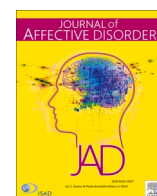




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Research paper

Prognostic factors and effect modifiers for personalisation of internet-based cognitive behavioural therapy among university students with subthreshold depression: A secondary analysis of a factorial trial



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ABSTRACT

Background: Internet-cognitive behavioural therapy (iCBT) for depression can include multiple components. This study explored depressive symptom improvement prognostic factors (PFs) and effect modifiers (EMs) for five common iCBT components including behavioural activation, cognitive restructuring, problem solving, self-monitoring, and assertion training.

Methods: We used data from a factorial trial of iCBT for subthreshold depression among Japanese university students ($N = 1093$). The primary outcome was the change in PHQ-9 scores at 8 weeks from baseline. Interactions between each component and various baseline characteristics were estimated using a mixed-effects model for repeated measures. We calculated multiplicity-adjusted p -values at 5 % false discovery rate using the Benjamini-Hochberg procedure.

Results: After multiplicity adjustment, the baseline PHQ-9 total score emerged as a PF and exercise habits as an EM for self-monitoring (adjusted p -values < 0.05). The higher the PHQ-9 total score at baseline (range: 5–14), the greater the decrease after 8 weeks. For each 5-point increase at baseline, the change from baseline to 8 weeks was bigger by 2.8 points. The more frequent the exercise habits (range: 0–2 points), the less effective the self-monitoring component. The difference in PHQ-9 change scores between presence or absence of self-monitoring was smaller by 0.94 points when the participant exercised one level more frequently. Additionally, the study suggested seven out of 36 PFs and 14 out of 160 EMs examined were candidates for future research.

Limitations: Generalizability is limited to university students with subthreshold depression.

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Conclusions: These results provide some helpful information for the future development of individualized iCBT algorithms for depression.

1. Introduction

Personalised medicine aims to optimize treatment for individuals and has been gaining increasing interest in psychiatry. In particular, depression is known to be a heterogeneous condition with various symptoms, severities, and courses (Herrman et al., 2022). Thus, depression requires optimised treatment approaches tailored to individual needs and characteristics (Hofmann, 2020). Identifying prognostic factors (variables that predict the prognosis regardless of the treatment) and effect modifiers (baseline variables predicting differential treatment responses) is essential for optimising depression treatments in personalised medicine (Noma et al., 2019).

Psychotherapies, especially cognitive behavioural therapy (CBT), are backed by robust evidence base supporting their efficacy (Cuijpers et al., 2021a, 2021b). However, psychotherapies in medical settings are limited in availability because of lacking resources and high costs. Over the past few decades, internet-based CBT (iCBT) has been researched and developed, as this could increase treatment availability to a larger population (Fairburn and Patel, 2017). Additionally, such digital strategies have accelerated the optimisation of treatment contents due to their ability to combine various CBT components and delivery methods while providing them in a consistent manner. A component network meta-analysis using individual participant data from 76 randomized controlled trials (RCTs) of iCBT identified potentially beneficial and harmful iCBT components (Furukawa et al., 2021).

Individual characteristics that enhance or weaken the effects of iCBT have been explored in recent years, as personal responses to psychotherapy vary widely (Furukawa et al., 2021; Karyotaki et al., 2021; Mohr et al., 2021). Studies have reported specific effect modifiers of iCBT, but these findings have not been consistent (Donker et al., 2013; Nolte et al., 2021). In addition, few effect modifiers for individual iCBT components have been identified (Furukawa et al., 2021).

We recently conducted a large-scale factorial trial of iCBT, consisting of six representative components of psychoeducation (PE), behavioural activation (BA), cognitive restructuring (CR), problem solving (PS), self-monitoring (SM), and assertion training (AT) among 1093 university students with subthreshold depression (Sakata et al., 2022). In the current study, we aimed to explore potential prognostic factors and effect modifiers for the five iCBT components that were randomly assigned after all participants received PE. These five components included BA, CR, PS, SM and AT.

2. Methods

2.1. Study design and procedures

This is a secondary analysis using the data from a fully factorial randomized trial, the Healthy Campus Trial, which examined the efficacy of five components of iCBT and their combinations for subthreshold depression among university students in Japan. The protocol and the main paper have been published elsewhere (Sakata et al., 2022; Uwatoko et al., 2018).

We recruited university students from five universities through posters, brochures, social media, and part-time employment websites between September 2018 and May 2021. The participants provided written informed consent. Additionally, all participants had to complete the psychoeducation (PE) component within two weeks after giving consent. After completing the PE lesson, participants were randomly assigned by a computer system to one of 32 combinations of the five smartphone-application-delivered CBT components. Allocation

corresponded with the presence or absence of SM, BA, CR, AT, and PS. Participants received weekly encouragement emails to reinforce their application use.

2.2. Participants

All individuals were screened for eligibility online. Inclusion criteria were 1) undergraduate and graduate students, 2) 18 to 39 years old, 3) having their own smartphone, and 4) meeting criteria for subthreshold depression. We defined subthreshold depression as scoring 5 to 14 points in the total score of the Patient Health Questionnaire-9 (PHQ-9) at screening. We also invited 10 % of the participants scoring 4 or less on the PHQ-9 but excluded them from the current analysis to only focus on the subthreshold depression population. Exclusion criteria were 1) not understanding the Japanese language, 2) currently receiving professional mental health treatments, 3) scoring 15 or more on the PHQ-9 total score, or scoring 10 to 14 on the PHQ-9 total score plus scoring two or three on item nine (suicidal ideation) at screening.

2.3. Intervention

All participants used our smartphone application for iCBT, “Resilience Training App.” The first component offered to all participants was psychoeducation (PE), explaining psychological stress and the importance of monitoring one's own emotional states. After completion of PE, participants were randomized to different combinations of the following iCBT components (Fig. 1).

- Behavioural activation (BA): provided activity record forms to increase the variety and frequency of new activities using a gamification “Action Marathon” facilitating a personal challenge to act.
- Problem solving (PS): taught detailed methods to break down presenting problems, consider many specific and achievable solutions, and choose an action for the best solution.
- Cognitive restructuring (CR): focused on automatic thoughts (i.e., initial thoughts occurring immediately after activating events) and expanded the range of one's thoughts through the application character interactions.
- Self-monitoring (SM): provided mind maps to systematically observe one's feelings, thoughts, behaviours, and physical reactions to different situations. Participants learned methods to reduce maladaptive reactions and learned adaptive responses.
- Assertion training (AT): presented communication methods to express one's feelings and thoughts frankly and appropriately for the situation without hurting others.

Each participant could take lessons of the assigned iCBT components for 8 weeks. A more detailed description of the interventions is in the study protocol (Uwatoko et al., 2018). Participants received ¥1000 or ¥2000 (approximately \$10 or \$20 USD) in Amazon gift vouchers by completing each survey at weeks 4 and 8.

2.4. Candidates for potential prognostic factors and effect modifiers

We collected data regarding 36 baseline variables which may work as prognostic factors or effect modifiers based on the literature (Maj et al., 2020; Kessler et al., 2017). We grouped these variables per the risk factor domains classification of Maj et al. (2020).

2.4.1. Demographics and lifestyle

- 1) Age
- 2) Sex
- 3) Domicile (home/lodging)
- 4) Part-time employment (none, <2 h/wk, 2–10 h/wk, >10 h/wk)
- 5) Involvement in club activities (none, <2 h/wk, 2–10 h/wk, >10 h/wk)
- 6) Smoking (none, 10, 20, or 30 plus cigarettes per day)
- 7) Drinking (none, <2 standard drinks per day, 2 or more standard drinks per day, problem drinking)
- 8) Exercise (rarely, sometimes, daily)
- 9) Breakfast (rarely, sometimes, daily)

2.4.2. Personality traits

Personality traits were measured by the Japanese Big Five Scale Short Form (JBFS-SF; 26 items) (Namikawa et al., 2012; Toyomoto et al., 2022). The JBFS-SF, based on the 60-item Big Five scale (JBFS) (Wada, 1996), consists of five personality traits: Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Each personal trait has four to seven adjectives rated on a 5-point Likert scale (range, 0 to 4). The reliability and validity of the original version and its short version have been established.

2.4.3. Protective factors/resilience

- 1) Social support was measured by the short form of the Social Support Questionnaire (SSQ; 12 items) (Sarason et al., 1987). The SSQ assesses the number of people providing support (quantity) and the satisfaction (quality) in six domains. The reliability and validity of the original scale and its Japanese version were demonstrated (Furukawa et al., 1999; Sarason et al., 1987).
- 2) Cognitive and behavioural skills were measured by the Cognitive Behavioural Therapy Skills Scale (CBT Skills Scale; 32 items) (Sakata et al., 2021). Each item is self-rated on a 4-point scale (range, 0 to 3), consisting of five CBT skill subscales: BA (8 items), PS (6 items), CR (6 items), AT (7 items), and SM (5 items). This scale has been shown to be valid and reliable among healthy university students (Sakata et al., 2021).

2.4.4. Symptoms and functioning

- 1) Depression was measured by Patient Health Questionnaire-9 (PHQ-9; 9 items) (Kroenke et al., 2001). The PHQ-9 is based on the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Each item is self-rated on a 4-point scale (range, 0 to 3). The total score ranges from 0 to 27 and a total of 15 or above suggests the presence of moderate or higher depression. The reliability and the validity of the Japanese version have been well established (Muramatsu et al., 2018; Umegaki and Todo, 2017).
- 2) Anxiety was measured by Generalised Anxiety Disorder-7 items (GAD-7) (Spitzer et al., 2006). Each item is scored on a 4-point scale (range = 0, 3) and produces a total score ranging from 0 to 21, with higher scores indicating worse anxiety. The reliability and validity of the Japanese version have been established (Doi et al., 2018).
- 3) Autistic tendencies were measured by the short form of the Autism Spectrum Quotient (AQ-J-10; 10 items) (Kurita et al., 2005). The AQ-J-10 is the short version of the Autism Spectrum Quotient (AQ) developed by Baron-Cohen et al. (2001). It produces a total score ranging from 0 to 10. The reliability and validity of the AQ-J and the AQ-J-10 have been established (Kurita et al., 2005).
- 4) Self-reported history of psychological/psychiatric treatment
- 5) Presenteeism was measured by the presenteeism subscale of World Health Organization Health and Work Performance Questionnaire (WHO-HPQ) (Kessler et al., 2003). It rates work performance during last 4 weeks on a scale of 0 (worst possible work performance) to 10 (top work performance). The Japanese version has been validated (Kawakami et al., 2020).

2.5. Statistical analysis

All analyses followed the intention-to-treat principle. Participants were analysed according to their randomly allocated interventions, regardless of actual treatment administration. We used a change in PHQ-9 scores from baseline to week 8 as the outcome variable, and we adopted the mixed-effects models for repeated measures (MMRM) design for analyses of the repeated outcomes. The model included fixed effects of treatment, week, baseline PHQ-9 score, university, age, treatment by week interaction, and adopted the unstructured covariance matrix for the multivariate outcomes. To explore if a factor was prognostic, we entered it as a covariate in the MMRM model. To explore if a

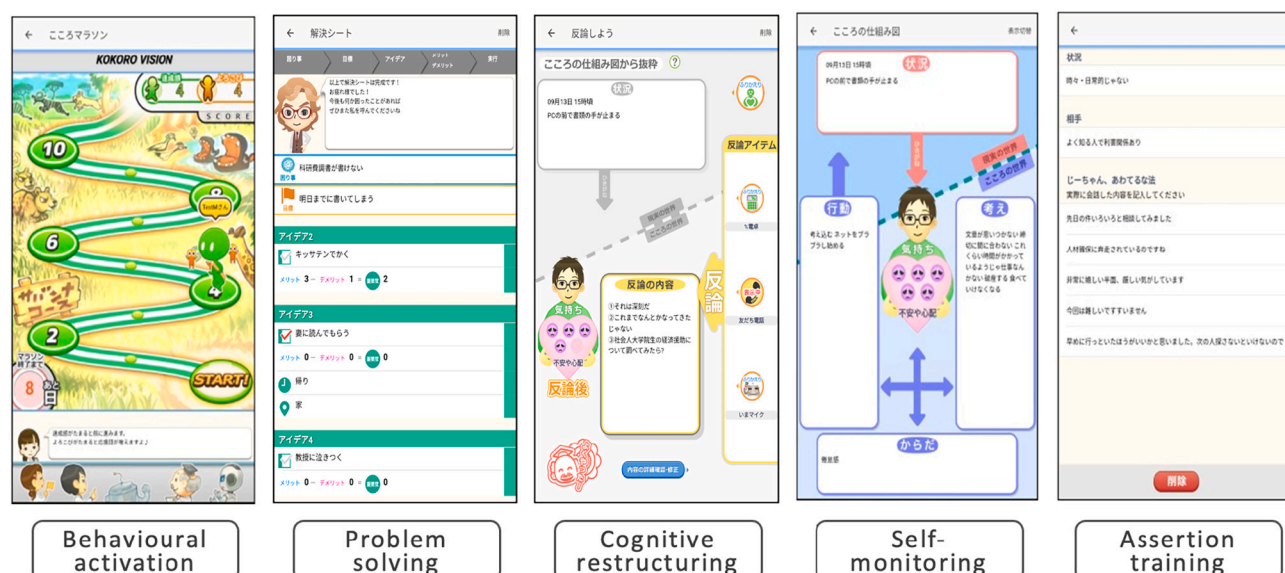


Fig. 1. Screenshots from each component of iCBT application “Resilience Training”.

factor was an effect modifier, we fitted an MMRM model including the covariate and its interaction for each treatment component. The change in the PHQ-9 corresponding with a unit change in the covariate represents the prognostic value of the covariate. The difference in change scores with or without the component represents the effect modification due to the interaction between the component and the covariate. These outcomes were estimated using least squares mean change scores based on the MMRM models. The supplement provides details of the statistical models and SAS program codes.

We considered a 2-sided $P < 0.05$ to be statistically significant. There is a risk of committing a Type I error due to multiple comparisons. The New England Journal of Medicine's guidelines recommend the Benjamini-Hochberg (BH) procedure for controlling the false discovery rate (FDR) in prespecified exploratory analyses (Aguinis et al., 2021; Benjamini and Hochberg, 1995). We examined the 36 covariates listed in Table 1 as potential PFs. For EMs, we included only the corresponding CBT skill competence for each component and therefore examined 32 covariates per component. Thus, we calculated multiplicity-adjusted p -values at 5 % FDR with the BH procedure for 36 covariates as PFs and 32 covariates as EMs per component. All analyses were performed with SAS Version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics and response at 8 weeks

In all, 5063 university students filled in the screening questionnaires. Of these, 3436 students were excluded from allocation because they did not meet inclusion criteria, did not attend informed consent sessions, or did not complete the psychoeducation component. Consequently, 1627 participants were randomly assigned to each of the 32 combinations, of whom, 533 participants with 4 or less on PHQ-9 and 1 participant who withdrew consent were excluded. Finally, 1093 with subthreshold depression were included in the current analysis.

Table 1 summarises baseline characteristics. The mean age was 21.7 (standard deviation [SD] = 3.03) and 58 % ($n = 641$) were female. Most participants were undergraduates. The mean baseline PHQ-9 score was 8.10 (SD = 2.76) and the mean endpoint PHQ-9 score was 6.16 (SD = 4.11), reduced by a mean of 1.93 (SD = 4.13) from baseline to 8 weeks. There was no significant difference in the proportions of students completing the lessons and answering the PHQ-9 by each component (Sakata et al., 2022).

3.2. Potential prognostic factors and effect modifiers

In a previous study, the primary analyses did not show significant differences by presence or absence of each component nor the presence of their interactions (Sakata et al., 2022). In this study we therefore explored the influence of participants' individual characteristics on the main effects.

Tables 2 to 4 show the statistically significant coefficient estimates of each covariate and each treatment by covariate interaction for the PHQ-9 change from baseline to 8 weeks before and after multiplicity adjustment by the Benjamini-Hochberg method. Prognostic factors and effect modifiers are grouped by demographics and lifestyle, personality traits, protective factors/resilience, and Symptom profile and severity.

3.2.1. Demographics and lifestyle

Table 2 shows the coefficient estimates for factors concerning demographics and lifestyles. After multiplicity adjustment, only the interaction of exercise habits for SM was significant ($\beta = 0.94$, 95 % CI = 0.48, 1.39).

3.2.2. Personality traits

Table 3 presents that no factor was significant in the multiplicity-adjusted p -values.

Table 1

Baseline characteristics ($N = 1093$).

	n	%	Mean	SD
Demographics and lifestyles				
Age			21.6	3.03
Sex (female)	641	58 %		
Undergraduate	829	76 %		
Married	21	2 %		
Living alone	686	62 %		
Part-time employment	845	77 %		
Involvement in club activities	745	68 %		
Smoking regularly	68	6 %		
Drinking alcohol regularly	466	42 %		
Exercise regularly	666	61 %		
Breakfast regularly	971	89 %		
Personality traits				
Openness			2.60	0.55
Conscientiousness			2.96	0.61
Extraversion			2.69	0.71
Agreeableness			3.33	0.55
Neuroticism			3.13	0.54
Protective factors/resilience				
Social support questionnaire				
Number			2.34	0.95
Satisfaction			3.59	0.97
Cognitive behavioural skills				
SM skill scores			7.60	3.11
BA skill scores			8.42	3.43
CR skill scores			9.78	4.21
AT skill scores			9.31	3.49
PS skill scores			10.4	3.13
Symptoms and functioning				
PHQ-9 total at baseline			8.10	2.76
PHQ-9 1st item (anhedonia)			0.79	0.63
PHQ-9 2nd item (depressed mood)			1.11	0.62
PHQ-9 3rd item (insomnia/hypersomnia)			1.51	0.94
PHQ-9 4th item (fatigue)			1.55	0.74
PHQ-9 5th item (appetite changes)			0.92	0.87
PHQ-9 6th item (feelings of worthlessness)			0.84	0.78
PHQ-9 7th item (trouble concentrating)			0.78	0.82
PHQ-9 8th item (psychomotor agitation/retardation)			0.37	0.63
PHQ-9 9th item (suicidal ideation)			0.23	0.48
GAD-7			6.40	3.33
Autism spectrum quotient			3.84	2.00
History of psychological/psychiatric treatment	130	12 %		
WHO-HPQ Presenteeism			4.41	2.14

PHQ-9: Patient Health Questionnaire-9, GAD-7: Generalised Anxiety Disorder-7, WHO-HPQ: World Health Organization-Health and Work Performance Questionnaire.

The summary statistics are shown either as the total number and proportion (n, %) or as the mean and its standard deviation (mean, SD).

3.2.3. Protective factors/resilience

The coefficient estimates on protective factors, as shown in Table 3, indicate that there was no significant factor after adjusting the p -values for multiple comparisons.

3.2.4. Symptom profile and severity

Table 4 shows that only the PHQ-9 total score was a statistically significant predictor for change in PHQ-9 without components ($\beta = -0.55$, 95 % CI = -0.69 , -0.41).

Table 2

Statistically significant prognostic factors and effect modifiers among demographics and lifestyles (N = 1093).

	Change in PHQ-9 without component		Difference in change in PHQ-9 when each component is present									
	Estimate (95%CI)	p	AT		BA		CR		PS		SM	
			Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p
Demographics												
Age	-0.17 (-0.30 to -0.04)	0.01	0.03 (-0.07 to 0.13)	0.57	0.10 (-0.002 to 0.20)	0.05	0.15 (0.05 to 0.25)	0.004	0.05 (-0.05 to 0.15)	0.34	0.05 (-0.05 to 0.15)	0.36
Sex (female)	-0.10 (-0.84 to 0.65)	0.80	0.26 (-0.35 to 0.88)	0.40	-0.30 (-0.91 to 0.31)	0.33	-0.38 (-0.99 to 0.24)	0.23	0.72 (0.11 to 1.33)	0.02	-0.09 (-0.70 to 0.53)	0.78
Lifestyles												
Part-time employment	0.21 (-0.07 to 0.49)	0.15	0.08 (-0.15 to 0.31)	0.48	-0.11 (-0.34 to 0.12)	0.33	-0.22 (-0.45 to 0.01)	0.06	-0.01 (-0.24 to 0.22)	0.95	-0.25 (-0.47 to -0.02)	0.04
Exercise	-0.60 (-1.17 to -0.03)	0.04	0.33 (-0.13 to 0.79)	0.16	-0.03 (-0.49 to 0.43)	0.90	-0.26 (-0.72 to 0.21)	0.28	-0.70 (-1.16 to -0.23)	0.003	0.94 (0.48 to 1.39)	<.001

Potentially beneficial variables are shown in green and potentially harmful variables are shown in orange according to p-values (p < 0.05).

p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring.

Table 3

Statistically significant prognostic factors and effect modifiers among personality traits and protective factors/resilience (N = 1093).

	Change in PHQ-9 without component		Difference in change in PHQ-9 when each component is present									
	Estimate (95%CI)	p	AT		BA		CR		PS		SM	
			Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p
Personality traits												
Extraversion	-0.28 (-0.80 to 0.23)	0.28	0.03 (-0.40 to 0.46)	0.89	-0.02 (-0.44 to 0.41)	0.93	-0.43 (-0.85 to -0.01)	0.05	-0.10 (-0.53 to 0.32)	0.64	0.42 (-0.01 to 0.84)	0.05
Protective factors/resilience												
SSQ number	-0.41 (-0.81 to -0.02)	0.04	0.30 (-0.02 to 0.61)	0.06	-0.03 (-0.34 to 0.29)	0.86	-0.08 (-0.39 to 0.24)	0.63	-0.04 (-0.36 to 0.27)	0.79	-0.07 (-0.39 to 0.24)	0.64
CR skill	-0.11 (-0.22 to 0.00)	0.05	0.09 (0.00 to 0.18)	0.05	-0.03 (-0.12 to 0.05)	0.45	-0.06 (-0.15 to 0.03)	0.20	-0.05 (-0.14 to 0.04)	0.28	0.11 (0.03 to 0.20)	0.01
BA skill	-0.11 (-0.20 to -0.02)	0.02	0.06 (-0.01 to 0.13)	0.11	0.03 (-0.04 to 0.10)	0.37	-0.02 (-0.10 to 0.05)	0.50	-0.06 (-0.13 to 0.01)	0.12	0.05 (-0.02 to 0.12)	0.17

Potentially beneficial variables are shown in green and potentially harmful variables are shown in orange according to p-values (p < 0.05).

p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring, SSQ: Social Support Questionnaire.

Table 4

Statistically significant prognostic factors and effect modifiers among symptoms and functioning (N = 1093).

	Change in PHQ-9 without component		Difference in change in PHQ-9 when each component is present									
	Estimate (95%CI)	p	AT		BA		CR		PS		SM	
			Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p	Estimate (95%CI)	p
Symptoms												
PHQ-9 total	-0.55 (-0.69 to -0.41)	<.001	0.05 (-0.06 to 0.16)	0.36	-0.01 (-0.12 to 0.10)	0.81	0.04 (-0.07 to 0.15)	0.48	0.09 (-0.02 to 0.20)	0.13	0.05 (-0.06 to 0.16)	0.40
PHQ-9 item5	-0.44 (-0.87 to -0.01)	0.04	0.16 (-0.19 to 0.51)	0.37	-0.02 (-0.37 to 0.34)	0.93	0.15 (-0.19 to 0.50)	0.39	0.22 (-0.13 to 0.57)	0.21	0.25 (-0.10 to 0.61)	0.16
PHQ-9 item9	0.34 (-0.50 to 1.18)	0.43	-0.58 (-1.23 to 0.07)	0.08	0.90 (0.25 to 1.55)	0.01	-0.26 (-0.90 to 0.38)	0.42	-0.02 (-0.66 to 0.63)	0.96	-0.18 (-0.83 to 0.46)	0.57
GAD7 total	0.10 (-0.01 to 0.21)	0.07	0.02 (-0.07 to 0.11)	0.71	-0.04 (-0.13 to 0.05)	0.44	0.01 (-0.08 to 0.10)	0.82	0.11 (0.20 to 0.02)	0.02	0.01 (-0.08 to 0.10)	0.76
AQ total	0.008 (-0.08 to 0.10)	0.87	-0.04 (-0.11 to 0.03)	0.27	0.04 (-0.04 to 0.11)	0.32	0.08 (0.01 to 0.15)	0.03	0.01 (-0.07 to 0.08)	0.89	0.002 (-0.07 to 0.07)	0.96
Functioning												
Presenteeism	-0.32 (-1.27 to 0.62)	0.50	0.20 (-0.55 to 0.96)	0.60	0.63 (-0.12 to 1.39)	0.10	0.08 (-0.68 to 0.84)	0.84	-0.86 (-1.61 to -0.10)	0.03	-0.22 (-0.98 to 0.54)	0.57

Potentially beneficial variables are shown in green colour and potentially harmful variables are shown in orange colour according to p-value (p < 0.05).

p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring, PHQ-9: Patient Health Questionnaire-9, GAD-7: Generalised Anxiety Disorder-7, AQ: Autism Spectrum Quotient.

4. Discussion

Our analyses based on a trial for university students with sub-threshold depression identified PHQ-9 total score as a potential prognostic factor and exercise habits as a potential effect modifier for SM.

Previous studies have found few prognostic factors and effect modifiers. For instance, a large IPD meta-analysis failed to reveal effect modifiers for iCBT components (Furukawa et al., 2018, 2021). Some individual studies identified them for iCBT overall, but not for individual iCBT components (Kessler et al., 2017; Karyotaki et al., 2021). To the best of our knowledge, this is the first study to explore the effect modifiers for each iCBT component in a single, large trial where a range of baseline covariates were consistently defined and systematically measured.

Regarding prognostic factors, we found that higher depression severity at baseline was associated with greater symptom reduction after eight weeks. This corresponded with a 0.55 (95%CI: 0.41 to 0.69) points

greater decrease for each 1-point increase in baseline PHQ-9 score, or 2.8 points greater decrease for each 5-point increase. One possible reason for this is that there is more room for improvement with higher depression severity. These findings are in line with recent meta-analyses for psychotherapies (Furukawa et al., 2018, 2021; Karyotaki et al., 2021; Mohr et al., 2021) and pharmacotherapies (Noma et al., 2019) for depression.

Our analyses also identified exercise habits as an effect modifier for self-monitoring. Specifically, the more frequent the exercise habits (rated in three levels between 0 and 2), the less effective SM was, resulting in a difference of 1.88 points (95%CI: 0.96 to 2.78) in the efficacy of SM between those with no exercise habits (0 points) and those with daily exercise habits (2 points). Exercise habits have been suggested as a protective factor, i.e., a factor that prevents the onset or continuation of depression (Maj et al., 2020). Learning to self-monitor one's thoughts and emotions did not appear to benefit those who exercise regularly.

The magnitude of these prognostic factor or effect modifier appears clinically meaningful, because the literature suggests that the smallest reduction in depressive symptoms important to patients, the minimum important change (MIC), is 1.7 points on the PHQ-9 (Kounali et al., 2022).

Previous studies have suggested that age, treatment history, or personality traits were possible prognostic factors or effect modifiers in psychological treatments of depression (Kessler et al., 2017; Maj et al., 2020) but the current study, after adjustment for multiple tests, was unable to replicate these findings. This may be because the current study was a secondary analysis, and the sample size was not large enough to detect these differences. Even multiplicity adjustment based on FDR generally decreases power because it is a conservative control for random errors. Considering that examining interactions requires a large sample and consequently some studies examining interactions choose to set the interaction *p*-value above the conventional 0.05, we may regard those factors found in unadjusted analyses as informative for future studies. Thus, seven out of 36 prognostic factors (i.e., age, exercise habits, social support, CBT skills, PHQ-9 total score, and PHQ-9 Item 5) and 14 out of 160 effect modifiers (i.e., age, sex, presenteeism, personality traits, anxiety, autistic tendencies, part-time job, CBT skills, exercise habits and suicidal ideation) may be potential candidates for future examination for various iCBT components.

Limitations

Our study has limitations of note. First, we targeted university students below the clinical depression threshold. Thus, it is unclear whether the current findings would apply to students with depressive disorders. Second, the use of an online questionnaire without any personal clinical assessment may not be an appropriate way to reliably explore even the presence of subthreshold depression (Robinson et al., 2017; Hobbs et al., 2021). Yet, these simpler tools can open the opportunity for regular screening and early intervention (Kroenke et al., 2010). Third, the variables of individual characteristics may well not have been exhaustive in this study. Nevertheless, we had pre-specified the key variables through careful discussion and literature review in our protocol. Lastly, this exploratory study examined many participant characteristics, and we calculated the multiplicity-adjustment *p*-values at 5 % FDR to guard against spurious findings. Even so, as the potential factors we proposed are hypothesis-generating, over-interpretations should be avoided, and future studies are needed for verification.

5. Conclusions

It is essential to individualize iCBT programs to maximize their effectiveness. We identified a possible effect modifier for one iCBT components and some effect modifier candidates for other components. Further studies are necessary to validate these findings, and eventually to construct iCBT packages tailored to individual user characteristics.

Availability of data and materials

Data are available on reasonable request. After the publication of the primary findings as specified in the protocol, the deidentified and completely anonymised individual participant-level dataset will be posted on the UMIN-ICDR website (<http://www.umin.ac.jp/icdr/ind-ex-j.html>) for access by qualified researchers.

CRediT authorship contribution statement

TAF, ERW, TU, TI, SM, TU, YL, and MS designed this trial. RT, MS, KY, YL, YN, HS, MS, HI, TS, TW, AT, TU, ES, and TAF acquired the data. HN conducted the statistical analyses. RT and TAF wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TAF reports personal fees from Boehringer-Ingelheim, DT Axis, Kyoto University Original, MSD, Shionogi and SONY, and a grant from Shionogi, outside the submitted work; In addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. MS reports personal fees from SONY outside the submitted work. NS received lecture fees from Meiji-seika Pharma for work that was not associated with this article. AT has received lecture fees from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, Meiji-Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, and Takeda Pharmaceutical. TM received lecture fees from Aikomi and LinkMedical for work outside the submitted work. HN reports personal fees from Boehringer Ingelheim, Kyowa Kirin, Toyota Motor Corporation, GlaxoSmithKline, Ono Pharmaceutical, SONY, and Terumo outside the submitted work. All the other authors have no competing interests to report.

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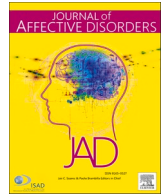
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Update

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Corrigendum

Corrigendum to “Prognostic factors and effect modifiers for personalisation of internet-based cognitive behavioural therapy among university students with subthreshold depression: A secondary analysis of a factorial trial” [J. Affect. Disord. 322 (2023) 156–162]

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P-values in Tables 2, 3, and 4 should have been adjusted for multiplicity, as shown correctly below and as discussed appropriately in the

text. The authors would like to apologise for any inconvenience caused.

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Table 2
Statistically significant prognostic factors and effect modifiers among demographics and lifestyles (N = 1093).

	Change in PHQ-9 without component			Difference in change in PHQ-9 when each component is present														
	Estimate (95%CI)	p	p*	AT			BA			CR			PS			SM		
				Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*
Demographics																		
Age	-0.17 (-0.30 to -0.04)	0.01	0.20	0.03 (-0.07 to 0.13)	0.57	0.80	0.10 (-0.002 to 0.20)	0.05	0.33	0.15 (0.05 to 0.25)	<0.01	0.12	0.05 (-0.05 to 0.15)	0.34	0.61	0.05 (-0.05 to 0.15)	0.36	0.76
Sex (female)	-0.10 (-0.84 to 0.65)	0.80	0.87	0.26 (-0.35 to 0.88)	0.40	0.74	-0.30 (-0.91 to 0.31)	0.33	0.82	-0.38 (-0.99 to 0.24)	0.23	0.57	0.72 (0.11 to 1.33)	0.02	0.21	-0.09 (-0.70 to 0.53)	0.78	0.90
Lifestyles																		
Part-time employment	0.21 (-0.07 to 0.49)	0.15	0.38	0.08 (-0.15 to 0.31)	0.48	0.77	-0.11 (-0.34 to 0.12)	0.33	0.82	-0.22 (-0.45 to 0.01)	0.06	0.46	-0.01 (-0.24 to 0.22)	0.95	0.96	-0.25 (-0.47 to -0.02)	0.04	0.56
Exercise habits	-0.60 (-1.17 to -0.03)	0.04	0.24	0.33 (-0.13 to 0.79)	0.16	0.75	-0.03 (-0.49 to 0.43)	0.90	0.85	-0.26 (-0.72 to 0.21)	0.28	0.98	-0.70 (-1.16 to -0.23)	<0.01	0.87	0.94 (0.48 to 1.39)	<0.01	<0.01

Potentially beneficial variables are shown in green and potentially harmful variables are shown in orange according to p-values ($p < 0.05$).
p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring.

Table 3
Statistically significant prognostic factors and effect modifiers among personality traits and protective factors/resilience (N = 1093).

Change in PHQ-9 without component				Difference in change in PHQ-9 when each component is present																	
				AT			BA			CR			PS			SM					
Estimate (95%CI)				Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*			
Personality traits																					
Extraversion				-0.28 (-0.80 to 0.23)	0.28	0.55	0.03 (-0.40 to 0.46)	0.89	0.89	-0.02 (-0.44 to 0.41)	0.93	0.99	-0.43 (-0.85 to -0.01)	0.05	0.46	-0.10 (-0.53 to 0.32)	0.64	0.88	0.42 (-0.01 to 0.84)	0.05	0.59
Protective factors/resilience																					
SSQ number				-0.41 (-0.81 to -0.02)	0.04	0.24	0.30 (-0.02 to 0.61)	0.06	0.75	-0.03 (-0.34 to 0.29)	0.86	0.99	-0.08 (-0.39 to 0.24)	0.63	0.97	-0.04 (-0.36 to 0.27)	0.79	0.96	-0.07 (-0.39 to 0.24)	0.64	0.86
CBT skills	CR skill			-0.11 (-0.22 to 0.00)	0.05	0.24	NA			NA			-0.06 (-0.15 to 0.03)			0.20	0.57	NA			NA
	BA skill			-0.11 (-0.20 to -0.02)	0.02	0.20	NA			0.03 (-0.04 to 0.10)			0.37	0.82	NA			NA	NA		

Potentially beneficial variables are shown in green and potentially harmful variables are shown in orange according to p-values ($p < 0.05$).
p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring, SSQ: Social Support Questionnaire.

Table 4
Statistically significant prognostic factors and effect modifiers among symptoms and functioning (N = 1093).

	Change in PHQ-9 without component				Difference in change in PHQ-9 when each component is present														
	Estimate (95%CI)	p	p*	AT			BA			CR			PS			SM			
				Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	Estimate (95%CI)	p	p*	
Symptoms																			
PHQ-9 total	-0.55 (-0.69 to -0.41)	<0.01	<0.01	0.05 (-0.06 to 0.16)	0.36	0.75	-0.01 (-0.12 to 0.10)	0.81	0.99	0.04 (-0.07 to 0.15)	0.48	0.81	0.09 (-0.02 to 0.20)	0.13	0.57	0.05 (-0.06 to 0.16)	0.40	0.76	
PHQ-9 item5	-0.44 (-0.87 to -0.01)	0.04	0.24	0.16 (-0.19 to 0.51)	0.37	0.75	-0.02 (-0.37 to 0.34)	0.93	0.99	0.15 (-0.19 to 0.50)	0.39	0.75	0.22 (-0.13 to 0.57)	0.21	0.57	0.25 (-0.10 to 0.61)	0.16	0.76	
PHQ-9 item9	0.34 (-0.50 to 1.18)	0.43	0.64	-0.58 (-1.23 to 0.07)	0.08	0.75	0.90 (0.25 to 1.55)	0.01	0.20	-0.26 (-0.90 to 0.38)	0.42	0.75	-0.02 (-0.66 to 0.63)	0.96	0.96	-0.18 (-0.83 to 0.46)	0.57	0.83	
GAD7 total	0.10 (-0.01 to 0.21)	0.07	0.27	0.02 (-0.07 to 0.11)	0.71	0.88	-0.04 (-0.13 to 0.05)	0.44	0.82	0.01 (-0.08 to 0.10)	0.82	0.98	0.11 (0.20 to 0.02)	0.02	0.21	0.01 (-0.08 to 0.10)	0.76	0.90	
AQ total	0.008 (-0.08 to 0.10)	0.87	0.89	-0.04 (-0.11 to 0.03)	0.27	0.75	0.04 (-0.04 to 0.11)	0.32	0.82	0.08 (0.01 to 0.15)	0.03	0.43	0.01 (-0.07 to 0.08)	0.89	0.96	0.002 (-0.07 to 0.07)	0.96	0.97	
Functioning																			
Presenteeism	-0.32 (-1.27 to 0.62)	0.50	0.70	0.20 (-0.55 to 0.96)	0.60	0.80	0.63 (-0.12 to 1.39)	0.10	0.65	0.08 (-0.68 to 0.84)	0.84	0.98	-0.86 (-1.61 to -0.10)	0.03	0.21	-0.22 (-0.98 to 0.54)	0.57	0.83	

Potentially beneficial variables are shown in green colour and potentially harmful variables are shown in orange colour according to p-value ($p < 0.05$).
p*: multiplicity-adjusted p-value, AT: assertion training, BA: behavioural activation, CR: cognitive restructuring, PS: problem-solving, SM: self-monitoring, PHQ-9: Patient Health Questionnaire-9, GAD-7: Generalised Anxiety Disorder-7, AQ: Autism Spectrum Quotient.