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A Prospective Longitudinal Study of Trajectories of Depressive Symptoms After Dysvascular Amputation

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Abstract

Objectives: Characterize the course of depressive symptoms during the first year after dysvascular amputation and identify factors that predict symptom trajectories.

Design: Prospective cohort study of individuals undergoing lower extremity amputation (LEA), surveyed at 4 time points (perioperative period, 6 weeks, 4 months, and 12 months postamputation). Multilevel modeling was used to describe and predict trajectories.

Setting: Four Veterans Affairs medical centers, a university hospital, and a level I trauma center.

Participants: Participants (NZ141; 74% retention) were a consecutive sample, eligible if they were undergoing their first unilateral LEA secondary to dysvascular disease.

Interventions: Not applicable.

Main Outcome Measure: Patient Health Questionnaire-9.

Results: Approximately 40% of participants endorsed at least moderate depressive symptoms at perioperative baseline. Individuals with greater depressive symptoms in the perioperative period concurrently reported greater pain, poorer self-rated health, and prior mental health treatment. In the first 6 weeks after amputation there was a substantial improvement in depressive symptoms, especially among individuals with greater symptoms at baseline. Depressive symptoms were generally stable after 6 weeks. None of the covariates assessed significantly predicted trajectories of depressive symptom improvement.

Conclusions: Watchful waiting may be the most appropriate course of action for many patients in the first 6 weeks after amputation. After 6 weeks, however, symptom levels tend to stabilize, suggesting that active intervention is called for if patients remain depressed at this point. Some

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patients may benefit from more proactive intervention, such as those with prior mental health treatment histories.

Keywords

Amputation; Depression; Rehabilitation

Dysvascular amputation is associated with elevated risk of depression,[1] with prevalence estimates ranging from 3% to 51%.[2,3] A review of the predominantly cross-sectional literature suggests elevated depression symptoms in the first 2 years after amputation, followed by levels consistent with population norms after 2 years.[1]

Two prospective longitudinal studies suggest unclear prevalence and course of depressive symptoms after dysvascular lower extremity amputation (LEA). Singh et al[3] evaluated a sample of 68 individuals with LEA of mixed etiologies, and rates of depressive symptoms were found to be elevated at inpatient admission, low at inpatient discharge approximately 54 days later, but elevated again at follow-up approximately 2.7 years later. Kratz et al[4] studied a subsample of 76 individuals with nontraumatic LEA who reported the highest rates of depression in the immediate postsurgical period, but reported no statistically significant changes in depressive symptom levels 1, 6, or 12 months later (despite a trend toward modest decreases in Patient Health Questionnaire-9 [PHQ-9] scores), suggesting that larger samples may be needed to reliably detect improvements.

With respect to factors that might increase risk for depressive symptoms after LEA, Singh et al[3] noted that depressive symptoms at 2.7-year follow-up were related to depressive symptoms at admission and medical comorbidities, but unrelated to age, sex, dysvascular etiology, prosthesis use, or living in isolation. In a subsample of individuals with LEA of nontraumatic etiology, Kratz et al[4] reported correlations between depressive symptoms and other factors measured concurrently: pain, posttraumatic stress symptoms, social isolation, social constraints, and aversive social support. Cross-sectional studies highlight other factors correlated with depression after amputation: higher-level (ie, transfemoral) amputation, poor self-rated health (SRH), more medical comorbidities, pain (in residual limb or other body parts), low social support, older age, lower income, less education, and being unmarried, divorced, or widowed.[2,5–8] However, the literature does not reveal whether these factors are correlates or prognostic indicators that predict the trajectory of depressive symptoms over time.

In the present study, depressive symptoms were assessed at multiple clinically meaningful time points during the first year postamputation, thereby allowing for modeling of trajectories of depressive symptom change over time, as well as assessment of the baseline factors that may predict improvement (or exacerbation) of symptoms.

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Methods

Study design

This study is a secondary analysis of a combined database from 2 multisite prospective cohort studies conducted with individuals undergoing their first major LEA due to

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complications of peripheral arterial disease (PAD) or diabetes mellitus (DM).[9] Participants were those with complete perioperative (ie, within 7 days before or after the amputation procedure) baseline data. Subsequent assessments were conducted in person or via telephone by trained study coordinators at each site 6 weeks, 4 months, and 12 months postsurgically. Studies were conducted in accordance with the procedures approved by human subjects review boards at each participating institution.

Participants

Participants (NZ141) were enrolled within 7 days of amputation. Participants were eligible if (1) they were age 18 years or older and (2) they underwent their first major LEA related to complications of DM or PAD. Participants were excluded if (1) they had inadequate cognitive or language function to consent or participate defined by >4 errors on the Short Portable Mental Status Questionnaire (SPMSQ) or (2) they were nonambulatory before the amputation for reasons unrelated to PAD or DM.

Measures

Amputation and demographic factors—Participants' age and marital status (married or partnered [1] vs not [0]) were self-reported, and amputation level (transmetarsal, transtibial, transfemoral) was extracted from the medical record.

Depressive symptoms and mental health treatment—The PHQ-9[10] was used to assess depressive symptoms.[11] The PHQ-9 asks participants to report how frequently they experienced each of 9 symptoms of depression over the past 2 weeks, ranging from 0 (not at all) to 3 (nearly every day). Possible sum scores range from 0 to 27 with higher scores representing greater depressive symptoms. Although sum scores were used in data analyses, symptom severity can be clinically categorized into none or minimal (scores 0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe depressive symptoms (20+).[10] Participants were also asked a yes or no question at baseline regarding whether they had received any prior treatment for depressive or anxiety symptoms.[12]

Pain intensity—Patients were asked to rate the average intensity of pain across a variety of body parts (eg, back, contralateral leg) experienced in the month prior to amputation on a scale ranging from 0 (no pain) to 10 (pain as bad as it could be). As the present study was primarily concerned with overall pain intensity, the highest pain intensity score (from any body part) was used. Pain intensity scores were dichotomized into severe pain (highest pain intensity rating of 7+) vs mild to moderate pain (highest pain intensity rating of 0–6), as in prior pain literature.[13–15]

Social support—Degree of social support was assessed using the brief version of the Modified Social Support Survey.[16,17] Participants are asked how often someone was available to provide 5 types of social support with response options ranging from 0 (none of the time) to 5 (all of the time). Total raw scores were standardized such that possible total scores range from 0 to 100, with higher scores indicating greater perceived social support.

Self-rated health—SRH was assessed via a single item modeled after the general health question from the Medical Outcomes Study 36-Item Short-Form Health Survey.[18] Participants were asked, "In general, would you say your health is…" with response options of very poor (1), poor (2), fair (3), good (4), and very good (5). This single-item index has been used extensively and has the advantage of ease and simplicity of administration.[19,20]

Data analysis

A series of multilevel modeling analyses were conducted using R statistical software version 3.4.1 (nlme package).[a],[b] These analyses modeled changes in PHQ-9 sum scores over time, with observations nested within individuals. Maximum likelihood estimation was used to model missing data (supplemental appendix S1, available online only at http://www.archives-pmr.org/).

Time was centered at baseline (ie, the perioperative period was coded as time 0 and therefore treated as the intercept). To allow for meaningful evaluation of parameter estimates, dichotomous variables were coded 1 or 0 and continuous variables were mean-centered as needed. We compared Akaike information criterion (AIC) and Bayesian information criterion (BIC) values across multiple alternative models, and retained the best model based on model fit statistics (comparing AIC and BIC values in the case of nonnested models and conducting χ^2 log-likelihood ratio tests in the case of nested models), before proceeding to add covariates to the model.

To determine the individual contribution of the variables described above, each covariate was first entered into the best-fitting model separately. Fixed effects associated with each covariate were evaluated by examining both the covariate term and the time-covariate interaction term. Any effects (covariate main effects or time-covariate interactions) that were significant at $P<.05$ were included in the final multivariate model.

Results

Participant characteristics

Of the 141 participants who met study criteria, 20 (14%) died within the study period and 16 (11%) withdrew or were lost to follow-up. At 12 months after amputation, 105 (74%) participants remained enrolled (fig 1). There were no significant differences in baseline depressive symptoms (PHQ-9 sum scores) between those who remained enrolled in the study at 12 month after amputation (n=105) and those who did not ($F_{1,139}$=.18, P=.68, n=36). Among this sample of predominantly white, male, married or partnered Veterans, approximately 40% endorsed at least moderate depressive symptoms at perioperative baseline and 38% reported prior treatment for anxiety or depression. At 12 months after amputation, approximately 23% endorsed at least moderate depressive symptoms (fig 2). See table 1 for study sample information.

[a] R statistical software v3.4.1; R Foundation.
[b] nlme package; Pinheiro J, Bates D, DebRoy S, Sarkar D, and R Core Team.

Modeling depression symptoms over time

Model selection—Multiple models were evaluated to determine the best fit for depression trajectories in this sample. Model fit statistics are provided in table 2. The piecewise model (with the first interval modeling change between perioperative baseline and 6 weeks after amputation, and the second interval modeling changes in depressive symptoms between 6 weeks, 4 months, and 12 months after amputation) fit the data best, as evidenced by its lower AIC and BIC values. Chi-square log-likelihood ratio tests indicated that the addition of a random slopes component for the first interval significantly improved model fit compared to the fixed slopes model ($\chi^2_2 = 20.00$, $P<.001$), but the addition of a random slopes component for the second interval failed to further improve model fit ($\chi^2_3 = 3.39$, $P=.34$). The piecewise model including random slopes for the first interval was therefore determined to be the most appropriate model to describe the trajectory of depressive symptoms in the year after amputation. This model indicates that participants had significant between-person variability in slopes in the first 6 weeks after amputation (the first interval) but little between-person variability in slopes between 6 weeks and 12 months after amputation (the second interval). Therefore, covariates were entered only for prediction of the slope in the first interval (which had significant variability) and not the second interval.

Piecewise linear model (without covariates)—In this piecewise model, mean depressive symptoms decreased during the first interval (perioperative period to 6-week follow-up), starting at a mean PHQ-9 score of 8.30 and dropping by an average of 1.69 points ($t_{334}=-4.50$; $P<.001$). In the second interval (6 weeks through 12 months), the group's mean PHQ-9 scores were effectively unchanged, increasing by 0.01 points ($t_{334}=.28$; $P=.78$) (fig 3). For the first 6-week interval, the estimated intercept and slope were negatively correlated at −.59, indicating that individuals with higher baseline depression scores experienced steeper decreases in symptoms over the first 6 weeks.

Factors associated with depressive symptom trajectories

Prior mental health treatment—In a model that included only a history of treatment for anxiety or depression, depressive symptoms declined in the first 6 weeks after amputation ($t_{334}=-4.49$, $P<.001$). The fixed effect of prior mental health treatment on the baseline value of depressive symptoms in the perioperative period was significant ($t_{139}=3.78$, $P<.001$), with participants with prior treatment reporting PHQ-9 scores 3.07 points higher than those without prior treatment. The interaction between prior treatment and time was not significant, indicating that those with and those without prior treatment did not improve at different rates in the first 6 weeks after amputation.

Pain—In a piecewise model that included only the presence of severe pain, those who endorsed severe pain at baseline had significantly higher PHQ-9 scores at baseline compared with those who did not endorse severe pain, with average PHQ-9 scores of 8.96 vs 5.87, respectively ($t_{139}=2.43$; $P=.02$). The interaction between severe pain and time was not significant, but the direction of the effect indicated that among those who endorsed severe pain at baseline, PHQ-9 scores decreased by 2.81 points between baseline and 6 weeks after amputation (t_{333}=−1.72; P=.09), compared to those with mild to moderate pain, who showed decreases of only 0.77 points.

Self-rated health—In a piecewise model that included only SRH, those who endorsed better SRH had significantly lower PHQ-9 scores (t_{139}=−2.22, P=.03): individuals with fair SRH (the average in this sample) had a mean baseline PHQ-9 score of 8.52, whereas individuals with good SRH had a mean score of 7.23. The interaction between SRH and time was not significant, indicating that those with better or worse SRH did not improve at different rates in the first 6 weeks after amputation.

None of the 3 single-covariate models indicated changes in mean PHQ-9 scores between 6 weeks and 12 months (see fig 4A, 4B, and 4C, respectively, for models controlling for treatment history, pain, and SRH).

Nonsignificant predictors—Age, marital status, social support, and amputation level did not significantly contribute to variance in baseline PHQ-9 scores (the intercept) or trajectories of depressive symptoms (the slope) over the first 6-week interval. As such, none of these were retained in the final multivariable model.

Multivariable model

The covariates that predicted PHQ-9 sum scores (P<.05) in the piecewise models (ie, prior treatment for anxiety or depression, severe pain, and SRH) were entered simultaneously in a multivariable piecewise multilevel model. In the multivariable model, depressive symptoms decreased in the first interval (t_{334}=−4.41, P<.001), with PHQ-9 scores dropping by an average of 2.32 points in the first 6 weeks after amputation. In this model, prior treatment for anxiety or depression (t_{137}=3.09, P<.001) was associated with higher baseline PHQ-9 scores, and higher perioperative SRH was associated with lower baseline PHQ-9 scores (t_{137}=−2.54, P=.01), while the presence of severe pain was no longer significantly associated with baseline PHQ-9 scores (t_{137}=1.20, P=.23) (table 3). In this model, after accounting for prior treatment for anxiety or depression, SRH, and severe pain, the correlation between the residuals around the estimated intercept and the residuals around the estimated slope was −.56, indicating that participants with more severe depression symptoms at baseline experienced greater improvements in their symptoms over the first 6 weeks.

Discussion

In this sample of individuals undergoing unilateral dysvascular LEA, greater depressive symptoms in the perioperative period tended to be associated with more severe pain, poorer SRH, and a prior history of mental health treatment for anxiety or depression. Overall, depressive symptoms improved in the first 6 weeks after amputation, especially among individuals who had more severe depression symptoms at baseline. However, there was little change from 6 weeks to 12 months after amputation. None of the covariates significantly predicted trajectories of improvement in mood symptoms.

The present findings are broadly consistent with 2 previous prospective longitudinal studies,[3,4] which indicated that depressive symptoms are highest during the perioperative period.

Our results extend prior research by clarifying how depressive symptoms change within the first year, indicating that symptoms significantly decrease within the first 6 weeks after dysvascular amputation and remain at lower levels throughout the first year.[4] This is similar to the trend described by Kratz et al[4] among 73 participants with nontraumatic amputations, but the present results were statistically significant in our larger sample (NZ141). Questions emerge when comparing the present findings to those of Singh et al,[3] who reported that depression rates were high at admission (23.5%), low at inpatient discharge (2.9%), and elevated again 2.7 years later (17.6%). Given that the present findings suggest stability in depressive symptoms from 6 weeks to 1 year after amputation, it is not clear when or why symptoms would rise again between 1 to 3 years after amputation. There may be meaningful differences between the samples (ie, civilian vs Veteran; traumatic vs dysvascular etiology) or the measures used that help to explain this. Relatedly, the present sample had higher rates of depression at all time points compared to the sample of Singh et al.[3] At 1 year after amputation, the prevalence of moderate to severe depressive symptoms in our sample was 23%, which is higher than the 9% estimate in the general population,[21] but more similar to the 18% meta-analytic estimate in men with diabetes.[22]

The present findings have implications for care of individuals undergoing initial dysvascular amputation. Although approximately 40% endorsed at least moderate depressive symptoms at perioperative baseline, many experienced substantial improvements in the first 6 weeks after amputation. Those with the greatest depressive symptom severity in the perioperative period showed the greatest improvements. It is not clear to what extent these improvements may be related to interventions for mood; this multisite study encompassed several different health care systems that do not share one common protocol for depressed mood. We suspect it is unlikely that mental health interventions were initiated quickly enough in a large enough subset of patients to fully account for the early improvements in mood seen here. The present findings suggest that a course of watchful waiting and setting positive expectations for most patients regarding mood improvement may be the most appropriate course of action in the perioperative period. After 6 weeks, symptom levels tended to stabilize, and so more active interventions may be indicated for those with elevated levels of depressive symptoms persisting 6 weeks after amputation. Additionally, although individuals with and without prior mental health treatment show similar rates of improvement in symptoms across the first 6 weeks, more close monitoring of those with a prior history of mental health treatment may be indicated, because they begin with greater depressive symptoms and tend to remain at higher levels over time. Patients with a prior history of treatment for anxiety or depression may therefore benefit from more quickly reconnecting with their mental health treatment team, reinitiating appropriate medication, or accessing other treatment and support.

Although not associated with trajectory in our sample, those with severe pain and poor SRH began and remained at increased risk for depressive symptoms, underscoring the importance of managing pain and medical comorbidities in this patient population. Our findings suggest that depression, pain, SRH, and history of mental health treatment should be assessed at baseline, and depression reassessed at 6 weeks after surgery. The 6-week window appears to be of clinical significance because this is a time interval when healing is occurring, and most patients are actively engaged in a rehabilitation process, which redirects the concern over the loss of an extremity into one of restoration of function and mobility. Although not well studied in the amputation population, this engagement may generate a sense of hope, which has been associated with improved outcomes.[23]

Study limitations

Although this is a large prospective longitudinal study of amputation, the sample size may still have been insufficient to detect some relationships. For instance, amputation level (often an important predictor of functional outcome) and pain in the perioperative period may be significant predictors of depressive symptom trajectories with a larger sample. In addition, the present study was missing data for individuals who died, withdrew, or were lost to follow-up. We included individuals with missing data (using maximum likelihood estimation); however, individuals who remained in the study for the duration contributed more information influencing estimates.

There was imprecision in the timing of the perioperative assessment due to practical constraints; some individuals completed the assessment within the week before their operation, whereas others completed it within 1 week after amputation. In both cases, participants were asked about depressive symptoms over the past 2 weeks, so all participants completed the measure with reference to at least 1 week of preamputation symptoms. A further limitation relates to the self-reported nature of the measures, which can introduce bias. Another limitation is that mood improvements in the first 6-week interval may not necessarily reflect natural recovery processes alone, but also unmeasured biopsychosocial interventions implemented in the perioperative period, some of which may specifically target depression (medications, counseling).

The present findings may not generalize to more diverse populations (in terms of sex, race, ethnicity, age, etc). This sample comprised individuals undergoing their first unilateral amputation, who did not have additional significant preexisting mobility limitations. Results might not generalize to a population of people with bilateral amputation or revision, for example, or to individuals with traumatic amputations.

Conclusion

The present study meaningfully contributes to our understanding of adjustment to amputation, as it sheds light on how and when depressive symptoms shift in the year after dysvascular amputation. These findings indicate that many individuals' depressive symptoms stabilize within 6 weeks after amputation (suggesting a watchful waiting approach) and then tend to remain stable, for better or worse (suggesting more active intervention at this stage). Future studies in samples with more variability in depressive trajectories over the first year may clarify how additional intervening factors that occur postsurgically can affect mental health symptom trajectories, and provide further guidance about optimizing interprofessional, patient-centered care after amputation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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List of abbreviations:

AIC	Akaike information criterion
BIC	Bayesian information criterion
DM	diabetes mellitus
LEA	lower extremity amputation
PAD	peripheral arterial disease
PHQ-9	Patient Health Questionnaire-9
SPMSQ	Short Portable Mental Status Questionnaire
SRH	self-rated health

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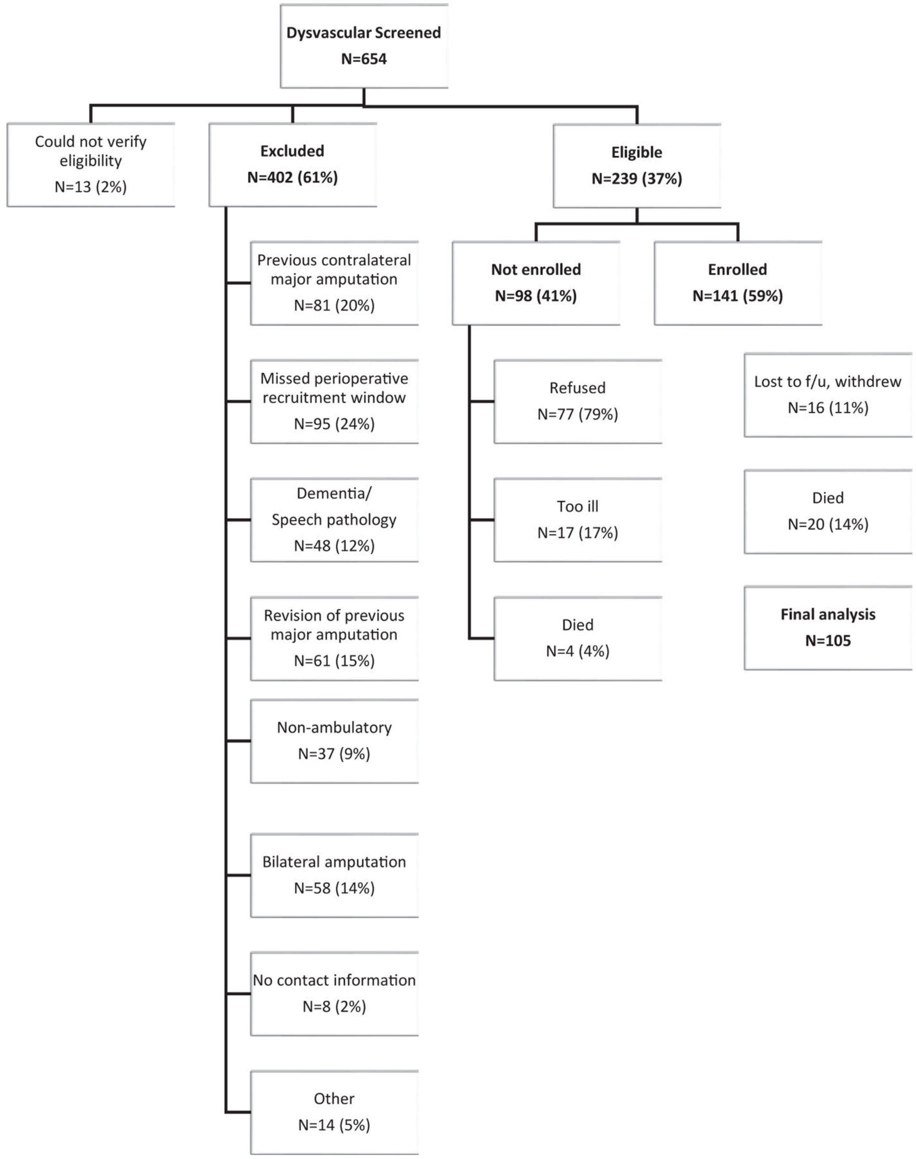

Fig 1.
STROBE diagram depicting participant flow. Abbreviations: STROBE, strengthening the reporting of observational studies in epidemiology.

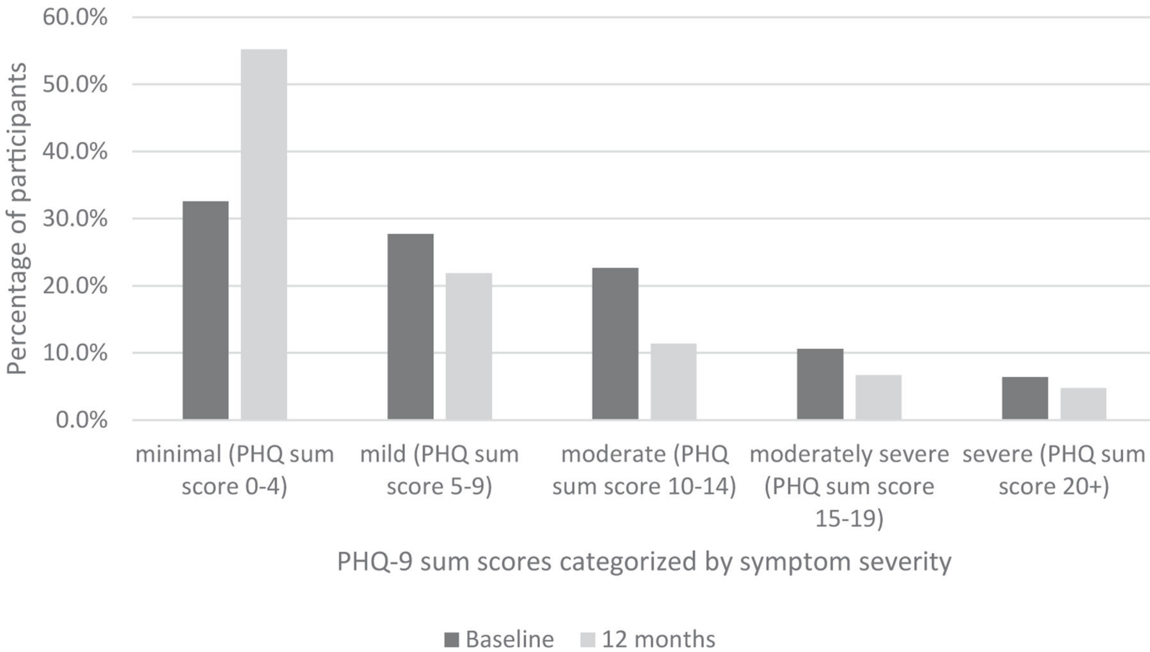

Fig 2.
Proportion of participant baseline and 12-month PHQ-9 sum scores, by symptom severity level.

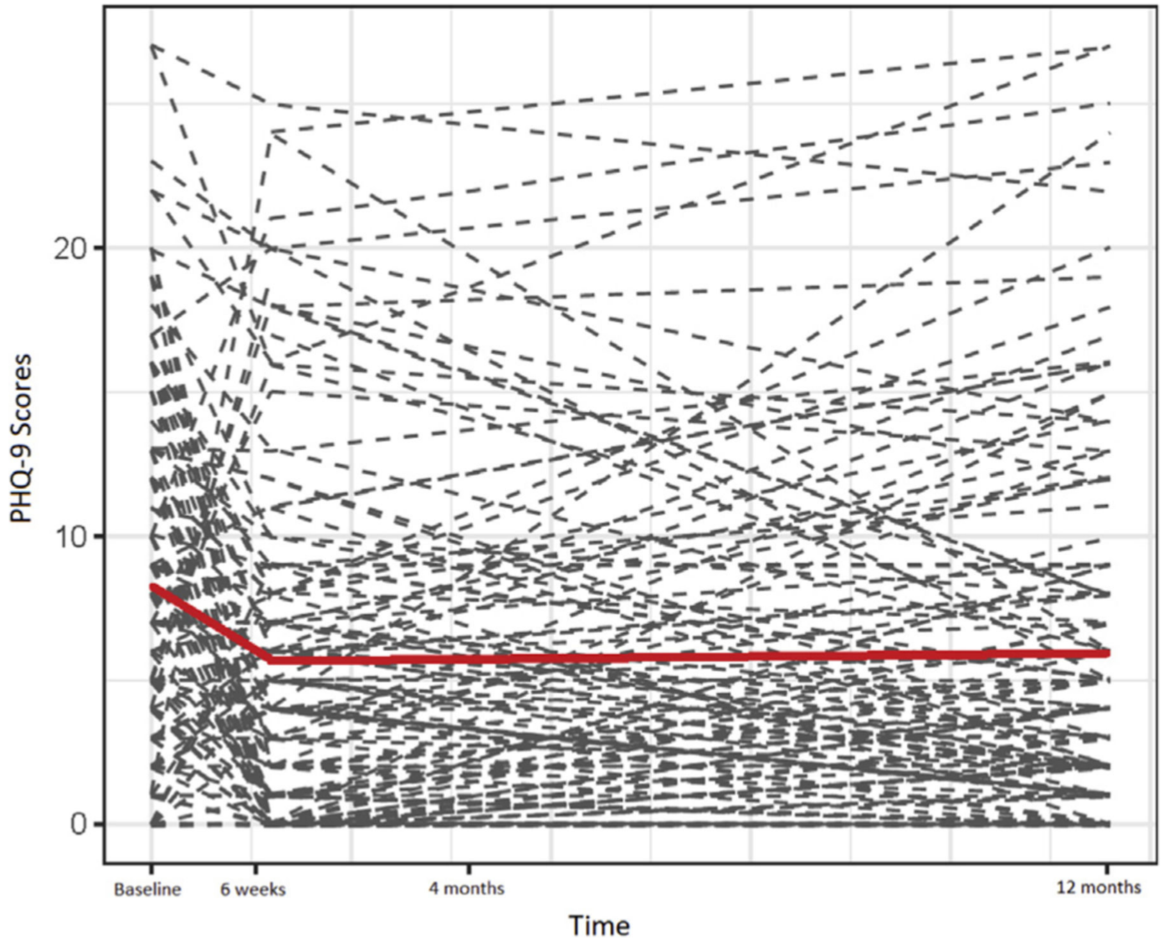

Fig 3.

Individual variability in slopes for time intervals (thick solid line represents fixed effect; thin dashed lines represent individual patient variation around the fixed effect).

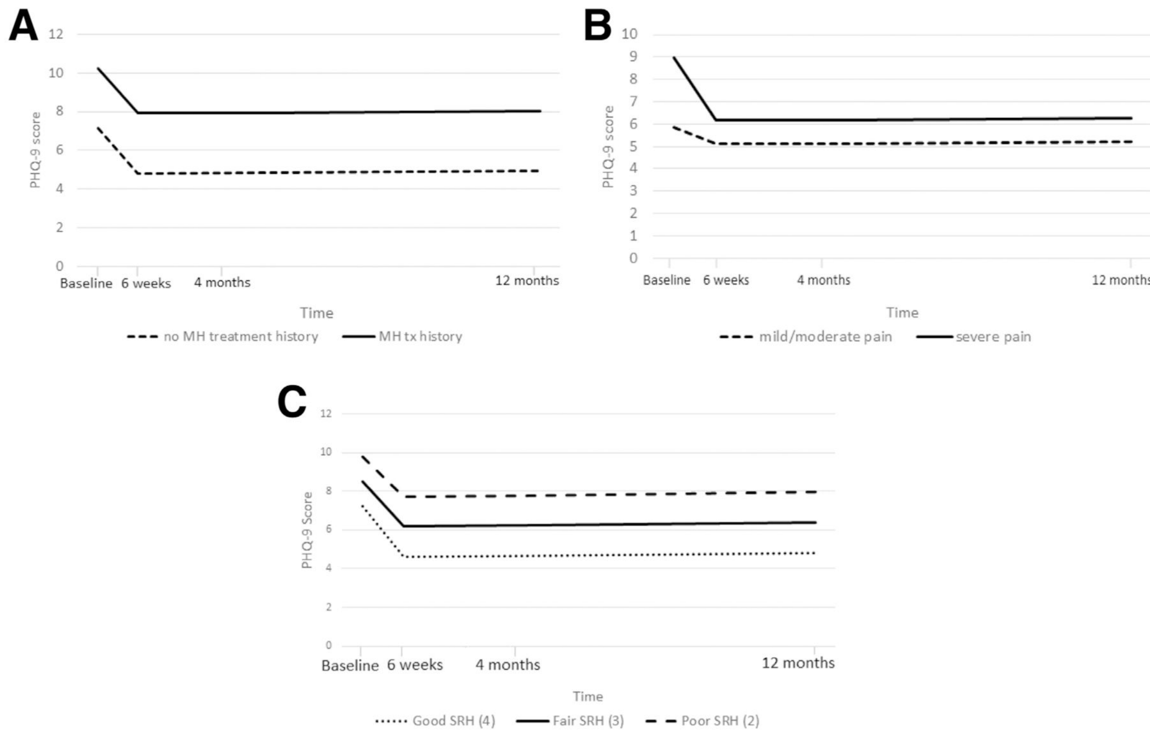

Fig 4.

Trajectories of depressive symptoms (PHQ-9 scores) during the first year postamputation: multilevel modeling analyses with (A) mental health treatment history; (B) presence of severe pain; and (C) SRH.

Table 1

Participant characteristics

Variables	n (%) or Mean ± SD	Possible Score Range
Men	139 (98.6)	
Age (y)	63.37±8.62	
White	104 (73.8)	
Married or partnered	74 (52.5)	
Veteran (vs civilian)	122 (86.5)	
Amputation level		
Transmetatarsal	36 (25.5)	
Transtibial	74 (52.5)	
Transfemoral	31 (22.0)	
DM or PAD diagnosis	122 (86.5)	
Prior treatment for anxiety or depression	53 (37.6)	
Severe average pain (≥7/10 rating)	111 (78.7)	
Social support (MSSS)	73.62±27.40	0–100
SRH	3.17±.90	1–5
Depressive symptoms (PHQ-9)		
Perioperative baseline	8.30±6.29	0–27
6 weeks after amputation	5.48±6.02	0–27
4 months after amputation	6.16±5.75	0–27
12 months after amputation	5.94±6.25	0–27

Abbreviation: MSSS, Modified Social Support Survey.

Table 2

Model fit statistics

Model Type	**AIC**	**BIC**
Linear, fixed slope	2980.36	2997.02
Linear, random slope	2983.26	3008.24
Quadratic	2979.72	3000.52
Cubic	2975.11	3000.06
Piecewise, fixed slope	2961.26	2982.07
Piecewise, random slope for 1st interval	2945.26	2974.39
Piecewise, random slope for 2nd interval	2964.47	2993.60
Piecewise, random slope for both intervals	2947.87	2989.48

Table 3

Fixed effects in linear piecewise multilevel modeling analyses predicting changes in PHQ-9 scores (final multivariable model including pain, SRH, and mental health treatment history)

Variable	Value	Standard Error	*df*	*t* Value	*P* Value
Intercept	10.00	1.78	334	5.60	<.0001
Baseline severe pain	1.12	.94	137	1.20	.24
Prior mental health treatment	2.52	.82	137	3.09	<.01
Baseline self-rated health	−1.11	.44	137	−2.54	.01
Slope for interval 1	−1.66	.38	334	−4.41	<.0001
Slope for interval 2	.01	.05	334	.30	.76

NOTE. Slope estimates reflect the rate of change in sum PHQ-9 scores per month.