Perceived Stress and Generalized Anxiety on Cardiovascular Health Measured by Ultrasound Carotid Intima-media Thickness

Everett Allen

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PERCEIVED STRESS AND GENERALIZED ANXIETY ON CARDIOVASCULAR HEALTH
MEASURED BY
ULTRASOUND CAROTID INTIMA-MEDIA THICKNESS

By

EVERETT B. ALLEN

B.A., Mathematical Sciences
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A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
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ABSTRACT

BACKGROUND: There are many studies that have documented the increasing impact of stress and anxiety on an individual’s health and well-being. Everyone handles stress and anxiety differently with these conditions having varying physiological effects. To better recognize whether or not a person may need help in tackling these conditions, scholars have developed reliable validated instruments. Two prominent instruments that effectively assess stress and anxiety levels are the Perceived Stress (PSS) and Generalized Anxiety Disorder (GAD-7) scales. Furthermore, the literature has shed light onto the importance of the carotid intima-media thickness (c-IMT) measurement as a tool in evaluating the risk of cardiovascular disease. After all, heart disease has been reported as being the number one killer of Americans in recent years. The specific aims of this study were to determine if there was an association between perceived stress / generalized anxiety and c-IMT (static association), and also if higher levels of perceived stress / generalized anxiety result in a significant increase in c-IMT (changes over time).

METHODS: Data was collected on about 700 participants comprised of employees from Emory University in Atlanta, Georgia. At baseline, six, twelve, and twenty-four months, the largest number of participants had completed and calculated their scores on the PSS and GAD-7 scales. At these same time points, participants had their IMT measured and recorded for the left and right common carotid arteries by a trained sonographer of the Emory Predictive Health Institute. Due to incomplete measurements and scores, only 228 participants were included for statistical analyses. This was still considered a suitable sample size given that this study only involved four measurement time points. Various statistical models were fitted for the data. All variables in the models were treated as categorical except for time which was continuous. Four separate models were built that included the variables perceived stress, age group, gender and time. In a similar manner, four models were built that included the variables generalized anxiety, age group, gender and time. AIC values, -2 log-likelihoods, partial correlations, p-values, and other relevant information were reported for these models. All statistical analyses were performed using the Statistical Analysis System (SAS), version 9.2.

RESULTS: The mean c-IMT measurements for the Emory participants were higher than established normal ranges. A strong correlation existed between the PSS and GAD-7 two-year averages when treated as continuous variables (.7316, p < .0001). Likewise, a meaningful relationship existed when both scales were categorical (.4154, p < .0001). The analyses revealed that the left and right mean IMT measurements for the common carotid arteries modeled a linear trend with an unstructured covariance the best. The partial correlations for perceived stress and generalized anxiety revealed weak, but significant positive associations with the mean c-IMT measurement. Although the slope coefficients were not significant for perceived stress, an increase from below average to above average perceived stress level still resulted in an increase in mean c-IMT measurement. Conversely, mild generalized anxiety was found to be statistically significant in the regression model of the left mean c-IMT. This was after controlling for age group and gender. The p-value for mild generalized anxiety was 0.0258, and the slope coefficient was 0.04856. IMT measurements were consistently higher for males on both sides compared to females. They were also higher on the left side compared to the right.
CONCLUSIONS: Failure to control anxiety could lead to c-IMT soaring to dangerous levels resulting in a myocardial infarction and/or cerebrovascular accident. Individuals should engage in healthy lifestyle practices that lower stress and anxiety levels to decrease the chances of cardiovascular disease. Based on this study’s findings, a person can certainly use their c-IMT readings, as well as their perceived stress and generalized anxiety scores, as indicators that lifestyle modifications may be needed.

INDEX WORDS: Perceived Stress, Generalized Anxiety Disorder, Carotid Intima-Media Thickness, Cardiovascular Health, Ultrasonography, Predictive Health
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Chapter 1
INTRODUCTION

1.1 Background

In today’s world, people are faced with greater responsibilities at work and in other areas of their lives. These increased responsibilities can lead to higher levels of stress and anxiety. They can also engender emotional and physical symptoms. Schnall and Landsbergis (1994) proposed possible pathways in which job strain in particular acts to influence the development of cardiovascular disease (p. 398). These pathways include some of the physiological and behavioral changes linked to stress (Theorell et al., 2006). Specifically, they are increases in blood pressure, cholesterol and smoking, as well as acceleration of coagulation processes and precipitation of arrhythmias (Schnall & Landsbergis, 1994). Based on the Stress in America survey by the American Psychological Association (2013), they found that overall about seventy percent of adults reported experiencing emotional and physical symptoms that ranged from feeling unmotivated and tired to feeling overwhelmed and nauseated (“High Stress Not Going Away,” para. 8). Equally important, the National Institute of Mental Health reports that “anxiety disorders affect about 40 million American adults age 18 years and older (about 18%) in a given year” (Introduction section, para. 1). It appears that stress and anxiety are affecting individuals in ways that can be detrimental to their health and well-being.

Many researchers over the past several decades have devoted their careers to truly understanding the roles that stress and anxiety play in overall health. A wealth of literature and scientific discoveries has come about as a result of their efforts. By the same token, useful tools have been developed to assess a person’s stress and anxiety levels. They are ultimately intended to identify individuals who may need help in dealing with these conditions. Examples of some of the measurement tools that have been created are the Perceived Stress and Generalized Anxiety Disorder scales. The Perceived Stress Scale (PSS) was developed in 1983 by psychology professor Sheldon Cohen and colleagues. Its purpose is to “measure
the degree to which situations in one’s life are appraised as stressful” (Cohen, Kamarck, & Mermelstein, 1983). Over two decades later, the Generalized Anxiety Disorder 7-item (GAD-7) scale was devised by several medical researchers who found at the time that there was no brief clinical measure for evaluating this condition. Unquestionably, these two instruments have proven to be very helpful in identifying likely cases of various stress and anxiety disorders.

Furthermore, there are several studies that have investigated the benefits of using intima-media thickness (IMT) measurement as a possible tool for determining one’s risk for cardiovascular disease. Some investigators have taken the research to higher levels by exploring the relationships that may exist between stress and anxiety with IMT and its progression. With the increase of research in this particular area, different technological instruments used to obtain IMT measurements have received greater attention.

1.2 Purpose of Study

The focus of this study was to ascertain whether or not any associations exist between perceived stress and generalized anxiety with the increased risk of cardiovascular disease overtime. IMT measurements, obtained from the Vivid 7 Ultrasound carotid IMT instrument, were used to determine cardiovascular risk for research participants of the Emory Predictive Health Institute. The usefulness of IMT measurement as a sound indicator of possible early atherosclerotic disease has been thoroughly studied in the literature. However, this study’s overarching goal was to produce evidence that shows how the c-IMT measurement can be used to prompt further investigation into factors that may influence it. For this psychosomatic study, the factors of main interest were perceived stress and generalized anxiety.

1.3 Research Questions

This research study sought to answer the following questions:

1. Is there an association between perceived stress and carotid IMT controlling for age and gender?

2. Do higher levels of perceived stress, controlling for age and gender, result in a significant increase in carotid IMT?
3. Is there an association between generalized anxiety and carotid IMT controlling for age and gender?

4. Do higher levels of generalized anxiety, controlling for age and gender, result in a significant increase in carotid IMT?
Chapter 2
REVIEW OF THE LITERATURE

2.1 Perceived Stress

Stress is an emotion experienced often by a person in their lifetime. It affects some people more
than others. The average person is able to recall at least one occasion in their life in which he or she
believed it to be stressful. This person can usually describe their emotional and physical responses to this
stressful event. Public health researchers have focused on stress over the past few decades, and have
come to understand the cost and burden of stress for Americans. Theorell and colleagues (2006)
provided a working definition of stress as “the non-specific reaction (energy mobilization) that arises in demanding
or challenging situations” (p. 4). They went on to further elaborate that stress explains how individuals
react to their environment, and that one’s coping mechanisms heavily influence his or her response to
stressors. Therefore, it is reasonable to suggest that stress is relative to the individual. That is to say,
levels of stress are based on subjective evaluation of the events (i.e., stressors) a person is experiencing in
their life. The ability or inability of a person to adapt successfully to stressors can result in different
physiological changes that may lead to disease. This is a concept from ancient Greek medicine as far
back as 2,500 years ago (Chrousos & Gold, 1992; Gold, Goodwin, & Chrousos, 1988; Stratakis, 1992).
In other words, when stressful events are viewed as threatening or otherwise demanding they are
presumed to increase risk of disease. This is also the case when coping resources are deemed inadequate
to address that threat or demand (Spacapan & Oskamp, 1988, p. 31). More specifically, certain studies
have shown that mental stress is related to decline in cardiovascular health that leads to conditions like
carotid atherosclerosis and other harmful diseases (Jennings et al., 2004; Yeung et al., 1991). It has
become increasingly important how cardiovascular health is impacted by mental stress in general, self-
perceived stress in particular.
Self-perceived stress has been associated with adverse changes in health behavior and risk of cardiovascular disease (Rod, Gronbaek, Schnohr, Prescott, & Kristensen, 2009). This type of mental stress is measured mainly by the scoring of an individual’s responses to questionnaires asking about the intensity and frequency of stress. The designs of these questionnaires can vary considerably. Nielsen and colleagues (2006), using a two-question survey for example, discovered that high levels of perceived stress was associated with a higher risk of ischemic heart disease among a large population sample of Danish men and women followed for 18 years (Nielsen et al., 2006). A prospective study on middle-aged Swedish men used a postal questionnaire instead to unveil that self-perceived psychological stress was an independent risk factor for coronary heart disease for these men (Rosengren, Tibblin, & Wilhelmsen, 1991). Moreover, the influence of perceived stress on cardiovascular health has been investigated in ethnic groups besides Caucasians. Japanese men and women from 1988 to 1990 completed a lifestyle questionnaire as part of the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk Sponsored by Monbusho. This questionnaire covered in part perception of mental stress. Results revealed that perceived mental stress was associated with increased death from cerebrovascular accident for women, and with coronary heart disease for both men and women (Iso et al., 2002).

2.2 The Perceived Stress Scale

Through the years, a validated instrument has been used for the assessment of perceived stress. This instrument, the Perceived Stress Scale (PSS), was created by renowned psychology professor Sheldon Cohen and his colleagues in 1983 (Appendix A). It is a 14-item instrument that is easily understandable, can be completed in minutes, and scored without difficulty. Scores for the PSS are calculated by reversing responses to the seven positively stated questions, and then adding all points together (Spacapan & Oskamp, 1988, p. 34). A person’s score can range from 0 to 45 for this particular scale. According to Cohen and colleagues (1983), they affirm that “the PSS measures the degree to which situations in one’s life are appraised as stressful” (p. 385). In addition to this, they state that “the PSS can be used to determine whether ‘appraised’ stress is an etiological (or risk) factor in behavioral disorders or disease” (Cohen, Kamarck, & Mermelstein, 1983, p. 393). The goal of each question within
this survey is to determine the degree to which a person sees their life as unpredictable, uncontrollable and overloading. These are recurring themes in the literature that Cohen and his colleagues found to be essential to the experience of stress (Cohen et al., 1983). After one to two months, the predictive validity of this scale is likely to decrease rapidly. This is due to the premise that daily hassles, major events, and changes in coping resources should influence levels of appraised stress (Cohen et al., 1983). There are two other versions of the PSS which include a 4-item and 10-item scale. The 14-item PSS discussed above was initially validated using a total of three samples: two of college students and one of participants in a community program whose objective was to curb smoking. Likewise, this particular scale along with the other two, was validated using a large (n=2,387) probability sample of the United States (Cohen et al., 1983; Spacapan & Oskamp, 1988, Chapter 3).

2.3 Generalized Anxiety Disorder and its Measurement

It has been well documented in the literature that along with stress there is anxiety. According to the Anxiety and Depression Association of America (2014), “stress is a response to a threat in a situation, and anxiety is a reaction to the stress.” Generalized Anxiety Disorder (GAD) is one of several clinically defined anxiety disorders. It is diagnosed when a person experiences symptoms that are characteristic to the disorder for at least six months. Individuals with this disorder constantly worry on a daily basis, in most cases unnecessarily, about matters ranging from finances and health to family and work (Anxiety and Depression Association of America [ADAA], 2014). The ADAA (2014) also states that “GAD affects 6.8 million adults, or 3.1% of the U.S. population, in any given year. Women are twice as likely to be affected.” A prominent risk factor for GAD is an increase in stress (Brantley, Mehan, Ames, & Jones, 1999). There are several studies in the literature that have linked anxiety and sustained levels of anxiety with risk of fatal coronary heart disease (CHD) and progression of carotid atherosclerosis. In the Normative Aging Study, for example, researchers found in their analyses a strong association between anxiety and fatal CHD; particularly sudden cardiac death. Out of 2271 men, there were 131 cases of fatal CHD during the follow-up period of which 26 were sudden death (Kawachi, Sparrow, Vokonas, & Weiss, 1994). In a systematic review of the association between anxiety and CHD, Kubzansky and colleagues
(1998) gathered and analyzed a sizable amount of literature that provided support for a possible association. As a result of their efforts, they were able to diagram potential mechanisms for the association between the aforementioned conditions (Kubzansky, Kawachi, Weiss, & Sparrow, 1998). Equally important, Paterniti et al. (2001) found in their study on 1389 subjects that sustained anxiety was associated with a two-fold increase of common carotid artery intima-media thickness (CCA-IMT) in both males and females. It was also found that men with high and stable levels of anxiety not only have a significant increase in CCA-IMT, but greater risk of plaque accumulation (p. 138).

With the prevalence of GAD in society, there was at one point in time no brief clinical measure for assessing it. A solution to this problem was given by Spitzer and colleagues (2006) through the creation of the GAD-7 scale (Appendix B). This instrument like the PSS is very brief, easy to understand, and can be scored by the respondent without any difficulty. As its name suggests, this scale is only seven questions. Each question is answered with the number 0, 1, 2 or 3 representing responses from “not at all” to “nearly every day.” Therefore, the score can total 0 all the way to 21.

The GAD-7 is found to be a valid and efficient screening tool for GAD (Spitzer, Kroenke, Williams, & Lowe, 2006). In similar fashion, this instrument is effective in measuring the degree at which anxiety psychologically affects a person. For example, the levels of anxiety severity are minimal (0 to 4), mild (5 to 9), moderate (10 to 14), and severe (15 to 21). According to Spitzer, Kroenke, Williams and Lowe (2006), they declare that “a score of 10 or greater on the GAD-7 represents a reasonable cut point for identifying cases of GAD” (p. 1095). As an illustration, a person with a score of 5 should not be very concerned, but the situation would be different if their score is 17. In this case, the person would need to seek professional help right away, and consider lifestyle adjustments.

2.4 Carotid Intima-Media Thickness

A measurement that is becoming widely accepted in assessing one’s cardiovascular risk is carotid intima-media thickness (c-IMT). There are a growing number of articles in the literature that support c-IMT as being a potentially useful screening tool. It is non-invasive, and as a result, does not jeopardize the safety of patients. Also, this measure is precise, reproducible, and cost effective (Aminbakhsh &
Mancini, 1999; Simon, Gariepy, Chironi, Megnien, & Levenson, 2002). It is mainly for these reasons why this measure is being used more in clinical research.

There are different methodological criteria taken into account for performing this measurement. Some researchers strongly feel that it is absolutely necessary to develop specific protocols for the measuring and recording of c-IMT (Probstfield et al., 1993). However, Simon and colleagues (2002) believe that the most effective way would be measurement at multiple carotid sites. They argue that there is greater likelihood of incorporating plaque thickness which could be indicative of increased risk for cardiovascular disease. It is important to note that an individual’s c-IMT measurement is primarily based on their age and gender (Gariepy et al., 1998; Rosfors et al., 1998). Even more, Gariepy and colleagues (1998) established “normal” values for IMT based on gender and age. In an earlier study by Lemne, Jogestrand, and Faire (1995), they also found that age was associated with IMT, but that this was evident for high-density lipoprotein cholesterol too. According to Simon et al., they have found that “the epidemiological data currently available indicate that a value of IMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease” (p. 161). Several studies like that of Rosfors et al. (1998) have observed through the use of the c-IMT measurement that carotid atherosclerosis may develop faster on the left than on the right side. Furthermore, studies have also shown that stress may significantly influence the progression of carotid atherosclerosis measured by c-IMT (Barnett, Spence, Manuck, & Jennings, 1997; Eller, Netterstrom, & Allerup, 2005).
3.1 Context of Study

Many researchers have contributed to the scientific literature in establishing the various roles that conventional risk factors like blood pressure, cholesterol, diabetes, and others play in influencing one’s cardiovascular health prospectively in time. However, relatively fewer investigators have specifically explored how technological advancements like ultrasound c-IMT can help predict the progression of heart disease, and serve well in identifying specific risk factors like perceived stress and generalized anxiety that can impact this change in health. This study’s main objective was to ascertain whether or not an individual’s perceived stress two-year average score, determined by the 14-item PSS, plays a significant role in predicting the mean IMT for the left and right common carotid arteries (CCAs) at baseline, six, twelve, and twenty-four months. In addition, it was investigated whether or not this perceived stress average score influenced the mean six-, twelve- and twenty-four month changes in the c-IMT. Emory research participants also had the opportunity to complete the GAD-7 scale. Therefore, participants’ average two-year GAD-7 scores were also taken into consideration as another possible predictor of one’s mean c-IMT and mean change in c-IMT.

3.2 Rationale of Study

The number one leading cause of death in 2010 for the United States was heart disease (Centers for Disease Control and Prevention [CDC], 2010). There is expanding evidence that suggest chronic stress and anxiety are heavily associated with an increased risk of heart disease. Stress engenders numerous widely known physiological and behavioral changes that can contribute to an increased risk of cardiovascular disease. Physiological changes may include an unsafe elevation of blood pressure, higher levels of LDL cholesterol, higher level of obesity, greater levels of stress hormone (e.g., cortisol, adrenalin), vascular inflammation, and others. Depending upon a person’s stress levels, unfavorable
behavioral changes can also lead to increased use of tobacco and alcohol, higher intake of unhealthy foods and calories, greater dependence on coffee, and development of poor sleeping habits (Theorell et al., 2006). The aforementioned behaviors play important parts in the physiological changes that many stressed people experience. Figure 3.1 illustrates this concept.

**Figure 3.1:** The Interplay of Physiological and Behavioral Changes as it relates to Stress and Cardiovascular Disease (CVD).

\[
CVD \ Risk = \text{Physiological Changes} \cong \text{Behavioral Changes} \leftarrow \text{Stress} \leftarrow \text{Stressors}
\]

- Blood pressure \rightarrow Tobacco
- Lipids \rightarrow Dietary habits
- Fibrinogen \rightarrow Calories
- Pulse \rightarrow Exercise
- Arrhythmia \rightarrow Type A
- Coagulation time \rightarrow Alcohol
- Obesity \rightarrow Coffee
- Stress hormones \rightarrow Sleeping patterns
- Vascular inflammation

*Figure 3.1.* The two pathways that connect stressors with the risk of cardiovascular diseases. Adapted from “Stress and Cardiovascular Disease,” by T. Theorell, T. S. Kristensen, M. Kornitzer, M. Marmot, K. Orth-Gomer, and A. Steptoe, 2006, *European Heart Network.*

Although age and gender primarily determine c-IMT, this measurement can prove to be an invaluable tool not only in detecting the presence of early atherosclerotic disease, but in linking other factors like stress and anxiety that could significantly influence this measurement. Emory University is an internationally known leading research institution in Atlanta, Georgia. It is likely that the faculty and staff are faced with the high expectation of maintaining the university’s stellar reputation of research excellence. This job expectation could reasonably bring about changes in stress and anxiety levels. On account of this, stress and anxiety were deemed as major factors that could potentially lead to an increased risk of cardiovascular disease for these participants.
3.3 Sample

Data was collected on about 700 participants comprised of employees from Emory University in Atlanta, Georgia. The human resources department identified these eligible employees. They were stratified to obtain a representative balance of employees across faculty, Fair Labor Standards Act (FLSA) exempt staff, and FLSA non-exempt staff. Every 10th employee from an alphabetic list of employees was invited to participate. Chosen employees were emailed an invitation to participate in the study with an included description of the program. Ultimately 10% of the solicited employees were enrolled in the cohort study out of approximately 30% who agreed to be contacted. Only adults with few known chronic conditions were allowed to be included in the cohort. The Emory University Institutional Review Board approved the recruitment strategy, consent forms and data collection protocols.

Participants were initially screened by telephone to ensure that they met the inclusion and exclusion criteria. Subsequently, prospects were sent via email or mail an informed consent form (Appendix C), and brochure about the Center for Health Discovery and Well Being (CHDWB) program. These individuals were asked at the first visit to sign the informed consent form. In addition to the typical elements, it contained information about the CHDWB goals, an outline of the prospective data collection and analysis plans, a description of all the specific measurements and assessments that could be performed, an outline of the educational program, and permission for entry into a research subject registry from which they may be contacted by other researchers for additional studies.

An option was given to research participants to complete the 14-item PSS (PSS14) at baseline, six, twelve, twenty-four, thirty-six, forty-eight, and sixty months. IMT readings were conducted during the same time points as well as an array of other measurements and surveys. Likewise, participants had the option to take the GAD-7 scale at each time point previously specified. The number of missing observations for certain variables of interest from enrolled participants increased tremendously as time progressed especially beyond twenty-four months. About a third (n=228) of the sample population of roughly 700 individuals had complete observations for the IMT, perceived stress, and generalized anxiety.
variables considered in the statistical analyses. Subjects missing a large portion of this data were eliminated from statistical analyses.

3.4 Statistical Analysis

Repeated IMT measurements and other information were taken on participants prospectively in time, so longitudinal data analyses were conducted. Anatomically, humans have a left and right CCA. Therefore, measurements were recorded for both sides at baseline, six, twelve, and twenty-four months by averaging the measurements for the near and far walls of the left and right carotid arteries. The likelihood of incorporating plaque thickness is much greater when IMT is measured in this way. It provides a better indication of those individuals who are at increased risk for cardiovascular disease (Simon, Gariepy, Chironi, Megnien, & Levenson, 2002). Measurements were recorded in millimeters. They were completed by a trained sonographer of Emory University using the Vivid 7 Ultrasound carotid IMT instrument. Statistical models for the mean IMT measurements and mean change in IMT measurements for both sides were fitted for the data.

In table 3.1, “normal” mean values are given for the PSS14 in the categories for gender and age group. This information was obtained from a large (n=2,387) probability sample of the United States collected by Louis Harris and Associates, Inc. in 1983 (Spacapan & Oskamp, 1988, Chapter 3).

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<td>18-29</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>949</td>
<td>1406</td>
</tr>
<tr>
<td>PSS14</td>
<td>Mean</td>
</tr>
<tr>
<td>18.8</td>
<td>20.2</td>
</tr>
<tr>
<td>S.D.</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Note. N = 2,387. S.D. = standard deviation. This table presents only the mean PSS14 values, along with the sample sizes and standard deviations, in each category for gender and age group. Adapted from “Perceived
According to Gariepy and colleagues (1998), a person’s age group and gender mainly determine their IMT measurements, so this is why special attention was given to these particular means. Also, age group and gender were controlled for in multivariate regression analyses performed. Spitzer and colleagues (2006) determined the ranges of values for the four generalized anxiety levels (p. 1095). As given earlier, they are as follows: minimal (0 to 4), mild (5 to 9), moderate (10 to 14), and severe (15 to 21).

In the regression analyses performed for this study, the variables perceived stress level, generalized anxiety level, age group, and gender were treated as categorical in the models. PSS14 and GAD-7 scores, calculated by participants at every time point, were each averaged for the first two years (i.e., the first four measurement time points) to obtain a two-year average score. These values gave the best overall indication of a participant’s perceived stress and generalized anxiety levels for this two-year time period. A dividing point was established to which participants were placed into one of two groups: below average stress or above average stress. This midpoint was calculated by performing the weighted average of all the mean values for gender and age group given in table 3.1. The calculated value of 19.63 served to represent the average perceived stress score. Participants were categorized based on whether their two-year average score for the PSS14 fell above or below 19.63. Likewise, participants were categorized based on their GAD-7 two-year average scores using the generalized anxiety levels established by Spitzer and colleagues in 2006. Furthermore, their ages at baseline, which ranged from 16 to 78 years old, and their genders were used to place them into the age groups given in table 3.2.

Parameter estimates, p-values, partial correlations and other information were calculated for some variables of interest. Also, correlations between the variables perceived stress and generalized anxiety were calculated and graphed with both treated as continuous and categorical. All statistical analyses were performed using the Statistical Analysis System (SAS), version 9.2.
### Table 3.2: “Normal” Left and Right IMT Intervals.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Right CCA IMT</th>
<th>Left CCA IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>.39 -.48</td>
<td>.42 -.49</td>
</tr>
<tr>
<td>31 to 40</td>
<td>.42 -.50</td>
<td>.44 -.57</td>
</tr>
<tr>
<td>41 to 50</td>
<td>.46 -.57</td>
<td>.50 -.61</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>.46 -.62</td>
<td>.53 -.70</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>.39 -.43</td>
<td>.30 -.47</td>
</tr>
<tr>
<td>31 to 40</td>
<td>.42 -.49</td>
<td>.44 -.51</td>
</tr>
<tr>
<td>41 to 50</td>
<td>.44 -.53</td>
<td>.46 -.57</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>.50 -.59</td>
<td>.52 -.64</td>
</tr>
</tbody>
</table>

*Note.* CCA = Common Carotid Artery. IMT = Intima-Media Thickness. Intervals are in millimeters. The lower and upper limits of the intervals represent the 25th lower and 75th upper percentiles of IMT distribution within the age groups specified. Abnormal IMT values (not shown in this table) are those exceeding the 75th percentile in each age group category. Adapted from “Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk,” by A. Simon, J. Gariepy, G. Chironi, J. L. Megnien, and J. Levenson, 2002, *Journal of Hypertension, 20*, p. 162.
Chapter 4
RESULTS

The statistical analyses yielded very interesting results. Graphs were created for the distributions of the left and right mean c-IMT measurements for each age category by gender on the Emory research participants. The means of these distributions were compared to the 25th and 75th percentiles displayed in table 3.2. The graphs are shown in figure 4.1. Figures 4.2 and 4.3 display graphical representations of the correlations between both scales. Figure 4.2 treats perceived stress and generalized anxiety two-year score averages as continuous variables. Figure 4.3 treats both as categorical variables by taking the two-year score averages and converting them into groups accordingly.

Figure 4.1: Left and Right IMT Intervals for Emory Participants.

Men

Figure 4.2: Distribution of RIGHT_MEAN_cIMT

Figure 4.3: Distribution of LEFT_MEAN_cIMT

\[ \bar{X} = 0.499 \quad \bar{X} = 0.579 \quad \bar{X} = 0.612 \quad \bar{X} = 0.709 \]
Women

Figure 4.1. A graphical representation of the left and right common carotid artery mean intima-media thickness ranges for four different age groups in both men and women. cIMT = carotid intima-media thickness. Left and right cIMT measurements are in millimeters (not shown). On the x-axis representing the age groups are 0 = ≤ 30, 1 = 31-40, 2 = 41-50 and 3 = >50. The lower and upper limits of the bars represent the 25th lower and 75th upper percentiles of IMT distribution within the age groups specified on the x-axis. The mean for each age group distribution is denoted by a diamond and outliers by a circle. The mean values are given below the graphs.

Figure 4.2: Correlation between PSS Score Averages and GAD-7 Score Averages.
Figure 4.2. A scatter plot with 95% Prediction Ellipse of the correlation between all PSS Averages and GAD-7 Averages for 227 of the 228 research participants considered. One participant has missing scores for several time points within the two-year period analyzed. The correlation is 0.7316 with p < .0001 (p-value not shown).

Figure 4.3: Correlation between PSS Score Group and GAD-7 Score Group.

Figure 4.3. A scatter plot with 95% Prediction Ellipse of the correlation between PSS Group and GAD-7 Group for 227 of the 228 research participants considered. One participant has missing scores for several time points within the two-year period analyzed. The correlation is 0.4154 with p < .0001 (p-value not shown).

The longitudinal study design and repeated measurements taken on each research participant required modeling of the mean c-IMT measurements at each time point. This was done for both the left and right CCAs. The mean changes in the left and right c-IMT measurements were also modeled. Line graphs were initially created from the data to obtain some insight into the patterns of change from baseline between the different perceived stress and generalized anxiety groups. Figure 4.4 shows the patterns of the mean c-IMT measurements from baseline for each side between the two perceived stress groups. On the other hand, figure 4.5 shows the patterns of the mean changes in c-IMT measurements for each side between these groups. These figures show the effects of only perceived stress level on mean c-IMT and mean change in c-IMT for the Emory participants. They do not control for the effects of the
variables age group and gender. Figures 4.6 and 4.7 display the aforementioned information in a similar manner for the three generalized anxiety groups.

**Figure 4.4:** Left and Right mean CCA IMTs at each measurement time point for both Perceived Stress Groups.

![Graph showing mean CCA IMTs](image)

*Figure 4.4.* LT = left. RT = right. CCA = common carotid artery. IMT = intima-media thickness. The graphs above display the patterns of change in the mean carotid IMT measurements from baseline for each side between the two perceived stress groups. They do not control for age group and gender. The top line represents participants who were categorized as having “below average” perceived stress, and the bottom line represents “above average.” Mean carotid IMT measurements are graphed at baseline, six, twelve, and twenty-four months.

**Figure 4.5:** Mean Changes in Left and Right CCA IMT at 6, 12 and 24 months for both Perceived Stress Groups.

![Graph showing mean change in CCA IMT](image)

*Figure 4.5.* LT = left. RT = right. CCA = common carotid artery. IMT = intima-media thickness. The graphs above display the patterns of mean change in the carotid IMT measurement from baseline for each side between the
two perceived stress groups. They do not control for age group and gender. The bottom line represents participants who were categorized as having “below average” perceived stress, and the top line represents “above average.” Mean change in carotid IMT measurement is graphed for six, twelve and twenty-four months.

**Figure 4.6:** Left and Right mean CCA IMTs at each measurement time point for the Generalized Anxiety Groups.

![Graph](image1)

**Figure 4.6.** LT = left. RT = right. CCA = common carotid artery. IMT = intima-media thickness. The graphs above display the patterns of change in the mean carotid IMT measurements from baseline for each side between the three generalized anxiety groups. They do not control for age group and gender. The middle line denotes minimal anxiety, the top line mild anxiety, and the bottom line moderate anxiety. Mean carotid IMT measurements are graphed at baseline, six, twelve, and twenty-four months.

**Figure 4.7:** Mean Changes in Left and Right CCA IMT at 6, 12 and 24 months for the Generalized Anxiety Groups.

![Graph](image2)
Figure 4.7. LT = left. RT = right. CCA = common carotid artery. IMT = intima-media thickness. The graphs above display the patterns of mean change in the carotid IMT measurement from baseline for each side between the three generalized anxiety groups. They do not control for age group and gender. The top line denotes minimal anxiety, the line below it represents mild anxiety, and the line that crosses the mild anxiety line represents moderate anxiety. Mean change in carotid IMT measurement is graphed for six, twelve and twenty-four months.

The research data was subsequently analyzed using a linear, quadratic and linear spline model assuming for each one an unstructured covariance matrix for the within subject random error vector. This type of covariance structure is fitting for when no assumptions are made about the variances and covariances. This was done to ascertain which model most appropriately represented the data by comparing the Akaike Information Criterion (AIC) and -2 log-likelihood values. Once this was determined, several other covariance structures were tested under this chosen model. These included compound symmetry, heterogeneous compound symmetry, first-order autoregressive, and heterogeneous first-order autoregressive. In a similar fashion, the AIC and -2 log-likelihood values were compared. The smallest AIC revealed the best covariance structure for the model. The MIXED procedure in SAS was employed to perform these analyses. It is an all-around great procedure for fitting linear models to longitudinal and clustered data (Fitzmaurice, Laird, & Ware, 2011). Tables 4.1 and 4.2 provide the smallest AIC and -2 log-likelihood values, regression models, p-values and partial correlations from the statistical analyses of the variables perceived stress and generalized anxiety, respectively, when controlling for age group and gender.

### Table 4.1: Regression Models, P-values and Other Information for Perceived Stress.

<table>
<thead>
<tr>
<th>For the Left Mean CCA IMT:</th>
<th>Effect</th>
<th>P-value</th>
<th>For the Right Mean CCA IMT:</th>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallest AIC value:</td>
<td>Intercept</td>
<td>&lt;.0001</td>
<td>Smallest AIC value:</td>
<td>Intercept</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>-3464.1</td>
<td></td>
<td></td>
<td>-3103.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2 Res Log Likelihood:</td>
<td>Stress Level</td>
<td>0.0880</td>
<td>-2 Res Log Likelihood:</td>
<td>Stress Level</td>
<td>0.2110</td>
</tr>
<tr>
<td>-3484.1</td>
<td></td>
<td></td>
<td>-3123.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Correlation:</td>
<td>Stress Level</td>
<td>0.1094</td>
<td>Partial Correlation:</td>
<td>Stress Level</td>
<td>0.072</td>
</tr>
<tr>
<td>0.0009</td>
<td></td>
<td></td>
<td>0.0299</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression Model:</td>
<td>Age ≤ 30</td>
<td>&lt;.0001</td>
<td>Regression Model:</td>
<td>Age ≤ 30</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
\[ Y = 0.6902 + 0.02707 \times (\text{Stress Level}) - 0.1999 \times (\text{Age} \leq 30) - 0.1731 \times (\text{Age 31} - 40) - 0.1025 \times (\text{Age 41} - 50) + 0.02113 \times (\text{Gender}) + 0.000418 \times (\text{Time}) \]

\[ Y = 0.6941 + 0.01828 \times (\text{Stress Level}) - 0.2030 \times (\text{Age} \leq 30) - 0.1690 \times (\text{Age 31} - 40) - 0.1052 \times (\text{Age 41} - 50) + 0.01499 \times (\text{Gender}) + 0.000302 \times (\text{Time}) \]

<table>
<thead>
<tr>
<th>For the mean change in Left CCA IMT:</th>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallest AIC value: -3099.6</td>
<td>Intercept</td>
<td>0.3307</td>
</tr>
<tr>
<td>-2 Res Log Likelihood: -3111.6</td>
<td>Stress Level</td>
<td>0.7548</td>
</tr>
<tr>
<td>Partial Correlation: 0.0116 p-value = 0.7619</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Regression Model: Z = 0.004138 + 0.001668 \times (\text{Stress Level}) - 0.00419 \times (\text{Age} \leq 30) - 0.00707 \times (\text{Age 31} - 40) - 0.00828 \times (\text{Age 41} - 50) - 0.00286 \times (\text{Gender}) + 0.000418 \times (\text{Time}) | Age \leq 30 | 0.7741 |
|                                                       | Age 31 - 40 | 0.3060 |
|                                                       | Age 41 - 50 | 0.1612 |
| Gender                                               | 0.5862     |
| Time                                                 | <.0001     |

<table>
<thead>
<tr>
<th>For the mean change in Right CCA IMT:</th>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallest AIC value: -2699.7</td>
<td>Intercept</td>
<td>0.9163</td>
</tr>
<tr>
<td>-2 Res Log Likelihood: -2711.7</td>
<td>Stress Level</td>
<td>0.6866</td>
</tr>
<tr>
<td>Partial Correlation: 0.0395 p-value = 0.3029</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Regression Model: Z = 0.000410 + 0.001898 \times (\text{Stress Level}) - 0.00167 \times (\text{Age} \leq 30) - 0.000499 \times (\text{Age 31} - 40) - 0.00413 \times (\text{Age 41} - 50) - 0.00035 \times (\text{Gender}) + 0.000304 \times (\text{Time}) | Age \leq 30 | 0.8969 |
|                                                       | Age 31 - 40 | 0.9346 |
|                                                       | Age 41 - 50 | 0.4273 |
| Gender                                               | 0.9394     |
| Time                                                 | 0.0025     |

Note. AIC = Akaike Information Criterion. CCA = Common Carotid Artery. IMT = Intima-media thickness. Y = left or right mean CCA IMT. Z = mean change in left or right CCA IMT. Dummy variables are used for stress level, age groups and gender. For stress level: 0 = below average stress, 1 = above average stress; Age groups: 0 = age group does not apply, 1 = age group does apply; Gender: 0 = female, 1 = male. Time is a continuous variable in each of the regression models. The data best reflects a linear trend with an unstructured covariance matrix for the within subject random error vector for all four cases in the table. Partial correlations are of perceived stress and the outcome variable, while adjusting for the variables age group and gender. P-values are for the significance of a particular variable, given other variables in the regression model.

Table 4.2: Regression Models, P-values and Other Information for Generalized Anxiety.
<table>
<thead>
<tr>
<th>Partial Correlation: 0.1373</th>
<th>Moderate Anxiety</th>
<th>0.7048</th>
<th>Partial Correlation: 0.1086</th>
<th>Moderate Anxiety</th>
<th>0.6767</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value &lt; .0001</td>
<td></td>
<td></td>
<td>p-value = 0.0011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression Model:</td>
<td></td>
<td></td>
<td>Regression Model:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y = 0.6903 +</td>
<td></td>
<td></td>
<td>Y = 0.6941 +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.04856*(Mild Anxiety)</td>
<td></td>
<td></td>
<td>0.03459*(Mild Anxiety)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ 0.02171*(Moderate Anxiety)</td>
<td></td>
<td></td>
<td>+ 0.02206*(Moderate Anxiety)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 0.2064*(Age ≤ 30) – 0.1715*(Age 31 – 40) – 0.09960*(Age 41 – 50) + 0.02503*(Gender) + 0.000409*(Time)</td>
<td></td>
<td></td>
<td>– 0.2088*(Age ≤ 30) – 0.1687*(Age 31 – 40) – 0.1049*(Age 41 – 50) + 0.01818*(Gender) + 0.000293*(Time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 30</td>
<td>&lt;.0001</td>
<td></td>
<td>Age ≤ 30</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Age 31-40</td>
<td>&lt;.0001</td>
<td></td>
<td>Age 31-40</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Age 41-50</td>
<td>&lt;.0001</td>
<td></td>
<td>Age 41-50</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.1119</td>
<td></td>
<td>Gender</td>
<td>0.2105</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>&lt;.0001</td>
<td></td>
<td>Time</td>
<td>0.0010</td>
<td></td>
</tr>
</tbody>
</table>

For the mean change in Left CCA IMT:

<table>
<thead>
<tr>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.1353</td>
</tr>
<tr>
<td>Mild Anxiety Level</td>
<td>0.1747</td>
</tr>
<tr>
<td>Moderate Anxiety Level</td>
<td>0.8922</td>
</tr>
</tbody>
</table>

For the mean change in Right CCA IMT:

<table>
<thead>
<tr>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.6550</td>
</tr>
<tr>
<td>Mild Anxiety Level</td>
<td>0.4886</td>
</tr>
<tr>
<td>Moderate Anxiety Level</td>
<td>0.7666</td>
</tr>
</tbody>
</table>

Regression Model:

Z = 0.006184 – 0.00996*(Mild Anxiety) + 0.002626*(Moderate Anxiety) – 0.00270*(Age ≤ 30) – 0.00555*(Age 31 – 40) – 0.00843*(Age 41 – 50) – 0.00383*(Gender) + 0.000408*(Time)

<table>
<thead>
<tr>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 30</td>
<td>0.8563</td>
</tr>
<tr>
<td>Age 31-40</td>
<td>0.4163</td>
</tr>
<tr>
<td>Age 41-50</td>
<td>0.1579</td>
</tr>
<tr>
<td>Gender</td>
<td>0.4707</td>
</tr>
<tr>
<td>Time</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Regression Model:

Z = 0.001702 – 0.00448*(Mild Anxiety) – 0.00508*(Moderate Anxiety) + 0.000063*(Age ≤ 30) + 0.001664*(Age 31 – 40) – 0.00427*(Age 41 – 50) – 0.00070*(Gender) + 0.000295*(Time)

<table>
<thead>
<tr>
<th>Effect</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 30</td>
<td>0.9962</td>
</tr>
<tr>
<td>Age 31-40</td>
<td>0.7823</td>
</tr>
<tr>
<td>Age 41-50</td>
<td>0.4176</td>
</tr>
<tr>
<td>Gender</td>
<td>0.8808</td>
</tr>
<tr>
<td>Time</td>
<td>0.0034</td>
</tr>
</tbody>
</table>

Note.  AIC = Akaike Information Criterion.  CCA = Common Carotid Artery.  IMT = Intima-media thickness.  Y = left or right mean CCA IMT.  Z = mean change in left or right CCA IMT.  Dummy variables are used for the mild and moderate anxiety levels, age groups and gender.  For anxiety levels:  0 = anxiety level is absent, 1 = anxiety level is present; Age groups:  0 = age group does not apply, 1 = age group does apply; Gender:  0 = female, 1 = male.  Time is a continuous variable in each of the regression models.  The data best reflects a linear trend with an unstructured covariance matrix for the within subject random error vector for all four cases in the table.  Partial correlations are of generalized anxiety and the outcome variable, while adjusting for the variables age group and gender.  P-values are for the significance of a particular variable, given other variables in the regression model.
Chapter 5  
**DISCUSSION AND CONCLUSION**

5.1 Discussion of Results

First and foremost, the distributions of the mean c-IMT measurements for the Emory participants in each age group for both sexes are higher than the normal ranges provided in table 3.2. This is the case for the left and right CCAs. The average values of the mean c-IMT measurements in each age group for both sides are slightly or significantly above the 75\textsuperscript{th} percentiles. These values are given in figure 4.1. These findings warranted an investigation to determine whether or not stress and anxiety could plausibly explain these abnormal measurements for the Emory research participants.

Sheldon Cohen et al. (1983) found in two samples of college students that “increases in social anxiety were associated with increases in perceived stress (.37 and .48, p < .001 for both)” (p. 392). This study among others established a link between anxiety and an individual’s subjective perception of stress. For this reason, efforts were undertaken to explore the correlations between the GAD-7 and PSS14 scales. Correlations were examined with both scales treated as continuous and categorical variables using the CORR procedure in SAS. As continuous variables, the correlation between the two-year average scores on both scales for all participants was calculated. The two-year average scores on both scales for the subjects were converted to categorical variables, and the correlation was subsequently calculated. A strong correlation exists between the two scales when treated as continuous variables (.7316, p < .0001). Just as important, a meaningful relationship exists when both scales are categorical (.4154, p < .0001). The correlations may be partly or completely attributable to the fact that some items in the two scales measure a similar or identical concept. For instance, both scales ask questions about nervousness and irritability.

Line graphs were initially created from the research data for specifically the variables perceived stress and generalized anxiety. These graphs do not control for the effects of the other variables age
group and gender. Surprisingly, the left and right mean c-IMT measurements are higher at each time point for participants who were categorized as experiencing “below average” levels of perceived stress. As a result, these graphs for perceived stress reveal that an “above average” level of perceived stress does not independently predict a higher mean c-IMT measurement. In fact, it predicts a lower mean c-IMT measurement for the Emory participants in comparison. In regards to the mean change in left c-IMT, the “below average” perceived stress group experienced a smaller six-month change in the left measurement. Interestingly, the mean twelve-month change in c-IMT was practically the same for both groups. However, the “below average” perceived stress group experienced greater changes in their left c-IMT measurements from the beginning of the second year onward. This same group, on the contrary, experienced significantly smaller changes at every time point for their right c-IMT measurements. There is a considerable decrease for the mean change in the right c-IMT particularly from six to twelve months. After this point, however, the mean change in right c-IMT continually increases.

As the generalized anxiety level increases from minimal to mild, so does the left and right mean c-IMT measurement at each time point. But from mild to moderate anxiety, this is definitely not the case. Left and right c-IMT measurements are actually the lowest for moderate anxiety compared to the other anxiety levels. This is more than likely due to the fact that there were only 4 out of 227 participants that fell within this anxiety category. In the same way, the mean changes in the left and right c-IMT measurements for the generalized anxiety groups are heavily influenced by the number of participants in each. The mean changes in c-IMT are higher at each time point for the minimal anxiety group (n=191), and lower for the mild anxiety group (n=32). In comparison, the mean changes in the left c-IMT steadily decreases from six to twelve to twenty-four months for the moderate anxiety group (n=4). Unlike the left side, the mean change in right c-IMT for the moderate anxiety group remains constant from six to twelve months. The mean changes sharply increase nevertheless after the first year.

A number of multivariate regression models were tested for data on the Emory Predictive Health Institute research participants. This was achieved through the MIXED procedure in SAS. As previously mentioned, the MIXED procedure is useful in fitting linear models for longitudinal and clustered data.
The analyses revealed that the left and right mean IMT measurements for the CCAs modeled a linear trend with an unstructured covariance the best. Results determined this to be the same for mean changes in the left and right c-IMT measurements. This applies to both perceived stress and generalized anxiety. A direct comparison of the AIC and -2 log-likelihood values from the linear, quadratic and linear spline models fitted for the data gave the above finding of a linear trend being the best fit for the data. The linear trend model was analyzed repeatedly with several other covariance structures, and all were compared with the unstructured covariance initially assumed. They were compound symmetry, heterogeneous compound symmetry, first-order autoregressive, and heterogeneous first-order autoregressive. All of the AIC and -2 log-likelihood values were negative. However, the linear trend model with the unstructured covariance had the largest negative AIC and -2 log-likelihood values which were desired in each of the four cases in tables 4.1 and 4.2.

The slope coefficients for the variables perceived stress and gender are found to be not significant in all four cases; given other variables in the regression model. This is because both variables have p-values that are > 0.05. Although the slope coefficients are not significant for perceived stress, an increase from below average to above average perceived stress level still results in an increase in mean c-IMT measurement. For instance, an increase from below average to above average perceived stress, results in the left mean c-IMT increasing 0.02707 mm; controlling for the effects of the other variables in the model. This is not significant because 0.02707 falls within the normal average increase per year of 0.01 to 0.03 mm (Simon et al., 2002). In contrast, the slope coefficients for the variables of the age groups (in decades) are very significant in the regression models of the left and right mean c-IMT. The slope coefficients for the age groups, on both sides, become smaller and smaller from one higher age group to another. Compared to persons older than 50 years of age, the left c-IMT measurement is expected to be 0.1999 mm less for a person 30 years of age or younger, 0.1731mm less for a person 31 – 40, and 0.1025 mm less for a person 41 - 50. These coefficients control for perceived stress level and gender. In other words, a person’s c-IMT measurement becomes larger as he or she ages. This is supported by findings of the AXA study on French male and female employees (Gariepy et al., 1998). This is reasonable
considering that with older age there is more stress and anxiety given issues one must deal with at various life stages. The body metabolizes macromolecules differently compared to one’s younger years. Also, adults tend to become more sedentary as they age. Therefore, these findings provide even more evidence that age is very significant in primarily determining c-IMT. The slope coefficients for the age groups are not significant, however, in the regression models of the mean change in left and right c-IMT. Partial correlations were calculated for perceived stress. The partial correlation assesses the strength of the linear relationship between two variables, while controlling for the effect of other variables. The partial correlation of 0.1094 between the variable perceived stress and the left mean c-IMT (outcome variable) is very significant with a p-value of 0.0009. The correlation of 0.072 between this same variable and the right mean c-IMT is also significant with a p-value of 0.0299. These values signify weak, but positive associations. The partial correlations are not significant for this variable in the regression models of the mean change in left and right c-IMT. These values are displayed in table 4.1.

In addition to the age group variables being statistically significant, mild generalized anxiety is too. This is after controlling for age group and gender in the regression model of the left mean c-IMT. The p-value for mild generalized anxiety is 0.0258, and the slope coefficient is 0.04856. Compared to a person with minimal anxiety level, this means that the left c-IMT measurement is expected to be 0.04856 mm higher for a person with mild generalized anxiety; after controlling for age group and gender. This is significant because 0.04856 is well above the normal average increase per year of 0.01 to 0.03 mm. The left mean c-IMT is not found to be significant between persons with minimal and moderate anxiety level (p-value=0.7048). The generalized anxiety levels are found to be not significant for the other three regression models including these variables. Nonetheless, the age groups are also very significant in the regression model of the right mean c-IMT. Partial correlations are very significant on both sides between the variable generalized anxiety and each of the outcome variables for the mean c-IMT. The correlation for the left side is 0.1373 with a p-value < .0001. The correlation is 0.1086 and the p-value 0.0011 for the right. These values represent weak, but positive associations like the variable perceived stress. It is worth
noting that the partial correlations are negative and not significant in the regression models of the mean change in left and right c-IMT. These values can be found in Table 4.2.

The PSS14 is a tool that looks to measure the degree to which certain events in individuals’ lives are appraised as stressful. The predictive validity of the PSS14 is expected to fall off rapidly after one or two months (Cohen, Kamarck, & Mermelstein, 1983). This is based on the premise by Cohen et al. (1983) that “levels of appraised stress should be influenced by daily hassles, major events, and changes in coping resources” (p. 387). They also argue that this scale is a better predictor of health outcomes than does a global measure of objective stressors (e.g., life-event scales), and is sensitive to chronic stress. This explains in part why the variable perceived stress is not significant for the regression models of the mean change in the c-IMT measurement. Beyond two months from each measurement time point, one’s perceived stress level cannot be reliably assessed. Thus, the affect that perceived stress level has on the mean 6-month, 12-month and 24-month change in the c-IMT cannot be truly determined. If a person uses the PSS14 to help predict their mean c-IMT on both sides, then it would be best utilized for predicting the mean c-IMT values within a sixty-day period. After this time period, another measure that assesses stress level should be considered.

Moreover, there were several research participants who had IMT measurements near or exceeding one millimeter. For these individuals, an increase in perceived stress and/or generalized anxiety level could result in a severe cardiovascular event or death. According to Simon and colleagues (2002), “the epidemiological data currently available indicate that a value of IMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease” (p. 161). Undoubtedly, there is the possibility that as these individuals’ perceived stress and/or generalized anxiety levels increase, so will their risk of cardiovascular disease.

Based on the statistical models built for the left and right mean c-IMT, males have higher c-IMT measurements on both sides compared to females. This is the case when comparing males and females at the same perceived stress and/or generalized anxiety levels in the same age group and at the same time. This provides further evidence that gender along with age plays a major role in c-IMT. Equally
important, these same models reveal that the left mean c-IMT measurement is consistently higher than the right. This is supported by findings of Rosfors and colleagues from 1998.

5.2 Study Strengths and Limitations

This study has several strengths, including its large sample size, collection of data using validated instruments, and the significant association that has been established with mild generalized anxiety level and left mean c-IMT. Data was collected on about 700 participants from the faculty and staff of Emory University. After examining each research participant’s data, 228 qualified for statistical analyses in the study. This still represented a suitable sample size considering that this study only involved four measurement time points. Well regarded instruments like the PSS14 and GAD-7 scales were utilized to assess participants’ stress and anxiety levels. These scales are brief, easy to understand, and can be completed entirely by the person. Likewise, IMT measurements were recorded utilizing the state-of-the-art Vivid 7 ultrasound carotid IMT instrument. This study found that mild generalized anxiety controlling for age group and gender has a significant effect on the left mean c-IMT. That is, it is an influential factor on cardiovascular health.

Several limitations of this study must be noted. The findings of this study are not generalizable to the greater population since Emory faculty and staff members were only allowed to participate. In addition, completing the PSS14 and GAD-7 scales were optional. Consequently, this tremendously decreased the amount of individuals that could be included in the statistical analyses. This was a result of participants having incomplete scores for one or both scales in the first two years of follow-up. Also, averaging the perceived stress and generalized anxiety scores for the first four measurement time points may have overlooked some information. However, this method provided the best overall indication of the participants’ perceived stress and generalized anxiety levels for this two-year time period. For the most part, participants’ scores did not drastically differ from one time point to the next. In analyzing the data, there was reason to believe that individuals may not have came back at exactly six, twelve and twenty-four months to have measurements and scores recorded. Hence, these recordings may be distorted.
5.3 Implications of Findings

The findings of this psychosomatic study further support the growing belief, and evidence in the literature, that generalized anxiety affects a person’s cardiovascular health. This has public health significance. This factor provides another possible link to the number one killer of Americans – heart disease. The results add supporting evidence that the c-IMT measurement tool could be also used to discover which factors in a person’s life may impact their cardiovascular health. For people who find that they have abnormal IMT readings, they should consult their healthcare provider for further evaluation. For the Emory research participants in particular, it is recommended that they continue to be proactive in their health and well-being. This is especially due to the fact that their IMT measurements are overall higher than the established norms. These abnormal readings could indicate early atherosclerotic disease. To decrease the chances of cardiovascular disease, individuals should engage in healthy lifestyle practices that lower stress and anxiety levels. Exercising several times a week, getting adequate amounts of sleep, engaging in enjoyable activities, striking a balance in one’s work life, and meditating are just a few examples.

5.4 Recommendations for Future Research

In this study, all variables of interest except for time were treated as categorical variables. Future studies should be conducted to test the influences of perceived stress and generalized anxiety on c-IMT when these are continuous variables. After all, there was a marked difference in correlation, although still significant, between the two scales when both were categorical versus continuous. Statistical analyses should include a time period much longer than the two years for this study. Also, models including both the perceived stress and generalized anxiety variables, along with age group and gender, should be analyzed using the MIXED procedure in SAS.

5.5 Conclusion

In short, the findings of this study suggest that the left mean c-IMT measurement is influenced in part by one’s generalized anxiety level when controlling for age group and gender. This reinforces the importance of how influences of the mind can affect the body, and why one should not ignore them. If
methodological issues in measuring c-IMT are resolved, then this information could possibly be used as a screening tool. Despite this fact, individuals can still use their c-IMT readings, as well as their perceived stress and generalized anxiety scores, as indicators that lifestyle modifications may be needed.
REFERENCES


APPENDIX A
PERCEIVED STRESS SCALE (14-ITEM VERSION)

Items and Instructions for Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don’t try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:

0. Never
1. Almost never
2. Sometimes
3. Fairly often
4. Very often

1. In the last month, how often have you been upset because of something that happened unexpectedly?
2. In the last month, how often have you felt that you were unable to control the important things in your life?
3. In the last month, how often have you felt nervous and “stressed”?
4. * In the last month, how often have you dealt successfully with irritating life hassles?
5. * In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?
6. * In the last month, how often have you felt confident about your ability to handle your personal problems?
7. * In the last month, how often have you felt that things were going your way?
8. In the last month, how often have you found that you could not cope with all the things that you had to do?
9. * In the last month, how often have you been able to control irritations in your life?
10. * In the last month, how often have you felt that you were on top of things?
11. In the last month, how often have you been angered because of things that happened that were outside of your control?
12. In the last month, how often have you found yourself thinking about things that you have to accomplish?
13. * In the last month, how often have you been able to control the way you spend your time?
14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

* Scored in the reverse direction.
# APPENDIX B

## GENERALIZED ANXIETY DISORDER 7-ITEM SCALE

### GAD-7 Anxiety

<table>
<thead>
<tr>
<th>Over the last two weeks, how often have you been bothered by the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious, or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to sleep or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid, as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Column totals \[ \text{Not at all} + \text{Several days} + \text{More than half the days} + \text{Nearly every day} = \]

Total score ______

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
APPENDIX C

EMORY UNIVERSITY

Consent to be a Research Subject

Title: The Center for Health Discovery and Well-Being® (CHDWB) Cohort Study

Principal Investigator: Gregory S. Martin, M.D.

Introduction:

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study. The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

Study Overview

The purpose of this study is to: 1) to obtain needed new information on factors that predict health over time, including diet, exercise, body function, body composition, social and psychological (mental) factors in individuals followed for several years; and 2) to test the effectiveness of personalized support of healthy lifestyles and stress reduction using a Predictive Heath Partner. The study also aims to discover new factors that may predict future disease and to define normal ranges of values for these new markers. Information from the study will allow researchers to better define “health” and predict future health, avoiding development of disease. This new information will be extremely valuable in developing new and better ways to prevent disease.

After agreeing to the stipulations in this consent form, you will be asked to participate in this study if you meet the following criteria:

- You are age 18 or older;
You have no history of hospitalization due to an acute or chronic disease within the previous year;
You have no history of severe psychosocial disorders within the previous year;
You have not needed the addition of new prescription medications to treat a disease condition within the previous year (with exception of changes of high blood pressure or diabetes medicines);
You have no history of substance or drug abuse or alcoholism within the previous year;
You have no active cancer or history of cancer other than localized cancer of skin during the previous 5 years;
You have no chronic disease that is poorly controlled medically; you have not had any illness in the previous 2 weeks before the baseline studies outlined below;
For the randomized Emory Cohort only – You have been employed at Emory at least part-time for at least two years.

**Procedures**
After you agree to the stipulations in this consent form, we will determine whether you meet the criteria given above and are eligible for proceeding with the study. We will also discuss with you the various membership models available to you.

For all of the membership packages, you will be asked to complete a series of health questionnaires and surveys at the CHDWB (described below). The information from these assessments will be entered into a computer based record that is confidential, and protected, consistent with all government regulations for handling such information. This information is used to assess your background information (such as age, gender, ethnic group, etc.), individual and family health history, social/spiritual profile, lifestyle profile, medication and supplement use profile, mental and behavioral health, and quality of life measurements using standard questionnaires.

**Questionnaires taken in the Center on our internet web-portal**

- Demographic Information. We will ask you information such as date of birth, place of birth, age, ethnicity, personal physician information, emergency contact information, household income, address and zip code.
- Occupational history and exposure. We will ask you information about your current and past jobs and the type of potential hazards you may have been exposed to.
- Individual and family health history. We will ask you about your family and your personal current and past medical diagnoses, hospitalizations, and surgeries.
- Current use of medications, supplements and herbs. We will ask if you are currently taking any over the counter or prescription substances.
- Health symptom assessment. We will ask you to respond to a list of questions and tell us how often you experience any of these symptoms.
- Perceived Stress Scale. We will ask you questions about how often and how intensely you experience stress in your life.
- Current alcohol and tobacco use. We will ask you questions about how often you use alcohol and tobacco products and if you have a desire to stop.
- Use of complementary and alternative medicine. We will ask if you partake in activities such as meditation, acupuncture, hypnosis, etc.
Surveys taken in the Center on our internet web-portal

- Block Food Frequency Questionnaire. We will ask you questions about the frequency and type of foods you eat and fluids you drink.
- Mini Cognitive Exam. We will ask you questions about your short term memory and the ability to recall and remember things.

Surveys taken either in the Center or at home on our internet web-portal

- Beck Depression Scale. We will ask you questions about how often and how intense you have feelings of being depressed.
- Enriched Social Support Inventory. We will ask you questions about how active you are within your family, work, and community and your perceived level of support.
- Epworth Sleepiness Scale. We will ask you questions about how sleepy you feel during different parts of the day.
- FACIT-Sp-Ex Survey. We will ask you about your ability to cope with chronic disease and if spirituality is part of your coping strategy.
- Family Assessment Device. We will ask you questions about your overall family functioning and support.
- General Anxiety Disorder Scale. We will ask you questions about feelings of anxiety.
- Mental health flourishing index. We will ask you questions about your perception of how well you feel and the emotions you have.
- Pittsburgh Sleep Quality Index. We will ask you questions about your perceived quality of sleep and how rested you feel upon awakening.
- SF-36v2. We will ask you questions about your physical activities, limitations, and emotional well being.
- CAPS Typical Week Physical Activity. We will ask you questions about the type and frequency of different physical activities.

At the end of your visit, you will receive a “Health Assessment Report.” Your Health Partner will review all of the measurements that were taken.

Individuals recruited as part of the randomized Emory Cohort will receive the Pioneer package as well as the Advanced blood work and metrics.

For the Explorer, Journey, Navigator and Pioneer packages the Health Partner will discuss how we can work together to make constructive changes, as requested, that may assist you to stay healthy longer. We call this process the “Personalized Health Action Plan”. We will partner with you to watch and see (discover) how these measurements relate to your health and certain behaviors. We hope to discover new relationships that were never previously appreciated. If this happens, you will have helped us to identify new tools for keeping people healthy. Your Health Partner is your key to learning and linking you to community resources like your doctor or other related groups depending on your unique results. The main goal of the Health Partner is to help you to focus on areas related to nutrition, physical activity, mental, emotional, and/or spiritual well being. The health partner will help you identify the best options for you. The
Health Partner’s primary role is supportive and not diagnostic. The partner will assist you with making the choices that you believe are best for you.

If you selected the Journey or the Pioneer package, the Health Partner can also follow-up with you at your preferred method (i.e., telephone, email, in person, etc.) and frequency (weekly, bi-weekly, monthly, bi-monthly, etc.) to see how you are doing. The Health Partner can offer more supportive guidance until your next scheduled visit at the Center.

For both the Navigator and Pioneer memberships, if any of your laboratory results are significantly out of range, you will be contacted immediately and instructed to seek medical attention by your regular primary care or other appropriate provider. If any of the other assessments show that you are not in optimal “good” health and would benefit from ongoing medical care, you will be asked to stop participating in the study until medical clearance is obtained stating that you are in sufficiently good health to continue.

In the Navigator and Pioneer memberships, the total amount of blood to be obtained during the first visit is approximately 100 mL (about 10 tablespoons). A small amount of urine will also be obtained. You must not eat or drink for at least 6 hours prior to the blood drawing visit at the CHDWB. We recommend that participants drink lots of water.

Advanced metrics are available with the Navigator and Pioneer memberships. These tests are performed in the Center by our trained personnel:

- Blood tests: Blood samples may be taken to measure oxidation, inflammation, fats, regenerative potential, immune markers and other novel proteins. Results of the routine blood tests will be made available to you. A code will be used to link your blood sample to your study results.
- Urine tests: A urine sample will be taken to measure oxidation and kidney function. Results of these tests will be made available to you. A code will be used to link your urine sample to your study results.
- Exercise capacity testing: Your ability to exercise under controlled conditions is an indication of heart capacity and fitness level. It can be measured by doing a test that involves walking fast on an inclined treadmill with a record of your heart rate, blood pressure, and rate of perceived exertion. Your assigned Health Partner or other trained staff at the Center will place a blood pressure cuff on your arm, and a heart rate monitor strap on your chest. The staff member will instruct you to perform a walking test on the treadmill. One of three exercise tests will be performed. The names of these tests are the “Bruce Protocol”, “Modified Bruce Protocol” and the “Modified Balke Protocol.” All tests are “sub maximal” tests. This means you will not exercise to exhaustion. The test will involve walking fast on an inclined treadmill until you reach 85% of your predicted maximum heart rate. This number is calculated by subtracting your age from 220. You can stop the test at any time if you are feeling exhausted, light-headed, or dizzy. The test will be stopped for medical reasons if for example, your blood pressure or heart rate goes beyond normal adult exercising limits. Your blood pressure, heart rate, and perceived exertion levels are measured continuously throughout the test. All staff performing these tests are CPR level 1 certified and an Automated External Defibrillator (AED) device is located adjacent to this area on standby at all times.
- Bone density and body composition: This is a painless and very safe exam done with
a special scanning machine. The scan involves a very small dose of radiation, about one tenth the dosage of a single chest x-ray. The bone densitometer will measure your bone mineral density and also the amount of fat and muscle present in your body. It will also compare your measurements to a reference population based on your age, weight, sex and ethnic background. The report will be given to you. This information can be used by your physician in making a diagnosis about the state of your bones and body fat amount. During the exam, you will be asked to lie flat on your back, breathe normally, and rest comfortably. The scan will take 15 to 20 minutes. We will also determine your height and body weight using scales, tape measures, and special calipers.

- **Eye Exam:** This will be a two step procedure to include both a visual acuity screening and fundus photographs. **Visual Acuity screening** - Measurements will be performed using both a distance chart and a near visual acuity reading card. These measurements are usually recorded at a preset distance, using your current prescription glasses for distance or near vision (reading glasses). The results are translated into a visual acuity score. The score is generally recorded as 20/20, 20/30, 20/50 or other (as examples). **Fundus Photographs** - These are pictures taken of the back of the eye. We will use a special fundus camera that works in dim light and does not require dilation of the pupils with drops. The camera takes photographs of the light sensitive tissue in the back of the eye, known as the retina.

- **Neurological and psychological testing:** You will take either a NexSig or NeuroTrax computerized test that lasts about 20-60 minutes. You will be asked a series of questions that measure your brains’ ability to process information and to recall items such as a list of numbers.

Additional metrics available for purchase include the following tests:

- **Ultrasound imaging of the carotid arteries:** In order to see whether you have any thickening of the arteries in your neck, we will take pictures of the arteries, during your screening visit using ultrasound or sonar which uses sound waves. You will be lying on a massage table with your head turned to each side; a probe will be placed and moved over the artery to take images of the carotid arteries. There are no known dangers of ultrasound.

- **Arterial compliance:** This test will measure how stiff your blood vessels are. You will be asked to keep your arm very still; a small plastic instrument will be placed on your skin over the blood vessels located on your wrist, middle crease of your arm, and at the top of your leg. You will lie down quietly on a bed and be connected to an ECG type device. This is where measurements will be taken. This is a non-invasive test that will take about 10 minutes.

- **Ultrasound imaging study of the arm artery:** You may not eat, drink (mainly anything with caffeine) or smoke on the morning before your visit. You will lie down quietly on a bed and be connected to an ECG machine. A cuff will be placed on your upper right arm to allow us to measure your blood pressure. Another blood pressure cuff will be placed on your upper left arm. A technician will measure the size of your left arm artery using an ultrasound or sonar probe placed just above the inside part of your elbow. Your left arm will be placed in a comfortable position throughout the procedure, which takes about 45 minutes. After obtaining the initial ultrasound pictures, the blood pressure cuff on your left arm will be inflated so as to stop the flow of blood and will be kept inflated for 5 minutes. This will be done once during each ultrasound study. During this period, you will likely experience mild discomfort at the cuff site and tingling of your left arm, as if it
has gone to sleep. After 5 minutes, this blood pressure cuff is quickly deflated and ultrasound pictures are taken again. The tingling in your arm will go away quickly as blood flow returns in your arm. At this point, after a 10-minute period, we will obtain additional ultrasound pictures.

**Risks and Discomforts**

Standard protocols for blood drawing, vital signs, body composition, vascular health and neurologic health will be followed and only trained personnel will do the procedures. However, there are certain risks that you need to be aware of.

1) Blood testing and genetic testing: A maximum of 100 mL of blood will be drawn at any one visit to the CHDWB. People with unstable asthma, chest pain, uncontrolled high blood pressure, or heart failure that cannot be controlled with drugs and people with infections or poorly controlled lung or heart abnormalities will not be studied in this study. Other risks may include feeling light headed, dizzy or possibly fainting. Rarely, bleeding can occur around the site where we draw your blood. This is not dangerous, but, if it occurs, it could result in a small bruise. Skin tape reactions may occur in a small portion of allergic subjects, but is generally well tolerated and causes no long term side effects. Due to the investigational nature of this study there may be other risks that are currently unknown. To maintain confidentiality, your blood samples and research results will be labeled with an identifying code and not your name. While there will be no direct linkage between your blood sample and your name, this code will allow researchers to link clinical information about you with your blood sample, without knowing your name.

2) Ultrasound imaging studies: The imaging study of your arm and neck arteries may cause some temporary discomfort from the probe. The blood pressure inflation, performed during brachial artery ultrasounds, lasts for 5 minutes and can result in temporary feelings of numbness and pins and needles in the arm that last for one or two minutes. However, this is generally well tolerated and causes no long term side effects.

3) Exercise capacity test: It should not be done in people with unstable asthma, chest pain, high blood pressure, or heart failure that cannot be controlled with drugs, or in people with high fever and several other lung or heart abnormalities. If you have any of these conditions the exercise test will not be done. Other risks may include feeling light headed, dizzy or possibly fainting. If you are not an active person, you may experience muscle cramping or soreness, fast breathing and sweating during or after the test. If the treadmill exercise capacity test induces or aggravate symptoms of any underlying lung or heart disease or causes chest pain, shortness of breath, flushing, hyper- or hypotension and/or cardiac arrhythmias, the test will be terminated and you will be treated and monitored appropriately by a CHDWB nurse and/or physician, or escorted to the Emory University Hospital Midtown emergency room as indicated.

4) Bone density and body composition studies: This procedure involves exposure to small amounts of radiation that will occur only as a result of your participation in this study. Women who may be pregnant should not participate in this study because of possible effects of radiation exposure on their unborn child. There are currently no studies that show an increase in the risk
of genetic mutation in the next generation of offspring. The radiation dose that you will receive is equal to or less than the natural environmental radiation the average person receives in the United States annually. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk from radiation exposure of this magnitude is considered to be negligible when compared to everyday risks.

5) Eye Exam: This procedure involves sitting at the camera with your chin on the chin rest and your forehead against the bar. The camera is mounted to a microscope that allows us to photograph the back of your eye. The camera projects a small light that focuses your retina and then a bright flash will capture the photograph. There is very little risk involved as this is a noninvasive photograph.

6) To minimize the risks associated with the psychological interviews and questionnaires, you will be asked to inform the interviewer when or if your levels of emotional distress are increasing during the evaluation process.

New Information
It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits
This study is not designed to benefit you directly. However, you may benefit from the assessments, the health assessment report, and from interaction with a Predictive Health Partner. All of these are designed to provide the participant with health related information that may encourage healthy behaviors. The study results may be used to help others in the future.

Compensation
You will not be offered payment for being in this study.

Confidentiality
Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records. These offices include the Emory Institutional Review Board, the Emory Office of Research Compliance, the Office for Clinical Research, the Clinical Trials Audit & Compliance Office and the Radiation Safety Committee. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

Research Information Will Not Go Into the Medical Record:
If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient, you do not have one.
Please note that an Emory Healthcare medical record will be created if you have any services or procedures done by an Emory provider or facility for this study.

If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign will not be placed in your Emory Healthcare medical record. Emory Healthcare may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These useful study results will not be placed in your Emory Healthcare medical record. Anyone who has access to your medical record will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory does not control results from tests and procedures done at other places, so these results would not be placed in your Emory Healthcare medical record. They will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. If you decide to be in this study, it is up to you to let them know.

**In Case of Injury**

*If you get ill or injured from being in the study, Emory would help you to get medical treatment. Emory and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proved that your injury or illness is directly caused by the negligence of an Emory or sponsor employee. “Negligence” is the failure to follow a standard duty of care.*

*If you become ill or injured from being in this trial, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.*

*If you believe you have become ill or injured from this research, you should contact Dr. Brigham at telephone number 404-686-6190. You should also let any health care provider who treats you know that you are in a research study.*

**Costs**
The sponsor will not pay for any items or services associated with the study. You will have to pay for the items or services that are part of this study. The suggested pricing is listed below:

<table>
<thead>
<tr>
<th>CHDWB services</th>
<th>Discovery</th>
<th>Explorer</th>
<th>Journey</th>
<th>Navigator</th>
<th>Pioneer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Partner Support</td>
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<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Personalized Health Action Plan</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Six Month Update</td>
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Additional Center for Health Discovery and Well Being® services

Services listed below are offered separately and can be purchased to supplement any plan listed above. The Discovery plan is required before adding additional services.

Health partner support  $250
Health Action Plan  $150
Comprehensive Blood Work  $350
Dexa Scan body composition  $200
Treadmill estimated VO2 max  $50
Basic metrics  $25
Cognitive function  $50
Advanced metrics  $250

Advanced blood work:
- Oxidative stress (redox potential)  $150
- Circulating progenitor cells (CD34) and cytokines (TNF-α)  $200

You will not be charged for any of the study procedures outlined above if you were selected as part of the randomized Emory Cohort.

Withdrawal from the Study
You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- You fail to comply with the scheduling or payment criteria outlined in your membership;
- or for any other reason.
**Contact Information**

Contact Gregory Martin, MD at 404-686-6190:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research
- if you would like to withdraw from the study

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at [http://www.surveymonkey.com/s/6ZDMW75](http://www.surveymonkey.com/s/6ZDMW75).

**Genetic Sample Consent**

This additional consent is for use of samples that may be taken from you for research.

Your samples will be stored in a secured freezer in the Emory Midtown Clinical Interaction Site of The Atlanta Clinical and Translational Science Institute. The samples of DNA and RNA that we will obtain will include identifiers that would link to you on a confidential basis. These samples may be shared with other investigators for related research. You can refuse to have your DNA samples stored and still be able to participate in the study. The genetic tests that may done on your blood samples will not be evaluated for known established diseases; rather we are testing whether certain newly described or future genes predict future disorders or can be associated with other markers of health and/or disease.

Any information collected or produced for research as part of this genetic study will not be reported to you.

Any information collected or produced for research as part of this genetic study will not be placed in your medical records (if you should have one at Emory) and will not be shared with any supervisor, health care professional or insurance agency.

Investigators that request access to your samples will have to submit a request in writing to the CHDWB Technical Advisory Group. That group will review and approve/deny every request and track usage of samples. The Technical Advisory Group is a panel of senior scientists and clinical investigators who function to provide expert information and advice in all operational matters related to the CHDWB.

Any samples released to investigators for research will be de-identified and will not contain your name.
You do not give up ownership of your tissue; you do give up ownership of any technology that may be developed from it. The information that is obtained from the analysis of your blood may be used scientifically and may be used by the sponsor in other research. The analysis of your blood samples may contribute to the creation of new diagnostic tests, new medicines, or other uses that may be commercially valuable to the CHDWB. You will receive no financial benefits and may not receive any health-related benefits from such development. The investigators and any other staff who may have access to your samples are not authorized to and are forever prohibited from using this material for any attempt at cloning a human being.

1a. I agree to allow my blood samples to be stored and accessed for future testing, including DNA tests: __________ (initials)

1b. I do not want my blood samples to be collected or stored for future testing. ________________ (initials)

Registry Consent

This additional consent is requesting your permission to store your personal information in our database indefinitely.

The study investigators may contact you to see if you are willing to volunteer for potential future studies performed by Emory and/or Georgia Tech researchers. If you choose to participate in a future study, you will be provided with information about that study and given a separate informed consent describing that study. We are only requesting your permission to store data about you and your health.

1a. I agree to allow my personal information to be stored in the research database indefinitely: __________ (initials)

1b. I do not want my personal information to be stored in the research database at all: __________ (initials)

2a. I agree to allow researchers to access my health-related data from Emory Healthcare and other Emory health plans for research: ____________ (initials)

2b. I do not want researchers to access my health-related data from Emory Healthcare and other Emory health plans for research: ________________ (initials)

You may change your mind at any time, please contact Gregory Martin, MD at 404-686-6190.

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

__________________________
Name of Subject
<table>
<thead>
<tr>
<th>Signature of Subject</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of Person Conducting Informed Consent Discussion</td>
<td>Date</td>
<td>Time</td>
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