ASSOCIATION OF CHRONIC SELF-PERCIEVED STRESS WITH MORTALITY AND HEALTH STATUS OUTCOMES IN PATIENTS WITH PERIPHERAL ARTERY DISEASE: INSIGHTS FROM THE PORTRAIT REGISTRY

A THESIS IN
Bioinformatics

Presented to the Faculty of the University Of
Missouri-Kansas City in partial fulfilment of
The requirements for the degree

MASTER OF SCIENCE

BY
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MBBS., AGA KHAN UNIVERSITY, 2012

Kansas City, Missouri
2019

ASSOCIATION OF CHRONIC SELF-PERCIEVED STRESS WITH MORTALITY AND HEALTH STATUS OUTCOMES IN PATIENTS WITH PERIPHERAL ARTERY DISEASE: INSIGHTS FROM THE PORTRAIT REGISTRY

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ABSTRACT

The prevalence of peripheral artery disease (PAD) is increasing worldwide and is estimated to affect about 360 million patients by 2030. Patients with PAD are at a higher risk of premature mortality and suffer from disability and functional impairment, both of which contribute to the direct and indirect socioeconomic burden of PAD. These trends are occurring despite emphasis towards control of traditional risk factors and interventions to decrease the impact of PAD on patient outcomes. Hence it is critical to identify and study novel risk factors that could impact outcomes in patients with PAD.

Chronic mental stress could be one such factor. Mental stress is a potent cardiovascular risk factor and has been associated with development and progression of coronary disease and worse outcomes, including higher risk of mortality and poorer quality of life in patients after a myocardial infarction. However, there is paucity of evidence for the association of chronic mental stress with outcomes in PAD.

To address this critical gap in understanding the link between mental stress and outcomes in PAD, we used data from the Patient-centered Outcomes Related to Treatment practices in peripheral Arterial disease: Investigating Trajectories (PORTRAIT), an international registry of patients presenting with symptoms of PAD. Mental stress was quantified at baseline, 3-, 6- and 12-month follow-up using the validated 4-item Perceived

Stress Scale (PSS-4). For each patient available PSS-4 scores from all time points were averaged to quantify a subject's average exposure to mental stress over one year. To examine the association of chronic stress with longitudinal mortality and health status outcomes, we did two separate landmark analysis. First to examine the impact of chronic stress on mortality we did a landmark analysis starting at 12-month follow-up. For each patient we defined chronic stress to be average of PSS-4 score at baseline through 12-months. Cox regression models adjusting for patients' demographics (age, sex, race), comorbid conditions (diabetes, hypertension, history of myocardial infarction, congestive heart failure, smoking status), baseline ankle-brachial index, invasive treatment for PAD, socioeconomic indicators (highest education level, avoidance of care due to cost and end of the month resources), were used to assess an independent association of average stress (over first year of follow-up) with all-cause mortality over the subsequent four years.

Second, to examine the association of chronic stress with 12-month health status outcomes we defined chronic stress exposure to be average PSS-4 score across baseline, 3- and 6-month follow-up assessments. This quantified a patient's exposure to chronic stress over first 6-months of follow-up. Health status was quantified at baseline and 12-months. PAD specific health status was assessed using the PAD Questionnaire (PAQ). Generic health status was assessed using the EuroQoL Visual Analog Scale (EQ5D VAS). Hierarchical multivariable regression models, with random effects for site and adjustment for country, patients' demographics, comorbid conditions, baseline ABI, treatment strategy and socioeconomic status-were used to examine independent association of average stress (baseline to 6-months) on recovery in health status at 12-months.

In in patients in whom accurate assessment of chronic mental stress and mortality could be made (n=757, mean age 68.5 ± 9.7, 42% females, 28% non-Caucasians), higher average stress scores over 12-months were associated with greater hazards of mortality, in the adjusted model *(hazard ratio per +1 unit increase in average PSS-4 1.08, 95% CI 1.01, 1.16 p=0.03*). Similarly, in patients who had complete assessment of chronic stress over 6-months and health status at baseline and 12-month follow-up (n=1060, mean age 67.7, 37% females, 17.7% non-Caucasian) higher averaged stress scores over 6-months were associated with poorer PAQ summary score at 12-months in completely adjusted models (*-1.4 points per +1-point increase in average PSS-4 95% CI -2.1, -0.6 p <0.001).*

Chronic stress in patients with PAD, is independently associated with higher mortality risk and poorer health status outcomes. These results set the stage for exploring interventions to examine if strategies to reduce chronic stress in patients with PAD improves outcomes.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis "Association of Chronic Self-Perceived Stress with Mortality and Health Status Outcomes in Patients with Peripheral Artery Disease: Insights from the PORTRAIT registry "presented by Ali Osama Malik, candidate for Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CONTENTS

ILLUSTRATIONS

TABLES

ACKNOWLEDGEMENTS

I want to thank the chair of my thesis committee, Dr. Kim Smolderen for her guidance and support throughout this process. Thank you to Mr. Jones for agreeing to be part of my thesis committee and for his guidance. Special thanks to Miss. Kensey Gosch for being the hero that I needed and probably did not deserve. I would have not been able to achieve anything without help and support from Miss Gosch. Thank you to Miss Christina Pacheco for all the support and help. A big thank you to Dr. David Cohen for inspiring and encouraging me. To Dr. Spertus- thank you so much for inspiring me, for believing in me, for helping me look at the “bigger picture” for encouraging me in my passions and above all making me a realize that an insignificant person with right intentions and passion to take it to the end, can make an impact.

CHAPTER 1

INTRODUCTION

Global Burden of Peripheral Artery Disease

Peripheral Artery Disease (PAD) is characterized by debilitating atherosclerotic occlusion of arteries in the lower extremities.[1,2] The prevalence of PAD is increasing worldwide, and PAD is now recognized as a growing global health concern.[3] It is estimated that by 2030, more than 300 million people worldwide will be affected by PAD.[4] The prevalence of PAD rises sharply with age and it affects a substantial proportion of the elderly population.[5]

PAD is a devastating disease and directly impacts a patient's functioning, productivity and increases risk of premature mortality.[1,6,7] These outcomes contribute to direct and indirect socioeconomic burden of PAD and represent a colossal public health issue. Over the past 20 years there has been a global increase in death and disability from PAD.[1,8] Average 5-year mortality for patients with PAD continue to be about 25%, comparable to mortality rates of patients after a myocardial infarction or heart failure.[9] Most of the patients with PAD die of cardiovascular causes.[10] This data underscores that patients with symptomatic PAD have a high cardiovascular risk and highlights the importance of interventions to attenuate the risk.

Additionally in the US, average annual cost for a patient with PAD is estimated to be about $11,000.[11] This direct cost of PAD compound lost wages, care by family members and lost opportunity costs, increasing the socioeconomic burden of PAD. It is important to realize that patients with PAD continue to suffer from these adverse outcomes despite significant advances in treatments including medications, supervised exercise and revascularization. Hence, it is critical to identify novel risk factors that put patients with PAD at higher risk so that interventions that seek to improve patients' outcomes can be designed.

Mental Stress, a Potent Cardiovascular Risk Factor

To understand the impact of stress on an individual's life it is important to conceptualize stress in terms of a relative imbalance between coping skills and external stimuli. Three different models of understanding the stress construct have been described. Stress has been viewed as a response, a stimulus and a transaction.[12,13]

Stress, in a response model is considered dependent to a stimulus. It ranges across a spectrum of response pattern and follows three stages; alarm, resistance and exhaustion. When confronted with a negative stimulus the alarm response initiates the sympathetic system to combat or avoid the stressor. The resistance response then activates the *fight or flight* reaction to the stressor, returning the system to homeostasis, reducing harm, or more generally, accommodating the stressor which can lead maladaptive responses such as sleep deprivation, hypertension, hyperglycemia etc., until the body's reserves are exhausted.[12]

The stimulus model of stress views stress as a significant life event or change that demands response, adjustment or adaption.[12] Holmes and Rahe created the Social Readjustment Rating Scale consisting of 42 life events scored according to the estimated degree of adjustment they would demand.[14] They theorized that stress was the independent variable in stress-coping equation, the cause of an experience, rather than the experience itself.

In order to explain stress as a dynamic process, Lazarus and Folkman introduced the transactional model of stress.[15] This model presents stress as a transaction between a person and his/her environment. Depending on the amount of demands that a person is confronted with and the amount of resources that they have to deal with the demands, stress may either be in abundance or avoided completely. Whenever confronted with a new situation, an individual analyzes if a situation is a threat or not. This is the primary appraisal. If the situation is perceived to be a threat,

a secondary appraisal occurs, where an individual decides if he/she can deal with the stressor. If the perceived demands outweigh the mental resources required to deal with them, stress occurs. Figure A2 describes the transactional model of stress.

Regardless of the construct used to define it, stress is a potent cardiovascular risk factor.[16] It occurs when external and internal stressors overcome an individual's mental reserves.[17] Exposure to chronic mental stress is associated with adverse health behaviors such as obesity[18], smoking[19] , lack of exercise[20] and use of illicit drugs.[21] Additionally, various pathophysiological processes that enhance atherosclerosis and development of cardiovascular disease are triggered by exposure to mental stress. These include, increase in blood pressure[22], platelet reactivity[23], endothelial dysfunction[24], hyperglycemia[25] and inflammation.[26] Additionally, in patients with a devastating disease such as PAD chronic stress further complicates management as stress is associated with decreased compliance and delays in seeking care. Through interplay of these mechanisms chronic stress is thought to increase overall cardiovascular risk and progression of atherosclerotic disease.

Higher exposure to mental stress at the time of myocardial infarction is independently associated with higher risk of mortality and poorer quality of life of patients.[27] In asymptomatic women, chronic stress due to marital issues was associated with about three times higher risk of development of cardiovascular disease.[28] Furthermore, mental stress at workplace was associated with higher risk of future events in patients with coronary artery disease.[29]

However, it is important to realize that mental stress is a modifiable risk factor for which evidence-based treatments exist.[30] Equipping patients with coping skills to reduce stress in their lives has been shown to be effective in improving quality of life in patients with coronary artery disease. Additionally, chronic stress management through cognitive behavioral therapy programs

as well through transcendental meditation in addition to standard care has been shown to reduce the risk of recurrent cardiovascular events and increased life expectancy after a myocardial infection.[31,32]

The Case for Studying Mental Stress as a Risk Factor in Peripheral Artery Disease

Patients with PAD suffer from adverse outcomes, including higher risk of mortality and disability. It is also known that about a third of the patients with PAD report high levels of self-perceived stress at initial presentation.[33] As stress has a strong relationship with development and progression of coronary artery disease and given similar mechanisms underlie the pathophysiological pathway to PAD, it is important to examine if there is an association of exposure to stress with outcomes in patients with PAD. Additionally, patients with PAD are at a high risk for adverse cardiovascular events. There is a paucity of data on impact of exposure to mental stress with outcomes in PAD. Some studies have examined the association of stress and anxious personality traits with health status of patients with PAD.[34,35] However, these studies either looked at cross-sectional associations and did not account for changes in stress levels over time. Additionally, no prior study has examined the association of chronic exposure to stress with mortality risk in patients with PAD.

To address these gaps in knowledge we sought to 1) examine the association of chronic exposure to stress with mortality in patients with PAD; 2) Examine the association of chronic exposure to stress with generic and disease specific health status of patients with PAD. We hypothesized that patients who had greater exposure to chronic stress would have higher risk of mortality and poorer generic and disease specific health status.

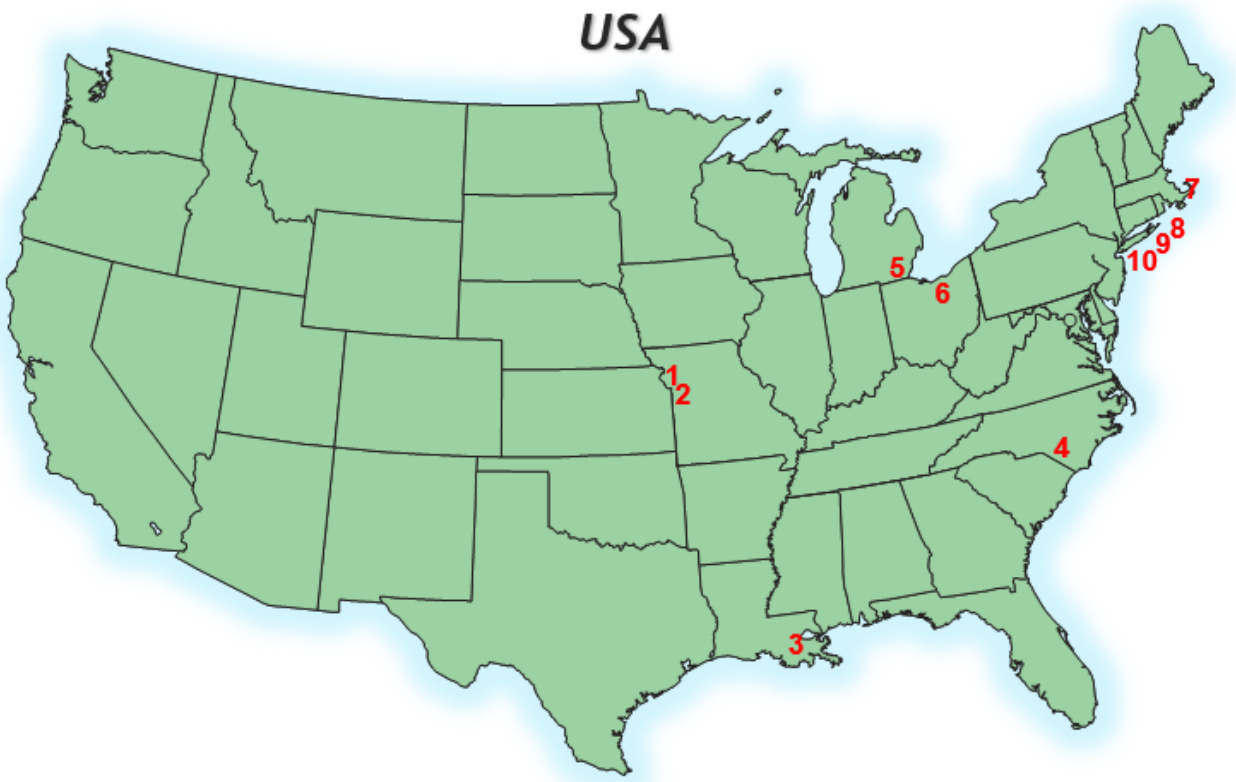
CHAPTER 2
METHODOLOGY

Study Design and Participants

The Patient Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories (PORTRAIT; NCT01419080) study is a prospective observational registry that enrolled patients with a new diagnosis or worsening of symptoms of PAD, that presented to subspecialty clinics in the US, Netherlands and Australia **(Figure 1).** Details of study design and methodology has been described extensively.[36] **Figure 2** illustrates the study design. For this analysis we used data from baseline, and all follow-up time points. Additionally, data on mortality (for US patients only) up to 5-year after enrollment was used. Patients were enrolled at the PAD specialty clinics that included general cardiology, interventional cardiology, interventional radiology, or vascular surgery offices. Baseline interview was conducted by trained study personnel to obtain information about patients' quality of life, symptoms and functioning. Standardized case report forms were used to abstract clinical information (medical history, PAD history, weight, height, and medications) from patients' medical records. Serial information about patients' health status and lifestyle factors was collected at 3, 6, and 12 months of follow-up through telephone interviews. Patients presenting to specialty clinic with symptoms of PAD and an ankle brachial index (ABI) ≤ 0.90 or a significant drop in post-exercise ankle pressure ($\geq$20mm of Hg) were enrolled. Patients with non-compressible ABI ≥ 1.30, critical limb ischemia, lower-limb revascularization in the 12 months prior to the PAD visit and those who were incarcerated, hard of hearing or unable to provide informed consent were excluded. **Table 1** describes the inclusion and exclusion criteria in detail. All participating centers obtained IRB approval and all patients provided informed consent at enrollment.

Figure 1: PORTRAIT enrolling sites.

(a) United States



1. Saint Luke's Mid America Heart Institute, Kansas City, MO
2. Truman Medical Center, Kansas City, MO
3. Ochsner St. Anna General Hospital, New Orleans, LA
4. Duke University Medical Center, Durham, NC
5. St. Joseph Mercy, Ann Arbor, MI
6. Cleveland Clinic, Cleveland, OH
7. Miriam Hospital, Providence, RI
8. Rhode Island HS, Providence, RI
9. Yale New Haven Hospital, New Haven, CT
10. Bridgeport Hospital, Bridgeport, CT

(b) Netherlands

1. St. Elisabeth Hospital, Tilburg
2. Twee Steden Hospital, Tilburg
3. Zorgsaam Terneuzen
4. Albert Schweitzer Hospital, Dordrecht
5. St. Antonius Hospital, Nieuwegein

(c) Australia

1. Queen Elisabeth Hospital, Adelaide

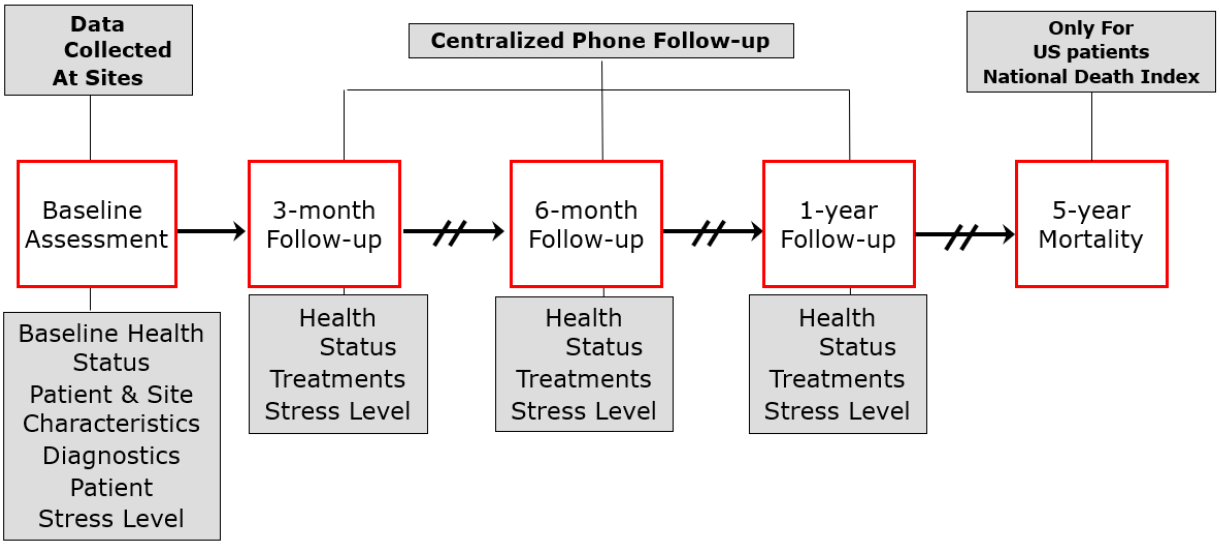


Figure 2. Study Design

Table 1. Inclusion and Exclusion Criteria for PORTRAIT study.

Inclusion Criteria	Exclusion Criteria
▪ Age ≥ 18 years ▪ New-onset or recent exacerbation of exertional leg symptoms, regardless of whether symptoms are typical or atypical (buttock, thigh, hip or calf pain, numbness or discomfort inhibiting the patient's ability to walk distances) ▪ Ankle-brachial index = resting ankle-brachial index assessment ≤0.90 or drop in post-exercise ankle pressure ≥20mmHg	▪ Non-compressible ankle-brachial index ≥1.30 ▪ Patient had a lower-limb revascularization procedure in the ipsilateral leg (=same leg) where the patient is currently having symptoms in the past year (atherectomy, endarterectomy, bypass surgery, angioplasty) ▪ A current episode of critical limb ischemia (ischemic rest pain, ulceration or gangrene) (Fontaine III, IV, or Rutherford grade IV-VI) ▪ Non-English speaking or non-Spanish speaking for US sites; Non-Dutch speaking for Dutch sites; Non-English speaking for Australian sites ▪ Hearing impairment ▪ Currently a prisoner ▪ Patient previously enrolled in PORTRAIT ▪ Unable to provide written informed consent

Assessment of Chronic Mental Stress

Each patient's perception of their ability to deal with the stress in their lives was quantified at baseline, 3-, 6- and 12-month follow-up using the 4-point Perceived Stress Scale (PSS-4). The PSS-4 is a reliable (Cronbach's alpha 0.67-0.79) and valid measure of a subject's self-evaluation of control and confidence in handling the stressful situations over the past month.[17] PSS-4 consists of four questions comprised of rating scale responses. Figure 2 lists the questions in the PSS-4. Scores range from 0-16, with higher scores indicating stress exceeding a subject's ability to cope. As the PSS-4 is a non-diagnostic instrument, there are no established thresholds, and scores are compared to a normative value in the general population.[17,37] In the English population a score ≥ 6 was found to depict patients with high levels of stress.[37] A score ≥ 6 was also found to be associated with adverse outcomes in patients after a myocardial infarction. Hence, in keeping with prior research we used a score of ≥ 6 to describe patients with high levels of self-perceived stress.[27]

Stress is an everyday phenomenon, and exposure to stress over time could incrementally increase a patient's cardiovascular risk. We wanted to examine the association of chronic stress with outcomes in PAD. Hence to depict each patient's chronic exposure to stress, we averaged the PSS-4 assessments. To examine the association with 12-month health status outcomes, we averaged the PSS-4 across first 6-month follow-up and for mortality assessment over 5-years we averaged PSS-4 scores over the first 12-month follow-up (figure 3)

Figure 3. Exposure to chronic stress for examining association with mortality and health status.

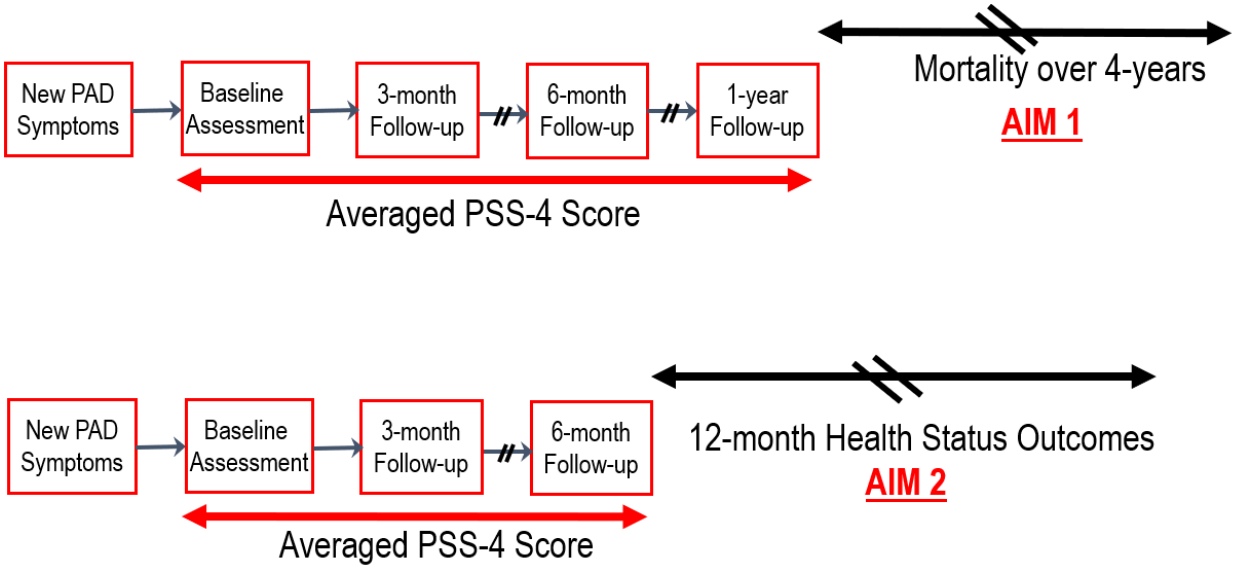


Figure 4. 4-Point Perceived Stress Scale

	Never	Almost Never	Sometimes	Fairly Often	Very Often
1)In the last month how often have you felt that you were unable to control the important things in your life?					
2) In the last month how often have you felt confident about your ability to handle your personal problems?					
3) In the last month how often have you felt that things were going your way?					
4) In the last month how often have you felt difficulties were piling up so high that you could not overcome them?					

Scoring

Question 1 and 4

0=Never
1=Almost never
2=Sometimes
3=Fairly Often
4=Very Often

Scoring

Question 2 and 3

4=Never
3=Almost never
2=Sometimes
1=Fairly Often
0=Very Often

Cohen S, 1983

Assessment of Health Status

Disease specific health status was assessed using the PAD Questionnaire (PAQ) **(Figure A-1).** PAQ is a 20-item multidimensional instrument that is a valid, reliable and responsive disease specific measure of patients with PAD.[38,39] A single item identifies the more symptomatic limb and remaining 19 are answered according to variable rating response scales to assess 6 domains, physical limitation, symptoms, symptom stability, social limitation, treatment satisfaction and QoL. The PAQ summary score (PAQ SS) integrates all domains except symptom stability and treatment satisfaction. Scores range from 0-100 with higher scores indicating less functional limitation, fewer symptoms, better treatment satisfaction, higher social functioning and better QoL. A change ≥ 8-points on the PAQ SS was found to be a clinically meaningful difference. The PAQ has been translated and validated in the Dutch population.[40]

Generic health status was assessed using the EuroQoL Visual Analog Scale (EQ5D VAS).[41] The VAS is a measure of perceived general health that consists of a single item "feeling thermometer", on which the patients rate their general health state from 0 (worst imaginable) to 100 (best imaginable).[41] Health status assessments from baseline and 12-months were used to examine impact of chronic stress on a patient's functionality, symptoms and quality of life.

Assessment of Mortality

Data on mortality was only available for patients from the US. Hence analysis to examine the association of chronic stress with mortality was only done in the US cohort of the PORTRAIT study. For the US patients vital status information over follow-up (median 49-months) was obtained for those who were alive 12 months following their enrollment through querying the National Death Index (NDI).[42] The NDI provides reliable and accurate data regarding vital status of patients from the US. All-cause mortality was the primary outcome for this analysis.[43]

To understand the common causes of death, international classification of disease (ICD) codes for the cause of death as listed in the NDI dataset were examined. After 1999, causes of death have been reclassified by ICD 10 codes in the NDI database.[43] We categorized causes of death as cardiovascular cause, presumed cardiovascular cause and non-cardiovascular death, as used in previous work.[44] Cardiovascular cause of death was considered if the ICD-10 code indicated myocardial infarction, ischemic heart disease, heart failure or cardiac arrest as the cause of death. Presumed cardiovascular cause of death was implied if the ICD-10 code indicated pulmonary embolism, cerebrovascular accident or PAD as cause of death. The remainder of causes of death were categorized as “other”.

Covariates

Socioeconomic status was assessed using patient responses to questions regarding their highest level of education (high school/college/post graduate), prior avoidance of care due to costs (yes/no) and typical financial resources left at the end of the month (some/just enough/not enough). Treatment strategy at 3 months following patients' PAD work-up was categorized as either invasive (including percutaneous or surgical interventions) or non-invasive (medical therapy only). Depressive symptoms at baseline were assessed using the 8-item Patient Health Questionnaire depression scale (PHQ-8), a screening instrument for major depression.[45] Scores range from 0-24 with higher score indicating greater depressive symptoms.[45] Score ≥ 10 are considered to imply clinically relevant symptoms that warrant further assessment.[45]

Statistical Analysis

For descriptive analyses the analytical cohort was dichotomized based on patients averaged stress scores over 6-months as high (average PSS-4 ≥ 6) vs. low (average PSS-4 <6). Patient demographics, PAD severity, treatment strategy and comorbidities at baseline were compared in patients with high and low chronic stress. Continuous variables were presented as means ± standard deviations and were compared across groups using independent t-tests for independent samples or Mann-Whitney U tests for non-normally distributed variables. Categorical variables were presented as frequencies with percentages and were compared using Chi-square tests.

To examine the association of chronic stress with patient's health status trajectories, mean PAQ and VAS scores at each assessment in patients with high and low levels of chronic stress were plotted. To examine the association of averaged stress scores with recovery in generic and disease specific health status at 12-months we did a land mark analysis starting at 6-

month follow up. We fit hierarchical multivariable regression models, with fixed effect for country and random effect for site to account for clustering at the site level, with exposure being average PSS-4 scores over 6-months and outcome being health status scores at 12-months. Several models were defined *a priori,* and a step-wise modelling approach was used. In model 1 the unadjusted association of average PSS-4 score with change in health status at 12-months, (except for adjusting for baseline health status) was assessed. In model 2 additional adjustment for patient demographics (age, sex and race) was done. As stress has been associated development of diabetes[22], hypertension[46], myocardial infarction[47], heart failure[48] and uptake of smoking[22], in model 3, additional adjustment for these covariates as well as PAD severity (assessed with baseline ABI) and treatment type (invasive/medical) was done. This was to assess if there remained an independent association after accounting for these factors; which could potentially have either a confounding or mediating effect, or both. Additionally, socioeconomic status has been associated with outcomes in patients with PAD.[49] Hence we constructed Model 4 with additional adjustment for socioeconomic status.

Accurate assessment of mortality was not available for patients from the Netherlands and Australia. Hence mortality analysis was limited to patients form the US. For the US-patients the association between average PSS-4 scores over 12 months with 4-year all-cause mortality after the initial 12-month follow up period was assessed, using a landmark analysis with time zero defined at 12-months. Patients who had died by 12-months (n=31) were excluded from this analysis. Kaplan-Meier curves to compare the age-adjusted risk of all-cause mortality over the following 4-years, in patients with high and low levels of stress were constructed, and statistical significance was tested using the log-rank test.

To examine the independent association of averaged PSS-4 score (as a continuous variable) with all-cause mortality over 4 years after the 12-month follow-up, hierarchical Cox regression models with a random effect for enrollment site were constructed. As with the health status linear regression models. four models were defined a priori. Model 1 unadjusted association (except for site and age) was examined. Model 2 was additionally adjusted for patient demographics (sex and race). Model 3 consisted of model 2 and further adjusted for comorbidities (diabetes, hypertension, history of myocardial infarction, congestive heart failure, current smoking status), baseline ABI and treatment type. Model 4 consisted of model 3 and further adjustment for socio-economic status variables (education, avoiding care due to costs, and end-of-the-month financial resources).

As chronic stress may overlap with depressive symptoms, we assessed the correlation of baseline PHQ-8 and PSS-4 scores using Pearson's correlation coefficient. Finally, in our completely adjusted models for examine health status and mortality we added baseline PHQ-8 score to assess whether chronic stress outside of the context of possible depression was associated with patient's health status and mortality risk.

All models included restricted cubic splines for estimating effects of continuous variables to accommodate non-linear relationships. In cases where no significant evidence of non-linearity was found, associations were re-estimated using linear effects to simplify interpretation. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC). All statistical tests were 2-tailed and significance was determined using $\alpha = 0.05$.

CHAPTER 3

RESULTS

Derivation of Study Cohort and Baseline Characteristics

After excluding patients who had missing baseline PSS-4 assessment (n=21), missing and patients who had missing health status assessment at 12-months (n=194), our final study cohort included 1060 patients. For examining the impact of stress on mortality, only data form patients from US was used, as accurate assessment of mortality was not available for non-US patients (n=303). Figure 5 shows the derivation of the analytical cohorts. Table A-1 compares the differences in the patients who were excluded and those who were not. Patients who were excluded had a higher mean PHQ-8 score and were less likely to have at least high school level of education and have hypertension. There were no significant differences in demographics or prevalence of other comorbidities. In our study cohort 198 patients had averaged PSS-4 score ≥ 6, and 862 patients had averaged PSS-4 scores <6. Mean age was 67.7 ± 9.3 years, 37.1% (n=393) of the patients were females and 82.3% (n=872) were white. Comorbidities were highly prevalent with 80.9% (n=858) patients having hypertension, 19.6% (n=208) having history of myocardial infarction, 32.5% (n=345) having diabetes, 9.7% (n=103) having congestive heart failure, 36.4% (n=386) being active smokers and 14.1% (n=149) having clinically relevant depressive symptoms (PHQ-8 ≥10). 9.7% (n=103) reported not having enough finances left at the end of the month to make ends meet, and 70.1% (n=743) reported having at least high school education.

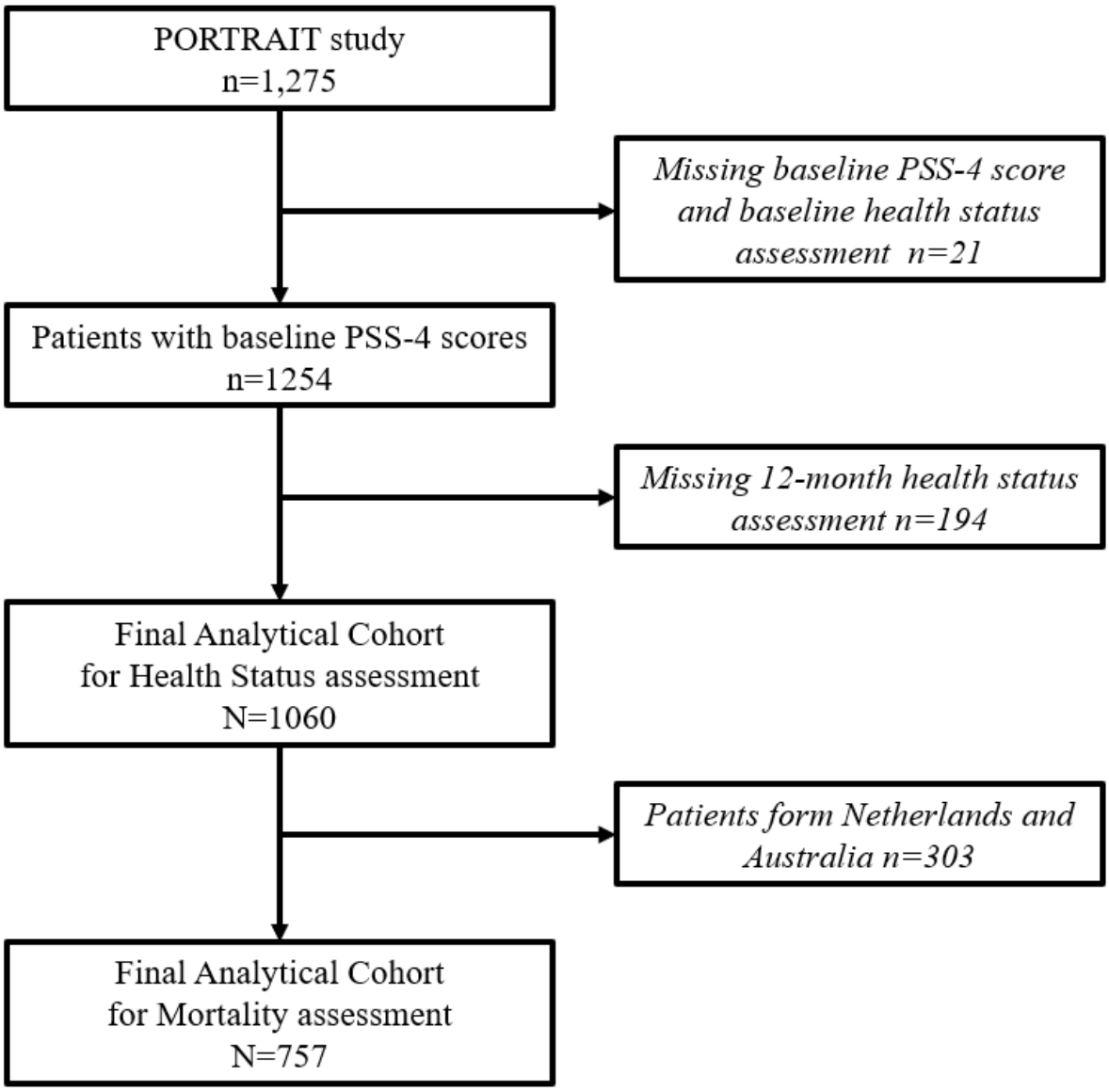


Figure 5: Derivation of analytical cohorts.

Table 3 describes the baseline demographic and clinical characteristics of patients stratified by high (≥6) and low (<6) average PSS-4 score. Patients with high average stress (n=198) were younger, more likely to be females and less likely to be white. Additionally, patients with high average stress had greater prevalence of diabetes, hypertension, congestive heart failure and were less likely to get invasive treatment. There were no significant differences in baseline ABI, and prevalence of cancer and history of myocardial infarction or stroke. More patients with high chronic stress reported not having enough finances left at the end of the month and avoiding care due to costs. Moreover, depressive symptoms were significantly more common in patients with higher stress.

Table 2. Baseline characteristics of patients with high vs low chronic stress level.

	PSS-4 Score ≥ 6 n=198	**PSS-4 Score <6 n=862**	**P value**
Demographics			
Age (Mean ± SD)	65.2 ± 9.5	68.2 ± 9.2	< 0.001
Female Sex (%)	44.9	35.3	0.01
White (%)	70.7	84.9	< 0.001
Comorbidities and treatment (%)			
Current smoker	40.9	35.4	0.32
Diabetes	41.9	30.4	0.001
Hypertension	85.4	79.1	0.02

Congestive Heart Failure	14.6	8.6	0.009
Chronic Kidney Disease	11.6	10.6	0.67
Cancer	11.6	9.6	0.40
Osteoarthritis	8.6	9.2	0.78
Sleep Apnea	11.6	7.8	0.08
Chronic Back Pain	13.6	14.0	0.88
Coronary Artery Disease	51.0	42.7	0.03
History of MI	23.7	18.7	0.11
History of stroke	11.6	11.6	0.81
Invasive Treatment Strategy	18.3	28.2	0.004
ABI (Mean ± SD)	0.65 ± 0.20	0.67 ± 0.18	0.20
Rutherford Classification of Symptoms (%)			
Mild Claudication	16.8	23.9	
Moderate Claudication	45.7	50.0	<0.001
Severe Claudication	37.6	26.1	
Socioeconomic Status (%)			
High school education	73.1	69.9	0.37
Not enough money left at month end	24.4	6.7	<0.001

Avoiding care due to cost	25.0	11.4	<0.001
Work for pay	46.2	36.4	0.25
Depressive Symptoms at Baseline			
PHQ-8 ≥ 10 (%)	41.0	8.2	< 0.001
PHQ-8 (Mean ± SD)	8.5 ± 6.4	3.6± 3.8	< 0.001

Ankle Brachial Index (ABI), Myocardial Infarction (MI), 8-point patient health questionnaire (PHQ-8),

Association of Chronic Stress with Health Status Outcomes

Overall in the study cohort the mean PAQ Summary Score at baseline and 12-month follow-up was 49.6 ± 21.6 and 70.1 ± 25.5 respectively. Mean VAS was 66.6 ± 19.0 at baseline and 70.2 ± 17.8 at 12-month follow-up. Figure 4 describes the trajectories of disease-specific and generic health status in patients with high and low levels of chronic stress. Patients who perceived high levels of chronic stress had poorer disease-specific health status (across all PAQ domains) as well as generic health status (VAS) at baseline and all follow-up assessments.

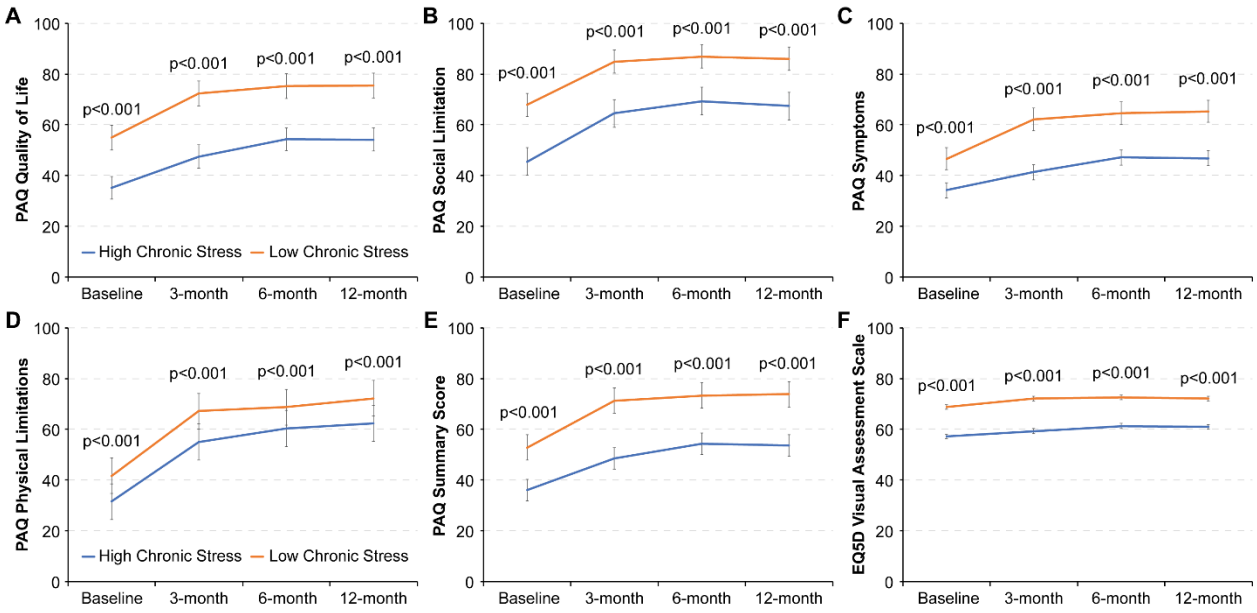


Figure 6. Trajectory of generic and disease-specific health status in patients with high and low chronic stress. [PAQ= Peripheral Artery Disease Questionnaire]

Figure 5 and 6 show the association of average PSS-4 scores with recovery in PAQ summary score and VAS at 12-months. In completely adjusted models accounting for potential confounding factors including patient demographics, comorbidities, disease severity, treatment type and socioeconomic status, higher stress scores were associated with lower PAQ SS (-1.4 points *per +1-point increase in average PSS-4* 95% CI -2.1, -0.6 p <0.001) and VAS (-1.2 points *per +1-point increase in average PSS-4* 95% CI -1.6, -0.8 p <0.001) at 12-months. After accounting for depressive symptoms (by adjusting for averaged PHQ-8 score), the association between chronic stress and 12-month change in PAQ summary score attenuated (-0.10 points per *+1-point increase in PSS-4* 95% CI -0.7, 0.5 p=0.75). However there remained a significant association of chronic stress with 12-month change in VAS (-0.5 points *per +1-point increase in PSS-4* 95% CI -0.9, 0.00 p=0.05).

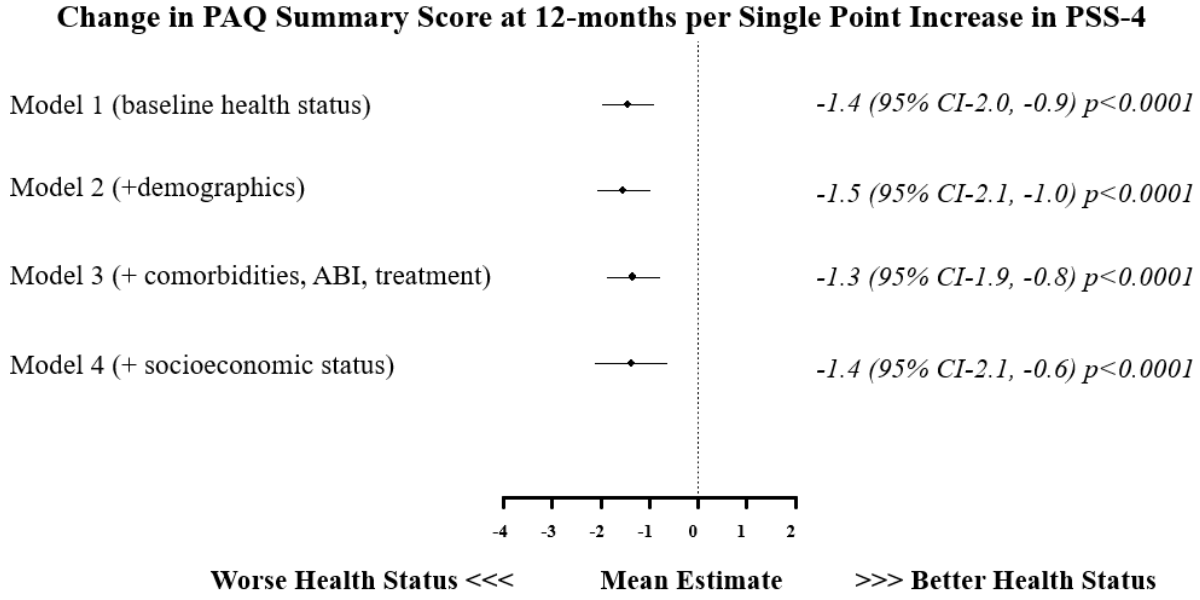


Figure 7. Association of a single point increase in averaged PSS-4 with disease specific health status in patients with peripheral artery disease. [PAQ= Peripheral Artery Disease Questionnaire]

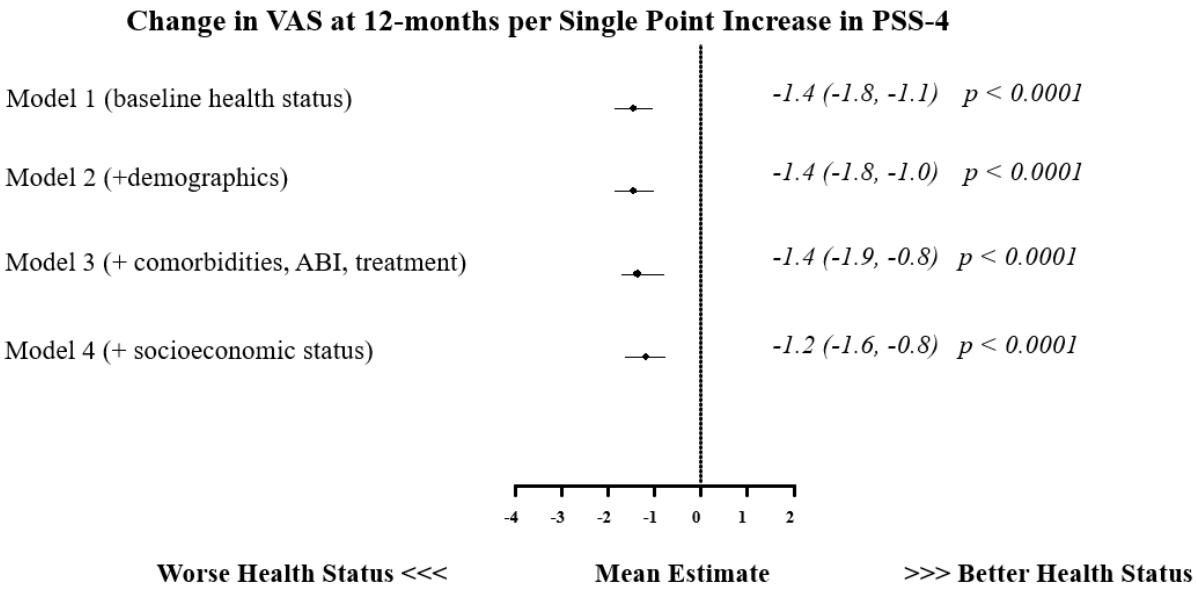


Figure 8. Association of a single point increase in averaged PSS-4 with generic health status in patients with peripheral artery disease.

Association of Chronic Stress with Mortality

In patients who were alive at 12-month follow up the crude (unadjusted) mortality rate over follow-up was was 20.50%. In Figure 7, age-adjusted Kaplan-Meir curves are presented by high vs. low stress level groups. The log-rank test for this comparison was p=0.01.

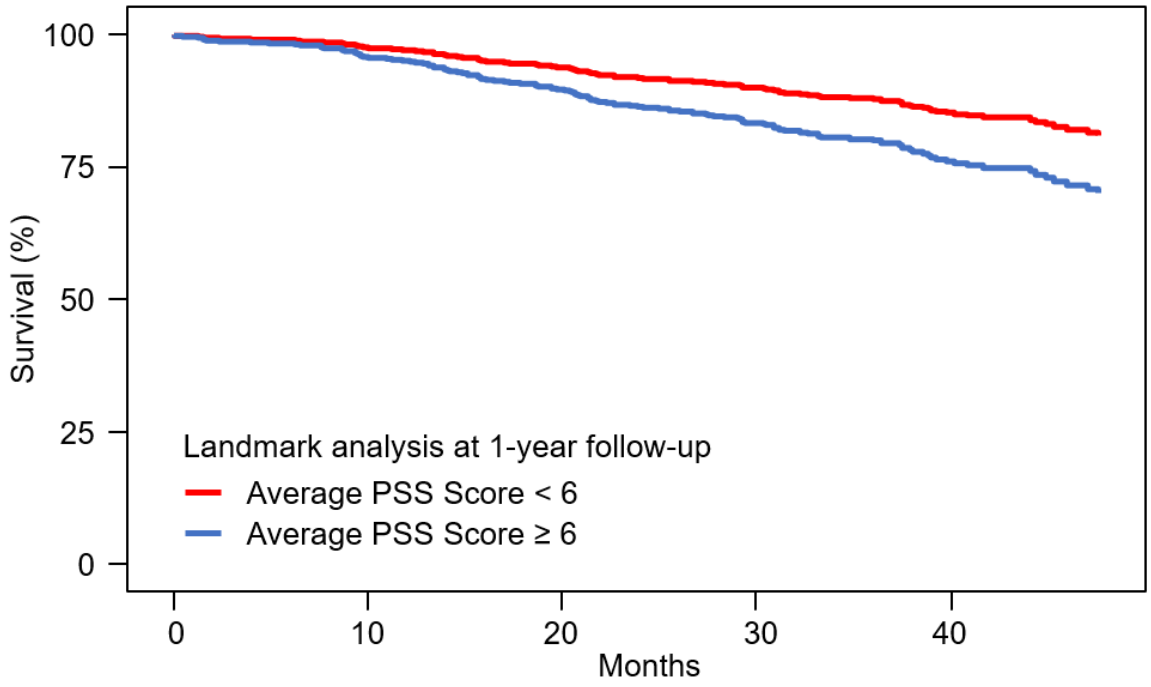


Figure 9. Kaplan Meier survival curve (landmarked at 1-year) in patients with high vs. low averaged stress scores over 1-year follow-up. (4-item Perceived Stress Scale [PSS-4])

Table 5 describes the association of higher average PSS-4 score *(per +1-unit increase)* with mortality. Higher average stress scores over 12-months were associated with greater hazards of mortality, in both only age adjusted model (*hazard ratio per +1 unit increase in average PSS-4* 1.09, 95% CI 1.03, 1.17 p=0.006) and completely adjusted model (*hazard ratio per +1 unit increase in average PSS-4* 1.08, 95% CI 1.01, 1.16 p=0.03).

Table 3. Association of + 1 unit increase in averaged PSS-4 score with all-cause mortality in patients with PAD.

Model	Hazard Ratio (95% CI)	p value
Model 1	1.09 (1.03, 1.17)	0.006
Model 2	1.10 (1.03, 1.18)	0.004
Model 3	1.08 (1.01, 1.158)	0.03
Model 4	1.08 (1.01, 1.16)	0.03

Model 1: unadjusted (except for age and enrollment site), Model 2: additionally, adjusted for sex and race, Model 3: additionally, adjusted for history of diabetes, hypertension, myocardial infarction, congestive heart failure, smoking status, baseline ABI and treatment type. Model 4: additionally, adjusted for SES (highest level of education, avoidance of care due to costs, end of the month financial distress).

To understand if chronic stress had a differential impact on mortality in patients across different age-groups, we did a post-hoc analysis to test the interaction of age with mortality. There was no interaction (p>0.1). However, patients with high chronic levels of stress in the age bracket 61-75 had higher event rates compared with patients having low chronic stress in the same age bracket (18.30-56.80% in high stress vs 8.50-25.50% in low stress groups). Table 4

describes the unadjusted event rates in patients with high and low chronic stress stratified by age groups.

Table 4. Unadjusted Kaplan Meier estimates of event rates in patients with high and low averaged stress score over 1-year follow-up, stress stratified by age quartiles.

	Age 42-60	**Age 61-69**	**Age 70-75**	**Age 76-95**
PSS-4 Score ≥ 6	9.3% (n=71)	18.3% (n=32)	56.8% (n=19)	34.2% (n=25)
PSS-4 Score < 6	8.5% (n=98)	8.5% (n=174)	25.5% (n=155)	34.3% (n=183)

4-item Perceived Stress Scale (PSS-4)

Table A-2 lists all the ICD-10 codes used for cause of death adjudication, stratified by cardiovascular causes, presumed cardiovascular causes and other causes. Cardiovascular causes accounted for 30% (n=46), presumed cardiovascular causes for 4.6% (n=7) and other causes accounted for 65% (n=100) of the deaths respectively.

PHQ-8 and PSS-4 scores were significantly correlated with a shared variance of 29% (Pearson's correlation coefficient 0.54 p<0.001). After accounting for depressive symptoms (by adjusting for averaged PHQ-8 score), the association between chronic stress and 12-month change in PAQ summary score attenuated (-0.10 points per *+1-point increase in PSS-4* 95% CI -0.7, 0.5 p=0.75). However there remained a significant association of chronic stress with 12-month change in VAS (-0.5 points *per +1-point increase in PSS-4* 95% CI -0.9, 0.00 p=0.05). For mortality assessment after adjusting for baseline PHQ-8 score the association of chronic stress with mortality, did not meaningfully change (*hazard ratio per +1 unit increase in average PSS-4* 1.09 95% CI 1.00, 1.18 p=0.06).

CHAPTER 4

DISCUSSION

With a growing population of patients presenting with PAD, it is critical to examine factors associated with worse outcomes as a strategy for identifying potential novel therapeutic strategies to further improve care. In high risk population, such as patients with PAD, decreasing risk of premature mortality is an important focus. Additionally, health status outcomes directly assess the impact of disease's symptoms, function and quality of life, and optimizing health status is an important goal of treatment.[50] In this real-world contemporary registry of patients with new or worsening PAD symptoms, we found that 19% of the patients had high chronic stress levels in the year following their PAD work-up. Higher exposure to chronic perceived stress was significantly associated with both an increased risk of mortality and poorer health status. This relationship was independent of patients' baseline ABI, major comorbidities, treatment type and socio-economic status. Our study demonstrates the prognostic importance of chronic stress in PAD and sets the stage for further exploration into stress reduction programs for PAD populations as a strategy to improve outcomes.

Previous studies have shown that perceived stress and a distressed personality are commonly present in patients with PAD and linked with worse health status and quality of life However these studies have only assessed generic measures of health status and only examined select populations without specifically quantifying patients' chronic mental stress. Our findings substantially extend these insights by using data for patients enrolled at similar time point for progression of PAD (development of new symptoms), use of validated instrument (PSS-4) to assess patients chronic self-perceived stress at multiple assessments over a 12-month follow-up period and looking at longitudinal association with health status and mortality.

Chronic mental stress is associated with development and progression of cardiovascular disease [51]. The mechanisms underlying this association are complex and multi-faceted **(Figure A-3).** These include development of adverse health behaviors such as physical inactivity[20], obesity[22] and smoking.[19] Stress is also associated with pathophysiological pathways leading to development of higher blood pressure[46], insulin resistance[22], enhanced activity of hypothalamic pituitary axis[25], platelet reactivity[23] and inflammation.[26] Moreover, patients with higher stress are less likely to be compliant with treatment and may present with vague symptoms causing treatment delays.[51] Through interplay of these complex processes, stress has been recognized as a strong independent determinant of outcomes in patients with atherosclerotic vascular disease.

Chronic stress can manifest itself in the context of other psychiatric conditions such as depression, or can present itself without having a clinical diagnosis for a mental condition and various idiosyncratic triggers can cause individuals to feel overwhelmed by stress such as marital[28] and financial strain[52], job insecurity[29], etc. It has been shown that high perceived stress is a potent risk factor for the development and progression of coronary artery disease and cardiovascular death.[47,53] Moderate to high mental stress levels at the time of myocardial infarction has been associated with a 40% higher risk of dying in the 2 years following the event.[27] However, interventions to mitigate the impact of stress have shown to improve outcomes. In patients discharged after a myocardial infarction, percutaneous coronary interventions or coronary artery bypass graft surgery, cognitive behavior therapy to equip patients to deal with stress in addition to standard care decreased the risk of mortality and recurrent events.[31] Similarly in patients with stable coronary artery disease transcendental meditation in addition to standard therapy reduced the risk of mortality.[32] Given the strength of the association found in our study and the fact that this risk factor has been largely ignored in the

PAD population, there appears to be an important need for studies to test the efficacy of stress management strategies on cardiovascular outcomes in patients with PAD. Patients with PAD are at high risk of adverse events. Control of traditional risk factors along with strategies to mitigate the impact of non-traditional risk factors such as stress could improve outcomes in this vulnerable population (Figure A-4).

This study should be interpreted within the context of the following limitations. First, the observational design of this study precludes any inferences about causation. In an absence of a randomized clinical trial, it cannot be determined if evidence-based strategies to manage chronic stress will result in improved health status and decrease mortality risk in patients with PAD. However, even after extensively adjusting for factors that could be along the causal pathway between exposure to stress and patient's health status, a significant and strong association with poorer health status and higher mortality risk with higher exposure to stress remained. This sets the stage for future efforts to explore if reduction in patient's chronic stress level can improve outcomes in PAD. Secondly, the sites that recruited patients for the PORTRAIT study may not be representative of other vascular clinics that were not represented in this study.

Conclusion

In a large multi-center contemporary registry of patients presenting with new or worsening symptoms of PAD, we found that high self-perceived stress levels are common in patients with PAD. There is a strong and independent association between higher chronic perceived stress levels in the year following a PAD diagnosis and a higher 4-year mortality risk. Additionally, across a broad spectrum of PAD-specific health status assessments quantifying the impact on patient's symptoms, functioning and quality of life as well as measures of generic health status, recovery in health status in patients with PAD was adversely impacted by higher

chronic self-perceived stress. These findings highlight the potential advantage of employing a more holistic treatment approach that includes assessment and management of patients' mental health, including the experience of chronic stress and such a strategy should be tested to improve the outcomes of patients with PAD.

APPENDIX

Table A-1. Baseline characteristics of patients who were included vs. those who were excluded from the study cohort.

	Included n=1060	**Excluded n=215**	**P value**
Demographics			
Age (Mean ± SD)	67.7 ± 9.3	67.3 ± 10.2	0.63
Female Sex (%)	37.1	41.4	0.23
White (%)	82.2	81.4	0.76
Comorbidities and treatment (%)			
Current smoker	36.4	40.9	0.22
Diabetes	32.6	36.3	0.29
Hypertension	80.9	74.4	0.03
Congestive Heart Failure	9.7	11.2	0.52
Chronic Kidney Disease	11.0	10.6	0.25
Cancer	10.0	10.7	0.76
Osteoarthritis	9.0	10.2	0.59
Sleep Apnea	8.5	6.0	0.23
Chronic Back Pain	14.0	12.1	0.47
History of MI	19.6	15.8	0.19
History of stroke	11.1	13.5	0.32
Invasive Treatment Strategy	24.4	26.6	0.42
ABI (Mean ± SD)	0.67 ± 0.19	0.66 ± 0.19	0.91

Socioeconomic Status (%)			
High school education	70.1	60.5	0.02
Not enough money left at month end	9.7	14.4	0.12
Avoiding care due to cost	13.9	14.4	0.80
Depressive Symptoms at Baseline			
PHQ-8 (Mean ± SD)	4.5 ± 4.8	5.9± 5.9	<0.001

Ankle Brachial Index (ABI), Myocardial Infarction (MI), 8-point patient health questionnaire (PHQ-8),

Table A-2. All ICD-10 codes for cardiovascular cause, probable cardiovascular cause and non-cardiovascular cause of death.

Cause of Death Categorization	ICD-10 codes
Cardiovascular	I251, I250, I219, I500, I255, I259, I119, I214, I248, I469, I509, I519,
Presumed Cardiovascular	I615, I739, I269, I64, I672
Non-Cardiovascular	I729, J151, J690, J841, K529, K566, K819, L039, M628, M869, N19, N288, N482, R092, R99, V092, X00, I272, I38, I210. G939, G062, J440, J961, J969, K559, N179, N185, N189, A047, B182, C169, C181, C189, C229, C23, C56, C80, C845, C911, C920, D381, D469, D649, D869, E117, A419, C259, C900, E149, G20, I48, C61, E119, E142, E785, G931, J449, C349
International Classification of Disease (ICD)	

Figure A-1. Peripheral Artery Disease Questionnaire.

The following questions refer to blockages in the arteries of your body, particularly your legs, and how that might affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Blockages in the arteries, often referred to as **peripheral vascular disease**, affect different people in different ways. Some feel cramping or aching while others feel fatigue. Which leg (or buttock) causes you the most severe **discomfort, fatigue, pain, aching, or cramps**?

the **Right** leg (buttock)	the **Left** leg (buttock)	**Both** are the same	Neither
☐	☐	☐	☐

2. Please review the list below and indicate how much limitation you have due to **your peripheral vascular disease** (discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)) over the past 4 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Walking around your home	☐	☐	☐	☐	☐	☐
Walking 1-2 blocks on **level ground**	☐	☐	☐	☐	☐	☐
Walking 1-2 blocks **up a hill**	☐	☐	☐	☐	☐	☐
Walking 3-4 blocks on level ground	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐
Vigorous work or exercise	☐	☐	☐	☐	☐	☐

7. How satisfied are you that everything possible is being done to treat your **peripheral vascular disease**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. How satisfied are you with the explanations your doctor has given you about your **peripheral vascular disease**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Overall, how satisfied are you with the current treatment of your **peripheral vascular disease**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

10. Over the past 4 weeks, how much has your **peripheral vascular disease** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

11. If you had to spend the rest of your life with your **peripheral vascular disease** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

12. Over the past 4 weeks, how often have you felt discouraged or down in the dumps because of your **peripheral vascular disease**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

13. How much does your **peripheral vascular disease** affect your lifestyle? Please indicate how your **discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)** may have limited your participation in the following activities over the past 4 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐

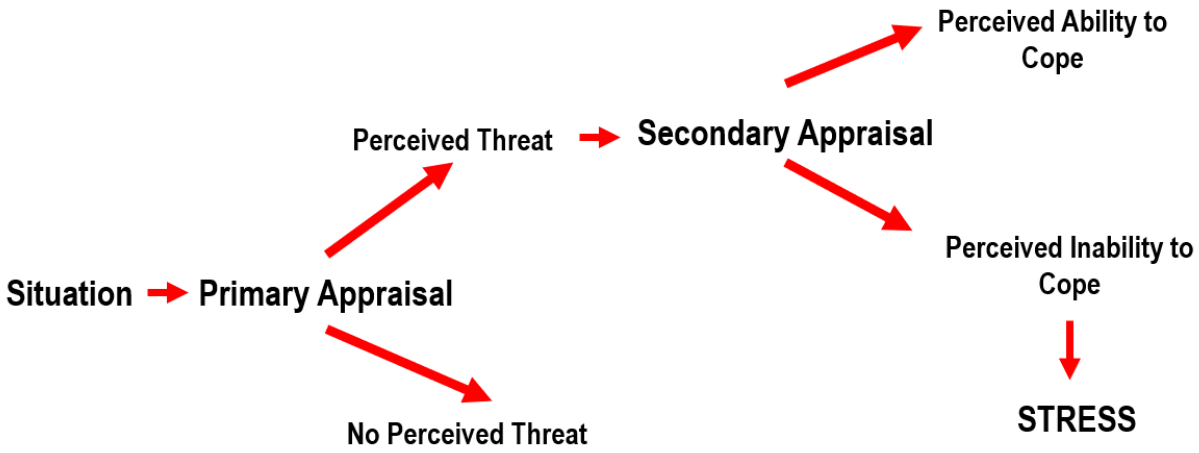


Figure A-2. Transactional Model of Stress

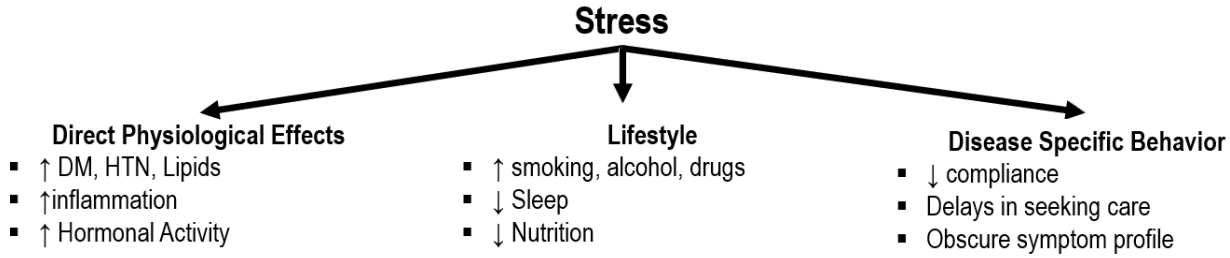


Figure A-3. Mechanisms by which chronic stress impacts risk of adverse outcomes in patients with peripheral artery disease.

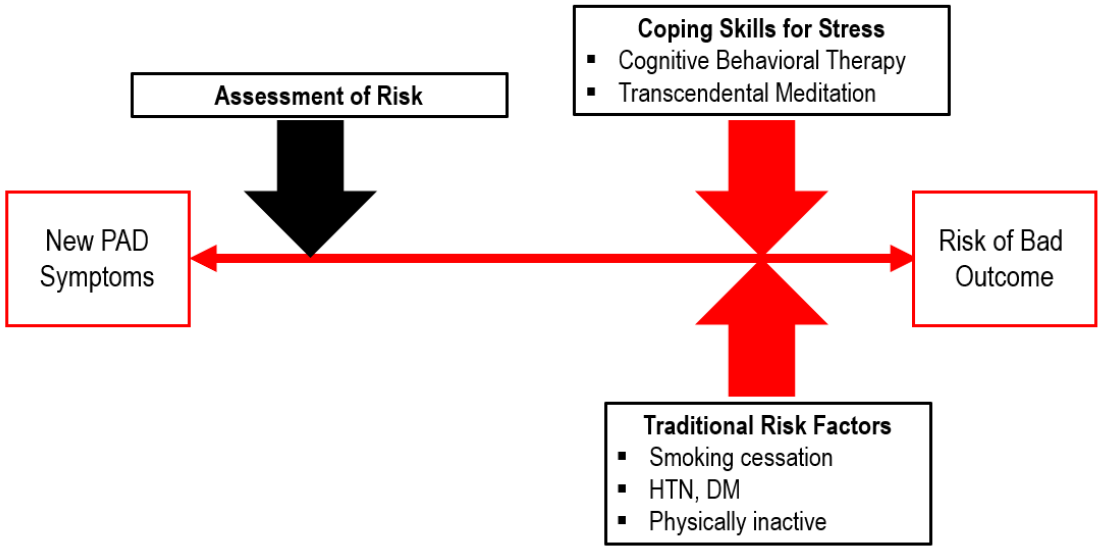


Figure A-4 Control of risk factors over time to improve outcomes in patients with peripheral artery disease.

Figure A-5 SAS code

EXCLUSIONS

```
AverageStressScore = mean(pssscore_b, pssscore_3, pssscore_6, pssscore_12);
label averagestressscore = 'Average PSS Score over 12 months';

if not missing(Averagestressscore) then do;
if averagesgressscore>=6 then avgpsspos = 1;
else avgpsspos = 0;
label avgpsspos = 'Average PSS Score >= 6';
format avgpsspos yesno.;
end;

if country = 1 then do;
        if trttype = 1 then invtrt_3 = 0;
        if trttype in (2,3) then invtrt_3 = 1;
end;
if country in (2,3) then invtrt_3 = invasivetrt_3;
run;
ods rtf file = "Exclusions &bettersysdate..rtf";
title 'Overall PORTRAIT Cohort';
proc sql;
select count (distinct ptid)
from portrait.patients;
quit;

title 'Have PSS Score at baseline';
proc sql;
select count (distinct ptid)
from portrait.patients
where not missing(pssscore_b);
quit;

title 'Have Baseline PAQ Summary Scores';
proc sql;
select count (distinct ptid)
from portrait.patients
where not missing(pssscore_b) and not missing(paqsumm_b);
quit;

title 'Have 12 month score';
proc sql;
select count (distinct ptid)
from portrait.patients
where  not missing(pssscore_b) and not missing(paqsumm_b) and not missing(paqsumm_12);
quit;
```

```
title;
ods rtf close;
```

BASELINE CHARACTERISTICS BY AVERAGE STRESS GROUPS

```
*Categorical variable - chi square test;
proc freq data=portrait.thesis;
tables sex*psspos_b/chisq;
run;

*Continuous variable - t test;
proc ttest data=portrait.thesis;
class psspos_b;
var age;
run;

%report;
%set(data=portrait.thesis, columns=psspos_b\_total_, statndec=2, stat=meanpmsd mediqr, stddiff
= t);
%table;
%section('Demographics');
%stat(age);
%freq(sex);
%freq(racewhite);
%freq(currentsmoker);
%freq(hxdm);
%freq(hxhtn);
%freq(hxchf);
%freq(hxckd);
%freq(hxcancer);
%freq(hxosteoarth);
%freq(hxsleepap);
%freq(hxbackpain);
%freq(hxcad);
%freq(hxmi);
%freq(hxcvatia);
%freq(invtrt_3);
%stat(abivalue);
%freq(educhs_b);
%freq(notenoughfinance);
%freq(Avoidcarecost_b);
%freq(workforpay);
%freq(phq8depr_b);
%stat(phq8score_b);
%endtable;
%endreport;
```

LINEAR REGRESSION MODELS FOR HEALTH STATUS

MODEL 1 UNADJUSTED

PAQ

```
title1 'PAQ Summary';
title2 'Unadjusted - no spline';
proc glimmix data=portrait.thesis;
class siteid;
model paqsumm_12  = averagestressscore_w paqsumm_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```

EQ5D VAS

```
proc glimmix data=portrait.thesis;
class siteid;
model eq5d_12  = averagestressscore_w eq5d_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```

MODEL 2 ADJUSTED FOR DEMOGRAPHICS

PAQ

```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country;
model paqsumm_12  = AverageStressScore_w paqsumm_b age sex racewhite country;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
```

EQ5D VAS

```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country;
model eq5d_12  = AverageStressScore_w eq5d_b age sex racewhite country;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```

MODEL 3 ADJUSTED FOR COMORBID CONDITIONS AND TREATMENT

PAQ

```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country currentsmoker hxhtn hxmi hxdm hxchf;
model paqsumm_12  = AverageStressScore_w paqsumm_b age sex racewhite country
currentsmoker hxhtn hxmi hxdm hxchf abivalue invtrt_3;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
```

```
ods select modelinfo tests3 estimates;
run;
```
EQ5D VAS
```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country;
model eq5d_12  = AverageStressScore_w eq5d_b age sex racewhite country;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```

MODEL 4 ADJUSTED FOR SOCIOECONOMIC STATUS
PAQ
```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country currentsmoker hxhtn hxmi hxdm hxchf notenoughfinance
educhs_B avoidcarecost_b;
model paqsumm_12  = AverageStressScore_w paqsumm_b age sex racewhite country
currentsmoker hxhtn hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B
avoidcarecost_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
```
EQ5D VAS
```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country currentsmoker hxhtn hxmi hxdm hxchf notenoughfinance
educhs_B avoidcarecost_b;
model eq5d_12  = AverageStressScore_w eq5d_b age sex racewhite country currentsmoker
hxhtn hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B avoidcarecost_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```

MODEL 5 ADJUSTED FOR BASELINE DEPRESSION
```
title2 'Adjusted for baseline depression score';
proc glimmix data=portrait.thesis;
class siteid sex racewhite country currentsmoker hxhtn hxmi hxdm hxchf notenoughfinance
educhs_B avoidcarecost_b;
model paqsumm_12  = AverageStressScore_w paqsumm_b age sex racewhite country
currentsmoker hxhtn hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B
avoidcarecost_b phq8score_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
run;
```
EQ5D

```
proc glimmix data=portrait.thesis;
class siteid sex racewhite country currentsmoker hxhtn hxmi hxdm hxchf notenoughfinance
educhs_B avoidcarecost_b;
model eq5d_12  = AverageStressScore_w eq5d_b age sex racewhite country currentsmoker
hxhtn hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B avoidcarecost_b
phq8score_b;
random intercept/subject=siteid;
estimate 'Average Stress Score per 1 pt increase' AverageStressScore_w 1/cl;
ods select modelinfo tests3 estimates;
```

MORTALITY

EXCLUSIONS

```
Data mortality2; set mortality;
if country = 1;
if not missing (pssscore_b);
AverageStressScore = mean(pssscore_b, pssscore_3, pssscore_6, pssscore_12);
label averagestressscore = 'Average PSS Score over 12 months';
* 48 month mortality;
if landmarkmo>48 then do;
        landmarkmo48=48; fdeath48=0;
end;
        else do landmarkmo48=landmarkmo; fdeath48=fdeath_ndi; end;
data numbermissing; set mortality2;
nummiss = nmiss(of pssscore_b pssscore_3 pssscore_6 pssscore_12);
run;
proc freq data=numbermissing;
tables nummiss;
run;
ods rtf file = "Missing mortality data &bettersysdate..rtf";
proc means data=mortality2 n nmiss;
var age sex racewhite currentsmoker hxhtn hxmi hxdm hxchf abivalue invtrt_3
notenoughfinance educhs_B avoidcarecost_b;
run;
data missing; set portrait.thesis;
nummiss = nmiss(of age sex racewhite currentsmoker hxhtn hxmi hxdm hxchf abivalue
notenoughfinance educhs_b avoidcarecost_b phq8score_b invtrt_3);
run;
proc freq data=missing;
```

MORTALITY BY AGE GROUPS

```
%cut(Data=mortality2, var=age, ngroups = 4, cutvar = agequart);
proc phreg data=mortality2;
class agequart avgpsspos/ref=first;
model landmarkmo48*fdeath48(0) = agequart|avgpsspos;
strata siteid;
estimate 'Age 42-61: Stressed vs not' avgpsspos 1  /exp cl;
```

```
estimate 'Age 61-69: Stressed vs not' avgpsspos 1 agequart*avgpsspos 1 0 0 /exp cl;
estimate 'Age 69-75: Stressed vs not' avgpsspos 1 agequart*avgpsspos 0 1 0/exp cl;
estimate 'Age 75-94: Stressed vs not' avgpsspos 1 agequart*avgpsspos 0 0 1/exp cl;
*ods select modelinfo nobs globaltests parameterestimates;
```

COX MODELS

```
model landmarkmo48*fdeath48(0) = averagestressscore|age/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
run;
```

UNADJUSTED

```
ods rtf file = "Mortality models &bettersysdate..rtf";
title 'Unadjusted';
proc phreg data=mortality2;
model landmarkmo48*fdeath48(0) = averagestressscore/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
run;
```

MODEL 1 ADUSTED FOR AGE

```
title 'Adjusted for age';
proc phreg data=mortality2;
model landmarkmo48*fdeath48(0) = averagestressscore age/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
run;
```

MODEL 2 ADJUSTED SEX AND RACE

```
proc phreg data=mortality2;
class sex racewhite/ref=first;
model landmarkmo48*fdeath48(0) = averagestressscore age sex racewhite/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
```

MODEL 3 ADJUSTED FOR COMORBIDITIES AND TREATMENT TYPE

```
proc phreg data=mortality2;
class sex racewhite currentsmoker hxhtn hxmi hxdm hxchf invtrt_3/ref=first;
model landmarkmo48*fdeath48(0) = averagestressscore age sex racewhite currentsmoker hxhtn
hxmi hxdm hxchf abivalue invtrt_3/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
run;
```

MODEL 4 ADJUSTED FOR SOCIOECONOMIC STATUS

```
proc phreg data=mortality2;
class sex racewhite currentsmoker hxhtn hxmi hxdm hxchf invtrt_3 notenoughfinance educhs_B
avoidcarecost_b/ref=first;
model landmarkmo48*fdeath48(0) = averagestressscore age sex racewhite currentsmoker hxhtn
hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B avoidcarecost_b/rl;
strata siteid;
```

```
ods select modelinfo nobs globaltests parameterestimates;
```
MODEL 5 ADJUSTED FOR BASELINE DEPRESSION
```
proc phreg data=mortality2;
class sex racewhite currentsmoker hxhtn hxmi hxdm hxchf invtrt_3 notenoughfinance educhs_B
avoidcarecost_b/ref=first;
model landmarkmo48*fdeath48(0) = averagestressscore age sex racewhite currentsmoker hxhtn
hxmi hxdm hxchf abivalue invtrt_3 notenoughfinance educhs_B avoidcarecost_b
phq8score_b/rl;
strata siteid;
ods select modelinfo nobs globaltests parameterestimates;
```
KAPLAN MEIER ANALYSIS

UNADJUSTED KM CURVE
```
title 'Unadjusted';
title2 'Stress binary';
proc lifetest data=mortality2 timelist = 0 to 48 by 6;
time landmarkmo48*fdeath48(0);
strata avgpsspos;
```
AGE ADJUSTED
```
proc phreg data=mortality2 plots(overlay)=survival;
  class avgpsspos;
  model landmarkmo48*fdeath48(0)=age avgpsspos;
  baseline covariates=mortality2 outdiff=Diff1 survival=_all_/diradj group=avgpsspos;
```

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VITA

Ali Osama Malik was born on July 28th 1988 in Islamabad, Pakistan. After middle school education at Bahria College and high school at Beconhouse School, he went on to medical school at the Aga Khan University Medical College in Karachi, Pakistan. He successfully completed his degree in 2012.

After completing his medical school Dr. Ali Malik went on to the University of Reno (Las Vegas campus) where he began his internal medicine residency, which was completed in 2017. During his time at University of Reno, Dr. Malik was inducted in the Alpha Omega Alpha Honors Medical Society. Dr. Malik, proceeded to work at the University of Nevada Las Vegas, as a chief resident during the academic year 2017-8. In 2018 Dr. Malik started a 2-year NIH-T32 research fellowship in cardiovascular outcomes research at the University of Missouri-Kansas City (UMKC) and Saint-Luke's Mid- America Heart Institute during which he was also enrolled in the Masters of Science in Bioinformatics program at the UMKC. Upon completion of his outcomes research fellowship, Dr. Malik will begin clinical cardiology training at University of Missouri-Kansas City and Saint Luke's Mid America Heart Institute. After completing his cardiology training, Dr. Malik will do additional training in Interventional Cardiology. Dr. Malik hopes to positively impact patients' lives' directly as a clinician and hopes to improve many lives indirectly through his research.

Dr. Malik is a member of the American College of Cardiology and the American Heart Association.