of Psychiatry 1998;172:23–28. [PubMed: 9534827]

Kessler, RC. Gender differences in major depression: Epidemiological findings. In: Frank, E., editor. Gender and its effects on psychopathology. Washington, DC: American Psychiatric Press; 2000. p. 61-84.

Kessler RC, Magee WJ. Childhood adversities and adult depression: Basic patterns of association in a US national survey. Psychological Medicine 1993;23:679–690. [PubMed: 8234575]

Kessler RC, Magee WJ. Childhood family violence and adult recurrent depression. Journal of Health and Social Behavior 1994;35(1):13–27. [PubMed: 8014427]

Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity, and recurrence. Journal of Affective Disorders 1993;29:85–96. [PubMed: 8300981]

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Archives of General Psychiatry 1994;51:8–19. [PubMed: 8279933]

Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the US comorbidity survey. British Journal of Psychiatry 1996;168(suppl 30):17–30.

Kessler RC, Walters EE. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the national comorbidity survey. Depression and Anxiety 1998;7:3–14. [PubMed: 9592628]

Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates and course of minor depression and major depression in the national comorbidity survey. Journal of Affective Disorders 1997;45:19–30. [PubMed: 9268772]

Klein DN, Lewinsohn PM, Rohde P, Seeley JR, Durbin CE. Clinical features of major depressive disorder in adolescents and their relatives: Impact on familial aggregation, implications for phenotype definition, and specificity of transmission. Journal of Abnormal Psychology 2002;111(1):98–106. [PubMed: 11866183]

Klein DN, Schatzberg AF, McCullough ME, Dowling F, Goodman D, Howland RH, Markowitz JC, Smith C, Thase ME, Rush AJ, LaVange L, Harrison WM, Keller MB. Age of onset in chronic major depression: Relations to demographic and clinical variables, family history, and treatment response. Journal of Affective Disorders 1999;55:149–157. [PubMed: 10628884]

Klerman GL, Weissman MM. The course, morbidity, and costs of depression. Archives of General Psychiatry 1992;49:831–834. [PubMed: 1417437]

Kovacs M. Gender and the course of major depressive disorder through adolescence in clinically referred youngsters. Journal of the American Academy of Child & Adolescent Psychiatry 2001;40(9):1079–1085. [PubMed: 11556632]

Kovacs M, Feinberg TL, Crouse-Novak M, Paulauskas SL, Pollock M, Finkelstein R. Depressive disorders in childhood: II. A longitudinal study of the risk for subsequent major depression. Archives of General Psychiatry 1984;41:643–649. [PubMed: 6732424]

Kovacs M, Obrosky DS, Sherrill J. Developmental changes in the phenomenology of depression in girls compared to boys from childhood onward. Journal of Affective Disorders 2003;74:33–48. [PubMed: 12646297]

Krueger RF. The structure of common mental disorders. Archives of General Psychiatry 1999;56:921–926. [PubMed: 10530634]

Kuehner C. Gender differences in unipolar depression: An update of epidemiological findings and possible explanations. Acta Psychiatrica Scandinavica 2003;108:163–174. [PubMed: 12890270]

Kupfer DJ, Frank E. The interaction of drug- and psycho-therapy in the long-term treatment of depression. Journal of Affective Disorders 2001;62:131–137. [PubMed: 11172880]

Kupfer, DJ.; Frank, E.; Wamhoff, J. Mood disorders: Update on prevention of recurrence. In: Mundt, C.; Goldstein, MJ., editors. Interpersonal factors in the origin and course of affective disorders. London, England: Gaskell/Royal College of Psychiatrists; 1996. p. 289-302.

Lara ME, Leader J, Klein DN. The association between social support and course of depression: Is it confounded with personality? Journal of Abnormal Psychology 1997;106(3):478–482. [PubMed: 9241950]

Lewinsohn PM, Allen NB, Seeley JR, Gotlib IH. First onset versus recurrence of depression: Differential processes of psychosocial risk. Journal of Abnormal Psychology 1999;108(3):483–489. [PubMed: 10466272]

Lewinsohn PM, Clarke GN, Seeley JR, Rohde P. Major depression in community adolescents: Age at onset, episode duration, and time to recurrence. Journal of the Academy of Child and Adolescent Psychiatry 1994;33(6):809–818.

Lewinsohn PM, Hoberman HM, Rosenbaum M. A prospective study of risk factors for unipolar depression. Journal of Abnormal Psychology 1988;97(3):251–264. [PubMed: 3192816]

Lewinsohn PM, Joiner TE, Rohde P. Evaluation of cognitive diathesis-stress models in predicting major depressive disorder in adolescents. Journal of Abnormal Psychology 2001;110(2):203–215. [PubMed: 11368074]

Lewinsohn PM, Rohde P, Seeley JR, Klein DN, Gotlib IH. Natural course of adolescent major depressive disorder in a community sample: Predictors of recurrence in young adults. American Journal of Psychiatry 2000;157:1584–1591. [PubMed: 11007711]

Lewinsohn PM, Steinmetz JL, Larson DW, Franklin J. Depression-related cognitions: Antecedent or consequence? Journal of Abnormal Psychology 1981;90(3):213–219. [PubMed: 7288016]

Lewinsohn PM, Zeiss AM, Duncan EM. Probability of relapse after recovery from an episode of depression. Journal of Abnormal Psychology 1989;98(2):107–116. [PubMed: 2708651]

Mitchell PB, Parker GB, Gladstone GL, Wilhelm K, Austin MV. Severity of stressful life events in first and subsequent episodes of depression: The relevence of depressive subtype. Journal of Affective Disorders 2003;73:245–252. [PubMed: 12547293]

Moldin SO, Reich R, Rice JP. Current perspectives on the genetics of unipolar depression. Behavior Genetics 1991;21(3):211–242. [PubMed: 1863257]

Mongrain M, Blackburn S. Cognitive vulnerability, lifetime risk, and the recurrence of major depression in graduate students. Cognitive Therapy and Research 2006;29(6):747–768.

Monroe SM, Roberts JE, Kupfer DJ, Frank E. Life stress and treatment course of recurrent depression: II. Postrecovery associations with attrition, symptom course, and recurrence over 3 years. Journal of Abnormal Psychology 1996;105(3):313–328. [PubMed: 8772002]

Nolen-Hoeksema S, Girgus JS, Seligman ME. Predictors and consequences of childhood depressive symptoms: A 5-year longitudinal study. Journal of Abnormal Psychology 1992;101(3):405–422. [PubMed: 1500598]

Oldehinkel AJ, van den Berg MD, Bouhuys AL, Ormel J. Do depressive episodes lead to accumulation of vulnerability ini the elderly. Depression and Anxiety 2003;18:67–75. [PubMed: 12964173]

O'Leary D, Costello F, Gormley N, Webb M. Remission onset and relapse in depression: An 18-month prospective study of course for 100 first admission patients. Journal of Affective Disorders 2000;57:159–171. [PubMed: 10708827]

O'Leary DA, Lee AS. Seven year prognosis in depression: Mortality and readmission risk in the Nottingham ECT cohort. British Journal of Psychiatry 1996;169:423–429. [PubMed: 8894191]

Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, dificulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. American Journal of Psychiatry 2001;158(6):885–888. [PubMed: 11384895]

Paykel ES, Tanner J. Life events, depressive relapse and maintenance treatment. Psychological Medicine 1976;6:481–485. [PubMed: 792937]

Philibert R, Caspers K, Langbehn D, Troughton EP, Yucuis R, Sandhu HK, Cadoret RJ. The association of the D2S2944 124 bp allele with recurrent early onset major depressive disorder in women. American Journal of Medical Genetics Part B(Neuropsychiatric Genetics) 2003;121B:39–43.

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry 1992;149(8):999–1010. [PubMed: 1353322]

Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. Remission and relapse in major depression: A two-year prospective follow-up study. Psychological Medicine 1995;25:1161–1170. [PubMed: 8637946]

Rao U, Hammen C, Daley SE. Continuity of depression during the transition to adulthood: A 5-year longitudinal study of young women. Journal of the American Academy of Child & Adolescent Psychiatry 1999;38(7):908–915. [PubMed: 10405510]

Rao U, Ryan ND, Birmaher B, Dahl RE, Williamson DE, Kaufman J, Rao R, Nelson B. Unipolar depression in adolescents: Clinical outcome in adulthood. Journal of the American Academy of Child & Adolescent Psychiatry 1995;34(5):566–578. [PubMed: 7775352]

Rice F, Harold GT, Thapar A. The genetic aetiology of childhood depression: A review. Journal of Child Psychology and Psychiatry 2002;43(1):65–79. [PubMed: 11848337]

Rohde P, Lewinsohn PM, Seeley JR. Are people changed by the experience of having an episode of depression? A further test of the scar hypothesis. Journal of Abnormal Psychology 1990;99(3):264–271. [PubMed: 2212276]

Segal ZV, Pearson JL, Thase M. Challenges in preventing relapse in major depression: Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. Journal of Affective Disorders 2003;77:97–108. [PubMed: 14607387]

Shea MT, Leon AC, Mueller TI, Solomon DA, Warshaw M, Keller MB. Does major depression result in lasting personality change? American Journal of Psychiatry 1996;153(11):1404–1410. [PubMed: 8890672]

Sheeber L, Hops H, Alperty A, Davis B, Andrews J. Family support and conflict: Prospective relations to adolescent depression. Journal of Abnormal Child Psychology 1997;25(4):333–344. [PubMed: 9304449]

Simpson HB, Nee JC, Endicott J. First-episode major depression: Few sex differences in course. Archives of General Psychiatry 1997;54:633–639. [PubMed: 9236547]

Spitzer, RL.; Williams, JBW.; Gibbon, M. Structured Clinical Interview for DSM-III-R. New York: Biometrics Research Department, New York State Psychiatric Institute; 1987.

Spotts EL, Neiderhiser JM, Ganiban J, Reiss D, Lichtenstein P, Hansson K, Cederblad M, Pedersen NL. Accounting for depressive symptoms in women: A twin study of associations with interpersonal relationships. Journal of Affective Disorders 2004;82:101–111. [PubMed: 15465582]

Staner L, Tracy A, Dramaix M, Genevrois C, Vanderelst M, Vilane A, Bauwens F, Pardoen D, Mendlewicz J. Clinical and psychosocial predictors of recurrence recovered bipolar and unipolar depressives: A one-year controlled prospective study. Psychiatry Research 1997;69:39–51. [PubMed: 9080544]

Stice E, Ragan J, Randall P. Prospective relations between social support and depression: Differential direction of effects for parent and peer support? Journal of Abnormal Psychology 2004;113(1):115–159.

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. American Journal of Psychiatry 2000;157(10):1552–1562. [PubMed: 11007705]

Swann AC, Secundo SK, Stokes PE, Croughan J, Davis JM, Koslow SH, Maas JW. Stress, depression, and mania: Relationship between perceived role of stressful events and clinical and biochemical characteristics. Acta Psychiatrica Scandinavica 1990;81:389–397. [PubMed: 1693033]

Teasdale JD, Dent J. Cognitive vulnerability to depression: An investigation of two hypotheses. British Journal of Clinical Psychology 1987;26:113–126. [PubMed: 3580646]

Wade TD, Kendler KS. The relationship between social support and major depression: cross-sectional, longitudinal, and genetic perspectives. Journal of Nervous and Mental Disease 2000;188(5):251–258. [PubMed: 10830561]

Wainwright NWJ, Surtees PG. Childhood adversity, gender and depression over the life-course. Journal of Affective Disorders 2002;72:33–44. [PubMed: 12204315]

Warner V, Weissman MM, Fendrich M, Wickramaratne P, Moreau D. The course of major depression in the offspring of depressed parents. Archives of General Psychiatry 1992;49:795–801. [PubMed: 1417432]

Wilhelm K, Parker G, Dewhurst-Savellis J, Asghari A. Psychological predictors of single and recurrent major depressive episodes. Journal of Affective Disorders 1999;54:139–147. [PubMed: 10403157]

Williams, JMG.; Watts, FN.; MacLeod, C.; Mathews, A. Cognitive psychology and emotional disorders. New York: Wiley; 1988.

Williamson DE, Ryan ND, Dahl RE, Jeannette L. Hamilton depression scores can be extracted from the K-SADS-P in adolescents. Journal of Child and Adolescent Psychopharmacology 1992;2(3):175–181.

Wittchen HU, Nelson CB, Lachner G. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychological Medicine 1998;28:109–126. [PubMed: 9483687]

World Health Organization. International Classification of Disease. 9. Geneva: World Health Organization; 1978.

Zeiss AM, Lewinsohn PM. Enduring deficits after remissions of depression: A test of the scar hypothesis. Behav Res Ther 1988;26(2):151–158. [PubMed: 3365205]

Zubenko GS, Hughes HB III, Stiffler JS, Zubenko WN, Kaplan BB. D2S2944 identifies a likely susceptibility locus for recurrent, early-onset, major depression in women. Molecular Psychiatry 2002;7:460–467. [PubMed: 12082563]

Zubenko GS, Zubenko WN, Spiker DG, Giles DE, Kaplan BB. Malignancy of recurrent, early-onset major depression: A family study. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2001;105:690–699. [PubMed: 11803516]

Table 1

Methodological differences in the reviewed studies.

study	sample	cross-sectional vs.longitudinal (follow-up time)	depression measure	how "recurrence" was examined	treatment
Alloy et al., 2006	347 college freshmen	Longitudinal (2.5 years)	DSM-III-R diagnosis	single-episode vs. recurrent	None noted
Alpert et al., 1994	116 depressed adult outpatients	Corss-sectional	DSM-III-R diagnosis	Number of episodes	Double-blind pharmacological
Barkow et al., 2003	725 depressed adults	Longitudinal (1 year)	ICD-10 diagnosis	Depression at time 2 vs. none	None noted
Berlanga et al., 1999	42 outpatients with a history of depression	Longitudinal (1 year)	DSM-IV diagnosis and HDRS score	a recurrence vs. no recurrence	Double-blind pharmacological
Birmaher et al., 2004	68 children and adolescents	Longitudinal (5 years)	DSM-III-R and HDRS	Single-episode vs. recurrent	None noted
Bland et al., 1986	763 first-degree relatives of 75 depressed inpatient probands	Cross-sectional for relatives, longitudinal (12—18 years) for probands	Feighner et al. criteria	Single-episode vs. recurrent	None noted for relatives, not described for probands
Bockting et al., 2005, 2006	187 adults with a history of recurrent depression	Longitudinal (2 years)	DSM-IV diagnosis	a recurrence vs. no recurrence	Treatment as usual vs. group CBT
Bos et al., 2005	102 outpatients with a history of depression	Cross-sectional	DSM-IV diagnosis	Single-episode vs. recurrent	None noted
Caspi et al., 2003	1037 young adults	Longitudinal (23 years total)	DSM-IV diagnosis	Depression at follow-up	None noted
Coryell et al., 1991	396 adults	Longitudinal (6 years)	RDC diagnosis	A recurrence vs. no recurrence	None noted
Deister & Marneros, 1993	106 adults with an affective disorder	Longitudinal (10 to 56 years)	DSM-III or DSM-III-R	Multiple recurrences or not	Not described
Duggan et al., 1995	79 first-degree relatives of inpatients with MDD	Cross-sectional	RDC diagnosis	Single-episode vs. recurrent	None noted
Fombonne et al., 2001a, 2001b	149 inpatient children	Longitudinal (20 years)	ICD-9	A recurrence vs. no recurrence	Not described
Giles et al., 1989	30 adults with a history of depression	Longitudinal (3 years)	RDC diagnosis and HDRS	A recurrence vs. no recurrence	Antidepressants or CBT
Gilman et al., 2003	1089 adults	Cross-sectional	DSM-III or DSM-IV	number of episodes predicting outcome	None noted
Gonzalez et al., 1985	113 outpatients with a history of depression	Longitudinal (1 to 3 years)	RDC diagnosis	A recurrence vs. no recurrence	Group or individual CBT
Hammen, 1991	14 depressed women	Longitudinal (1 year)	DSM-III-R	A recurrence vs. no recurrence	None noted
Hammen, 2003	816 women	Cross-sectional	DSM-IV	A recurrence vs. no recurrence	None noted
Harkness et al., 1999	59 depressed outpatients	Cross-sectional	RDC diagnosis, BDI and HDRS	Single-episode vs. recurrent	Individual CBT
Iacoviello et al., 2006	159 initially non-depressed college freshmen	Longitudinal (2.5 years)	DSM-III-R diagnosis	Predicting number of episodes	None noted
Joffe et al., 1999	135 depressed adults	Cross-sectional	HDRS	Number of episodes	pharmacological
Kaminski & Garber, 2002	185 high-risk adolescents	Longitudinal (6 years)	DSM diagnosis	Single-episode vs. recurrence	None noted
Kendler et al., 1993	1733 female twins	Longitudinal (15 months)	DSM-III-R diagnosis	Both	None noted
Kessing 1998, 2004; Kessing et al., 1998, 2000	20,350 first-admission patients with an affective disorder	Longitudinal (admissions from 1971 to 1993)	ICD-8	Number of hospital re-admissions	Not described
Kessler et al., 1993	8098 adults	Cross-sectional	DSM-III-R	Single-episode vs. recurrent	None noted
Kessler & Magee 1993	1024 adults with a history of depression	Longitudinal (3 years)	"A" criterion of DSM-III-R	A recurrence vs. no recurrence	None noted
Klein et al., 1999	289 depressed outpatients	Cross-sectional	DSM-III-R and HDRS	Single-episode vs. recurrent	Double-blind pharmacological
Kovacs et al., 1984, 2001	65-92 depressed children	Longitudinal (6-10 years)	DSM-III	Single-episode vs. recurrent	None noted
Lewinsohn et al., 1989	2046 adults	Cross—sectional	RDC and CES-D	Single-episode vs. recurrent	None noted

study	sample	cross-sectional vs.longitudinal (follow-up time)	depression measure	how "recurrence" was examined	treatment
Lewinsohn et al., 1988,1994, 1999, 2000	Up to 1709 adolescents, 362 with a history of depression	Longitudinal (8 months to 10 years)	DSM-III-R or BDI	both	None noted
Mitchell et al., 2003	270 depressed adults (inpatient or outpatient)	Cross-sectional	DSM-IV	Single-epsidoe vs. recurrent	Not described
Mongrain & Blackburn, 2006	97 graduate students	Longitudinal (16 months)	DSM-IV diagnosis	a recurrence vs. no recurrence	None noted
Monroe et al., 1996	67 adults with recurrent depression	Longitudinal (17 weeks following recovery)	RDC, BDI and HDRS	A recurrence vs. no recurrence	Pharmacotherapy and/or IPT
Nolen-Hoeksema et al., 1992	508 3rd -grade children	Longitudinal (5 years)	CDI	Depression at multiple time points	None noted
Oldehinkel et al., 2003	26 elderly adults with a history of depression	Longitudinal (2 years)	DSM-IV and HDRS	Single-episode vs. recurrent	None noted
O'Leary & Lee, 1996	118 depressed patients treated with ECT	Longitudinal (7 years)	HDRS	Readmission for a recurrence or not	Not described
O'Leary et al., 2000	100 depressed adult inpatients	Longitudinal (18 months)	ICD-10 or HDRS	A recurrence vs. no recurrence	Not described
Paykel et al., 1976; Ramana et al., 1995	57 adults (inpatient or outpatient)	Longitudinal (15 months following remission)	RDC, DSM-III-R and ICD-10 diagnosis, and HDRS	A recurrence vs. no recurrence	Not described
Rao et al., 1995	28 depressed adolescents	Longitudinal (7 years)	RDC and DSM-III- R diagnoses	a recurrence vs. no recurrence	None noted
Rao et al., 1999	155 women (age 18 at intake)	Longitudinal (5 years)	DSM-III-R	both	None noted
Rohde et al., 1990	49 adults	Longitudinal (2 years)	CES-D	One depressive episode	None noted
Shea et al., 1996	28 adults	Longitudinal (6 years)	RDC diagnosis	One depressive episode	None noted
Staner et al., 1997	24 adults with a history of depression	Longitudinal (1 year)	RDC diagnosis	A recurrence vs. no recurrence	Antidepressant prophylaxis
Simpson et al., 1997	195 first-episode depressed adults	Longitudinal (5 years)	RDC diagnosis and HDRS	Single-episode vs. recurrent	None noted
Swann et al., 1990	85 depressed adults	Cross-sectional	RDC diagnosis	Single-episode vs. recurrent	None noted
Wade & Kendler, 2000	1898 female twins	Longitudinal (5 years)	DSM-III-R	Depression in the past year	None noted
Wainwright and Surtees, 2002	3491 adults	Cross-sectional	DSM-IV	Single-epsiode vs. recurrent	None noted
Wilhelm et al., 1999	164 adults	Longitudinal (15 years)	DSM-III and DSM-III-R	Single-episode vs. recurrent	None noted
Zeiss & Lewinsohn, 1988	66 depressed adults	Cross-sectional	MMPI-D	Depression at two time points	psychotherapy
Zubenko et al., 2001	407 first-degree relatives and 835 extended relatives of 81 probands with recurrent depression	Cross-sectional	DSM-IV	Single-episode vs. recurrent	None noted

CBT = cognitive behavioral therapy, IPT = interpersonal psychotherapy, DSM = Diagnostic and Statistical Manual, HDRS = Hamilton Depression Rating Scale, ICD = International Classification of Diseases, CES-D = Center for Epidemiologic Studies Depression Scale, BDI = Beck Depression Inventory, RDC = Research Diagnostic Criteria, ECT = electro-convulsive therapy, CDI = Children's Depression Inventory, MMPI-D = Minnesota Multiphasic Personality Inventory Depression scale T-scores