PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial
AUTHORS	Tsuji, Katsunori; Ochi, Eisuke; Okubo, Ryo; Shimizu, Yoichi; Kuchiba, Aya; Ueno, Taro; Shimazu, Taichi; Kinoshita, Takayuki; Sakurai, Naomi; Matsuoka, Yutaka

VERSION 1 – REVIEW

REVIEWER	Lisa Loughney DCU, Ireland
REVIEW RETURNED	01-May-2019

GENERAL COMMENTS	Thank you for inviting me to review this protocol study paper. It is a really interesting research question. However I feel more detail is required on the intervention (mainly what did the support sessions involve and what were participants told about the app). Some suggestions are noted below: Checklist item 3: I am not sure I have enough detail on intervention. What is being discussed at the support sessions? What are participants been told to do? How is intensity being measured? it is unclear whether the intervention is one 10-min session or one 10-min lower body and then one 10-min of more exercises (see page 11, lines 6-19) Checklist 15: the introduction can be edited to be more concise and provide the reader with a quick and clear understanding of the work.

REVIEWER	Justin Jeon Yonsei University, Exercise Medicine Center for Diabetes and Cancer Patient
REVIEW RETURNED	01-May-2019

GENERAL COMMENTS	The current manuscript is a protocol paper to investigate effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors. The manuscript is clear and well written. However, some of the methodologies lack details and may reconsider their methodologies. Please see my comments below:

	1. The topic of study is up to date and interesting. 2. The study aim is clearly described. 3. Page 9. line 41-42. How are authors going to measure whether potential participants engage more than moderate intensity exercise for 30min on 2 separate days per week? How about 20 min three times or 10 min everyday? How are authors going to determine whether it is moderate or light or vigorous? 4. Page 9 line 57 how does primary physician judge whether exercise is risky or not? Does exercise mean the current habit-B program? Will physician have a prior knowledge of the exercise program? 5. Why Resting heart rate below 60 bpm would be removed. If they did not have conduction disorder or any specific reasons for bradycardia, they would be most healthy person. Seviiri M 2018 AND Aune et al. 2017 6. Page 10 Line 26 The process of randomization is not clear enough (is app going to be used to assign group? It is not clear. 7. Page 11 line 26-49, it mentioned the theory of Bandura was applied for the program development. Was this validated previous in Breast Cancer Survivors among Japanese or Asian? 8. Which wearable device? (country, company, feature? pedometer? accelerometer?) 9.What device will be used for fitness/physical function tests? Grip strength? Leg Press?etc. 10.The study will collect many biological sample? WHY? What parameters will be analyzed and how? 11. How will study handle missing samples? 12. How will study analyze drop out? per protocol or intention-to-treat? 13. May reconsider, how they will test primary outcome? t-test may not be ideal 14. Why so many secondary outcome measures? How are they going to correct for multiple testing?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Thank you for inviting me to review this protocol study paper. It is a really interesting research question. However I feel more detail is required on the intervention (mainly what did the support sessions involve and what were participants told about the app). Some suggestions are noted below:
Reply: Thank you for this positive comment. We have responded to the points you raised and have revised the manuscript accordingly.

Checklist item 3: I am not sure I have enough detail on intervention. What is being discussed at the support sessions? What are participants been told to do? How is intensity being measured? it is unclear whether the intervention is one 10-min session or one 10-min lower body and then one 10-min of more exercises (see page 11, lines 6-19)
Reply: In accordance with your comment, we have revised the Methods and Analysis as suggested. Basically, the exercise support will comprise 6 weeks of exercise counseling/exercise guidance (Once a week, 6 times in total, 30 min per session) and 12 weeks of ICT interventions, which are provided via personalized e-mail message (Once a week, 12 times in total) and a newly developed exercise app (during each exercise session). Regarding the exercise counseling and guidance, we introduce and develop social cognitive theory (please see Page 9, Lines 21 to Page 10, Lines 8). In addition, we

have added screenshots of the new exercise app (Figure 3). As shown in the new Figure 4, the exercise intervention will be a single 10-min session.

Checklist 15: the introduction can be edited to be more concise and provide the reader with a quick and clear understanding of the work.
Reply: In accordance with your comment, we have deleted the redundant sentences to make the Introduction clearer.

Reviewer #2
The current manuscript is a protocol paper to investigate effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors. The manuscript is clear and well written. However, some of the methodologies lack details and may reconsider their methodologies. Please see my comments below:
Reply: Thank you for this positive comment. We have responded to all the points you raised and have revised the manuscript accordingly.

1. The topic of study is up to date and interesting.
2. The study aim is clearly described.

Reply: Again, we appreciate these positive comments.

3. Page 9. line 41-42. How are authors going to measure whether potential participants engage more than moderate intensity exercise for 30min on 2 separate days per week? How about 20 min three times or 10 min everyday? How are authors going to determine whether it is moderate or light or vigorous?

Reply: We conducted interviews to confirm the exercise habits, including exercise duration and intensity. The criteria for determining exercise habits are based on the National Health and Nutrition Survey Japan. We have added this information in the Methods and Analysis. (please see page 8, line 20)

4. Page 9 line 57 how does primary physician judge whether exercise is risky or not? Does exercise mean the current habit-B program? Will physician have a prior knowledge of the exercise program?

Reply: As described in page 11, the chief of primary surgeons participated in developing the habit-B program. The core project members (KT, EO, YM) explained the risk of the habit-B exercise program to primary surgeons in detail. Then, the primary surgeons will empirically determine the risk of the current habit-B program for cancer survivors who have cardiovascular disease (CVD) such as myocardial infarction, stroke, and angina.

5. Why Resting heart rate below 60 bpm would be removed. If they did not have conduction disorder or any specific reasons for bradycardia, they would be most healthy person. Seviiri M 2018 AND Aune et al. 2017

Reply: The target population of this study is sedentary. In subjects with bradycardia, exercise may pose a risk for adverse events such CVD. Therefore, we decided to exclude them out of consideration of safety.

6. Page 10 Line 26 The process of randomization is not clear enough (is app going to be used to assign group? It is not clear.

Reply: In accordance with your comment, we have added the following details about the randomization process (please see page 8, lines 8-12).

“Participants will be assigned by the minimization method, a form of dynamic randomization, using two prognostic factors: VO_{2peak} and age. Based on the allocation sequences, the contents of the app that participants use during the trial will be assigned automatically to either the habit-B program or control.”

7. Page 11 line 26-49, it mentioned the theory of Bandura was applied for the program development. Was this validated previous in Breast Cancer Survivors among Japanese or Asian?

Reply: Unfortunately, to our knowledge, there has been no previous validation study of this theory in breast cancer survivors in Japan. Hence, we referred to and followed this theory.

8. Which wearable device? (country, company, feature? pedometer? accelerometer?)

Reply: We will use the Fitbit Versa smart watch (Fitbit Inc., San Francisco, CA). This information has been added in the Methods and Analysis (please see page 16, lines 5-12).

9. What device will be used for fitness/physical function tests? Grip strength? Leg Press?etc.

Reply: We have added this information as follows: “…leg press machine (Powertec Leg Press P-LP16, Powertec, Paramount, CA), Grip strength (TKK 5401 Grip-D; Takei, Niigata, Japan).

10. The study will collect many biological sample? WHY? What parameters will be analyzed and how?

Reply: Yes, we will measure the gut microbiota and blood compositions of n-3 polyunsaturated fatty acids. Since these parameters are topics of interest in exercise science (Monda V et al 2017; Żebrowska A et al, 2015), we will measure the potential biological parameters as a preliminary study.

References

Monda V et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.

Żebrowska A et al. Omega-3 fatty acids supplementation improves endothelial function and maximal oxygen uptake in endurance-trained athletes. Eur J Sport Sci. 2015;15(4):305-14.

11. How will study handle missing samples?

Reply: We plan not to impute missing values for any outcomes in the primary analysis and patients with missing outcome data will be excluded from the analysis population. We have carefully designed and implemented the study plan to avoid unnecessary missing data, but if we find the possibility of missing data that may substantially affect the effect estimation and testing, we will specify the methods to deal with missing data in the Statistical Analysis Plan before the study data is fixed. We have added the following sentence in the Data Analysis section

“Our primary analysis is intention-to-treat analysis and patients without outcome data will be excluded from the analyses.”

12. How will study analyze drop out? per protocol or intention-to-treat?

Reply: Our primary analysis for efficacy endpoints is an intention-to-treat analysis, and patients with missing outcome data will be excluded from the analyses. To support the interpretation of the results from the primary analyses, we plan to compare the proportion of the patients who drop out between the two groups. If we find the possibility of missing data due to drop out that may substantially affect the effect estimation and testing, we may add supplementary analyses of each outcome. The detailed methods for supplementary analyses will be specified in Statistical Analysis Plan before the study data is fixed. We have added the following sentences into Data Analysis section

“Our primary analysis is intention-to-treat analysis and patients without outcome data will be excluded from the analyses.” and “The detailed methods for supplementary analyses will be specified in the Statistical Analysis Plan before the study data is fixed.”

13. May reconsider, how they will test primary outcome? t-test may not be ideal
Reply: We plan to use the t-test for the primary analysis. However, if the distribution of the primary outcome deviates from a normal distribution, we will consider performing non-parametric tests with the Wilcoxon rank-sum test as a supplementary analysis.

14. Why so many secondary outcome measures? How are they going to correct for multiple testing?
Reply: We will measure these biological parameters as a preliminary study. The purpose of analyzing the secondary outcomes is to support the interpretation of the primary results on VO_2 peak and to obtain clues for the future direction of development of the proposed exercise program, regardless of whether the study shows efficacy. We have no intention to provide a definitive conclusion on secondary outcomes, and therefore we will not correct for multiple testing on secondary outcomes.

VERSION 2 – REVIEW

REVIEWER	Lisa Loughney RCSI, Ireland
REVIEW RETURNED	09-Jul-2019

GENERAL COMMENTS	Thank you for inviting me to review this interesting study. I have some concerns about the following: 1. this RCT compares home exercise vs. usual care. However, the usual care are given a wearable device which will muddy findings. I note that the control group will be monitored with an objective physical activity monitor. This will provide data for this group. I would worry that the wearable device will not provide the authors with "a usual care control group". The monitor could be issued to both groups at baseline and 12 weeks and would provide output on what the participants are doing in terms of daily PA. 2. Is the randomisation correct based on fitness? This needs to be reviewed. 3. the inclusion/exclusion criteria (sedentary and BMI less than 30 may make recruitment difficult) However this may not be the case in Japan.

REVIEWER	Justin Jeon Yonsei University, South Korea
REVIEW RETURNED	18-Jun-2019

GENERAL COMMENTS	Authors improved the manuscript adequately. My only suggestion is to adjust their inclusion criteria for resting heart rate from 60 to 50bpm. Previous studies showed as many as 50% of the general public had resting heart rate below 60bpm. Therefore, this exclusion criteria may hinder them. Also they need to mention about beta-blocker, which lowers resting heart rate.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1
1. this RCT compares home exercise vs. usual care. However, the usual care are given a wearable device which will muddy findings. I note that the control group will be monitored with an objective physical activity monitor. This will provide data for this group. I would worry that the wearable device will not provide the authors with "a usual care control group". The monitor could be issued to both groups at baseline and 12 weeks and would provide output on what the participants are doing in terms of daily PA.

Reply: In accordance with your comment, we have changed our manuscript throughout to “treatment as usual with wearable device” (Page 3, Line 10, Page 21, Line 14, and Figure 1).

2. Is the randomisation correct based on fitness? This needs to be reviewed.
Reply: Yes, as describe in page 12 and Figure 2, we will use VO2peak for assignment adjustment factors as below;
“After enrollment and the additional input of the VO2peak value, patients will be randomly assigned. In the process of random assignment, VO2peak (obtained from the baseline measurement performed after obtaining informed consent) and age will be used as assignment adjustment factors, and automatic assignment will be performed using the data center’s assignment feature.”

3. the inclusion/exclusion criteria (sedentary and BMI less than 30 may make recruitment difficult) However this may not be the case in Japan.
Reply: We agree with the reviewer’s suggestion. Previous studies have been shown that adult obesity rates are lowest (only 3.7% more than 30kg/m2, OECD Obesity-Update 2017) and sitting times are highest (medians ≥360 min/day, Bauman et al., 2011) in Japan. Hence, we believe that our criteria should be appropriate. We can recruit the eligible women actually.

Reviewer #2
Please leave your comments for the authors below
Authors improved the manuscript adequately. My only suggestion is to adjust their inclusion criteria for resting heart rate from 60 to 50bpm. Previous studies showed as many as 50% of the general public had resting heart rate below 60bpm. Therefore, this exclusion criteria may hinder them. Also they need to mention about beta-blocker, which lowers resting heart rate.
Reply: Thank you for this positive comment. In accordance with your comment, we have decided to change the exclusion criteria for resting heart rate from 60 to 50 bpm as following sentences (please see page 9, lines 6 and 9).
“(5) abnormal electrocardiogram in preoperative testing, resting heart rate (HR) below 50 beats/min or above 100 beats/min, or stage III hypertension or above (diastolic blood pressure over 110 mmHg or systolic blood pressure over 180 mmHg); and (6) judged unfit for the trial by a primary physician for other reasons such as the administration of beta-adrenergic blocking agents.”