Original Paper

Title: Efficacy of the Digital Therapeutic Mobile App "BioBase" to Reduce Stress and Improve Mental Wellbeing Among University Students: a Randomized Controlled Trial

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Abstract

Background: UK university students are experiencing increasing levels of anxiety. A programme designed to increase awareness of one's present levels of wellbeing and suggest personalized health behaviours may reduce anxiety and improve mental

wellbeing in students. The efficacy of a digital version of such a programme, providing biofeedback and therapeutic content based on personalized wellbeing metrics, is reported here.
Objective: The aim of this study was to test the efficacy and sustained effects of using a mobile app (BioBase) and paired wearable device (BioBeam), compared to a wait-list control group, on anxiety and wellbeing in university students with elevated levels of anxiety and stress.
Methods: The study employed a randomized, wait-list controlled, trial with assessments at baseline, 2-weeks, post-intervention (4 weeks), and at follow-up (6 weeks). Participants were eligible if they were current full-time undergraduate students and (1) at least 18 years of age, (2) scored >14 points on the DASS-21 stress subscale or > 7 points on the DASS-21 anxiety subscale, (3) owned an iOS smartphone, (4) did not have any previous psychiatric or neurological conditions, (6) were not pregnant at the time of testing, and (7) were able to read and understand English. Participants were encouraged to use BioBase daily and complete at least one course of therapeutic content. A p value ≤.05 was considered statistically significant.
Results: We found that a 4-weeks intervention with the BioBase programme significantly reduced anxiety and increased perceived wellbeing, with sustained effects at a 2-weeks follow-up. Furthermore, a significant reduction in depression levels was found following 4-weeks usage of Biobase.
Conclusions: This study shows the efficacy of a biofeedback digital intervention in reducing self-reported anxiety and increasing perceived wellbeing in UK university students. Results suggest that digital mental health interventions could constitute a novel approach to treat stress and anxiety in students, which could be combined, or integrated with, existing therapeutic pathways.

Trial Registration: OSF: https://osf.io/2w5sy/

Keywords: anxiety; wellbeing; digital interventions; biofeedback; mental health; mobile phones; technology**.**

Introduction

Stress and anxiety in UK university students has been steadily rising in the past decade [1]. Research demonstrates that by the mid-point of their course, 9% of previously symptom-free students develop depression and 20% become anxious to

clinically significant levels [2]. Nearly half (48%) of the students registered at a UK university-based general practice report high levels of anxiety [3]. Internationally, levels of students' anxiety are also increasing, with university counselling services experiencing increasingly higher demand since 2010 [4–7]. Longitudinal studies report that students experience higher stress on entering university, which continues to increase during their studies, and does not return to previous levels after graduation [8,9].

Strikingly, only 25-36% of students with mental health issues seek treatment [10–12], largely due to the perceived stigma associated with these conditions [11,13]. A study investigating self-reported barriers to help-seeking behaviours and engagement in therapeutic pathways in students at risk of suicide found that a lack of time and a preference for self-management were among the main factors contributing to students' choice not to seek treatment [14]. Untreated mental health issues among university students have been shown to have immediate and significant repercussions on overall quality of life, increasing the likelihood of dropping out of university and committing suicide [1]. Importantly, untreated mental health issues during university years also have negative impact following graduation, affecting relationships, levels of productivity, and the likelihood of substance abuse [15].

Although on-site facilities are crucial for managing students' mental health, their underutilisation [16] suggests that novel approaches are needed to overcome accessibility barriers. Studies calling for more timely and preventative therapeutic interventions have highlighted the need for digital interventions [17–19]. The use of digital interventions, such as internet-based self-help resources and mobile applications, have been on the rise in the past decade, due to their increased accessibility, availability and anonymity [20–24], as well as their cost-effectiveness [25]. Due to the widespread use of mobile phones, mobile applications could constitute effective therapeutic support for periods when students are away from the university, as well as increasing the capacity of on-site counselling services [26,27]. Mobile applications, paired with biosensors and wearable devices, are also effective in gathering passive data (e.g. physical activity; [28]) and self-report measures (e.g. mood journaling). Accordingly, apps are increasingly used as a real-time monitoring tool, with personalised feedback, insights and therapeutic content offered to users within the context of mental health interventions [29] and illness prevention [30].

A number of these digital interventions have proven effective in treating a variety of mental health disorders, ranging from anxiety and depression, to substance use disorder [31]. For example, an intervention lasting 2 weeks comprising of brief, daily conversations and mood tracking with a CBT-oriented conversational agent (Woebot), found that, in comparison with an information-based digital control group, those in the Woebot group significantly reduced their symptoms of depression, while participants in both groups showed significantly reduced levels of anxiety [32]. Furthermore, an 8-week intervention in US university students with the mobile-app Calm was found to produce a significantly greater degree of stress reduction than that seen in a wait-list control group [23]. Despite these promising results, studies investigating the efficacy of a combined

intervention, including both passive data collection as well as active therapeutic content, are still lacking.

The app BioBase (BioBeats, Ltd) aims at increasing individuals' wellbeing by combining elements of Mindfulness, biofeedback interventions (such as diaphragmatic breathing exercises), Cognitive Behavioural Therapy (CBT) and Behavioural Activation Theory [33–35]. Specifically, its psycho-educational content is based on the Job Demands-Resources model, which has been shown to be associated with students' wellbeing and stress management [36]. Alongside therapeutic content, data on physical activity, sleep quality and heart-rate is collected via a wrist worn wearable device ('BioBeam') and made available to individuals using the app, in order to foster an increased awareness of users' current wellbeing. Furthermore, available in-app tools include an ecological momentary assessment tool based on the Circumplex Model of Affect [37], allowing individuals to log their mood in the moment, and reflect back on their entries at a later date to gain insights into longer-term patterns of emotion. The app also includes diaphragmatic breathing exercises and relaxation techniques for in-the-moment stress reduction. In an initial feasibility study conducted with the BioBase app in a sample of full-time employees [38], it was found that 4 weeks of usage of BioBase significantly reduced anxiety and increased self-reported mental wellbeing. The study also found higher levels of baseline stress were associated with greater reductions in anxiety and increases in mental wellbeing, suggesting that usage of BioBase could be most beneficial for individuals with increased anxiety. However, the lack of a control group and the specificity of the selected population did not allow us to draw more general conclusions about the effects of using BioBase on self-reported anxiety and stress.

Hence, the purpose of this study was to test the efficacy of a 4-weeks intervention delivered via a mobile app and wearable device (i.e. the BioBase programme) in comparison with a wait-list control group on anxiety and general mental wellbeing in university students with elevated anxiety or stress. The study also examined sustained effects (at 6 weeks from baseline) of the intervention on anxiety and wellbeing. Finally, in the current study, measures of depression were collected to investigate the impact of the BioBase programme on depressive symptoms.

We hypothesised that university students in the intervention group, but not in the wait-list control, would have significant improvements in anxiety and wellbeing following a 4-weeks intervention with BioBase. We also predicted that anxiety and wellbeing would have sustained effects in the intervention group, but not in the wait-list control, at 2-weeks following the end of the intervention. Furthermore, it was hypothesised that being enrolled in the BioBase programme would reduce depressive symptoms after 4 weeks of usage.

Methods

Ethics Approval

This study was approved by an Institutional Ethics Committee at the University of Exeter (UEBS Research Ethics Committee, ethics application number: eUEBS002252). All participants provided informed, electronic consent prior to their enrollment in the study. Data from this study, including the pre-registration protocol, is available on the Open Science Framework website (https://osf.io/2zd45).

Study design

The current study was a randomised, wait-list control trial with assessments conducted at baseline, 2 weeks, post-intervention (4 weeks), and at follow-up (6 weeks). Participants randomly assigned to the intervention group took part in a 4-week wellbeing intervention (the BioBase programme). Those assigned to the wait-list control group received the intervention after 8 weeks.

Recruitment

Participants were recruited using institutional participant pools at different UK universities as well as via social media, mailing lists, flyers and through university staff. Recruitment took place between October and November 2019 and potential participants were screened for eligibility via a Qualtrics survey. Inclusion criteria comprised being a full-time university student attending a university in the United Kingdom and (1) being aged between 18 and 25 years, (2) having scored >14 points on the Depression, Anxiety and Stress Scale-21 items (DASS-21; [39]) stress subscale or > 7 points on the DASS-21 anxiety subscale, (3) owning an iPhone 6 or above, (4) not having any previous psychiatric or neurological conditions, (5) not being pregnant at the time of testing, and (6) being able to read and understand English. Participants were also excluded if they were currently in therapy or were using counselling services. Individuals taking part in the initial screening survey were entered into a lottery to win a £50 Amazon Voucher.

Randomization and Blinding

The original design was devised as a single-blind study; however, due to logistical reasons (i.e. clarity of communications between the research team and participants) it was decided to unblind the design.

Eligible participants (n=262) were sent a reminder email prompting them to confirm their willingness to take part in the study. 130 participants were randomly assigned to the intervention group and 132 participants were randomly assigned to

the wait-list control group based on minimisation factors: gender (2 categories: male and female), age (7 categories: 18, 19, 20, 21, 22, 23, 24 and 25 years of age), DASS-21 anxiety subscale (5 categories: Normal, Mild, Moderate, Severe, Extremely severe) and DASS-21 stress subscale (5 categories: Normal, Mild, Moderate, Severe, Extremely severe). DASS-21 categories were used for inclusion (i.e. participants scoring within the normal range at screening were excluded from the study and those scoring normal at baseline were excluded from the analysis) and minimisation purposes only. The first participant was allocated at random. Each subsequent participant's group membership was allocated such that their addition to that group would lead to a closer match between the groups according to the minimisation factors at screening. The random number list used to create the two groups was generated using the R "Minirand" package. Following randomisation, the intervention group received their BioBeams (which are not functional until paired with a registered BioBase account) via post at their selected address.

Intervention Group

After randomization, participants in the intervention group were emailed the first set of questionnaires to complete (Figure 1). At the end of the questionnaires, they were given details on how to download and register on the BioBase app.

The BioBase programme is a multidimensional mobile application comprising psycho-educational content on mental health and wellbeing, mood tracking (via an Ecological Momentary Assessment, EMA; [40]) and in-the-moment exercises (e.g. deep breathing and relaxation techniques). Furthermore, passive data on sleep, heart-rate and physical activity is collected via a wearable device (BioBeam) and presented to the users via a dashboard view.

The psycho-educational content is delivered via forty-two five-minutes long modules, each tackling different aspects of psychological and emotional distress (see Table 2, Supplementary Materials for a detailed description of the modules). The content is organised in three different courses, based on the job demands-resources model [41]. Each course relates to a different aspect of the model (i.e. demands, control and support) and it comprises 14 modules. Demands and control are widely recognised as relevant workplace stressors [42,43], whilst social support has been shown to positively impact perceived wellbeing [44]. Embedded in these modules are elements of cognitive behavioural therapy (CBT) and self-compassion (see Table 1, Supplementary Materials). Digitally-delivered CBT interventions have been proven efficacious in reducing levels of anxiety and depression [45] and similarly, self-compassion has been shown to predict symptom severity in anxious and depressed individuals [46]. By incorporating these therapeutic elements the courses aim to foster an individual's recognition of internal physiological and emotional processes as a trigger for stress, and identify effective coping strategies (e.g. setting achievable goals aligned with the individual's personal values).

The EMA tool allows an individual to report their mood in the moment by choosing a mood from a list of options, each with different valence (positive or negative) and arousal (high or low). Furthermore, individuals can specify any

ecological component surrounding the moment they chose to declare their mood (i.e. where they were, whether they were alone or with somebody and what activities they were engaged with). EMAs are a valuable mood-tracking tool in the context of digital interventions specifically aimed at reducing levels of anxiety and depression (see [47] for a review).

The deep-breathing tool is designed as a quick intervention aimed at reducing stress and increasing relaxation and consists of ten guided deep diaphragmatic breaths. Respiration biofeedback has been shown to lead to a reduction of symptoms of depression and anxiety (see [48] for a review on results of biofeedback interventions). Similarly, the body scan has been devised as a standalone quick relaxation intervention, due to its effectiveness in reducing anxiety and depression (for a detailed review, see [49]).

Finally, passive data collection on physical activity (i.e. number of steps performed every 20 seconds), sleep duration and quality (via a triaxial accelerometer with a sample rate of 100 Hz), and heart-rate (via a photoplethysmography sensors) was obtained via the BioBeam wearable. This information was made available to participants via an in-app dashboard. Increased sleep awareness and implementation of sleep hygiene techniques have been recognised as a mediating factor in anxiety [50], thus supporting the notion that insights into individuals' sleeping patterns may prove beneficial in stress reduction. Furthermore, as physical inactivity is associated with greater levels of anxiety (e.g. [51]), awareness of and insight into one's own activity patterns may foster improvements in individuals' wellbeing.

Participants were not prompted to use the app in any specific fashion and were left to freely engage with it for the whole intervention (i.e. 4 weeks). Participants were, however, encouraged to continuously wear the BioBeam and engage with the therapeutic content (modules and tools) on a daily basis for at least 5 minutes. App usage was discontinued after the 4-weeks intervention ended.

Wait-List Control Group

The wait-list control group received the baseline questionnaire at the same time as the intervention group, followed by an email stating that they would be provided with the app and the wearable device in 8 weeks. Throughout the 8 weeks during which the intervention group used BioBase, the wait-list control participants received the 2, 4 and 6-weeks questionnaires, preceded by a reminder email to complete them. After 8 weeks, participants received a BioBeam at their selected address as well as an email with instructions on how to download and register the app.

Measures and Incentives

Both groups completed four surveys via an online platform (Qualtrics). The surveys consisted of the following questionnaires: the State-Trait Anxiety Inventory (STAI-S-6; [52]), the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; [53]), the Depression Anxiety Stress Scales (DASS-21) and the Patient Health Questionnaire (PHQ-9; [54]). The DASS-21 Stress and Anxiety Subscales were used as a screening tool for participants' inclusion in the study, whereas the depression subscale, together with the PHQ-9, was used as an outcome measure for depression. Demographic characteristics of the sample were collected at baseline. At the end of the study, each participant received a monetary incentive of £40 (£10 per each completed set of questionnaires at T0, T1, T2 and T3) plus an additional £5 if they decided to send back the wearable device received as part of the intervention.

Primary Outcome

The primary outcome of the study were responses on the State-Trait Anxiety Inventory (STAI; [52]). The STAI-S-6 is a short version of the 10-item state subscale of the State-Trait Anxiety Inventory. It is a 6-item scale, measuring state anxiety, with responses ranging from 1 ("Not at all") to 4 ("Very much"). Scaled scores are obtained by multiplying the summed responses to each item by 20 and subsequently dividing the score by 6 (range 20-80).

Secondary Outcome

The secondary outcome of the current study was the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; [53]), measuring perceived wellbeing. WEMWBS is a 14-item scale assessing subjective well-being and psychological functioning. Scoring is obtained by summing each response, ranging from 1 ("None of the time") to 5 ("All of the time) (range 14-70). WEMWBS has been validated for use in the UK with those aged 16 and above [53].

Additional measures

Anxiety and stress were further measured via the DASS-21 subscales to ensure participants were still reporting elevated levels of stress or anxiety at baseline as well as during the screening procedure. Moreover, depression levels were investigated via the DASS-21 Depression subscale and the PHQ-9 questionnaire, a widely employed clinical tool. Whilst DASS-21 focuses on 1-week periods, PHQ-9 instructs individuals to report changes in the previous 2-weeks. Given that the focus on longer periods may mitigate the effects of random fluctuations in mood, both measures were collected.

Statistical Analysis

Power

A power analysis, based on a previous feasibility pilot study, was conducted in order to estimate the required sample size for the randomised controlled trial. Accounting for potential drop-out, the estimated sample size was at least 200 participants (100 per group), providing .95 power to detect a large effect size of .96 with an alpha of .05 in a final sample of at least 55 participants per group.

Data Exclusion

Given that the inclusion criteria for the current study comprised indication of anxiety or stress (as indexed by DASS-21 Anxiety and Stress subscales scores), 15 participants from the intervention group and 16 from the wait-list control group who initially scored above the normal range at screening but who scored in the normal range at baseline (T0) were excluded from statistical analysis. Participants were further excluded from final analyses if they did not download or open the app during the 4-weeks intervention as well as if they did not complete all questionnaires.

Data analysis

The current study employed a mixed design with a between-subjects variable (Group) with 2 levels: intervention vs wait-list control and a within-subjects variable (time) with 4 different levels: baseline, 2 weeks, 4 weeks and 6 weeks. Given the advantages of Linear Mixed Models (LMMs) in dealing with lack of homogeneity of variance and incomplete datasets across time points [55], LMMs were used to analyse our primary and secondary outcomes. Specifically, Group and Time were the fixed effects and Time/Subjects were the nested random effects. Planned comparisons (paired-samples t-tests) were conducted to explore the direction of significant interactions between Group and Time. Effect sizes for planned comparisons were calculated using Cohen's d (pooled SD) to allow maximum comparability with previous research [56]. The p-values reported below have not been corrected for multiple comparisons but remain significant if corrected. Data were analysed and plotted using the "tydiverse" , "ggplot2" [57] , "lmer4" [58] and "lmerTest" [59] packages for R.

Results

Participant Enrollment and Demographics

Figure 2 illustrates the flow of participants through the study and reasons for exclusion. Of 805 participants that were screened via an online questionnaire for inclusion and exclusion criteria, 262 participants were deemed eligible and were randomised into either the intervention (n=130) or wait-list control (n=132) group. 59 participants from the intervention group and 64 from the control group completed the final questionnaire at T3 and were included in the analysis. Engagement data from the participants in the intervention group showed participants engaged with the app 21.9 of 29 days on average (median=26 days, IQR= 13 days, range: 2-29 days). On average, participants engaged with the app 5.33 (SD=5.03) minutes per day (range: 2.13- 28.68) over the 29 days of the intervention (see Figure 1 and 2, Supplementary Materials). However, no correlation was found between the total amount of engagement with the app and differences, from baseline to T2 (4-weeks), in the main outcome measures (see Figure 3 and 4, Supplementary materials).

Participants in the two groups did not differ significantly with respect to age, gender nor their levels of stress and anxiety at baseline (see Table 1 below). 59 participants from the intervention group and 70 from the control group partook in the second questionnaire (Intervention group: 38 females, age-range: 18-25, M=19.9, SD=1.9; Wait-list control: 48 females, age-range: 18-25, M=19.9, SD=1.89 ; Figure 2), 55 and 61 (respectively) in the third (Intervention group: 36 females, age-range: 18-25, M=19.9, SD=1.82 ; Wait-list control: 43 females, age-range: 18-25, M=19.93, SD=1.95) and finally 59 and 64 participants completed the follow-up questionnaire (Intervention group: 38 females, age-range: 18-25, M= 19.92, SD=1.86; Wait-list control: 43 females, age-range: 18-25, M=20, SD=1.90).

Table 1. Summary of participant characteristics at baseline (T0).

Characteristics	Intervention Group (N=72) Mean (*SD*)	Wait-list Control (N=74) Mean (*SD*)	*p*
Gender (number)			
Females	45	47	
Males	27	27	1
Age	19.9 *(1.83)*	19.84 *(1.76)*	.83
DASS-21 Anxiety	15.39 *(6.68)*	14.46 *(7.23)*	.42
DASS-21 Stress	21.08 *(7.02)*	19.86 *(7.66)*	.32

Primary Outcomes

STAI-S-6 – Baseline to follow-up

The primary hypothesis was that, in comparison with the wait-list control group, the intervention group treated with Biobase would show a significant reduction in anxiety levels (measured via STAI-S-6) at the end of the intervention (i.e. 4 weeks following baseline measures). Furthermore, it was hypothesized that such effect would be sustained at follow-up (i.e. 2 weeks after the end of the intervention). A linear mixed model with STAI-S-6 as the dependent variable and Group and Time (as well as their interaction) as independent variables was carried out. This analysis revealed a significant main effect of Time (at both week 4 and week 6), with scores being lower in comparison with baseline. Furthermore, a significant interaction between Group and Time (at both week 4 and week 6) on perceived anxiety levels (see Table 2 below for a summary of the LMMs) was observed.

In order to further explore the significant interaction between Time and Group, planned comparisons were conducted separately in the intervention and wait-list control groups comparing STAI-S-6 values at baseline with week 4 and follow-up (6-weeks) respectively. Findings revealed that STAI-S-6 at week 4 was significantly lower in the intervention group but not in the control group (see Table 3 for a summary of descriptive statistics and planned comparisons and Figure 3) and that such reduction was still present at follow-up in the intervention group only.

One of our secondary hypotheses was that, in line with the results from Fitzpatrick and colleagues [32], the BioBase intervention would show efficacy in decreasing self-reported levels of anxiety after 2 weeks of treatment compared to the control group. However, no interaction between Time and Group was found at week 2, suggesting that changes in anxiety did not occur within the first two weeks of the intervention (Table 2).

Table 2. Summary of the Linear Mixed Model on STAI-S-6 scores over the four time points in the intervention and wait-list control groups.

	STAI-S-6		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	53.61	47.07 – 60.15	<.001
Group	-1.90	-5.99 – 2.19	.36
T 1 - 2 weeks	-6.35	-12.87 – 0.17	.06
T 2 - 4 weeks	-12.25	-18.90 – -5.59	**<.001**
T 3 - 6 weeks	-11.32	-17.84 – -4.81	**.001**
Group:TimeT1	3.44	-0.65 – 7.52	.10

Group:TimeT2	7.09	2.94 – 11.24	**.001**
Group:TimeT3	4.56	0.49 – 8.63	**.03**
Random Effects			
σ2	16.82		
τ00 Time:Participants ID	49.44		
τ00 Participants ID	67.20		
ICC	0.87		
N Time	4		
N ID	123		
Observations	491		
Marginal R^2 / Conditional R^2	0.037 / 0.879		

Table 3. Mean, SD and planned comparisons on STAI-S-6 scores over the duration of the study (T0, T1, T2 and T3) in the intervention and wait-list control groups.

	STAI-S-6 - planned comparisons					
	Intervention			**Wait-list control**		
Time	*Mean (SD)*	*T-test*	*Effect size*	*Mean(SD)*	*T-test*	*Effect size*
T0 - Baseline	51.71*(10.78)*			49.81*(10.96)*		
T1 - Week 2	-	-	-	-	-	-
T2 - Week 4	46.31(*11.32)*	$t_{(54)}$=3.507 p<.001	d=0.67	51.33*(10.35)*	$t_{(60)}$=-1.449 p=.15,	d=0.26
T3 - Week 6	44.95(*12.52)*	$t_{(58)}$=4.35 p<.001	d=0.81	47.61*(13.29)*	$t_{(63)}$=1.542 p=.13	d=0.27

Secondary Outcomes

WEMWBS - Baseline (T0) – follow-up (T3)

One of the secondary hypotheses was that participants in the intervention group only, would report higher levels of wellbeing (as measured by WEMWBS) at both the end of the intervention and at follow-up. A linear mixed model with WEMWBS as the dependent variable and Group and Time (as well as their interaction) as the independent variables revealed a significant main effect of Time

(at both week 4 and week 6), suggesting that perceived wellbeing increased over time regardless of groups. Furthermore, a significant interaction between Group and Time (week 4 and week 6) was found (see Table 4), which was further analysed with planned comparisons. T-tests were conducted separately in the intervention and wait-list control group comparing WEMWBS values at baseline (T0) and following the 4-weeks intervention as well as at follow-up (week 6). Results showed that in the intervention group only, WEMWBS values significantly increased between baseline and week 4, suggesting a higher perceived wellbeing in the intervention group (see Table 5 and Figure 4). WEMWBS values significantly increased between baseline and follow-up in both groups, but with higher values on average in the intervention group, suggesting an increase in perceived wellbeing.

Table 4. Summary of the Linear Mixed Model on WEMWBS scores over the four time points in the intervention and wait-list control groups.

		WEMWBS	
Predictors	*Estimates*	*CI*	*p*
(Intercept)	36.40	31.65 – 41.16	**<.001**
Group	2.07	-0.90 – 5.04	.17
T 1 - 2 weeks	2.69	-1.25 – 6.64	.18
T 2 - 4 weeks	7.41	3.38 – 11.44	**<.001**
T 3 - 6 weeks	8.94	4.99 – 12.88	**<.001**
Group:TimeT1	-1.57	-4.05 – 0.90	.21
Group:TimeT2	-3.96	-6.47 – -1.45	**.002**
Group:TimeT3	-3.65	-6.11 – -1.18	**.004**
Random Effects			
σ2	5.00		
τ00 Time:Participants ID	19.25		
τ00 Participants ID	46.28		
ICC	0.93		
N Time	4		
N ID	123		

Observations	533
Marginal R^2 / Conditional R^2	0.029 / 0.794

Table 5. Mean, SD and planned comparisons on WEMWBS scores over the duration of the study (T0, T1, T2 and T3) in the intervention and wait-list control groups.

	WEMWBS - planned comparisons					
	Intervention			**Wait-list control**		
Time	*Mean (SD)*	*T-test*	*Effect size*	*Mean(SD)*	*T-test*	*Effect size*
T0 - Baseline	38.47*(7.54)*			40.55*(7.76)*		
T1 - Week 2	-	-	-	-	-	-
T2 - Week 4	42.15*(9.02)*	$t_{(54)}$=-3.385 p=.001	d=0.65	40.51*(8.64)*	$t_{(62)}$=0.814 p=.42	d=0.15
T3 - Week 6	47.76*(8.31)*	$t_{(58)}$=-6.260p<.001	d=1.16	42.19*(8.37)*	$t_{(63)}$=-2.127 p=.04	d=0.38

Additional measures

In order to explore the potential of the BioBase programme to reduce depression over the 4-week period of use, depression was measured via the PHQ-9 questionnaire and a linear mixed model with depression scores as the dependent variable and Group and Time (as well as their interaction) as the independent variables was carried out. This analysis revealed that depressive symptoms decreased at 4-weeks from the start of the intervention, regardless of groups, but that in the intervention group this effect was more pronounced (as suggested by the significant interaction between Group and Time at week 4). This significant interaction (Table 6) was further analysed via planned comparisons on depression scores in the intervention and wait-list control group at baseline and following the 4-weeks intervention. Findings revealed that in the intervention group only, PHQ-9 values significantly decreased between baseline and week 4, suggesting a lower perceived level of depression (see Table 7 and Figure 5). Changes in the Depression subscale of the DASS 21 were also explored. This analysis revealed a main effect of Time at both week 2 and week 4 (see Table 1, Supplementary Materials), with depression levels reducing over time irrespective of groups. Whilst the same pattern

highlighted by the PHQ-9 scores was observed (Intervention group: Baseline: M=18.58, SD=10.87; Week 4: M=12.76, SD=8.77; Wait-list control: Baseline: M=16.44, SD=9.67; Week 4: M=12.16, SD=8.90), there was no significant interaction between Group and Time. Such finding could be due to the intrinsic characteristics of the scales (i.e. DASS-21 focuses on 1-week periods, while PHQ-9 asks individuals to report changes in the previous 2-weeks).

Table 6. Summary of the Linear Mixed Model on PHQ-9 scores over the duration of the intervention (T0, T1 and T2) in the intervention and wait-list control groups.

	PHQ-9		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	12.65	9.73 – 15.58	**<.001**
Group	-0.87	-2.70 – 0.95	.35
T 1 - 2 weeks	-1.34	-3.53 – 0.84	.23
T 2 - 4 weeks	-4.91	-7.15 – -2.67	**<.001**
Group:TimeT1	0.46	-0.90 – 1.83	.51
Group:TimeT2	2.07	0.67 – 3.46	**.004**
Random Effects			
σ2	4.25		
τ00 Time:Participants ID	3.22		
τ00 Participants ID	19.22		
ICC	0.84		
N Time	3		
N ID	123		
Observations	368		
Marginal R^2 / Conditional R^2	0.026 / 0.845		

Table 7. Mean, SD and planned comparisons on PHQ-9 scores over the duration of the intervention (T0, T1 and T2) in the intervention and wait-list control groups.

	PHQ-9 - planned comparisons					
	Intervention			**Wait-list control**		
Time	*Mean (SD)*	*T-test*	*Effect size*	*Mean(SD)*	*T-test*	*Effect size*
T0 - Baseline	11.78*(5.2)*			10.91*(4.93)*		
T1 - Week 2	-	-	-	-	-	-
T2 - Week 4	8.71*(4.45)*	$t_{(54)}$=5.139 p<.001	d=0.99	9.85*(5.38)*	$t_{(60)}$=1.392 p =.17	d=0.25

Discussion

Principal Results

The aim of the current study was to investigate the efficacy of Biobase, a 4-weeks app-based intervention, in reducing anxiety and increasing wellbeing in university students with high self-reported levels of stress or anxiety. Results revealed that using the Biobase programme for 4 weeks led to reduced self-reported anxiety and increased self-reported wellbeing. Such results were sustained at follow-up, with participants in the intervention group maintaining lower levels of self-reported anxiety and higher levels of wellbeing at 6 weeks from the study start date. Effect sizes ranged from moderate to large throughout the different outcomes.

Comparison with Prior Work

The primary hypotheses of the current study were that in the intervention group only, levels of anxiety would decrease following enrollment in the Biobase programme and that this reduction would be sustained after 2-weeks from the end of the intervention. In line with our first primary hypothesis, we found that self-

reported levels of anxiety were significantly reduced in the intervention group after 4-weeks of app usage. This finding is in line with results from previous studies using digital interventions in both student [23] and non-student [32] populations. As mentioned in the Introduction, Huberty and colleagues [23] found that the mobile application Calm, consisting of a guided mindfulness meditation programme, was effective in reducing stress levels among university students. In contrast to the Biobase 4-weeks programme of 5 mins a day however, the Calm intervention was an 8-week programme, requiring participants to first complete a 1-week course and then actively engage with the therapeutic content for at least 10 minutes a day. The efficacy of the Biobase programme despite the reduced 'dosage' may be related to the nature of the BioBase programme: the therapeutic content is only one aspect of the hypothesised factors at play in anxiety reduction. Interactions with the app dashboard (showing participants their levels of activity, sleep quality, mood declarations over time and heart-rate), as well as usage of the tools, are hypothesized to be causally efficacious in addition to the traditional therapeutic content. Future studies using BioBase could shed light on the individual contribution of each of these aspects in reducing anxiety levels.

These results are also in line with previous findings[38], suggesting a significant reduction in anxiety following a 4-week intervention with the BioBase programme in a sample of full-time employees. However, in this previous study, the effect of the intervention was not assessed beyond the end of the programme. In the current study, we showed that the effect of the intervention persisted for two weeks following the end of the programme. This result, in line with previous research [23], highlights the efficacy of mobile applications to reduce stress and anxiety over time, and their potential to supplement existing therapeutic support [18,27,29,30]. Future studies should investigate the extent to which these effects persist over longer timeframes, with the aim of identifying optimal guidelines for engagement to maximise outcomes.

A secondary hypothesis was that reduction in anxiety would be present following 2-weeks of enrollment in the BioBase programme in the intervention group (but not in the wait-list control group). However, we did not find evidence of efficacy at 2-weeks. This finding is in contrast with a previous study conducted in the young adult population [32], using a CBT-based intervention to reduce anxiety and depression, which found significant results following a 2-weeks long interactions with a web-based conversational agent. Nevertheless, the current study significantly differed in both methods of delivery (app vs web-based) as well as type of intervention. Whilst Fitzpatrick and colleagues employed a daily intervention, comprising specific time windows of interaction with the therapeutic content, the current study had a more ecological approach, with the BioBase programme being available to participants at all times yet not being a daily commitment. Thus, the reason behind the lack of efficacy following a 2-weeks enrollment in the programme may be due to differences in perceived benefit from the participants' perspective, i.e. it may be easier to recognise the impact of a daily conversational intervention versus a natural, progressive engagement with a multidimensional programme. Further

research, comparing different kinds of interventions, would be needed to shed light on these findings.

In terms of secondary outcomes, it was hypothesised that perceived wellbeing would increase following a 4-weeks intervention with BioBase and that this effect would be sustained at follow-up (6-weeks). As predicted, we found that participants in the intervention group reported higher levels of perceived wellbeing after 4-weeks, which were still significant at 2-weeks from the end of the intervention. Nevertheless, we also found a main effect of time, with levels of perceived wellbeing being higher at T2 and T3, regardless of the grouping. Further studies with single- or double-blind designs could investigate the impact of being enrolled in a study on perceived wellbeing.

Finally, additional measures of depression were obtained via the PHQ-9 questionnaire and DASS-21 Depression subscale in order to assess the feasibility of the BioBase programme in reducing depressive symptoms. Results showed that participants taking part in the current study reported lower depression levels after 4-weeks of BioBase usage and sustained effects at follow-up (as measured via the PHQ-9). Nevertheless, despite showing the same pattern of reduction, the same results were not significant for the DASS-21 Depression subscale. Such discrepancy may be due to differences in sensitivity of the two measures, given the focus on periods of different length, and further research is needed to shed light on these findings. Furthermore, given that the trial was conducted in November-December 2019, it is possible that the reduction in DASS Depression scores observed in the wait-list control group could be due to changes in university work demands, such as coursework deadlines and exams, over this period.

This result is nonetheless particularly relevant when assessing the lack of engagement of individuals at risk of suicide with established pathways of support. Specifically, the possibility to access a digital mental health intervention which could be efficacious in reducing depressive symptomatology could represent a novel approach in students at risk of suicide [1,14]. Future studies should specifically investigate the efficacy of such intervention in a student population with individuals suffering from self-reported depressive symptoms.

Limitations

A limitation of the current study is the lack of a blinding procedure. As mentioned in the Methods, the current study was an unblinded, randomised controlled trial, with participants in the control group being aware of the fact that they were not currently partaking in the intervention. This was a consequence of the type of control group employed. However, both groups received the same kind of communications and were prompted to respond to the questionnaires in the same way. A targeted standardised email was sent every week, with the timeline of the study and key dates as a reminder to participants. Whilst these measures reduced the possibility that unblinding could influence the results of the current study, future studies should investigate the extent to which being enrolled in an intervention leads to improvements in anxiety and wellbeing by employing a single-blind design, with an information-based control group.

Moreover, due to lack of data on ethnicity, or information on the characteristics of the students underusing mental health services, it was not possible to assess the generalizability of our sample. Further studies should further investigate this, by replicating the current study whilst controlling for these variables.

Furthermore, in the current study it was not possible to differentiate the effect of the different components of the BioBase programme. Whilst this is a characteristic of digital interventions [60], future studies should explore what components of the BioBase programme are most efficacious for which individuals.

Additionally, the current study targeted subclinical levels of anxiety, therefore participants with a psychiatric diagnosis of anxiety were excluded. This decision was made in order to explore symptom reduction and wellbeing increase without the confounding factors of being currently in treatment for anxiety. It could be the case, however, that effect sizes were underestimated if BioBase is more efficacious in participants with higher anxiety levels. Further research is needed to better understand the potential effects of BioBase in individuals with a clinical diagnosis of anxiety or stress.

In terms of the follow-up measure, the current study employed a 6-weeks follow-up, aimed at investigating sustained effects of the intervention. However, it should be noted that further research is needed to explore long-lasting effects of the intervention (e.g. 8 weeks).

Finally, in the current study, no specific criterion was used in regard to app usage. Given that we wanted to observe how participants would naturally engage and interact with the programme, there was no strict indication nor control on participants' way to use the app. Nevertheless, the majority of the sample engaged with the intervention, with only three people not downloading or installing the app. Future research could explore whether a more controlled intervention, with specific engagement criteria, could lead to more efficacious results whilst still maintaining ecological validity.

Conclusions

In the current study, we showed that a 4-weeks digital intervention was efficacious in reducing anxiety and increasing wellbeing in a student population with high levels of self-reported stress and anxiety. These effects were sustained after 2-weeks from the end of the intervention, thus suggesting prolonged efficacy over time. To the best of our knowledge, this is the first study showing efficacy of a multidimensional digital programme, comprising therapeutic content, biofeedback and mood-journaling, in reducing anxiety and increasing wellbeing in a student population. These findings are particularly relevant given the documented preference of students to self-help, rather than accessing on-site facilities, when facing mental health issues. Furthermore, the common use of mobile phones makes this type of intervention both accessible and scalable for higher education institutions who aim to extend the support provided to their students [27]. Future research should investigate the feasibility of including digital mental health interventions in the existing therapeutic pathways, thus encouraging preventative as well as intervention-driven approaches to mental health, tailored to the needs of the individuals.

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Conflicts of Interest

DP was the CEO of BioBeats, the provider of the BioBase programme. DM was the CTO of BioBeats, the provider of the BioBase programme. SP, NH, JK and GB were employees of BioBeats, the provider of the BioBase programme. The company owners were not involved in the analysis, which was conducted by SP and reviewed by JK.

References

1. Thorley, C., & Degrees, N. B. Improving Student Mental Health in the UK's Universities. 2017;

2. Andrews B, Wilding JM. The relation of depression and anxiety to life-stress and achievement in students. Br J Psychol 2004 Nov;95(Pt 4):509–521. PMID:15527535

3. Edwards DJ, Rainey E, Boukouvala V, Wells Y, Bennett P, Tree J, Kemp AH. Novel ACT-based eHealth psychoeducational intervention for students with mental distress: a study protocol for a mixed-methodology pilot trial. BMJ Open 2019 Jul 16;9(7):e029411. PMID:31315873

4. Beiter R, Nash R, McCrady M, Rhoades D, Linscomb M, Clarahan M, Sammut S. The prevalence and correlates of depression, anxiety, and stress in a sample of college students. J Affect Disord 2015 Mar 1;173:90–96. PMID:25462401

5. New, Jake. Colleges struggle to provide ongoing treatment as demands for mental health services increases [Internet]. [cited 2019 Oct 14]. Available from: https://www.insidehighered.com/news/2017/01/13/colleges-struggle-provide-ongoing-treatment-demands-mental-health-services-increases

6. Novotney A. Students under pressure [Internet]. https://www.apa.org. [cited 2019 Oct 14]. Available from: https://www.apa.org/monitor/2014/09/cover-pressure

7. Pierceall EA, Keim MC. Stress and Coping Strategies Among Community College Students. Community College Journal of Research and Practice Routledge; 2007 Sep 6;31(9):703–712.

8. Bewick B, Koutsopoulou G, Miles J, Slaa E, Barkham M. Changes in undergraduate students' psychological well-being as they progress through university. Studies in Higher Education Routledge; 2010 Sep 1;35(6):633–645.

9. Newbury-Birch D, Lowry RJ, Kamali F. The changing patterns of drinking, illicit drug use, stress, anxiety and depression in dental students in a UK dental school: a longitudinal study. Br Dent J 2002 Jun 15;192(11):646–649. PMID:12108944

10. Eisenberg D, Hunt J, Speer N, Zivin K. Mental health service utilization among college students in the United States. J Nerv Ment Dis 2011 May;199(5):301–308. PMID:21543948

11. Eisenberg D, Downs MF, Golberstein E, Zivin K. Stigma and help seeking for mental health among college students. Med Care Res Rev 2009 Oct;66(5):522–541. PMID:19454625

12. Blanco C, Okuda M, Wright C, Hasin DS, Grant BF, Liu S-M, Olfson M. Mental health of college students and their non-college-attending peers: results from the National Epidemiologic Study on Alcohol and Related Conditions. Arch Gen Psychiatry 2008 Dec;65(12):1429–1437. PMID:19047530

13. Cardwell JM, Lewis EG, Smith KC, Holt ER, Baillie S, Allister R, Adams VJ. A cross-sectional study of mental health in UK veterinary undergraduates. Vet Rec 2013 Sep 21;173(11):266. PMID:23956162

14. Czyz EK, Horwitz AG, Eisenberg D, Kramer A, King CA. Self-reported barriers to professional help seeking among college students at elevated risk for suicide. J Am Coll Health 2013;61(7):398–406. PMID:24010494

15. Hunt J, Eisenberg D. Mental health problems and help-seeking behavior among college students. J Adolesc Health 2010 Jan;46(1):3–10. PMID:20123251

16. Marsh CN, Wilcoxon SA. Underutilization of Mental Health Services Among College Students: An Examination of System-Related Barriers. J College Stud Psychother

Routledge; 2015 Jul 3;29(3):227–243.

17. Randall EM, Bewick BM. Exploration of counsellors' perceptions of the redesigned service pathways: a qualitative study of a UK university student counselling service. Br J Guid Counc Routledge; 2016 Jan 1;44(1):86–98.

18. Lungu A, Sun M. Time for a Change: College Students' Preference for Technology-Mediated Versus Face-to-Face Help for Emotional Distress. Telemed J E Health 2016 Dec;22(12):991–1000. PMID:27223266

19. Prentice JL, Dobson KS. A review of the risks and benefits associated with mobile phone applications for psychological interventions. Canadian Psychology/Psychologie canadienne Educational Publishing Foundation; 2014;55(4):282.

20. Kählke F, Berger T, Schulz A. Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial. journal of methods … [Internet] Wiley Online Library; 2019; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/mpr.1766

21. Mak WWS, Chan ATY, Cheung EYL, Lin CLY, Ngai KCS. Enhancing Web-based mindfulness training for mental health promotion with the health action process approach: randomized controlled trial. J Med Internet Res 2015 Jan 19;17(1):e8. PMID:25599904

22. Donker T, Batterham PJ, Warmerdam L, Bennett K, Bennett A, Cuijpers P, Griffiths KM, Christensen H. Predictors and moderators of response to internet-delivered Interpersonal Psychotherapy and Cognitive Behavior Therapy for depression. J Affect Disord 2013 Oct;151(1):343–351. PMID:23953024

23. Huberty J, Green J, Glissmann C, Larkey L, Puzia M, Lee C. Efficacy of the Mindfulness Meditation Mobile App "Calm" to Reduce Stress Among College Students: Randomized Controlled Trial. JMIR mHealth and uHealth JMIR mHealth and uHealth; 2019;7(6):e14273.

24. Mowbray CT, Mandiberg JM, Stein CH. Campus mental health services: Recommendations for change. American Journal of [Internet] Wiley Online Library; 2006; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1037/0002-9432.76.2.226

25. Herrman H, Saxena S, Moodie R. Promoting Mental Health: Concepts, Emerging Evidence, Practice [Internet]. PsycEXTRA Dataset. 2004. [doi: 10.1037/e538802013-009]

26. The invisible problem? Improving students' mental health - HEPI [Internet]. HEPI. 2016 [cited 2019 Oct 14]. Available from: https://www.hepi.ac.uk/2016/09/22/3592/

27. Price M, Yuen EK, Goetter EM, Herbert JD, Forman EM, Acierno R, Ruggiero KJ. mHealth: a mechanism to deliver more accessible, more effective mental health care. Clin Psychol Psychother 2014 Sep;21(5):427–436. PMID:23918764

28. He Y, Li Y. Physical Activity Recognition Utilizing the Built-In Kinematic Sensors of a Smartphone. Int J Distrib Sens Netw SAGE Publications; 2013 Apr 1;9(4):481580.

29. Donker T, Petrie K, Proudfoot J, Clarke J, Birch M-R, Christensen H. Smartphones for smarter delivery of mental health programs: a systematic review. J Med Internet Res

2013 Nov 15;15(11):e247. PMID:24240579

30. Ebert DD, Cuijpers P, Muñoz RF, Baumeister H. Prevention of Mental Health Disorders Using Internet- and Mobile-Based Interventions: A Narrative Review and Recommendations for Future Research [Internet]. Frontiers in Psychiatry. 2017. [doi: 10.3389/fpsyt.2017.00116]

31. Waltz E. Pear approval signals FDA readiness for digital treatments. Nat Biotechnol 2018 Jun 6;36(6):481–482. PMID:29874220

32. Fitzpatrick KK, Darcy A, Vierhile M. Delivering Cognitive Behavior Therapy to Young Adults With Symptoms of Depression and Anxiety Using a Fully Automated Conversational Agent (Woebot): A Randomized Controlled Trial. JMIR Ment Health 2017 Jun 6;4(2):e19. PMID:28588005

33. Larsson A, Hooper N, Osborne LA, Bennett P, McHugh L. Using Brief Cognitive Restructuring and Cognitive Defusion Techniques to Cope With Negative Thoughts. Behav Modif 2016 May;40(3):452–482. PMID:26685210

34. Marlow SL, Lacerenza CN, Paoletti J, Burke CS, Salas E. Does team communication represent a one-size-fits-all approach?: A meta-analysis of team communication and performance. Organ Behav Hum Decis Process 2018 Jan 1;144:145–170.

35. Bennett-Levy J, Richards D, Farrand P, Christensen H, Griffiths K. Oxford Guide to Low Intensity CBT Interventions. OUP Oxford; 2010. ISBN:9780199590117

36. Barr, T., Sessa, V., Sumner, K., & Bragger, J. Applying the Job Demands-Resources Model towards Understanding Student Stress. Computers in Human Behavior 2015;77(C):317–325.

37. Posner J, Russell JA, Peterson BS. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. Dev Psychopathol 2005 Summer;17(3):715–734. PMID:16262989

38. Effectiveness of a smart phone application BioBase for reducing anxiety and increasing mental wellbeing: a pilot feasibility and acceptability study [Internet]. JMIR Preprints. [cited 2020 Feb 12]. Available from: https://preprints.jmir.org/preprint/18067

39. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. Psychology Foundation of Australia; 1996. ISBN:9780733414237

40. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1–32. PMID:18509902

41. Bakker AB. The Job Demands-Resources model: state of the art. Journal of Managerial Psychology Emerald Group Publishing Limited; 2007 Jan 1;22(3):309–328.

42. Karasek RA. Job Demands, Job Decision Latitude, and Mental Strain: Implications for Job Redesign. Adm Sci Q [Sage Publications, Inc., Johnson Graduate School of Management, Cornell University]; 1979;24(2):285–308.

43. Häusser JA, Mojzisch A, Niesel M, Schulz-Hardt S. Ten years on: A review of recent research on the Job Demand–Control (-Support) model and psychological well-being. Work & Stress Routledge; 2010 Jan 1;24(1):1–35.

44. Haslam C, Jetten J, Cruwys T, Dingle G, Haslam SA. The new psychology of health: Unlocking the social cure. Routledge; 2018.

45. Proudfoot J, Ryden C, Everitt B, Shapiro DA, Goldberg D, Mann A, Tylee A, Marks I, Gray JA. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry 2004 Jul;185:46–54. PMID:15231555

46. Van Dam NT, Sheppard SC, Forsyth JP, Earleywine M. Self-compassion is a better predictor than mindfulness of symptom severity and quality of life in mixed anxiety and depression. J Anxiety Disord 2011 Jan;25(1):123–130. PMID:20832990

47. Schueller SM, Aguilera A, Mohr DC. Ecological momentary interventions for depression and anxiety. Depress Anxiety 2017 Jun;34(6):540–545. PMID:28494123

48. Schoenberg PLA, David AS. Biofeedback for psychiatric disorders: a systematic review. Appl Psychophysiol Biofeedback 2014 Jun;39(2):109–135. PMID:24806535

49. Blanck P, Perleth S, Heidenreich T, Kröger P, Ditzen B, Bents H, Mander J. Effects of mindfulness exercises as stand-alone intervention on symptoms of anxiety and depression: Systematic review and meta-analysis. Behav Res Ther 2018 Mar;102:25–35. PMID:29291584

50. Chou T-L, Chang L-I, Chung M-H. The mediating and moderating effects of sleep hygiene practice on anxiety and insomnia in hospital nurses. Int J Nurs Pract 2015 May;21 Suppl 2:9–18. PMID:26125570

51. Stubbs B, Koyanagi A, Hallgren M, Firth J, Richards J, Schuch F, Rosenbaum S, Mugisha J, Veronese N, Lahti J, Vancampfort D. Physical activity and anxiety: A perspective from the World Health Survey. J Affect Disord 2017 Jan 15;208:545–552. PMID:27802893

52. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). British Journal of Clinical Psychology Wiley Online Library; 1992;31(3):301–306.

53. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, Parkinson J, Secker J, Stewart-Brown S. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation [Internet]. Health and Quality of Life Outcomes. 2007. p. 63. [doi: 10.1186/1477-7525-5-63]

54. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 [Internet]. Journal of General Internal Medicine. 2001. p. 606–613. [doi: 10.1046/j.1525-1497.2001.016009606.x]

55. Hesselmann G. Applying linear mixed effects models (LMMs) in within-participant designs with subjective trial-based assessments of awareness--a caveat. Front Psychol Frontiers; 2018;9:788.

56. Field A. Discovering Statistics Using IBM SPSS Statistics. SAGE; 2017. ISBN:9781526422965

57. Wickham H. ggplot2: Elegant Graphics for Data Analysis. Springer; 2016. ISBN:9783319242774

58. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Usinglme4 [Internet]. Journal of Statistical Software. 2015. [doi: 10.18637/jss.v067.i01]

59. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Softw [Internet] The Foundation for Open Access Statistics; 2017;82(13). Available from: https://orbit.dtu.dk/en/publications/id(2e6e11c6-6a44-43df-b809-d96b897d9bf2).html

60. Whitton AE, Proudfoot J, Clarke J, Birch M-R, Parker G, Manicavasagar V, Hadzi-Pavlovic D. Breaking Open the Black Box: Isolating the Most Potent Features of a Web and Mobile Phone-Based Intervention for Depression, Anxiety, and Stress. JMIR Ment Health 2015 Jan;2(1):e3. PMID:26543909