Considering comorbidities and individual differences in testing a gaming Behavioral Activation app for perinatal depression and anxiety; A pilot study

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Abstract

Background: Mobile Behavioral Activation (BA) is efficacious for the treatment of perinatal depression, however, the effect of comorbidity on symptom trajectories remains underexplored which is important given that at least 10% of women in the perinatal period experience comorbid anxiety and depression (CAD).

Objective: Our objective was to assess whether there are differences in symptom trajectories in pregnant participants with Comorbid Anxiety and Depression (CAD) as compared to those same with depression only (i.e., Major Depressive Disorder; MDD) during intervention with a Behavioral Activation (BA) mobile gaming app.

Methods: Pregnant adults with either CAD (n = 10) or MDD (n = 7) used a BA app for 10 weeks and completed biweekly symptom severity questionnaires for depression and anxiety. We assessed whether baseline diagnoses were associated with differential symptom trajectories across the study with mixed effects longitudinal models.

Results: When controlling for baseline symptoms, results revealed a significant interaction between baseline diagnosis and the quadratic component of study week on anxiety (? = 0.06, SE = 0.02, t(63) = 2.94, p = .005), revealing a tendency for anxiety in CAD group to increase initially and then decrease at an accelerated rate, whereas MDD symptoms were relatively stable across time. There was a significant effect of linear time on PHQ-9 (? = -0.39, SE = 0.11, t(68) = -3.51, p = .001), showing that PHQ-9 declined steadily across time for both groups. There was a significant effect of baseline diagnosis on PHQ-9 (? = -8.53, SE = 3.93, t(13) = -2.17, p = .05), suggesting that those with MDD had higher PHQ-9 scores post- treatment compared to those with CAD when holding other predictors constant.

Conclusions: Findings underscore the need to consider comorbidities and individual variations in participants when developing scalable mobile interventions for perinatal populations. Clinical Trial: Not applicable

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Considering comorbidities and individual differences in testing a gaming Behavioral Activation app for perinatal depression and anxiety

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ABSTRACT

Introduction: Mobile Behavioral Activation (BA) is efficacious for the treatment of perinatal depression, however, the effect of comorbidity on symptom trajectories remains underexplored which is important given that at least 10% of women in the perinatal period experience comorbid anxiety and depression (CAD). Our objective was to assess whether there are differences in symptom trajectories in pregnant participants with Comorbid Anxiety and Depression (CAD) as compared to those same with depression only (i.e., Major Depressive Disorder; MDD) during intervention with a Behavioral Activation (BA) mobile gaming app. **Methods:** Pregnant adults with either CAD (n = 10) or MDD (n = 7) used a BA app for 10 weeks and completed biweekly symptom severity questionnaires for depression and anxiety. We assessed whether baseline diagnoses were associated with differential symptom trajectories across the study with mixed effects longitudinal models. **Results:** When controlling for baseline symptoms, results revealed a significant interaction between baseline diagnosis and the quadratic component of study week on anxiety (β = 0.06, SE = 0.02, $t(63)$ = 2.94, p = .005), revealing a tendency for anxiety in CAD group to increase initially and then decrease at an accelerated rate, whereas MDD symptoms were relatively stable across time. There was a significant effect of linear time on PHQ-9 (β = -0.39, SE = 0.11**,** $t(68)$ = -3.51, p = .001), showing that PHQ-9 declined steadily across time for both groups. There was a significant effect of baseline diagnosis on PHQ-9 (β = -8.53, SE = 3.93, $t(13)$ = -2.17, p = .05), suggesting that those with MDD had higher PHQ-9 scores post- treatment compared to those with CAD when holding other predictors constant. **Conclusions:** Findings underscore the need to consider comorbidities and individual variations in participants when developing scalable mobile interventions for perinatal populations.

Key Words: Perinatal Anxiety; Perinatal Depression; Behavioral Activation; Digital Mental Health

INTRODUCTION

During the perinatal period, 19-40% of women experience anxiety or depression, and at least 10% experience comorbid anxiety and depression (CAD; [1,2]). Despite its prevalence, CAD in perinatal populations is relatively underexplored [3]. CAD is associated with greater symptom severity, decreased treatment response, and longer episode duration [2,3]. Therefore, more research is needed assessing treatment considerations for perinatal individuals with CAD.

Behavioral Activation (BA) is a behavioral intervention that aims to boost engagement in pleasurable activities, emphasizing value-driven behaviors and avoidance reduction, and is efficacious for the treatment of perinatal depression and anxiety [4]. There is increasing interest in the development of scalable digital mental health interventions for perinatal populations [5]. Few studies focus on individual differences in mobile BA treatment outcomes [6]. Vanderkruik and colleagues' [7] pilot study on the feasibility and acceptability of a BA gaming app for pregnant women suggests its potential to decrease depression symptoms during pregnancy, though the effect of comorbidity on symptom trajectories remain unexplored [7]. In the present study, we assess differences in anxiety and depression symptom trajectories in participants with either CAD or depression only (i.e., Major Depressive Disorder; MDD).

METHODS

Recruitment

Participants (pregnant adults, native English speakers, smartphone users, at least moderately depressed; [7]) were recruited between 2021–2022 via clinician referrals

and social media. Ineligibility criteria included imminent risk of self-harm, current substance abuse, psychotic disorder, or active mania. All participants (N = 18) met DSM-5 criteria for a current Major Depressive Episode, ten of whom additionally met criteria for generalized anxiety disorder (GAD) as assessed by the Mini International Neuropsychiatric Interview (MINI; [8]). One participant was dropped from enrollment due to active substance use, resulting in a final sample of N = 17.

The X Institutional Review Board approved study procedures. Participants were instructed to use the app for the 10-week study period and invited to complete daily "Adventures" (e.g. exercising, cleaning) in their real life to earn points and progress in the game. Participants completed surveys for depression and anxiety symptoms biweekly and post-treatment [7].

Measures

Eligibility was assessed at baseline with the MINI [8] a semi- structured interview conducted by a trained research assistant [7]. Participant grouping (CAD vs. MDD) was determined at baseline using MINI diagnostic criteria, where CAD were individuals who met DSM-5 criteria for GAD (excessive and difficult to control anxiety and worry for most days for *at least six-months* and three of the following symptoms; restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension , sleep disturbance; [8]) and MDD (a depressed mood for most of the day or anhedonia for *at least two-weeks* as well as five of the following symptoms; significant unintentional weight or appetite change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate or excessive guilt, decreased ability to concentrate or make decisions, and recurrent thoughts of death or suicidal ideation; [7]), whereas those in the MDD group only met criteria for MDD.

Self-reported anxiety and depression symptoms within the *past two-weeks* were measured

with the Generalized Anxiety Disorder-7 (GAD-7; [9]) and Patient Health Questionnaire-9 (PHQ-9; [10]), respectively.

Statistical Analysis

Given the scope of this pilot study, we chose a hypothesis-generating approach with the intent of informing future studies, though we expected to see less favorable depression and anxiety symptom trajectories (according to GAD-7 and PHQ-9, respectively) for CAD relative to the MDD group. The analyses were conducted in R(4.3.0). Demographic variables, group differences in reductions of anxiety and depression symptoms, and individual symptom trajectories by group were analyzed with descriptive statistics. Independent group-*T* tests explored differences in baseline measures of depression and anxiety by baseline diagnosis.

To assess individual variation in depression and anxiety symptom decreases over time within each group, we plotted individual participant data to visualize trajectories of change for anxiety and depression symptoms across time. To determine whether treatment outcomes changed differentially across time by baseline diagnosis while controlling for baseline depression and anxiety symptom levels, we used mixed effects longitudinal models. In separate models PHQ-9 and GAD-7 (hereafter referred to as depression and anxiety symptoms, respectively) were the dependent variables. Fixed predictors were baseline diagnosis group (CAD vs. MDD), time (linear and quadratic components of week in study), baseline depression or anxiety symptoms for the analysis of each of their respective dependent variables, and all two- and three-way interactions of Group, Time, and baseline depression and anxiety symptoms. Participant-

level covariates of baseline age and baseline week gestation were also included. The random effect was participant intercept. We progressively removed nonsignificant covariates and higher-order terms and reran the model. We checked the model residuals to ensure conformance to model assumptions of normality and calculated the proportion of variance in the dependent variable attributable to the fixed effects.

RESULTS

Out of 17 participants, 58.82% participants (*n* = 10) had CAD and 41.12% had MDD (*n* = 7) at baseline. Participants were primarily white, heterosexual, married, employed, and educated, with private health insurance (Table 1). There were no significant group differences in age (*MCAD* 33.4, *SDCAD* = 3.0; *MMDD* = 35.8, *SD*MDD = 2.7), weeks gestation at baseline (*M*CAD = 18.1, *SD CAD* = 8.4; *M*MDD = 15.1, *SD*MDD = 5.9), or baseline depression symptoms (*MCAD* = 12.8, *SDCAD* = 3.3; *MMDD* = 11.7, *SDMDD* = 3.5). There was no significant difference in baseline past two-week anxiety symptoms (*MCAD* = 10.7, *SDCAD* = 2.7; *MMDD* = 7.0, *SDMDD* = 2.7; Table 2). That is, while both diagnostic groups have similar past 2- week levels of anxiety, only the CAD group met full DSM-5 criteria GAD which requires a duration of at least 6-months of symptoms. The CAD group was 3.6 times more likely to be using psychotropic medications (CAD = 60%, MDD = 28.6%) though with this sample size, it did not reach statistical significance. The CAD group was 1.2 times more likely to be in therapy (CAD = 50%, MDD = 42.9%); findings did not reach significance.

There was no significant difference between the depression symptom mean change score for treatment completers from baseline to post-treatment for the CAD group compared to the MDD group (*MCAD* = -5.7, *SDCAD* = 4.3; *MMDD* = -6.0, *SDMDD* = 1.7; t(8) = 0.11, p = .92, 95% CI

for difference in means [-4.9-6.4]). There was also no significant difference in the anxiety

symptom mean change score for treatment completers from baseline to post-treatment for the CAD group compared to MDD group (*MCAD* = -4.0, *SDCAD* = 4.2; *MMDD* = 2.3, *SDMDD* = 6.5; t(8)

= -1.87, p = .09, 95% CI for difference in means [-14.1-1.5])).

Principal Results

When assessing individual-level trajectories of depression and anxiety symptom scores across study week by participant, we see within group variation both for depression and anxiety symptom scores (Figure 1). In the MDD group, most individuals' anxiety symptoms decreased over time, though one individual demonstrated an *increase* in anxiety. Some CAD individuals' anxiety increased before decreasing across time. While overall depression symptoms decreased over time, a few individuals in both groups displayed spikes in symptoms.

For mixed effects models, nonsignificant higher order terms and covariates were removed, and models rerun. Relevant to the assessment of any association of baseline diagnosis to change in anxiety across time controlling for baseline anxiety, there was a significant interaction between baseline diagnosis and quadratic study week (β = 0.06, *SE* = 0.02, *t*(63) = 2.94, *p* = .005). This interaction reflected a tendency for the CAD group anxiety symptoms to increase initially and then decrease at an accelerated rate, whereas the MDD groups' anxiety symptoms were relatively stable across time or even showed a slight "U" shape pattern across time (Figure 2). Overall, the fixed effects accounted for 33.9% of the total variance in the anxiety symptom scores. All other fixed effects of interest were nonsignificant (Table 3). For the assessment of baseline diagnosis on depression across time controlling for baseline depression, there was a significant effect of linear time on depression symptom scores (β = - 0.39, *SE* = 0.11**,** *t*(68) = -3.51, *p* < .001), showing that depression symptoms decline steadily across time for both groups. We also found a significant effect of baseline diagnosis on depression symptoms post-treatment (β = -8.53 , *SE* = 3.93, *t*(13) = -2.17, *p* = .05), suggesting

that being in the MDD group was associated with slightly higher depression symptom scores post-treatment compared to the CAD groups' post-treatment depression symptom scores across time (Figure 2), holding other predictors, (e.g., baseline depression symptoms), constant.

DISCUSSION

Principle Results

Our findings provide preliminary support for considering individual differences in baseline diagnostic characteristics when developing personalized mobile interventions, particularly in the context of treating perinatal individuals with psychological comorbidities. Individuals with CAD may experience an increase in anxiety symptoms prior to seeing any decrease in symptoms; future treatment personalization studies should assess whether notifying patients of this possibility improves treatment adherence. Findings of individual variability in anxiety and depression over time point to an opportunity for future more highly powered studies investigating risk for increasing anxiety and depression across treatment during pregnancy.

Regarding our hypothesis that the CAD group may have less favorable treatment trajectories, we instead found that depression symptoms decreased linearly across time for *both* groups, and that the MDD group had higher depression symptom scores post-treatment compared to the CAD groups' post-treatment scores across, providing evidence of the app's effectiveness in treating depression in individuals with different comorbidity profiles.

Limitations & Conclusions

This pilot study has several limitations (e.g., modest sample size, no control group; discussed further in X et al. [7]). Nevertheless, findings provide preliminary support for considering individual differences and comorbidities when developing scalable mobile interventions for perinatal populations. Further research involving an adequately powered

randomized control trial may further illuminate individual differences affecting the impact of mobile interventions.

Declarations

Author Contributions

LC, RV, GH, contributed to the study conception and design. Material preparation & data collection were performed by RV, LK, & CF. Analyses were performed by GH and CS and JL provided consultation. The first draft of the manuscript was written by GH with contributions from RV and CS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Funding was acquired by RV, supervision was provided by JL, RP, RM, LC, & RV.

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Conflicts of Interest

Gabriella E. Hamlett, MA: None

Chloe Schrader: None

Craig Ferguson, MS: None Lauren

A. Kobylski: None Rosalind

Picard, ScD: None Joseph J.

Locacio, PhD: None Richard J.

McNally, PhD: None

Lee S. Cohen, MD – *as of 2/26/2024*:

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Abbreviations

BA: Behavioral Activation

CAD: Comorbid Anxiety and Depression

GAD: Generalized Anxiety Disorder

GAD-7:Generalized Anxiety Disorder-7

PHQ-9: Patient Health Questionnaire-9

MDD: Major Depressive Disorder

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TABLES & FIGURES

Table 1. Demographics & Participant Characteristics

	Comorbid Anxiety and Depression (n=10)	Depression Only (n=7)	Total (N=17)
Age	33.4 (3.0)	35.8 (2.7)	34.4(3.1)
Weeks Gestation	18.1 (8.4)	15.1 (5.9)	16.8 (7.3)
Race/Ethnicity			
White	10 (100%)	2 (28.6%)	12 (70.6%)
Black or African American	0 (0%)	3 (42.9%)	3 (17.6%)
Asian	0 (0%)	2 (28.6%)	2 (11.8%)
Non-Hispanic or Latina	9 (90%)	6 (85.7%)	15 (88.2%)
Hispanic or Latina	1 (10%)	1 (14.3%)	2 (11.8%)
Sexual Orientation			
Heterosexual	7 (70%)	7 (100%)	14 (82.4%)
Bisexual	2 (20%)	0 (0%)	2 (11.8%)
Queer	1 (10%)	0 (0%)	1 (5.9%)
Marital Status			
Married	9 (90%)	3 (42.9%)	12 (70.6%)
Divorced	0 (0%)	1 (14.3%)	1 (5.9%)
Never Married	1 (10%)	3 (42.9%)	4 (23.5%)
Employment Status			
Employed	7 (70%)	7 (100%)	14 (82.4%)
Student	3 (30%)	0 (0%)	3 (17.6%)
Disabled/Unable to Work	0 (0%)	0 (0%)	0 (0%)
Insurance Status			
Private Health Insurance	10 (100%)	6 (85.7%)	16 (94.1%)
Medicaid	0 (0%)	1 (14.3%)	1 (5.9%)
Education Level			
Post Graduate Training	7 (70%)	5 (71.4%)	12 (70.6%)
Bachelor's Degree	3 (30%)	1 (14.3%)	4 (23.5%)
Some College	0 (0%)	0 (0%)	0 (0%)
High School Diploma	0 (0%)	0 (0%)	0 (0%)
Some High School	0 (0%)	1 (14.3%)	1 (5.9%)
Treatment			
Psychiatric Medication in Last Two Months	6 (60%)	2 (28.6%)	8 (47%)
Psychosocial Treatment in Last Two Months	5 (50%)	3 (42.9%)	8 (47%)

Figure 1. Individual symptom Trajectories of Anxiety (GAD-7) and Depression (PHQ-9) By Baseline Diagnosis

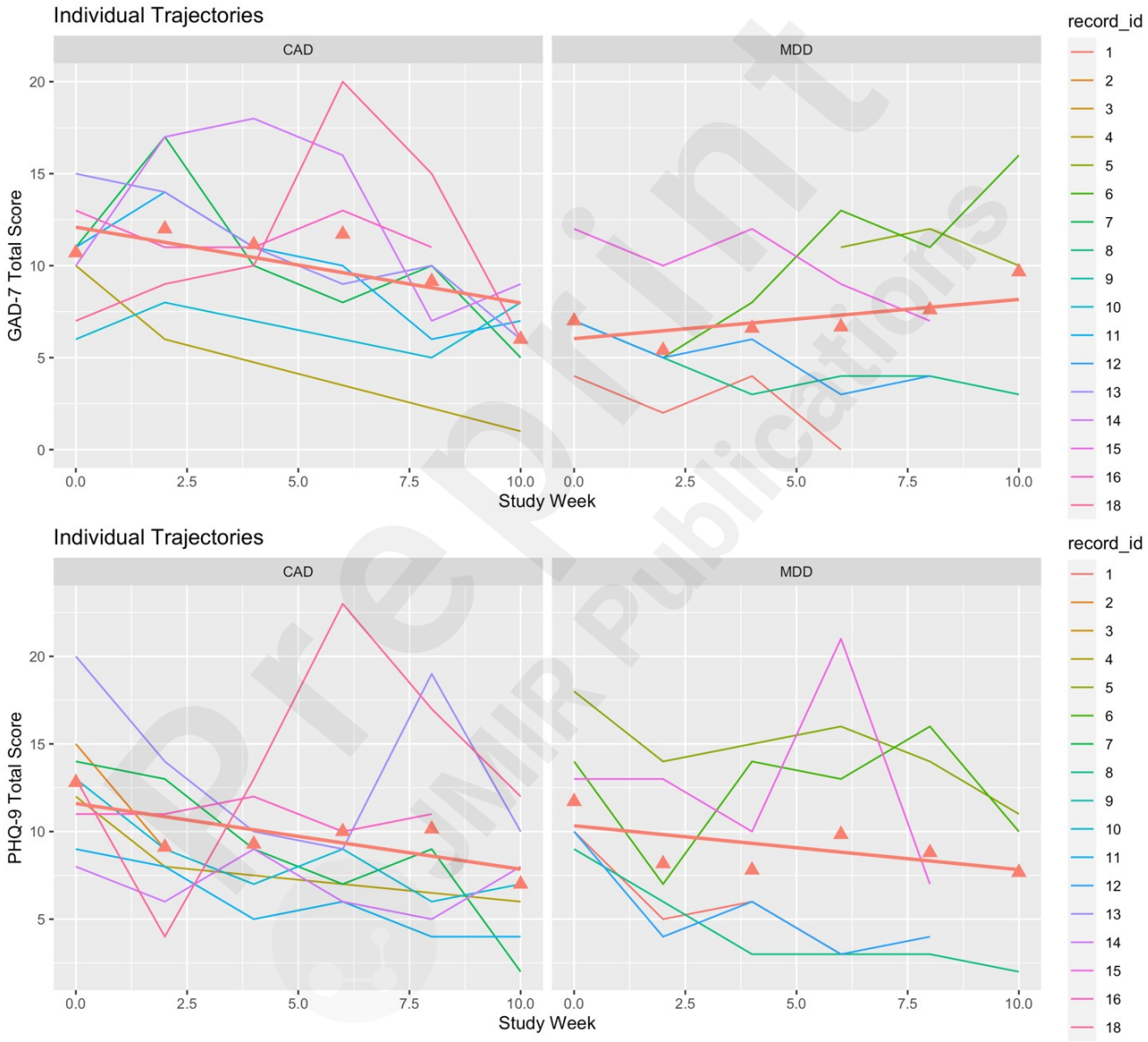

Figure 1 shows raw score symptom trajectories for each subject for Anxiety outcomes (GAD-7) and depression outcomes (PH-Q-9) by baseline diagnosis, where CAD = Comorbid Anxiety and Depression and MDD = Major Depressive Disorder. The red triangles denote the mean at a given study week, and the corresponding red straight line is a least squares regression line fit to the means.

Figure 2. Model Fixed Effect Predicted Values of GAD-7 and PHQ-9 Over Time

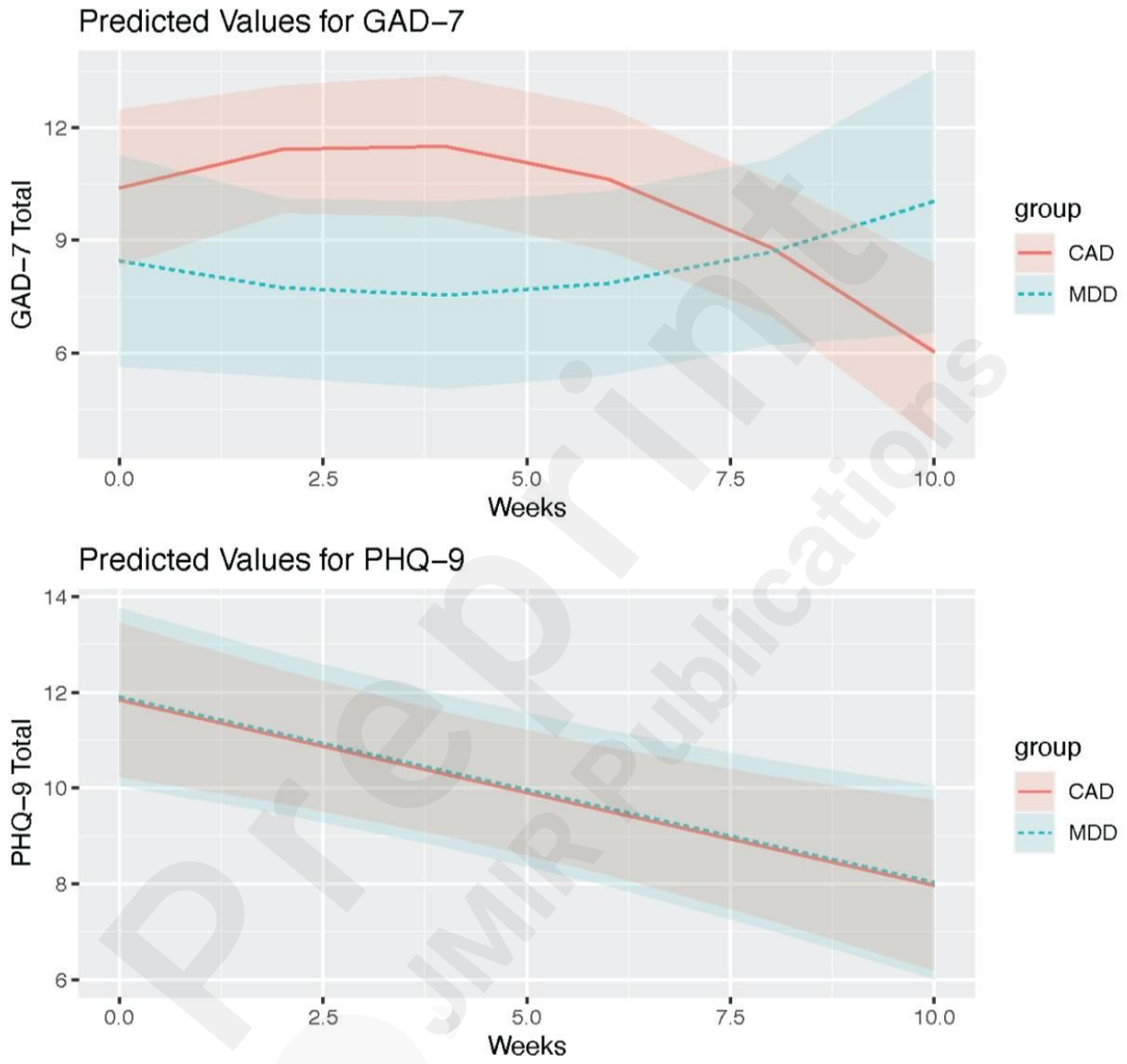

Figure 2 shows effects plots for the two mixed effects models predicting anxiety (GAD-7; top panel) and depression (PHQ-9; bottom panel) across time where CAD = Comorbid Anxiety and Depression and MDD = Major Depressive Disorder. Model fixed effect predicted values are shown and 95% confidence bands around the lines.

Table 2. Mean Changes from pre- to post in Anxiety and Depression

	Comorbid Anxiety and Depression (CAD)				Depression Only (MDD)			
	Pre-Tx (n = 10) (*M, SD*)	**Completers Pre-Tx (n = 7) (*M, SD*)**	**Post-Tx (n = 7) (*M, SD*)**	**Completers Mean Change Score (n = 7) (*M, SD*)**	**Pre-Tx (n = 7) (*M, SD*)**	**Completers Pre-Tx (n = 3) (*M, SD*)**	**Post-Tx (n = 3) (*M, SD*)**	**Completers Mean Change Score (n = 3) (*M, SD*)**
PHQ-9	12.8, 3.7	12.7, 3.9	7.0, 3.4	-5.7, 4.3	11.7, 3.5	13.7, 4.5	7.7, 4.9	-6.0, 1.7
GAD-7	10.7, 2.7	10.0, 2.9	6.0, 2.6	-4.0, 4.2	7.0, 2.7	7.3, 0.6	9.7, 6.5	2.3, 6.5

Table 2 shows pre-treatment (pre-tx) means for the whole sample and for the completers, and post-tx means for completers. Mean change score reflects the change in means from pre-tx to post-tx for tx-completers. PHQ-9 = Patient Health Questionnaire to assess depression symptoms; GAD-7 = Generalized Anxiety Disorder Scale to assess anxiety symptoms

Table 3. Mixed Models Fixed Effects Results

Table 3 shows fixed effects results from both mixed effects models. Interaction effect indicated with *. PHQ-9 = Patient Health Questionnaire to assess depression symptoms; GAD-7 Generalized Anxiety Disorder Scale to assess anxiety symptoms. Time = Linear time, $Time^2$ = quadratic time. Relevant significant result in bold.

	β	***SE***	**t**	***df***	***p***
GAD-7 Model					
Intercept	5.06	2.62	1.93	15	0.072
Baseline Diagnosis	-1.94	1.81	-1.07	32	0.292
Time	0.75	0.44	1.72	63	0.091
$Time^2$	-0.12	0.04	-2.76	62	0.007
Baseline GAD-7	0.53	0.23	2.35	13	0.035
Baseline Diagnosis * Time	-1.24	0.69	-1.81	62	0.076
Baseline Diagnosis * $Time^2$	0.18	0.07	2.61	62	**0.011 ***
PHQ-9 Model					
Intercept	4.37	2.52	1.73	12	0.108
Baseline Diagnosis	-8.53	3.93	-2.17	13	**0.049 ***
Baseline PHQ-9	0.57	0.18	3.07	11	0.011
Time	-0.39	0.11	-3.51	68	**0.001 ***
Baseline Diagnosis * Baseline PHQ-9	0.65	0.31	2.12	13	0.054

Supplementary Files

Figures

Raw score symptom trajectories for each subject for Anxiety outcomes (GAD-7) and depression outcomes (PH-Q-9) by baseline diagnosis, where CAD = Comorbid Anxiety and Depression and MDD = Major Depressive Disorder. The red triangles denote the mean at a given study week, and the corresponding red straight line is a least squares regression line fit to the means.

Effects plots for the two mixed effects models predicting anxiety (GAD-7; top panel) and depression (PHQ-9; bottom panel) across time where CAD = Comorbid Anxiety and Depression and MDD = Major Depressive Disorder. Model fixed effect predicted values are shown and 95% confidence bands around the lines.