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Trajectories of Depressive Symptoms in Response to Prolonged Stress in Medical Interns

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Abstract

Objective—The high degree of heterogeneity in the development of depression under stress is unaccounted for in traditional statistical modeling. We employ growth-mixture modeling to identify classes of individuals at highest-risk for depression under stress.

Methods—Medical internship was used as a prospective stress model. Interns from US residency programs completed demographic, psychological and depressive symptom assessments two-months prior to internship and at 3-month intervals throughout internship year.

Results—2,278(59%) of interns chose to take part in the study. Three classes of depressive symptoms were identified: 1) Stress-Resilient Class: 62% of participants report low depressive symptoms before and throughout internship year; 2) Stress-Neutral Class: 22% of participants report mild depressive symptoms before and throughout internship year; and 3) Stress-Sensitive Class: 16% of participants report low depressive symptoms before internship stress, and high levels of depressive symptoms throughout internship year. Individuals in the Stress-Sensitive class were more likely to be female, in a surgical specialty, and have a history of depression, difficulty early family environment and high neuroticism scores compared to individuals in the Stress-Resilient class.

Conclusions—Trajectory based analysis allows for the identification of a high-risk group, within a heterogeneous population, that accounts for the link between stress and depression.

Keywords

affective disorders; stress; biostatistics

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Introduction

Major depression affects approximately 16% of Americans at some point in life¹. According to the World Health Organization, depression is far and away the leading cause of disease-associated disability among individuals 15 to 44 years old. Life stress is one of the strongest, most consistent risk factors for major depression²⁻³ with approximately 80% of depressive episodes preceded by a major stressor⁴. However, the majority of individuals encountering stressful life events do not become depressed, indicating that there is variation in how individuals respond to stress⁵.

The high degree of heterogeneity in the development of depression in response to stress constitutes an important public health problem, with significant implications for how to effectively focus resources on those individuals at highest risk for depression under stress. A large body of work has examined demographic and psychological factors that correlate with the development of depression under stress and has advanced our understanding of this condition⁶⁻⁸. However, drawing conclusions about the relationship between these factors and symptoms of depression is often not possible due to limitations imposed by the methodology employed (e.g., retrospective or cross-sectional study designs which can not distinguish the cause and effect relationship between potential risk factors and depression under stress)⁹. There are a limited number of longitudinal studies assessing the relationship between stress and depression, and most of these have not gathered baseline psychological data from before the onset of stress¹⁰⁻¹¹. Further, these studies have employed a mixed-effects growth model which assumes the same mean trajectory of depressive symptoms over time for all participants. This approach tends to obscure interindividual heterogeneity and cannot identify distinct trajectories of depressive symptoms under stress⁹. In contrast, trajectory-based models (also known as growth-mixture modeling or latent class growth models), allow for the identification of distinct classes of developmental trajectories of depressive symptoms and the identification of factors that predict class membership.

In this study we aimed to overcome prior study limitations by utilizing a trajectory-based model to examine depressive symptom trajectory classes and predictors of class membership before and during a naturalistic prolonged stressor, medical internship. Medical internship is a rare situation where a dramatic increase in stress and depressive symptoms can be predicted¹²⁻¹³.

Aims of the study

The present study sought to 1) determine individual trajectories of depressive symptoms over the course of medical internship via employment of growth-mixture modeling; and 2) identify personal factors that predict trajectory class membership.

Material and Methods

Participants

4,175 interns entering traditional internal medicine, general surgery, pediatrics, and psychiatry residency programs during the 2007, 2008, 2009 and 2010 academic years were

sent an email two months prior to commencing internship and invited to participate in the study. For 314 subjects, our email invitations were returned as undeliverable and we were unable to obtain a valid email address. Of those with a valid email address, 59% (2278/3861) of the remaining invited subjects agreed to participate in the study (Table 1). The Institutional Review Board at participating hospitals approved the study. Subjects were given \$30 (2007 cohort) or \$40 (2008, 2009 and 2010 cohorts) gift certificates for their participation.

Data Collection

All surveys were conducted through a secure online website designed to maintain confidentiality, with subjects identified only by numbers. No links between the identification number and the subjects' identities were maintained.

Depressive symptoms were measured using the depression module of the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a self-report component of the PRIME-MD inventory designed to screen for depressive symptoms¹⁴. For each of the 9 depressive symptoms, interns indicated whether, during the previous 2 weeks, the symptom had bothered them "not at all," "several days," "more than half the days," or "nearly every day." Each item yields a score of 0 to 3, so that the PHQ-9 total score ranges from 0 to 27. PHQ scores of 5 or greater, 10 or greater, 15 or greater and 20 or greater correspond to mild, moderate, moderately severe and severe depression, respectively¹². Scores below 5 are low and considered not clinically relevant. A score of 10 or greater on the PHQ-9 has a sensitivity of 93% and a specificity of 88% for the diagnosis of major depressive disorder¹⁵. Diagnostic validity of the PHQ-9 is comparable to clinician-administered assessments¹⁴.

Assessments

Subjects completed a baseline survey two months prior to commencing internship that assessed general demographic factors (age, sex, ethnicity, marital status), medical education factors (medical specialty), personal factors (baseline PHQ-9 depressive symptoms, self-reported history of depression) and psychological measures (Neuroticism (NEO-Five Factor Inventory¹⁶), Early Family Environment (Risky Families Questionnaire¹⁷) and Cognitive Styles (modified Sociotropy-Autonomy Scale¹⁸)). The Neuroticism subscale of the NEO-Five Factor Inventory evaluates characteristics such as anxiety, moodiness, worry, envy and jealousy. Higher scores on the Neuroticism subscale indicate an increase likelihood of experiencing negative emotions, especially in response to environmental stress. The Risky Families Questionnaire evaluates early family environment. Higher scores indicate a more chaotic, harsh and abusive early family environment where lower scores indicate a more organized, supportive and nurturing early family environment. The Sociotropy-Autonomy Scale assesses two cognitive personality constructs. Individuals with high Sociotropy scores require external validation in order to experience satisfaction for their achievements whereas those with high autonomy scores derive greater satisfaction from activities and goals that are achieved independent of others approval. Participants were contacted via email at months 3, 6, 9 and 12 of their internship year and asked to complete the PHQ-9.

Statistical Analyses—Mplus Version 6.1 was used to determine distinct classes of depression trajectories via growth mixture modeling with latent variables¹⁹. Growth-mixture modeling combines a person-oriented approach with traditional variable-oriented growth curve modeling, permitting continuous latent growth factors (i.e., intercept and slope) to be related to time¹⁹. While conventional growth modeling assumes a single population and estimates a mean growth curve, growth-mixture modeling uses categorical latent variables to capture different classes of trajectories within a population. Growth-mixture models are estimated with maximum likelihood with robust standard errors, which permits analysis of data missing at random. Evidence for different trajectory classes exists when models with two or more latent classes provide a better fit to the data than models with one class. Since the standard chi-square difference test (likelihood ratio test) cannot be used with mixture models²⁰, information criteria, which compute an index that is a function of the log-likelihood, are commonly used. In this study, we use the Akaike Information Criterion (AIC)²¹ and the Bayesian Information Criterion (BIC)²². The number of latent trajectories was chosen based on the lowest AIC and BIC along with size and substantive interpretation of the classes. Because, as expected, the PHQ score means across did not reflect a linear growth trend, a quadratic model was used. An initial quadratic growth curve analysis on the entire sample of interns (one-class model), provided a point of comparison for increases in numbers of classes. Next, two- to five-class models were assessed. Once the best fitting number of classes was determined, we tested various sub-models that relax the restriction that the growth factor (i.e., intercept, slope, and quadratic term) variances are equivalent across classes. Baseline covariates were added to the model to aid in prediction of individual's trajectory class membership. For the time invariant covariates a series of multinomial logistic regressions were conducted to determine if baseline characteristics influence the probability of class membership.

Results

Consistent with previous studies, there was a dramatic increase in PHQ depression symptom (*Mean (S.D.)*) score from baseline (2.45 (3.05)) to 3 months (6.06 (4.87)), 6 months (5.99 (4.75)), 9 months (6.29 (4.98)), and 12 months (5.81 (4.98)) of internship¹³. To assess for the presence of distinct trajectory classes, one-through five-class model were tested (Table 2). The four- and five-class solutions did not have a replicated log-likelihood indicating that these solutions were unstable, thus these models were rejected. Among the remaining three models, it was determined that three-class solution was the best fitting as indicated by the lowest AIC and BIC values. We then tested variations of the three-class model that relax the restrictions on the intercept, slope, and quadratic variances equivalency across classes (Models 3A, 3B, and 3C in Table2), and it was determined that the three-class solution with no quadratic growth factor variance in any class, with the intercept and slope variance freely estimated in Class 2, with no slope factor variance in Class 1, was the best-fitting model as indicated by the AIC and BIC values

Figure 1 shows the average trajectory in each latent class. Class 1 (Stress-Resilient; 62% of participants) subjects report low depressive symptoms before internship stress and continue with relatively low depressive symptoms through the intern year. Class 2 (Stress-Neutral; 22% of participants) report a mild level of depressive symptoms before internship, and

continue to report mild symptoms throughout internship. Class 3 (Stress-Sensitive; 16% of participants) subjects report low depressive symptoms before internship, but report a dramatic increase in depressive symptoms with the onset of internship stress.

Predictors of Depression Trajectory

In order to identify variables that predict membership in the different classes, covariates were introduced into the three-class model (Table 3). The introduction of covariates improves model fit as indicated by lower values of the AIC and BIC when compared to the three-class model without covariates (Table 2). A personal history of depression, high neuroticism, adverse early family environment, female gender and surgical specialty predicted membership in the Stress-Sensitive Class, compared to the Stress-Resilient Class. A personal history of depression, high neuroticism, and adverse early family environment also predicted membership in the Stress-Neutral Class, compared to the Stress-Resilient Class.

Discussion

Using the trajectory-based analysis we demonstrate, for the first time, that there are distinct trajectories of depressive symptoms in response to a prolonged stressor, medical internship. Interns separate into three distinct classes of depressive symptoms during the stressful condition. Specifically, subjects in the largest trajectory class in our sample (Stress-Resilient) report low depressive symptoms prior to the onset of stress and again throughout the year of high stress. Subjects in the second largest trajectory class (Stress-Neutral) report mild depressive symptoms before the onset of stress and again throughout the year of stress. These groups are similar in that depressive symptoms do not fluctuate in response to stress, but differ in that the Stress-Neutral class is experiencing clinically mild depressive symptoms on an ongoing bases and the Stress-Resilient class experiences no clinically relevant depressive symptoms. In contrast, subjects in the smallest trajectory class (Stress-Sensitive) report low depressive symptoms before the onset of stress but high depressive symptoms throughout the year of stress. Over the course of internship year, 81% of the Stress-Sensitive class had a PHQ-9 depression score indicating a probable diagnosis of Major Depression during at least one follow-up assessment, compared to 53% and 4.2% of those in the Stress-Neutral or Stress-Resilient class, respectively.

In addition to identifying distinct classes of depressive symptoms under conditions of stress, we have also identified a number of important pre-internship predictors of class membership. History of depression, high neuroticism, difficulty early family environment, female gender and surgical specialty increased the likelihood of membership in the Stress-Sensitive class, in comparison to the Stress-Resilient class. Additionally, history of depression, high neuroticism, and adverse family environment increased likelihood of membership in the Stress-Neutral class, characterized by mild depressive symptoms throughout the year, compared to the Stress-Resilient class.

There are several important implications that follow from this study. First, our prospective study design and statistical approach has identified a sub-sample of individuals most vulnerable to depressive symptoms under conditions of stress. While prior studies have

consistently demonstrated an overall association between stress and depression^{6-8, 23-24}, our findings suggest that the increase in depressive symptoms in response to stress is a precipitant to depressive symptoms in only a small sub-sample of individuals (Stress-Sensitive class), rather than a common increase across the full population. Second, we identify a pre-internship demographic and psychological profile that predicts membership in this high-risk sub-sample. Although the demographic and psychological profile has historically been shown to associate with depression⁶⁻⁸, our prospective study design demonstrates that these factors predict a significant increase in depressive symptoms under conditions of stress. These findings have important clinical and health economic implications as it allows residency programs to focus limited prevention and intervention resources on the small subset of trainees most vulnerable to responding poorly to internship stress. If replicated in samples exposed to other forms of prolonged stressors (e.g., military members, patients' with chronic medical conditions), this finding will have broad utility for identification and resource allocation. For example, the incidence of depression for those with the profile found in the Stress-Sensitive class could be decreased by a targeted preventative intervention, which are most effective for those at greatest risk for the disease²⁵. It is important to note however, that factors shown to predict class membership are only risk factors and do not determine an individual's course or trajectory for internship year. An alternative to a targeted prevention intervention is a universal screening within the first few months of internship with referral for clinically significant symptoms, as depressive symptoms that are high at 3 months of internship appear to remain elevated throughout internship year.

Beyond the clinical implication of these findings, growth mixture modeling captures important information about how individuals experience depressive symptoms under stress. For example, depression scores for the Stress-Sensitive class from pre-internship to internship year change dramatically, whereas for the other classes they remained relatively stable across the year. If we employed standard regression analyses and looked at the overall population average we would be missing this important variability and heterogeneity among groups. Growth mixture modeling identifies classes with more homogenous, or more similar severity of depressive symptoms over time.

The identification of distinct trajectory classes with less fluctuation and greater stability in depressive symptoms can provide a more homogenous population for studies investigating the biological basis of depression. For instance, the Stress-Sensitive class of individuals may provide a platform to better understand the biologic effects of stress induced depression. Similarly, investigating biological markers in individuals demonstrating mild but persistent symptoms of depression over time, independent of environmental stressor (Stress-Neutral), may provide an opportunity to gain insight into dysthymia, which likely has different biologic and genetic underpinnings compared to stress-induced depression. Investigating classes of individuals with depressive symptoms that are more homogenous will likely increase our ability to detect biological contributors to the disease²⁶.

While it is well established that women experience higher rates of depression compared to men^{1,27}, there is conflicting evidence on whether the relationship between stress and depression differs between men and women²⁸⁻³¹. In our study, we find that female gender

increased the likelihood of membership in the Stress-Sensitive class. This finding adds to an emerging pattern of results, with prospective studies finding evidence for gender difference in stress sensitivity and retrospective studies finding no evidence for gender difference, suggesting that recall bias may be playing an important role in the different results³¹. The prospective study of stress and depression may be an important direction for advancing our understanding of sex differences in depression³².

There are several limitations to our study. First, our study was restricted to interns completing their first year of postgraduate medical training. Thus, it is unknown if similar classes of depressive symptom trajectories hold true for other populations experiencing a stressor. Second, only 59% of invited individuals chose to participate in the study. Previous work demonstrates minimal demographic differences in age and sex between those who chose to take part in the study and those who did not¹³. However, other unmeasured factors may account for study participation (i.e., incentives or interest in the topic) or non-participation (i.e., lack of time) and could potentially be a source of study bias. Thus, our results should be extrapolated with caution. Third, while we included covariates in the study that have previously predicted increased depressive symptoms in medical interns¹³, other potentially important predictors of depression in this population likely exist. Fourth, although multiple studies have demonstrated the validity, sensitivity, and specificity of the PHQ-9 inventory¹⁴⁻¹⁵, it is important to note that we assessed depression through a self-report inventory rather than a diagnostic interview. However, we chose this method as opposed to in person assessment given that medical trainees are less likely to honestly report depressive symptoms when assessments are not anonymous³³. Lastly, the employed modeling framework, although it has numerous strengths, is not without its limitations. One criticism of growth-mixture models in general is that because standard chi-square difference tests cannot be used in this setting³⁴, formal tests of model fit to the data cannot be conducted³⁵. Therefore, growth-mixture modeling cannot prove the existence of latent classes, but only describe the putative growth trajectory classes³⁶⁻³⁸. Additionally, although the determination of the trajectory classes are relatively robust to missing data, if data are not missing at random, the point estimates of the parameters may be biased, although it is unlikely that such bias would be substantial³⁹.

Our study provides evidence of distinct classes of depressive symptoms in response to stress and identifies a set of pre-stress factors that predict trajectory class membership. The trajectory based analysis allows for the identification of a high-risk group in a heterogeneous population, a finding for which there is significant implications for clinical intervention and potentially provides an improved platform for identifying biological risk for stress-related depression.

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Significant Outcomes

- Growth-mixture modeling identifies and characterizes distinct classes of depressive symptoms under conditions of stress and a number of important pre-stress predictors of class membership.
- Our findings suggest that the increase in depressive symptoms in response to stress is a precipitant to depressive symptoms in only a small sub-sample of individuals, rather than a common increase across the full population as suggested by previous studies
- The identification of a high-risk group has important clinical and health economic implications as it allows the focus of limited prevention and intervention resources on the small subset of individuals most vulnerable to responding poorly to stress.

Limitations

- Only 59% of potential subjects agreed to take part in the study.
- Depressive symptoms were assessed through a self-report inventory rather than a diagnostic interview.
- Our study was restricted to interns completing their first year of postgraduate medical training. Thus, it is unknown if similar classes of depressive symptom trajectories hold true for other populations experiencing a stressor.