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Brief report

# Sex differences in clinical predictors of depression: A prospective study

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ABSTRACT

*Background:* Estimating the likelihood of future major depressive episodes (MDEs) would assist clinicians in decision-making regarding the optimal length of treatment for MDE. Unfortunately, little data are available to guide clinical practice.
*Methods:* We followed 200 females and 152 males who responded to treatment for a MDE for 2 years to determine risk factors for future MDE. Cox Proportional Hazard Regression modeled time to first relapse into MDE and mixed effect logistic regression modeled monthly depression status.
*Results:* Females were more likely than males to experience a MDE in any month of the study, and marginally more likely to experience a relapse. By 12 months, 60% of females had relapsed compared to 51% of males (median time to relapse 8 vs. 13 months, respectively). Several factors predicted worse outcome for both men and women: reported childhood abuse, earlier age of onset of first MDE, bipolar disorder, unemployment, and more years of education. For females, but not males, suicidal ideation predicted MDE relapse and both suicidal ideation and prior suicide attempts were associated with more time in a MDE.
*Limitations:* The naturalistic treatment of participants, exclusion of individuals with current comorbid alcohol or substance use disorder, and a follow up period of two years are limitations.
*Conclusions:* Women are more vulnerable to relapse and spend more time depressed compared to men. Identification of general and sex-specific risk factors for future depression may provide clinicians with useful tools to estimate need for ongoing pharmacotherapy in MDE.



## 1. Introduction

When first prescribed antidepressants, patients often ask how long they will need to take medication and whether symptoms will recur. Unfortunately, little data is available to guide counseling, even though anchors for clinical decision-making are sorely needed. Further, although depression prevalence differs in men and women, few studies have examined whether risk for future depression differs across sexes and if so, whether clinical moderators exist.

Predictors of relapse or recurrence of depression include being single (Coryell et al., 1991; Mueller et al., 1999), lower socio-economic status (Kessler et al., 1994; Rao et al., 1995), childhood abuse (Gopinath et al., 2007; Suija et al., 2011), number of episodes (Bockting et al., 2006; Gonzales et al., 1985; Kessing, 1998; Kessing et al., 2004; Lewinsohn et al., 1989; Maj et al., 1992; Mueller et al., 1999; Winokur et al., 1993), life events (Kendler et al., 1993), comorbidities (Hart et al., 2001; Ilardi et al., 1997; Giles et al., 1989; Grilo et al., 2010), neuroticism (Berlanga et al., 1999; Duggan et al., 1995; Kendler et al., 1993), and suicide attempts (Wilhelm et al.,1999).

While several studies have found females are at higher risk for future major depressive episodes (MDE) than males (Kessing, 1998; Mueller et al., 1999) others have not (Coryell et al., 1991; Kovacs et al., 1984; Kessing et al., 2004; Kovacs, 2001; Rao et al., 1995; Simpson et al., 1997; Wilhelm et al., 2002). In addition, Winokur et al. (1993) found that females with unipolar depression were more likely to have a future MDE; but no sex differences in bipolar participants. None of these studies examined specific clinical risk factors that might contribute to sex differences.

We examined whether risk for future depression differed for men and women and whether clinical predictors differed across sexes. Our sample is one of the largest to date, surpassed only by the NIMH Collaborative Study ($n=955$) (Mueller et al., 1999), the STAR-D study ($n=943$) (Nierenberg et al., 2010), and the Zurich Youth Cohort ($n=591$) (Angst and Merikangas, 1997). We hypothesized that females would be at greater risk for future MDE, based on the higher point prevalence of depression for women (Kessler et al., 1994). Since a search engine-assisted literature search uncovered no studies of moderators of risk for future MDE, we

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explored whether baseline demographic, developmental or clinical moderators would differentially predict relapse into depression or time spent depressed across sexes.

## 2. Methods

### 2.1. Participants

Written informed consent, as approved by the Institutional Review Board, was obtained from 200 females and 152 males, ages 18–75, who had responded to treatment for MDE. Exclusion criteria included current alcohol or substance abuse, neurological illness or active medical conditions that could confound clinical characterization.

### 2.2. Materials and procedures

Ratings were conducted by trained clinicians with at least a Master's Degree. Axis I diagnoses were made using the SCID (Spitzer et al., 1990). Childhood physical or sexual abuse were rated as present or absent. Depression symptoms were rated using the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Subjects provided age of onset of their first MDE, number of previous MDEs, and family history of depression. The Scale for Suicide Ideation (SSI) (Beck et al., 1979) measured suicidal ideation. Suicide attempts were recorded using the Columbia Suicide History Form (Oquendo et al., 2003). Life stressors at study entry were evaluated with the St. Paul-Ramsey Questionnaire. Follow up assessments occurred at 3 months, 1 year and 2 years and determined whether patients had suffered any MDEs in the intervening period, and if so, during which month(s).

### 2.3. Statistical methods

Baseline characteristics of men and women were compared using *t*-tests and chi square statistics. To analyze time to first relapse into depression, Cox Proportional Hazard Regression was used. A separate survival analysis model was fit for each candidate risk factor, with sex, the risk factor, and their interaction as predictors.

We also tested predictors of time spent depressed during follow-up, using monthly depression status data. 7275 person-months were observed for 352 subjects. A survival analysis model was fit for each candidate risk factor, with sex, the risk factor, and their interaction as predictors and presence/absence of MDE measured in person-months, as the response. The longitudinal logistic regression with correlated errors was performed in SAS 9.2 using proc glimmix with an AR(1) correlation structure between residuals at consecutive time-points for the same subject. Risk factors were considered significant for both sexes if the main effect of the risk factor was significant but not the interaction. A significant interaction between sex and the risk factor was interpreted as denoting a differential risk factor, and the main effect's odds or hazard ratio and significance level determined whether the risk factor was significant for males, females or neither. Since this study is exploratory, we did not adjust for multiple testing.

## 3. Results

The sample was mostly female and moderately depressed before response to treatment (Table 1). Time to drop-out or last visit was similar for females and males (25 vs. 24 months, respectively, Wilcoxon test $W=15686$, $p=0.6067$). Women had higher depression scores, earlier onset of mood disorder, and more frequently reported childhood abuse and family history of depression.

Females were marginally more likely than males to experience a MDE during follow-up, (HR=1.30, 95%CI: 1.00–1.70, $z=1.9$, $p=0.0547$). By 12 months, 60% of females had relapsed compared to 51% of males. Estimated median times to first relapse, based on the Kaplan–Meier method, were 8 months for females (95%CI: 6–10) and 13 months (95%CI: 8–19) for males. Females were more likely than males to experience a MDE in any given month (OR=1.47, 95%CI=1.16–1.86, $t=3.21$, df=350, $p=.0014$).

### 3.1. Risk factors common to males and females

More education, earlier age of onset and childhood abuse predicted relapse for both sexes. Time spent depressed was significantly higher in those unemployed at baseline, with more education, earlier onset of disease, and with bipolar disorder (Table 2).

### 3.2. Risk factors specific to females

For women, suicidal ideation was associated with a higher likelihood of both relapse of depression and of being depressed during follow-up (HR=1.02, $z=2.66$, $p=.0077$; and OR=1.02, $t=3.24$, df=320, $p=.0013$), while past suicide attempts predicted more time spent depressed (OR=1.39, $t=2.09$, df=438, $p=.0372$) and tended to confer risk for relapse (HR=1.39, $z=1,91$, $p=.0557$). For men, neither of these factors increased relapse risk. Interaction terms in all these models were significant (Table 2).

## 4. Discussion

As hypothesized, females are more likely than males to relapse during a 2-year period. This finding is consistent with some (Kessing, 1998; Mueller et al., 1999; Winokur et al., 1993), but not all (Coryell et al., 1991; Gonzales et al., 1985; Kovacs et al., 1984; Kovacs, 2001; Rao et al., 1995; Simpson et al., 1997) previous work. Negative findings generally have emerged from analyses of smaller sample sizes, possibly due to limited power. Consistent with others (Hart et al., 2001), perhaps the most remarkable finding is the brevity of time between episodes, 8–13 months, supporting the notion that affective disorders are best conceptualized as chronic, relapsing conditions.

### 4.1. Risk factors common to males and females

Those with reported childhood abuse had earlier reappearance of MDE than those without such history, evidence for the lasting impact of childhood adversity. Childhood abuse is a predictor of MDE in clinical samples of men and women (Gopinath et al., 2007; Suija et al., 2011). However, neither study assessed time to future MDE or length of the new episode, nor did they examine effects of childhood abuse by sex. Whether childhood abuse has different effects in men and women has not been studied extensively. A handful of population studies report no differences in outcomes for males and females reporting abuse (Eisenberg et al., 2007; Fergusson et al., 2008; for review see Gershon et al., 2008), although not all agree (Robinson et al., 2001; Banyard et al., 2004).

Life events did not predict risk, although events were measured at baseline only, since we were seeking moderators. This finding is in contrast to some evidence (Keller et al., 2007) that links life events to depression onset, even suggesting that different life events predict subsequent depressive symptom patterns. Nonetheless, more recent work (Kendler et al., 2011) suggests life