January 2024

Latent Health Status Trajectory Modelling In Patients With Symptomatic Peripheral Artery Disease

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LATENT HEALTH STATUS TRAJECTORY MODELLING IN PATIENTS WITH SYMPTOMATIC PERIPHERAL ARTERY DISEASE

A Thesis Submitted to the Yale University School of Medicine

in Partial Fulfillment of the Requirements for the Doctor of Medicine Degree and

Masters of Health Science Degree

by

Scott Grubman 2024

LATENT HEALTH STATUS TRAJECTORIES IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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For patients with peripheral artery disease (PAD) and symptoms of intermittent claudication, treatment is geared towards maximizing health status and minimizing disease progression. We aimed to phenotype health status trajectories over the first 12 months of specialty care and examine factors associated with nonresponsiveness to treatment. Adults with new or worsening exertional leg symptoms presenting to vascular clinics in the United States, Australia, and Netherlands 2011-2015 were included. Patients with non-compressible ankle-brachial index, critical limb ischemia, barriers to consent, or lacking at least one follow-up interview were excluded. The Peripheral Artery Questionnaire (PAQ; range 0-100, higher = better) was used to capture disease-specific health status at baseline and during 3-, 6-, and 12-month follow-up visits. Latent trajectory modeling was used to delineate latent trajectory subgroups based on heterogeneity in longitudinal PAQ scores. Trajectories were classified as either "Responsive" or "Nonresponsive" by achievement of

a mean ≥10-point improvement by the 12-month visit. Medical and psychosocial factors associated with a Nonresponsive trajectory were assessed by hierarchical multivariable logistic regression with a random effect for site. Of 2,917 eligible patients, 1,204 (41.3%) were included in the final cohort. The cohort was 62.5% male with a mean age of 67.5±9.4. Latent trajectory modelling revealed 5 subgroups: the High (n=401, 33.3%), Intermediate (n=400, 33.2%), Low (n=150, 12.5%), Sustained Response (n=98, 8.1%), and Transient Response (n=155, 12.9%) groups with +16.8, +59.4, +24.0, +8.6, and +7.6 score changes at 12-months, respectively. Following a Nonresponsive trajectory (Low or Transient Response) was associated with depressive symptom burden, however the effect did not remain significant after sequential adjustment for age, sex, race, country, baseline PAQ, and revascularization. Individuals with new or worsening PAD symptoms receiving specialty care exhibit diverse recovery trajectories. Roughly 1 in 4 experiences no meaningful improvement in health status at 12 months. Addressing psychosocial factors alongside medical comorbidities in an integrated care system may improve outcomes in PAD.

ACKNOWLEDGEMENTS

I extend heartfelt gratitude to Drs. Mena-Hurtado, MD, and Smolderen, PhD, for their unwavering mentorship, guidance, and advocacy throughout my completion of the work comprising this thesis as part of the Yale VAMOS lab. I would also like to thank Dr. Geirsson, MD, for lending his continued expertise and perspective to the thesis committee and the refinement of my project. I would also like to thank the amazing members of the VAMOS lab—particularly Gaëlle Romain, PhD, Jake Cleman, MD, and Lindsey Scierka, MD, for fostering a collaborative and supportive environment for learning and growth on my research journey.

This work received funding through the Yale School of Medicine One-Year Medical Student Research Fellowship with grant support from the National Heart, Lung and Blood Institute of the National Institutes of Health. The content is the sole responsibility of the authors and does not represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Table of Contents

INTRODUCTION **1**

Peripheral Artery Disease 1
Intermittent Claudication 2
Treatment Options 2
Patient Reported Outcomes and Health Status 3
Latent Variables and Latent Trajectory Modelling Techniques 4

STATEMENT OF PURPOSE **6**

METHODS **6**

Student Contributions 6
Ethics Statement 7
Human Subjects Research 7
Methods Description 7
Study Population *7*
Study Outcome *9*
Latent Trajectory Modeling *9*
Statistical Methods 10
Determining Latent Trajectory Shape *10*
Determining Number of Latent Trajectory Subgroups *11*
Determining Random Effect Structure *11*
Model Adequacy Testing *12*
Other Statistical Analysis *12*
Handling of Missing Data *13*
Software *14*

RESULTS **14**

Study population *14*
Latent Trajectory Modelling *15*
Responsive vs. Nonresponsive Trajectories *15*

DISCUSSION **16**

CHALLENGES AND LIMITATIONS **19**

CONCLUSIONS **20**

DISSEMINATION **21**

FIGURES AND TABLES **22**

REFERENCES **37**

INTRODUCTION

Peripheral Artery Disease

Lower extremity peripheral artery disease (PAD) is marked by atherosclerosis from the aortoiliac to pedal arteries. An ankle brachial index (ABI) ≤0.9 or toe-brachial index ≤0.7 in patients with artificially elevated ABI values is diagnostic for PAD.[1] PAD is the third most common manifestation of systemic atherosclerotic disease behind only coronary artery disease and stroke.[2] The condition affects an estimated >230 million worldwide, and disproportionally impacts those living in low to middle income countries in regions such as southeast Asia or the western Pacific.[1,2] PAD is highly prevalent in the United States, affecting an estimated 8.5 million individuals over the age of 40 domestically.[3] Given screening for PAD is not often conducted in the primary care setting and a large portion of patients with PAD remain asymptomatic, it is likely many individuals suffering from PAD go underdiagnosed and undertreated.[4-6] Even in those who are asymptomatic, PAD is associated with an increased risk for amputation, heart attack, stroke, and death.[7,8]

Risk factors for PAD include those common to coronary atherosclerotic disease including age, male sex, hypertension, hypercholesterolemia, diabetes, chronic kidney disease, and smoking.[3] Additional, PAD has also been associated with sedentary lifestyle and markers of systemic inflammation.[9] There is some evidence PAD is heritable. For instance, a study of 1,464 twins enrolled in the Swedish Twin Registry monozygotic twins had the odds ratio (OR) for concordance (OR=17.7), followed by dizygotic twins (OR=5.7) with an estimated 58% of the effect attributable to genetics.[10] PAD burden also differs substantially by race and ethnicity. For instance, amongst a study of 403 patients from the Houston Veterans Affairs Medical Center and the Harris County Hospital District, rates of

PAD were nearly two-fold higher in the African Americans compared to either Whites or Hispanics.[6] Moreover, based on national readmissions data from 2011-2017, Hispanics represented 12-16% of annual admissions with PAD and had higher rates of amputations (32% vs. 21%, d=0.31) than their non-Hispanic White counterparts.[11]

Intermittent Claudication

PAD may cause an array of debilitating symptoms related to large vessel obstruction and resultant oxygen supply and demand mismatch in leg skeletal muscle including intermittent claudication, rest pain, ulcer formation, and tissue loss.[12] Intermittent claudication, or exertional leg pain that resolves with rest, is the most common symptom of PAD and can significantly impact patients' functional capacity and quality of life.[13] Intermittent claudication may present with atypical symptoms, which may be more likely based on a patient's age, sex, comorbid conditions, and other behavioral or patient-specific factors.[14] Under current clinical classification systems, the presence of PAD with either typical or atypical claudication corresponds to Fontaine II or Rutherford I-III disease.[15]

Treatment Options

For patients presenting to specialty care for intermittent claudication, first-line treatments include cardiovascular risk factor management (e.g. treatment of hypertension, diabetes, dyslipidemia), lifestyle modifications (e.g. counseling on smoking cessation), and supervised exercise programs.[1] Because only a small portion of patients with intermittent claudication go on to develop critical limb ischemia (CLI), invasive revascularization is typically reserved for improving health status in those with particularly-limiting symptoms

refractory to conversative management, rather than for limb salvage.[16] Revascularization can be performed endovascularly using an evolving array of catheters, balloons, and stents to expand the lumen and modify plaque.[15] Surgery remains an important alternative for patients with PAD, and can be performed via endarterectomy, bypass, or through hybrid approaches.[17] Several studies have demonstrated an association between the reception of early revascularization (e.g. ≤3 months of initial presentation) and health status benefits for patients at an aggregate level, however identifying which individuals in the clinic stand to gain the most from more invasive treatment remains a challenge that limits the shared decision-making process.[18-21]

Patient Reported Outcomes and Health Status

Patient reported outcome measures (PROMs) are assessment tools that, as their name implies, come directly from the patient without interpretation or modification from a healthcare professional—often taking the form of a survey or questionnaire.[22] PROMs are frequently used to capture patients' health status, which is defined as the combination of a patient's self-perceived physical, emotional, and social wellbeing. Health status measures are used across many domains of medicine, and have increasingly been utilized in randomized controlled trials and prospective studies in patients with PAD to assess the effectiveness of different treatment options from the patient perspective.[18,20,21] PROMs measuring health status are particularly crucial for the study of those with intermittent claudication, as these health status measures are closely aligned with the overarching goals of treatment: reducing symptom burden and improving quality of life. One such PROM is the Peripheral Artery Questionnaire (PAQ). The PAQ is a 20-item survey among the most

reliable, sensitive, and well-validated measures of disease-specific health status in patients with PAD.[23-27] PAQ scores serve as a composite metric spanning the subdomains of physical limitation, symptoms, symptom stability, social and emotional function, treatment satisfaction, and quality of life. PAQ scores range from 0 to 100, with higher scores indicating better PAD-specific health status.

Latent Variables and Latent Trajectory Modelling Techniques

Studies measuring health status over time at the aggregate level provide limited insight into individual clinical trajectories, rehabilitations phenotypes, and their multi-risk profiling. Whereas traditional longitudinal modelling approaches can provide good a "birds-eye" view of the average effects or general patterns over time for a population, latent variables can be used to characterize clinical phenotypes at a more granular level based on patterns of change in a continuous variable over time. Latent variables are unobserved, meaning they are estimated during the modelling process. Longitudinal finite mixture modelling (FMM) is one application of latent variables in which one assumes the population being studied actually consists of a finite mixture of subgroups, each consisting of individuals that tend to behave more similarly to each other than they do to the wider population. In each of the three common applications of FMM discussed below, each subgroup is represented by a different level of a latent categorical variable included in the model.[28] The sample of patients in each subgroup in a longitudinal FMM can be referred to as latent trajectory subgroup.

In its simplest form, longitudinal FMM is referred to as group-based trajectory modelling (GBTM). In GBTM all individuals in a latent trajectory subgroup are

considered to be homogenous. Furthermore, equal variance is assumed across time and between latent subgroups.[28] GBTM was first applied to model physical aggression over time in adolescents in the Montreal Longitudinal-Experimental Study.[29] It has since been applied in various medical contexts—including in the study of cardiovascular disease. For instance, GBTM has been used to separately examine trajectories of both heart rate and serum sodium in patients with heart failure and to explore associations between these latent subgroups and adverse outcomes.[30,31] Latent class growth analysis (LCGA) is a slightly more complex form of longitudinal FMM compared to GBTM. Unlike GBTM, variance is freely estimated across both time and latent subgroups.

Growth mixture modeling (GMM) is the most complex form of FMM, and unlike GBTM and LCGA does not assume homogeneity within subgroups. Instead, GMM accounts for intra-group (random) effects alongside inter-group (fixed) effects. However, the increased sophistication and potential to fit complex study populations of GMM comes at the cost of model complexity and increased computational demand.[28] A model that might take minutes to hours to estimate using GBTM may take hours or days using GMM. As such, GMM is less frequently encountered in the medical literature.

All 3 modelling approaches (GBTM, LCGA, and GMM) were considered for this project. However, as patients with peripheral artery disease are known to be a highly heterogenous population with diverse disease experiences and evolving symptoms, the authors ultimately decided the increased flexibility and fewer restrictions imposed by GMM were worth the relatively high computational costs. Interestingly, as will be discussed in the methods section, the systematic GMM framework utilized by this study

involved the initial estimation of GBTMs. GBTMs were then expanded to GMMs by adding random effects and testing different variance-covariance structures.

STATEMENT OF PURPOSE

Leveraging the GMM approach to latent trajectory modelling, the present study aimed to 1) phenotype typical health status trajectories over the first year of care for patients with PAD presenting with new or worsening intermittent claudication and 2) investigate baseline medical and psychosocial factors associated with following a responsive vs. nonresponsive health status trajectory, as distinguished by achievement of meaningful health status improvement at 12 months.

METHODS

Student Contributions

The study question was generated by SG and further refined by KS and CM. SG was responsible for overall study design under the guidance of KS and CM. SG was responsible for preparation of institutional review board and internal study proposals. SG was responsible for all statistical coding, including that for data cleaning, preliminary data analysis, latent trajectory modelling, multiple imputation, and hierarchical mixed multivariate logistic regression analysis. Example code for data cleaning, preliminary analysis, and multiple imputation was provided by GR along with coding and statistical troubleshooting support. SG generated all tables and figures, prepared all presentations, abstracts, posters, related to this thesis work. SG was responsible for writing this thesis and a manuscript pending journal submission.

Ethics Statement

This study involved patients enrolled in the prospective PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) registry, which has been detailed elsewhere.[32] The PORTRAIT study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of all participating sites. The present study was granted exception status by the Yale University institutional review board. Two authors (SG, GR) had full access to the data and take responsibility for its integrity and analysis.

Human Subjects Research

All patients enrolled in the PORTRAIT study provided written informed consent prior to participation. Data were collected and stored in a Health Insurance Portability and Accountability Act – compliant manner. All data were accessed securely.

Methods Description

Study Population

Patients ≥18-years-old with new or worsening PAD symptoms (Fontaine II or Rutherford I-III) and a resting ankle-brachial index (ABI) ≤0.90 or with significant drops in post-exercise ankle pressure (≥20 mmHg) presenting to 16 specialty clinics across the United States, the Netherlands, and Australia between June 2011 and December 2015 were included as part of the PORTRAIT study. Patients were excluded for noncompressible ABI (≥1.30), ipsilateral leg revascularization within a year, current critical limb ischemia (Fontaine III-IV or Rutherford IV-VI), current incarceration, hearing impairment, language

barriers (non-English, Spanish, or Dutch-speaking), inability to provide written informed consent, prior enrollment in the study, or for not completing at least one follow-up interview.

Baseline demographics, medical comorbidities, and PAD diagnostic criteria were collected by medical record abstraction. Socioeconomic factors including self-reported race, marital status, completion of secondary education, employment status, insurance status, and degree of economic burden from accessing care (5-point Likert scale ranging from "not at all" to "severe") were collected during a standardized interview prior to treatment initiation.

A baseline psychosocial profile consisting of patient-reported depressive symptoms, anxiety symptoms, perceived stress symptoms, and degree of social support was obtained through administration of the 8-Item Patient Health Questionnaire (PHQ-8), the Generalized Anxiety Disorder 2-Item (GAD-2), the Perceived Stress Scale (PSS), and the ENRICHD Social Support Instrument (ESSI), respectively.[33-37] The PHQ-8 consists of 8 items each scored from 0 to 3, with a higher score indicating more frequent depressive symptoms.[34] The GAD-2 is a brief anxiety screening tool with 2 items, each scored 0 to 3; a higher score indicates more frequent anxiety symptoms.[35] The PSS is a 10-item questionnaire with scores ranging from 0 to 40, with a higher score indicating more perceived stress.[36] The ESSI consists of 7-items, and scores can be interpreted as indicating either "low" or "adequate" levels of social support.[37]

To evaluate the potential influence of an initial invasive vs. non-invasive treatment plan on health status trajectories, data on reception of early revascularization was collected. Early revascularization was defined as reception of any lower-extremity percutaneous

transluminal angioplasty, stenting, endarterectomy, or surgical bypass procedure prior to or at the 3-month follow-up visit. In the United States, treatment data was captured through medical record abstraction and during the 3-month interview. In the Netherlands and Australia, treatment modality was captured through focused interviewing at the 3-month visit alone.

Study Outcome

The primary outcome for this study was PAD-specific health status, as captured by the Peripheral Artery Questionnaire (PAQ) summary score at baseline and during 3-, 6-, and 12-month follow-up visit interviews. The PAQ is a 20-item patient reported outcome measure that is among the most reliable, sensitive, and well-validated measures of disease-specific health status in patients with PAD.[23-27] The summary score serves as a composite across the subdomains of physical limitation, symptoms, symptom stability, social and emotional function, treatment satisfaction, and quality of life. The PAQ summary score ranges from 0 to 100, with higher scores indicating better PAD-specific health status.

Latent Trajectory Modeling

A latent trajectory model was constructed and used to identify subgroups of patients following distinct PAQ summary score trajectories over the first 12 months of specialty care. To enhance methodological replicability and transparency, the modelling process followed that proposed by Lennon *et. al.* to determine optimal trajectory shape, the number of latent subgroups, and random effect and variance-covariance structure in a stepwise, iterative manner (detailed below in Statistical Methods).[38] At each of the aforementioned

decision points, multiple candidate models were estimated and compared using Bayesian Information Criterion (BIC)—a measure of model fit and parsimony for which smaller values are favored. The final analytic model (*Model H*) was subjected to several adequacy assessments prior to analysis including an average posterior probability >0.7, an odds of correct classification of >5 within each class, and mismatch approximating 0.[38]

Responsive vs. Nonresponsive Trajectories

Mean PAQ score changes from baseline to 12 months were obtained for each latent trajectory subgroup specified. Trajectory subgroups were categorized as either "Responsive" or "Nonresponsive" based on whether or not they achieved a mean PAQ increase of ≥10 points at 12 months. This threshold was chosen as the previously established minimally clinically important difference (MCID) for the PAQ summary score in this population.[39] An MCID represents the smallest increment of change in a patient reported outcome measure considered meaningful from the patient perspective.

Statistical Methods

Determining Latent Trajectory Shape

Latent trajectory shape was first selected by estimating several scoping models (*intercept, quadratic, cubic, quartic)* using the '*hlme'* linear mixed model function from the '*lcmm'* package, with a consistent number of groups (3) and a model name representing the degree of the trajectory polynomial shape with respect to time. These provisional models included fixed effects only. The authors believed starting with 3 groups was appropriate as it would capture health status trajectories that were positive, intermediate,

and negative over time. Polynomial degrees ranged from intercept-only to quartic. To avoid local maxima, initialization values were drawn from a random matrix of coefficients from corresponding 1 group models for each structure. This process was repeated 200 times for each model specification, with 20 iterations allowed for each repetition. The repetition with the lowest log likelihood was estimated with an allowance of to 500 iterations for convergence. Coefficients were allowed to freely vary between all latent classes. The model shape with the lowest Bayesian Information Criterion (BIC), a measure balancing model fit with complexity, was selected to represent the optimal degree polynomial for the final analytic model—in this case, a cubic model was favored.

Determining Number of Latent Trajectory Subgroups

The number of latent trajectory subgroups was chosen by estimating and comparing fixed effect-only models with cubic shape with anywhere G=1 to G=5 groups (*cubic1-cubic5*). Models with G≥5 were not run due to concern over lack of interpretability and subgroup sizes too small to be clinical meaningful or interpretable. The *cubic5*, G=5 model was selected for further refinement and inclusion of random effects based on its favorable BIC.

Determining Random Effect Structure

Models with increasing complex random effect structures ranging from degree 0 (intercept-only) to cubic were estimated with either a constrained variance-covariance between groups (i.e. “fixed”) or class-specific variance-covariance (“not fixed”). The final analytic model was chosen based on several criteria: convergence within 500 iterations,

lower BIC, higher relative entropy, latent subgroup sizes ≥5% of the total cohort, and clinical plausibility upon graphing of both predicted and smoothed mean trajectories over 12 months.

Model Adequacy Testing

Model adequacy was assessed using the '*LCTMtoolkit'* function, ensuring an odds of correct classification (OCC) >5 within each class, an average posterior probability of assignment (APPA) >0.7, and mismatch approximating 0. After checking OCC, APPA, and mismatch values, patients were assigned modally to class for which they have the highest posterior probability of assignment.

Other Statistical Analysis

Characteristics of the overall cohort and of each individual trajectory subgroup identified by *Model H* were compared. Continuous variables were reported as means with standard deviations (SD). Categorical variables were reported as counts with percentages. Differences between trajectory subgroups were assessed using one-way analysis of variance for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Differences were considered statistically significant at $p<0.05$. Subsequent pairwise comparisons were made using standardized differences (Cohen's *d*).[40,41] Standardized differences correspond to "small", "moderate", and "large" effect sizes at |d| thresholds of 0.2, 0.5, and 0.8, respectively. Pairwise differences with $|d|\geq0.2$ were considered significant and reported.

Baseline characteristics were also compared between Responsive and Nonresponsive pooled groups using standardized mean differences as above. Predictors of following a Responsive vs. Nonresponsive trajectory were assessed by a hierarchical multivariate logistic regression with a random effect by site. Medical risk factors for PAD (hypertension, dyslipidemia, diabetes, smoking, chronic kidney disease) and psychosocial markers that could plausibly modulate health status (PHQ-8 score, GAD-2 score, PSS score, low social support on ESSI, and moderate/severe economic burden imposed by accessing care) were included as covariates in the model. The model was sequentially adjusted for demographic variables (age, sex, white vs. nonwhite race, country), then baseline PAQ score, and finally reception of early revascularization. The results were reported as odds ratios (OR) with 95% confidence intervals (95% CI) and p-values.

Handling of Missing Data

The latent trajectory modelling process used the full information maximum likelihood method, which accommodated for missing PAQ scores.[42] No PAQ scores were missing at baseline, 44 (3.7%) were missing at 3 months, 116 (9.6%), were missing at 6 months, and 135 (11.2%) were missing at 12 months. The maximum missingness rate for covariates in the logistic regression was 5.8% for GAD-2 score. These missing data were handled through multiple imputation by chained equations, with point estimates and variances pooled across 50 imputed datasets using Rubin's combination rules.[43,44] The quadratic rule was used to ensure the minimum number of imputations required for stable measures of uncertainty and replicability of results was exceeded.[45]

Software

Latent trajectory modelling was performed with R Statistical Software version 4.2.2 (R Core Team. 2022. Vienna, Austria: R Foundation for Statistical Computing) using the packages '*lcmm 2.0.0'* and '*LCTMtools'*.[38,42,46] All further analyses were performed using STATA version 17 (StataCorp. 2021. College Station, TX: StataCorp LLC).

RESULTS

Study population

Of 2,917 eligible patients, a total of 1,713 (58.7%) were excluded (**Figure 1**). The final cohort of 1,204 patients was 62.5% male, 82.1% white, and had a mean age of 67.5±9.4 years (**Table 1**). At the time of baseline interview, 69.2% of patients had completed secondary education, 15.0% were currently employed, 56.7% were married, 23.8% were living alone, and 16.6% had low social support. Only 0.7% lacked insurance, however 11.4% reported accessing specialty care was either a "moderate" or "severe" financial burden. The study cohort had high rates of medical comorbidities including hypertension (80.4%), dyslipidemia (79.6%), diabetes (33.0%), and chronic lung disease (17.3%). Many patients had a history of prior heart attack (18.9%) or stroke (7.8%) and over half (51.1%) had a smoking history. Nearly 1 in 8 (11.9%) had a history of a depressive disorder. A total of 313 (26.0%) patients received revascularization within 3 months of initiating specialty care.

Latent Trajectory Modelling

At the end of the stepwise modeling process, *Model H* was selected to serve as the final analytic model due to its favorable BIC, adequate trajectory subgroup sizes (smallest > 5% of total cohort), and clinical plausibility. Selection criteria used in this process are detailed in **Table 2**. *Model H* identified 5 latent trajectory subgroups, coined the Low (n = 150, 12.5%), Intermediate (n = 400, 33.2%), High (n = 401, 33.3%), Sustained Response (n = 98, 8.1%), and Transient Response (n = 155, 12.9%) trajectory subgroups based on their respective appearances (**Figure 2).** Baseline characteristics stratified by individual latent trajectory subgroup are compared in **Table 3**.

Responsive vs. Nonresponsive Trajectories

The High, Intermediate, and Sustained Response latent trajectory subgroups had predicted mean PAQ changes from baseline to 12 months of +16.8 , +24.0, and +59.4 points, respectively, and were therefore considered Responsive trajectories. The Low and Transient Response trajectory subgroups had PAQ changes that did not meet the MCID threshold for improvement at only +8.6 and +7.6 points, respectively, and were therefore considered Nonresponsive.

Compared to their Nonresponsive counterparts, patients following Responsive trajectories were more often male (65.9% vs. 52.8%, *d*=0.268), white (85.0% vs. 73.8%, *d*=0.280), married (60.1% vs. 46.5%, *d*=0.275), employed (17.0% vs. 9.2%, *d*=0.231) and less often experienced either low social support (13.9% vs. 24.5%, *d*=0.275) or moderate to severe economic burden from medical care (9.3% vs. 17.8%, *d*=0.305) (**Table 4**). They also had lesser rates of medical comorbidities including hypertension (78.2% vs. 86.9%,

d=0.230), diabetes (30.3% vs. 41.0%, *d*=0.230), and sleep apnea (6.5% vs. 13.8%, *d*=0.245). Patients following Responsive trajectories less often carried a formal diagnosis of alcohol use disorder (4.7% vs. 9.8%, *d*=0.200) or depression (9.7% vs. 18.4%, *d*=0.252) and had more favorable baseline PHQ-8, GAD-2, and PSS scores (all $d \geq 0.2$). Of note, while patients who received early revascularization experienced a +30.9 (±24.6) point change at 12 months compared to +16.7 (±23.5) in patients who had not, there was no difference in the number of patients who received early revascularization between patients following Responsive and Nonresponsive trajectories (26.0% vs. 25.9%, *d*=-0.003).

On hierarchical multivariate logistic regression, following a Nonresponsive trajectory was initially significantly associated with higher depressive symptom burden at baseline as measured by PHQ-8 score (OR=1.14, 95% CI=1.10-1.19, p<0.001) (**Table 5**). This association was largely unchanged after adjustment for age, sex, race, and country (OR=1.14, 95% CI=1.09-1.18, p<0.001), however did not remain significant after further adjustment for baseline PAQ score alone, or for both baseline PAQ score and reception of early revascularization (**Figure 3**).

DISCUSSION

Using a patient-centered longitudinal modelling approach, this study of 1,204 individuals presenting with new or worsening symptoms of peripheral artery disease demonstrated that paths towards recovery after initiating specialty care are diverse. Approximately 1 in 4 individuals in the study belonged to a latent health status trajectory subgroup demonstrating no meaningful improvement of disease-specific health status at 12 months. Nonresponsiveness to treatment was found to be associated with a higher depressive symptom burden at baseline, not with medical comorbidities such as smoking

status, hypertension, dyslipidemia, diabetes, or chronic kidney disease. This association was at least partially explained by baseline PAQ score as evidenced by the results of our hierarchical multivariate logistic regression.

Our findings are novel as they capture and characterize the diverse health status trajectories patients with new or worsening symptoms of PAD experience at the level of the individual patient. We demonstrate that baseline psychosocial factors including depressive symptoms and disease-specific health status are associated with patient-perceived responsiveness to treatment in a way that traditional cardiovascular risk factors are not—despite their emphasis in current treatment paradigm and integral role to the development and progression of atherosclerotic plaque.

The observation that higher depressive symptom burden at baseline predicts poor recovery trajectory after initiating specialty care prior to adjusting for baseline PAQ score is consistent with growing evidence pointing to depression as an independent risk factor for claudication symptoms, major adverse cardiovascular events, and mortality in patients with PAD.[47-49] It is also in line with previously established associations between higher depressive symptom burden and diminished health status benefits from interventions such as revascularization in the PAD population.[50] The negative effect of depression on outcomes in PAD is likely at least partially explained by psychosocial barriers to medication adherence, exercise, or other optimal health-related behaviors in patients with depression.[51] Vascular inflammatory markers associated with chronic stress conditions have also been shown to predict quality-of-life changes after endovascular treatment in patients with PAD, suggesting the relationship between the conditions is likely more complex.[52] The attenuation of the association between depressive symptomatology and

baseline PAD-specific health status observed in this study supports that the two processes are inter-related, and likely exert an interactive effect on patient-perceived treatment benefits. The importance of deepening our understanding of the interaction between PAD and depression is underscored by their high co-prevalence: roughly 1 in 5 patients with PAD has been found to be diagnosed with depression, and some suggest the condition is underdiagnosed and undertreated in those with PAD.[53]

Although the association between several traditional cardiovascular risk factors and following a Responsive vs. Nonresponsive latent health status trajectory did not reach statistical significance in our study, it is worthwhile to note that the presence of several comorbidities—hypertension, diabetes, chronic kidney disease, and smoking—appeared to broadly favor following a Nonresponsive latent health status trajectory in our analysis. These conditions are all closely linked to an increased risk of adverse outcomes including amputations and mortality in PAD.[54,55] Moreover, the presence of these medical comorbidities may contribute to the persistence or worsening of ischemic symptoms by contributing to the development of atherosclerotic plaque or microvascular dysfunction.[54,56-59] This hypothesis is supported by the observation that patients with concurrent PAD and diabetes tend to have lower disease-specific health status than their counterparts with PAD alone.[60]

Despite advances in our understanding of PAD, substantial gaps and disparities persist.[61] Preventative therapies are broadly underutilized, with another study of PORTRAIT participants demonstrating that less than a third of active smokers received a referral for cessation counseling upon initiation of care and 72% continued to smoke at 12 months.[62] Although a recent Scientific Statement from the American Heart Association

focused on screening for socioeconomic factors and improving the delivery of preventative services in PAD, no emphasis was placed on the evaluation and treatment of psychological factors that may hinder treatment response in the PAD population. The implementation of additional system-level changes to PAD care models, such as integrated psychosocial care, may present an opportunity to improve patient-centered outcomes and is an exciting potential avenue of further research.

CHALLENGES AND LIMITATIONS

The results of this study should be considered in the context of several challenges and limitations. First, there was a relative underrepresentation of female, nonwhite, and uninsured individuals in the study cohort, which limits the generalizability of our results to these populations. As highlighted in a recent Scientific Statement from the American Heart Association, the prevalence of PAD differs across ex, race, and ethnicity.[61] For instance, the authors found while studies screening for PAD using ABI ≤0.9 often find equivalent prevalence between sexes (~3-4.5% in those aged ≥40 years), studies involving symptomatic PAD often demonstrated a higher prevalence in men.[61]

Moreover, this study did not involve patients who were either asymptomatic or had active critical limb ischemia, as defined by the presence of rest pain, non-healing ulcers, or tissue loss in the afflicted limb. These patients have different manifestation of PAD compared to those suffering from intermittent claudication. Thus, findings from this study cannot be applied to these subsets of patients with PAD.

Similarly, as this study only collected PAQ scores during the first 12 months of treatment, extrapolation beyond this timepoint is not possible. Our understanding of longer-term health status outcomes in patients with PAD remains limited, although some evidence

suggests early PAQ scores (measured at baseline and 3-month) may maintain prognostic significance for predicting 5-year survival in patients with symptomatic PAD.[63]

Finally, the observational nature of our findings prohibits causal inference by introducing the possibility of confounding between observed and/or unobserved covariates. For instance, it is difficult to decipher the exact relationship between disease-specific health status (PAQ) and depressive symptomatology (PHQ-8) and their collective relationship with belonging to a responsive vs. nonresponsive latent trajectory subgroup from the results of this study alone. It is also baseline PAQ score is related to an unmeasured factor, such as macrovascular disease severity or the presence of microvascular dysfunction, that might make symptoms more or less refractory to medical, endovascular, or surgical intervention. For instance, patients with PAD and multilevel disease have previously been observed to have the lowest adjusted average PAQ summary score over the first year or specialty treatment, although overall patients with claudication had similar health status on presentation by level of disease.[64]

CONCLUSIONS

This work demonstrates that health status trajectories for patients with symptomatic PAD are heterogenous. Not all patients can or should be expected to follow the same clinical pattern after initiating specialty care. Roughly a quarter of patients demonstrated poor health status responsiveness to treatment after one year, which was found to be associated with factors including worse depressive symptoms at baseline and baseline PAQ score. Further emphasis should be placed on screening for psychosocial barriers to treatment response.

DISSEMINATION

The work comprising this project was presented as a poster at the Yale School of Medicine Student Research Day on May 9, 2023. It was also presented as a poster at the American Heart Association's Scientific Sessions in Philadelphia, Pennsylvania on November 11, 2023. A manuscript based on this work is pending submission for publication in a peer-reviewed journal.

FIGURES AND TABLES

Table 1: Baseline demographic, psychosocial, medical, and treatment characteristics with missingness rates for final analytic cohort.

Variable	Overall (n=1,204)	Missing (n, %)
Age (mean, SD)	67.54 (9.37)	0
Male	753 (62.5)	0
White	989 (82.1)	0
Married	679 (56.7)	6 (0.5)
Living Alone	341 (28.3)	0
Secondary Education	826 (69.2)	10 (0.8)
Employed	180 (15.0)	4 (0.3)
Insured	1,195 (99.3)	0
Economic Burden of Care		8 (0.7)
Moderate/Severe	137 (11.5)	
Somewhat	132 (11.0)	
A Little	140 (11.7)	
Not at All	787 (65.8)	
Smoking History	615 (51.1)	0
Hypertension	968 (80.4)	0
Dyslipidemia	958 (79.6)	0
BMI (mean, SD)	28.98 (6.10)	262 (21.8)
Diabetes	397 (33.0)	0
Diabetic Neuropathy	40 (3.3)	0
Heart Failure	124 (10.3)	0
Atrial Fibrillation	136 (11.3)	0
Heart Attack	228 (18.9)	0

Stroke	94 (7.8)	0
Chronic Kidney Disease	133 (11.0)	0
Chronic Lung Disease	208 (17.3)	0
Sleep Apnea	100 (8.3)	0
Cancer	121 (10.0)	0
Chronic Back Pain	165 (13.7)	0
Osteoarthritis	112 (9.3)	0
Depression	143 (11.9)	0
Alcohol Use Disorder	72 (6.0)	0
EQ-5D (mean, SD)	66.09 (19.36)	70 (5.8)
PHQ-8 (mean, SD)	4.71 (5.00)	29 (2.4)
GAD-2 (mean, SD)	1.04 (1.58)	9 (0.7)
Low Social Support	198 (16.6)	9 (0.7)
PSS (mean, SD)	3.97 (3.43)	15 (1.2)
Early Revascularization	313 (26.0)	0
PAQ Baseline (mean, SD)	49.22 (21.72)	0
PAQ 3 Months (mean, SD)	66.67 (24.70)	44 (3.7)
PAQ 6 Months (mean, SD)	69.73 (24.42)	116 (9.6)
PAQ 12 Months (mean, SD)	70.25 (25.42)	135 (11.2)

All values are presented as n (%), unless otherwise specified. Abbreviations: BMI = body mass index; EQ-5D = European Quality of Life-5 Dimension; ESSI = ENRICHD Social Support Instrument; GAD-2 = Generalized Anxiety Disorder 2-Item; PAQ = Peripheral Artery Questionnaire; PHQ-8 = 8-Item Patient Health Questionnaire (PHQ-8); PSS = Perceived Stress Scale (PSS); SD = Standard deviation.

Table 2: Selection criteria used in latent trajectory modelling process

Model	G	Cov	BIC	*X*	% G1	% G2	% G3	% G4	% G5
intercept	3	-	41001.1	0.70	13.2	58.6	28.2	-	-
linear	3	-	40380.4	0.74	13.7	58.3	28.0	-	-
quadratic	3	-	39990.2	0.76	57.1	14.0	28.9	-	-
cubic	3	-	39930.2	0.76	30.1	55.6	14.2	-	-
quartic	3	-	39940.7	0.77	56.2	14.0	29.7	-	-
cubic1	1	-	41622.9	1.00	100	-	-	-	-
cubic2	2	-	40153.7	0.84	71.1	28.9	-	-	-
cubic3	3	-	39930.2	0.76	30.1	55.6	14.2	-	-
cubic4	4	-	39889.1	0.71	13.1	14.0	19.4	53.5	-
cubic5	5	-	39857.5	0.73	13.0	2.2	15.3	28.7	40.8
Model A	5	-	39857.5	0.73	13.0	2.2	15.3	28.7	40.8
Model B	5	-	39857.5	0.73	13.0	15.3	28.7	2.2	40.8
Model C	5	fixed	39746.5	0.73	58.1	4.7	4.0	23.0	10.2
Model D	5	free	39736.2	0.68	43.0	2.4	9.9	36.5	8.2
Model E	5	fixed	39791.4	0.70	2.6	7.6	24.3	12.5	53.0
Model F	5	free	39723.7	0.69	3.9	9.8	39.5	42.9	3.9
Model G	5	fixed	39810.8	0.70	8.1	12.5	54.2	2.2	23.1
Model H	5	free	39723.2	0.67	12.9	12.5	33.3	8.1	33.2
Model I	5	fixed	39826.4	0.69	15.7	5.1	18.6	10.2	50.3
*Model J**	5	free	-	-	-	-	-	-	-

Final analytic model highlight grey. *Model failed to converge.
Abbreviations: BIC=Bayesian Information Criterion; Cov=covariance structure (fixed or free); G=groups; *X*=model entropy.

Table 3: Baseline characteristics stratified by individual trajectory subgroup

Variable	Transient Response	Low	High	Sustained Response	Intermediate	p-Value	Pairwise Comparisons
Age (mean, SD)	68.33 (9.81)	65.20 (10.56)	68.66 (8.71)	65.78 (10.30)	67.42 (8.93)	0.001	a,e,g,h
Male	88 (56.8)	73 (48.7)	298 (74.3)	53 (54.1)	241 (60.3)	< 0.001	b,e,g,h,i
White	116 (74.8)	109 (72.7)	350 (87.3)	86 (87.8)	328 (82.0)	< 0.001	b,c,e,f,g,i
Married	85 (56.3)	54 (36.5)	258 (64.3)	52 (53.1)	230 (57.5)	< 0.001	a,e,f,g,h,i
Living Alone	42 (27.1)	54 (36.0)	101 (25.2)	26 (26.5)	118 (29.5)	0.145	
Secondary Education	118 (76.1)	94 (64.4)	285 (72.0)	69 (70.4)	260 (65.2)	0.047	a,d,i
Employed	17 (11.0)	11 (7.3)	71 (17.7)	21 (21.6)	60 (15.1)	0.006	c,e,f,g
Insured	153 (98.7)	147 (98.0)	401 (100.0)	97 (99.0)	397 (99.3)	0.039*	e
Economic Burden							
Moderate/Severe	16 (10.3)	38 (25.5)	34 (8.6)	11 (11.2)	38 (9.5)	< 0.001	a,e,f,g,i
Somewhat	21 (13.5)	17 (11.4)	35 (8.9)	10 (10.2)	49 (12.3)		
A Little	17 (11.0)	25 (16.8)	30 (7.6)	11 (11.2)	57 (14.3)		

Not at All	101 (65.2)	69 (46.3)	296 (74.9)	66 (67.3)	255 (63.9)		
Smoking History	86 (55.5)	57 (38.0)	210 (52.4)	49 (50.0)	213 (53.3)	0.014	a,e,g
Hypertension	135 (87.1)	130 (86.7)	298 (74.3)	77 (78.6)	328 (82.0)	0.001	b,e,i
Dyslipidemia	129 (83.2)	122 (81.3)	313 (78.1)	74 (75.5)	320 (80.0)	0.53	
BMI (mean, SD)	29.04 (6.07)	30.59 (7.86)	27.85 (4.98)	28.72 (6.20)	29.53 (6.18)	< 0.001	e,i
Diabetes	58 (37.4)	67 (44.7)	112 (27.9)	23 (23.5)	137 (34.3)	< 0.001	b,c,e,f,g,j
Diabetic Neuropathy	6 (3.9)	9 (6.0)	6 (1.5)	2 (2.0)	17 (4.3)	0.042*	e,i
Heart Failure	21 (13.5)	16 (10.7)	32 (8.0)	10 (10.2)	45 (11.3)	0.34	
Atrial Fibrillation	24 (15.5)	13 (8.7)	45 (11.2)	7 (7.1)	47 (11.8)	0.238	
Heart Attack	35 (22.6)	38 (25.3)	61 (15.2)	16 (16.3)	78 (19.5)	0.05	b,e,
Stroke	17 (11.0)	18 (12.0)	25 (6.2)	6 (6.1)	28 (7.0)	0.094	e
Chronic Kidney Disease	23 (14.8)	20 (13.3)	35 (8.7)	5 (5.1)	50 (12.5)	0.047	b,c,f,j
Chronic Lung Disease	24 (15.5)	40 (26.7)	46 (11.5)	19 (19.4)	79 (19.8)	< 0.001	a,e,h,i
Sleep Apnea	21 (13.5)	21 (14.0)	19 (4.7)	8 (8.2)	31 (7.8)	< 0.001	b,d,e,g

Cancer	21 (13.5)	19 (12.7)	32 (8.0)	13 (13.3)	36 (9.0)	0.15	
Chronic Back Pain	18 (11.6)	33 (22.0)	38 (9.5)	13 (13.3)	63 (15.8)	0.002	a,e,i
Osteoarthritis (hip or knee)	14 (9.0)	15 (10.0)	33 (8.2)	9 (9.2)	41 (10.3)	0.898	
Depression	18 (11.6)	38 (25.3)	26 (6.5)	8 (8.2)	53 (13.3)	< 0.001	a,b,e,f,g,i
Alcohol Use Disorder	13 (8.4)	17 (11.3)	10 (2.5)	12 (12.2)	20 (5.0)	< 0.001	b,e,g,h,j
PHQ-8 (mean, SD)	6.01 (5.41)	9.52 (6.28)	2.23 (2.74)	5.15 (4.83)	4.78 (4.51)	< 0.001	a,b,d,e,f,g,h,i
GAD-2(mean, SD)	1.28 (1.62)	2.34 (2.06)	0.46 (1.04)	1.09 (1.54)	1.02 (1.52)	< 0.001	a,b,e,f,g,h,i
Low Social Support (ESSI)	23 (15.0)	51 (34.2)	31 (7.8)	12 (12.2)	81 (20.4)	< 0.001	a,b,e,f,g,i
PSS (mean, SD)	4.10 (3.32)	6.75 (4.15)	2.70 (2.77)	4.43 (3.48)	4.03 (3.08)	< 0.001	a,b,e,f,g,h,i
Early Revascularization	51 (32.9)	28 (18.7)	105 (26.2)	53 (54.1)	76 (19.0)	< 0.001	a,c,d,f,h,I,j

*Fisher's exact test used. All values are presented as n (%), unless otherwise specified. For pairwise comparisons, letters listed denote comparisons where standardized difference $|d| \geq 0.2$: a = Transient Response vs. Low; b = Transient Response vs. High; c = Transient Response vs. Sustained Response, d = Transient Response vs. Intermediate; e = Low vs. High; f = Low vs. Sustained Response; g = Low vs. Intermediate; h = High vs. Sustained Response, i = High vs. Intermediate; j = Sustained Response vs. Intermediate. BMI=body mass index; EQ-5D=European Quality of Life-5 Dimension; ESSI=ENRICHD Social Support Instrument; GAD-2=Generalized Anxiety Disorder 2-Item; PAQ=Peripheral Artery Questionnaire; PHQ-8=8-Item Patient Health Questionnaire (PHQ-8); PSS=Perceived Stress Scale (PSS).

Table 4: Baseline characteristics stratified by reponsiveness to treatment at 12 months

	Nonresponsive (n=305, 25.3%)	Responsive (n=899, 74.7%)	Cohen's *d*
Age (mean, SD)	66.79 (10.29)	67.79 (9.03)	-0.104
Male	161 (52.8)	592 (65.9)	0.268
White	225 (73.8)	764 (85.0)	0.28
Married	139 (46.5)	540 (60.1)	0.275
Living alone	96 (31.5)	245 (27.3)	0.093
Secondary Education	212 (70.4)	614 (68.8)	0.036
Employed	28 (9.2)	152 (17.0)	0.231
insured	300 (98.4)	895 (99.6)	0.118
Economic Burden of Care			
Moderate/Severe	54 (17.8)	83 (9.3)	0.305
Somewhat	38 (12.5)	94 (10.5)	
A Little	42 (13.8)	98 (11.0)	
Not at All	170 (55.9)	617 (69.2)	
Smoking History	143 (46.9)	472 (52.5)	0.113
Hypertension	265 (86.9)	703 (78.2)	0.23
Dyslipidemia	251 (82.3)	707 (78.6)	0.092
BMI (mean, SD)	29.77 (6.99)	28.70 (5.73)	0.167
Diabetes	125 (41.0)	272 (30.3)	0.225
Diabetic Neuropathy	15 (4.9)	25 (2.8)	0.111
Heart Failure	37 (12.1)	87 (9.7)	0.079

Atrial Fibrillation	37 (12.1)	99 (11.0)	0.035
Heart Attack	73 (23.9)	155 (17.2)	0.166
Stroke	35 (11.5)	59 (6.6)	0.172
Chronic Kidney Disease	43 (14.1)	90 (10.0)	0.126
Chronic Lung Disease	64 (21.0)	144 (16.0)	0.128
Sleep Apnea	42 (13.8)	58 (6.5)	0.245
Cancer	40 (13.1)	81 (9.0)	0.131
Osteoarthritis (hip or knee)	29 (9.5)	83 (9.2)	0.009
Chronic Back Pain	51 (16.7)	114 (12.7)	0.114
Depression	56 (18.4)	87 (9.7)	0.252
Alcohol Use Disorder	30 (9.8)	42 (4.7)	0.2
PHQ-8 (mean, SD)	7.74 (6.10)	3.68 (4.07)	0.783
GAD-2 (mean, SD)	1.80 (1.92)	0.78 (1.36)	0.614
Low Social Support (ESSI)	74 (24.5)	124 (13.9)	0.272
PSS (mean, SD)	5.40 (3.97)	3.48 (3.08)	0.542
Early Revascularization	79 (25.9)	234 (26.0)	0.003

All values are presented as n (%), unless otherwise specified. BMI = body mass index; EQ-5D = European Quality of Life-5 Dimension; ESSI = ENRICHD Social Support Instrument; GAD-2 = Generalized Anxiety Disorder 2-Item; PAQ = Peripheral Artery Questionnaire; PHQ-8 = 8-Item Patient Health Questionnaire (PHQ-8); PSS = Perceived Stress Scale (PSS); SD = Standard deviation.

Table 5: Hierarchical Multivariate Logistic Regression for Nonresponsive Trajectory Membership

Variable	OR	[95% CI]		*p*	OR	[95% CI]		*p*
Hypertension	1.44	0.93	2.24	0.102	1.25	0.80	1.95	0.326
Dyslipidemia	1.02	0.68	1.53	0.916	0.97	0.64	1.46	0.878
Diabetes	1.26	0.92	1.71	0.151	1.22	0.90	1.67	0.204
Chronic Kidney Disease	1.42	0.91	2.22	0.121	1.32	0.84	2.06	0.227
Smoking	1.18	0.73	1.91	0.498	1.38	0.84	2.27	0.208
PHQ-8	1.14	1.10	1.19	<0.001*	1.14	1.09	1.18	<0.001*
GAD-2	1.09	0.97	1.21	0.150	1.09	0.98	1.22	0.125
PSS	1.02	0.97	1.08	0.371	1.02	0.97	1.08	0.402
Low Social Support (ESSI)	1.12	0.76	1.65	0.571	1.09	0.74	1.62	0.658
Moderate/Severe Economic Burden	0.91	0.79	1.04	0.166	0.91	0.79	1.04	0.154
Age	-	-	-	-	1.01	0.99	1.03	0.256
Female Sex	-	-	-	-	1.22	0.90	1.67	0.206
White Race	-	-	-	-	0.77	0.51	1.17	0.219
United States	-	-	-	-	[reference group]			
Netherlands	-	-	-	-	-	0.27	0.79	0.005*
Australia	-	-	-	-	-	0.82	3.50	0.153
Baseline PAQ	-	-	-	-	-	-	-	-

Early Revascularization	-	-	-	-	-	-	-	-
Variable	OR	[95% CI]		*p*	OR	[95% CI]		*p*
Hypertension	1.01	0.62	1.62	0.979	1.01	0.63	1.64	0.953
Dyslipidemia	1.09	0.70	1.71	0.696	1.08	0.69	1.70	0.725
Diabetes	1.11	0.79	1.56	0.542	1.11	0.79	1.56	0.530
Chronic Kidney Disease	1.30	0.80	2.12	0.285	1.27	0.78	2.07	0.328
Smoking	1.07	0.62	1.85	0.797	1.09	0.63	1.87	0.764
PHQ-8	1.03	0.99	1.08	0.147	1.03	0.99	1.08	0.171
GAD-2	1.10	0.97	1.24	0.132	1.10	0.97	1.24	0.139
PSS	0.99	0.93	1.05	0.665	0.99	0.93	1.04	0.618
Low Social Support (ESSI)	0.99	0.65	1.51	0.973	0.97	0.64	1.48	0.893
Moderate/Severe Economic Burden	0.92	0.79	1.07	0.284	0.93	0.80	1.08	0.322
Age	1.02	1.00	1.04	0.073	1.02	1.00	1.04	0.085
Female Sex	0.90	0.64	1.27	0.550	0.89	0.63	1.25	0.499
White Race	0.64	0.41	1.01	0.055	0.67	0.43	1.05	0.081
United States	[reference]				[reference]			
Netherlands	0.63	0.35	1.11	0.106	0.61	0.35	1.08	0.093
Australia	1.70	0.79	3.65	0.175	1.54	0.71	3.35	0.277
Baseline PAQ	0.94	0.93	0.95	<0.001*	0.94	0.93	0.95	<0.001*

Early Revascularization	-	-	-	-	0.70	0.48	1.03	0.069

*=statistically significant at p<0.05. CI = confidence interval; ESSI=ENRICHD Social Support Instrument; GAD-2 = Generalized Anxiety Disorder-2; OR = odds ratio; PAQ = Peripheral Artery Questionnaire; PHQ-8 = Patient Health Questionarre-8 item; PSS = Perceived Stress Scale.

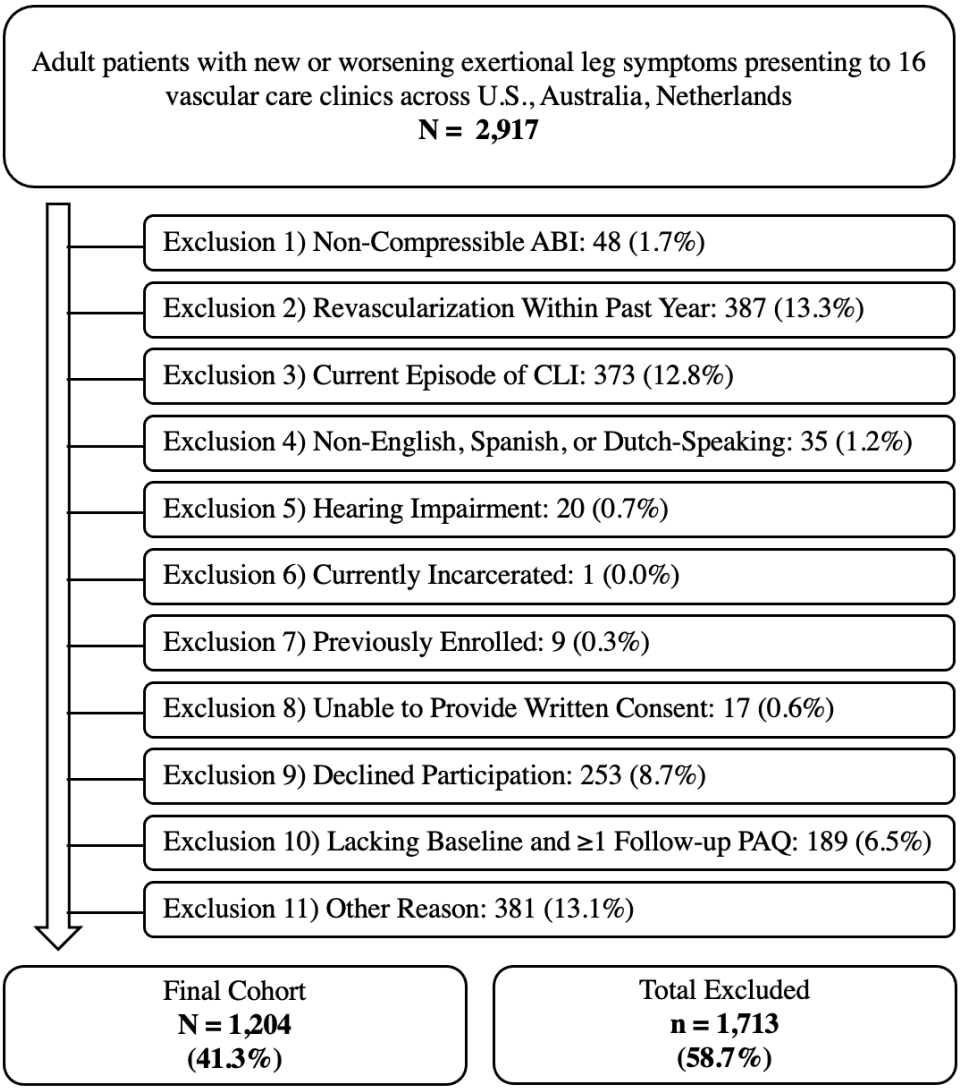

Figure 1: Study cohort flow diagram. ABI = ankle brachial index; CLI = critical limb ischemia; PAQ = Peripheral Artery Questionnaire.

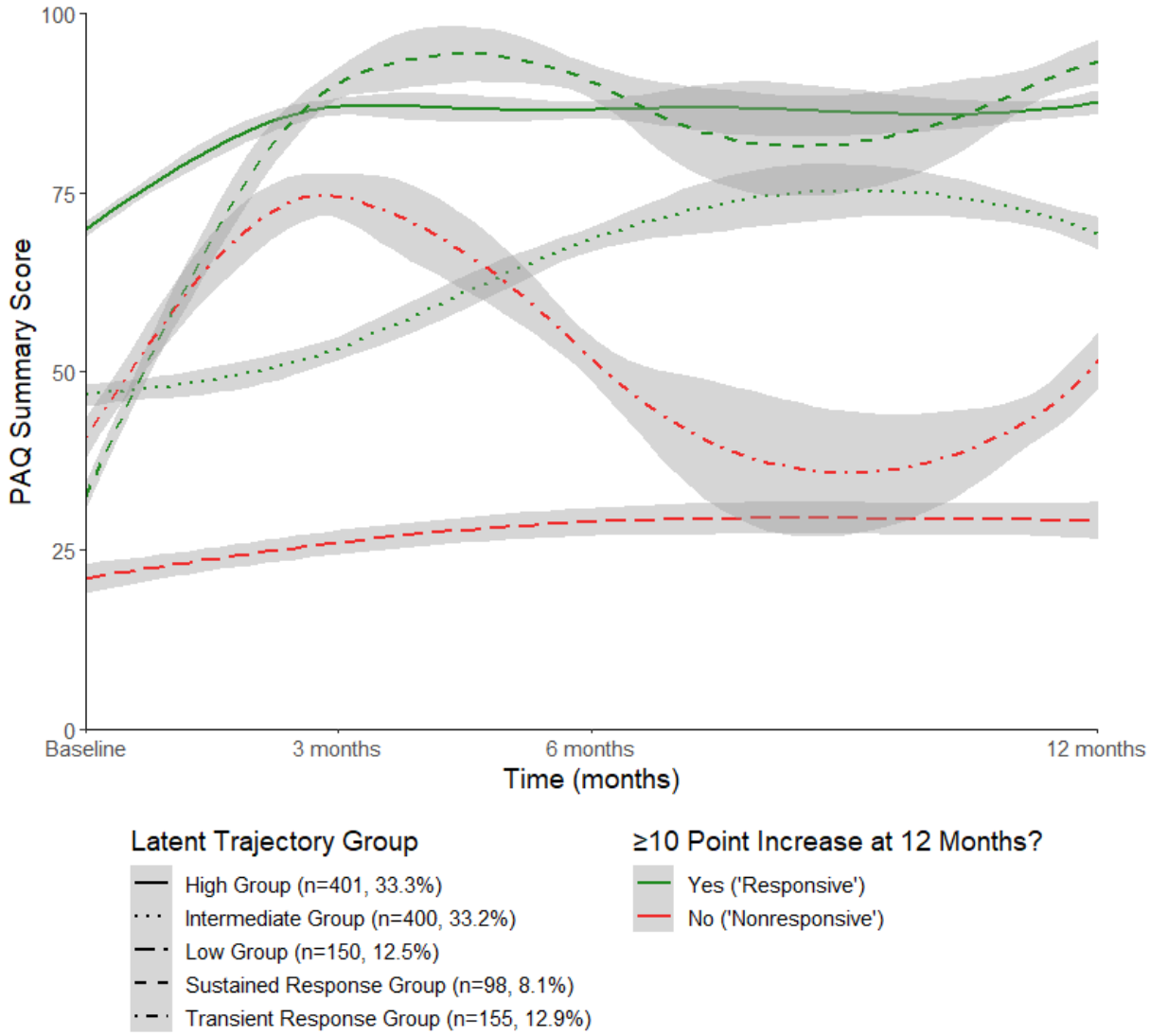

Figure 2: Responsive and Nonresponsive one year latent health status trajectories in patients with symptomatic peripheral artery disease. Lines represent smoothed means with shaded 95% confidence interval. PAD = peripheral artery disease; PAQ = Peripheral Artery Questionnaire.

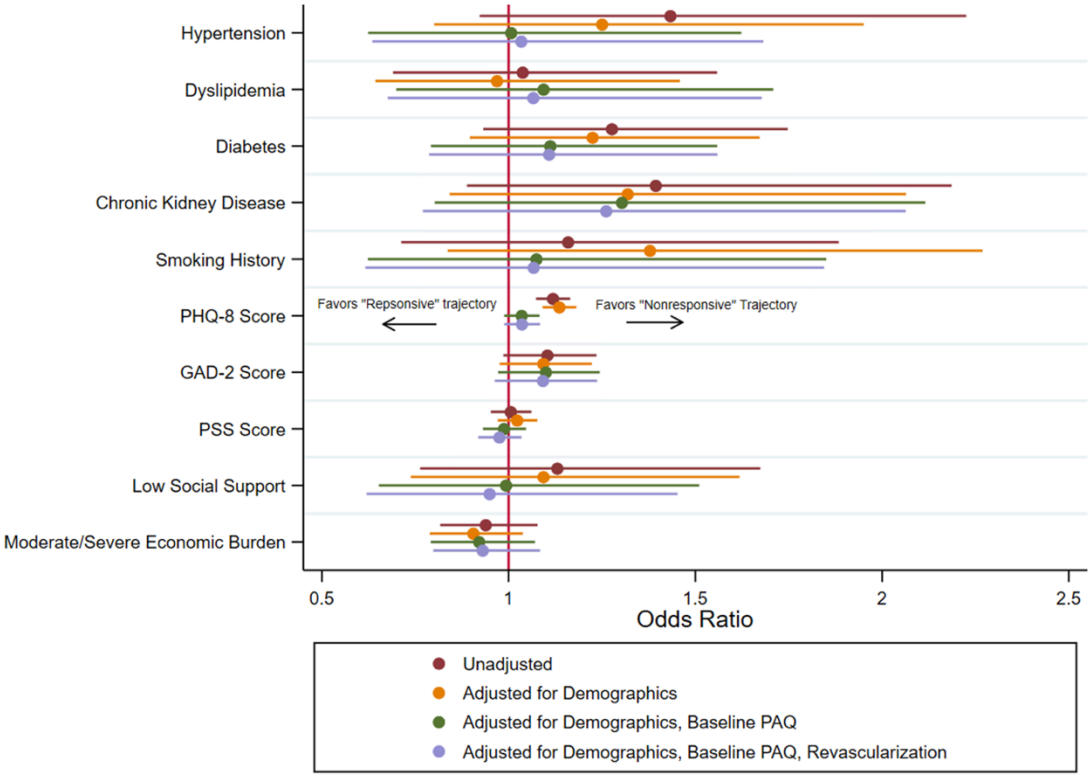

Figure 3: Hierarchical multivariate logistic regression predicting Responsive vs. Nonresponsive health status trajectory for patients with peripheral artery disease receiving specialty care. Models sequentially adjusted for demographics (age, sex, white vs. non-white race, country), baseline PAQ, and early (≤3 months) revascularization. GAD-2 = Generalized Anxiety Disorder 2-Item; PHQ-8 = 8-Item Patient Health Questionnaire (PHQ-8);; PSS = Perceived Stress Scale (PSS).

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