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Predictors of first episode unipolar major depression in individuals with and without sub-threshold depressive symptoms: A prospective, population-based study

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Abstract

Background—The aim of this study is to assess predictors of first-episode major depression in a community-based sample of adults with and without sub-threshold depression.

Method—Data were from Waves 1 & 2 of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Participants meeting criteria for a sub-threshold depressive episode (sMDE; $n = 3,901$) reported lifetime depressed mood/loss of interest lasting at least two weeks and at least two of the seven other DSM-IV symptoms of MDD. Predictors of MDE 3 years later were compared in those with and without ($n = 31,022$) sMDE.

Results—Being female, history of alcohol or substance use, and child abuse increased the odds of developing MDD to a greater degree in individuals without sMDE relative to those with sMDE. Among those with sMDE and additional risk factors (low education, substance use), younger age was associated with marginally increased risk of MDD.

Conclusion—Several demographic risk factors may help identify individuals at risk for developing MDD in individuals who have not experienced an sMDE who may be candidates for early intervention. Future work should assess whether preventative interventions targeting substance/alcohol use and child abuse could reduce the risk of depression.

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Conflicts of Interest

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Contributors

Amy T. Peters proposed the hypotheses and analytic plan, conducted the analyses, and drafted the manuscript. Stewart A. Shankman assisted with the conceptualization of the study design, hypotheses, and analytic plan. Thilo Deckersbach was responsible for reviewing/editing the manuscript and providing supervision on the data analyses. Amy E. West was responsible for the overall study design and reviewing/editing the manuscript.

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Keywords

depression; sub-threshold; risk factors

Introduction

Major depressive disorder (MDD) is among the most common mental disorders. MDD is associated with significant impairment in individual functioning, as well as a costly burden in terms of economic expenditures (McLaughlin, 2011; Organization, 2008). Importantly, the public health impact of depression is likely much wider than estimates based on full syndromal MDD, as there is a growing recognition of the negative impact of sub-threshold depression (Lewinsohn et al., 2000; Pincus et al., 1999). Lifetime prevalence rates of sub-threshold depression may be as high as 26% (Lewinsohn et al., 2004) and symptoms of sub-threshold depression are associated with significant impairment in functioning (Lewinsohn et al., 2000). In at least one study, impairment associated with sub-threshold depression is comparable to that of MDD (Gotlib et al., 1995). Sub-threshold depression is also associated with elevated risk for developing MDD (Georgiades et al., 2006; Keenan et al., 2008; Pine et al., 1999; Shankman et al., 2009). However, not all individuals with sub-threshold symptoms escalate to full syndrome MDD. Identifying individual factors that further specify the nature of risk for developing MDD has the potential to improve the accuracy and efficiency of screening procedures and target prevention programs in a manner that is most likely to reduce the risk of symptom escalations.

Surprisingly, relatively few studies have utilized longitudinal designs to identify the characteristics of individuals with sub-threshold symptoms who are more likely to develop MDD. A study of adults in primary care found an 18.35% rate of MDE onset after one year. Severity of depressive symptoms, family history of MDD, and having a chronic general medical illness were associated with increased risk of onset (Cuijpers et al., 2005). In a subsequent study of older adults with elevated scores on a depression screening measure, Cuijpers et al found that 20.1% of individuals developed MDD or dysthymia by 6 year follow up. Low appetite and trouble sleeping conferred a higher likelihood of developing a mood disorder (Cuijpers et al., 2006). More recently, predictors of escalation to full-syndrome depressive disorders were examined in a community sample of 225 adolescents with a conversion rate from sub-threshold to major depression of 67% (Klein et al., 2009). Severity of depressive symptoms, medical conditions/symptoms, history of suicidal ideation, history of anxiety disorder, and familial loading for MDD predicted escalation. A later study from the same project investigated specific combinations of risk factors to improve the sensitivity and specificity of predicting MDD onset (Hill et al., 2014). Adolescents with a history of sub-threshold depression were at highest risk of escalation to MDD if they fell into either of two clusters; those with friend support and an anxiety or substance use disorder, or those with better friend support, but multiple major life events, and an anxiety disorder.

Although existing studies have helped to identify common demographic and clinical risk factors for the transition from sub- to full-threshold depression, several important

methodological gaps remain. First, the generalizability of previous findings is unclear, as there is an essential lack of studies based on nationally representative community samples with a prospective follow-up. Findings from age-specific cohorts, or from individuals seeking treatment in primary care, may not be representative of the overall population. Second, the onset of MDD is not necessarily predated by a sub-threshold depressive episode. Data from existing studies do not clarify whether variables that predict the first onset of MDD are unique to individuals with sub-threshold symptoms, or are risk factors for MDD across all individuals. Third, risk factors for MDD may vary as a function of age (Jaffee et al., 2002). Individuals with adolescent or young adult onset are likely to be more severe (Korten et al., 2012), thus rates and risk factors for conversion to MDD may be magnified during certain periods in adulthood. An ideal sample is one that is well powered to assess the moderating effect of age on rates and risk factors across the lifespan.

The aims of the current study are three-fold. To aid in replication efforts we will first examine prospective predictors of first episode MDD over a three-year follow up period using the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; (Grant BF, 2007; Grant BF, 2003), a large, nationally representative, community-based sample. The primary aim is to examine whether predictors of first episode MDD pertain more strongly to individuals who experienced a sub-threshold depressive episode (sMDE) or broadly predict the development of a first major depressive episode (MDE) in individuals regardless of whether they have experienced an sMDE. Next, we will evaluate whether predictors of MDD onset vary according to age. Predictors were selected that were associated with escalation in previous studies (e.g. medical burden, family history (Cuijpers et al., 2006; Cuijpers et al., 2005; Klein et al., 2009)), part of a standard mental health assessment (anxiety, substance/alcohol use, child abuse), or are typically assessed in routine clinical screenings (demographics). Importantly, any positive findings from the selected predictors have the potential for immediate clinical translation and impact since they represent characteristics that are common, affordable, and feasible to assess.

Method

Study Design

Data for this study were sourced from the 1st and 2nd waves of the NESARC (Grant BF, 2007; Grant BF, 2003). Full details regarding data acquisition methods have been reported previously (Grant BF, 2007; Grant BF, 2003). Briefly, this nationally representative sample was drawn from non-institutionalized individuals across the United States using a combination of face-to-face and computer-assisted interviews. The Wave 1 survey was administered between 2001 and 2002. 43,093 respondents completed the Wave 1 survey with an overall response rate of 81%. A longitudinal follow-up to the Wave 1 survey was conducted approximately 3 years later. In Wave 2, all Wave 1 participants were re-interviewed, barring those unavailable due to death, migration, active military duty during follow-up period, or physical/mental incapacity. 34,653 individuals completed follow-up interviews with an overall response rate of 86.7%.

Participants

Participants were 18 years or older at time of enrollment in Wave 1. Individuals met criteria for the sMDE group at Wave 1 if they ever in their life experienced an episode of depressed mood or loss of interest or pleasure lasting at least two weeks during which they also experienced at least two of the seven other DSM-IV symptoms of an MDE, but never experienced any full-syndrome mood disorder (MDD, dysthymia, bipolar I disorder, and bipolar II disorder). This definition is consistent with other studies on sub-threshold depression (Cuijpers et al., 2006; Cuijpers et al., 2005; Hill et al., 2014; Klein et al., 2009). Of the 43,093 respondents who completed the Wave 1 survey, $n = 8,170$ participants met criteria for a lifetime full-syndrome mood disorder, and were excluded from the analysis. This left a total sample of $N = 34,923$ participants. Of these participants, $n = 3,910$ met criteria for a lifetime sMDE at Wave 1. This resulted in $n = 31,022$ participants without a lifetime sMDE or full-threshold mood disorder at Wave 1 as a comparison group. At Wave 2, $n = 1,314$ of this sample met criteria for a full-threshold unipolar major depressive episode (participants who escalated to bipolar disorder I or II or dysthymia were not included). Demographic and clinical characteristics of the sample are reported in Table 1.

Diagnostic Measures

At Wave 1 and Wave 2, participants were interviewed with the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV), which distinguished lifetime and present episodes of psychiatric disorders. At Wave 2, the AUDADIS-IV provided information regarding the onset and course of disorders since the previous interview to yield the incidence of new cases of psychiatric diagnoses during the period of follow up. The following axis I disorders were evaluated at both waves: major depression, dysthymia, bipolar I disorder, bipolar II disorder, panic disorder with/without agoraphobia, agoraphobia without panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), alcohol abuse or dependence, and drug abuse or dependence (evaluated drugs: amphetamines, opioids, sedatives, tranquilizers, cocaine, inhalants/solvents, hallucinogens, cannabis, heroin, and other drugs). Inter-rater reliabilities for all full-threshold diagnoses ranged from good to excellent (Grant et al., 2005a; Grant et al., 2004; Grant et al., 2005b).

Predictors of Escalation to Full Syndrome

Predictors included four demographic variables (age, sex, race, and education), four variables reflecting non-mood psychiatric disorders or medical problems (lifetime anxiety disorder, lifetime alcohol use disorder, lifetime drug use disorder, and number of medical conditions in the 12 months before Wave 1), and two family history variables (any 1st degree family history of depression and history of childhood abuse).

Data Analytic Approach

All statistical analyses were completed using SPSS statistics version 21 complex sampling procedures, which adjusts variance and point estimates for the multi-stage sampling design and differential selection probabilities used to ascertain the NESARC sample (see (Grant BF, 2007; Grant BF, 2003). The NESARC data were weighted to: (1) reflect the probabilities of selection of primary sampling units (PSUs) within stratum and for the

selection of housing units within the sample PSUs; (2) account for oversampling of young adults; (3) account for the selection of one sample person from each household; (4) adjust for non-response at the household level and person level. The NESARC data are adjusted on a variety of socio-demographic variables including region, age, sex, race, and ethnicity to be representative of the U.S. population. Standard error and confidence interval estimates were also estimated using SPSS Complex Samples module, which uses appropriate statistical techniques to adjust for sample design characteristics. Weighted percentages and means with their standard error using the Wave 2 sampling weights are presented; actual sample sizes are reported.

The dependent variable in all models was a binary outcome reflecting presence of a first onset of MDD by Wave 2. To replicate previous studies, univariate predictors were each entered as independent variables in separate binary logistic regression models to evaluate transition to MDD. Categorical predictors were dummy coded as follows: sex (female = 1, male = 0), race (non-white race = 1, white = 0), lifetime anxiety (yes = 1, no = 0), lifetime substance use (yes = 1, no = 0), lifetime alcohol use (yes = 1, no = 0), family history of depression (yes = 1, no = 0), child abuse (yes = 1, no = 0). Continuous predictors were mean-centered. Predictors from this first step were then entered simultaneously into a separate multivariate logistic regression model to examine which variable contributed uniquely to the prediction of first onset of MDD.

To test our primary aim (whether predictors of developing MDD differed among individuals with and without sMDE), an interaction term between each predictor and sMDE status was added to the univariate models. Given the large number of predictors evaluated, interactions were not tested simultaneously to avoid exaggerated minor fluctuations associated with an over-fitted model (Hawkins, 2004). Significant interactions were then followed-up with simple slopes (Aiken and West, 1991). For binary moderators, simple slopes were tested at each level of the moderator. For continuous moderators, simple slopes were tested one standard deviation above (high), below (low), and at the mean (average). To test our secondary aim, age was included in the models to test two-way interactions (predictor x age) and three-way interactions (predictor x sMDE status x age). All continuous predictors were mean-centered when included in an interaction term. Given the large sample and the number of models run to address the study aims, an alpha-threshold was set at .01 to adjust for multiple comparisons. 95% confidence intervals for OR are reported.

Results

Risk of Escalation

Of the 3,901 participants who had sMDE by Wave 1, 184 (4.72% [un-weighted]) developed MDD by Wave 2. Of $n = 31,022$ participants without sub-threshold depression at Wave 1, $n = 1,130$ (3.24%) developed MDD at Wave 2. Sub-threshold depression at Wave 1 was associated with significantly greater risk of developing MDD ($p < .001$, $OR = 1.49$, $CI: 1.36-1.62$).

Predictors of First Episode MDD

In univariate models, 9 of 10 variables predicted the development of MDD at Wave 2 (Table 2). Across all participants, demographic characteristics that conferred heightened risk of developing MDD included younger age ($p<.001$, OR=.99), being female ($p<.001$, OR=2.13), fewer years of education ($p<.001$, OR=.98), and non-white race ($p=.003$, OR=1.16). A lifetime anxiety disorder ($p<.001$, OR=2.01), lifetime drug use disorder ($p<.001$, OR=1.33), lifetime alcohol use disorder ($p=.008$, OR=1.11), history of child abuse ($p<.001$, OR=3.58), and any 1st degree family history of depression were also predictive of developing MDD ($p<.001$, OR=1.62). Lifetime co-morbid medical conditions did not predict the development of MDD. All variables remained significant predictors of developing MDD in the multivariate model except for a lifetime drug use disorder.

Predictors of First Episode MDD in Individuals With and Without Sub-threshold Depression

Interaction terms between univariate predictors and sub-threshold depression status at Wave 1 indicated that the effect of several predictors on risk for developing MDD differed between individuals with sMDE and those without (Table 3). Sex was the only demographic predictor that differed in magnitude between individuals with and without sMDE. Being female increased the likelihood of developing MDD to a greater degree among individuals *without* sMDE ($p<.001$, OR=2.25) relative to individuals with sMDE ($p<.001$, OR=1.31). There was no interaction between sMDE status and age, education, or race.

Regarding the diagnostic variables, there was an interaction between lifetime alcohol use and sMDE status. Among individuals without sMDE, a lifetime alcohol use disorder increased the odds of developing MDD ($p=.001$, OR=1.17). Surprisingly, among individuals with sMDE, a lifetime alcohol use disorder decreased the odds of developing MDD ($p=.003$, OR=.76). There was also an interaction between past year medical conditions and sMDE status. Similarly, among individuals without sMDE, more past year medical conditions increased the odds of developing MDD ($p<.001$, OR=1.01). Among individuals with sMDE, more past year medical conditions decreased the odds of developing MDD ($p=.009$, OR=.95). There was no interaction between sMDE status and lifetime anxiety disorder or lifetime drug use disorder.

History of childhood abuse also interacted with sMDE status. Although childhood abuse was associated with increased likelihood of developing MDD in both groups, childhood abuse increased the odds of developing MDD to a greater degree in individuals without sMDE ($p<.001$, OR=3.91) relative to those with sMDE ($p<.001$, OR=2.11).

Age-Varying Influences on Predictors of First Episode MDD

Two predictors interacted with age and sMDE status in predicting onset of MDD (Table 3). There was a significant three-way interaction between age, education, and sMDE status. In individuals with sMDE, there was a significant effect of younger age at low ($p=.022$, OR=.98) and average ($p=.009$, OR=.98) levels of education, but not among individuals with high education ($p=.173$, OR=.99). Among individuals without sMDE, there was a significant

effect of younger age at low ($p<.001$, OR=.99), average ($p<.001$, OR=.98), and high ($p<.001$, OR=.98) levels of education.

There was also a significant three-way interaction between age, lifetime drug use, and sMDE. Among individuals with sMDE, the effect of younger age was stronger for individuals with lifetime drug use ($p<.001$, OR=.95) than those without lifetime drug use ($p=.002$, OR=.99). However, among individuals without sMDE, the effect of younger age on developing MDD did not differ in individuals with a lifetime drug use ($p=.159$, OR=.99) from those without a history of drug use ($p<.001$, OR=.99).

Discussion

The current study investigated risk factors predicting first MDE in individuals with and without a lifetime history of sMDE in a prospective, population-based sample. Approximately 5% of participants escalated to MDD over three years. The strongest predictor of onset of MDD overall was a history of childhood abuse, consistent with a large literature that children who suffer from abuse are more likely than others to develop depression and anxiety disorders (Carr et al., 2013; Hovens et al., 2012; Martins et al., 2014; Norman et al., 2012). Results in this community-based sample of adults are also broadly consistent with prior work that younger age, being female, fewer years of education, being of non-white race, co-morbid psychiatric conditions, and family history of depression are *independent* risk factors for the development of MDD (Cuijpers et al., 2006; Cuijpers et al., 2005; Hill et al., 2014; Klein et al., 2009). Importantly, this study is the first to utilize a comparison group to demonstrate that these demographic and clinical characteristics confer different magnitude of risk in individuals with and without a history of sub-threshold depressive symptoms.

Four variables indicated distinct processes involved in the onset of MDD in individuals who have experienced sub-threshold depression and those who have not: female sex, lifetime alcohol use disorder, lifetime substance use disorder, and childhood abuse. These variables were stronger predictors of first-episode MDD in individuals without a history of sMDE, showing larger effect size estimates (odds of developing MDD) compared to odds in the sMDE sample. This finding is somewhat surprising given that sMDE is in itself a risk factor for MDD (Klein et al., 2009; Lewinsohn et al., 2000), and the accumulation of multiple distinct risk factors has been shown to increase the sensitivity and specificity of predicting first-onset of MDD (Klein et al., 2009). One interpretation is that the sMDE group is already at increased risk of MDD onset, simply by virtue of having a history of sub-threshold depressive symptoms, and additional demographic or clinical characteristics only moderately increase this risk. In contrast, when pre-existing signs of mood dysregulation are not present, sex, alcohol use, drug use, and child abuse play a bigger role in specifying who is at elevated odds to become depressed. Further, because alcohol use, drug use, and child abuse are less common among individuals who do not show signs of depression, the power of these variables to predict a future MDD may be more specific than in an sMDE group where such issues are more prevalent.

Our findings indicated possible age-varying influences on predictors of first-episode MDD, consistent with the broader literature that depression is most likely to develop during early adulthood (Kolaitis, 2012). Specifically, we found a statistically significant three-way interaction between age, education, and sMDE status, as well as between age, drug use, and sMDE status. From a clinical perspective, these findings could suggest that problem-solving barriers to education or promoting positive coping strategies in lieu of the use of illicit substances may help promote resilience among people who show signs of depression during the high-risk period of early adulthood (Uebelacker et al., 2012). However, it is worth noting that the effect sizes regarding these three-way interactions with age were very small and it is unclear whether the effects would result in measurable clinical impact. Much higher rates of conversion from sub- to full-threshold depression have been found in younger cohorts (Hill et al., 2014; Klein et al., 2009). In addition, given that this sample consists primarily of middle-aged adults, it seems plausible that the assessed age range represents a more firmly consolidated stage of development that is less prone to age-related fluctuations in mood relative to younger or older adults (Karel, 1997; Mirowsky, 2013). Further, the small effect sizes with respect to age in this sample stand in contrast to findings regarding sex, child abuse, family history, and anxiety, which demonstrate effects of a moderate to large magnitude in this sample of adults. Thus, sex, child abuse, family history, and anxiety status may be the particularly salient risk factors to assess and target in the prevention of depression among adults.

This study has important implications for understanding the etiology of MDD. In ours, and other studies, the incidence of MDD in individuals with sub-threshold symptoms is higher than in those without. Therefore, sub-threshold depression may be viewed as part of the prodromal phase of MDD. However, not everyone with sMDE develops MDD, and, not all subjects pass through a sub-threshold phase prior to MDD onset. Thus, there is great variability and little specificity with which we can identify subgroups at highest risk. Our results help to specify the process by which individuals with prodromal symptoms and their seemingly healthy counterparts go on develop MDD by identifying how other clinical indicators interact with depressive symptoms in the process. One of this study's strengths is leveraging a large, nationally representative sample of adults with good retention over the follow-up period. This sample allowed us to conduct multivariate models exploring complex interactions with sufficient power; an improvement over past designs conducted in smaller, prospective cohorts (Cuijpers et al., 2006; Cuijpers et al., 2005; Hill et al., 2014; Klein et al., 2009). Importantly, our design allowed for the comparison of distinct effects of predictors in individuals with sMDE and non-sMDE individuals; a feature that from a clinical perspective promotes a more nuanced understanding of risk factors in and outside the context of pre-existing mood dysregulation.

This study also has several limitations. First, it would have been ideal to gather intermittent assessments over the follow-up to collect more specific information regarding time of MDD onset and temporal concordance with stressors that occurred during the follow-up. Second, the NESARC had limited assessment of social and interpersonal stressors, which have repeatedly been implicated in the development, maintenance, and recurrence of MDD (e.g. Asselmann et al., 2015; Sheets and Craighead, 2014)). Third, the definition of sub-threshold depression emphasizes symptom count over duration. Because the NESARC did not provide

detailed information regarding duration of depressive symptoms within a full- or sub-threshold depressive episode, the findings from the current study data do not necessarily generalize to alternative clinical manifestations of sub-threshold MDD (e.g., meeting full symptom count criteria for less than 2 weeks). Fourth, family history assessment in the NESARC only pertained to depression. We could not evaluate whether family history of other mood disorders (e.g. bipolar disorder (Serra et al., 2015)) or other psychological disorders affected risk for depression. Family history assessments, such as this one, are understood to have good specificity but poorer sensitivity (Milne et al., 2008). Fifth, the administration procedures for the AUDADIS-IV were such that depression diagnosis exclusion criteria for a general medical conditions, substance-use disorders, and bereavement were only asked if the participant endorsed a minimum of 5 of 9 depressive symptoms, prohibiting us from excluding sMDE cases due to these causes. Last, although the study included a wide age range (18–65), this prospective cohort did not include children or adolescents, nor were data available in the NESARC to evaluate the age of sMDE onset at Wave 1 as a predictor. Given elevated rates of transition from sub- to full-threshold mood disorders in youth, an important future direction is to compare predictors of MDD with and without sMDE in younger cohorts.

In conclusion, although a sub-threshold depressive disorder is one of the best established risk factors for the onset of full-syndrome depressive disorders, many individuals do not go on to develop MDD. This may be particularly true for nationally representative community samples, such as this one, where rates of conversion from sub- to full-threshold MDD are much lower than rates reported in clinical settings (Lewinsohn et al., 2004). Equally, many individuals without signs of sub-threshold mood dysregulation go on to later develop depression. Importantly, through this study we identified four variables that were stronger predictors of the first-onset of MDD in healthy individuals relative to sMDE: female sex, lifetime alcohol use disorder, lifetime substance use disorder, and childhood abuse. In addition, we identified that younger age may account for a small amount of variance for transition to MDD among adults with pre-existing symptoms who are of low education or have a history of using substances. Collectively, these data may be useful in identifying subgroups of individuals who are especially high-risk for developing depression and good candidates for prevention/early intervention programs. In particular, these findings help to specify the clinically important warning signs of depression among individuals who are not showing emerging depressive symptoms.

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Highlights

- Several demographic and clinical predictors vary in strength and specificity of predicting first episode major depression between individuals with and without a lifetime history of sub-threshold depression.
- Female sex, lifetime alcohol use disorder, lifetime substance use disorder, and childhood abuse are stronger predictors of first episode major depression in individuals without a history of sub-threshold symptoms.
- How likely risk factors are to predict the first episode major depression may vary according to age. For example, low education and substance use are two risk factors that were stronger predictors of first episode major depression in younger adults with depressive tendencies.
- The strongest predictor of first onset of MDD in both individuals with and without a history of sub-threshold depression was a history of childhood abuse.

Table 1

Demographic and Clinical Characteristics of Participants with and without sMDE

	sMDE (n = 3,901)		No Mood Disorder (n = 31,022)	
	Escalated to MDD (n = 184)	No MDD (n = 3,717)	Escalated to MDD (n = 1,130)	No MDD (n = 29,892)
Age ^{M (SE)}	43.13 (.69)	46.85 (.16)	42.01 (.21)	46.02 (.07)
Female	133 (67%)	2,410 (61%)	800 (67%)	15,742 (47%)
Race	149 (88%)	2,900 (86%)	871 (84%)	22,282 (82%)
Education ^{M (SE)}	9.63 (.07)	9.82 (.02)	9.41 (.03)	9.57 (.01)
LT Anxiety Disorder	56 (33%)	853 (23%)	174 (17%)	2,715 (9%)
LT Alcohol Use Disorder	42 (29%)	1162 (35%)	291 (29%)	6,910 (26%)
LT Substance Use Disorder	20 (14%)	403 (12%)	98 (9%)	1,890 (7%)
Number of Medical Conditions ^{M (SE)}	1.67 (.07)	1.93 (.08)	4.37 (.14)	3.47 (.06)
1 st Degree Family History MDD	84 (52%)	1577 (46%)	267 (27%)	5,228 (18%)
Childhood Abuse	17 (10%)	193 (5%)	119 (10%)	857 (3%)

Note: All percentages are un-weighted. M (SE) denotes Mean (Standard Error)

Table 2**Predictors of First Episode Major Depressive Disorder**

Predictor	Univariate Models					Multivariate Model				
	<i>b</i>	95% CI	OR	<i>p</i>		Lower	Upper	Lower	Upper	<i>p</i>
Age	-.01	-.014	.99	<.001	-.015	-.016	-.013	.99	<.001	
Sex	.75	.68	2.13	<.001	.78	.70	.86	2.18	<.001	
Race	.14	.05	1.16	.003	.20	.10	.29	1.21	<.001	
Education	-.03	-.04	.98	<.001	-.04	-.05	-.03	.96	<.001	
Anxiety Disorder	.70	.61	2.01	<.001	.51	.41	.61	1.66	<.001	
AUD ^a	.11	.03	1.11	.008	.12	.03	.21	1.13	.007	
SUD ^b	.29	.19	1.33	<.001	.06	-.06	.18	1.06	.311	
Medical Conditions	.008	.016	.99	.074	.02	.01	.03	1.02	<.001	
Childhood Abuse	1.28	1.17	3.58	<.001	1.09	.97	1.21	2.98	<.001	
Family History	.48	.41	1.62	<.001	.30	.22	.38	1.35	<.001	

^a AUD = Alcohol Use Disorder^b SUD = Substance Use Disorder

Table 3
Predictors of First Episode Major Depressive Disorder as a Function of Sub-threshold Status

Demographic Variables	<i>b</i>	95% CI		OR	<i>p</i>
		Lower	Upper		
Model 1 - Age					
Age x Sub-threshold Status	<.01	-.007	.006	1.00	.945
Model 2 - Sex					
Sex x Sub-threshold Status	-.54	-.72	-.37	.58	<.001
Age x Sex x Sub-threshold Status	.004	-.004	.01	1.00	.362
Model 3 - Race					
Race x Sub-threshold Status	.02	-.27	.30	1.02	.913
Age x Race x Sub-threshold Status	-.02	-.05	.003	.98	.083
Model 4 - Education					
Education x Sub-threshold Status	-.01	-.04	.02	.99	.630
Age x Education x Sub-threshold Status	.003	.001	.005	1.01	.007
Co-morbidity					
Model 5 - Lifetime Anxiety Disorder					
Anxiety Disorder x Sub-threshold Status	-.24	-.44	-.04	.79	.021
Age x Anxiety Disorder x Sub-threshold Status	-.003	-.02	.01	.99	.657
Model 6 - Lifetime Alcohol Use Disorder					
Alcohol Use Disorder x Sub-threshold Status	-.44	-.66	-.22	.65	<.001
Age x Alcohol Use Disorder x Sub-threshold Status	-.02	-.04	-.003	.98	.021
Model 7 - Lifetime Substance Use Disorder					
Substance Use Disorder x Sub-threshold Status	-.16	-.45	.12	.85	.255
Age x Substance Use Disorder x Sub-threshold Status	-.05	-.08	-.03	.95	<.001
Model 8 - Past Year Medical Conditions					

	<i>b</i>	95% CI	OR	<i>p</i>
	Lower		Upper	
Medical Conditions x Sub-threshold Status	-.06	-.104	-.024	.94 .002
Age x Medical Conditions x Sub-threshold Status	<.01	-.001	.001	1.00 .290
Family History Variables				
Model 9 - Childhood Abuse				
Childhood Abuse x Sub-threshold Status	-.62	-.84	-.39	.54 <.001
Age x Childhood Abuse x Sub-threshold Status	.02	.002	.05	1.02 .035
Model 10 - 1 st Degree Family History of MDD				
Family History x Sub-threshold Status	-.21	-.39	-.03	.81 .026
Age x Family History x Sub-threshold Status	-.003	-.01	.01	.99 .595

* Note: All lower order main effects and interaction terms were included in each model. Model terms that were not pertinent to the specific aims of this study are not presented for parsimony.