Stress, Anxiety, and Somatic Symptoms: A Comparison of Biomarkers in a Clinical Sample

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Stress, Anxiety, and Somatic Symptoms: A Comparison of Biomarkers in a Clinical Sample

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Stress, Anxiety, and Somatic Symptoms:
A Comparison of Biomarkers in a Clinical Sample

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Introduction

Anxiety Disorders

Anxiety is a significant mental health problem in the United States. Characterized by excessive and persistent fear and worry resulting in significant distress and dysfunction, anxiety disorders constitute the most prevalent class of disorders in the country, with a lifetime prevalence of 28.8% (Alegria et al., 2007; Kessler, 2005). These disorders typically follow a chronic and recurrent course (Barlow, 2002) and comorbidity is common; more than half of individuals with a primary diagnosis of an anxiety disorder present with an additional anxiety disorder or depression and more than 25% also experience a co-occurring substance use disorder (Ohayon, 2006). Those who suffer from anxiety disorders experience the effects of their condition far beyond their particular symptoms or diagnoses; anxiety disorders exert a “ripple effect” that impacts almost every sphere of the sufferer’s interpersonal and professional worlds. Anxiety disorders are associated both with increased absenteeism and decreased productivity in the workplace (Kessler & Frank, 1997), increased likelihood of living below the poverty line, decreased self-reported quality of life, and the tendency to experience increased family and relational distress (Tolin, Gilliam, & Dufresne, 2010). Given that these disorders impact more than 1-in-4 individuals in the U.S., effects are also felt more broadly by society. Anxiety disorders account for 30% of our nation’s mental healthcare expenditures totaling 42.3 billion per year in 1990 U.S. dollars (Ohayon, 2006; Greenburg et al., 1999), and equal to 69.6 billion per year when adjusted to 2010 U.S. dollars. Even more importantly, the majority (54%) of these annual costs accrue from treatment by primary care practitioners, emergency room staff, or other non-psychiatric
providers, placing a general strain upon the most overtaxed areas of our nation’s healthcare system (Wang et al, 2005; Lepine, 2002; Greenburg et al., 1999). This over-utilization of the health care system may stem from the association between anxiety, stress, and somatic symptoms.

**Somatic Symptoms**

Although often considered mainly within the context of depressive symptomatology, somatic symptoms are inherent to anxiety disorders and in certain cases they are a key part of their accurate diagnosis (American Psychiatric Association, Diagnostic and Statistical Manual, Fourth Edition, Text-Revision, 2000). Researchers in Norway considered this association when they analyzed data from an epidemiological study of 50,377 participants age 20 or over. The study used self-report to assess for the presence of anxiety disorders, depression and a range of somatic symptoms (e.g., fatigue, dizziness, chest pain, headache, heart palpitations) while excluding those who reported confirmed diagnoses of medical disorders (e.g., myocardial infarction, hypertension). In participants with anxiety disorders, they reported an odds ratio (OR) of 3.0 for reporting 5 or more somatic symptoms; this was not significantly different than the OR for participants with depression (OR=2.7). Notably, the highest OR (5.0) for 5 or more somatic symptoms reported was observed in participants with comorbid anxiety and depression (Haug et al., 2004). There is evidence that cognitive and affective biases associated with anxiety and depression contribute to an increased reporting of somatic symptoms, and anxiety is thought to heighten negative appraisal of somatic sensation while depression is believed to increase recall of prior negative symptoms (Suls & Howren, 2012). Cognitive processing theory offers meaningful insight into the
mechanisms by which interpretation and recall of somatic symptoms may be altered by anxiety; at the same time, the occurrence of somatic symptoms outright may also be explained by activation of the stress response.

**Stress Response**

The stress response is a collection of evolved physiological pathways which activate in response to a perceived threat and serve to restore and maintain homeostasis within an organism. This physiological constellation is known as the hypothalamic-pituitary-adrenal (HPA) axis (Graeff & Zangrossi, 2010; Chrousos, 2009). The HPA axis in turn is comprised of two highly interconnected but physiologically distinct neuroendocrine systems. One of these systems is the glucocorticoid (GC) system. When the HPA axis is activated, the paraventricular nuclei (PVN) of the hypothalamus release arginine vasopressin (AVP) and corticotropin releasing hormone (CRH), signaling the anterior pituitary gland to manufacture and release adrenocorticotropic hormone (ACTH). ACTH acts on receptors of the adrenal cortex, causing those cells to release the glucocorticoid molecule cortisol into the circulation; thus cortisol serves as the endpoint effector of the GC system (Chrousos, 2009; Kim & Gorman, 2005). Cortisol levels are typically assayed through direct measurement in plasma, urine, or saliva.

The other system of the HPA is the locus ceruleus-norepinephrine (LC-NE) system (Graeff and Zangrossi, Jr., 2010) which primarily modulates the sympathetic branch of the autonomic nervous system (Kim & Gorman, 2005). As with the GC system, the LC-NE system begins with stimulation of the hypothalamic PVN, neurons of which project both to the locus ceruleus (LC) of the pons and to other noradrenergic
brainstem nuclei of the autonomic nervous system (ANS). Sympathetic fibers of the ANS innervate peripheral sites throughout the human body, allowing for autonomic regulation of a host of physiological processes (cardiovascular, respiratory, gastrointestinal, renal, etc.) including release of catecholamines (epinephrine and norepinephrine) from the medulla of the adrenal gland directly into the blood stream as endpoint effectors (Chrosous & Gold, 1992). This neural infrastructure allows the body to rapidly respond to stressors with the characteristic “flight or fight” response. Increased attention, focus, and arousal as well as cardiovascular, respiratory, and circulatory changes are all characteristic features of sympathetic nervous system (SNS) stimulation (Chrosous, 2009). Historically, researchers have assessed the SNS response by somewhat invasive or obtrusive methods: either by direct plasma assay of norepinephrine levels or by recording external, observable symptoms of SNS activation (e.g., heart rate, skin conductance, or blood pressure). Recently researchers have begun to utilize assay of a relatively novel molecule, salivary alpha-amylase (sAA), as a biomarker of SNS activity. Reports on both animal and human research provide support for the association between salivary alpha-amylase levels and plasma norepinephrine, suggesting that sAA can be used as a reliable marker of LC-NE stress response activation (Nater and Rohleter, 2009; Rohleder, N., Nater, U., Wolf, J., Ehlert, U., & Kirschbaum, C., 2006). Moreover, assessing for noradrenergic and sympathetic activation in addition to GC activity provides a more complete window into the mechanisms of stress activation and contributes to the methodological quality of studies examining psychosocial aspects of stress (Hellhammer, Wust, & Kudielka, 2009).

Cortisol
Salivary assay of cortisol is a long-standing method for estimating HPA axis activation (Gozansky, Lynn, Laudneslager, & Kohrt, 2005) and is preferred over urinary or plasma assay as a convenient and non-invasive technique for assessing HPA axis activity in psychiatric research (Meewisse, 2007; Kiraly, 1997; van Eck, M., Berkhof, H., Nicolson, N., & Sulon, J., 1996). Cortisol levels may be influenced by a multitude of factors. In their meta-analysis of studies using healthy human participants, Michaud and colleagues (2008) reported that particular factors relating to the stressor type, such as controllability or chronicity of exposure influences the cortisol increase in response to a stressor. Numerous biological factors may likewise contribute to variation in salivary cortisol levels, such as recent food intake, recent exercise, time of day of sampling, or season of the year (Hansen, A., Garde, A., & Persson, R., 2008). In female study participants, phase of menstrual cycle, peri-/post-menopause status, and use of oral contraceptives can all influence cortisol levels (Kirschbaum & Hellhammer, 2007). Particularly germane to psychological research, the use of medications such as antidepressants has been shown to alter HPA axis activity through their influence upon serotonergic and other pathways (Manthey et al., 2011).

*Alpha-Amylase*

Salivary alpha-amylase (sAA) is a salivary enzyme with digestive functions secreted by the parotid gland; its levels directly vary with systemic norepinephrine release (Nater and Rohleder, 2009). There is a burgeoning literature exploring associations between anxiety and sAA. In a pilot study, 10 volunteers underwent a 15-minute mental arithmetic test; researchers observed statistically significant correlations between sAA levels, heart rate, and self-report state anxiety. No corresponding
associations between these measures and cortisol levels were found (Noto et al., 2005). Kang (2010) experimentally induced an anxious state in 16 healthy college students and reported statistically significant elevations of sAA and blood pressure in the anxious group compared to controls. Other studies have extended research on the association between anxious arousal and sAA from community samples to specific clinical populations. Using a sample of untreated patients diagnosed with generalized social anxiety disorder (gSAD), researchers noted significantly higher basal sAA levels in the diagnosed group than among matched controls without a comparable difference in cortisol levels (van Veen et al., 2008). Another research team observed sharp increases in waking sAA levels among PTSD patients, the opposite of what was seen in controls, suggesting an atypical diurnal profile of sAA in their sample (Thoma et al., 2011). Meanwhile, Tanaka and colleagues (2012) observed elevated sAA in a subgroup of their sample of panic disorder patients. While promising, the existing literature has yet to consider the factors of symptom chronicity or Axis I comorbidity in their methodology. Given the high prevalence of these two features within the anxiety disorders population, research is warranted that addresses what effect, if any, chronicity and psychiatric comorbidity may have on the stress response in an anxiety disorder sample.

Present Study

The aim of this study was to examine the associations between psychosocial factors (trait anxiety, health anxiety, depression, comorbid psychopathology, symptom chronicity, mood state), salivary biomarkers for both the GC and LC-NE axes of the HPA stress response (cortisol and alpha amylase), and report of somatic symptoms in a clinical outpatient population. We hypothesize that higher levels of trait anxiety, as measured on
the STAI-T, will be associated with greater levels of salivary cortisol and sAA. We also hypothesize that factors such as comorbid psychopathology and chronicity of symptoms will moderate the relationship between trait anxiety and salivary biomarkers, with higher levels of these moderators strengthening the association. An additional hypothesis is that higher levels of stress as measured by salivary cortisol and salivary alpha amylase levels will be associated with increased number and frequency of somatic symptoms. Our final hypothesis is that higher levels of trait anxiety will also be associated with increased number and frequency of somatic symptoms.

Methods

Participants

Participants were men and women experiencing anxiety symptoms who presented to an outpatient research facility specializing in the treatment of anxiety disorders. Included participants were 1) between 18-65 years of age, 2) able to provide legal, informed consent, 3) fluent in English, and 4) attending their first initial assessment session at the ADC at time of recruitment. As the first session at the ADC is an evaluation session, recruiting participants from their initial session avoided any effects of treatment on results.

To maximize the generalizability of the study, exclusion criteria were limited to only those psychiatric or medical conditions that either preclude the provision of valid consent or compromise the ability of the patient to complete study procedures. Exclusion criteria included 1) a lifetime diagnosis of schizophrenia or psychotic disorder, 2) a primary diagnosis of pervasive developmental disorder including autism spectrum
disorders, 3) mental retardation, 4) chronic organic brain disease, 5) females who were pregnant or nursing, and 6) active suicidal or homicidal ideation.

Procedure

This study utilized a cross-sectional, correlational design with a convenience sample. As noted above, participants were recruited through the normal patient flow at the ADC. Upon arrival for their appointment at the ADC, patients were informed of this study and asked if they would like to be approached by a member of the study staff after their appointment or during a break. Eligible patients who were interested in participating underwent an informed written consent procedure; patients who provided consent then began study procedures. Participants first provided a saliva sample via either expectoration or passive drool into a 2-ml polyethylene vial designed for salivary collection and assay. All participants were provided a short section of drinking straw to facilitate saliva collection.

Following the provision of a saliva sample, participants completed a packet of self-report questionnaires and psychosocial measures. This packet included the State-Trait Anxiety Inventory-Trait Subscale (STAI-T; Spielberger, Gorsuch, & Lushene, 1970; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988), and the Health Anxiety Inventory (HAI; Salkovskis, Rimes, Warwick, & Clark, 2002). The packet also included a Physical Health Questionnaire and a Saliva Collection Questionnaire that were specifically designed for this study. Consent for and completion of these procedures
required approximately 45 minutes. Participants were asked to complete all measures in the packet in a single session. Where time did not allow this, participants were permitted to take the packet home for completion, returning the completed packet to the center staff upon arrival before their third ADC appointment, before direct treatment interventions are generally introduced.

In addition, participants permitted access to their medical charts to retrieve demographic, diagnostic, and depression data by research staff. Saliva samples were frozen as soon as possible after collection and maintained in a study-specific container in a locked frozen storage unit until such time as the samples were sent to a subcontracted laboratory (Salimetrics, LLC), State College, PA) for analysis.

Personal identifying information was removed from all collected data. Each participant’s measures and saliva sample were assigned a unique study identification number and stored separately from their written consent form in locked files at the research lab. A master file linking participant identity and study identification number was maintained in a different room on a desktop computer with multiple password protections enabled. The protocol for this study was approved by the Institutional Review Boards of both Hartford Hospital and the University of Connecticut through cooperative agreement prior to data collection.

Physiological Measures

Salimetrics, Inc., a laboratory that specializes in biochemical salivary assays, performed all laboratory tests. All samples were weighed and assayed for the presence of cortisol and alpha amylase. Results of each assay were reported in standard units of concentration as a continuous ratio variable (e.g., µg/dL, U/ml).
Psychosocial Measures

The State-Trait Anxiety Inventory-Trait Subscale (STAI-T; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a 20-item scale that assesses the stable tendency to experience anxiety (Spielberger et al., 1983). Responses regarding how a participant generally feels are rated on a Likert scale ranging from 1 (almost never) to 4 (always). The STAI-T is one of the most frequently used self-report measures of trait anxiety, and adequate reliability and validity have been established (Oei, Evans & Crook, 1990). The STAI-T exhibited good internal consistency when used with this sample ($\alpha=.876$).

The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) is a brief scale designed to measure present experience of the two primary dimensions of mood. Participants rate the 20 items on a 5-point scale asking how they feel “right now”. In validation studies, the Positive Affect (PA) and Negative Affect (NA) scales were internally consistent (alphas range from .86 to .90). Discriminant validity between the scales was also supported (correlations ranged from -.12 to -.23). Test-retest reliability at 8 weeks was .54 for the PA scale, and .45 for the NA scale. Factorial and external validity of the scales was also supported. The PANAS has also demonstrated sensitivity to intraindividual mood fluctuations with short-term time frame instructions. Confirmatory factor analyses supported the two factors, and the influence of gender, education, and age were nonsignificant (Crawford & Henry, 2004). Good internal consistency was demonstrated in this sample ($\alpha=.859$).

The Health Anxiety Inventory (HAI; Salkovskis, Rimes, Warwick, & Clark, 2002) is a self-report measure of health anxiety and hypochondriasis. It includes 64 items with four statements each, about which participants select the statement that best
describes their feelings over the past six months (e.g., ‘a) I do not worry about my health, b) I occasionally worry about my health, c) I spend much of my time worrying about my health, d) I spend most of my time worrying about my health’). In addition, participants rate their tendency to avoid 10 situations due to fear or discomfort, on a 9-point Likert scale from 0 (“Would not avoid it”) to 8 (“Would always avoid it”). Finally, participants rate the frequency with which they seek reassurance regarding their health from 9 different sources, on a scale from 0 (“Never”) to 8 (“Daily”). The HAI has been reported to show adequate to good internal consistency from .71 to .92, and one-week test-retest reliability of .90 (Salkovskis, Rimes, Warwick, & Clark, 2002). In our sample, the HAI demonstrated very good internal consistency (α= .959)

The Physical Health Questionnaire (PHQ) was designed specifically for this study. In completing the PHQ, participants were asked to report all chronic medical conditions from which they suffer by choosing from a broad-based inventory of illness categories. Given a similarly exhaustive list of symptoms participants likewise reported the number and frequency of physical health symptoms that they experience. Further, they answered questions about current health behaviors such as smoking, caffeine consumption, sleep hygiene, and physical exercise. Participants also provided specific information on their frequency of illness and utilization of the health care system (physician appointments, ER visits) over the last 30 days.

The Saliva Collection Questionnaire (SCQ) was also designed specifically for this study. The SCQ asked participants to report on the numerous factors that have been shown to influence salivary assays generally, as well as those that may specifically affect salivary cortisol or sAA concentrations (e.g.: food intake, recent exercise, smoking, oral
contraceptive use, etc.). This information provides important data regarding potential covariates for each participant as well as sample integrity.

The Anxiety Disorders Interview Schedule for DSM-IV, Adult Version: (ADIS; Brown, DiNardo, & Barlow, 2004) is a semi-structured diagnostic interview for the assessment of current Axis I anxiety and mood disorders. While the ADIS is primarily designed to focus on anxiety and mood disorders, the interview also includes sections assessing the broader range of psychopathology as comorbidity frequently occurs with anxiety disorders. Per standard practice at the Anxiety Disorders Clinic, patients complete a screen of key symptoms prior to the assessment interview, which clinicians use to determine relevant portions of the ADIS for full administration.

The Beck Depression Inventory-II (BDI-II; Beck & Beck, 1972) is a 21-item self-report measure of cognitive and affective depressive symptoms used to assess depression. The BDI-II has well-established psychometric properties (internal consistency $\alpha = 0.92$) and is one of the most frequently used and cited depression rating scales (Beck, Epstein, Brown & Steer, 1988). Internal consistency with this study’s sample was comparable to that of prior psychometric reporting ($\alpha = .910$).

Because this study did not exclude participants on the basis of Axis I comorbidity, data on the participants’ number of comorbid Axis I diagnoses were obtained from patient files. For the purpose of analysis, these data were operationalized as an ordinal variable with 3 categories (e.g., a) no comorbid Axis I diagnoses, b) 1 comorbid Axis I diagnosis, and c) more than 1 comorbid Axis I diagnosis) for subsequent statistical analyses.

Data Analytic Plan
All electronic data were entered and stored on password protected computers. Data were cleaned and checked for computational or data entry errors prior to analysis. Missing data reduced the sample size in some analyses. In response to missing data, pairwise deletion was utilized. Analyses were conducted using the statistical software package SPSS version 19.0. The overall data analytic strategy was to use Pearson correlations and regression coefficients to examine the association between psychosocial measures, cortisol, sAA, and somatic symptoms. First, the total score on each psychosocial measure was associated with the assayed levels of salivary cortisol and salivary alpha amylase. Second, levels of cortisol and sAA were associated with each measure of physical health. Third, the total score on each psychosocial measure was associated with the measure of reported somatic symptoms. Linear regression was then utilized to examine associations between psychosocial measures and stress biomarkers, controlling for confounding variables where appropriate (see below). Moderator analyses examined the potential interactions of possible 3rd variables and were conducted using the custom dialog MODPROBE for SPSS developed by Hayes and Matthes (2009). Poisson (log-linear) regression was utilized to examine associations between stress biomarkers and somatic symptoms. Poisson regression was also utilized to examine associations between psychosocial measures and somatic symptoms.

The variable of somatic symptoms investigated in this study was assessed as count data (i.e., the number of particular occurrences in a fixed period of time). Methodologically, this presents certain challenges; certain assumptions of ordinary least squares (OLS) regression such as conditional normality and homogeneity of variance (homoscedasticity) are typically not held with count data, which is often positively
skewed, kurtotic, and heteroscedastic. This can result in under-estimations of both regression coefficients and statistical significance when OLS regression is used with count data (Cohen, Cohen, West & Aiken, 2003). Poisson regression is a form of Generalized Linear Modeling (GLM) with more flexible assumptions better suited for analysis of count data. Poisson regression models were utilized for regressions involving count data criteria in this study. However, use of a log-linear analysis such as Poisson regression, while advantageous, also presents certain challenges to the reporting and interpretation of results. For example, in OLS regression it is customary to report standardized regression coefficients (beta-weights) or the squared multiple correlation ($R^2$) to provide information on effect size and variance accounted for by the particular variable under examination. Because it utilizes a log-linear regression derived by maximum likelihood estimation, standardized coefficients cannot be used and no direct analogue of $R^2$ exists. In this study, we instead follow the recommendations of Coxe and colleagues (2009) and report a change in deviance score ($R^2_{DEVIANCE}$) as an indirect analogue of $R^2$. This score is obtained by calculating the ratio of the deviance value of the regression model with the variable of interest over the deviance value with the variable of interest omitted, then subtracting this ratio from 1 (see equation 1 below).

$$R^2_{DEVIANCE} = 1 - \frac{\text{deviance (fitted model)}}{\text{deviance (intercept only)}}$$  \hspace{1cm} (1)

The resultant $R^2_{DEVIANCE}$ score offers a measurement of improvement in model fit (i.e., reduction in deviance) attributable to the variable under examination and reports this using a standard 0 to 1 metric comparable to the familiar $R^2$ statistic of OLS analysis.
Concentrations of stress biomarkers in saliva are influenced by multiple biological and behavioral variables. We examined the associations between the biological variables and age, gender, body mass index (BMI), presence of oral contraceptive medication, presence of selective serotonin reuptake inhibitor (SSRI) medication, and presence of beta-adrenergic blocking or stimulating medication. Similarly, the behavioral variables of exercise, smoking, alcohol/recreational drug use, caffeine consumption, and eating within 1 hour of sampling were also examined. If any of these variables were significantly related to the biological measures (p < .05), they were entered as covariates prior to all analyses. In addition, any psychosocial variables that were significantly associated (p < .05) were also entered as covariates prior to all analyses. Salivary alpha amylase data typically exhibits a positive skew and it is common methodological practice to transform the data prior to analysis (Nater & Roehleder, 2009). Thus, for all analyses, square root transformed sAA data were utilized.

Power Analysis

Prior to the completion of data collection, a statistical power analysis was completed for this study using Lenth’s online java applet (Lenth, 2006-09). Given an alpha coefficient .05, a proposed sample size of 35, and an analysis consisting of multiple regression analyses with up to 4 regressors, this study was sufficiently powered (.8237) to detect a medium effect (r = .3) as defined by Cohen (1992).
Results

Demographics: Participant Characteristics

The demographic characteristics of study participants included in the analyses are presented in Table 1. Participants consisted of 46 adults ranging in age from 18-65 (median age=35). Gender was split unevenly with 33 women (71.7%) and 13 (28.3%) men. This gender ratio of 2.54:1 is generally consistent with overall anxiety disorder prevalence by gender (Kessler et al., 2005). The majority of participants (91.3%) were White. Employment status was reported by 43 participants (93.5%) and was distributed as follows: full time 28.3%, part time 28.3%, not working 15.2%, student 13.0%, on disability 6.5%, and retired 2.2%. Forty-two participants (91.3%) reported their educational attainment as follows: Doctoral degree 4.3%, Master’s or equivalent 17.4%, Bachelor’s or equivalent 34.8%, Associate’s Degree or other post-secondary education 21.7%, and High School Diploma 13.0%. Forty participants (87.0%) reported income data, with median total household income of $70,000 or greater.

Clinically, 42 participants (91.3%) reported on the nature and extent of the anxiety disorder which constituted their presenting problem at the ADC. With regard to problem duration, 67.4% reported having experienced their primary anxiety disorder for more than 10 years, 15.2% reported a duration of 5-10 years, and 8.7% reported a duration of 1 year or less. An onset of symptoms during childhood/adolescence was reported by 49.8% of participants, with adult onset reported in 41.5% of participants. Eight participants (17.4%) reported no prior treatment and 34 participants (73.9%)
reported at least one encounter with a mental health professional prior to intake at the ADC. A history of inpatient hospitalization was reported by 19.6% of participants.

Diagnostically, initial evaluations were available on 44 participants (95.7%) at time of chart review for data collection. Clinical comorbidity was a common feature of this sample, with 26 participants (59.1%) carrying 2 or more Axis I diagnoses.

Diagnostic Differences

Primary diagnoses of study participants are reported in Table 2. One-way ANOVA was used to examine differences in trait anxiety, health anxiety, number of DSM-IV anxiety disorder symptom criteria endorsed, depression, positive/negative affect, and stress biomarkers by diagnostic category. There were no statistically significant differences between diagnostic groups in trait anxiety ($f(8,25)=2.220; p=.061$), health anxiety ($f(8,26)=1.896; p=.104$), number of DSM-IV anxiety disorder symptom criteria endorsed ($f(8,31)=.591; p=.777$), depression ($f(8,32)=1.492; p=.199$), positive affect ($f(8,25)=.442; p=.884$), negative affect ($f(8,24)=1.105; p=.452$), cortisol ($f(8,31)=1.033; p=.433$), and salivary alpha-amylase ($f(8,31)=.990; p=.463$).

Hypothesis 1: Psychosocial Variables and Stress Biomarkers

STAI-T and Cortisol. Linear regression was used to examine the association between trait anxiety and salivary cortisol level, both of which were examined as continuous variables. Controlling for diurnal variation of baseline cortisol, age, gender, body mass index (BMI), presence of oral contraceptive medication, presence of selective serotonin reuptake inhibitor (SSRI) medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, and psychosocial
factors when appropriate, no association was observed between trait anxiety and salivary cortisol in the sample ($\beta = -.090; p = .609$).

**STAI-T and sAA.** Linear regression was used to examine the association between trait anxiety and sAA level, both of which were examined as continuous variables. Controlling for diurnal variation of baseline sAA, age, gender, body mass index (BMI), presence of beta adrenergic blocking medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, and psychosocial factors when appropriate, no association was observed between trait anxiety and sAA in the sample ($\beta = .033; p = .853$).

**Hypothesis 2: Comorbidity and Chronicity as Moderators of Anxiety-Stress Associations**

**Comorbidity, STAI-T, and Cortisol.** MODPROBE was used to examine the interaction between trait anxiety and extent of comorbid psychopathology as associated with cortisol. Controlling for diurnal variation of baseline cortisol, age, gender, body mass index (BMI), presence of oral contraceptive medication, presence of selective serotonin reuptake inhibitor (SSRI) medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling and psychosocial factors when appropriate, no significant interaction was observed ($\Delta R^2 = .006; p = .666$).

**Comorbidity, STAI-T, and sAA.** MODPROBE was used to examine the interaction between trait anxiety and extent of comorbid psychopathology as associated with sAA. Controlling for diurnal variation of baseline sAA, age, gender, body mass index (BMI), presence of beta adrenergic blocking medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling,
and psychosocial factors when appropriate, no significant interaction was observed ($\Delta R^2=.016; p=.463$).

**Chronicity, STAI-T, and Cortisol.** MODPROBE was used to examine the interaction between trait anxiety and chronicity of presenting problem as associated with cortisol. Controlling for diurnal variation of baseline cortisol, age, gender, body mass index (BMI), presence of oral contraceptive medication, presence of selective serotonin reuptake inhibitor (SSRI) medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, and psychosocial factors when appropriate, no significant interaction was observed ($\Delta R^2=.082; p=.187$). The data trend suggested that greater chronicity weakened the association between trait anxiety and cortisol (see Figure 2).

**Chronicity, STAI-T, and sAA.** MODPROBE was used to examine the interaction between trait anxiety and chronicity of presenting problem as associated with sAA. Controlling for diurnal variation of baseline sAA, age, gender, body mass index (BMI), presence of beta adrenergic blocking medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, and psychosocial factors when appropriate, a significant interaction was observed ($\Delta R^2=.166; p=.038$). Greater chronicity strengthened the association between trait anxiety and sAA in the sample (see Figure 3).

**Hypothesis 3: Stress Biomarkers and Somatic Symptoms**

**Number and Frequency of Somatic Symptoms and Cortisol.** Poisson regression was used to examine the association between the number and frequency of somatic
symptoms experienced and cortisol. Controlling for health anxiety, diurnal variation of baseline cortisol, age, gender, body mass index (BMI), presence of oral contraceptive medication, presence of SSRI medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, health anxiety, depression, and current mood state when appropriate, a significant association was observed ($R^2_{\text{DEVIANCE}} = .035; B = -1.215; p = <.001$).

Number and Frequency of Somatic Symptoms and sAA. Poisson regression was used to examine the association between the number and frequency of somatic symptoms, a count variable, and sAA level, which was examined as a continuous variable. Controlling for diurnal variation of baseline sAA, age, gender, body mass index (BMI), presence of beta adrenergic blocking medication, exercise, smoking, alcohol/recreational drug use, caffeine consumption, eating within 1 hour of sampling, health anxiety, depression, and current mood state when appropriate, a significant association was observed between sAA and the number and frequency of physical symptoms in the sample ($R^2_{\text{DEVIANCE}} = .020; B = .005; p = <.001$).

Hypothesis 4: Trait Anxiety and Somatic Symptoms

Number and Frequency of Physical Symptoms and STAI-T. Poisson regression was used to examine the association between the number and frequency of physical symptoms, a count variable, and trait anxiety, which was examined as a continuous variable. Controlling for age, gender, health anxiety, depression, and current mood state when appropriate, an association was observed between trait anxiety and the number and
frequency of physical symptoms in the sample ($R^2_{DEVIANCE} = .112; \beta = .031; \ p = <.001$). The multivariate regression with covariates is reported in Table 4.

**Discussion**

To our knowledge, this is the first study to examine associations between psychosocial factors (trait anxiety, health anxiety, depression, comorbid psychopathology, symptom chronicity, mood state), salivary biomarkers of both the GC and LC-NE axes of the stress response (cortisol and alpha amylase), and somatic symptoms in a diagnostically heterogeneous anxiety disorder population. Based on prior stress and anxiety research, we hypothesized that greater levels of trait anxiety would be associated with greater levels of salivary cortisol and sAA. Multiple regression/correlation analyses conducted with our sample did not support this hypothesis, however, the extremely low correlations observed strongly suggested the influence of a moderating variable. When the moderator of chronicity was tested, the resultant interaction term was significant and similarly significant associations between trait anxiety and the stress biomarker sAA were observed. Greater chronicity was associated with stronger association between trait anxiety and sAA. Statistical significance was not observed however in regards to the moderator model of problem chronicity, trait anxiety and the stress biomarker cortisol. Nonetheless a trend was observed such that greater chronicity appeared to reduce the association between cortisol and trait anxiety, a trend that is consistent with the glucocorticoid hypo-reactivity in response to chronic stress reviewed and reported elsewhere (Kirschbaum and Hellhammer, 2007; van Eck et al., 2005).
The finding that chronic anxiety is associated with persistent sympathetic arousal has long been demonstrated in the literature (White and Gildea, 1937; Holden and Barlow, 1986). Moreover, there is similarly long-standing evidence that sympathetic arousal is a robust symptom that can be observed across anxiety disorders. Barlow et al. (1985) studied 108 patients across diagnostic categories and observed reports of panic at a high frequency. When these reports were subjected to the scrutiny of the clinical interview, a full third or greater of patients in each category additionally met DSM panic disorder criteria. More recent research has also suggested that different associations with anxiety exist across the two biomarkers under examination in this study. Using an experimental stress paradigm with a small non-clinical sample, Noto et al. (2005) reported an association between STAI state anxiety scores and sAA but not cortisol in response to a stress paradigm, while Van Veen et al. (2008) examined a sample of untreated generalized social anxiety disorder patients and found similar relationships at baseline. More recently, Tanaka et al. (2012) observed a similar relationship of associations using an electrical shock paradigm in a sample of panic disorder patients. Our findings appear consistent with these prior observations, and to our knowledge, this study is the first to observe such findings in a diagnostically heterogeneous and comorbid sample.

The two pathways of the HPA and LC-NE axes represent interrelated yet wholly distinct aspects of the physiological stress response (Chrousos, 2009). In the healthy organism, each path enervates the other such that stimulation of one necessarily leads to stimulation of the other in tandem. However, introduction of an anxiety disorder with a chronic course into the organism could in principle bring about pathophysiological
alterations to the organism’s neuro-endocrinology. This perspective draws from earlier neuroscience research elegantly reviewed by Kandel (2001) whose own work with animal models demonstrated that associative learning occurs as a result of changes at the cellular level within the nervous system. In particular, it was demonstrated that repeated exposure to a noxious stimulus led to a potentiation of the protective withdrawal response in a simple organism. His work further demonstrated that this learned behavior was mediated by changes in the synaptic membrane composition of the relevant neurons, affecting neurotransmitter concentrations. It is possible that learned anxiety is mediated by neurology in humans through means of an analogous, but naturally more complex, model that similarly potentiates sympathetic activation.

A pertinent negative finding was the lack of association observed between trait anxiety and cortisol in our sample. A similar finding was reported in a study of a non-clinical sample (Taylor et al., 2008), while in the clinical realm Meewisse and colleagues (2007) meta-analyzed 38 studies of cortisol levels in persons with PTSD and reported that overall cortisol levels did not differ between PTSD and control groups. This finding is also consistent with the burgeoning literature on sAA and cortisol comparisons (Tanaka et al., 2012; van Veen et al., 2008; Noto et al., 2005). Such a pattern is consistent with observed associations between chronic stress and hypocortisolism in both animal models and human studies (Fries, Hesse, Hellhammer, & Hellhammer, 2005). As Hellhammer and colleagues (2009) point out in their review of salivary cortisol as a biomarker in social and behavioral research, salivary cortisol alone appears insufficient to explain psychological factors and stress activation. The symptom chronicity that has been
reported in this sample could have had the effect of cortisol response attenuation in our study’s participants.

Another interesting finding in this study pertains to comorbid psychopathology in the sample. We originally hypothesized that comorbid psychopathology would moderate the relationship between trait anxiety and concentrations of stress biomarkers. This was not observed in our moderator analyses but interestingly, a direct association between the numbers of Axis I diagnoses and sAA was observed ($\beta = .433; p = .006$) without any similar association between this same variable and cortisol ($\beta = .010; p = .955$). The “full plate syndrome” is a phenomenon that is more commonly considered in the realm of Industrial/Organizational psychology (Tannenbaum, 2012); employees who over-commit and overextend themselves professionally become overwhelmed and can experience increased stress, acute onset of depressive symptoms and decreased productivity. In the clinical realm, this same phenomenon might be at work via comorbid psychopathology, wherein additional phobias, intrusive thoughts, persistent apprehensions, or other clinical symptoms are experienced as cumulative and contribute to the patient’s overall psychopathological burden. This finding may reflect the robustness of sympathetic arousal association with chronic anxiety in the context of a diagnostic “full plate.”

A statistically significant association between both stress biomarkers and somatic symptoms was observed in this study. Higher levels of sAA were associated with a greater number of somatic symptoms endorsed, while higher cortisol levels were associated with a lesser number of said symptoms. The review by Chrosous (2009) outlines the manifold physiological domains that experience dysfunction and risk lasting damage within the chronically stressed individual: cardiovascular, gastro-intestinal,
angiokinetic, metabolic, and immunological processes can all experience pathological alterations in function. Prolonged dysregulation of the stress response can also initiate or exacerbate numerous disease processes by triggering a prolonged inflammatory response (Glaser & Kiecolt-Glaser, 2009). These inflammation-associated symptoms appear to be reflected in a broad range of somatic symptoms included in our questionnaire and experienced by participants. Though not formally hypothesized in this study, the paradoxical relationship between cortisol and symptom report appears to echo the indirect relationship observed between stress and anxiety as moderated by the factor of chronicity. More prolonged dysfunction of the stress system would theoretically be observed in more chronic sufferers such that these individuals would present both with a greater number of somatic symptoms and with attenuated cortisol activity.

An association between trait anxiety and somatic symptoms was likewise observed in this sample. Trait anxiety as reflected by STAI-T score was positively associated with the number and frequency of somatic symptoms experienced. Obtaining a self-assessment of physical health in patients with anxiety disorders is necessarily fraught. Because of its close association with the stress response, so much of the experience of anxiety has a somatic component. It is possible that cognitive and affective biases secondary to anxiety drove the reporting of physical symptoms. Anxious individuals may also have a lower threshold for experiencing pain or other symptoms. Our use of the Health Anxiety Inventory allowed us to control for this significant covariate of physical health reporting; in this study, an association between trait anxiety and reported symptoms was still observed. The directionality of the relationship nonetheless remains in question. Anxiety can present secondary to physical health
symptoms, with pain and physical impairment leading to feelings of worry. Additionally, there is also the possibility that reported physical symptoms have an organic cause. Epidemiological studies have noted the co-occurrence of anxiety and disease, particularly inflammatory conditions such as arthritis, allergies, and gastro-intestinal disease (El-Gabalawy et al., 2011). Other studies, both those considering large-scale epidemiological data and those examining specific clinical populations, have observed associations between anxiety and the pathogenesis of disease, from cardiovascular disease (Pereiro et al., 2012; Roest et al., 2010) to diabetes mellitus (Agyemang et al., 2011) to arteriosclerosis, a stiffening of the arteries that is a precursor of vascular diseases such as hypertension (Logan et al., 2012).

Limitations

Although there are particular strengths to this study, such as the relative novelty of the sAA biomarker used and broad diagnostic inclusion criteria for participation, there are certain limitations that should be noted. Convenience sampling in a clinical setting introduces selection bias such that only those individuals who present to the clinic constitute the actual sampling frame. This includes those whose income and insurance status permit them to access outpatient care. Similarly, only individuals with symptoms that are sufficiently severe to seek care but not so severe as to prevent their ability to travel to the research site will be eligible for recruitment. This introduces a potential restriction of range in the variables of interest. Moreover the sample was predominantly White, educated, and middle-class. These factors undermine the representativeness of the sample with respect to the population of individuals with anxiety disorders. An additional limitation was present in the reliance upon self-report for physical health data. Although participants were instructed to be complete and thorough in their reporting, we
cannot be certain that these instructions were followed in every case. This risk may be compounded by another limitation of the study: the timing of procedures. Participants were recruited during or immediately after their initial intake appointments with the ADC. These appointments, which were approximately 2 to 3 hours in length, consisted of the completion of ADC intake measures and meeting with licensed clinicians and possibly students engaged in formal diagnostic interviewing. Transitioning directly from this process to study procedures consisting of additional questionnaire completion may have resulted in fatigue. Completing questionnaires while fatigued can in theory influence the validity of the responses given.

The saliva sampling method used was intended to obtain a basal stress level, however the context of the clinic with its interviewing and assessment procedures may have elicited arousal in participants prior to our study’s procedures. Methodologically, multiple time point saliva sampling is favored as it provides more information on the diurnal variations of each individual’s biomarker levels, while longitudinal designs necessarily provide data on variations between days throughout a discrete period of time.

The particular constellation of observed associations in this study would suggest a mediation model however, violation of the particular conditions necessary to consider mediation testing prevent this. In particular, the absence of feedback effects is a necessary prerequisite of mediation testing (Baron & Kenny, 1986). In this study, stress may contribute to the occurrence of a somatic symptom in an individual, but such a symptom may contribute to that individual’s perceived stress as well. A similar reciprocity may be posited with regard to the anxiety/stress and anxiety/physical health relationships. The relatively small sample size of our study likewise prevented the use of
alternative path modeling techniques. A further limitation of the study is the use of a cross-sectional design, which prevents consideration of causation with respect to the associations that were observed. Although causal mechanisms cannot be implied, our study’s findings do nonetheless support the assertion that relationships exist between anxiety, stress, and physical health, which warrants further examination.

Future Directions

In conclusion, consideration of the stress response is important to our understanding of anxiety disorders and physical health symptoms. Our findings support the use of sAA with individuals suffering from anxiety disorders as a biomarker of the stress response associated with anxiety. Our results indicate that anxiety chronicity acts as a moderator of the stress response and that comorbid Axis I diagnoses contribute to stress activation in people experiencing anxiety disorders. These findings have meaningful clinical implications in both research and practice. Based on our findings, individuals suffering from anxiety disorders may benefit from interventions that target the cognitive and physiological elements of anxious arousal. Cognitive-behavioral therapy, with its focus on cognitive processing biases and its use of stress-reduction techniques such as deep breathing exercises and progressive muscle relaxation, has the potential to provide useful tools to individuals with anxiety disorders and co-occurring baseline arousal of the stress response. The use of salivary biomarkers in turn may have promise as an objective measure of intervention effects; in this way, biomarkers of the stress response may enhance the existing means of assessing therapeutic progress based on clinician rating or patient self-report. A reduction in somatic symptoms may reduce
the likelihood of patients seeking treatment from primary care physicians for mental health problems and thereby reduce the burden on this facet of the health care system.

Continued investigation of the relationship between stress, anxiety, and physical health using salivary biomarkers is clearly indicated. Continuing to use broader inclusion criteria with respect to chronicity and comorbidity serves the science as it transitions from lab-based, internally valid designs to more ecologically representative ones. Longitudinal studies with greater sample sizes will permit more sophisticated statistical modeling. Future research can also examine anxiety interventions from the perspective of stress and physical health outcomes. Given that anxiety disorders are the most prevalent class of psychiatric disorder, treatment interventions that can ameliorate psychological stress activation and its attendant somatic dysregulation have the potential to meaningfully impact public health.
References


Appendices

**Appendix A: Tables and Figures**

Table 1: Sample Descriptive Statistics

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Figure 1: Study Participants by Diagnostic Category

Table 2: Regression of Stress Biomarkers on Psychosocial Measures

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<th>Cortisol on</th>
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<th>p-value</th>
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<td>STAI-T</td>
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<td>HAI</td>
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<td>.753</td>
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<td>PANAS-PA</td>
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<td>.209</td>
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<td>.667</td>
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<td>Comorbidity</td>
<td>.010</td>
<td>.955</td>
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<table>
<thead>
<tr>
<th>sAA on</th>
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<th>p-value</th>
</tr>
</thead>
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<tr>
<td>STAI-T</td>
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<td>.853</td>
</tr>
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<td>-.163</td>
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</tr>
<tr>
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<td>.702</td>
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<td>.006**</td>
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Table 3: Regression of Somatic Symptoms on Stress Biomarkers

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<tr>
<th>Somatic Sx</th>
<th>Biomarker</th>
<th>R²</th>
<th>DEVIANCE</th>
<th>B-Coefficient</th>
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<td>.005</td>
<td>&lt;.001**</td>
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Table 4: Regression of Somatic Symptoms on Psychosocial Measures

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<tr>
<th>Somatic Sx on</th>
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<th>SE</th>
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Figure 2: Symptom Chronicity moderates the relationship between Trait Anxiety and Cortisol (not statistically significant)

Figure 3: Symptom Chronicity moderates the relationship between Trait Anxiety and sAA
Appendix B: Study Measures

ANXIETY STUDY PHQ

1. Please indicate if you have any of the following chronic medical conditions or symptoms? Please check all that apply.

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<td>Chronic Fatigue Syndrome</td>
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</tr>
<tr>
<td>Arthritis/rheumatoid arthritis</td>
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<tr>
<td>Heart disease</td>
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<tr>
<td>History of heart attack</td>
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<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Heart disease</td>
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</tr>
<tr>
<td>Migraines</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Asthma</td>
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<tr>
<td>Emphysema</td>
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<tr>
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<tr>
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<tr>
<td>History of stroke</td>
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<tr>
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<td>Abnormal breathing tendencies</td>
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<tr>
<td>Chronic Bronchitis (disorder)</td>
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</tr>
<tr>
<td>Fibromyalgia</td>
<td></td>
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<tr>
<td>Coagulation (bleeding/clotting disorder)</td>
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<tr>
<td>Ulcer</td>
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</tr>
<tr>
<td>Epilepsy/seizures</td>
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<tr>
<td>Other – please describe:</td>
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2. Have you ever been diagnosed with any type of cancer (e.g., lung, breast, cervical, ovarian, prostate, skin, colon)?

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<th>Type of Treatment</th>
<th>Approximate</th>
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</table>
3. Has anyone in your family ever been diagnosed with any type of cancer (e.g., lung, breast, cervical, ovarian, prostate, skin, colon)?

_____ No

_____ Yes- please indicate the following:

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<th>Type of Treatment</th>
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4. Please describe any significant medical conditions your mother, fathers, sisters, or brother have had (please refer to question 1 for examples of conditions).

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Age</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

5. Are you currently being treated for any medical illnesses?

_____ No
6. Do you currently take any medications in addition to those listed in your intake packet?
   _____ No
   _____ Yes - please list:
   _______________________________________________________________

7. About how many days have you been sick in the past month? ___________ days

8. About how many visits have you made to your doctor in the past month? _______ visits

9. About how many visits have you made to the ER in the past month? __________ visits

10. Do you have any trouble doing physical activity due to physical illness?
    _____ No
    _____ Yes – on average, how many days per month? __________

11. Are you sexually active?
    _____ No
    _____ Yes – if you use birth control, please list type of birth control: __________

12. If female, what is your menopausal status?
    _____ Pre-menopausal
    _____ Peri-menopausal (i.e., currently in menopause)
    _____ Post-menopausal
13. If female, have you experienced any of the following? Please check all that apply.

_____ Severe cramps during menstruation

_____ Missed periods for reasons other than pregnancy – if yes, how many times in the past year?

_____ times

_____ Miscarriages – if yes, about how many? __________

14. Do you currently smoke cigarettes?

_____ No

_____ Yes – how many cigarettes/day? _________

17. Do you currently drink alcoholic beverages?

_____ No

_____ Yes – on average, about how many drinks do you consume per day __________

18. Do you currently drink any caffeinated beverages?

_____ No

_____ Yes – Please describe:

a) on average, about how many drinks (cups) do you consume per day __________

b) what kinds (e.g., coffee, tea, soda, energy drinks etc) ______________________

19. Do you currently use illicit/illegal drugs?

_____ No

_____ Yes – Please circle all that apply: Opiates, cocaine, marijuana, benzodiazepines, steroids, hallucinogens, barbiturates

20. Do you currently engage in regular exercise?

_____ No

_____ Yes - please describe:

a) type of exercise (e.g., running, walking, weight training, etc)
b) about how many times per week:

____________________________________________________________________

c) for about how long:

____________________________________________________________________

d) how intense (e.g., mild, moderate, strenuous):

21. On average, how many hours do you currently sleep per night (This may be different than the number of hours you spend in bed)? _____ Hours of sleep per night

22. Do you experience any of the following?

_____ Trouble falling asleep each night – if yes, on average, how long (minutes) does it take to fall asleep: ______ minutes

_____ Wake up in the middle of the night – if yes, how often? ________ times

_____ Discomfort while sleeping - Circle all that apply: snoring, hot/cold, long pauses between breaths, restlessness, pain, leg twitching

23. On average, how would you rate your quality of sleep (please circle one)? Poor, Fair, Good, Very Good, Excellent

24. How satisfied are you in general with your medical care (circle one)? Poor, Fair, Good, Very Good, Excellent

25. Please indicate how often you have felt the symptoms below:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Never/Almost Never</th>
<th>Less than 3-4 Times per Year</th>
<th>Every Month or so</th>
<th>Every Week or so</th>
<th>More than Once a Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eyes water</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Condition</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>2</td>
<td>Itchy eyes or skin</td>
<td></td>
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<td></td>
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<tr>
<td>3</td>
<td>Choking sensations</td>
<td></td>
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<tr>
<td>4</td>
<td>Sneezing spells</td>
<td></td>
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<tr>
<td>5</td>
<td>Running nose</td>
<td></td>
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<tr>
<td>6</td>
<td>Congested nose</td>
<td></td>
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<tr>
<td>7</td>
<td>Bleeding nose</td>
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<td>8</td>
<td>Cold hands or feet even in hot weather</td>
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<tr>
<td>9</td>
<td>Hemorrhoids</td>
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<tr>
<td>10</td>
<td>Back pains</td>
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<td>11</td>
<td>Sensitive or tender skin</td>
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<td>12</td>
<td>Acne or pimples on face or body</td>
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<td>13</td>
<td>Sweat even in cold weather</td>
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<td>14</td>
<td>Feeling pressure in head</td>
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<td>15</td>
<td>Numbness or tingling in any part of body</td>
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<tr>
<td>16</td>
<td>Twitching of eyelid</td>
<td></td>
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<tr>
<td>17</td>
<td>Hands tremble or shake</td>
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<td>18</td>
<td>Sore muscles</td>
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<td>19</td>
<td>Sore throat</td>
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<tr>
<td>20</td>
<td>Heart burn</td>
<td></td>
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<tr>
<td>21</td>
<td>Trouble hearing</td>
<td></td>
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<tr>
<td>22</td>
<td>Nausea</td>
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<tr>
<td>23</td>
<td>Indigestion</td>
<td></td>
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<td>24</td>
<td>Diarrhea</td>
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<tr>
<td>25</td>
<td>Constipation</td>
<td></td>
<td></td>
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<tr>
<td>26</td>
<td>Hearing problems</td>
<td></td>
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<td></td>
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<tr>
<td>27</td>
<td>Abdominal pain</td>
<td></td>
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<tr>
<td>28</td>
<td>Changes in vision</td>
<td></td>
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<td>29</td>
<td>Ringing in ears</td>
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<tr>
<td>30</td>
<td>Fatigue/weakness</td>
<td></td>
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<tr>
<td>31</td>
<td>Excess thirst or urination</td>
<td></td>
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<tr>
<td>32</td>
<td>Problems with teeth/gums</td>
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<tr>
<td>33</td>
<td>Chest pain/discomfort</td>
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<tr>
<td>34</td>
<td>Cough/wheezing</td>
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<tr>
<td>35</td>
<td>Difficulty breathing</td>
<td></td>
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<tr>
<td>36</td>
<td>Nighttime urination</td>
<td></td>
<td></td>
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<tr>
<td>37</td>
<td>Easy bruising</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>38</td>
<td>Leaking urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Sexual function problems</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Never/Almost Never</th>
<th>Less than 3-4 Times per Year</th>
<th>Every Month or so</th>
<th>Every Week or so</th>
<th>More than Once a Week</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>40.</td>
<td>Muscle or Joint Pain</td>
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<tr>
<td>41.</td>
<td>Hay fever (allergic rhinitis)</td>
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<td>2</td>
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<tr>
<td>42.</td>
<td>Rash or mole change</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>43.</td>
<td>Headaches</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>44.</td>
<td>Memory loss</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>45.</td>
<td>Unexplained weight loss/gain</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<tr>
<td>46.</td>
<td>Out of breath</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>47.</td>
<td>Other – Please describe ___________</td>
<td>0</td>
<td>1</td>
<td>2</td>
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Saliva Collection Questionnaire

Please provide the following information about factors that may influence stress markers in saliva.

1. Height: ___ feet, ___ inches

2. Weight: _______ pounds

3. Do you smoke cigarettes?
   ___No
   ___Yes - How many cigarettes have you smoked today? ________

4. What time did you last smoke a cigarette? ________ a.m. / p.m.

5. How recently have you eaten any food? ________ a.m. / p.m.

6. Have you had any caffeine today?
   ___No
   ___Yes - What type (coffee, tea, soda, etc.) ____________and how much _______(cups)?

7. When was the last time you had any dental work, including regular teeth cleaning?
   Month: ________________    Day: ________    Year: ________

8. Do you have any periodontal disease (gum disease, gingivitis, periodontitis)?
   ___No
   ___Yes
9. What time did you wake up this morning? ___________ a.m.

10. How long did you sleep last night? _______ hours _______ minutes

11. Have you done any physical exercise today?
   ___No
   ___Yes - What type? ________________________ For How Long? _________minutes

12. Have you consumed any alcohol in the past 24 hours?
   ___No
   ___Yes - Number of Drinks _____

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way right now, that is, at the present moment. Use the following scale to record your answers:
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>1.</td>
<td>Interested</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td>Distressed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3.</td>
<td>Excited</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.</td>
<td>Upset</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5.</td>
<td>Strong</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6.</td>
<td>Guilty</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7.</td>
<td>Scared</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8.</td>
<td>Hostile</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9.</td>
<td>Enthusiastic</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10.</td>
<td>Proud</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11.</td>
<td>Irritable</td>
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<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>12.</td>
<td>Alert</td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13.</td>
<td>Ashamed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14.</td>
<td>Inspired</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15.</td>
<td>Nervous</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16.</td>
<td>Determined</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17.</td>
<td>Attentive</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18.</td>
<td>Jittery</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19.</td>
<td>Active</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20.</td>
<td>Afraid</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>
HAI

Each question is this section consists of a group of four statements. Please read each group of statements carefully and then select the one which best describes your feelings, over the past six months. Identify the statement by ringing the letter next to it i.e. if you think that statement (a) is correct, ring statement (a); it may be that more than one statement applies, in which case, please ring any that are applicable.

1.  a.  I do not worry about my health.
     b.  I occasionally worry about my health.
     c.  I spend much of my time worrying about my health.
     d.  I spend most of my time worrying about my health.

2.  a.  I notice aches/pains less than most other people (of my age).
     b.  I notice aches/pains as much as most other people (of my age).
c. I notice aches/pains more than most other people (of my age).

d. I am aware of aches/pains in my body all the time.

3. a. As a rule I am not aware of bodily sensations or changes.  
b. Sometimes I am aware of bodily sensations or changes.  
c. I am often aware of bodily sensations or changes.  
d. I am constantly aware of bodily sensations or changes.

4. a. When I have an unexplained bodily sensation or change I rarely worry about it.  
b. When I have an unexplained bodily sensation or change I sometimes worry about it.  
c. When I have an unexplained bodily sensation or change I often worry about it.  
d. When I have an unexplained bodily sensation or change I always worry about it.

5. a. Resisting thoughts of illness is never a problem.  
b. Most of the time I can resist thoughts of illness.  
c. I try to resist thoughts of illness but am often unable to do so.  
d. Thoughts of illness are so strong that I no longer even try to resist them.

6. a. I never worry about dying.  
b. I occasionally worry about dying.  
c. I often worry about dying.  
d. I worry about dying most of the time.

7. a. When I have an unexplained bodily sensation or change, I rarely think that it is a sign of illness.  
b. When I have an unexplained bodily sensation or change, I sometimes think that it is a sign of illness.  
c. When I have an unexplained bodily sensation or change, I often think that it is a sign of illness.  
d. When I have an unexplained bodily sensation or change, I always think that it is a sign of illness.

8. a. As a rule I am not afraid that I have a serious illness.  
b. I am sometimes afraid that I have a serious illness.  
c. I am often afraid that I have a serious illness.  
d. I am always afraid that I have a serious illness.

9. a. I do not have images (mental pictures) of myself being ill.  
b. I occasionally have images of myself being ill.  
c. I frequently have images of myself being ill.  
d. I constantly have images of myself being ill.

10. a. It usually feels extremely unlikely that I will develop a serious illness in the near future.  
b. It usually feels unlikely that I will develop a serious illness in the near future.  
c. It usually feels as though there is some likelihood that I will develop a serious illness in the near future.  
d. It usually feels likely that I will develop a serious illness in the near future.

11. a. If I notice an unexplained bodily sensation or change I don’t check to see how it develops.  
b. If I notice an unexplained bodily sensation or change I check it occasionally to see how it is developing.  
c. If I notice an unexplained bodily sensation or change I check it frequently to see how it is developing.
developing.

d. If I notice an unexplained bodily sensation or change I constantly check on it.

12. a. The idea that I have a serious illness is senseless.
    b. The idea that I have a serious illness might be sensible.
    c. The idea that I have a serious illness is probably sensible.
    d. The idea that I have a serious illness is realistic.

13. a. I do not avoid situations which trigger thoughts of death or dying.
    b. I sometimes avoid situations which trigger thoughts of death or dying.
    c. I often avoid situations which trigger thoughts of death or dying.
    d. I always avoid situations which trigger thoughts of death or dying.

14. a. If I notice an unexplained bodily sensation I ignore it.
    b. If I notice an unexplained bodily sensation I focus on it from time to time.
    c. If I notice an unexplained bodily sensation I focus on it often.
    d. If I notice an unexplained bodily sensation I constantly focus on it.

15. a. I don’t usually examine my body.
    b. I often examine my body.
    c. I examine my body daily.
    d. I examine my body constantly.

16. a. I do not have any difficulty taking my mind off thoughts about my health.
    b. I sometimes have difficulty taking my mind off thoughts about my health.
    c. I often have difficulty in taking my mind off thoughts about my health.
    d. Nothing can take my mind off thoughts about my health.

17. a. I am lastingly relieved if my doctor tells me there is nothing wrong.
    b. I am initially relieved but the worries sometimes return later.
    c. I am initially relieved but the worries always return later.
    d. I am not relieved if my doctor tells me there is nothing wrong.

18. a. If I hear about an illness I never think I have it myself.
    b. If I hear about an illness I sometimes think I have it myself.
    c. If I hear about an illness I often think I have it myself.
    d. If I hear about an illness I always think I have it myself.

19. a. If I notice an unexplained bodily sensation or change I rarely try to find out the cause.
    b. If I notice an unexplained bodily sensation or change I sometimes try to find out the cause.
    c. If I notice an unexplained bodily sensation or change I often try to find out the cause.
    d. If I notice an unexplained bodily sensation or change I always try to find out the cause.

20. a. My health worries do not interfere with my life.
    b. Occasionally my health worries interfere with my life.
    c. Often health worries interfere with my life.
    d. I am unable to do anything because of my health worries.

21. a. I never believe that I am going to die soon.
    b. I sometimes believe that I am going to die soon.
    c. I often believe that I am going to die soon.
    d. I constantly believe that I am going to die soon.
<table>
<thead>
<tr>
<th>Question</th>
<th>Option A</th>
<th>Option B</th>
<th>Option C</th>
<th>Option D</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.</td>
<td>a. I am never afraid of visiting my doctor because of my health worries.</td>
<td>b. I am sometimes afraid of visiting my doctor because of my health worries.</td>
<td>c. I am often afraid of visiting my doctor because of my health worries.</td>
<td>d. I am too afraid to visit my doctor because of my health worries.</td>
</tr>
<tr>
<td>23.</td>
<td>a. Worries about my health do not stop me thinking about other things.</td>
<td>b. Worries about my health sometimes stop me thinking about other things.</td>
<td>c. Worries about my health often stop me thinking of other things.</td>
<td>d. I am so worried about my health that I can think of nothing else.</td>
</tr>
<tr>
<td>24.</td>
<td>a. If I notice an unexplained bodily sensation I never feel a need to distract myself from it.</td>
<td>b. If I notice an unexplained bodily sensation I sometimes try to distract myself from it.</td>
<td>c. If I notice an unexplained bodily sensation I often try to distract myself from it.</td>
<td>d. If I notice an unexplained bodily sensation I always try to distract myself from it.</td>
</tr>
<tr>
<td>25.</td>
<td>a. The idea that I have a serious illness never seems sensible.</td>
<td>b. The idea that I have a serious illness sometimes seems sensible.</td>
<td>c. The idea that I have a serious illness often seems sensible.</td>
<td>d. The idea that I have a serious illness always seems sensible.</td>
</tr>
<tr>
<td>26.</td>
<td>a. My previous illnesses were properly treated.</td>
<td>b. My previous illnesses could have been slightly better treated.</td>
<td>c. My previous illnesses could have been much better treated.</td>
<td>d. My previous illnesses were seriously mismanaged.</td>
</tr>
<tr>
<td>27.</td>
<td>a. If I have a bodily sensation or change I rarely wonder what it means.</td>
<td>b. If I have a bodily sensation or change I often wonder what it means.</td>
<td>c. If I have a bodily sensation or change I always wonder what it means.</td>
<td>d. If I have a bodily sensation or change I must know what it means.</td>
</tr>
<tr>
<td>28.</td>
<td>a. I do not avoid situations where illness is prominent.</td>
<td>b. I sometimes avoid situations where illness is prominent.</td>
<td>c. I often avoid situations where illness is prominent.</td>
<td>d. I always avoid situations where illness is prominent.</td>
</tr>
<tr>
<td>29.</td>
<td>a. I usually feel at very low risk for developing a serious illness.</td>
<td>b. I usually feel at fairly low risk for developing a serious illness.</td>
<td>c. I usually feel at moderate risk for developing a serious illness.</td>
<td>d. I usually feel at high risk for developing a serious illness.</td>
</tr>
<tr>
<td>30.</td>
<td>a. I rarely have images of myself dying or dead.</td>
<td>b. I occasionally have images of myself dying or dead.</td>
<td>c. I frequently have images of myself dying or dead.</td>
<td>d. I constantly have images of myself dying or dead.</td>
</tr>
<tr>
<td>31.</td>
<td>a. If I notice an unexplained bodily sensation I never mention it to others.</td>
<td>b. If I notice an unexplained bodily sensation I sometimes mention it to others.</td>
<td>c. If I notice an unexplained bodily sensation I often mention it to others.</td>
<td>d. If I notice an unexplained bodily sensation I always mention it to others.</td>
</tr>
<tr>
<td>32.</td>
<td>a. As a rule, I do not think about what it would be like if I were seriously ill.</td>
<td>b. I sometimes think about what it would be like if I were seriously ill.</td>
<td></td>
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</table>
c. I frequently think about what it would be like if I were seriously ill.

d. I constantly think about what it would be like if I were seriously ill.

33. a. I do not usually feel at all vulnerable to serious illness.
   b. I usually feel slightly vulnerable to serious illness.
   c. I usually feel moderately vulnerable to serious illness.
   d. I usually feel extremely vulnerable to serious illness.

34. a. If I notice an unexplained bodily sensation or change I never try to reassure myself about it.
   b. If I notice an unexplained bodily sensation or change I sometimes try to reassure myself about it.
   c. If I notice an unexplained bodily sensation or change I often try to reassure myself about it.
   d. If I notice an unexplained bodily sensation or change I always try to reassure myself about it.

35. a. I never think I have a serious illness.
   b. I sometimes think I have a serious illness.
   c. I often think I have a serious illness.
   d. I usually think that I am seriously ill.

36. a. It usually feels extremely unlikely that I will become ill (in any way) in the next few weeks.
   b. It usually feels unlikely that I will become ill (in any way) in the next few weeks.
   c. It usually feels as though there is some possibility that I will become ill (in any way) in the next few weeks.
   d. It usually feels likely that I will become ill (in any way) in the next few weeks.

37. a. As a rule I am not afraid of developing a serious illness.
   b. I am sometimes afraid of developing a serious illness.
   c. I am afraid of developing a serious illness most of the time.
   d. I am afraid of developing a serious illness all the time.

38. a. It is extremely unlikely that I have an undiagnosed serious illness.
   b. It is fairly unlikely that I have an undiagnosed serious illness.
   c. It is fairly likely I have an undiagnosed serious illness.
   d. It is very likely I have an undiagnosed serious illness.

39. a. If I think about developing a serious illness I feel a little scared.
   b. If I think about developing a serious illness I feel moderately scared.
   c. If I think about developing a serious illness I feel very scared.
   d. If I think about developing a serious illness I feel terrified.

40. a. When I have a pain, I rarely think that it is a sign of illness.
   b. When I have a pain, I sometimes think that it is a sign of illness.
   c. When I have a pain, I often think that it is a sign of illness.
   d. When I have a pain, I always think that it is a sign of illness.

41. a. It usually feels extremely unlikely that I will die soon.
   b. It usually feels as if there is a fair chance that I will die soon.
   c. It usually feels as though I will probably die soon.
   d. It usually feels as though I am going to die soon.
42. a. If I notice an unexplained bodily sensation I never do anything to try to get rid of it.
   b. If I notice an unexplained bodily sensation I sometimes try to get rid of it.
   c. If I notice an unexplained bodily sensation I often try to get rid of it.
   d. If I notice an unexplained bodily sensation I always try to get rid of it.

43. a. If I notice an unexplained bodily sensation I don’t find it difficult to think about other things.
   b. If I notice an unexplained bodily sensation I sometimes find it difficult to think about other things.
   c. If I notice an unexplained bodily sensation I often find it difficult to think about other things.
   d. If I notice an unexplained bodily sensation I always find it difficult to think about other things.

44. a. If I hear about a certain illness it never causes me to worry about other illnesses.
   b. If I hear about a certain illness it sometimes causes me to worry about other illnesses.
   c. If I hear about a certain illness it often causes me worry about other illnesses.
   d. If I hear about a certain illness it always causes me to worry about other illnesses.

45. a. My family/friends would say I do not worry enough about my health.
   b. My family/friends would say I have a normal attitude to my health.
   c. My family/friends would say I worry too much about my health.
   d. My family/friends would say I am a hypochondriac.

46. a. My GP would say I do not worry enough about my health.
   b. My GP would say I have a normal attitude to my health.
   c. My GP would say I worry too much about my health.
   d. My GP would say I am a hypochondriac.

47. a. I think I worry too little about my health.
   b. I think I have a normal attitude to my health.
   c. I think I worry too much about my health.
   d. I think I am a hypochondriac.

For the following questions, please think about what it might be like if you had a serious illness of a type which particularly concerns you (such as heart disease, cancer, multiple sclerosis and so on). Obviously you cannot know for definite what it would be like; please give your best estimate of what you think might happen, basing your estimate on what you know about yourself and serious illness in general.

48. a. If I had a serious illness there is a good chance that I would still be able to have a reasonable quality of life.
   b. If I had a serious illness there is a small chance that I would still be able to have a reasonable quality of life.
   c. If I had a serious illness there is only a very small chance that I still would be able to have a reasonable quality of life.
   d. If I had a serious illness there is no chance that I would still be able to have a reasonable quality of life.

49. a. If I developed a serious illness there is a small chance that it would be very painful.
   b. If I developed a serious illness there is a moderate chance that it would be very painful.
   c. If I developed a serious illness there is an extremely high chance that it would be very painful.
   d. If I developed a serious illness it would definitely be very painful.

50. a. If I developed a serious illness there is a small chance that it would be fatal.
   b. If I developed a serious illness there is a moderate chance that it would be fatal.
   c. If I developed a serious illness there is an extremely high chance that it would be fatal.
   d. If I developed a serious illness it would definitely be fatal.
51. a. If I developed a serious illness there is a small chance that it would involve prolonged suffering.
b. If I developed a serious illness there is a moderate chance that it would involve prolonged suffering.
c. If I developed a serious illness there is an extremely high chance that it would involve prolonged suffering.
d. If I developed a serious illness it would definitely involve prolonged suffering.

52. a. If I had a serious illness I would still be able to enjoy things in my life quite a lot.
b. If I had a serious illness I would still be able to enjoy things in my life a little.
c. If I had a serious illness I would be almost completely unable to enjoy things in my life.
d. If I had a serious illness I would be completely unable to enjoy life at all.

53. a. If I developed a serious illness there is a good chance that modern medicine would be able to cure me.
b. If I developed a serious illness there is a moderate chance that modern medicine would be able to cure me.
c. If I developed a serious illness there is a very small chance that modern medicine would be able to cure me.
d. If I developed a serious illness there is no chance that modern medicine would be able to cure me.

54. a. If I developed a serious illness my family and friends would not act in a pitying way towards me (or it would not bother me if they did).
b. If I developed a serious illness my family and friends would act in a fairly pitying way towards me.
c. If I developed a serious illness my family and friends would act in a very pitying way towards me.
d. If I developed a serious illness my family and friends would act in an exceedingly pitying way towards me.

55. a. If I had a serious illness my belief in my own worth would not change.
b. If I had a serious illness my belief in my own worth would be slightly affected.
c. If I had a serious illness my belief in my own worth would be strongly affected.
d. If I had a serious illness my belief in my own worth would be destroyed.

56. a. A serious illness would ruin some aspects of my life.
b. A serious illness would ruin many aspects of my life.
c. A serious illness would ruin almost every aspect of my life.
d. A serious illness would ruin every aspect of my life.

57. a. If I developed a serious illness my family and friends would not reject me.
b. If I developed a serious illness my family and friends might reject me.
c. If I developed a serious illness my family and friends would probably reject me.
d. If I developed a serious illness my family and friends would definitely reject me.

58. a. If I had a serious illness I would not feel that I had lost my dignity.
b. If I had a serious illness I would feel that I had lost a little of my dignity.
c. If I had a serious illness I would feel that I had lost quite a lot of my dignity.
d. If I had a serious illness I would feel that I had totally lost my dignity.

59. a. I would not feel ashamed if I developed a serious illness.
b. I would feel slightly ashamed if I developed a serious illness.
c. I would feel moderately ashamed if I developed a serious illness.
d. I would feel deeply ashamed if I developed a serious illness.

60. a. If I developed a serious illness I would be able to tolerate loss of independence.
    b. If I developed a serious illness I would have some difficulty tolerating loss of independence.
    c. If I developed a serious illness I would have considerable difficulty tolerating loss of independence.
    d. If I developed a serious illness I would find loss of independence completely intolerable.

61. a. If I developed a serious illness, my family would be able to cope without me.
    b. If I developed a serious illness, my family would have some problems coping without me.
    c. If I developed a serious illness, my family would have great difficulty coping without me.
    d. If I developed a serious illness, my family would be completely unable to cope without me.

62. a. If I developed a serious illness my family and friends would care.
    b. If I developed a serious illness my family and friends would care to some extent.
    c. If I developed a serious illness my family and friends would not care very much.
    d. If I developed a serious illness my family and friends would not care at all.

63. a. If I developed a serious illness there are many people who would be able to support me.
    b. If I developed a serious illness there are several people who would be able to support me.
    c. If I developed a serious illness there are one or two people who would be able to support me.
    d. If I developed a serious illness there is no-one who would be able to support me.

64. a. I would cope very well if I developed a serious illness.
    b. I would cope fairly well if I developed a serious illness.
    c. I would cope badly if I developed a serious illness.
    d. I would be unable to cope if I developed a serious illness.

Choose a number from the scale below to show how much you would avoid each of the situations listed below because of fear or other unpleasant feelings. Then write the number you chose in the space provided.

0 ……….. 1 ……….. 2 ……….. 3 ……….. 4 ……….. 5 ……….. 6 ……….. 7 ……….. 8

Would not avoid it Slightly avoid it Definitely avoid it Markedly avoid it Always avoid it

1. Consulting your family doctor

2. Visiting a friend in hospital.
3. Visiting a relative in hospital

4. Going to a hospital for treatment

5. Talking about illness

6. Reading about illness

7. Visiting a hospital for other reasons (e.g. delivering a message)

8. Watching TV programs about illness

9. Listening to radio programs about illness

10. Thinking about illness

Choose a number from the scale below which best describes how often you seek reassurance about your health, from each of the sources described below. Then write the number you have chosen in the space provided.

0………1………2………3………4………5………6………7………8
Never Rarely Sometimes Often Daily

1. Friends

2. Family

3. Reading books

4. Checking body for changes

5. Family doctor

6. Nurses

7. Hospital outpatient clinic

8. Hospital casualty
9. Other (specify)

.................................................................................................................................
The purpose of this packet is to help us get more information about you and your concerns. Please answer all of these questions to the best of your ability. If you do not understand a question, please circle it and ask your clinician about it.

Name: ___________________________ Age: ___________ Date of Birth: ___________

Gender (circle one): Male 1 Female 2

Ethnicity (circle one): Hispanic or Latino 1 Not Hispanic or Latino 2

Race (circle all that apply): Black or AA 1 White 2 Native Hawaiian or Pacific Islander 3 Asian 4 American Indian/Alaska Native 5

Relationship Status (circle one): Single 1 Married 2 Living Together 3 Divorced or Separated 4 Widowed 5 Civil Union 6 Other 7

Religion (circle one): Catholic 1 Protestant 2 Jewish 3 Other 4 None 5

Employment Status (circle one): Not working 0 Part-time 1 Full-time 2 On disability 3 Student 4 Retired 5

What is your job? _____________________________________________________________

How far did you go in school? (circle one):

Ph.D., MD, or equivalent 1 MA, MS, or equivalent 2 Some graduate school 3 Some BA, BS, or equivalent 4 Some AA or some college 5 High school graduate 6 Some high school 7 Grammar school 8

Current household income (circle one):

$70,001 and up 1 $60,000-70,000 2 $50,001-60,000 3 $40,001-50,000 4 $30,001-40,000 5 $20,001-30,000 6 $10,001-20,000 7 $10,000 and less 8
## TREATMENT HISTORY

Please list all outpatient psychologists, psychiatrists, counselors, or therapists that you have had.

<table>
<thead>
<tr>
<th>Dates</th>
<th>Clinician’s Name</th>
<th>City and Phone Number</th>
<th>Did you receive therapy? (Check if yes)</th>
<th>Did you receive medication? (Check if yes)</th>
<th>May we contact this person? (Write YES or NO)</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

Please list all inpatient psychiatric hospitalizations that you have had.

<table>
<thead>
<tr>
<th>Dates</th>
<th>Hospital</th>
<th>City and Phone Number</th>
<th>May we contact this hospital? (Write YES or NO)</th>
</tr>
</thead>
<tbody>
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Please sign here to authorize us at the Anxiety Disorders Center, Institute of Living to contact the people and/or hospitals you have indicated above. This is for the purpose of continuity of care and will cover all dates of admission and/or discharge. Your signature authorizes us to obtain and disclose all information, including admission and discharge statements, assessments, progress notes, psychological testing, lab reports, and physical examinations. Your signature authorizes us to communicate via fax, mail, or verbally. Authorization for this communication expires in one year. Refusal to grant consent will not jeopardize your right to obtain present or future treatment except where disclosure is necessary for treatment. This consent can be revoked at any time except to the extent that disclosure in good faith has already occurred in reliance on this consent.

Your Name (print) ____________________________ Signature ____________________________ Date ____________

Witness (signature): ____________________________
Please list all medications you are currently taking.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Current Dose</th>
<th>How long have you taken the medication?</th>
<th>Who prescribes this medication?</th>
</tr>
</thead>
<tbody>
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</table>

Please list all medications you have taken in the past, but are no longer taking.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Highest Dose</th>
<th>How long did you take the medication?</th>
<th>Who prescribed this medication?</th>
</tr>
</thead>
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ADIS-IV SCREENING QUESTIONNAIRE

This form will ask you about problems that you may have had. Please respond to each question by circling "Yes," "No," or "Maybe/Unsure."

1. PD: Do you have times when you feel a sudden rush of intense fear or discomfort?  
   YES  NO  MAYBE/UNSURE

2. AG: Do you feel panicky in any situations or avoid them because you might feel panicky?  
   YES  NO  MAYBE/UNSURE

3. AG: Are you apprehensive about entering situations due to the fear that you may develop such symptoms as diarrhea, vomiting, dizziness, etc.?  
   YES  NO  MAYBE/UNSURE

4. SoP: In social situations where you might be observed or evaluated by others or when you are meeting new people, do you feel fearful, anxious, or nervous?  
   YES  NO  MAYBE/UNSURE

5. SP: Are you overly concerned that you may say something that might embarrass or humiliate yourself in front of others, or that others may think badly of you?  
   YES  NO  MAYBE/UNSURE

6. GAD: Over the last several months, have you been continually worried or anxious about a number of events or activities in your daily life?  
   YES  NO  MAYBE/UNSURE

7. OCD: Are you bothered by thoughts, images, or impulses that keep recurring to you that seem inappropriate or nonsensical but that you can't stop from coming into your mind?  
   YES  NO  MAYBE/UNSURE

8. OCD: Do you feel driven to repeat some behavior or to repeat something in your mind over and over again to try to feel less uncomfortable?  
   YES  NO  MAYBE/UNSURE

9. CH: Do you have a lot of difficulty discarding things that others would be able to discard easily?  
   YES  NO  MAYBE/UNSURE

10. CH: Is your home so cluttered that it is hard to use the rooms for their intended purpose?  
    YES  NO  MAYBE/UNSURE

11. SpP: Do you fear or feel a need to avoid such things as flying, seeing blood, getting a shot, heights, closed places, or certain kinds of animals or insects?  
    YES  NO  MAYBE/UNSURE

12. PTSD: Have you ever experienced or witnessed a traumatic or life-threatening event such as assault, rape, seeing someone badly injured or killed, combat, accidents, or natural or man-made disasters?  
    YES  NO  MAYBE/UNSURE

13. MDE: Have you ever experienced a period of two weeks or more when you felt depressed, sad, empty, or lost interest or pleasure in your usual activities?  
    YES  NO  MAYBE/UNSURE

14. DyD: Over the past two years, have you frequently had days where you felt down, blue, or depressed for most of the day?  
    YES  NO  MAYBE/UNSURE
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Answer</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. MaE: Have you ever experienced a period of several days or more when you felt unusually or excessively high or irritable?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>16. Hyp: Over the last several months, have you continually feared or believed that you might have a serious physical disease or illness?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>17. Som: Have you had a lot of physical problems in your life?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>18. MixAD: Do you often have days when you feel somewhat down or depressed or maybe anxious or keyed up?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>19. ETOH: Has there ever been a period of time when you drank too much alcohol?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>20. SA: Do you drink a large amount of beverages that contain caffeine?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>21. SA: Have you ever used any other substances such as marijuana or cocaine?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>22. Conv: Have you ever experienced a loss or change in your physical functioning such as paralysis, seizures, or severe pain?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>23. Psy: Has there ever been a period of time when you had strange or unusual experiences such as hearing or seeing things that other people didn't notice, hearing voices when no one was around, or seeing visions that no one else saw?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
<tr>
<td>24. Psy: Has there ever been a period of time when you had the feeling that something odd was going on around you, that people were doing things to test you or antagonize or hurt you so that you felt you had to be on guard constantly?</td>
<td>YES</td>
<td>NO</td>
<td>MAYBE/UNSURE</td>
</tr>
</tbody>
</table>
BDI-II

Please read each group of statements carefully, then pick out the one statement in each group which best describes the way you have been feeling during the past 2 weeks including today. Circle the number beside the statement you have picked. Do not leave any statements blank. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1. Sadness
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can’t stand it.

2. Pessimism
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel that I am a total failure as a person.

4. Loss of Pleasure
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don’t enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can’t get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0 I don’t feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings
0 I don’t feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self Dislike
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self Criticism
0 I don’t criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts and Dying
0 I don’t have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don’t cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying but I can’t.

11. Agitation
0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it’s hard to stay still.
3 I am so restless or agitated I have to keep moving or doing something.

12. Loss of Interest
0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It’s hard to get interested in anything.

13. Indecisiveness
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.
14. Worthlessness
0  I do not feel I am worthless.
1  I don't consider myself as worthwhile or useful as I used to.
2  I feel more worthless compared to other people.
3  I feel utterly worthless.

15. Loss of energy
0  I have as much energy as ever.
1  I have less energy than I used to have.
2  I don't have enough energy to do very much.
3  I don't have enough energy to do anything.

16. Change in Sleeping Pattern
0  I have not experienced any change in my sleeping pattern.
  1a I sleep somewhat more than usual.
  1b I sleep somewhat less than usual.
  2a I sleep a lot more than usual.
  2b I sleep a lot less than usual.
  3a I sleep most of the day.
  3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability
0  I am no more irritable than usual.
1  I am more irritable than usual.
2  I am much more irritable than usual.
3  I am irritable all the time.

18. Changes in Appetite
0  I have not experienced any changes in my appetite.
  1a My appetite is somewhat less than usual.
  1b My appetite is somewhat greater than usual.
  2a My appetite is much less than before.
  2b My appetite is much greater than usual.
  3a I have no appetite at all.
  3b I crave food all the time.

19. Concentration difficulty
0  I can concentrate as well as ever.
1  I can't concentrate as well as usual.
2  It's hard to keep my mind on anything for very long.
3  I find I can't concentrate on anything.

20. Tiredness or Fatigue
0  I am no more tired or fatigued than usual.
1  I get more tired or fatigued more easily than usual.
2  I am too tired or fatigued to do a lot of the things I used to do.
3  I am too tired or fatigued to do most of the things I used to do.

21. Loss of interest in Sex
0  I have not noticed any recent changes in my interest in sex.
1  I am less interested in sex than I used to be.
2  I am much less interested in sex now.
3  I have lost interest in sex completely.
SELF-EVALUATION QUESTIONNAIRE
STAI T-1

DIRECTIONS: A number of statements which people used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate **HOW YOU GENERALLY FEEL**. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

<table>
<thead>
<tr>
<th></th>
<th>Not At</th>
<th>Some</th>
<th>Moderat</th>
<th>Very</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel pleasant.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>2. I feel nervous and restless.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel satisfied with myself.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>4. I wish I could be as happy as others seem to be</td>
<td>1</td>
<td>2</td>
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<td>4</td>
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<tr>
<td>5. I feel like a failure</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>6. I feel rested</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>7. I am calm, cool, and collected</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>8. I feel that difficulties are piling up so that I cannot</td>
<td>1</td>
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<tr>
<td>9. I worry too much over something that really doesn’t</td>
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<tr>
<td>10. I am happy</td>
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<td>2</td>
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<td>11. I have disturbing thoughts</td>
<td>1</td>
<td>2</td>
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<tr>
<td>12. I lack self-confidence</td>
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<td>2</td>
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<tr>
<td>13. I feel secure</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>14. I make decisions easily</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>15. I feel inadequate</td>
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<td>2</td>
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<tr>
<td>16. I am content</td>
<td>1</td>
<td>2</td>
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<tr>
<td>17. Some unimportant thought runs through my mind</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>18. I take disappointments so keenly that I can’t put</td>
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<td>2</td>
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<tr>
<td>19. I am a steady person</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>20. I get in a state of tension or turmoil as I think over my recent concerns and interests</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
PROBLEM DESCRIPTION

Please tell us about the problem(s) you would like help with.

How long have you been experiencing the problem(s)? (circle one)

One month or less
1
1 to 6 months
2
6 months to 1 year
3
1 to 5 years
4
5 to 10 years
5
More than 10 years
6

How old were you when you began having the problem(s)? ____________________________