Inflammation and Depression Profile at Non-Small Cell Lung Cancer Diagnosis Predicting Depression Trajectories

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Abstract

Background: Lung cancer is a product of inflammation and a dysfunctional immune system, and depression has similar dysregulation. Depression disproportionately affects lung cancer patients and has been shown to be significantly associated with systemic inflammation responses. Independently, systemic inflammation, depression, and the depressive symptom trajectory are predictive of non-small cell lung cancer (NSCLC) survival, but the impact of comorbid depressive symptoms with high inflammation at diagnosis on the depressive symptom trajectory is unknown. Studied is the depressive symptom trajectory of four baseline depressive symptom/inflammation profile groups (LoDep/LoInf, LoDep/HiInf, HiDep/LoInf, HiDep/HiInf), with the hypothesis that patients with high depression and high inflammation at baseline would show a uniquely different trajectory of depressive symptoms, one that is elevated compared to all other groups, including patients with high depression but low inflammation.

Methods: Newly diagnosed stage-IV non-small cell lung cancer (NSCLC; *N*=182) patients were enrolled (ClinicalTrials.gov Identifier: NCT03199651). Clinical characteristics, cell count, and albumin data for inflammation biomarker calculation were abstracted from patient electronic medical records from first clinic visit or soon thereafter. Linear mixed models were used to test for differences in the depressive symptom trajectory from diagnosis through 8 months for each baseline depressive symptom/inflammation profile group.

Results: Linear mixed models confirmed a significant interaction between Profile 4 (HiDep/HiInf) and time ($F(24,945) = -.04$, $p = .001$), indicating Profile 4

(HiDep/HiInf) membership at diagnosis was a significant predictor of the depressive symptom trajectory in both the simple model and the model adjusting for significant sociodemographic and clinical covariates. Tests of this interaction were insignificant for all other profiles, including Profile 3 (HiDep/LoInf).

Conclusions: Novel data show that the interaction of elevated baseline depressive symptoms and inflammation contribute differentially to a worsened depression trajectory from diagnosis to 8 months. Biological and psychological domains often viewed as disparate were found to be predictive of distinct vulnerability to the continuation of elevated depressive symptoms for patients with a high depression and high inflammation comorbidity compared to all other groups at diagnosis, including those with high depression but low inflammation. These findings indicate depression intervention is exceedingly important for these vulnerable patients, as the continuing trajectory of depressive symptoms predicts NSCLC overall survival (Andersen et al., 2022). Further, there is a compelling case for identifying vulnerable patients early (e.g., at diagnosis) and delivering depression intervention in the early months of cancer treatment following diagnosis to improve their psychological functioning and perhaps, reduce inflammation.

Keywords: lung cancer, depression, inflammation, depression trajectory, systemic inflammation response, cohort

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Introduction

Among all cancer patients, non-small cell lung cancer (NSCLC) patients are uniquely vulnerable with the occurrence of co-morbid depression and inflammation, as the incidence of depressive symptoms is high, and lung cancer is an inflammatory disease (Lee & Singh, 2021; Walker et al., 2020; Wong et al., 2017). Depression and inflammation are similarly characterized by biologic dysregulation and separately predictive of NSCLC overall survival (Andersen et al., 2022; Jin et al., 2020; Mandaliya et al., 2019; McFarland et al., 2021; Xu et al., 2019; Zhang et al., 2020; Zhou et al., 2021). Data show their covariation (Beurel et al., 2020), but the impact of co-occurrence is unknown.

Non-small cell is the most prevalent lung cancer type, comprising ~85% of lung cancer cases, with ~77% presenting with advanced-stage (stage IV) disease at diagnosis (Noone, 2018). Cancer at this stage has metastasized, is most symptomatic, and is least amenable to treatment (Morgensztern et al., 2010). With the prevalence of advanced disease and poor prognosis (~5 months) (Li et al., 2019) considered, NSCLC patients are particularly vulnerable to depressive symptoms (Lee & Singh, 2021). An estimated 36% of NSCLC patients have moderate to severe depressive symptoms at diagnosis (Lee & Singh, 2021; Walker et al., 2020; Wong et al., 2017), and levels thereafter range from none/mild to severe. (Linden et al., 2012; Lo et al., 2010; McFarland, 2019). Across cancer types, depression is a rate limiting factor impacting patients' quality of life, treatment adherence, and, potentially, treatment response (Arrietta et al., 2014; Sullivan et al., 2016). Depression assessed at diagnosis is prognostic for mortality in cancer patients, with the strongest effects found for those with lung cancer (Walker et al., 2020;

Wang et al., 2020). Concerning effects of depression post diagnosis, the *continuing trajectory* of depressive symptoms from diagnosis through two years predicts NSCLC overall survival (HR=1.09 per unit increase of depressive symptoms, 95% CI=1.03–1.15, p=.002), above and beyond baseline depression, sociodemographics, smoking status, cell type, and receipt of targeted treatments and immunotherapies (Andersen et al., 2022). Taken together, data support psychological, behavioral, and biologic toxicities of depression potentially capable of influencing survival.

Lung cancer is characterized by biologic toxicity, with inflammation arising from multiple sources (e.g., tobacco/smoking-induced inflammation, inflamed tumor microenvironment) combined with a dysregulated immune system (Brown et al., 2019; Mandaliya et al., 2019; Walser et al., 2008). In NSCLC patients, higher systemic inflammation responses (SIRs) are reliably associated with lower overall survival ($p<.001$) compared to those with lower SIRs (Jin et al., 2020; Mandaliya et al., 2019; McFarland et al., 2021; Xu et al., 2019; Zhang et al., 2020; Zhou et al., 2021). Thus, studies suggest systemic inflammation has adverse effects on both lung cancer incidence and survival.

Meta-analyses have suggested elevated depressive symptoms and major depressive disorder (MDD) covary with decreased adaptive immune responses, evidenced by reduced pharmaceutical and treatment responsiveness (Miller & Raison, 2016), tryptophan degradation (Sforzini et al., 2019), and others (Majd et al., 2020). Depression has also been shown to covary with cytokines that advance disease progression (pro-inflammatory cytokines, e.g., c-reactive protein) in depressed individuals compared to responses in non-depressed controls (Dowlati et al., 2010;

Osimo et al., 2019). Further, biologic therapies which increase inflammation (e.g., interferon-alfa treatment) can cause major depressive disorder (MDD) (Chiu et al., 2017; Lotrich, 2022).

In non-cancer populations, biomarkers of inflammation include pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF- α). Activation and regulation of immune activity is characterized by *anti*-inflammatory cytokines (e.g., IL-4, IL-10) counterbalancing these pro-inflammatory responses. Thus, elevations in *pro*-inflammatory cytokines indicate increased inflammation and immune dysregulation (Dowlati et al., 2010). In the case of lung cancer, systemic inflammatory responses (SIRs) – neutrophils, lymphocytes, monocytes, and platelets – are key factors in inhibiting disease incidence, proliferation, metastisis, angiogenesis, immunosuppression, and nutritional depletion (Zhou et al., 2021), and thus cellular ratios of SIRs are regularly used. Briefly, the cellular inflammatory response is characterized by increases in circulating neutrophils (N) accompanied by falls in circulating lymphocytes (L). The neutrophil-to- lymphocyte ratio (NLR) is viewed as a biomarker reflecting the inflammatory imbalance of pro-tumor efficacy (N) and anti-tumor capacity (L) of the host (Kumar et al., 2018; Zhou et al., 2021). The platelet-to-lymphocyte ratio (PLR) is important as platelet elevation accelerates tumor progression (Xu et al., 2019; Zhang et al., 2020). Unique is the advanced lung cancer inflammation (ALI) index, which considers albumin and body mass index (BMI) as measures of nutritional status along with NLR. ALI is a robust indicator of systemic inflammation in lung cancer patients as it merges multiple relevant measures (Hua et al., 2019). SIRs are prognostic biomarkers for multiple tumor types, and meta analyses have confirmed elevated NLR and PLR and lower ALI levels (each

indicating higher inflammation) at diagnosis to predict NSCLC overall survival at two years (Ayers et al., 2021; Ding et al., 2016; Hua et al., 2019; Jin et al., 2020; Sacdalan et al., 2018).

Using these biomarkers, we recently tested the association of depression and SIRs in newly diagnosed NSCLC patients (N = 186) and found depression to be associated with all SIRs – NLR, PLR, and ALI. Specifically, patients with moderate/severe depressive symptoms were 2 to 3 times more likely to have prognostically poor inflammation biomarker levels, with the strongest association found using ALI (p = .009) (Andersen, et al., 2023). Of note, patients with low/no depression at baseline were as likely to have low ALI (lower scores = higher inflammation) as high. In contrast, significantly more patients with moderate/severe depression at baseline had prognostically worse, low ALI (70%) rather than high (30%) (see Figure 1). A plausible interpretation of this data is a differential effect of depression severity which "adds" to patients' basal level of inflammation arising from other sources. This may be a contributing mechanism to the uniquely high rates of depression found in lung cancer patients at diagnosis (Lee & Singh, 2021; Walker et al., 2020; Wong et al., 2017) and the toxicity of the depression trajectory thereafter predicting lower survival (Andersen et al., 2022).

The present study seeks to extend these findings. It is unknown if the covariation of depression and inflammation found at diagnosis would have relevance to patients' depressive symptoms in post-diagnosis months as they begin and continue with cancer treatment. If significant differences in trajectories of those with or without depression and those with or without high inflammation is observed, it would provide evidence that the

presence of this baseline covariance—particularly high depressive symptoms and high inflammation—contributes to depression maintenance. The value in baseline depression and inflammation profiles at diagnosis as predictors of the depression trajectory among patients with lung cancer is clear: if particular profiles impart risk for prognostically worse depression trajectories, there is a compelling case for identifying vulnerable patients early (e.g., at diagnosis) and delivering depression intervention in the early months of cancer treatment following diagnosis to improve their psychological functioning and perhaps, reduce inflammation. Study of the consequences of co-morbid depression and inflammation in lung cancer patients is timely as new therapies come on line and treatment guidelines rapidly change (Ettinger et al., 2022). Biopsychological studies of lung patients have been few and come largely from prior decades of chemotherapy-only treatments (Sullivan et al., 2016), making examination of the impact of the association between depressive symptoms and systemic inflammation responses (SIRs) on the depression trajectory novel.

For this extended analysis, the same sample was used (*N*=186). Patients' depressive symptoms—from baseline through month 8—were assessed. Using the same dichotomous scoring of baseline depressive symptoms (PHQ-9, cutoff: 8) with inflammation (ALI, cutoff: 24), the four patient groups previously identified were studied: Profile 1: low depression and low inflammation (LoDep/LoInf), Profile 2: low depression and high inflammation (LoDep/HiInf), Profile 3: high depression and low inflammation (HiDep/LoInf), and Profile 4: high depression and high inflammation (HiDepHiInf) patients. We anticipated that the depression trajectories of the two groups having low depressive symptoms at baseline (Profiles 1 and 2) would maintain low (or

possibly slightly improved) depressive symptoms across time, regardless of baseline ALI levels. The key test resides in the trajectories of the two high depressive symptom groups, one with low inflammation and the other with high. It was predicted that the group with both high depression and high inflammation (Profile 4) would show a significantly and uniquely different trajectory of depressive symptoms, one that is elevated compared to all other groups, including patients with high depression but low inflammation (Profile 3).

Methods

Design

A single-group longitudinal design was used. Advanced-stage (stage-IV) NSCLC patients were enrolled in the Beating Lung Cancer in Ohio (BLCIO) cohort study approved by the Institutional Review Board of the James Cancer Hospital and Solove Research Institute of the Comprehensive Cancer Center at the Ohio State University (Clinicaltrials.gov Identifier: NCT03199651). Accrual occurred from July 2017 to February 2020 and used the following inclusion criteria: new diagnosis of pathologically confirmed stage IV NSCLC; any performance status and any illness or condition comorbidity; age ≥ 18 years; English-speaking; and willingness to respond to surveys, provide biospecimens, and access to medical records. Exclusion criteria were prior treatment with definitive chemo-radiotherapy, receipt of any NSCLC treatment for over one month before enrollment, diagnosis >90 days prior to accrual, second-opinion or consult-only cases, and presence of disabling hearing, vision, or psychiatric impairments preventing consent or survey completion.

Participants

One hundred eighty-two (*N*=182) patients with NSCLC were studied. See Table 1 for demographic and clinical characteristics of the total sample. Patient age ranged from 34-86 years, and the mean age was 63.25 years. The majority were Caucasian (82.8%), male (59.3%), and partnered (59.3%). Approximately half (54.9%) reported completing some education beyond high school and most were unemployed (75.8%). The most prevalent cancer cell type in the sample was adenocarcinoma (78.6%) followed by squamous (12.6%), and 91.2% of patients subsequently received treatment for their cancer. First lines of treatment included chemotherapy (16.5%), immunotherapy (22.5%), targeted therapy (17.0%), chemotherapy + immunotherapy (33.0%), chemotherapy + targeted therapy (2.2%), and no treatment (8.8%). The majority of patients were within the overweight or obese Body Mass Index (BMI) categories (60.4%). Most endorsed a lifetime history of smoking (84.6%), and 17.0% reported current smoking.

Procedures

Participants were accrued and enrolled at patients' first thoracic oncology clinic appointment. Verbal and written consent was obtained by research personnel with signatures witnessed. Clinical characteristics, cell count, and albumin data for inflammation biomarker calculation were abstracted from patient electronic medical records from first clinic visit or soon thereafter (mean = 11.82 days). Interviewers from a professional survey center contacted patients by telephone monthly following accrual, and participants were compensated $15 for completion of each telephone survey. Study flow (Figure 3) is provided.

Measures

Depressive symptoms. The Patient Health Questionnaire-9 (PHQ-9, range 0-27; Kroenke & Spitzer, 2002) is a self-report measure assessing frequency and severity of Major Depressive Disorder (MDD) symptoms. The measure includes 9 items rated on a 4-point Likert scale (0=not at all, 3=nearly every day) with four levels of summed symptom classification: none/mild (0-7), moderate (8-14), moderate to severe (15-19), and severe (20-27). The total score can be dichotomized as an indicator of depressive symptom severity: low (< 8) and high (≥ 8) (Andersen et al., (in press); Andersen et al., 2014). Cronbach's alpha was .80.

Systemic inflammation biomarker. Advanced Lung Cancer Inflammation Index was calculated by multiplying BMI [i.e., weight (kg)/height $(m)^2$] by the quotient of albumin (g/dL) and neutrophil-to-lymphocyte ratio (NLR) (i.e., ALI=BMI*Albumin/NLR). NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. Considering methods and findings from prior studies and meta analysis of ALI as a predictor of overall survival (Hua et al., 2019; Jafri et al., 2013), 24 was used as an accepted and empirically-supported cutoff for analyses, with ALI ≤ 24 indicating higher levels of inflammation.

Covariates. Age, race, sex, partner status, education level, and employment status were considered. Also considered were clinical and disease variables as follows: lifetime smoking history, cancer cell type, and first line treatment to be received (if any) as abstracted from medical records.

Analytic Plan

Sample descriptive data for sociodemographic (age, race, sex, partner status, education level, employment status) and clinical and disease characteristics (lifetime smoking history, BMI, cancer cell type, first line of treatment) are reported.

Four depression/inflammation groups using cutoff inflammation values and depression scores at baseline were identified: Profile 1 (LoDep/LoInf), Profile 2 (LoDep/HiInf), Profile 3 (HiDep/LoInf), and Profile 4 (HiDep/HiInf). Cutoffs indicating low and high levels of depression (low: PHQ<8) and inflammation (low: ALI>24) identified as standard from prior studies and meta-analyses were used (Andersen et al., (in press); Andersen et al., 2014, Hua et al., 2019). Published data with this sample using this cutoff confirmed lower ALI levels (higher inflammation) to be predictive of worse 2 year overall survival (HR = 0.53; p = 0.005) for this sample (Andersen et al., 2023) (see Figure 2).

Pearson correlations and biserial correlations between depressive symptoms and sociodemographic characteristics were examined. One-way ANOVAS were used to test for associations between depressive symptoms and clinical and disease characteristics. Normality of PHQ-9 score distribution was examined with a histogram. Boxplots of standardized PHQ-9 scores tested for outliers in both the overall sample and each profile group.

Linear mixed models were estimated to test for differences in depressive symptom trajectories for the four baseline depression/inflammation profile groups from baseline to 8 months. Linear mixed models (i.e., mixed effects models) examine variation of coefficients between multiple groups of observations and are appropriate for analysis

of dependent data, including data from repeated measures designs. Further, this modeling allows testing of both fixed and random effects, as well as correlated residual errors. Two models were tested. Model 1 was the simple model without controlling for covariates to allow for comparison of best model fit. Model 2 included sociodemographic, clinical, and disease characteristics significantly associated with depressive symptoms at one or more timepoints ($p < .05$) within the model as controls.

The following were included as fixed effects in each model: baseline depression/inflammation profile Group (LoDep/LoInf, LoDep/HiInf, HiDep/LoInf, and HiDep/HiInf), Time (baseline, 1 month, 2 months…8 months), and the interaction between Group and Time. Both models included patient ID (intercept) as a random effect to allow for individual values of baseline depressive symptoms. Additionally, the specification that observations closer in time are more strongly correlated with observations more distant in time was applied by use of a first order autoregressive [AR(1)] covariance structure was included in both models. Models were compared for best fit using Akaike (AIC) and Bayesian (BIC) information criterions. Comparatively lower AIC and BIC coefficients indicate better model fit.

Covariates for analysis were selected based on a cutoff of $p < .05$ to avoid overfitting the model. Significant interactions were probed by comparing simple main effects. To test the assumption of linearity, standardized fitted values for each model were plotted against the standardized residuals with a locally weighted smoothing (LOESS) curve. An approximately linear relationship around zero indicates the assumption is met. Q-Q plots of the standardized residuals for both models were examined to test the normality of residuals assumption. An approximately linear arrangement of data indicates that the

assumption is met. The plots of standardized fitted values against the standardized residuals were examined for change in variance around zero to test for signs of heteroscedasticity. Analyses were performed using R 4.1.1. (Team RC, 2021).

Results

Preliminary

Sample size at each follow-up were as follows: $N = 156$ (1 month), $N = 144$ (2 months), $N = 127$ (3 months), $N = 121$ (4 months), $N = 108$ (5 months), $N = 98$ (6 months), $N = 98$ (7 months), $N = 97$ (8 months). Descriptive statistics of mean and standard deviation for sociodemographic, clinical, and disease characteristics for the sample are provided in Table 1. Age ($r(1129)=-.109$, $p<.001$), partner status ($r(1129)=-.14$, $p<.001$), education status ($r(1129)=-.12$, $p<.001$), lifetime lifetime smoking history ($F(1, 1129)=19.68$, $p<.001$) were found to be significantly correlated ($p < .05$) with depressive symptoms (PHQ-9) and were included as controls in Model 2. A positively skewed distribution of PHQ-9 scores was observed, thus a square root transformation of scores was used. Associations between candidate control variables and linear mixed model outcome variable (square root transformed PHQ-9) are provided in Table 2. Five outliers of square root transformed PHQ-9 scores were observed in the overall sample but were retained due to the lack of outliers in the individual profile boxplots.

Descriptive statistics of depressive symptoms at baseline for each profile group are provided in Table 3. Standardized predicted values plotted against standardized residuals revealed that the linearity assumption was met for both models. Standardized residuals were then examined with Q-Q plots for each model which indicated that the normality assumption was also met for both models. No signs of heteroscedasticity were

observed in the plots of standardized predicted values against the standardized residuals, indicating that the assumption of homoscedasticity was met. Fit statistics of each model are reported in Table 4. Akaike and Bayesian information criterions indicated that the absence of covariates in Model 1 improved model fit compared to Model 2.

Primary

Statistics for both linear mixed models predicting depressive symptom trajectories are reported in Table 5.

Model 1. The simple model without covariates showed baseline depression and inflammation profile group was a significant predictor of depressive symptoms for the two profiles with high depressive symptoms at baseline (Profile 3, HiDep/LoInf; Profile 4, HiDep/HiInf) across the 8-month follow-up period ($F(3,178) = 1.54$, $p < .001$; $F(3,178) = 1.12$, $p < .001$). Specifically, patients in Profile 3 and Profile 4 reported higher depressive symptom severity than patients in Profile 1 (LoDep/LoInf). Profile 2 (LoDep/HiInf) was not a significant predictor of depressive symptoms across the 8-month follow-up period ($F(3,178) = .176$, $p = .331$). Time was not a significant predictor of depressive symptoms with the inclusion of Profile 2 (LoDep/HiInf) ($F(8,945) = -0.01$, $p = .266$). Interactions between Profile 2 (LoDep/HiInf) and time ($F(24,945) = .00$, $p = .786$) and between Profile 3 (HiDepLoInf) and time ($F(24,945) = -.03$, $p = .102$) were not significant. As hypothesized, there was a significant interaction between Profile 4 (HiDepHiInf) and time ($F(24,945) = -.04$, $p = .001$), indicating Profile 4 (HiDep/HiInf) membership at baseline was a significant predictor of the depressive symptom trajectory.

Model 2. Controlling for age, partner status, education level, and lifetime smoking history, baseline depression/inflammation profile was a significant predictor of

depressive symptoms for profiles with high depressive symptoms at baseline (Profile 3, HiDep/LoInf; Profile 4, HiDep/HiInf) across the 8-month follow-up period ($F(3,173) = 1.51$, $p < .001$; $F(3,173) = 1.11$, $p < .001$), confirming the Model 1 results. Profile 2 (LoDep/HiInf) was not a significant predictor of depressive symptoms across the 8-month follow-up period ($F(3,173) = .17$, $p = .347$). Time was not a significant predictor of depressive symptoms with the inclusion of Profile 2 (LoDep/HiInf) ($F(8,945) = -0.01$, $p = .263$). Similar to Model 1, interactions between Profile 2 (LoDep/HiInf) and time ($F(24,945) = .00$, $p = .768$) and between Profile 3 (HiDep/LoInf) and time ($F(24,945) = -.03$, $p = .101$) were not significant. Again, there was a significant interaction between Profile 4 (HiDep/HiInf) and time ($F(24,945) = -.04$, $p = .001$). This indicates Profile 4 (HiDep/HiInf) membership as a significant predictor of the depressive symptom trajectory, controlling for age, partner status, education level, and lifetime smoking history.

To illustrate the depressive symptom trajectory at the patient level, Figure 4 displays depressive symptoms from baseline through 8 months for each depressive symptom/inflammation profile group. Raw group means at each time point are displayed, and superimposed locally estimated scatterplot smoothing (LOESS) curves indicate the depressive symptom trajectory for each group. Boxplots of depressive symptoms from baseline through 8 months for each baseline depressive symptom/inflammation profile (Figure 5) are also provided, also indicating group *n* at each followup. Figures 5 and 6 display flat trajectories of low depressive symptoms across time for Profile 1 (LoDep/LoInf) and Profile 2 (LoDep/HiInf). Greater variability of the depressive symptom trajectory are observed in spaghetti (Figure 4) and boxplots (Figure 5) of

Profile 3 (HiDep/LoInf) and Profile 4 (HiDep/HiInf). Larger standard error and higher standard deviation are displayed in plots of Profile 3 (HiDep/LoInf), while tighter standard error and standard deviation is observed in plots of Profile 4 (HiDep/HiInf), increasing confidence for the reported effect.

Discussion

Independently, depression and systemic inflammatory biomarkers are known predictors of advanced NSCLC survival (Andersen et al., 2022; Kazandjian et al., 2019) and have been shown to be significantly associated at diagnosis (baseline) (Andersen et al., 2023). Novel data show that the interaction of elevated baseline depressive symptoms (PHQ-9) and high inflammation (ALI) contribute differentially to a worsened depression trajectory from diagnosis to 8 months, adjusting for sociodemographic and lifetime smoking history variables. Biological and psychological domains often viewed as disparate were found to be predictive of distinct vulnerability to the continuation of elevated depressive symptoms for patients with a high depression and high inflammation comorbidity compared to all other groups at diagnosis, including those with high depression but low inflammation.

As anticipated, depression trajectories of the two groups with low depressive symptoms at baseline (Profiles 1 and 2) were not significantly different, regardless of inflammation level ($F(24,945) = .00$, $p = .786$; $F(24,945) = .00$, $p = .768$). Results confirmed our hypothesis of comorbid high depressive symptoms and high inflammation at baseline as predictive of worsened depression trajectory compared to all other groups ($F(24,945) = -.04$, $p = .001$; $F(24,945) = -.04$, $p = .001$), including patients with high depressive symptoms but low inflammation ($F(24,945) = -.03$, $p = .102$; $F(24,945) =$

-.04, p = .001). This effect was observed in both the simple linear mixed model and the model controlling for age, partner status, education level, and lifetime smoking history as covariates.

These data are in the context of immune-based therapies being established as standard of care in patients with NSCLC (Ettinger et al., 2022). As these therapies yield improved treatment outcomes and survival, patient quality of life, treatment followup (return to clinic; Arrietta et al., 2014), and treatment response are of increasing salience, and each are negatively impacted by depressive symptoms (Sullivan et al., 2016). Further, data have shown the *continuing trajectory* of depressive symptoms from diagnosis through two years predicts NSCLC overall survival (HR=1.09 per unit increase of depressive symptoms, 95% CI=1.03–1.15, p=.002; Andersen et al., 2022), meaning patients vulnerable to maintained high depressive symptoms across time are at increased risk of mortality above and beyond that associated with NSCLC occurance.

A large proportion of patients—35% found here—had significant depressive symptoms prior to receipt of immune-based therapy, and 25% had attendant high inflammation, a profile now shown to have a differentially worse depression trajectory. That is, patients with both high inflammation and high depressive symptoms at baseline are at increased risk of maintaining depressive symptoms from diagnosis through 8 months compared to other groups. The mechanism whereby depression (including maintained depression) leads to reduced treatment response or poorer survival is likely multifactorial, but the current literature supports a model in which attendant inflammation exerts an inhibitory effect on immune function (Andersen et al., 2023; Dowlati et al., 2010; Osimo et al., 2019; Zhou et al., 2021). These data support further investigation of

maintained depression and its mechanisms in relation to the efficacy of current therapeutic modalities. The necessity of depression intervention at time of diagnosis for NSCLC patients with comorbid high depression and inflammation is also clear.

Important findings are considered with regards to generalizability, methodology, and measures used. Patients were contained in one geographical region (Ohio), and 50% were from rural Appalachia counties. Most were receiving cancer treatment at the time of the study, and each was diagnosed with advanced lung cancer. Measure completion across followup reflected longer survival of over half the sample (*N*= 97 at 8 month followup) than average NSCLC mortality (~5 months; Li et al., 2019). Results may not be generalizable to other patients with NSCLC, earlier staged disease, other cancers, or receiving treatment at other clinics. The sample also had comparatively low ethnic and racial diversity (18% vs. 22% nationally in the US) (US Census Bureau, 2021), potentially limiting generalizability.

Other strengths and weaknesses are considered. Uniform timing of data collection during the difficult diagnostic period was clinically and methodologically important, and there were no age or functional status exclusions. With disease prognosis considered, longitudinal study of NSCLC patients is salient. The cohort study has an 80% mean completion rate of available *N* across followups from diagnosis up to 24 months, and the sample was at least equal to if not larger than those found in multiple SIR meta analyses (Ayers et al., 2021; Jin et al., 2020; Sacdalan et al., 2018; Xu et al., 2019) and sufficient for this first test of depression trajectories from diagnosis through 8 months predicted by baseline profiles of depression and inflammation. ALI is an accurate and precise survival predictor (Winther-Larsen et al., 2021; Andersen et al., 2023), and the PHQ-9 has

equivalent psychometric strengths (Mitchell et al., 2016). A robust range of depressive symptoms were present in this sample. Diagnostic interviews were not done, with the number of patients with MDD unknown. However, MDD criterion symptoms (e.g., low mood, anhedonia, cognitive difficulties, hopelessness, and suicidality) were endorsed by the patients, as has been the case in other studies of depressed NSCLC patients (Andersen et al., 2022; Andersen et al., 2020; Presley et al., 2021; Valentine et al., 2022).

In conclusion, NSCLC patients are uniquely vulnerable to the occurrence and effects of comorbid depression and inflammation. A notable proportion of NSCLC patients present with depression at diagnosis, and these data provide a new understanding of the impact of depression/inflammation comorbidity on the depression trajectory. That is, patients with high depressive symptoms *and* high inflammation at diagnosis are uniquely vulnerable to maintenance of moderate to severe depressive symptoms, significantly more so than other groups, including those with high depression and low inflammation at diagnosis. Depression intervention at time of diagnosis is exceedingly important for these vulnerable patients, as the continuing trajectory of depressive symptoms predicts NSCLC overall survival (Andersen et al., 2022). Intensive study of the interaction of the depression trajectory and measures of biology, inflammation, and immunity among patients with NSCLC is needed to extend these findings and discover their impact and mechanisms, with the long term aim to improve patients' quality of life, treatment responses, and longevity.

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Appendix A: Tables

Table 1. Sociodemographic and disease characteristics of NSCLC sample (N=182)

	n (%) or Mean ± *SD*
Sociodemographic	
Age	63.25 ± 10.66
Range	34-86
Race	
Caucasian	150 (82.4%)
Non-Caucasian	32 (17.6%)
Ethnicity (% Hispanic)	3 (1.6%)
Sex (% Male)	108 (59.3%)
Partner Status (% married/partnered)	108 (59.3%)
Education	
≤ High School	82 (45.1%)
> High School	100 (54.9%)
Employment Status (% Not Employed)	138 (75.8%)
Disease and Clinical	
BMI Category	
Underweight or Healthy weight	72 (39.6%)
Overweight	53 (29.1%)
Obese	57 (31.3%)
Smoking (% Ever)	154 (84.6%)
Never	28 (15.4%)
Former	123 (67.6%)
Current	31 (17.0%)
Cancer Cell Type	
Adenocarcinoma	143 (78.6%)
Squamous	23 (12.6%)
Adenosquamous	4 (2.2%)
Large Cell	4 (2.2%)
Not Otherwise Specified / Other	8 (4.4%)
Treatment (% Subsequently receiving treatment)	166 (91.2%)
First Line Treatment	
No Treatment	16 (8.8%)
Chemotherapy	30 (16.5%)
Immunotherapy	41 (22.5%)
Targeted Therapy	31 (17.0%)
Chemotherapy + Immunotherapy	60 (33.0%)
Chemotherapy + Targeted Therapy	4 (2.2%)

Table 2. Associations between candidate control variables and the linear mixed model outcome variable, standardized PHQ-9) (N = 186)

Sociodemographic	
Age	-.109*
Race	.049
Sex	.045
Partner Status	-.141*
Education Level	-.124*
Employment Status	-.077
Disease and clinical ^	
Lifetime Smoking History	19.680*
Cancer Cell Type	2.927
First Line of Treatment	.602

Note. Levels for dichotomous variables are reported in Table 1
* Significant at the .05 level, two-tailed
^ ANOVA F-values reported

Table 3. Baseline PHQ-9 and ALI scores for depression/inflammation profile group

	Mean ± *SD*	**Mean ± *SD***
Depression/Inflammation Profile	PHQ-9	ALI
Profile 1: LoDep/LoInf (n=50)	3.706 ± 2.023	43.471 ± 14.144
Standardized	1.801 ± .686	
Profile 2: LoDep/HiInf (n=68)	3.22 ± 2.376	13.027 ± 5.709
Standardized	1.574 ± .871	
Profile 3: HiDep/LoInf (n=19)	11.378 ± 3.898	41.497 ± 16.820
Standardized	3.332 ± .533	
Profile 4: HiDep/HiInf (n=45)	13.421 ± 4.880	9.993 ± 6.581
Standardized	3.608 ± .652	

Note. Cutoffs: PHQ-9 <8 = LoDep, ALI > 24 = LoInf. PHQ-9 symptom classifications: none/mild (0-7), moderate (8-14), moderate to severe (15-19), and severe (20-27).

Table 4. Fit statistics of Model 1 (simple) and Model 2 (Model 1 + significant covariates) for Akaike Informattion Criterion (AIC) and Bayesian Information Criterion (BIC)

	AIC	**BIC**
Linear mixed model		
Model 1	1813.860	1869.121
Simple		
Model 2	1833.238	1913.547
Significant covariates included		

Note. Lower comparative AIC and BIC coefficients indicate better model fit

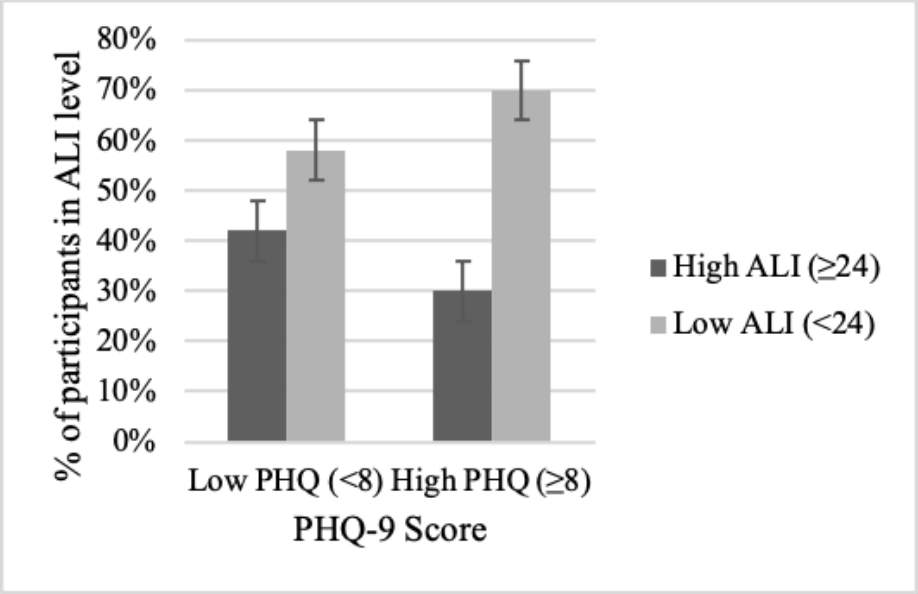
Table 5. Linear mixed model analyses testing baseline depression/inflammation profiles as predictors of the group depressive symptom trajectory from baseline to 8 months (N = 182)

Model	Predictor	*F*	*df*	*p*
Model 1 Simple model	Profile 2 (LoDep/HiInf)	.176	178	.331
	Profile 3 (HiDep/LoInf)	1.539	178	.000*
	Profile 4 (HiDep/HiInf)	1.120	178	.000*
	Time	-.009	945	.266
	Profile 2 (LoDep/HiInf) X Time	.003	945	.786
	Profile 3 (HiDep/LoInf) X Time	-.027	945	.102
	Profile 4 (HiDep/HiInf) X Time	-.042	945	.001*
Model 2 (Model 1 + Covariates)	Age	-.008	173	.254
	Partner Status	-.094	173	.541
	Education Level	-.033	173	.821
	Smoking History, Former	.151	173	.469
	Smoking History, Current	.410	173	.111
	Profile 2 (LoDep/HiInf)	.172	173	.347
	Profile 3 (HiDep/LoInf)	1.508	173	.000*
	Profile 4 (HiDep/HiInf)	1.111	173	.000*
	Time	-.009	945	.263
	Profile 2 (LoDep/HiInf) X Time	.003	945	.768
	Profile 3 (HiDep/LoInf) X Time	-.027	945	.101
	Profile 4 (HiDep/HiInf) X Time	-.042	945	.001*

Note. Profile 1 (LoDep/LoInf) is used for comparison in the linear mixed models

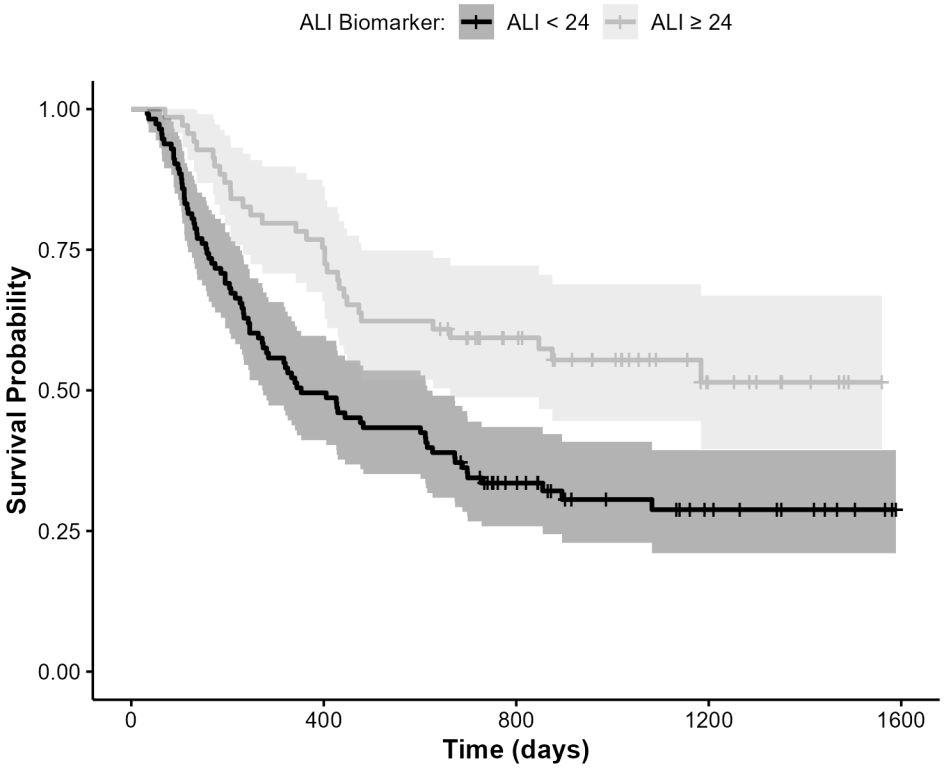
Appendix B: Figures

Figure 1. NSCLC patients classified into PHQ/ALI subgroups



Note. Patients with no/low depressive symptoms were as likely to have low ALI as to have high ALI (left side). In contrast, for patients with moderate/severe depressive symptoms, significantly more patients had prognostically worse, low ALI rather than high ALI (right side). Percentage data are provided with error bars.
From Andersen, Blevins, Park, …. & Carson. (2023). Depression in association with neutrophil-to-lymphocyte, platelet-to-lymphocyte, and advanced lung cancer inflammation index biomarkers predicting lung cancer survival. *PLoS ONE 18*(2), e0282206.

Figure 2. Kaplan Meier survival curve for NSCLC patients stratified by ALI systemic inflammation, ALI < 24 and ALI ≥ 24 (n=182), showing worse survival probability ($p<0.005$) for patients having greater inflammation (i.e., below ALI cutoff)



Note. From Andersen, Blevins, Park, …. & Carson. (2023). Depression in association with neutrophil-to-lymphocyte, platelet-to-lymphocyte, and advanced lung cancer inflammation index biomarkers predicting lung cancer survival. *PLoS ONE 18*(2), e0282206.

Figure 3. Study flow

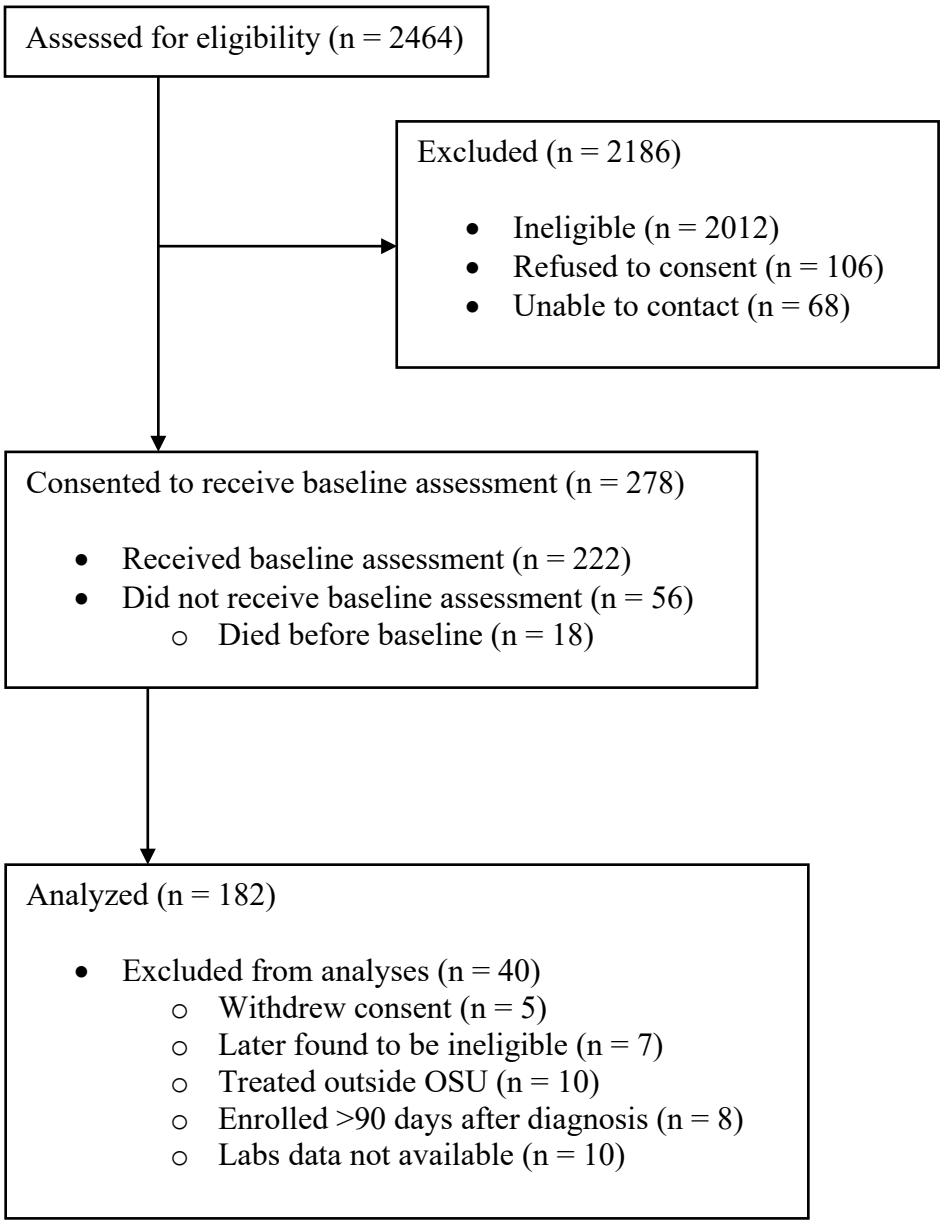
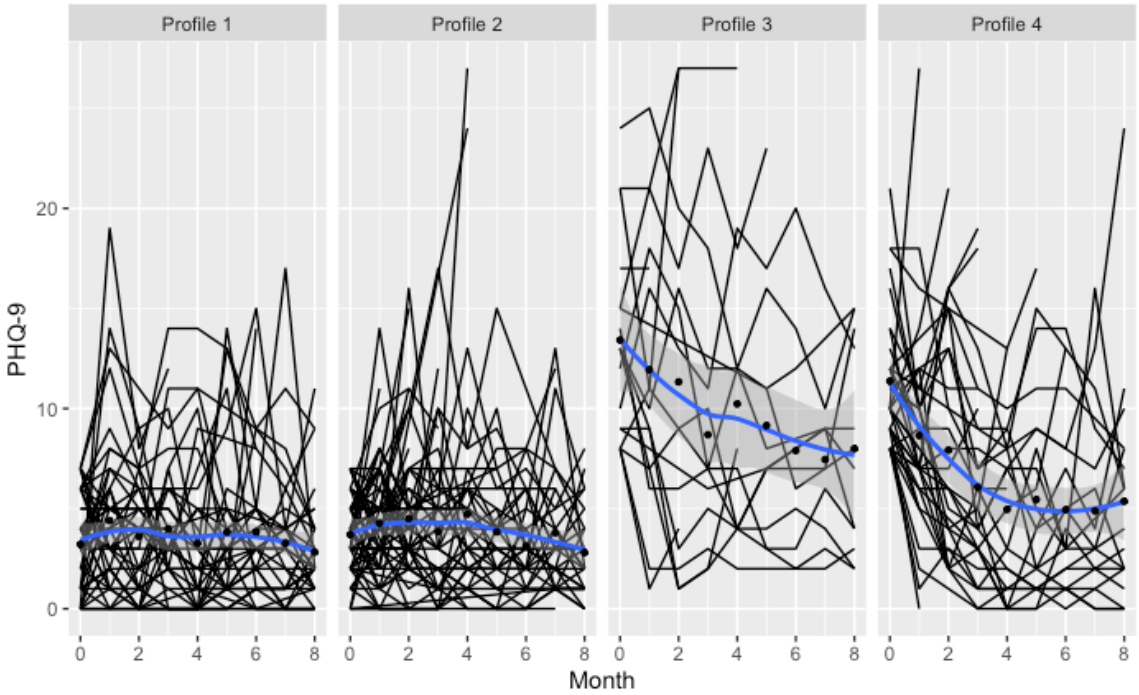


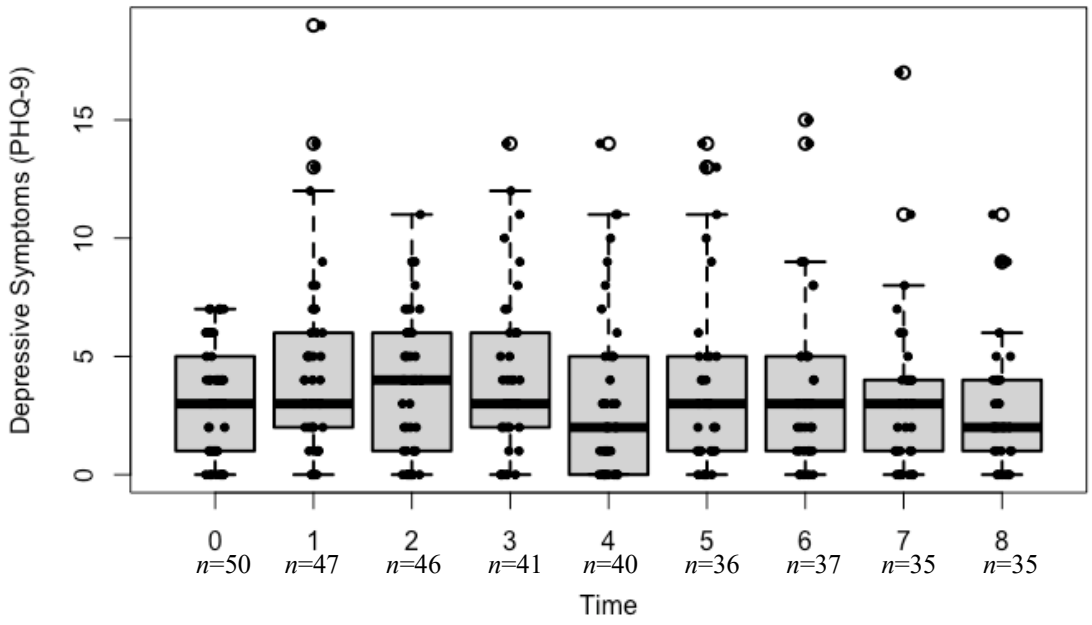
Figure 4. Spaghetti plots with superimposed LOESS curves showing the depressive symptom trajectory from baseline through 8 months for each basline depressive symptom/inflammation profile



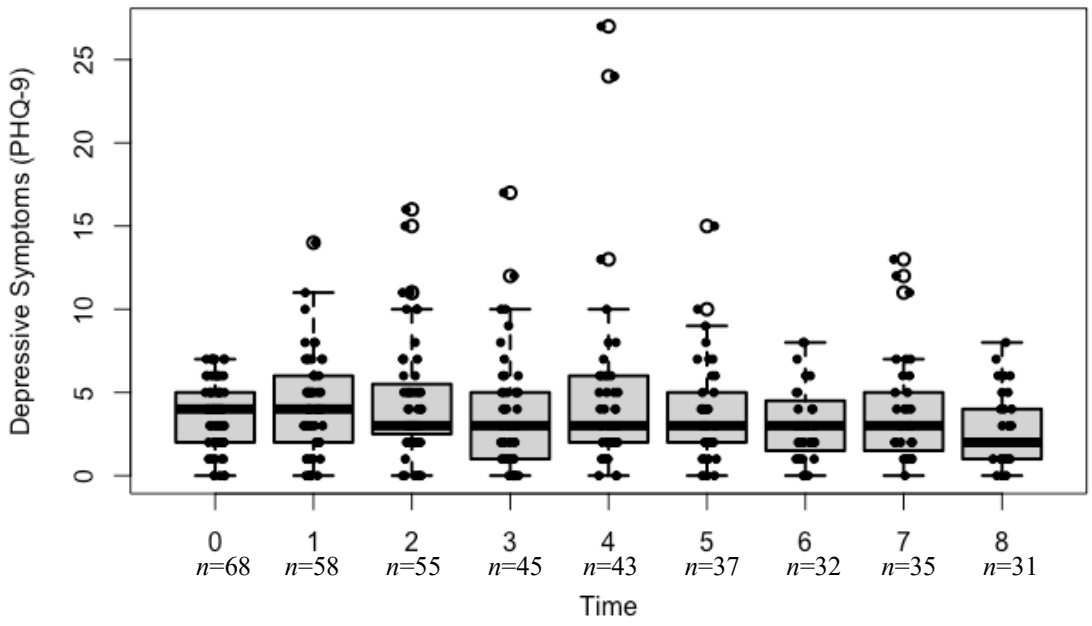
Note. Profile 1 = low depressive symptoms and low inflammation (n=50), profile 2 = low depressive symptoms and high inflammation (n=68), profile 3 = high depressive symptoms and low inflammation (n=19), profile 4 = high depressive symptoms and high inflammation (n=45). Black dots = raw means; shading = standard errors; blue lines = locally estimated scatterplot smoothing (LOESS).

Figure 5. Boxplots showing depressive symptom trajectory for each baseline depressive symptom/inflammation profile from baseline through 8 months

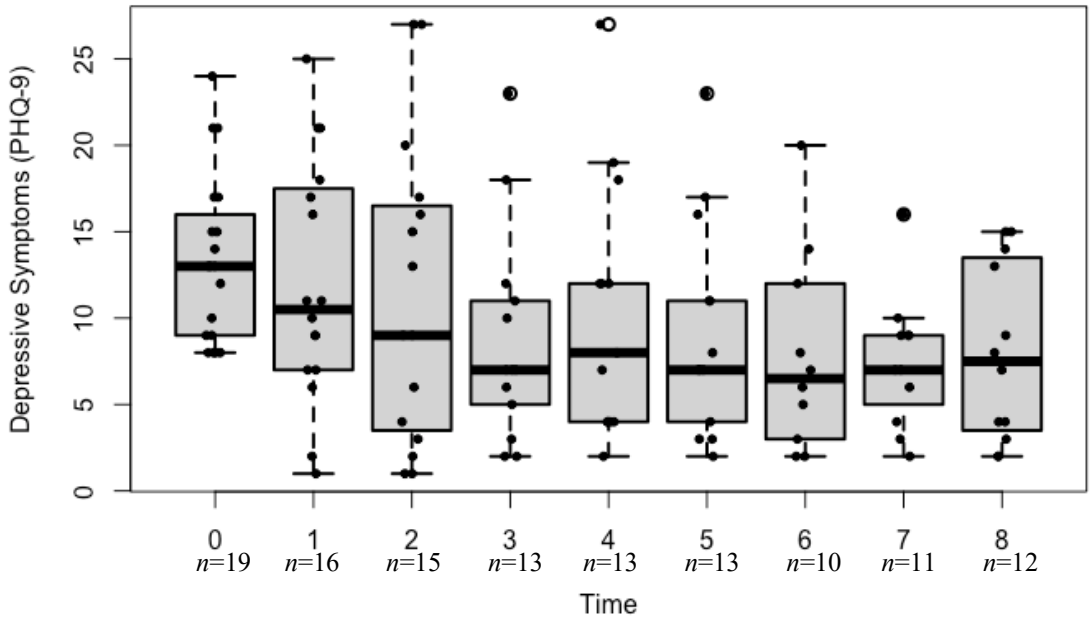
Profile 1 (LoDep/LoInf)



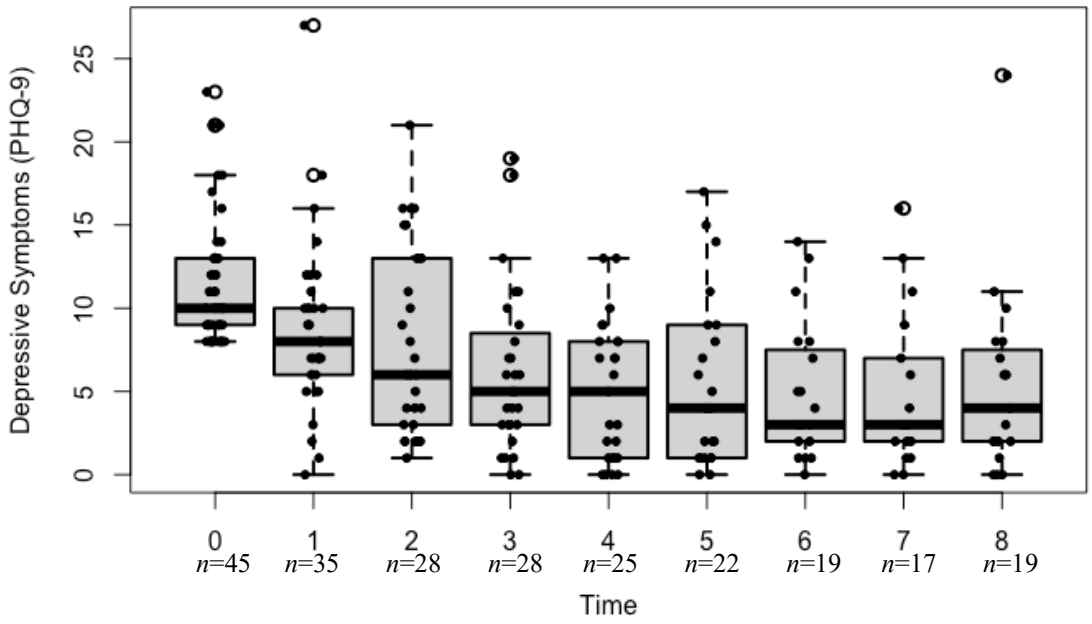
Profile 2 (LoDep/HiInf)



Profile 3 (HiDep/LoInf)



Profile 4 (HiDep/HiInf)



Appendix C: Measures

The Patient Health Questionnaire-8

Subject ID

Assessment

Feelings in the Past Two Weeks
BLCIO PHQ-9

Over the past TWO WEEKS, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	⊙	⊙	⊙	⊙
2. Feeling down, depressed or hopeless	⊙	⊙	⊙	⊙
3. Trouble falling or staying asleep, or sleeping too much	⊙	⊙	⊙	⊙
4. Feeling tired or having little energy	⊙	⊙	⊙	⊙
5. Poor appetite or overeating	⊙	⊙	⊙	⊙
6. Feeling bad about yourself--or that you are a failure or have let yourself or your family down	⊙	⊙	⊙	⊙
7. Trouble concentrating on things, such as reading the newspaper or watching television	⊙	⊙	⊙	⊙
8. Moving or speaking so slowly that other people could have noticed? Or the opposite--being so fidgety or restless that you have been moving around a lot more than usual	⊙	⊙	⊙	⊙
9. Thoughts that you would be better off dead or hurting yourself in some way	⊙	⊙	⊙	⊙

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

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
⊙	⊙	⊙	⊙

Sociodemographic Questionnaire

BLCIO

II. SOCIODEMOGRAPHICS

Next, I have some general background questions.

1. What is your gender?
   - o MALE (1)
   - o FEMALE (2)
   - o OTHER (3)
   - o DON'T KNOW (98)
   - o REFUSED (99)

2. Are you of Latina, Latino, or Hispanic ancestry?
   - o YES (1)
   - o NO (0)
   - o DON'T KNOW (98)
   - o REFUSED (99)

3. What is your racial/ethnic group? Please say yes or no for each option. Are you...
   - □ Caucasian/White
   - □ African-American/Black
   - □ Asian
   - □ American Indian/Alaskan Native
   - □ Native Hawaiian/Other Pacific Islander
   - □ Other (please specify)
   - □ DON'T KNOW
   - □ REFUSED

4. What is your marital status? Are you...
   - o Currently married (1)
   - o Single, never married (2)
   - o Separated or divorced (3)
   - o Widowed (4)
   - o DON'T KNOW (98)
   - o REFUSED (99)

5. Are you currently living with a significant other, that is, a husband, wife, or long-term romantic partner?
   - o YES (1)
   - o NO (0)
   - o DON'T KNOW (98)
   - o REFUSED (99)

6. IF MARRIED: How long have you been married?
   IF LIVING WITH A PARTNER: How long have you been living together?
   RESPONSES: _____
   o DON'T KNOW (98)
   o REFUSED (99)

   INTERVIEWERS: IF 1 YEAR OR LESS, ENTER 1.

   (Programming instructions: item asked of those who are "currently married" in Q4 and/or answered "yes" to Q5)

7. How many children under the age of 18 are living in your home?
   RESPONSES: _____
   o DON'T KNOW (98)
   o REFUSED (99)

8. What is the highest level of formal education that you have completed?
   o 8th grade or less (1)
   o Some high school (2)
   o Completed high school/GED (3)
   o Technical, vocational, or certificate program (4)
   o Some college (no degree) (5)
   o Associate's degree (6)
   o Bachelor's degree (7)
   o Some graduate school (8)
   o Master's degree (9)
   o Doctoral degree (MD, PhD, JD) (10)
   o DON'T KNOW (98)
   o REFUSED (99)

9. What is your current job status? Are you…
   o Retired, but working part or full time (1)
   o Retired (2)
   o Employed full time (that is, 30 or more hours a week) (3)
   o Employed part-time (that is, less than 30 hours a week) (4)
   o Temporarily unemployed, seeking employment (5)
   o Disabled (6)
   o Homemaker, raising children, care of others (7)
   o Other (please specify) (8)
   o DON'T KNOW (98)
   o REFUSED (99)

10. On average, how many hours per week do you currently work for pay?
    RESPONSES: _____
    o DON'T KNOW
    o REFUSED

11. How many days in the last month did you take sick days or time off because of physical health problems or emotional difficulties?
RESPONSES: _____
o DON'T KNOW (98)
o REFUSED (99)

(Programming instructions: item asked of those who currently employed (answered 1, 3, or 4 to Q9))

12. IF EMPLOYED: What is your occupation?

IF NOT EMPLOYED: What was your occupation at your last full time job?

INTERVIEWERS: PROBE FOR SPECIFICS ABOUT TYPE OF WORK IF NEEDED.

RESPONSES: _____
o DON'T KNOW (98)
o REFUSED (99)

13. Could you please tell me how much income you and the other members of your household received in 2016, before taxes? We don't need the exact amount; please just tell me which of these broad categories it falls into:
o $15,000 or less (1)
o $15,001 - $25,000 (2)
o $25,001 - $35,000 (3)
o $35,001 - $50,000 (4)
o $50,001 - $75,000 (5)
o $75,001 - $100,000 (6)
o $100,001 - $150,000 (7)
o $150,001 - $200,000 (8)
o $200,001 - $250,000 (9)
o More than $250,000 (10)
o DON'T KNOW (98)
o REFUSED (99)

Current, Ever and Past Cigarette and E-cigarette use - Baseline

Cigarettes:

1. Have you EVER smoked a cigarette EVEN ONE TIME?
    - Yes
    - No (go to question #16)
    - DON'T KNOW
    - REFUSED

2. How old were you the first time you smoked part or all of a cigarette? (PATH ID: AC1006)
   ASK: Respondents who have ever smoked a cigarette.
   INTERVIEWER NOTES: Enter age in years.

   |___|___| YEARS

    - DON'T KNOW
    - REFUSED

3. About how long has it been since you last smoked a cigarette? (PATH ID: AC1009)
   ASK: Respondents who ever smoked a cigarette.
   INTERVIEWER NOTES: If it was earlier today, enter 1 day.

   |___|___| DAYS

   |___|___| MONTHS

   |___|___| YEARS

    - DON'T KNOW
    - REFUSED

4. Have you ever smoked cigarettes fairly regularly? (PATH ID: AC1100)
   ASK: Respondents who have ever smoked a cigarette.
    - Yes
    - No (go to question #7)
    - DON'T KNOW
    - REFUSED

5. How old were you when you first started smoking fairly regularly? (PATH ID: AC1007)
   ASK: Respondents who have ever smoked fairly regularly.
   INTERVIEWER NOTES: Enter age in years.

   |___|___| YEARS

    - DON'T KNOW
    - REFUSED

6. About how long have you or did you smoke fairly regularly? Do not count the time you stayed off cigarettes. (PATH ID: AC9002)
   ASK: Respondents who ever smoked fairly regularly

   |___|___| DAYS

   |___|___| MONTHS

   |___|___| YEARS

   - DON'T KNOW
   - REFUSED

7. Do you now smoke cigarettes every day, some days per week, occasionally, rarely, or not at all?
   ASK: Those who have ever smoked a cigarette
   - Every day
   - Some days per week (go to question #9)
   - Occasionally (go to question #9)
   - Rarely (go to question #9)
   - Not at all (go to question #16)
   - DON'T KNOW
   - REFUSED

~~8.~~ On average, about how many cigarettes do you now smoke each day? A pack usually has 20 cigarettes in it. (PATH ID: AC1021)
   ASK: Only those who smoke cigarettes every day:
   _____(number)
   - DON'T KNOW
   - REFUSED