Acceptability of a structured diet and exercise weight loss intervention in breast cancer survivors living with an overweight condition or obesity: A qualitative analysis

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Abstract

Background: Weight loss increases survivorship following breast cancer diagnosis. However, most breast cancer survivors (BCS) do not meet diet and exercise recommendations.

Aim: The purpose of this study was to explore the barriers and facilitators of BCS who had lymphedema and who participated in a 22-week weight loss lifestyle intervention.

Methods and results: Participants completed semi-structured interviews about barriers and facilitators to intervention adherence. Interviews were transcribed verbatim and a thematic analysis was conducted. Participants (n = 17) were 62 ± 8.0 years of age with a mean body mass index of 34.0 ± 7.1 kg/m². Four themes emerged: (1) facilitators of intervention adherence, (2) barriers of intervention adherence, (3) continuation of healthy habits post intervention, and (4) recommendations for intervention improvements. Facilitators of intervention adherence were education, social support, routine, motivation, goal-setting, meal-provisioning, self-awareness, and supervised exercise. Barriers to intervention adherence were personal life, health, meal dissatisfaction, seasonality, unchallenging exercises, and exercising alone. All women planned to continue the acquired healthy habits post intervention. Recommendations to improve the study included addressing the exercise regime, meal-provisioning, and dietary intake monitoring methods.

Conclusion: Future strategies to engage BCS in weight loss interventions should promote group exercise, offer individualized meal-provisioning and exercise regimes, provide transition tools, and allow participants to choose their self-monitoring method.

KEYWORDS
acceptability, breast cancer, diet, exercise, oncology, qualitative, weight loss

1 INTRODUCTION

Breast cancer (BC) is the most common cancer worldwide in females, with an incidence rate of over 2 million in 2018.1 Weight gain, which ranges between 6 and 23 kg, occurs in the majority of women following BC treatment.2-4 Females who are premenopausal, have an advanced stage of the disease, receive chemotherapy, radiotherapy, or hormone therapy, and receive longer duration and higher doses of...
treatment are more likely to gain weight. This weight gain is problematic given that living with obesity or an overweight condition is associated with an increased risk of all-cause and BC-related mortality. In Canada, according to the 2005 Canadian Community Health Survey, 30% of female breast cancer survivors (BCS) are living with an overweight condition and 18.5% are living with obesity. Weight loss, through diet and physical activity (PA), is feasible and crucial in this population to improve survival. A diet low in fat and high in fruits and vegetables is associated with a reduction in all-cause and BC-related mortality. PA equally improves BCS outcomes, notably by reducing all-cause mortality, BC-specific mortality, and BC recurrence and new primaries. Cancer survivors should follow the Canadian Society for Exercise Physiology’s recommendation to perform at least 150 min of moderate-intensity exercise per week. For BCS specifically, at least five servings of fruit and vegetables per day in conjunction with this exercise is associated with higher survival rates. Yet, only 18% of BCS consume five or more fruits and vegetables per day and only 16% to 37% perform at least 150 min of moderate-intensity PA per week.

Obtaining and understanding experiences of female BCS who participated in a weight loss intervention can provide valuable insight on how to help BCS meet diet and PA recommendations in the long run, and thereby increase survivorship. Therefore, the aim of this qualitative study is to explore BCS’ experiences after participating in a 22-week lifestyle weight loss intervention that included supervised, structured training sessions and meal-provisioning.

2 | MATERIALS AND METHODS

2.1 | Program

This qualitative study was conducted following a lifestyle weight loss intervention among BCS and reports on secondary data from a larger study. The protocol for this study and the larger study were approved by the Human Research Ethics Committee of Concordia University (Certificate #30009486). Briefly, participants were recruited from the Lymphedema Clinic at the McGill Nutrition and Performance Laboratory and from the PERFORM Centre affiliated with Concordia University (Montreal, Quebec, Canada). To be eligible, participants must have been in remission for 10 years (±7 years) prior to starting the study. The intervention lasted 22 weeks.

At baseline, fitness goals were determined by the clinical exercise physiologist. Nutritional goals were determined by the registered dietitian. The overall goal was to reduce 5% to 7% of the total body weight. Each participant underwent a nutrition and fitness assessment prior to starting the program. The results obtained from the fitness assessment allowed the clinical exercise physiologist to determine the exercising heart rate range, such that the participants would reach the appropriate exercise intensity during their training sessions. The results obtained from the nutrition counseling allowed the registered dietitian to provide advice on the eating habits.

At each exercise session, participants performed to achieve a maximum of 60% of their heart rate reserve. This was chosen as a threshold because vigorous intensity corresponds to >60% of the heart rate reserve, as defined by the American College of Sports Medicine. The first 10 weeks consisted of an individually conducted progressive training program with exercise physiology interns twice per week for 1 hour per session (Table S1). For the remaining 12 weeks, training sessions were twice per week and were not supervised. Participants who were unable to attend a training session due to scheduling conflicts communicated with the assigned trainers to reschedule during the same week. Missed sessions that were unable to be rescheduled within the same week were canceled and not accumulated in the next period.

Additionally, the first 12 weeks included dietitian sessions and provisioning of 10 meals per week supplemented by participants’ own foods. For the remaining 10 weeks, participants attended two out of the three offered group-cooking classes instead of meal-provisioning. Meal adherence was assessed using the smartphone dietary self-monitoring tool Keenao (Montreal, Canada). This application (app) identifies food items using artificial intelligence. Users estimate portion sizes, and dietitians can adjust the entries as needed. In brief, the dietitian met with each participant to demonstrate how to use the app. Participants were asked to capture their food intake three times during the same week (two weekdays and one day during the weekend). The data was linked to the dietitian’s account who monitored their food intake. Nutrition counseling was also provided during the intervention and when appropriate goals were created with participants.

Cohort 1 (n = 12) participated from January 2019 to June 2019 and cohort 2 (n = 9) from September 2019 to February 2020. Participants were compensated with a 3-month PERFORM Centre membership post intervention. Informed consent was obtained from all participants.

2.2 | Interviews

All participants (n = 21) who took part in the lifestyle intervention were contacted by telephone inviting them to participate in an exit survey to obtain information about their experiences in the parent study.

Semi-structured one-on-one interviews were used. Interview questions were structured prior to the calls to encourage participants to critically reflect on both positive and negative intervention aspects. Individual interviews (Table S2) were moderated by researchers (HB, VB, SS), who had no clinical relationship with the participants. The interview questions were based on the Theory of Planned Behavior (TPB). In brief, this theory suggests that behavior change is influenced by one’s intention to change, which is predicted by three TPB constructs: attitudes towards the behavior, subjective norms, and perceived behavioral control. TPB outlines why an individual may choose to engage or not in a specific behavior. This theory was therefore appropriate given that the aim of this research was to...
determine why or why not individuals chose to engage in healthy eating and physical activity behaviors. Each participant was telephoned a maximum of three times. After a third non-response, efforts for recruitment were terminated. The interviews were conducted in either English or French depending on the participant’s first language. Cohort 1 interviews were conducted in June 2019. Cohort 2 interviews were conducted in March 2020. All interviews were recorded by the TapeACall Pro app (TelTech, New Jersey, USA) and were transcribed verbatim in their respective language by Transcription Heroes (Toronto, Canada). Given that the researchers had sufficient knowledge of both the English and French language, the data were received and analyzed by researchers in the language in which the interview was conducted.

2.3 | Data analysis

A thematic analysis was used to analyze the data. All transcripts were placed into a qualitative data management software (Taguette Version 9.0, European Organization for Nuclear Research, Switzerland).

Data from both cohorts were merged for analysis. Transcripts from both cohorts were transcribed simultaneously by Transcription Heroes and subsequently sent to the researchers. This ensured that both cohorts were dealt with equally and that cohort 1 was not set as the priority cohort over cohort 2, despite cohort 1 interviews having been performed at an earlier time. In the first step of the analysis, HB reviewed all transcripts line by line to become familiar with the data and reviewed the transcripts for accuracy. An open coding method was subsequently used by HB to generate themes that were derived directly from the data rather than from predetermined categories. Themes were determined using the following method: within each theme, if a concept was mentioned by a minimum of two participants, sentences were grouped together as a sub-theme. Once the sub-themes were established, those with a similar overall theme were combined, forming the main themes. There was significant repetition among transcripts, and no new themes were added from the last four to five interviews, suggestive of adequate sampling and probable saturation. Themes were reviewed with MS followed by TC. If a disagreement arose, the original transcripts were reviewed and discussed until a consensus was reached. Specific quotations were extracted to illustrate each of the main themes. To ensure confidentiality, identifying information was removed from quotes, and each participant was given an arbitrary number as their identifier.

3 | RESULTS

By the end of the study, women lost an average of 2.4 kg (±3.3 kg, \( P = .007 \)) after 10 weeks. Interviews were conducted with 17 (16 completed the study, and dropped out after 15 weeks for a non-intervention-related reason) of the 21 eligible participants for the study (Table S3). Four participants were unable to be reached by telephone. Interviews lasted between 15 and 30 min.

Four themes emerged: (1) facilitators of intervention adherence, (2) barriers of intervention adherence, (3) continuity of healthy habits post-intervention, and (4) recommendations for intervention improvements (Table S4). Common barriers and facilitators for diet and/or exercise adherence were examined.

4 | THEME 1: FACILITATORS OF INTERVENTION ADHERENCE

4.1 | Both diet and PA

4.1.1 | Education

Through the education and guidance received from the dietitian in addition to the trainers, all participants reported gaining knowledge and confidence in their abilities to consume a healthier diet and pursue PA goals. Participants valued the provided meals, dietitian sessions, cooking classes, and recipes, and explained that these elements educated them on portion sizes, healthy foods that they were otherwise unfamiliar with (ie, legumes, barley, quinoa), and the required skills needed to create and maintain a healthier lifestyle. For example, they learned to cook with healthy oils and whole grains, to replace meat protein with other protein sources, and about hidden sources of sugar and salt. This acquired knowledge was a reported facilitator for meal preparation and portioning in second half of the intervention when participants had to prepare their own meals. The knowledge and positive health behaviors learned during the study even prompted some women to educate their entourages on healthy eating.

Participants equally explained that the supervised training sessions taught them how all exercise machines worked and the purpose of using them. They emphasized this effective teaching-enabled exercise maintenance during the unsupervised conditions of the intervention. Participants also stated that the trainers’ guidance on how to safely use machines to meet their fitness needs within their physical limitations increased their skills and self-motivation to exercise. These acquired skills and knowledge facilitated the PA component of the intervention.

4.1.2 | Social support

All women stated that they felt supported by their friends and family. Participants additionally felt supported, encouraged, and motivated by all intervention team members (dietitian, trainers, researchers), and other participants. Support from these sources was reported to facilitate intervention adherence and increase motivation.

4.1.3 | Routine and structure

Participants explained that the structure of the study enabled them to change their lifestyle habits. The intervention structure promoted a
routine of eating three meals per day and exercising twice per week. The women reported that this stable routine made it easier to execute diet and PA changes.

4.1.4 | Motivation

Participants residing far from the study site reported that the motivation acquired from the positive study environment promoted their intervention continuation despite long travel times. Several others mentioned that commitment to the study and to improving their own health contributed to their motivation to continue. The motivation acquired from all of these various sources facilitated intervention adherence.

4.2 | Diet alone

4.2.1 | Goal-setting

Some participants made weekly goals using the S.M.A.R.T. goal framework (specific, measurable, attainable, relevant, time-based) with the dietitian to increase consumption of healthier foods. This goal-setting was reported to facilitate making dietary changes.

4.2.2 | Meal-provisioning

Participants expressed that the food-provisioning simplified the diet aspect of the intervention, as it eliminated having to think about meal preparation. This facilitated the diet component of the intervention.

4.2.3 | Increased self-awareness

Participants became more self-aware of the time that they were eating and reasons why they were eating, for example, being more conscious of the foods consumed while watching television. They also learned to differentiate between physical and emotional hunger. Women explained that this increased self-awareness facilitated reducing their caloric intake because they were no longer mindlessly consuming calories. To note, self-awareness was not addressed during the intervention and was therefore individually driven.

4.3 | PA alone

4.3.1 | Individualized, supervised exercise sessions

Participants claimed that the supervised training sessions were a crucial facilitator. The participants felt more motivated to attend the gym knowing that someone was waiting for them. Participants also appreciated the gradual increase in exercise difficulty and the individualized alternative exercises provided by trainers if needed.

5 | THEME 2: BARRIERS OF INTERVENTION ADHERENCE

5.1 | Both diet and PA

5.1.1 | Personal life

Work schedules, doctor’s appointments, flooding in the home, and other events in the participants’ personal lives were challenges for intervention adherence. Participants’ personal lives were reported as higher priorities compared to meeting intervention requirements.

5.1.2 | Physical health

Physical health (notably fatigue, illness, or body pain) was an obstacle for meeting intervention requirements. These conditions were reported to reduce motivation for meal preparation and gym attendance.

5.2 | Diet alone

5.2.1 | Meal dissatisfaction

Although, in general, participants learned new recipes and cooking techniques, not all enjoyed the meals provided, which thereby decreased their adherence to the dietary intervention. Despite becoming accustomed to the provided meals, several women initially expressed difficulty to consume unfamiliar foods. Two women reported adding salt to their meals, and three participants expressed their desire for meals to be individualized to their likes/dislikes.

5.3 | PA alone

5.3.1 | Poor weather conditions

A challenge to attending the exercise sessions was poor weather conditions (ie, ice and snow blizzards). Women reported cleaning snow and ice off of their vehicles and poor driving conditions as obstacles for gym attendance during the winter months.

5.3.2 | Unchallenging exercise regimes

Two women reported feeling demotivated towards the end of the study due to the exercises not being challenging enough. This was
5.3.3 | Exercising alone

Participants reported that exercising alone was difficult. They found acquiring motivation to perform PA challenging without someone else performing PA with them.

6 | THEME 3: CONTINUITY OF HEALTHY HABITS POST INTERVENTION

All participants planned to maintain their dietary changes and PA levels post intervention. Participants expressed willingness to maintain the newly acquired cooking skills and to consume appropriate foods and portion sizes. Several women reported that they continue to cook the program’s recipes and reuse the program’s meal containers to aid with food portioning. Participants also planned to continue to engage in PA for 1 hour, two to three times per week. Many participants expressed gratitude for the 3-month PERFORM Centre membership to facilitate this continuation. Some participants made appointments with PERFORM Centre trainers and planned to renew this membership. Other participants reported either downloading cellphone apps to help them meet their PA goals, joining a gym near their house, joining exercise classes, and/or continuing to exercise at home.

7 | THEME 4: RECOMMENDATIONS FOR INTERVENTION IMPROVEMENTS

The women suggested minor modifications to the exercise machines used, particularly the bike, as it was associated with rear-end pain. Alternative suggestions included the treadmill or a bike with a backrest. Many women were disappointed with the limited gym access and number of cooking classes. Participants reported wanting more direction on appropriate supplemental foods (snacks and suppers) to consume. They also recommended increasing meal-provisioning to 21 for 7 days to better accommodate those lacking time for food preparation.

Participants equally suggested gathering their food preferences beforehand to personalize meal plans. Further, women expressed concern over the use of the smartphone diet self-monitoring tool used in the study to assess dietary intake (Keenoa). Participants felt this app was hard to use, citing issues downloading it onto their cellphones and not being provided with alternative tracking methods. Participants felt a standard food journal (paper-to-pen) should have been used when app issues arose. and in general some preferred paper-to-pen over the app. Lastly, participants expressed the desire to have exercise programs with different intensities, especially for those with previous exercise experience.

8 | DISCUSSION

This study provides a detailed analysis of BCS’ experiences in a lifestyle weight loss intervention that included meal-provisioning and supervised, structured training sessions. Perspectives on intervention’s barriers and facilitators were attained. This study found that by participating in nutrition and exercise education, participants acquired the necessary knowledge and subsequently confidence in their abilities to execute healthier habits. This confidence-building is crucial because lack of confidence can hinder intervention adherence.19,21 Furthermore, knowledge on food preparation and recipes is a reported facilitator for diet interventions.22,23 Similar to other BCS lifestyle change trials, participants in this study also expressed encouraging friends and the family to adopt healthier lifestyles.22,24

Participants valued the supervised, individualized, and gradual progression of the exercise component of the intervention and the study trainers’ support. In agreement with previous studies, supervised exercise, trainer support, and individualization are common facilitators in exercise interventions.25-27 On the other hand, lack of individualization and unchallenging exercises are reported as barriers to intervention adherence.27,28 However, due to the one-on-one training and gradual progression of difficulty in the exercise regime, these were seldom reported in this intervention. Individualized exercise and diet interventions are more effective and sustainable than a “one-size-fits-all” approach and are therefore preferable.29,30 Despite exercise individualization, two participants reported feeling unchallenged due to having prior exercise experience, resulting in decreased motivation for intervention continuation. Participants in this study were permitted to achieve an exercise intensity of only 60%, a limit that may have been easier to attain for participants with previous exercise experience. To avoid this in future clinical interventions, screening or inclusion criteria should focus on both present and past exercise experience. With this information, participants with an exercise history can either be excluded from the study or provided with modified, more challenging, plans that allow for higher intensities. This will ensure exercises are challenging for all participants.

Other diet and PA trials have similarly used one-on-one consultations and/or group sessions with dietitians and trainers to help participants meet intervention requirements. However, in these previous studies, participants felt that they had inadequate time with these professionals, which led to participants feeling undersupported.20,25-27

Participants in this study did not express similar sentiments, likely due to the fact that the nutrition and exercise education given, totaling ~27 hour, may have been adequate to help them feel confident in their own abilities and be self-sufficient.

All intervention participants had the support of their friends, family, and intervention team members. Social support is a well-known facilitator for diet and exercise interventions and, when lacking, is a major obstacle to intervention adherence.20,21,23,28,31 The importance of social support is emphasized in a meta-analysis on weight loss intervention adherence by Lemstra et al, who concluded that social support improves adherence rates by 29%.22
Routine and goal-setting assisted the women in changing their lifestyle habits. Routine is a reported facilitator to help participants stay on track in both diet and PA trials.\textsuperscript{23,31} Goal-setting is an equal facilitator in diet and PA trials.\textsuperscript{20,27,28} As reported by participants in a study by Kerkelä et al, goal-setting helped individuals to plan their next steps and track their improvements.\textsuperscript{27} Goal-setting is also associated with increasing participant motivation.\textsuperscript{33} Motivation is another recognized facilitator for intervention adherence and was equally found in this analysis.\textsuperscript{25,27,28}

Meal-provisioning was the novel aspect of this intervention. In previous diet interventions, participants reported inadequate time to prepare appropriate meals and inadequate intervention support related to cooking and appropriate recipes, and requested that meals be provided.\textsuperscript{19-22,28,31} These challenges resulted in difficulty with intervention adherence. The diet intervention in this study aimed to overcome these obstacles, thereby facilitating dietary changes. While providing meals is a well-accepted enabling factor, several women expressed the desire for more meal individualization. This request is fitting, given that a randomized control trial performed by Celis-Morales et al concluded that providing a personalized nutrition plan to each participant led to greater and more sustainable dietary behavior changes.\textsuperscript{34} Future studies should therefore consider gathering participant preferences, providing more meal choices, and tailoring meals to each participant to enhance the meal-provisioning component. Moreover, as the participants recommended, extending meals to 7 days a week and adding more flavor to meals should be considered. Developing self-awareness related to food also helped participants meet their diet requirements. Similarly, participants partaking in a weight loss study by Rogerson et al reported that self-awareness and mindfulness allowed them to make conscious eating decisions, facilitating weight loss.\textsuperscript{23}

A reported barrier for intervention adherence was seasonality. Seasonality has similarly been found by others as an obstacle for participating in PA interventions.\textsuperscript{19,25,35} Specifically, Hefferon et al found that 48% participants reported poor weather as an obstacle for gym attendance.\textsuperscript{35} Participants also explained that exercising alone was discouraging. This theme is also apparent in a BCS diet and exercise trial by Balneaves et al, where participants recommended having a program partner or a modified version for a partner to do at home to provide support and reinforcement of the acquired habits.\textsuperscript{22} Lack of companionship is additionally a reported barrier in other exercise interventions.\textsuperscript{19,26} Group exercising and support from other study members increases motivation and facilitates exercising, and therefore should be encouraged in future exercise interventions.\textsuperscript{22,26-28} A study by Mascarenhas et al demonstrated that group exercise sessions through video-conferencing significantly increased PA levels among participants.\textsuperscript{36} This strategy can be tested in BCS in order to overcome both the barrier of seasonality and lack of companionship. Other factors hindering exercise were other family commitments and work schedule, which are well-known barriers to changing both diet and exercise behaviors.\textsuperscript{25,27,35} Interestingly, in other diet and PA interventions, several psychological factors were reported as barriers, notably lack of self-control, being unready to change, lack of confidence, and lack of motivation.\textsuperscript{19-21,31,35} Moreover, in weight loss trials with female BCS specifically, participants recommended a psychological component for future trials.\textsuperscript{22,24} However, these results were not observed in this study. Although readiness to change was not explicitly explored in this study, this non-observation of psychological factors could be indicative that participants were ready to change and through the intervention’s supportive environment gained both adequate confidence and motivation to change their lifestyle habits.

Regarding post-intervention continuity, in accordance with a BCS study by Sheppard et al, participants agreed that they intended to continue the acquired dietary and PA habits.\textsuperscript{24} However, while only 23% of individuals in the Sheppard et al study expressed that they would join a fitness club, 76% of participants in this study reported that they will join another gym, exercise class, or use their PERFORM Centre membership.\textsuperscript{24} This discrepancy may be explained by participants in this study being given an additional 3-month membership to the PERFORM Centre as a tool to ease them from the intervention setting back to their self-selected environment. The importance of providing transition tools is further supported by BCS participants of a diet and PA trial that expressed the desire for a place to continue exercising together post intervention.\textsuperscript{22} Future PA interventions should therefore provide similar transition tools for participants.

Future trials may require more instructions for cellphone app use as dietary intake monitoring tools. If this app cannot be downloaded, an alternative monitoring method is needed, such as writing dietary intake down by hand, which was not used in this study. As mentioned, some participants preferred this method. Self-monitoring is associated with a healthier dietary intake and an increased amount of PA.\textsuperscript{37,38} Therefore, interventions should consider participant preference for self-monitoring method to increase likeliness of self-monitoring and subsequent development of the desired lifestyle changes. This recommendation is further supported by Pew Research Center data, which reported that, in 2012, only 8% of cellphone users aged 65+ and 25% aged 50 to 64 downloaded an app on their phones.\textsuperscript{39} Moreover, only 11% of Canadians aged 65+ and 23% aged 55 to 64 used at least one cellphone app to monitor health.\textsuperscript{60} This is indicative that older adults may not be as adept with app download and use. Consequently, they may prefer another method of dietary self-monitoring.

### 8.1 Study limitations

This study has limitations. Firstly, this was a single-arm study and there was no pre-intervention assessment performed, even though this was a qualitative study. A pre-intervention would have allowed for an assessment on the participants’ motivation prior to and post intervention. Secondly, no data was collected on the participants’ socioeconomic status. Since lower socioeconomic statuses are associated with lower adherence to lifestyle interventions, such information would have furthered our interpretation of the results.\textsuperscript{32} Thirdly, all participants were older adults. Although the employment status of the participants was unknown, based on the participant mean age and...
several women reporting being either retired or semi-retired, it is plausible that many participants were not currently employed. Younger employed participants may therefore have different perspectives. Moreover, all participants were female and BCS. The findings may therefore not be applicable to other cancer survivors and males. The limitation of sex is supported by a systematic review concluding that each sex responds differently to and have different preferences for weight loss programs. The participants were also all volunteers. Consequently, results may be skewed to the perceptions of only those who had positive intervention experiences. Fourthly, all women reported having a supportive entourage. Social support can be a facilitator or barrier to intervention adherence. Therefore, the results may be applicable to only those with supportive social networks. Lastly, no data analysis on participant cancer treatment and subsequent physical health was performed. Therefore, it is unknown if cancer treatment(s) could have contributed to the physical health barrier reported by participants.

8.2 | Clinical Implications

These results are meaningful as they can be used to convey the necessary support and tools for BCS to sustain lifestyle changes that ultimately promote healthy body weights. Future BCS weight loss trials should promote group exercise sessions, include a tailored exercise regime, include individualized meal provisioning, provide transition tools, and allow participants to choose their preferred self-monitoring method.

9 | CONCLUSION

This study obtained experiences of female BCS participating in a structured diet and PA weight loss intervention with the novel aspect of meal-provisioning. Several facilitators and barriers for intervention adherence and intervention improvements were identified. The evaluated structured diet and exercise intervention overcame barriers found in previous research, notably lack of time for meal preparation, lack of intervention support, and psychological obstacles. The analysis findings are important to guide future BCS weight loss interventions.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.
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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.