Ph.D. Dissertation of Philosophy in Medical Science

The evaluation of clinical efficacy with multidimensional mechanisms analysis of a novel digital therapeutic for obesity: a randomized controlled trial

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Abstract

Background - Since lifestyle modification is the cornerstone of the obesity treatment, digital therapeutics (DTx) became one of the compelling and easily accessible treatment modalities.

Objective - This research proposes to validate the treatment efficacy, understand behavioral changes by eating behavioral analysis, identify the predictive digital phenotypes for engagement and clinical outcomes, and examine genetic precision medicine of a novel digital therapeutic for obesity (dCBT-O).

Method – This was an open-label, active-comparator, randomized controlled trial. Seventy female participants with body mass index (BMI) scores above 24kg/m² and no clinical problems besides obesity were randomized into experimental and control groups. The experimental group (dCBT-O group; 45 participants) was connected with a therapist intervention using a digital healthcare service that provided daily feedback and assignments for 8 weeks. The control group (25 participants) also used the digital healthcare service but practiced self-care without therapist intervention. Regarding the validating treatment efficacy, the primary outcomes of this study were objectively measured: weight in kg as well as other body compositions at 0, 8, and 24 weeks. Also, several eating behavioral phenotypes were assessed by buffet test-meal and food diary in app to examine the healthy behavioral change. Regarding the predictors for treatment efficacy, multidimensional digital phenotypes within time-series data were analyzed by elastic net regression method and obesity-related SNPs were genotyped from dCBT-O group.

Result – Both weight (–3.1%, SD 4.5, vs –0.7%, SD 3.4; $p = 0.036$) and fat mass (–6.3%, SD 8.8, vs –0.8%, SD 8.1; $p = 0.021$) reduction at 8 weeks in the dCBT-O group were significantly higher than in the control group. Applying the machine learning approach, sixteen types of digital

phenotypes (i.e., lower intake of high calorie food and evening snack, higher interaction frequency with mentors) predicted engagement rates, thirteen different digital phenotypes (i.e., lower intake of high calorie food and carb, higher intake of low calorie food) predicted the short-term weight change, and eight measures of digital phenotypes (i.e., lower intake of carb and evening snack, higher motivation) predicted the long-term weight change. The dCBT-O was also successful in promoting healthy eating behaviors that led to physiological and psychological adjustment for the metabolic mechanisms and consequences of healthy eating behavior. Lastly, CETP and APOA2 SNPs were significantly associated with the change in BMI (p = 0.028 and p = 0.005, respectively) at 24 weeks and eating behavioral phenotypes (p = 0.007 for healthy diet diversity and p = 0.036 for healthy diet proportion, respectively), the clinical efficacy markers of this study.

Conclusion – These findings confirm that the multidisciplinary approach via digital modalities enhances the clinical efficacy of digital-based interventions for obesity. Moreover, it contributes to better understand the mechanisms of human eating behavior related to weight control. This line of research may shed light on the development of advanced prevention and personalized digital therapeutics.

Keywords: Digital Therapeutics, Obesity, Eating Behavior, Digital Phenotyping, Genetic Analysis

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Chapter 1. Introduction

What is digital therapeutics?

Digital therapeutics (DTx) is “an evidence-based therapeutic intervention using high-quality software programs to prevent, manage, or treat a medical disorder or disease” (1). DTx emerged as a novel therapeutic approach for the prevention, management, or treatment of chronic, behavior-changeable diseases in recent years. Due to the public health emergency posed by coronavirus disease 2019, the Food and Drug Administration (FDA) has relaxed its regulations to expand access to digital health devices for remote monitoring and management of illness (1). Currently, DTx products target behavior-modifiable problems such as type 2 diabetes and weight management. For example, Welldoc Communications, a system to provide a mobile phone-based diabetes management software connected to web-based data analytics, serves as an interactive platform for patients and healthcare providers that provides real-time information and analysis (2). There are also other digital healthcare companies for diabetes and weight control; Noom, Omada, Livongo, Lark, Voluntis, and so on. Herein, I would discuss evidence-based therapeutic interventions driven by high-quality software programs. Only telephone calls, short message services (SMS), or online web-based servers are excluded from the definition of DTx.

Mostly, DTx systems draw upon the evidence-based principles of behavioral or psychological intervention protocols known as cognitive behavioral therapy (CBT) (1). CBT uses evidence-based techniques to change problematic behaviors and unhelpful cognitive distortions, and to improve emotional regulation and coping skills to solve the current problems (3). Frequent clinical assessments in the context of diverse psychological conditions using digital modalities are highly beneficial to enhance the efficacy of CBT interventions (4). In fact, collecting assessment data in face-to-face conditions is a burdensome task involving retrospective reports.

These reports have high risks of being systematically biased by recall and neglecting important contextual components or acute changes in certain periods (4). In contrast, collecting assessment data using smartphones and wearables is convenient and time-sensitive, allowing the real-time evaluation of context-rich information. Thus, the integration of digital technologies and CBT techniques has become the cutting-edge approach in DTx components, allowing individualized and stepped-care interventions (5).

DTx for obesity and eating-related problems: an emphasis on a multidisciplinary approach

Since obesity and eating behavioral problems are complex diseases with a multifactorial etiology, a biopsychosocial approach including medical treatment and lifestyle changes is required to treat them effectively (6). As shown in Figure 1, both physical and mental health conditions are the major components of lifestyle modification. To achieve a healthy lifestyle through a lifestyle modification intervention, high motivation is mandatory as a prerequisite for high adherence (7, 8). A patient can also attain stimulus control capability by manipulating eating-related cues in the environment, using cognitive techniques to investigate maladaptive thinking, and building coping skills related to emotional regulation and stress management (9). These psychological mechanisms contributing to mental health are closely associated with physical health and contribute to clinical outcomes.

Mental health should be considered a vital component of DTx for obesity and eating-related problems. However, most previous self-management DTx studies were limited by only focusing on behavioral aspects apart from mental health components, such as self-monitoring of glucose and body weight, medication adherence, logging a food diary, and physical activity (10, 11). The majority of mobile health interventions only showed effective improvements in primary outcomes for physical health measures, such as

hemoglobin A1c or body weight (12-15). They did not determine psychological components such as self-efficacy, quality of life, depression, and other measures. A multidisciplinary approach including psychological components is needed to develop DTx which successfully derives healthier lifestyle modification to deal with obesity and other eating behavioral problems.

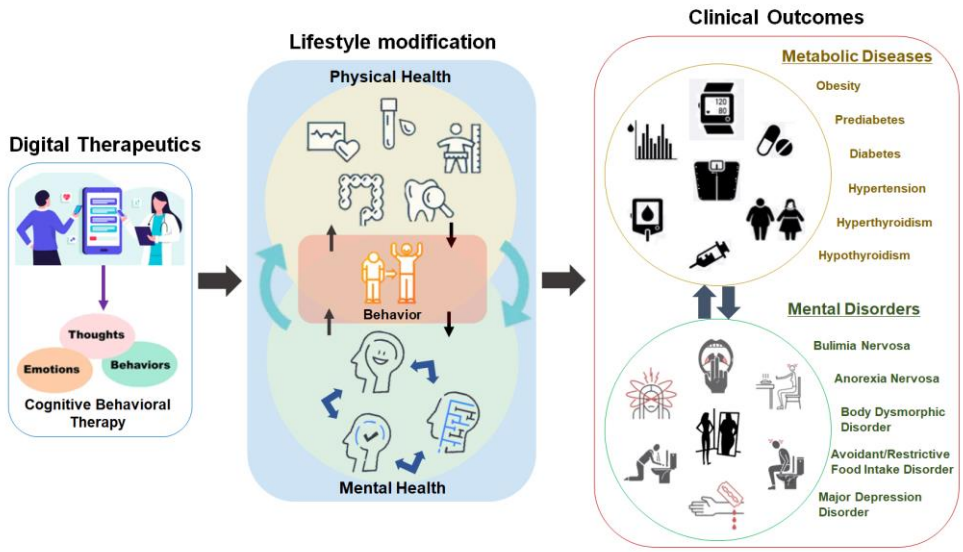


Figure 1. Interaction between mental and physical health for lifestyle modification via digital therapeutics

Recent randomized controlled trials related to DTx for obesity and eating-related problems

To encourage an informed discourse about the efficacy of DTx for obesity and eating-related problems, I reviewed several randomized controlled trials (RCTs) of DTx conducted from 2017 to 2020 (Table 1). The combinations of keywords used for eligible articles were “digital intervention”, “obesity”, “eating behavior”, “eating disorder”, “weight control”, and “randomized controlled trial.” in Google Scholar. All founded research were included following the PRISMA guidelines.

Table 1. RCTs for digital-based interventions for obesity and eating behavior problems from 2017 to 2020

Ref. No.	Author (Year)	N / Population	Study design			Delivery digital device			Outcomes					Adherence (estimated)
			Intervention	Duration	Control	SmP	Web	Wearable	B.W.	Anthr.	L.T.	B.T.	Psych.	
18	Spring et al., (2017)	N=96 / Adults with obesity	Technology-supported	6 months	Self-guided, standard	O	O	X	△	↓↓	-	-	-	O
16	Nezami et al., (2018)	N=51 / Mother with overweight & obesity, a child aged 3-5 years	Smart group (mobile supported)	6 months	Placebo	O	X	X	↓↓	-	-	-	-	85%
19	Spring et al., (2018)	N=212 / Adults aged 18-65 years	Temporally simultaneous intervention	12 weeks	Sequential (digital sham), control	O	X	X	-	-	-	△	-	82%
20	Kim et al., (2019)	N=136 / Older adults (mean age 60) with diabetes	Mobile-based glucose diary	24 weeks	Usual care (paper diary)	O	X	X	X	X	↓↓	-	X	-
17	Fitzsimmons-Craft et al., (2020)	N=690 / Women with eating disorders	CBT-guided Self-help	8 months	Usual care	O	X	X	-	-	-	↓↓	↓	31%
21	Lowe et al., (2020)	N=141 / Women + men (adults) with BMI 27~43 kg/m^2	Time-restricted eating	12 weeks	Consistent meal timing	O	X	O	X	LBM ↓↓	X	-	X	84%

RCT, randomized controlled trial; Ref., reference; No. number; N, number of participants; SmP, smartphone; B.W., body weight; Anthr., anthropometrics; L.T., lab test; B.T., behavioral test; Psych., psychological assessments; LBM, lean body mass; BMI, body mass index; CBT, cognitive behavioral therapy; O, used; -, not assessed; ↓↓, (statistically) significantly decreased; ↓, reported decreasing trend; △, mixed results among the measures; X, no difference.

Regarding the study population, only one DTx RCT was conducted among young children (16). In fact, the intervention was not directly delivered to the children, but supported their caregivers to reduce sugar-sweetened beverage intake. In terms of the target diseases, four RCTs investigated DTx for obesity treatment, while only one study focused on eating disorders (17).

Only one study applied psychological evidence-based strategies (i.e., CBT) in their intervention protocols, considering cognitions, emotions, and behaviors for lifestyle modification (17). Other studies utilized only behavioral strategies such as self-monitoring or restricting time (16, 18-21).

To test the efficacy of the interventions, two studies used a three-arm parallel-group design (18, 19), while other studies used a two-arm parallel-group design (16, 17, 20, 21).

Regarding the digital devices utilized in the research, two studies combined two different modalities (i.e., smartphone + web or smartphone + wearable) to deliver the intervention (19, 21). All studies applied smartphones as their core intervention devices (16-21).

Although obesity and eating behavioral problems are known to have complex backgrounds, most studies evaluated clinical efficacy with only one or two measures (16-19). A few studies applied several assessments to validate their intervention efficacy, but they did not show significant outcomes in general (20, 21). All clinical outcomes significantly improved after the digital intervention period.

It is also important to evaluate the adherence rate of an intervention since adherence is a key component for understanding the clinical efficacy of DTx. An engagement rate of over 80% was shown in most studies (16, 19, 21). However, the only study that adapted self-help strategies in the digital intervention presented an adherence rate of 31% (17).

<u>Part I.</u> Validating the treatment efficacy and finding its predictive markers: development of a dCBT-O

To date, the most effective standard obesity treatment is weight-loss lifestyle modification based on a combination of behavioral and cognitive approaches and nutrition and physical education. Clinical psychological treatment approaches are pivotal and involve engaging patients in lifestyle modification and motivating them to successfully lose weight with the help of a multidisciplinary team (6). Cognitive behavioral therapy for obesity is aimed at not only losing weight but also preventing weight regain, thereby avoiding the dissatisfactory long-term results of earlier behavioral treatments. It firmly distinguishes between weight loss and weight maintenance, allowing patients to practice effective weight-maintenance strategies (e.g., avoiding unrealistic weight goals and addressing obstacles to weight maintenance) (22). One study applied a 12-week CBT program for obese people, resulting in a 6% reduction in body fat relative to the control group (23). Moreover, a 20-week CBT intervention involving a 10-week main program followed by a 10-week less intensive care program significantly improved body composition and improved soft drink consumption habits compared to the control group (24).

Although cognitive behavioral programs involving weekly clinic visits are known to be the most effective treatments for obesity, they place high demands due to time, cost, distance, status of endorsement, and difficulties securing child care (25). A previous study found that people would prefer cost-effective and time-saving methods to lose weight (26). Researchers have thus explored alternative methods for carrying out weight loss programs, such as television, computer, and smartphone applications (apps) to meet individual needs and to make obesity treatment more accessible. Among these, self-monitoring via smartphone apps has shown the greatest potential to make diet tracking easier and engaging because of its convenience and accessibility (27). Despite the use of smartphone apps for

self-monitoring, a “law of attrition” in digital health interventions still holds, whereby users stop using technology-based components over time. Because the effectiveness of treatments via digital tools is closely associated with the user’s extent of engagement (28), a high attrition rate is a critical issue in the assessment of the efficacy of digital intervention programs. Therefore, based on behavioral modification principles, periodic prompts that encourage healthy behaviors are one method to remind and motivate people to change their health behaviors. A systematic review of the use of technology tools to send periodical notifications about users’ behavior changes found them to be more effective than non-technological notifications or no notifications (29). However, this review only focused on the effectiveness of digital interventions for behavior change as a whole and did not investigate how to enhance engagement with the intervention.

The goal of Part I was to test a novel approach to losing weight and maintaining the new weight after participation in an intensive and comprehensive human coaching program based on CBT modules via digital tools such as the Noom Coach app and InBody dials. The Noom Coach app is one of the most popular smartphone apps currently available; it has received higher quality assessment scores than other smartphone apps (30). It allows participants to log their food intake, exercise activities, and weight, and to engage in in-app group activities, read in-app articles, and interact with a human coach via in-app messages. In-app group activity lets participants communicate with other participants and share their experience of healthy lifestyle trials; in-app articles deliver practical information about healthy lifestyles written by physicians, nutritionists, and clinical psychologists; and in-app messages enable participants to receive individualized feedback from human coaches based on their own records presented on the web-based dashboard. A web-based dashboard is provided to the coaches to monitor participants’ data. InBody dial is a home body composition analyzer linked to a mobile application, allowing users to

conveniently measure their body composition. Furthermore, this part addressed the self-sustainability of the promoted lifestyle change after the intervention.

<u>Part II.</u> Eating behavioral analysis using buffet test-meal and food diary in app: understanding human eating behavior change by dCBT-O

From a psychological perspective, there are three fundamental questions related to studying human eating behaviors: How much do we eat based on the energy density (ED) of food (food intake)? How much do we choose to eat from specific ED of food groups (food proportion)? How diverse are the categories of ED of food we eat (food diversity)? Food intake refers to the amount of food consumed within the consideration of ED of food. This is one of the most remarkable eating behavior phenotypes, since an energy imbalance, the main feature of overweight condition and obesity, occurs when the intake exceeds the expenditure (31). Food proportion refers to the percentage of food group sections composing the total food intake (32). There are controversial results regarding the relationship between food proportion and bodyweight, showing all three possible outcomes (positive, negative, and no significant associations) (31, 33, 34). Thus, it is important to consider the ED of food with food proportion, since it significantly influences energy intake and fullness (35). It is known that the high ED of food intake increases energy intake compared to the low ED of food (i.e., fruits, vegetables, whole grains). Accordingly, changing habitual diet from high ED of food to low ED of food can be an important component for reducing energy intake and prompting effective weight loss (36). Food diversity is related to the distribution or diversity of dietary patterns among different food groups (37). Although few studies have investigated the role of food diversity in health outcomes, there is an increasing recognition that food diversity can be particularly relevant to obesity and blood glucose

control in diabetes (32, 38). Moreover, it may be a principal indicator for evaluating the nutritional status of the diet as a whole. The concept of human eating behavior is described in Figure 2.

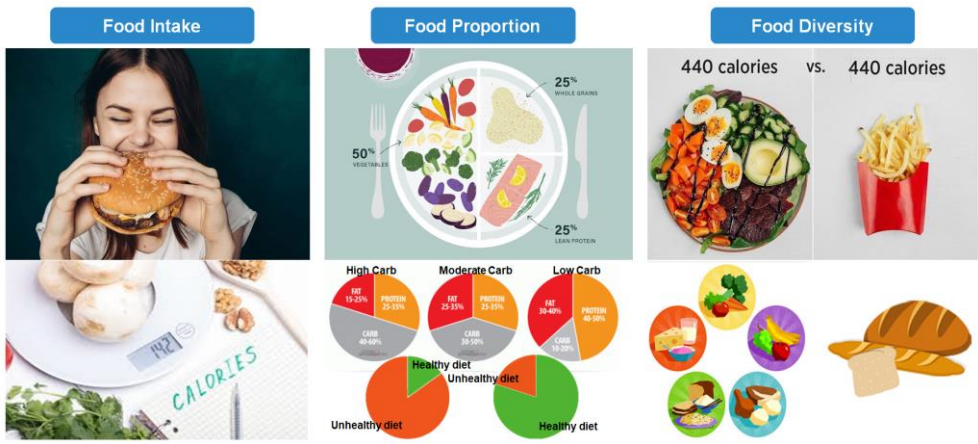


Figure 2. Several phenotypes of human eating behavior

There is no doubt that emotions and eating behaviors interact with each other. For instance, emotion could influence food intake and choice by altering appetite or food availability, while emotional transitions can also result from food intake and choice (39). In addition, people regulate eating behaviors according to contextual aspects such as social settings (31), food variety (40), food palatability (41), memory of recent eating (42), and motives for eating regulation (43). The great majority of research on eating behaviors within psychology is about managing food intake, choice, and variety, since these can be associated with obesity and eating disorders. Regarding physiological aspect, eating behavior is closely also interacting with the changes in energy balance which is modulated by the metabolic changes, such as insulin resistance. Previous studies have revealed that insulin resistance (IR) is closely related to eating behavior associated with obesity and metabolic diseases such as type 2 diabetes (T2D) mellitus and cardiovascular disease, and cognitive impairment. Moreover, IR is associated with the central nervous system, regulating eating behavior (44,

45). A previous study also reported that IR patterns correlated positively with eating behaviors such as overeating and food craving, potentially stimulating altered regulation of the homeostatic system (46). Accordingly, reducing the food calorie intake decreases both body weight and IR (47, 48). In further human brain studies, insulin activation selectively impaired the prefrontal cortex and hypothalamus of overweight and obese people (46, 49). However, the role of IR during changes in eating behavior, food intake, proportion, and diversity for weight loss has not been comprehensively investigated.

To comprehend human eating behaviors, it is critical to establish assessment methods for analyzing food intake, proportion, and diversity (50). Since the nature of eating behavior is complicated, an optimal protocol for its assessment has not yet been defined. In fact, current protocols to analyze eating behavior lack precision and have systematic limitations. Some past studies insisted upon approaches that consider both internal validity (reproducibility) and external validity (resemblance to real-world eating behavior) (51). Thus, a comprehensive assessment indicating ideal circumstances (high internal validity) and real-world conditions (high external validity) will promote the efficacy and safety of new medical interventions for obesity using RCTs (52). Regarding the categorization of the food into either healthy or unhealthy groups, it is practical to classify them based on the multiple components such as ED of food and glycemic index (GI). In addition, the cognitive and physiological aspects of eating behavior should be considered to comprehensively understand the consumption patterns of individuals under these food conditions.

Part II aims to investigate the treatment efficacy of digital lifestyle modification regarding eating behavioral phenotypes and the role of psychological characteristics and IR in improvements of healthy eating behaviors. The conceptual framework of eating behavior with its assessment methods and related factors are shown in Figure 3.

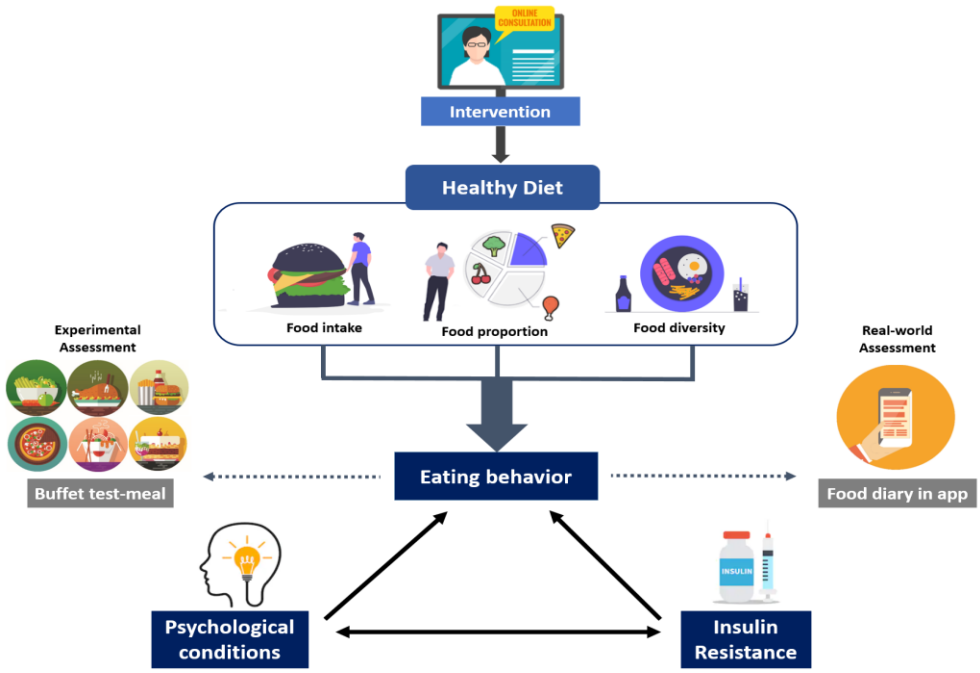


Figure 3. Conceptual framework of eating behavior with assessment methods and related factors.

<u>Part III.</u> Digital phenotyping using machine-learning analysis: identifying a predictive model for engagement in application and clinical outcomes of dCBT-O

While delivering an intervention via a mobile app, the users must be actively and frequently engaged with mobile apps to succeed within the treatment. Thus, identifying predictive markers that can inform engagement in mHealth interventions could potentially strengthen its effectiveness. Previous studies have found that social and gamified components' involvement or offering personalized feedback from human factors effectively enhances user engagement for app-based interventions (53, 54). In fact, identifying the major principles that can predict users' engagement and health outcomes is important for exploring systemic elements to strengthen user engagement in digital intervention. Engagement with digital technology is intricate because it is not stationary but a progressive process

(55). It is also multifaceted in its environment, reflecting the quality of the user's practice, their communication features, and their willingness to use the app over time or repeatedly (56). Of special interest to this present issue, it is noted that intrinsic motivation is a significant precursor for engagement (57). Moreover, a wide range of cognitive and emotional states such as self-interest and self-efficacy are closely related to the user's engagement (56). Therefore, it is important to examine motivation, behavior, emotion, and cognition to understand the changes of users' engagement and predict the clinical outcomes. This will intensify the treatment's efficacy and find good responders for precision medicine. However, finding the major indicator that predicts who will benefit the most from digital intervention is insufficient. This resulted in only a minor portion of users obtaining advantages from the digital healthcare system (58, 59). Thus, it is necessary to explore how comprehensive and multidimensional digital phenotypes detect individual differences and determine the user's engagement in the digital intervention. A conceptual framework of mHealth components, including examples of digital phenotypes, is presented in Figure 4.

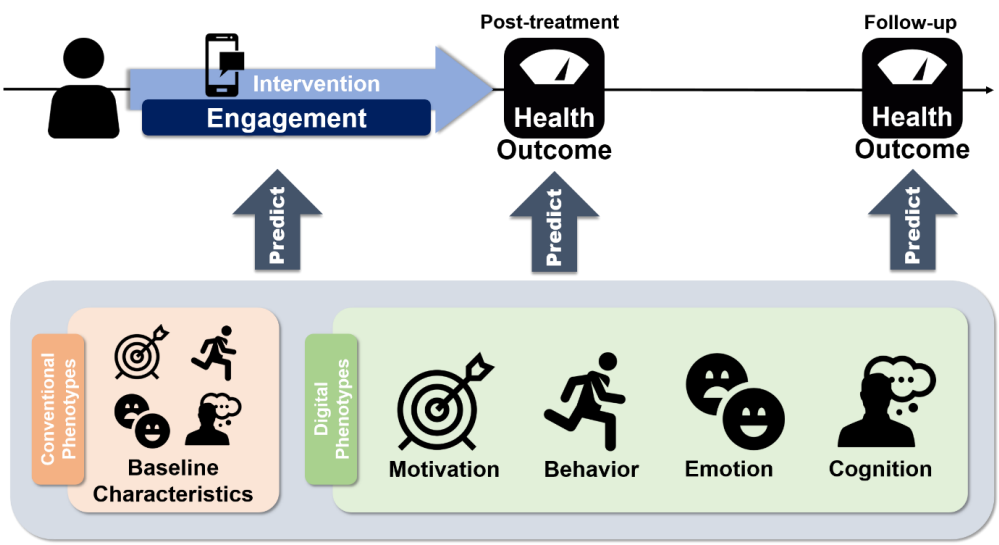


Figure 4. A conceptual framework of mHealth components and examples of digital phenotypes.

Another major issue in the digital era is the interpretation and filtering of data for clinical decisions. Although the rapid growth of digital technologies has led to comprehensive and abundant information about one's health status, analytical methods to clarify and simplify it have not advanced at a compatible pace (60). This could be addressed as the main bottleneck in current digital phenotyping studies. Some pioneering research has demonstrated statistical methods to derive insights (which predict outcome) from various digital phenotypes (61-63). However, the data are mostly heterogeneous and mixed with structured and unstructured frames containing random sampling, artifacts, and inconsistent completion, making traditional statistical models difficult. This can lead to limited or biased results from the data and a lack of replicability of the conclusions. Compared to conventional analytical methods, machine-learning analysis can obtain information from scattered and intricate data, offering insights to promote clinical decision-making. A recent study has shown that mortality prediction models using intensive care unit (ICU) data based on a machine learning approach were superior to conventional methods (64). The algorithms supporting individual-specific predictions might enhance the usability of machine-learning prediction models. The elastic net is a penalized regression method that automatically selects significant variables by reducing the regression coefficients of unimportant features to zero. This algorithm merges feature elimination from least absolute shrinkage and selection operator (LASSO) regression and feature coefficient reduction from the ridge regression to enhance the model's predictions. To elaborate, LASSO regression uses L1 regularization which penalizes less important features of the dataset and makes their respective coefficient zero. On the other hand, ridge regression uses L2 regularization which shrinks the parameter to possess a low variance, but it never leads to a coefficient tending to zero unlike the LASSO regression. Thus, the LASSO regression

is beneficial for automatic variable selection of the models by eliminating the coefficient (shrinks to zero) but can lead to lower accuracy due to the loss of information compared to the ridge model (65). Similarly, the ridge regression method can decrease the complexity of a model but is not a better fit for the feature reduction like LASSO regression (66). To improve these limitations found in both LASSO and ridge regression methods, the elastic net automates certain parts of model selection and leads to dimensionality reduction which makes it a computationally efficient model. Thus, the key roles of an elastic net are grouping and variable selection, making it most appropriate regression method where the dimensional data is greater than the number of samples used (67). Here, since the number of conventional and digital phenotypes are greater than the sample size in this part of the study, I applied an elastic net analytic method for the machine learning algorithm. This could aid in the adaptation of machine learning models as clinical decision-support tools.

Part III investigated multidimensional information at different time points using various assessment methods to monitor and predict the primary outcome's engagement and efficacy. This part plays a significant role in establishing the most practical and effective mHealth intervention paradigm.

Part IV. Genetic analysis for predicting the clinical responses: genetic precision medicine of dCBT-O

Recently, genome-wide association studies (GWAS) have identified a large number of single nucleotide polymorphisms (SNPs) associated with obesity phenotypes (68). One of the commonly used phenotypes to assess obesity is the BMI and it is known that approximately 40-70% of inter-individual differences in BMI are associated with genetic factors (69). In addition, several previous studies have stated that there are several gene-diet interactions associated with changes in anthropometric and metabolic measures (70, 71). Although the prevalence of obesity depends on multi-

dimensional components, most of the current literature reviews the associations between obesity candidate genes and single-dimensional phenotypes.

With the increasing prevalence of obesity, various types of obesity interventions have also been developed. Nevertheless, obesity interventions are not successful for all individuals, suggesting that genetic traits contribute to the variability in weight loss in response to each type of intervention. This suggests that a personalized approach based on individual characteristics, such as genetics, is required to effectively treat obesity. In a previous study, the degree of weight loss after exercise was found to be more similar between identical twin pairs when compared to dizygotic twin pairs (72). Moreover, weight loss in response to Roux-en-Y gastric bypass (RYGB) was also similar among first-degree relatives when compared to unrelated individuals (73). Clinical research on obesity medications reported that the Taq1A variant of the DRD2 gene may be used as a marker to predict weight loss response to naltrexone/bupropion (NB) (74). Moreover, the variation in genetic risk score (GRS) for lean body mass (LBM) may affect appetite changes and body composition in response to dietary fat intake (75). However, there have been no studies that investigated SNP genotypes that modulate the clinical outcomes in response to digital therapeutics for obesity. Part IV aimed to examine the associations between SNP genotypes and clinical efficacy using multi-dimensional components of digital therapeutics (Figure 5). Thus, the candidate SNPs were investigated to identify which genotype modulated the changes in clinical outcomes in response to dCBT-O.

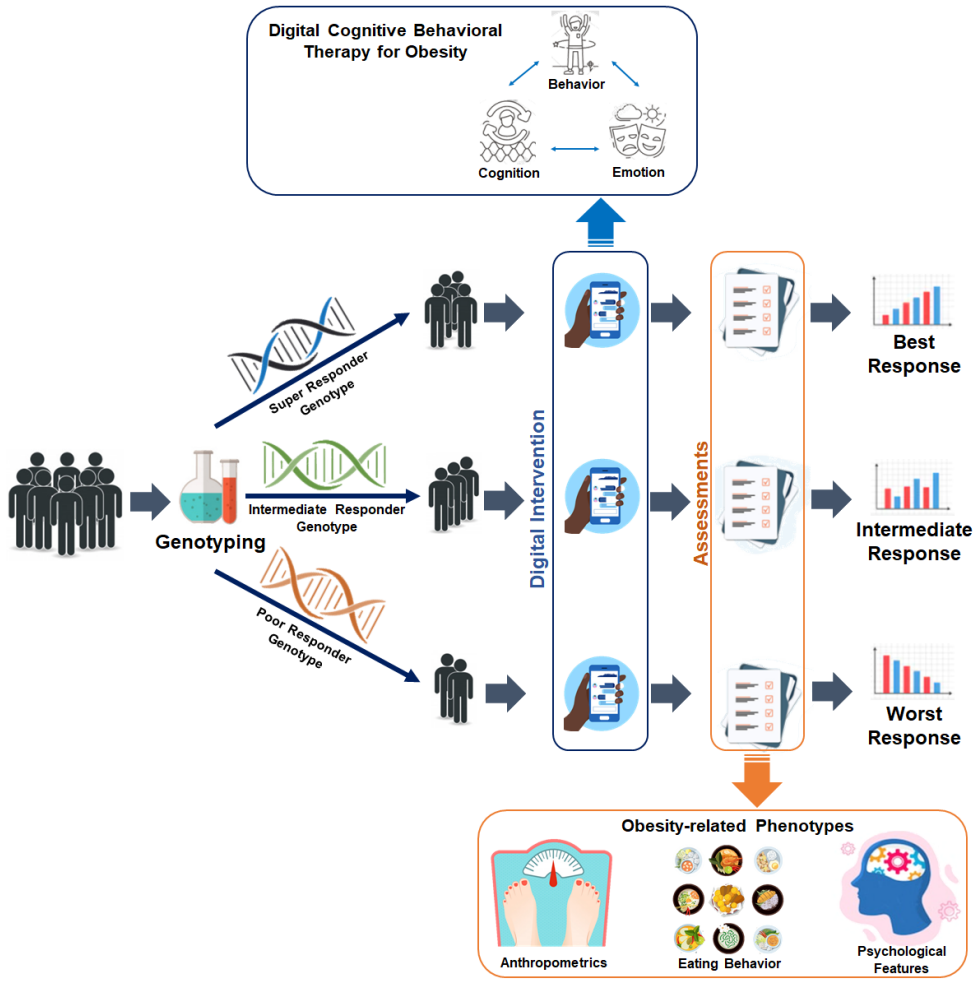


Figure 5. Diagram for Precision Medicine in Digital Cognitive Behavioral Therapy for Obesity (dCBT-O)

Overall, I aimed to research on validating the newly developed dCBT-O and finding the predictive model for engagement in app and clinical efficacy by digital phenotyping using machine-learning analysis. Also, to comprehensively understand the behavioral changes due to dCBT-O, I examined eating behavioral analysis via two different assessments: buffet test-meal (direct observation) and food diary in app (real-world setting). Lastly, I investigated the candidate SNPs to find the major genotypes which regulate the responses of dCBT-O. The overview of my thesis structure is described in Figure 6.

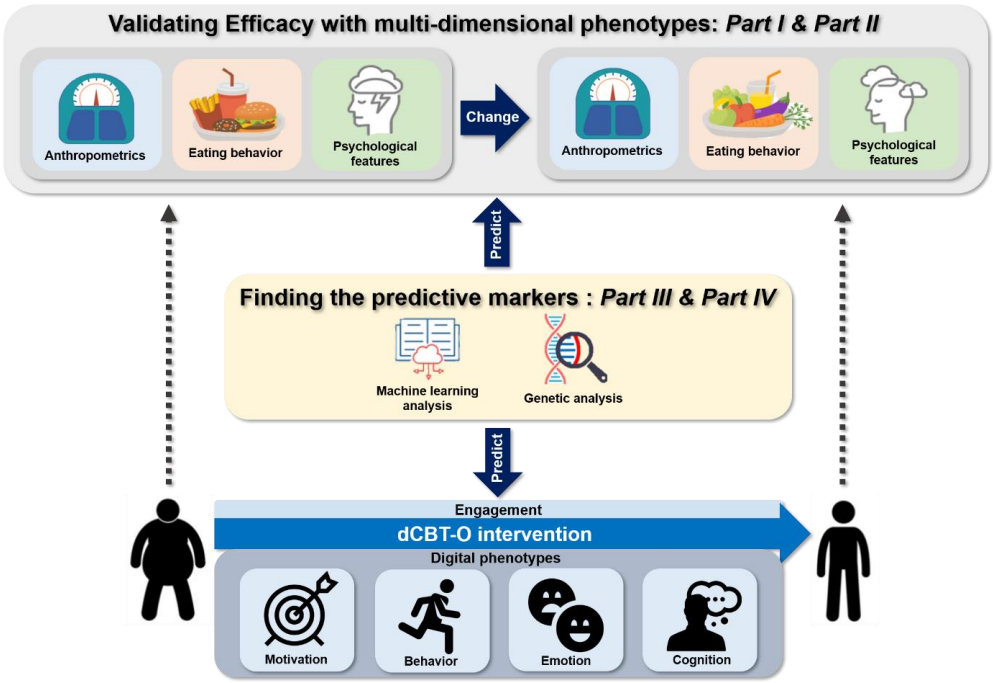


Figure 6. Overview and the structures of this thesis paper

The hypotheses of each part are as the followings;

<u>Part I.</u> Validating the treatment efficacy and finding its predictive markers: development of a dCBT-O

- The individuals randomized to the dCBT-O group would lose weight and better maintain their weight loss than individuals in the control group.

<u>Part II.</u> Eating behavioral analysis using buffet test-meal and food diary in app: understanding human eating behavior change by dCBT-O

- The digital lifestyle modification successfully promotes healthy eating behavior change.
- Improved healthy eating behavior is associated with psychological and metabolic phenotypes.

<u>Part III.</u> Digital phenotyping using machine-learning analysis: identifying a predictive model for engagement in application and clinical outcomes of

dCBT-O

- A higher engagement rate in the app is associated with higher weight loss after the dCBT-O.
- Machine learning analysis identifies digital behavioral phenotypes for both engagement rate in app and clinical outcomes of dCBT-O.

<u>Part IV.</u> Genetic analysis for predicting the clinical responses: genetic precision medicine of dCBT-O

- According to the candidate SNPs for obesity phenotypes, the anthropometrics, obesity-related behavioral phenotypes, and psychological characteristics may differ in response to the dCBT-O.

Chapter 2. Method

Participants

Seventy female subjects were recruited between September and October 2017 through both online and offline boards of a university campus in Seoul and a social network service. Eligibility criteria included age between 18 and 39 years, body mass index of 25 to 40kg/m^2, smartphone usage, and scores in the highest 40% on the Situational Motivation Scale (SIMS; scores above 68 out of 112 total). Participants were ineligible if they had a history of major medical problems such as diabetes, angina, or stroke; a major psychiatric disorder involving hospitalization or medication in the past; and a current, planned pregnancy within the next 6 months. The flow of participants from recruitment to final assessment at 24 weeks is shown in Figure 7.

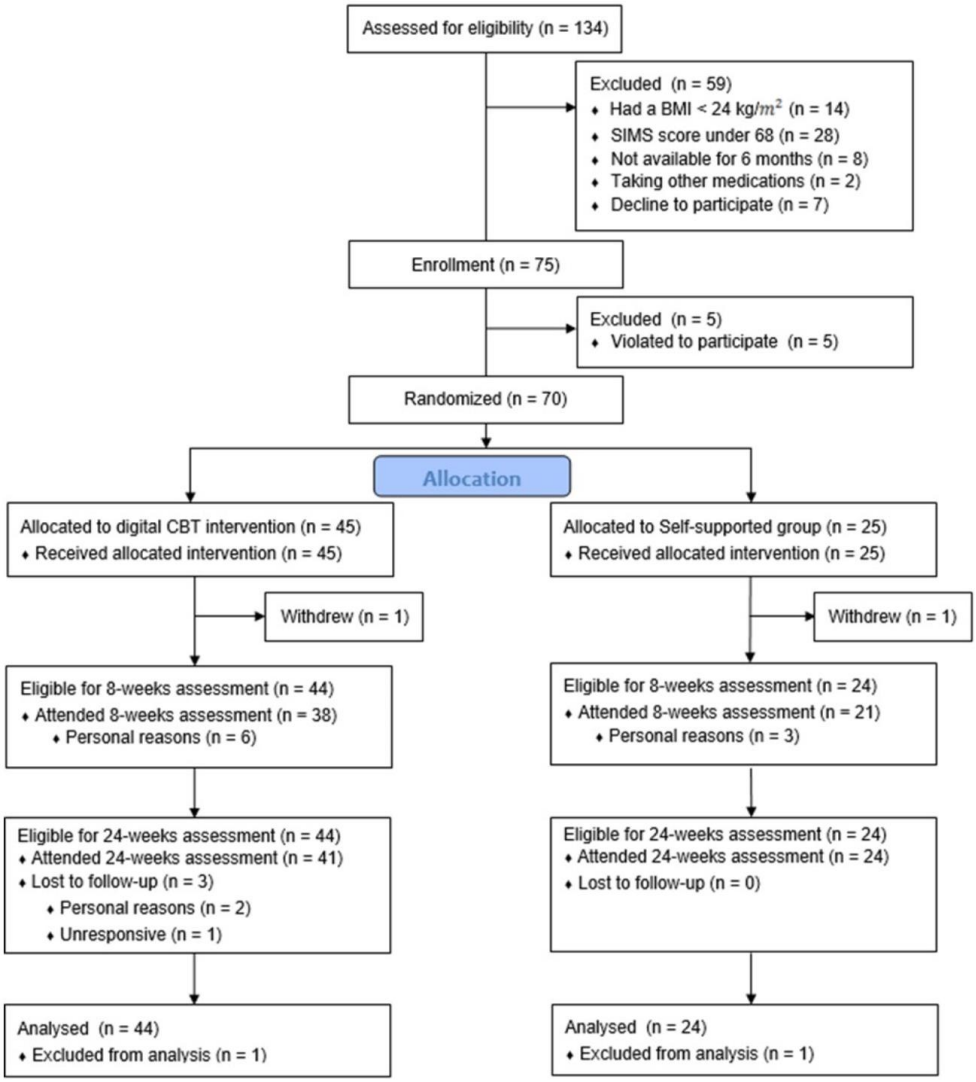


Figure 7. dCBT-O CONSORT flow diagram‡
‡Modified from master thesis of Meelim Kim

Study Design

This was an open-label, active comparator RCT. Following initial screening, all participants were asked to attend an orientation session where the study was described in more detail. Written informed consent and baseline measurements were obtained in person. The randomization was designed to randomly assign 75 participants in total to a control (App only) group or a dCBT-O (App+human CBT) group at a ratio of 1 to 2 so as to deliver a

more powerful trial within resource constraints and to maximize the statistical power of predictor analysis (within-group analysis) (76). Randomization was performed by the project manager by drawing lots. All participants were asked to visit at baseline, 8, and 24 weeks for objective measurements and completion of questionnaires, and they were each paid $4 for attending each of the appointments. This study was conducted from September 2017 to April 2018. The Institutional Review Board of Seoul National University Hospital approved the study with approval number H-1707-122-872. The study protocol was registered at ClinicalTrials.gov NCT03465306 on January 15, 2018.

Procedures

Anthropometric measurements were assessed by InBody H20B (InBody Co., Ltd., Seoul, South Korea) at baseline, 8, and 24 weeks in light street clothing and without socks and shoes. Blood samples were taken in the morning after overnight fasting to avoid daily variations in activities. After the blood test, breakfast session (buffet test-meal) took place between 8:00 a.m. and 10:00 a.m. It was composed of 24 food items (12 food items for a healthy diet and 12 food items for an unhealthy diet; Table 2). The energy density of food was the major criterion to classify healthy and unhealthy diet foods. Then, the glycemic index (GI) of each food has also been considered to justify this classification of diet foods. Thus, healthy diet foods have low energy density and GI, while unhealthy diet foods have relatively high energy density and GI (77, 78). Prior to the meal, the participants were given an explanation about the foods available at the test-meal and told they could decide which foods to eat, and as much or as little as they wanted, offering unlimited amounts of food. All participants had 30 minutes to eat, but they were not required to eat for this entire time if they finished earlier. The majority of the participants consumed their meals within 15–20 minutes. They were also informed that they could ask for

additional servings of any of the foods provided. During the meal, the total weight of each food consumed was measured from pre- to post-meal, and nutrient values were calculated using nutrition facts label information to determine total meal intake.

Table 2. Serving sizes of food served during the buffet test-meal assessment.

Healthy Diet Foods[a]	**Energy density (kcal per 100g or mL)**	**Nutritional Information Carb / Protein / Fat (%)**	**Glycemic Index (GI)**
Solid foods			
Whole grain bread (without butter or spreads)	250	76 / 10 / 14	51
Brown rice	152	90 / 7 / 3	50
Boiled egg	150	0 / 35 / 65	30
Banana	93	96 / 4 / 0	46
Braised chicken	90	34 / 30 / 36	45
Vegetable salad†	83.9	69 / 12 / 19	22
Apple	52	100 / 0 / 0	36
Nabak kimchi†	18	100 / 0 / 0	
Liquid foods			
Soymilk	50	0 / 33 / 67	30
Low-fat milk	40	49 / 29 / 22	26
Seagram's sparkling water	0	0 / 0 / 0	0
Water	0	0 / 0 / 0	0
Unhealthy Diet Foods[aa]			
Solid foods			
Sneakers chocolate	483	52 / 9 / 39	90
French butter croissant	415	43 / 9 / 48	70
Combination pizza	392	52 / 18 / 30	80
Grilled spam	340	57 / 13 / 30	
Egg tart	321	88 / 6 / 7	
Pickle†	300	65 / 9 / 26	63

Chicken tender stick	288	33 / 49 / 18	
Seasoned sesame leaves†	116	59 / 26 / 15	
Liquid foods			
Orange juice (sweetened)	160	33 / 49 / 18	57
Sprite	110	100 / 0 / 0	
Coca Cola	80	100 / 0 / 0	63
Apple juice (sweetened)	63	100 / 0 / 0	

[a]Healthy Diet Foods: for solid food, energy density ≤ 250 and GI ≤ 55; for liquid food, energy density ≤ 50 and GI ≤ 55. [aa]Unhealthy Diet Foods; for solid food, energy density ≥ 250 and GI ≥ 55; for liquid food, energy density ≥ 50 and GI ≥ 55. †Regarding the natural characteristics of vegetable and fruit groups, we adjusted the criteria of healthy and unhealthy diet classification to energy density ≤ 100 and GI ≤ 50 for healthy diet foods; energy density ≥ 100 and GI ≥ 50 for unhealthy diet foods.

The basics of the tutorial and login procedures for both the Noom app and InBody H20B (InBody Co., Ltd., Seoul, South Korea) were demonstrated to all participants during the orientation of the study. The Noom app was mainly used to keep a food diary and deliver messages between the therapist and participants, while InBody H20B was used to monitor and collect the body composition data of the participants. The dCBT-O group was given daily feedback and assignments from a psychologist based on the CBT modules for 8 weeks and could access the digital tools from the intervention period to the 24-week follow-up. The control group was instructed to use only a food diary without therapist intervention until the 24-week follow-up but was given the same digital tools and instruction as the dCBT-O group. Thus, the control group underwent the same standard of care arm trial as the dCBT-O group, except that it was asked to practice self-care.

Measurements

Anthropometrics The primary outcome was change in body weight. Other measures such as change in BMI and body fat mass were secondary outcomes.

Digital phenotypes There are six types of behavioral phenotypes assessed in apps: food restriction, overeating and binge eating, late-night meals, snacking, food choice, and activity rate. Food restriction was evaluated using kcal per meal per day. Overeating and binge eating were assessed by kcal per meal per day, and the speed per meal (79) —the late-night meal was investigated using the dinner kcal and the time per meal. Snacking was estimated using snack kcal. Food choice was examined based on the type of food per meal, total amount of sodium and sugar, number of food types per meal, and percentage of nutritional types (carb, protein, and fat). The activity rate was measured as the number of steps and the total hours of exercise. Automatic thoughts were grouped into six categories: selective abstraction, arbitrary inference, overgeneralization, magnification or minimization, personalization, and absolutism. There were 20 automatic thoughts, and participants could add thoughts related to food or eating behaviors. Example statements for automatic thoughts are listed in Table 3. I assessed five negative emotions closely related to problematic eating habits: irritation, loneliness, nervousness, boredom, and depression (80, 81). The participants were asked to report each type of negative emotion scores using a visual analog scale (VAS) between 0 and 100. The motivation was assessed using four dimensions: will, rank of importance, confidence, and satisfaction. These different types of motivation were scored using a 10-point Likert scale (1–10).

Table 3. The categorization of digital phenotypes and items used for each phenotype.

Part 1. Behavior

	Main Question	Sub-Categories	Responses
The Place to Eat	Where did you eat?	Breakfast	1 (Skipped the meal) 2 (At home) 3 (At the office) 4 (At the restaurant)
		Morning snack	
		Lunch	

		Afternoon snack	5 (In the traffic) 6 (Others)
		Dinner	
		Late-night snack	

	Main Question	Sub-Categories	Responses
The Time Period to Eat	What time of the day did you eat?	Breakfast	1 (Skipped the meal) 2 (6:00am~) 3 (7:00am~) 4 (8:00am~) 5 (9:00am~) 6 (10:00am~) 7 (11:00am~) …. 17 (21:00pm~), 18 (Others)
		Morning snack	
		Lunch	
		Afternoon snack	
		Dinner	
		Late-night snack	

	Main Question	Sub-Categories	Responses
The Speed of Eating	How long did you take to eat?	Breakfast	1 (Skipped the meal) 2 (less than 5mins) 3 (5mins. ~ 10mins.) 4 (10mins. ~ 15mins.) 5 (15mins. ~ 20mins.) 6 (more than 20mins.)
		Morning snack	
		Lunch	
		Afternoon snack	
		Dinner	
		Late-night snack	

	Main Question	Sub-Categories	Responses
The Type of Food	What type of food did you eat?	Breakfast	1 (Skipped the meal) 2 (Liquid) 3 (Fruits/Finger food) 4 (Full set diet)
		Morning snack	
		Lunch	
		Afternoon snack	
		Dinner	
		Late-night snack	

Part 2. Cognition

Main Question	The list of thoughts	Checked

The thoughts that came to your mind during the day	- It is free, so you can eat a lot. - If you leave food, it is a waste, so you must eat it all. - There is no difference between eating less or more since I have already exceeded the recommended calories per day. - If I do not eat, he/she will be disappointed. - If I become thinner, other people will like me more. - If I leave food, other people will think I am spoiled. - When I gain weight, others will ignore me. - If I do not eat, other people will think I am timid. - I cannot help it since I failed my diet again. - I failed to lose weight since I could not do the exercise I was supposed to do today. - I am ruined since I passed the recommended calories per day. - I am going to gain a lot of weight again since I ate OOO. - It is okay if I skip dinner. - I can have a lot for dinner since I ate a little for lunch. - It is okay to eat a lot since I am going to exercise. - I can have as much as I want for lunch since I skipped my breakfast. - Eating a lot of fruits is okay. - If I enjoy eating, it's 0 kcal. - If you eat as much as you want, the stress can be resolved. - Spicy food does not make you gain weight.	0 – No 1 - Yes

Part 3. Emotion

Main Question	The list of emotions	Responses
How did you feel today?	Irritated	VAS 0-100
	Lonely	
	Anxious	
	Bored	
	Depressed	

Part 4. Motivation

Main Question	The list of dimensions in motivation	Responses
How much weight do you wish to lose?	Will	VAS 1-10
How important is it to lose body weight?	Rank of importance	
How confident do you feel about losing weight?	Confidence	
How helpful is this weight loss program to you?	Satisfaction	

The engagement criteria (the number logged into app) of the program were completing actions such as responding to the daily assessment (responses per day), logging meals (meals per week), green foods as defined by Noom (82) (logged per week), and exercise (times per week), registering exercise time (minutes per week), recording steps taken (steps per week), logging weigh-ins (times per week), reading articles (articles per week), group posts (posts per week), and group comments (comments per week), sending messages to the coach (messages per week), and making group likes (likes per week). These criteria were used to assess the use of the app using objective measures for each participant.

Physiological phenotypes Blood samples were collected at the baseline and 8 weeks after a 10-h fast. I examined serum insulin, leptin, glucose concentrations, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total cholesterol, and triglyceride levels to assess the changes in these indices in relation to the change in body weight.

Psychological phenotypes Participants' situational motivation toward the weight loss program was assessed using an adapted version of the SIMS. The SIMS typically measures four types of motivation to engage in a task

(herein, the weight loss program) at a specific point in time, with four items per subscale: intrinsic motivation, identified regulation, external regulation, and motivation. The SIMS has demonstrated acceptable levels of reliability and validity in past research. The Body Shape Questionnaire-8C (BSQ-8C) is a brief form of the BSQ consisting of eight items extracted from the full version measuring the extent of psychopathology of concerns about body shape. Higher values on the BSQ indicate more body dissatisfaction. Depression was assessed using the Korean version of the Beck's Depression Inventory (K-BDI-II) scoring system. A total score from 0 to 9 indicated no depression; 10 to 15, mild depression; 16 to 23, moderate depression; and 24 to 63, severe depression. Anxiety was measured using the 20-item Trait Anxiety Scale (TAI) of the State-Trait Anxiety Inventory with higher scores indicating greater trait anxiety. The Rosenberg Self-Esteem Scale (RSES) measure of self-esteem was used in this research with a 10-item scale consisting entirely of negatively worded items. Thus, higher scores implied lower self-esteem. Eating behavior notions were measured with the Dutch Eating Behavior Questionnaire (DEBQ), which identifies three distinct psychologically based eating behaviors: restrained eating, emotional eating, and external eating. It contains 33 items, with higher scores indicating a greater tendency to present subscale behavior. The frequency of occurrence of automatic negative thoughts associated with depression was assessed by the Automatic Thoughts Questionnaire (ATQ-30). The scores ranged from 30 to 150, where higher scores indicate more frequent automatic negative thoughts. All the psychological questionnaires were in Korean.

Eating behavioral phenotypes Food intake is the quantity of food consumed by the subject. The food intake phenotypes were composed of nine indices for the buffet test-meal method: total calories (FIB-T), caloric intake of healthy diet foods (FIB-H), that of unhealthy diet foods (FIB-UH), the intake amount of carbohydrate (FIB-Carb), protein (FIB-Pro), fat (FIB-Fat), sugar (FIB-Su), sodium (FIB-So), and saturated fat (FIB-Sf), and nine

indices for the food diary in the app: total calories (FID-T), the amount of carbohydrates (FID-Carb), protein (FID-Pro), fat (FID-Fat), sodium (FID-So), and calorie intake for breakfast (FID-B), lunch (FID-L), dinner (FID-D), and snacks (FID-S). For example, the intake amount of carbohydrate (FIB-Carb) is the absolute value of the total amount of carbohydrate intake during the buffet meal-test. Food proportion is defined as the proportion of each food type (healthy/unhealthy or carbohydrate/protein/fat) consumed by the subject, composing the total food intake. The food proportion phenotypes consisted of five markers for buffet test-meal assessment: the proportion of chosen amounts from highly healthy diet foods (FPB-H), unhealthy diet foods (FPB-UH), carbohydrate (FPB-Carb), protein (FPB-Pro), and fat (FPB-Fat); and three markers for the food diary in the app assessment: carbohydrate (FPD-Carb), protein (FPD-Pro), and fat (FPD-Fat). For example, the healthy diet proportion score (FPB-H, 0%–100%) = [(amount of healthy diet food intake) / (amount of total dietary intake)] × 100; unhealthy diet proportion score (FPB-UH, 0%–100%) = [(amount of unhealthy diet food intake) / (amount of total dietary intake)] × 100. Food diversity is the diversity of dietary patterns chosen by the subject among the buffet food item groups served; it is not the same as the proportion of foods consumed. Food diversity phenotypes refer to the number of food categories consumed from a previously selected list. Thus, these categories were derived from the buffet test-meal method only and defined as follows: total food diversity score (FDB-T, 0%–100%) = [(the number of food items consumed from all 24 food items provided) / 24] × 100; healthy diet diversity score (FDB-H, 0%–100%) = [(the number of food items consumed from the 12 healthy food items provided) / 12] × 100, and unhealthy diet diversity score (FDB-UH, 0%–100%) = [(the number of food items consumed from the 12 unhealthy food items provided) / 12] × 100. The classifications of the overall eating behavior index are presented in Table 4.

Table 4. Classifications of the eating behavior indices.

Measurement Method	Food Intake Phenotype (FI)	Food Proportion Phenotype (FP)	Food Diversity Phenotype (FD)
Buffet test-meal (B) = Laboratory setting = Objective (direct measurements)	**1) Total Intake** (FIB-T) **2) Type of Diet Intake** 2a) Healthy Diet Intake (FIB-H) 2b) Unhealthy Diet Intake (FIB-UH) **3) Macronutrient intake** 3a) Carb (FIB-Carb) 3b) Protein (FIB-Pro) 3c) Fat (FIB-Fat) **4) Micronutrient Intake** 4a) Sugar (FIB-Su) 4b) Sodium (FIB-So) 4c) Saturated Fat (FIB-Sf)	**1) Type of Diet Proportion** 1a) Healthy Diet Proportion (FPB-H) 1b) Unhealthy Diet Proportion (FPB-UH) **2) Macronutrient Proportion** 2a) Carb Proportion (FPB-Carb) 2b) Protein Proportion (FPB-Pro) 2c) Fat Proportion (FPB-Fat)	**1) Total Food Diversity Score** (FDB-T) **2) Healthy Diet Diversity Score** (FDB-H) **3) Unhealthy Diet Diversity Score** (FDB-UH)
Diary app (D) = Real-world setting = Subjective (self-report)	**1) Total Intake** (FID-T) **Macronutrient Intake** 1a) Carb (FID-Carb) 1b) Protein (FID-Pro) 1c) Fat (FID-Fat) **2) Micronutrient Intake** 2a) Sodium (FID-	**1) Macronutrient Proportion** 1a) Carb Proportion (FPD-Carb) 1b) Protein Proportion (FPD-Pro) 1c) Fat Proportion (FPD-Fat)	

	So)
3) Total Intake Per Meal	
	3a) Breakfast (FID-B)
	3b) Lunch (FID-L)
	3c) Dinner (FID-D)
	3d) Snack (FID-S)

Interventions

The intervention of this study was a multi-factorial, daily-based personalized coaching implemented by a psychologist using CBT modules via the digital platform. The dCBT-O contents were based on programs proposed to clinicians (83) as a guide. I monitored and assessed various factors related to the behavior, cognition, mood, and motivation of each participant assigned to the dCBT-O group. Participants in the dCBT-O group therefore received daily self-report assessments in a Google survey form via text message on their phone. Participants were also instructed to log their dietary intake and physical exercise on a daily basis. Additionally, they were asked to measure their weight, BMI, and fat mass twice a week with InBody H20B as soon as they woke up in the morning and were instructed to log their meals and physical activity by self-report on the Noom Coach app on a weekly basis. After participants' responses to the components related to the four factors were collected, digital mobile tools collected the data to allow the therapist to securely monitor participants' progress through a web-based dashboard. The participants received at least three individual messages from the coach every day except on weekends and holidays via the Noom Coach app. Furthermore, the therapist individually sent a daily report, a weekly report, and a mid-week report (on Week 4) to the participants for the purpose of goal-setting and to strengthen their motivation. Weekly group

missions were provided to the dCBT-O group based on the expectation that social supports (e.g., communicating needs and building positive support) would intensify the motivation. When the participants were inactive for more than 3 consecutive days or asked for thorough counseling, the therapist phoned them and conducted motivational interviews. The motivational interviews could be implemented only once a week per person. The duration of the phone call did not exceed 15 minutes.

All contents of the coaching messages, group missions, and articles were managed by a supervisor of the digital healthcare coach, who has a master-level degree in clinical psychology and has trained as a behavioral therapist using CBT modules such as self-monitoring, goal setting, problem solving, nutritional and physical activity education, stimulus control, challenging automatic thoughts, thought restructuring, and relapse prevention. Throughout the intervention, I expected the participants in the dCBT-O group to experience a lifestyle change by finding a healthy pattern of living that fit each participant's context. The diagram of the dCBT-O process and features of the digital platforms are presented in Figures 8 and 9.

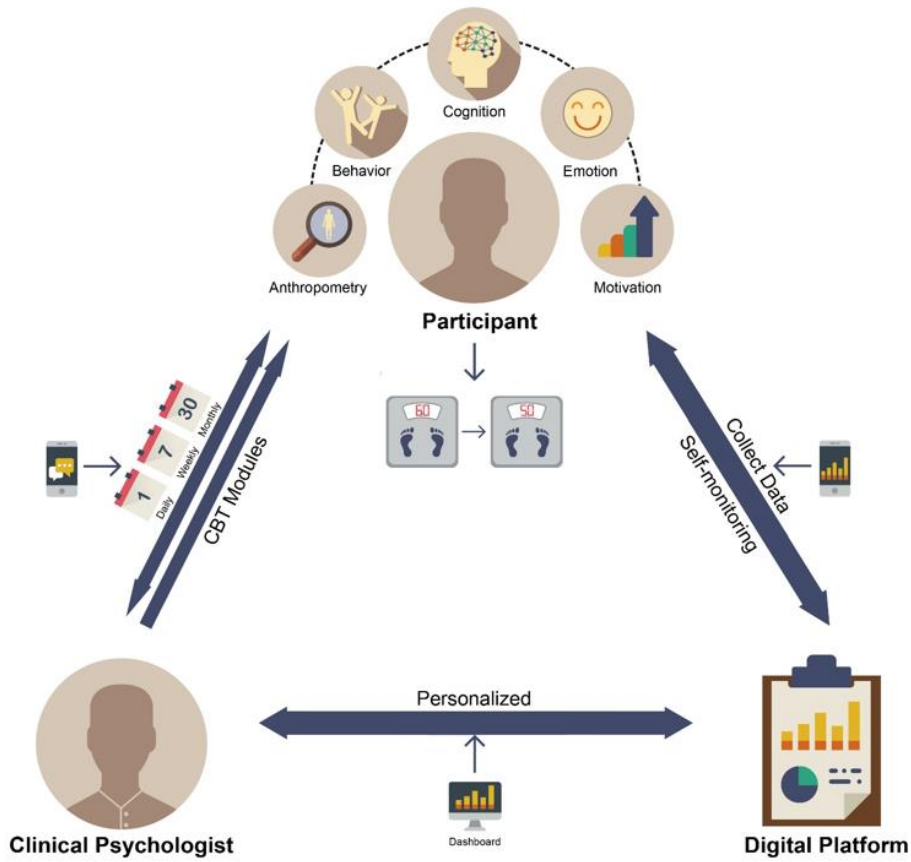


Figure 8. Diagram of the dCBT-O process.

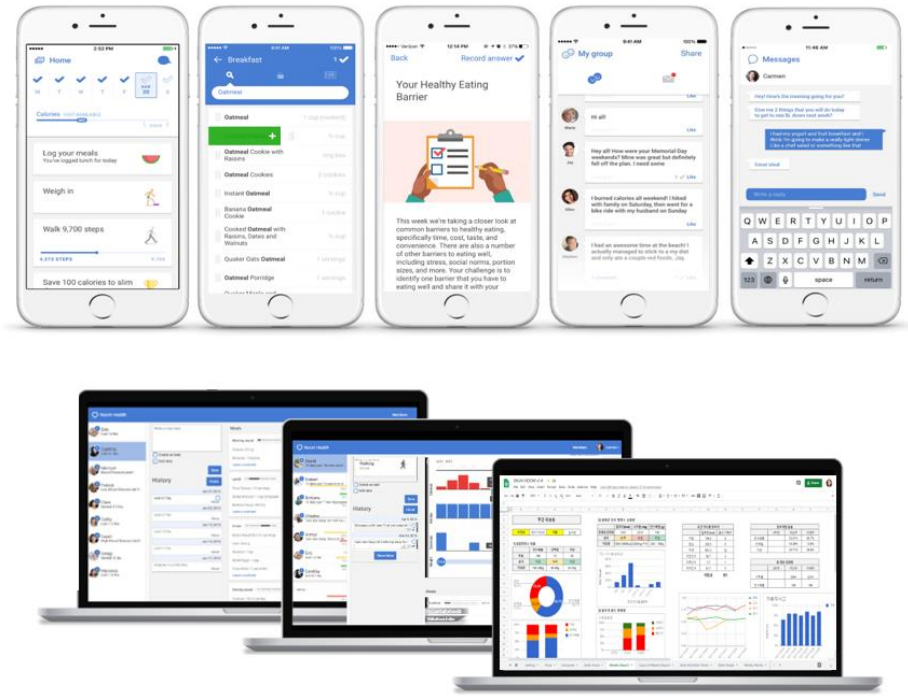


Figure 9. The features of the digital platform for the participants (top) and the therapist (bottom)

Statistical Analysis

<u>Part I.</u> Validating the treatment efficacy and finding its predictive markers

The sample size was selected to provide the study with a statistical power of 80% to detect clinically meaningful differences in weight loss of 5 kg with an SD of 7 kg in treatment effect, based on previous studies (84). Assuming an average attrition rate of 10%, a sample of at least 70 subjects was selected. For differences in baseline characteristics, independent sample *t*-tests were used for continuous variables, and a chi-square test of independence was used for categorical data assessing the demographic patterns of subjects. The analysis was conducted following per-protocol principles. The participants who attended at either 8 or 24 weeks were included in the analysis of the applicable period without missing imputations. There were no outliers in the dataset. To investigate differences

in the outcomes between the two groups, changes in the outcomes of weight, BMI, and fat mass were analyzed using an independent-sample *t*-test. Receiver-operating characteristic (ROC) curve analysis was undertaken to identify the optimum trade-off between sensitivity and specificity for cut-offs in weight change distribution. For the ROC analysis in the present study, I set a cut-off of 3% loss of initial body weight as a "good response" at 24 weeks for the dCBT-O group data. The Youden index was used for the optimal cut-off. The results regarding the proportion of people who reached 5% weight loss threshold are also reported to permit comparison with other previous studies. All analyses were conducted using SPSS Statistics software, version 25 (IBM Corp.), and two-tailed statistical significance was set at $p = .05$. For multiple comparison correction, a threshold of $p < 0.001$ was used (the p threshold of 0.05 divided by 42, corresponding to two different time periods and 21 phenotypes).

***Part II.* Eating behavioral analysis using buffet test-meal and food diary app**

The mean and SD were used to describe baseline characteristics. Differences between the two groups were detected using both independent-samples t-test and two-way ANOVA for continuous variables and a chi-square test for dichotomous variables. A paired-samples *t*-test was conducted to examine the statistical differences between baseline and post-intervention within a group. Effect sizes were estimated using Cohen's d. The power analysis was also conducted (85). Multivariate regression analysis was used to investigate which baseline measures had a predictive role in healthy eating behavioral change at eight weeks. The coefficient of variation (CV) was used to determine the standardized measure of distribution dispersion. Additional statistical analysis using a false discovery rate (FDR) method was applied to adjust for multiple comparisons. As there were less than 20% missing values in the set of overall changes variables,

both mean and regression imputation were performed.

<u>Part III.</u> Digital phenotyping using machine-learning analysis

In this part, the data from only dCBT-O group (n=45) was analyzed to predict three target outcomes: (a) the number of mobile activities during the experiment session, (b) the weight change rate between pre-session (week 0) and post-session (week 8), and (c) the weight change rate between post-session and follow-up. The weight change rates were calculated as the ratio of the weight difference to the baseline weight as $\frac{weight_{before} - weight_{after}}{weight_{before}}$.

Correlations between the number of logs and weight change rates were analyzed to determine the relationship between engagement and health outcomes. A machine-learning algorithm using an elastic net (86) was conducted. The elastic net is a penalized regression method that automatically selects significant variables by reducing the regression coefficients of unimportant features to zero.

Using 41 behavioral, cognitive, motivational, and emotional measures, I tried to reveal which measure contributes to predicting behavioral changes before and after treatment. The analysis procedure for out-of-sample regressions is similar to that in a previous study (87, 88). To conduct out-of-sample regression, I used leave-one-out cross-validation (LOOCV), which trains a model with data except for a single point and then evaluates the point's prediction. Root mean squared errors (RMSE) computed for all possible train test splits are averaged to the leave-one-out cross-validation error, which is the measure for evaluating the model fit. To acquire generalizable coefficients, I conducted model fitting 1,000 times for each possible alpha value (α), which is the ratio between the ridge and LASSO penalty terms. Figure 10 shows the RMSE with 100 alpha values (from 0.01 to 1 with an interval of 0.01), and I chose the alpha value that minimizes RMSE across all participants. After choosing the model with the best fit, I

analyzed the regression coefficients. Then, to identify predictors for engagement and health outcomes, I computed mean beta coefficients across 1000 iterations, and only phenotypes that survived more than 5% of 1000 iterations are chosen for predictors for each model (87, 89).

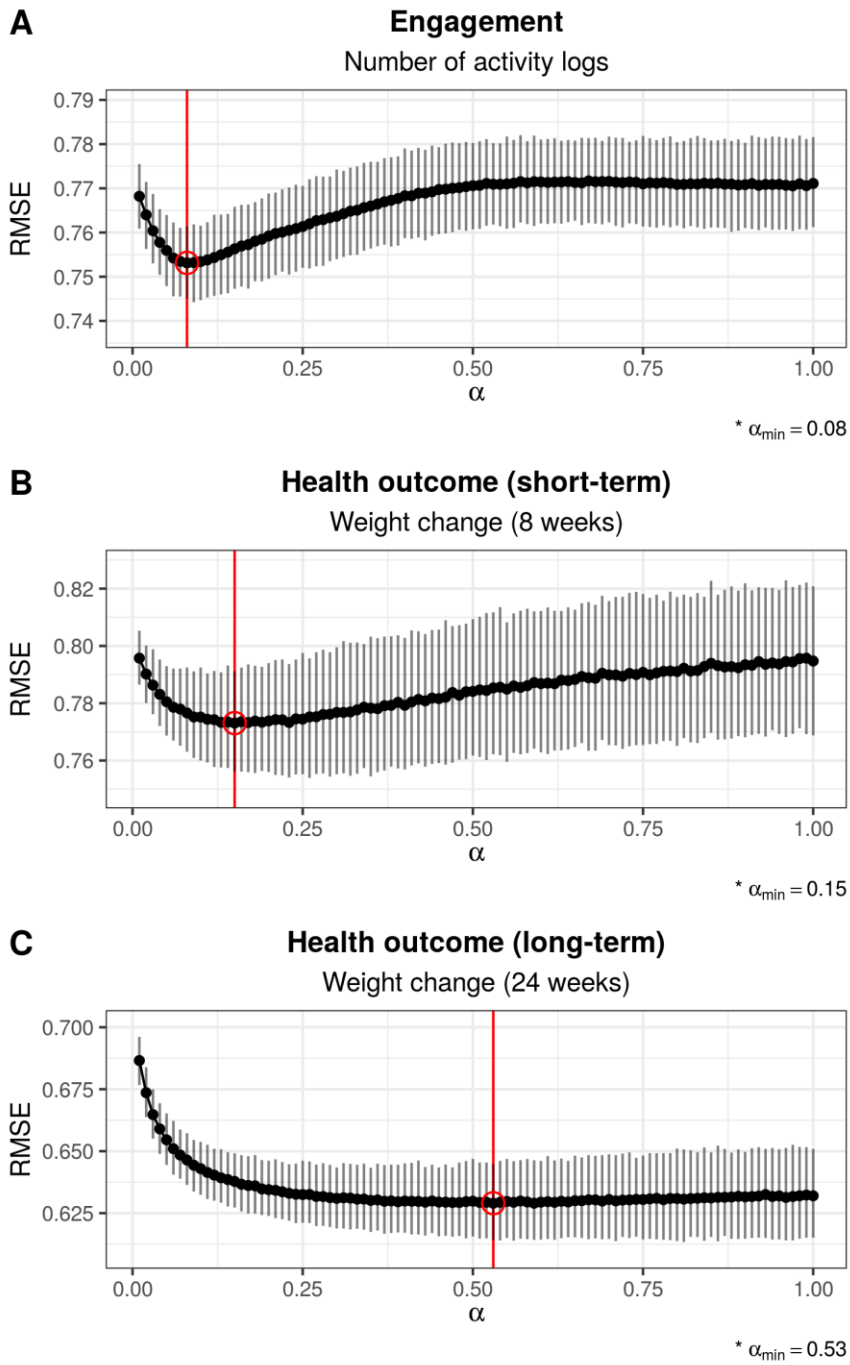


Figure 10. Cross-validation results on the model performance of three elastic net models based on different mixing parameter values (alpha). Each point indicates the mean value of simulated root mean squared errors (RMSE) for each alpha value, and the error bar indicates 95% quantile ranges on the simulated RMSEs. The alpha value with the minimum RMSE was chosen for each model.

Part IV. *Genetic analysis for predicting the clinical responses*

Blood DNA was extracted using the ExgeneTM Tissue SV (GeneAll, Seoul, Korea). All DNA samples were amplified and randomly portioned into 25-125 bp fragments, which were in turn purified, re-suspended, and hybridized with the Theragen Precision Medicine Research Array (Theragen PMRA array), which is a customized array based on the Asian Precision Medicine Research Array (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Following hybridization, the bound target was washed under stringent conditions to remove non-specific background signals and minimize noise resulting from random ligation events. Subsequently, I genotyped 820,000 SNPs using the Theragen PMRA array, according to the manufacturer's instructions, therefor obtaining genome-wide coverage in five major populations, as well as imputation accuracy for GWAS markers of 0.90 and 0.94 with minor allele frequencies (MAF) of > 1% and > 5% for 7.4 million imputed markers in an Asian population. To reduce potential concerns regarding batch effects and the possibility of false associations, I applied highly stringent quality control measures to select SNPs for use in the case and control datasets. Quality control procedures were performed on each of the 820,000 SNPs before the association tests were conducted. The SNP set was filtered based on the genotype call rates (≥ 0.95) and MAF (≥ 0.10). The Hardy-Weinberg equilibrium (HWE) was calculated for individual SNPs using an exact test. All the SNPs reported in this manuscript were shown to have HWE *p*-values of > 0.01. After filtering, 560,795 polymorphic SNPs were analyzed on chromosomes 1 through 22. The obesity-related SNPs that were reported in Asian were found on the GWAS catalogue and SNPedia. Then, the 83 obesity-related SNPs of the

GENESTYLE MEDIFIT were selected based on the significant association more than twice among the six different categories: appetite control, stress, inflammation, fat and sugar metabolism, and energy consumption. A *p*-value of < 0.05 was considered statistically significant for all two-sided tests and multivariate comparisons. Linear regression analysis was used to examine the additive effects of each SNP on anthropometric, eating behavioral, psychological, and physiological measures. To verify the interaction between SNPs in the identified model, an ANOVA test was performed. I applied Welch's test and the Games-Howell test for post hoc analysis to address violations in Levene's test. In addition, I analyzed the data from only the dCBT-O group (n=45) while considering imputation and excluded those samples with only baseline data.

Chapter 3. Results

There were no significant differences between the randomization groups on key demographic characteristics (Table 5). However, the DEBQ-Emotional (p = 0.001) and DEBQ-External (p = 0.049) scores of the two groups did differ at baseline. These differences between the groups were found after lots were drawn for the randomized control procedure. Participants had a mean (*SD*) age of 21.8 (3.3) years and a mean (*SD*) BMI of 28.0 (3.2).

Table 5. Baseline Characteristics of Participants in Both Groups[a]‡

Characteristic	Control (*n* = 25)	dCBT-O (*n* = 45)
Age, years, mean (*SD*)	21 (2.7)	22.3 (3.5)
Weight, kg, mean (*SD*)	71.9 (7.7)	74.5 (9)
BMI, kg/m^2, mean (*SD*)	27.7 (2.9)	28.2 (3.4)
Fat Mass, kg, mean (*SD*)	29.3 (6.0)	30.2 (6.8)
Fat Percent, %, mean (*SD*)	40.5 (4.8)	40.4 (5.4)
Lean Body Mass, kg, mean (*SD*)	23.8 (3.3)	24 (2.6)
Fasting Glucose, mg/dL, mean (*SD*)	87 (8.1)	87.3 (7.4)
Triglyceride, mg/dL, mean (SD)	92.2 (35.9)	93.2 (42.6)
Total Cholesterol, mg/dL, mean (SD)	184.7 (24.9)	191.1 (30.4)
ALT, U/L, mean (*SD*)	12.7 (6.9)	15.3 (11.9)
AST, U/L, mean (*SD*)	17.0 (4.7)	16.9 (4.8)
GGT, U/L, mean (*SD*)	15.3 (8.5)	21.3 (32.8)
Leptin, ng/ml, mean (*SD*)	37.5 (14.7)	42.49 (15.3)
Fasting Insulin, μU/mL, mean (*SD*)	12.6 (6.1)	16.1 (9.1)
HOMA-IR	2.8 (1.5)	3.5 (2.1)
SIMS, score, mean (*SD*)	77 (5.8)	76.1 (5.7)
BSQ-8C, score, mean (*SD*)	34.8 (8.9)	36.24 (7.5)
K-BDI-II, score, mean (*SD*)	14.7 (9.6)	13.6 (9)
TAI, score, mean (*SD*)	47.8 (11)	48 (10.4)

RSES, score, mean (*SD*)	21.9 (6.4)	19.8 (5.6)
DEBQ-Restrained score, mean (*SD*)	30.6 (7.3)	29.9 (6.6)
DEBQ-Emotional score, mean (*SD*) †	29.1 (11.6)	38 (10.1)
DEBQ-External score, mean (*SD*) †	32 (7)	34.9 (4.8)
ATQ-30, score, mean (*SD*)	57.6 (26)	57.2 (22.3)
YFAS, score, mean (*SD*)	2.24 (1.7)	2.96 (1.7)
Residence status		
Living with family	10 (40)	27 (60)
Living alone	8 (32)	8 (18)
Living with roommates	7 (28)	9 (20)
Others	0	1 (2.2)
Number of Attempts to Lose Weight by Different Methods		
None	0	1 (2.2)
Once	3 (12)	4 (8.9)
Twice	12 (48)	15 (33.3)
Three times	3 (12)	13 (28.9)
Four times	4 (16)	8 (18)
Five times	2 (8)	4 (8.9)
Six times	1 (4)	0

[a]Values are expressed as No. (percentage) unless otherwise indicated; †There was a statistical difference between two groups at baseline; ‡Modified from master thesis of Meelim Kim; CBT = Cognitive Behavioral Therapy; BMI = Body Mass Index; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; GGT = Gamma-Glutamyl Transpeptidase; HOMA-IR = Homeostasis Model for Assessment of Insulin Resistance (Insulin resistance = [Insulin (μU/mL) × Glucose (mg/dL)] / 405); SIMS = Situational Motivation Scale; BSQ-8C = Body Shape Questionnaire; K-BDI-II = Beck Depression Inventory-II in Korean; TAI = Trait-Anxiety Inventory; RSES = Rosenberg Self Esteem Scale; DEBQ = Dutch Eating Behavior Questionnaire; ATQ-30 = Automatic Thoughts Questionnaire; YFAS = Yale Food Addiction Scale.

<u>Part I.</u> Validating the treatment efficacy and finding its predictive markers

Primary outcome (weight change) was assessed at two time points:

immediately after lifestyle change dCBT-O (8 weeks) and long-term follow-up without dCBT-O (24 weeks), to investigate the self-sustaining effect of lifestyle change induced by 8 weeks of dCBT-O. Of the randomized participants, 65 (92.9%) were assessed for the primary outcome, body weight, at 24 weeks, and 5 (7.1%) were lost to follow-up. Figure 11 represents the mean weight change along with other anthropometric measures, BMI, body fat mass, and body lean mass, at each study time point. Participants in the dCBT-O group showed significant changes in body weight at 8 weeks compared to the control group (−3.1 (4.5%) vs. −0.7 (3.4%), p = 0.036) but not at 24 weeks. The proportion of subjects who showed "good response" was 45% (17 out of 38) in the dCBT-O group and 29% (6 out of 21) in the control group at 8 weeks (p = 0.223), while at 24 weeks it was 54% (22 out of 41) in the dCBT-O group and 42% (10 out of 24) in the control group (p = 0.351). In addition, the number reaching the conventional 5% weight loss from the baseline in the dCBT-O group was significantly higher than in the control group at 8 weeks (32% (12 out of 38) vs. 4% (1 out of 21), P = 0.017) but not at 24 weeks (44% (18 out of 41) vs. 29% (7 out of 24), p = 0.239). Changes in the BMI (−3.1 (4.6%) vs. −0.7 (3.5%), p = 0.043) and body fat mass (−6.3 (8.8%) vs. −0.8 (8.1%), p = 0.021) of the dCBT-O group were also significant compared to the control group at 8 weeks but not at 24 weeks. Body lean mass did not significantly differ between the two groups at both 8 and 24 weeks. Examining within-group changes, only the dCBT-O group achieved significant weight changes as well as BMI and body fat mass at both 8 and 24 weeks and significant changes in lean body mass not at 8 weeks but at 24 weeks.

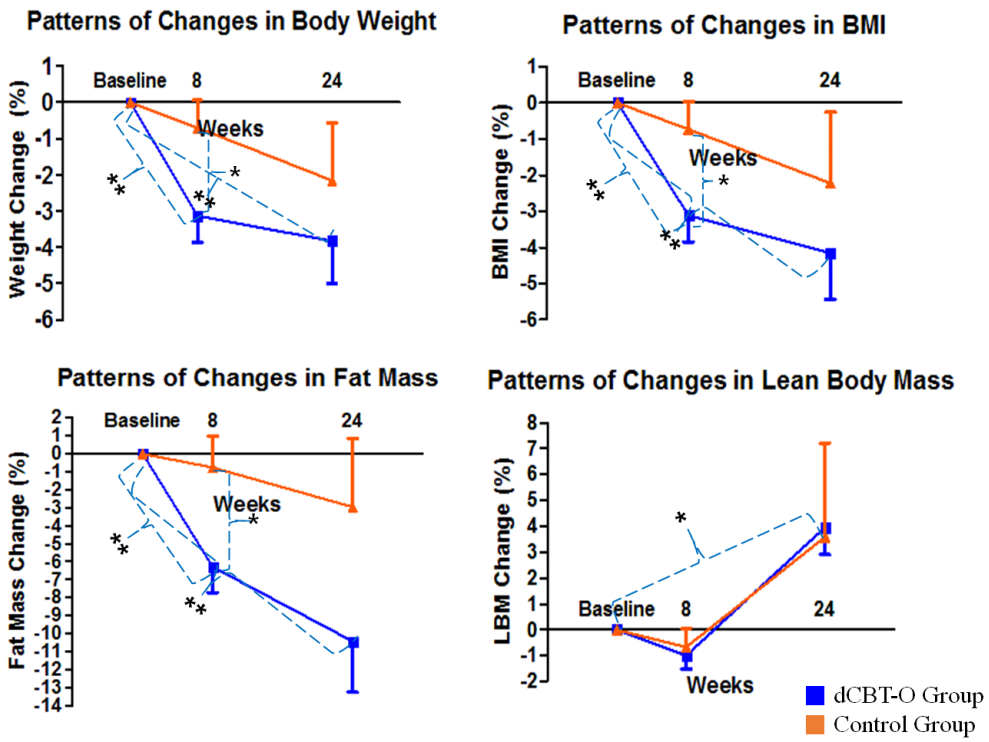


Figure 11. Patterns of changes in primary outcomes (anthropometric measures)‡
‡Modified from master thesis of Meelim Kim; *$p < 0.05$; **$p < 0.01$

Table 6 shows the sensitivity and specificity of the baseline psychological characteristics showing significant correlations with weight change, the primary outcome. The definition of "optimal statistical prediction threshold" is weight loss of more than 3% of the initial body weight. This is an important threshold because this treatment was CBT as a lifestyle modification without any biological intervention. Both motivation and self-esteem had the greatest area under the curve (0.63). The Areas Under the Curve (AUC) of depression and anxiety were 0.61 and 0.62, respectively. To predict a "good response," the cut-off for motivation (SIMS score = 76.5) provided a good trade-off between sensitivity (59%) and specificity (74%). Additionally, the cut-off for depression (K-BDI-II score = 7.5), anxiety (TAI score = 41.5), and self-esteem (RSES score = 24.5) provided optimal sensitivity and specificity to predict a good response. Overall, motivation showed the best predictive performance.

Table 6. ROC-curve analysis for predicting efficacy of dCBT-O by psychological status

	ROC Analysis			
	AUC (95% CI)	**Optimal cut off**	**Sensitivity (%)**	**Specificity (%)**
Weight Change (%)				
Motivation (SIMS score)	0.63 (0.46-0.80)	76.5	59%	74%
Depression (K-BDI-II score)	0.61 (0.44-0.78)	7.5	78%	50%
Anxiety (TAI score)	0.62 (0.45-0.78)	41.5	87%	41%
Self-esteem (RSES score)	0.63 (0.46-0.79)	24.5	35%	91%

ROC = Receiver Operating Characteristic; AUC = Area Under Curve; SIMS = Situational Motivation Scale; K-BDI-II = Beck Depression Inventory-II in Korean; TAI = Trait-Anxiety Inventory; RSES = Rosenberg Self Esteem Scale.

The high motivation subgroup (SIMS scores > 76.5) showed a 65% probability of successful 3% weight loss (13 out of 20), whereas the low motivation subgroup (SIMS scores < 76.5) showed a 36% probability of successful 3% weight loss (9 out of 25). Optimal predictive performance was achieved by combining both motivation and depression scores. The high motivation-low depression subgroup (SIMS scores > 76.5 and K-BDI-II < 7.5) showed a 100% probability of successful 3% weight loss (6 out of 6). Other subgroups showed a lower probability of successful 3% weight loss (low motivation and low depression subgroup 55%, high motivation and high depression subgroup 50%, or low motivation and high depression subgroup 25%; Figure 12).

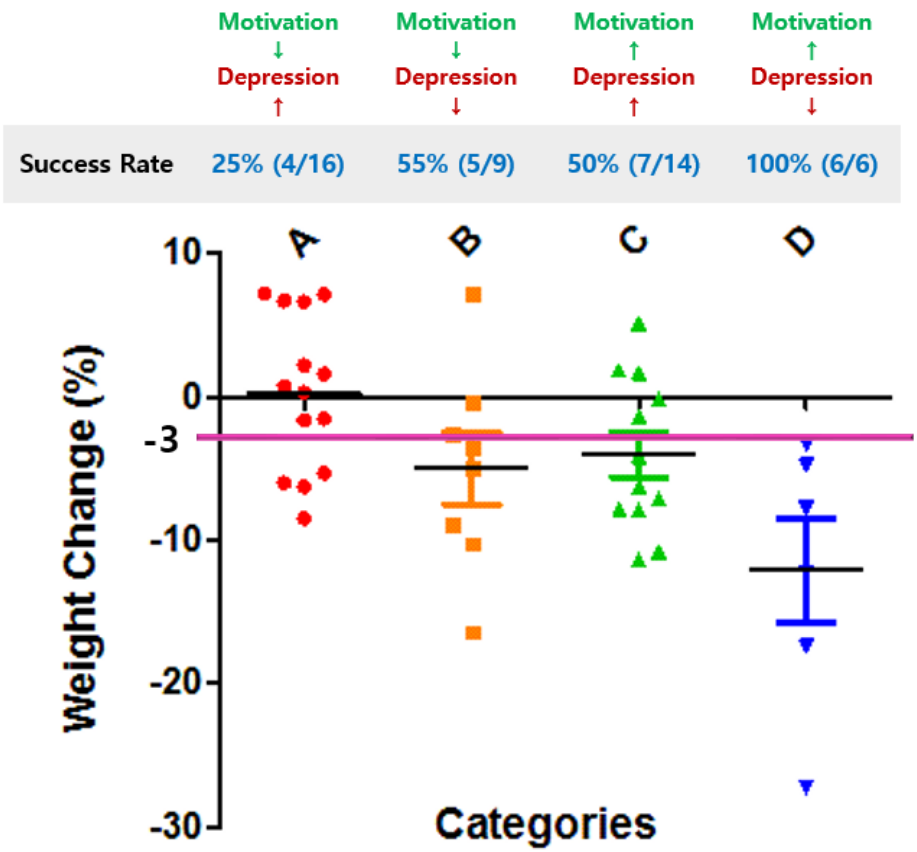


Figure 12. The clinical efficacy of the dCBT-O by optimal cut-off score with the predictive markers

Even when the strict statistical threshold for multiple comparison corrections was applied, changes in weight, BMI, and fat mass from baseline to 8 weeks in the dCBT-O group were considered significant ($p < 0.001$). The changes in the scores of DEBQ-RE from baseline to 8 weeks and in the K-BDI-II and DEBQ-EX scores from baseline to 24 weeks in the dCBT-O group were also significant after multiple corrections ($p < 0.001$). Furthermore, the changes in the scores of BSQ-8C from baseline to 8 weeks and 24 weeks in both the dCBT-O and control groups were considered significant after multiple corrections ($p < 0.001$). Some of the results in Part I have been modified from master thesis of Meelim Kim.

<u>Part II.</u> Eating behavioral analysis using buffet test-meal and food diary app

Figure 13 shows each behavioral phenotype's overall results for both healthy and unhealthy diets from the buffet test-meal assessment. Regarding eating behavior phenotypes from the buffet test-meal, participants in the dCBT-O group showed a significant change in FIB-H (Cohen's d = 0.60, dCBT-O: M = 26.06, SD = 68.95 vs. Control: M = −8.00, SD = 46.41; p = 0.03) and FDB-H (Cohen's d = 0.66, dCBT-O: M = 4.62, SD = 11.54 vs. Control: M = −2.78, SD = 10.85; p = 0.01) at eight weeks compared to the control group. For the eating behavior phenotypes from food diary data, the changes in mean FID-B (Cohen's d = 0.60, dCBT-O: M = 26.75, SD = 154.56 vs. Control: M = −41.63, SD = 46.98; p = 0.03) of the dCBT-O group were significant compared to the control group at eight weeks. No significant differences were observed in other eating behavior phenotypes. The observed power of FIB-H, FDB-H, and FID-B were 69.2%, 76.2%, and 78.5%, consecutively. Additional analysis applying regression imputation also showed that the participants in the dCBT-O group had a significant change in FDB-H at eight weeks compared to the control group (p = 0.01). Moreover, additional analysis using two-way ANOVA showed significant changes in mean FID-D of dCBT-O group compared to the control group at eight weeks (p = 0.04). All other results regarding additional imputation, statistical analysis, and FDR method were not significant (Table 7 and 8).

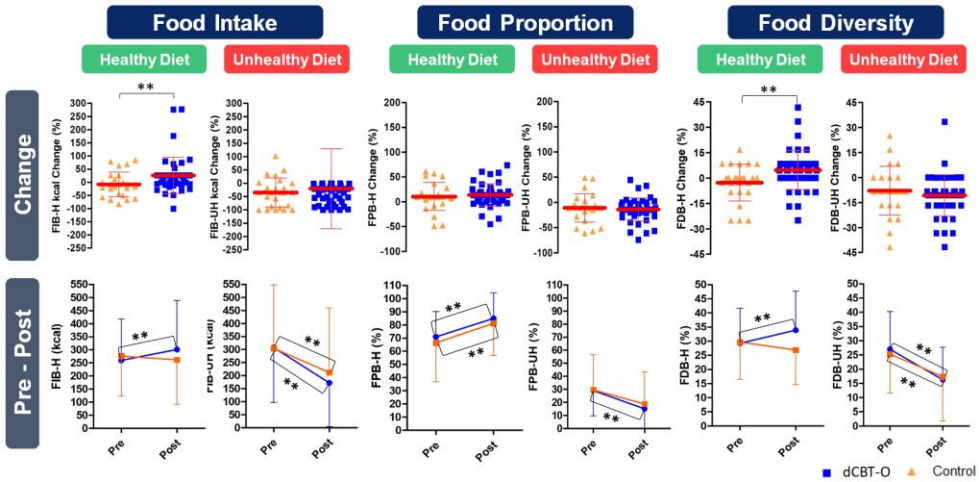


Figure 13. Overall results of each behavioral phenotype in both healthy and unhealthy diets from buffet test-meal assessment; $^{**}p < 0.01$

Table 7. Comparison of main outcomes from buffet test-meal assessment by intervention condition.

Outcome	N^{a}	Control	N^{aa}	dCBT-O	*p* (2-tailed)			
					M.I. t-test	R.I. t-test	M.I. Two-way ANOVA	R.I. Two-way ANOVA
Food Intake								
FIB-H, kcal,	25	26.1	45	−8		0.147	0.897	0.881
mean (*SD*)	25	(68.9)	45	(46.4)	0.031*	0.087	0.35	0.347
FIB-UH, kcal,		−35		−20.2	0.636			
mean (*SD*)		(54.2)		(150)				
Food Proportion								
FPB-H, %,	25	10.7	45	14		0.77	0.821	0.857
mean (*SD*)	25	(28.1)	45	(22.7)	0.601	0.1	0.699	0.741
FPB-UH, %,		−10.7		−14	0.601			
mean (*SD*)		(28.1)		(22.7)				
Food Diversity								
FDB-H, %,		−2.8		4.6				
mean (*SD*)	25	(10.8)	45	(11.5)	0.011*	0.01*	0.206	0.217
FDB-UH, %,	25	−7.9	45	−10.7	0.396	0.36	0.205	0.201
mean (*SD*)		(14.5)		(12.4)				

[a]Number of participants in control group, [aa]Number of participants in dCBT-O group, M.I.

= Mean Imputation, R.I. = Regression Imputation, *p* values were not corrected for multiple comparisons, *$p < 0.05$

Table 8. Comparison of main outcomes from the food diaries in app assessment by intervention condition.

Outcome	N^a	Control	N^{aa}	dCBT-O	*p* (2-tailed)			
					M.I. t-test	R.I. t-test	M.I. Two-way ANOVA	R.I. Two-way ANOVA
Breakfast, kcal, mean (*SD*)	25	−41.6 (47)	45	26.8 (154.6)	0.035*	0.03	0.389	0.406
Lunch, kcal, mean (*SD*)	25	1.7 (48.4)	45	−13 (43.5)	0.195	0.263	0.361	0.351
Dinner, kcal, mean (*SD*)	25	5.4 (50.9)	45	−12.5 (55)	0.184	0.178	0.039*	0.042*
Snack, kcal, mean (*SD*)	25	−43.87 (47.4)	45	−34.1 (73.6)	0.553	0.491	0.965	0.992

[a]Number of participants in control group, [aa]Number of participants in dCBT-O group, M.I. = Mean Imputation, R.I. = Regression Imputation, *p* values were not corrected for multiple comparisons, *$p < 0.05$; **$p < 0.01$

In addition, only the dCBT-O group showed significant changes in the FIB-H (Cohen's d = 0.73, M = 135.33, SD = 185.70; $p < 0.001$), FPB-UH (Cohen's d = 0.54, M = 13.98, SD = 25.87; $p = 0.003$), and FDB-H (Cohen's d = −0.35, M = −4.66, SD = 13.32; $p = 0.049$) after the 8-week intervention. The dCBT-O and control groups showed significant changes in FIB-UH, FPB-H, FDB-UH, and FDB-T. According to the eating behavior phenotypes from the food diary assessment in the app, only the dCBT-O group showed significant decreases in both the FID-L (Cohen's d = −0.39, M = −68.85, SD = 174.90; $p = 0.008$) and FID-D (Cohen's d = −0.43, M = −111.97, SD = 257.86; $p = 0.005$) at eight weeks compared to the baseline. Both groups achieved significant FID-S changes in the last week compared to the first week (dCBT-O: Cohen's d = −0.62, M = −73.32, SD = 117.74; $p < 0.001$ vs.

Control: Cohen's d = −0.59, M = −124.26, SD = 211.07; p = 0.006). Figure 14 shows the results of food intake changes per meal assessed by the food diary in the app (details in Table 9 and 10).

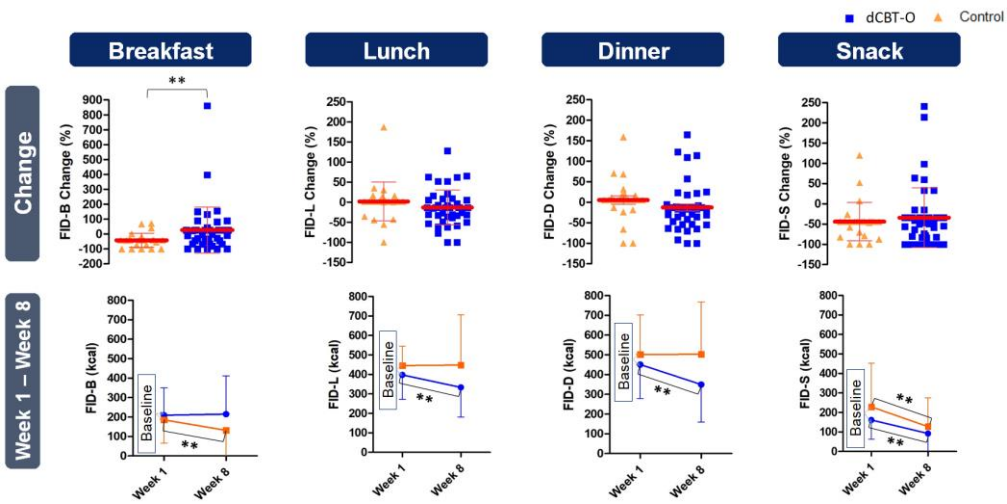


Figure 14. Overall results of each behavioral phenotype in both healthy and unhealthy diets from buffet test-meal assessment; ** p < 0.01

Table 9. Changes in main outcomes from the first buffet to the second buffet for both groups.

Outcome	First buffet	Second buffet	*p* (2-tailed)
dCBT-O Group			
Food Intake			
FIB-H, kcal, mean (*SD*)	259.7 (157.5)	301.4 (187.5)	0.01*
FIB-UH, kcal, mean (*SD*)	307.6 (210.4)	172.3 (168.3)	0.000**
Food Proportion			
FPB-H, %, mean (*SD*)	70.9 (19.4)	84.9 (19.4)	0.000**
FPB-UH, %, mean (*SD*)	29.1 (19.4)	15.1 (19.4)	0.000**
Food Diversity			
FDB-H, %, mean (*SD*)	29.3 (12.4)	33.9 (13.9)	0.01*
FDB-UH, %, mean (*SD*)	27 (13.2)	16.3 (11.4)	0.000**
Control Group			
Food Intake			
FIB-H, kcal, mean (*SD*)	276.3 (153.6)	262 (170.5)	0.566
FIB-UH, kcal, mean (*SD*)	304.6 (242.8)	212 (247.3)	0.013*

Food Proportion			
FPB-H, %, mean (*SD*)	66.4 (29.6)	81.2 (24.4)	0.01*
FPB-UH, %, mean (*SD*)	29.6 (26.8)	18.8 (24.4)	0.068
Food Diversity			
FDB-H, %, mean (*SD*)	29.7 (13.2)	26.9 (12.3)	0.212
FDB-UH, %, mean (*SD*)	25.3 (13.7)	17.4 (15.6)	0.012*

P values were not corrected for multiple comparisons, *$p < 0.05$; **$p < 0.01$

Table 10. Changes in main outcomes from the first week to the last week of food diary in app for both groups.

Outcome	Week 1	Week 8	*p* (2-tailed) [a]
dCBT-O Group			
Breakfast, kcal, mean (*SD*)	210 (139.7)	215.3 (196.6)	0.851
Lunch, kcal, mean (*SD*)	397.5 (126)	333.7 (152)	0.008**
Dinner, kcal, mean (*SD*)	450.7 (171.7)	190.1 (28.3)	0.005**
Snack, kcal, mean (*SD*)	161.9 (98.1)	92.2 (99.7)	0.000**
Control Group			
Breakfast, kcal, mean (*SD*)	185.4 (118.9)	131.5 (177)	0.028*
Lunch, kcal, mean (*SD*)	445.8 (99)	448.3 (258)	0.962
Dinner, kcal, mean (*SD*)	501.6 (200.8)	502.7 (264.8)	0.98
Snack, kcal, mean (*SD*)	229.3 (222.9)	127.6 (147.4)	0.006**

P values were not corrected for multiple comparisons, *$p < 0.05$; **$p < 0.01$

Restrained eating behavior, measured by the DEBQ (DEBQ-RE) at baseline, was significantly correlated with FDB-H change at eight weeks ($p = 0.006$). Participants who had greater dietary restraint intention or behavior at baseline were more likely to increase the number of food categories among the healthy diet foods after the 8-week intervention. The change in the level of body shape satisfaction, assessed by the BSQ-8C during the 8-week intervention, showed a significant positive correlation with FIB-H change ($p = 0.02$) and FDB-H change ($p = 0.04$). The calorie intake and number of healthy diet food categories increased as the level of body shape satisfaction increased. The change in IR (fasting insulin) was also significantly correlated with FIB-H change ($p = 0.019$) and FDB-H change ($p = 0.026$).

Thus, participants with greater calorie intake and more categories among healthy diet foods showed a greater decrease in IR during the 8-week intervention. Other parameters showed significant or meaningful results. These outcomes remained significant after adjusting for the age and BMI. All results of the regression analysis are presented in detail in Table 11.

Table 11. Predictive markers and mechanisms related to changes in major eating behavioral phenotypes

Phenotype	Regressor	β	*p*-value
Predictors			
FDB-H	DEBQ-restrained eating behavior	0.403	0.006*
Mechanisms			
FIB-H change	BSQ-8C change	- 0.346	0.020*
	Fasting Insulin change	- 0.349	0.019*
FDB-H change	BSQ-8C change	- 0.308	0.040*
	Fasting Insulin change	- 0.332	0.026*

*= significant ($p < 0.05$) after adjusting for the age and BMI; P values were not corrected for multiple comparisons

Considering the CV among the two different assessments, the CV of FIB-T (46%) was greater than that of FID-T (28%) after dCBT-O. The CV of these two assessments was similar to other nutritional indices such as carbohydrate (FIB-Carb vs. FID-Carb; 45% vs. 34%), protein (52% vs. 41%), fat (77% vs. 45%), and sodium (59% vs. 47%). In addition, there was no significant correlation between FIB-T and FID-T or among other indices after dCBT-O ($p = 0.806$).

Part III. Digital phenotyping using machine-learning analysis

Figure 15 shows the correlations between the number of logs (engagement)

and weight change (health outcomes). For the weight change during the 8-week intervention, two variables were highly correlated (r = -0.59, t = -4 − 32, df = 35, $p < 0.0001$; Figure 15A), which indicates that participants who had engaged in the in-app activity more actively lost weight. This result was the same for the weight change between baseline and follow-up (r = -0.52, t = -3 − 59, df = 35, $p = 0.00099$; Figure 15B). These short-term and long-term health outcomes were highly correlated with each other (r = 074, t = 6.60, df = 35, $p < 0.0001$; Figure 15C).

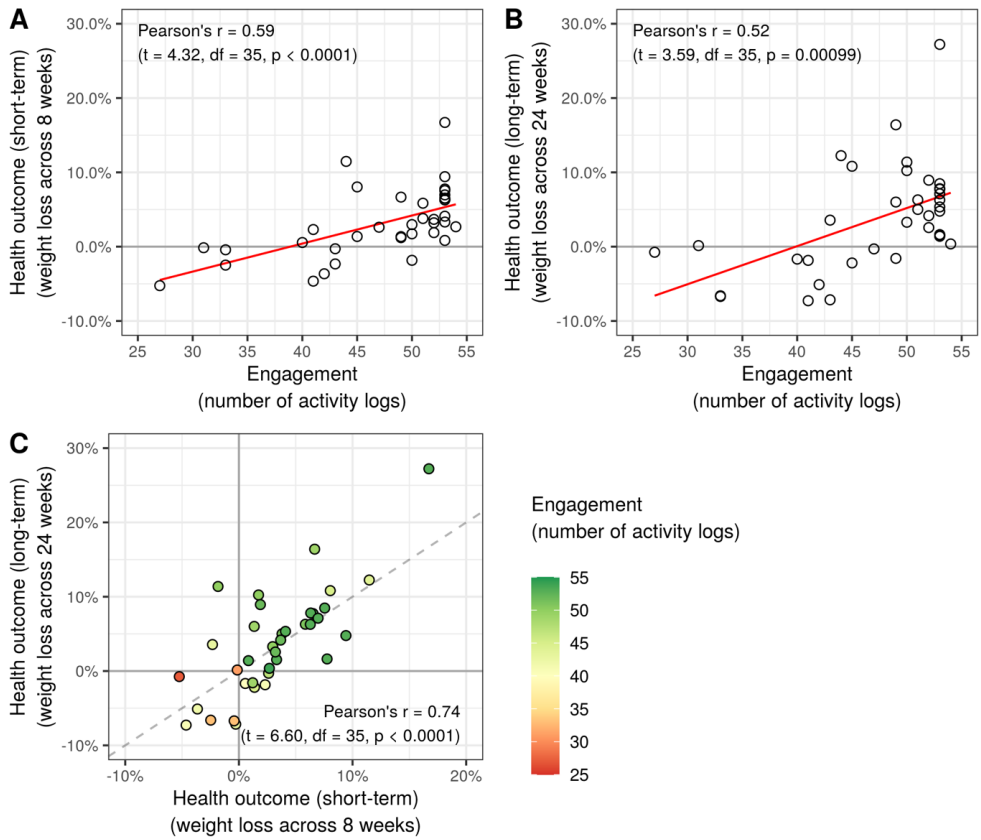


Figure 15. Relationships between engagement and health outcomes. The health outcome larger than zero indicates weight loss compared to baseline.

Through the leave-one-out cross-validations with different values for the mixing parameter (alpha), I chose the best value for each model that showed the minimum RMSE between the data and predicted outcomes. The

estimated mixing parameters, alphas, were 0.08, 0.15, and 0.53 for predicting engagement, short-term health outcome, and long-term health outcome, respectively (see Figure 9). The alpha estimate for the long-term health outcome was much higher than that in the other two models, suggesting that the multivariate pattern is more parsimonious. Its coefficients are prone to shrink to zero while predicting long-term weight change.

Figure 16 illustrates the multivariate profiles of conventional and digital phenotypes to predict in-app engagement and the health outcomes of digital healthcare. In-app engagement, computed as the number of daily activity logs, was significantly associated with lower self-esteem, lower body satisfaction, and higher external eating behaviors, measured as conventional phenotypes. For digital phenotypes, engagement was predicted by lower intake of food with a high-calorie density index (CDI), higher food intake in the morning (breakfast, morning snack), lower food intake after that (lunch, dinner, evening snack), higher sugar intake, higher intake of moderate or low CDI food, and higher frequency of interactions with the therapist. Higher emotional and motivational measures in digital phenotypes were also involved, such as irritation, boredom, depression, satisfaction, will, and confidence.

For short-term health outcomes, lower emotional eating behavior, lower self-esteem, lower anxiety, higher external eating behavior, and higher motivation predicted the weight change rate for eight weeks. The 8-week weight change was also predicted by lower intake of high-CDI food, lower carb, lower sodium, lower fat intake, higher afternoon snack intake, lower dinner intake, higher intake of low CDI food, and higher frequency interactions with a healthcare mentor. Furthermore, short-term health outcomes were positively associated with emotional and motivational features in digital phenotypes, such as boredom, irritation, will, satisfaction, and confidence.

In contrast, fewer phenotypes are involved in the prediction of long-term health outcomes. Lower self-esteem, lower food addiction, lower body satisfaction, higher motivation, and higher restricting eating behavior in conventional phenotypes predicted the 24-week weight change. For digital phenotypes, the long-term health outcome was predicted by lower carb intake, lower lunch and evening snack intake, lower fat intake, lower steps in a day, higher satisfaction, higher will, and higher confidence.

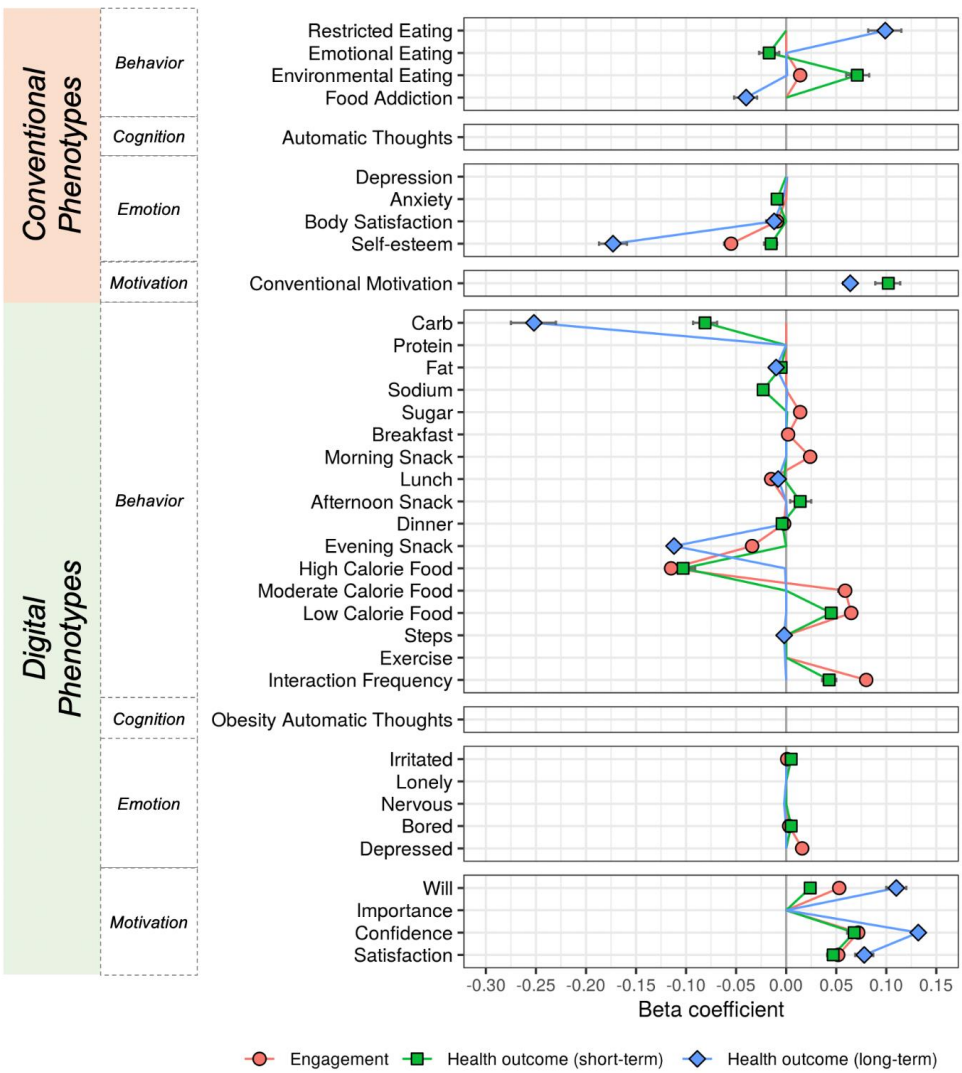


Figure 16. Multivariate patterns of conventional and digital phenotypes for predicting engagement (red) as well as short-term (green) and long-term (blue) health outcomes. Points indicate the averaged beta coefficients across 100 repetitions of net elastic analysis

(see Methods for details). A positive beta estimate of a phenotype indicates an association between the phenotype and higher in-app activities (engagement) or more weight loss (health outcomes). The points, which contain zero in the simulated 95% ranges, are omitted.

Common predictors across dependent variables were associated with different phenotypes (Figure 17 and Table 12). Engagement and health outcomes were commonly affected by lower self-esteem in conventional phenotypes and higher in-app motivational measures in digital phenotypes. In other words, decreased self-esteem before the intervention and inclined motivation during the intervention highly predicted more in-app activities and more weight loss following the intervention. Furthermore, common predictors between engagement and short-term health outcomes include the behavioral dimension of digital phenotypes, such as the frequency of coach interaction and low/high-calorie food intake. For predicting short-term and long-term health outcomes, carb intake was the most commonly influential predictor. Conversely, conventional and digital phenotypes' motivational measures were positively associated with health outcomes (see Figure 18).

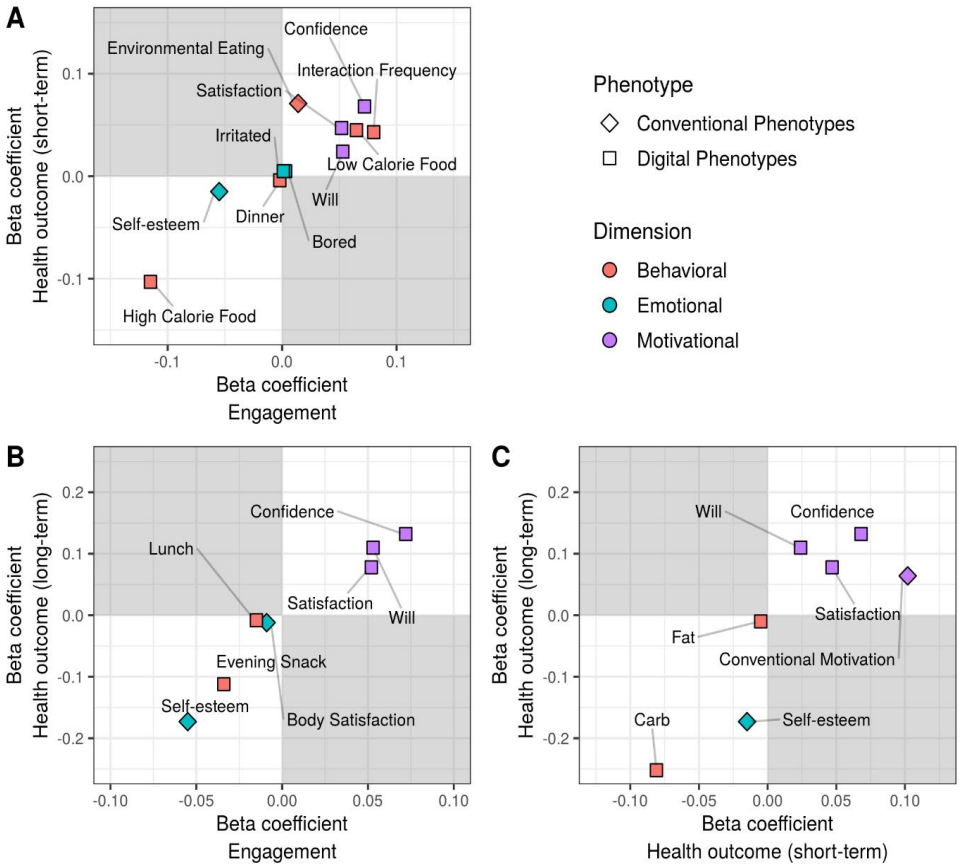


Figure 17. Common predictors between engagement and health outcomes. Each axis indicates the beta estimate for predicting engagement and health outcomes. A positive beta coefficient indicates a positive association with engagement but negative associations with health outcomes (weight changes).

Table 12. Common and specific predictors of conventional and digital phenotypes for predicting engagement and health outcomes.[a]

	Common predictors	**Predictors specific to each dependent variable**		
		Engagement	**Health outcome (short-term)**	**Health outcome (long-term)**
Conventional phenotypes	Self-esteem ↓	Body Satisfaction ↓ Environmental Eating ↑	Emotional Eating ↓ Anxiety ↓ External Eating ↑	Food Addiction ↓ Body Satisfaction ↓ Conventional Motivation ↑

				Conventional Motivation ↑	Restrictive Eating ↑
Digital phenotypes	Behavioral	-	High-Calorie Food ↓ Night Snack ↓ Lunch ↓ Dinner ↓ Breakfast ↑ Sugar ↑ Morning Snack ↑ Moderate Calorie Food ↑ Low-Calorie Food ↑ Interaction Frequency ↑	High-Calorie Food ↓ Carb ↓ Sodium ↓ Fat ↓ Afternoon Snack ↓ Low-Calorie Food ↑ Interaction Frequency ↑	Carb ↓ Night Snack ↓ Lunch ↓ Fat ↓ Steps ↓
	Emotional	-	Irritated ↑ Bored ↑ Depressed ↑	Irritated ↑ Bored ↑	-
	Motivational	Satisfaction ↑ Will ↑ Confidence ↑	-	-	-

[a]Common predictors in the first column were involved in all models. The cognitive dimension of digital phenotypes is omitted due to a lack of significance.

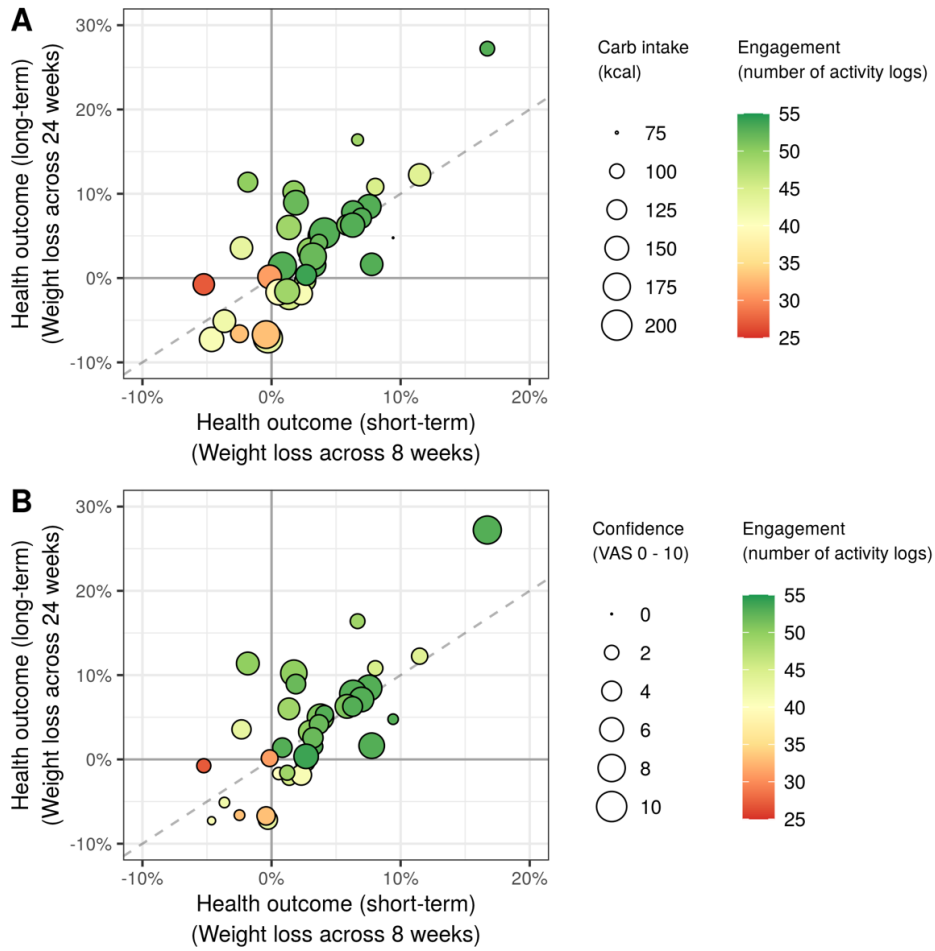


Figure 18. Two examples of common predictors between short-term and long-term health outcomes: carb intake and confidence in digital phenotypes.

Regarding the model performance of the three prediction models, the machine-learning approaches successfully predicted the engagement rate (mean R^2 = 0.416, SD = 0.006), short-term weight change (mean R^2 = 0.382, SD = 0.015), and long-term weight change (mean R^2 = 0.590, SD = 0.011). Especially in predicting long-term weight change, approximately 59% of the outcome variance is explained by the prediction model. In sum, these model performances suggest that the multivariate profiles in conventional and digital phenotypes provide the phenotypes that are significantly associated with engagement and health outcomes.

Part IV. *Genetic analysis for predicting the clinical responses*

After analyzing 83 obesity-related SNPs with multi-dimensional phenotypes (anthropometric, eating behavior, psychological, and physiological phenotypes), I selected those showing significant association ($p < 0.05$) with BMI and at least one phenotype among eating behavioral phenotypes (i.e., food intake, food proportion, or food diversity) (clinical efficacy markers from Part I and Part II). The genotype frequency stratified by each SNP, cholesterol ester transfer protein (CETP) rs9939224, and apolipoprotein A-II (APOA2) rs5082 genotypes are presented in Table 13. No significant deviation from HWE was observed ($p > 0.05$).

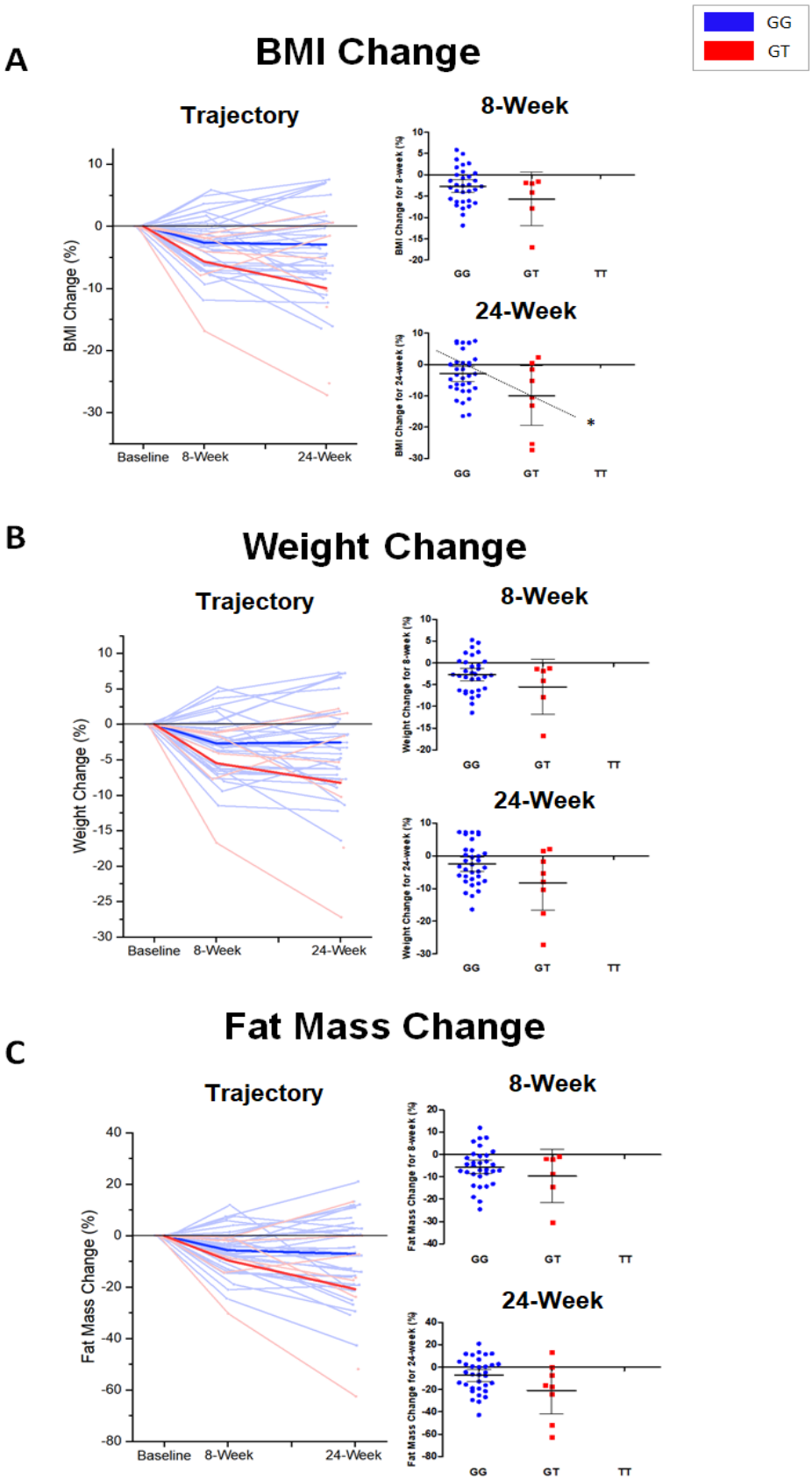
Table 13. Genotype and allele frequencies.

CETP rs9939224	**G/G**	**G/T**	**T/T**	***p*-value**
N	36	8	1	
Genotype frequency	80.00%	17.78%	2.22%	> 0.05
APOA2 rs5082	**A/A**	**A/G**	**G/G**	***p*-value**
N	37	7	1	
Genotype frequency	82.22%	15.56%	2.22%	> 0.05

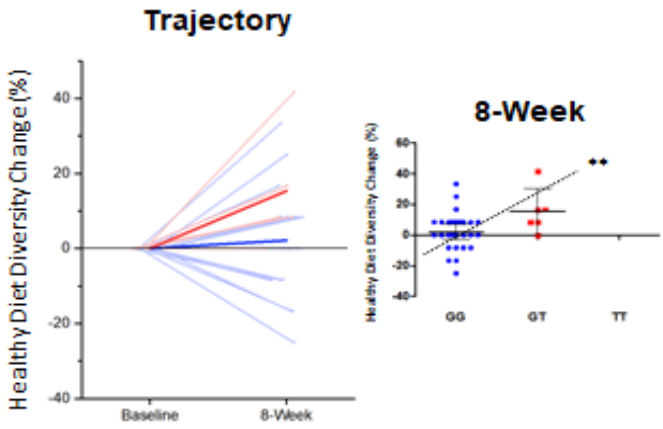
Regarding the primary outcome, the CETP GG genotype was shown to lead to a -2.62% and -2.91% variance in BMI after 8 and 24 weeks, respectively. The CETP T allele was shown to lead to a -5.68% and -9.94% variance in BMI after 8 and 24 weeks, respectively. Moreover, the CETP T allele was significantly associated with a greater BMI decrease at 24 weeks ($p = 0.028$; GG group BMI -2.91%, GT group BMI -9.94%; Figure 19A). The CETP GG group exhibited a -2.69% and -2.56% change in weight after 8 and 24 weeks, respectively, while the CETP T allele group exhibited a -5.48% and -

8.24% change in weight, respectively. Thus, the changes in weight were shown to exhibit a decreasing trend at 24 weeks in the CETP T allele group (p = 0.052; GG group weight change -2.56%, GT group weight change -8.24%; Figure 19B). Finally, we found that the CETP GG group exhibited a -5.65% and -7.26% change in fat mass after 8 and 24 weeks, respectively, whereas the CETP T allele group exhibited a -9.70% and -20.78% change in fat mass at 8 and 24 weeks, respectively. Accordingly, the CETP T allele group presented a decreasing trend in regard to fat mass at 24 weeks (p = 0.057; GG group fat mass change -7.26%, GT group fat mass change -20.78%; Figure 19C).

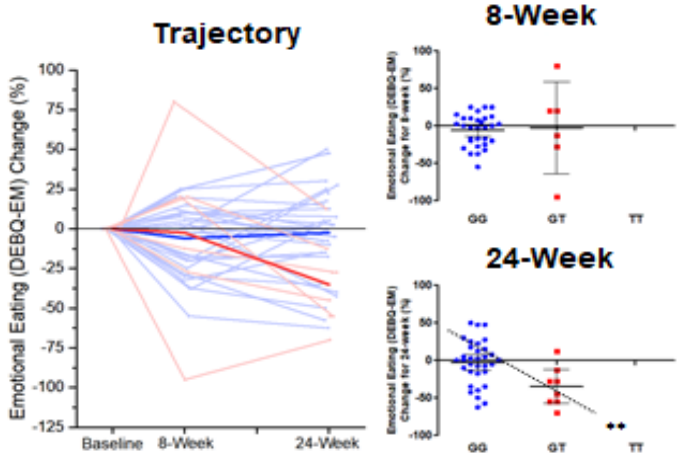
When considering dietary behaviors, I found that the CETP T allele group exhibited a significantly improved healthy diet diversity after dCBT-O when compared to the CETP GG group (p = 0.007; GG group FDB-H change 2.15%, GT group FDB-H change 15.27%; Figure 19D). In addition, the CETP GG group demonstrated a -5.83% and -2.65% variance in emotional eating behavior after 8 and 24 weeks, respectively, while the CETP T allele group showed a -2.5% and -35% variance in emotional eating behavior after 8 and 24 weeks, respectively. Accordingly, emotional eating behavior was shown to be significantly promoted in the CETP T allele group at 24 weeks when compared to the CETP GG group (p = 0.007; GG group DEBQ-EM -5.83%, GT group DEBQ-EM -35%; Figure 19E). Lastly, the CETP GG group showed a +11.47% and +5.53% variation in restrained eating behavior after 8 and 24 weeks, respectively, whereas the CETP T allele group exhibited a +4.12% and +4.80% variation in restrained eating behavior after 8 and 24 weeks, respectively. The change in restrained eating behavior in the CETP T allele group exhibited an increasing trend when compared to the CETP GG group at 24 weeks (p = 0.091; GG group DEBQ-RE +5.53%, GT group DEBQ-RE +4.80%; Figure 19F).


GG
GT
A
BMI Change
Trajectory
BMI Change (%)
Baseline
8-Week
24-Week
8-Week
BMI Change for 8-week (%)
24-Week
BMI Change for 24-week (%)
*
B
Weight Change
Trajectory
Weight Change (%)
Weight Change for 8-week (%)
Weight Change for 24-week (%)
C
Fat Mass Change
Trajectory
Fat Mass Change (%)
Fat Mass Change for 8-week (%)
Fat Mass Change for 24-week (%)

D **Healthy Diet Diversity Change**



E **Emotional Eating Change**



F **Restrained Eating Change**

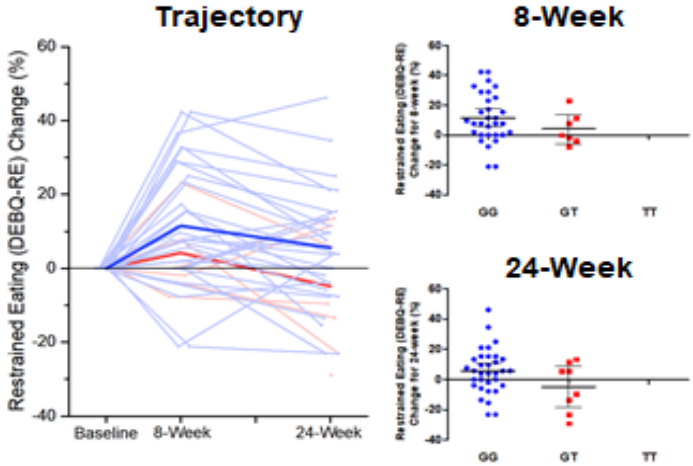
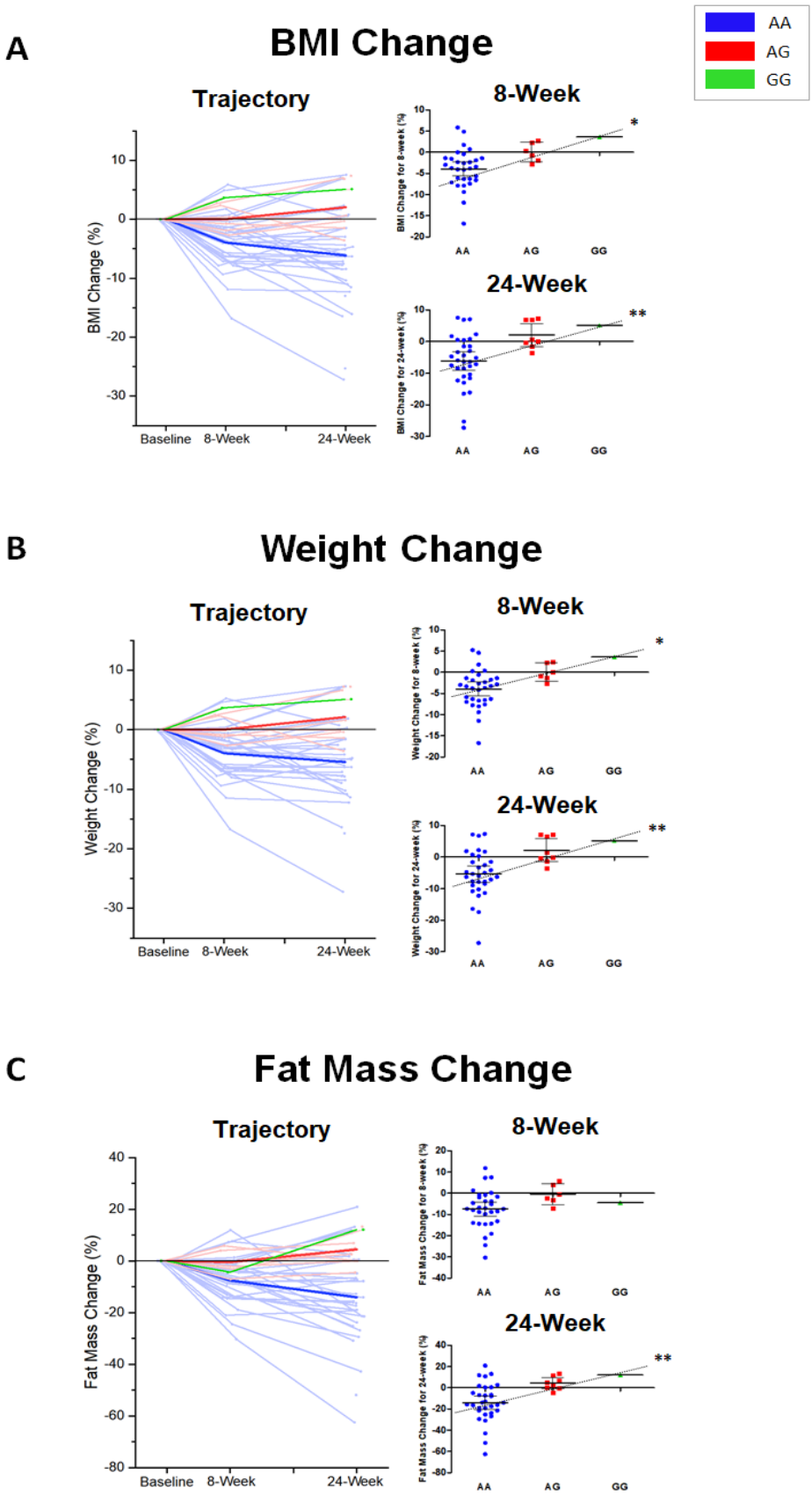


Figure 19. Association between CETP rs9939224 and obesity-related phenotypes; *p < 0.05; **p < 0.01

According to the analysis, the APOA2 AA group exhibited a -3.93% and -6.17% change in BMI after 8 and 24 weeks, respectively. The APOA2 AG group showed a -0.02% and +2.05% change in BMI after 8 and 24 weeks, respectively. The APOA2 GG group showed a +3.65% and +5.11% change in BMI after 8 and 24 weeks, respectively. Thus, the APOA2 G allele was shown to be significantly associated with an increasing trend in BMI (p = 0.012 and p = 0.005 at 8 and 24 weeks, respectively; Figure 20A). In addition, the APOA2 AA group showed a -3.96% and -5.39% change in weight at 8 and 24 weeks, respectively. On the other hand, the APOA2 AG group showed a -0.03% and -2.14% change in weight at 8 and 24 weeks, respectively, while the APOA2 GG group exhibited a +3.65% and +5.11% change in weight at 8 and 24 weeks, respectively. Therefore, the APOA2 G allele was shown to be associated with an increasing trend in weight (p = 0.01 and p = 0.004 at 8 and 24 weeks, respectively; Figure 20B). In regard to changes in fat mass, the APOA2 AA group exhibited a -7.47% and -14.13% change in fat mass after 8 and 24 weeks, respectively, whereas the APOA2 AG and APOA2 GG groups presented a -0.50% and -4.31% and -4.42% and +12.05% change in fat mass, respectively, at 8 and 24 weeks. Therefore, the APOA2 G allele was associated with a significant increase in fat mass at 24 weeks (p = 0.0035) but not after 8 weeks (Figure 20C). Regarding dietary behaviors, the APOA2 AA group exhibited a +18.60% change in FPB-H at 8 weeks, while the APOA2 AG group showed a -10.02% change. The APOA2 GG group showed no change between the measurements taken at baseline and 8 weeks. Thus, the APOA2 AA genotype significantly promoted healthy diet proportions after dCBT-O when compared to the AG and GG genotype at 8 weeks post-intervention (p = 0.036; Figure 20D).


A
BMI Change
AA
AG
GG
Trajectory
BMI Change (%)
Baseline
8-Week
24-Week
8-Week
BMI Change for 8-week (%)
24-Week
BMI Change for 24-week (%)
B
Weight Change
Trajectory
Weight Change (%)
Weight Change for 8-week (%)
Weight Change for 24-week (%)
C
Fat Mass Change
Trajectory
Fat Mass Change (%)
Fat Mass Change for 8-week (%)
Fat Mass Change for 24-week (%)

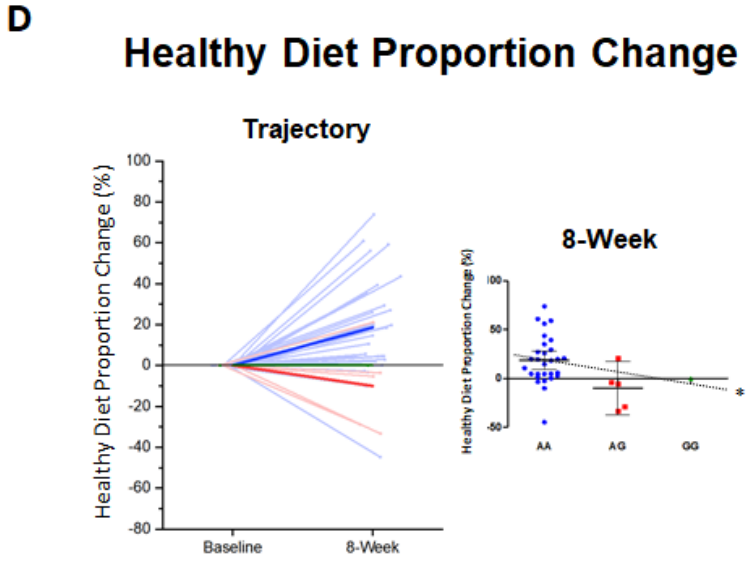


Figure 20. Association between APOA2 rs5082 and obesity-related phenotypes; *$p < 0.05$; **$p < 0.01$

To test for a gene-gene effect between the CETP and APOA2 genotypes, they were classified into three interaction groups: best (good × good), intermediate (good × bad), and worst (bad × bad) response. Linear regression analysis revealed that the primary outcome (BMI change) was significantly different between the three interaction genotype groups ($p < 0.05$). Moreover, the BMI change was significantly unfavorable in the worst-response group (+2.62%) when compared to both the intermediate (-4.49%; $p = 0.007$) and best (-11.45%; $p = 0.038$) response groups (Figure 21).

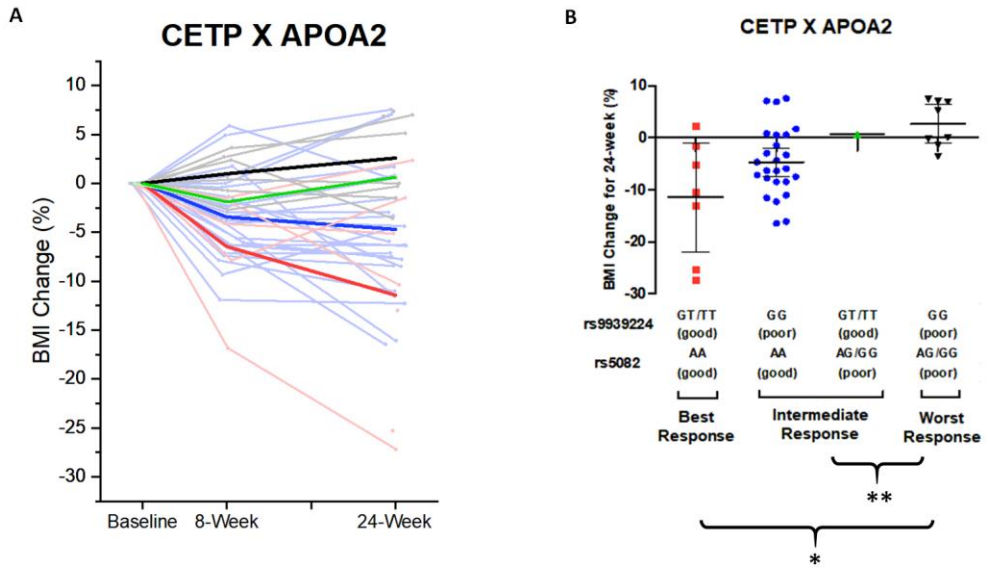


Figure 21. The effects of the interactions between CETP and APOA2 on BMI change after dCBT-O; *$p < 0.05$; **$p < 0.01$

Several other SNPs were also associated with changes in clinical outcomes (Table 14). For example, BMI change at 24 weeks, which was the primary outcome, was significantly associated with FTO rs1421084 ($p = 0.044$), LIPC rs1800588 ($p = 0.004$), and COMT rs737865 ($p = 0.049$). Furthermore, several SNPs were associated with the baseline phenotypes (Table 15). For instance, MC4R rs17782313 was associated with anthropometric (body weight, $p = 0.003$; BMI, $p = 0.001$; body fat percentage, $p = 0.014$) and psychological measures (depression; $p = 0.048$) at baseline.

Table 14. Associations between other SNPs and changes in clinical outcomes

SNP	Phenotype classification	Phenotype (unit)	Period	*P*	Beta
rs1042713	Eating behavioral change	Δ Total intake (%)	at 8 weeks	0.05	0.34
rs1042714	Biological change	Δ GGT (U/L)	at 8 weeks	0.01	-0.45
		Δ Insulin (μU/mL)	at 8 weeks	0.05	0.34
rs10487505	Psychological change	Δ TAI (score)	at 24 weeks	0.04	-0.33
rs1051168	Anthropometric change	Δ BMI (%)	at 8 weeks	0.01	0.44
		Δ Weight (%)	at 8 weeks	0.01	0.44

		Δ Fat Mass (%)	at 8 weeks	0.01	0.43
	Biological change	Δ ALT (U/L)	at 8 weeks	0.01	0.44
		Δ AST (U/L)	at 8 weeks	0.04	0.36
		Δ Leptin (ng/ml)	at 8 weeks	0.02	0.40
	Psychological change	Δ RSES (score)	at 24 weeks	0.01	-0.40
rs10778213	Psychological change	Δ RSES (score)	at 8 weeks	0.01	0.40
rs10838738	Biological change	Δ TG (mg/dL)	at 8 weeks	0.02	-0.40
	Eating behavioral change	Δ Sodium (%)	at 8 weeks	0.04	0.35
rs10937273	Psychological change	Δ RSES (score)	at 8 weeks	0.04	0.34
		Δ BSQ-8C (score)	at 24 weeks	0.00	0.51
rs1121980	Eating behavioral change	Δ Unhealthy Diet Intake (%)	at 8 weeks	0.04	-0.36
		Δ Healthy Diet Proportion (%)	at 8 weeks	0.02	0.40
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.02	-0.40
		Δ Healthy Diet Diversity (%)	at 8 weeks	0.00	0.54
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.03	-0.38
rs1137101	Biological change	Δ Glucose (mg/dL)	at 8 weeks	0.03	0.37
	Eating behavioral change	Δ Healthy Food Intake (%)	at 8 weeks	0.04	0.37
		Δ Total Intake (%)	at 8 weeks	0.05	0.34
		Δ Protein Intake (%)	at 8 weeks	0.00	0.50
		Δ Fat Intake (%)	at 8 weeks	0.01	0.43
		Δ Saturated Fat (%)	at 8 weeks	0.02	0.41
rs11642841	Eating behavioral change	Δ Unhealthy Diet Intake (%)	at 8 weeks	0.04	-0.36
		Δ Healthy Diet Proportion (%)	at 8 weeks	0.02	0.40
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.02	-0.40
		Δ Healthy Diet Diversity (%)	at 8 weeks	0.03	0.38
rs12463617	Anthropometric change	Δ LBM (%)	at 8 weeks	0.02	-0.37
	Psychological change	Δ TAI (score)	at 8 weeks	0.05	0.33

rs12772424	Anthropometric change	Δ LBM (%)	at 24 weeks	0.01	0.40
	Eating behavioral change	Δ Fat Intake (%)	at 8 weeks	0.05	0.34
		Δ Saturated Fat (%)	at 8 weeks	0.05	0.34
rs12999373	Anthropometric change	Δ Fat Mass (%)	at 8 weeks	0.03	0.35
	Biological change	Δ Leptin (ng/ml)	at 8 weeks	0.02	0.41
rs13113518	Eating behavioral change	Δ Carbohydrate Intake (%)	at 8 weeks	0.04	0.35
		Δ Protein Intake (%)	at 8 weeks	0.04	0.35
rs1339000	Eating behavioral change	Δ Healthy Diet Proportion (%)	at 8 weeks	0.01	0.43
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.01	-0.43
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.03	-0.37
	Psychological change	Δ K-BDI-II (score)	at 24 weeks	0.02	-0.37
rs1421084	Anthropometric change	Δ BMI (%)	at 24 weeks	0.05	0.31
		Δ Weight (%)	at 24 weeks	0.04	0.32
	Eating behavioral change	Δ Healthy Diet Intake (%)	at 8 weeks	0.01	0.42
		Δ Healthy Diet Diversity (%)	at 8 weeks	0.03	0.39
	Psychological change	Δ RSES (score)	at 24 weeks	0.04	-0.32
rs174547	Eating behavioral change	Δ Healthy Diet Intake (%)	at 8 weeks	0.02	-0.39
rs17782313	Psychological change	Δ BSQ-8C (score)	at 8 weeks	0.02	0.37
rs1799724	Anthropometric change	Δ BMI (%)	at 8 weeks	0.02	-0.39
		Δ Weight (%)	at 8 weeks	0.02	-0.38
			at 24 weeks	0.05	-0.31
		Δ Fat Mass (%)	at 8 weeks	0.02	-0.38
		Δ LBM (%)	at 24 weeks	0.04	-0.32
	Biological change	Δ Leptin (ng/ml)	at 8 weeks	0.02	-0.40
rs1800588	Anthropometric change	Δ BMI (%)	at 24 weeks	0.04	0.31
		Δ Weight (%)	at 24 weeks	0.02	0.35
		Δ Fat Mass (%)	at 24 weeks	0.05	0.31
	Eating behavioral change	Δ DEBQ-RE (score)	at 8 weeks	0.04	-0.33
rs1800774	Biological change	Δ GGT (U/L)	at 8 weeks	0.05	-0.34

rs1815739	Biological change	Δ Cholesterol (mg/dL)	at 8 weeks	0.03	-0.38
rs1864163	Eating behavioral change	Δ Healthy Diet Diversity (%)	at 8 weeks	0.03	0.38
rs1942880	Biological change	Δ TG (mg/dL)	at 8 weeks	0.01	0.42
	Eating behavioral change	Δ Carbohydrate Intake (%)	at 8 weeks	0.00	0.50
rs1993709	Biological change	Δ Insulin (μU/mL)	at 8 weeks	0.00	0.65
	Psychological change	Δ K-BDI (score)	at 24 weeks	0.02	0.37
		Δ RSES (score)	at 24 weeks	0.02	0.37
		Δ TAI (score)	at 24 weeks	0.02	0.35
rs2016520	Psychological change	Δ K-BDI-II (score)	at 8 weeks	0.01	0.40
		Δ RSES (score)	at 8 weeks	0.04	0.34
			at 24 weeks	0.01	0.39
		Δ TAI (score)	at 8 weeks	0.03	0.35
			at 24 weeks	0.02	0.35
rs2069762	Eating behavioral change	Δ Healthy Diet Proportion (%)	at 8 weeks	0.04	-0.36
	Psychological change	Δ RSES (score)	at 24 weeks	0.02	-0.36
		Δ TAI (score)	at 24 weeks	0.04	-0.32
rs2075650	Anthropometric change	Δ BMI (%)	at 8 weeks	0.00	-0.50
		Δ Weight (%)	at 8 weeks	0.00	-0.51
		Δ Fat Mass (%)	at 8 weeks	0.00	-0.51
			at 24 weeks	0.04	-0.32
	Biological change	Δ Leptin (ng/ml)	at 8 weeks	0.01	-0.43
rs2229094	Biological change	Δ HOMA-IR	at 8 weeks	0.02	-0.35
rs2229616	Biological change	Δ HOMA-IR	at 8 weeks	0.02	0.33
	Psychological change	Δ RSES (score)	at 8 weeks	0.00	0.46
rs239345	Psychological change	Δ TAI (score)	at 24 weeks	0.01	-0.39
rs2568958	Eating behavioral change	Δ Unhealthy Diet Intake (%)	at 8 weeks	0.02	-0.39
rs2794520	Psychological change	Δ RSES (score)	at 24 weeks	0.01	0.39
rs2808630	Biological change	Δ Insulin (μU/mL)	at 8 weeks	0.04	0.36
	Psychological change	Δ RSES (score)	at 24 weeks	0.03	0.33
rs3093664	Biological change	Δ GGT (U/L)	at 8 weeks	0.00	-0.51
rs328	Psychological change	Δ K-BDI-II (score)	at 8 weeks	0.03	-0.36
rs34872471	Psychological change	Δ BSQ-8C (score)	at 24 weeks	0.04	-0.32
rs35610689	Eating behavioral change	Δ Carbohydrate Intake (%)	at 8 weeks	0.03	0.37
rs429358	Anthropometric	Δ BMI (%)	at 8 weeks	0.02	-0.39

	change	Δ Weight (%)	at 8 weeks	0.01	-0.41
		Δ Fat Mass (%)	at 8 weeks	0.02	-0.38
	Biological change	Δ Leptin (ng/ml)	at 8 weeks	0.02	-0.40
	Eating behavioral change	Δ Fat Intake (%)	at 8 weeks	0.05	0.35
		Δ Unhealthy Diet Intake (%)	at 8 weeks	0.05	0.34
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.03	0.37
rs4722167	Psychological change	Δ K-BDI-II (score)	at 8 weeks	0.01	0.44
		Δ RSES (score)	at 8 weeks	0.02	0.38
		Δ TAI (score)	at 8 weeks	0.04	0.34
rs4818	Biological change	Δ Glucose (mg/dL)	at 8 weeks	0.04	-0.35
rs519113	Eating behavioral change	Δ Total intake (%)	at 8 weeks	0.02	0.39
		Δ Unhealthy Diet Intake (%)	at 8 weeks	0.02	0.42
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.05	0.35
		Δ Fat Intake (%)	at 8 weeks	0.03	0.38
rs5370	Biological change	Δ Cholesterol (mg/dL)	at 8 weeks	0.01	-0.43
rs5400	Anthropometric change	Δ LBM (%)	at 8 weeks	0.04	0.34
rs6265	Eating behavioral change	Δ Sodium (%)	at 8 weeks	0.02	0.39
rs659366	Psychological change	Δ BSQ-8C (score)	at 24 weeks	0.05	0.31
rs671	Eating behavioral change	Δ Total intake (%)	at 8 weeks	0.00	0.61
		Δ Unhealthy Diet Intake (%)	at 8 weeks	0.00	0.50
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.02	0.39
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.01	0.46
		Δ Carbohydrate Intake (%)	at 8 weeks	0.00	0.53
		Δ Protein Intake (%)	at 8 weeks	0.00	0.53
		Δ Fat Intake (%)	at 8 weeks	0.00	0.57
		Δ Saturated Fat (%)	at 8 weeks	0.00	0.53
rs711752	Biological change	Δ AST (U/L)	at 8 weeks	0.03	0.38
	Psychological change	Δ K-BDI-II (score)	at 8 weeks	0.01	0.40
rs713598	Eating behavioral	Δ Healthy Diet	at 8 weeks	0.05	-0.35

	change	Proportion (%)			
rs7310409	Psychological change	Δ BSQ-8C (score)	at 8 weeks	0.02	-0.38
			at 24 weeks	0.05	-0.31
rs737865	Anthropometric change	Δ BMI (%)	at 24 weeks	0.05	0.31
	Biological change	Δ Glucose (mg/dL)	at 8 weeks	0.02	-0.41
		Δ Insulin (μU/mL)	at 8 weeks	0.03	0.05
	Eating behavioral change	Δ Healthy Diet Diversity (%)	at 8 weeks	0.02	-0.40
rs762551	Eating behavioral change	Δ Healthy Diet Intake (%)	at 8 weeks	0.02	-0.41
rs7673908	Anthropometric change	Δ Fat Mass (%)	at 8 weeks	0.04	-0.34
	Eating behavioral change	Δ Fat Intake (%)	at 8 weeks	0.04	0.36
		Δ Protein Intake (%)	at 8 weeks	0.05	0.35
		Δ Saturated Fat (%)	at 8 weeks	0.02	0.39
rs780094	Biological change	Δ ALT (U/L)	at 8 weeks	0.05	-0.34
rs791595	Biological change	Δ Cholesterol (mg/dL)	at 8 weeks	0.03	0.37
		Δ Glucose (mg/dL)	at 8 weeks	0.04	0.36
rs8044769	Eating behavioral change	Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.04	0.36
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.01	0.44
rs822393	Psychological change	Δ BSQ-8C (score)	at 24 weeks	0.00	-0.43
		Δ RSES (score)	at 8 weeks	0.02	-0.38
		Δ TAI (score)	at 8 weeks	0.03	-0.35
rs9308762	Biological change	Δ AST (U/L)	at 8 weeks	0.05	0.34
	Eating behavioral change	Δ Sugar (%)	at 8 weeks	0.00	-0.49
rs9930506	Eating behavioral change	Δ Healthy Diet Intake (%)	at 8 weeks	0.02	0.42
		Δ Healthy Diet Proportion (%)	at 8 weeks	0.01	0.43
		Δ Healthy Diet Diversity (%)	at 8 weeks	0.00	0.52
		Δ Unhealthy Diet Intake (%)	at 8 weeks	0.04	-0.36
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.01	-0.43

		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.02	-0.40
rs9939506	Eating behavioral change	Δ Healthy Diet Proportion (%)	at 8 weeks	0.04	0.35
rs9939609	Eating behavioral change	Δ Healthy Diet Intake (%)	at 8 weeks	0.02	0.39
		Δ Healthy Diet Proportion (%)	at 8 weeks	0.00	0.50
		Δ Healthy Diet Diversity (%)	at 8 weeks	0.00	0.59
		Δ Unhealthy Diet Intake (%)	at 8 weeks	0.01	-0.44
		Δ Unhealthy Diet Proportion (%)	at 8 weeks	0.00	-0.50
		Δ Unhealthy Diet Diversity (%)	at 8 weeks	0.01	-0.44
rs9989419	Anthropometric change	Δ LBM (%)	at 24 weeks	0.00	0.48
	Psychological change	Δ BSQ-8C (score)	at 8 weeks	0.00	-0.51
		Δ K-BDI-II (score)	at 24 weeks	0.04	0.33
		Δ RSES (score)	at 24 weeks	0.01	0.40
		Δ TAI (score)	at 24 weeks	0.02	0.37

Δ = The change value of the clinical outcomes; BMI = Body Mass Index; LBM = Lean Body Mass; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; GGT = Gamma-Glutamyl Transpeptidase; HOMA-IR = Homeostasis Model for Assessment of Insulin Resistance (Insulin resistance = [Insulin (μU/mL) × Glucose (mg/dL)] / 405); BSQ-8C = Body Shape Questionnaire; K-BDI-II = Beck Depression Inventory-II in Korean; TAI = Trait-Anxiety Inventory; RSES = Rosenberg Self Esteem Scale; DEBQ-RE = Dutch Eating Behavior Questionnaire-Restrained Eating

Table 15. Associations between other SNPs and the phenotypes at baseline

SNP	Phenotype classification	Phenotype	P-value
rs1042714	Anthropometric	Fat Percent	0.047
rs10778213	Anthropometric	Fat Percent	0.02
		Fat Mass	0.004
		LBM	0.005
rs10937273	Anthropometric	Weight	0.006

		BMI	0.001
		Fat Percent	0.011
	Biological	Leptin	0.007
rs1121980	Anthropometric	Fat Mass	0.038
rs11642841	Anthropometric	Weight	0.027
		BMI	0.007
		Fat Percent	0.018
rs13113518	Anthropometric	Fat Mass	0.006
	Psychological	BSQ-8C	0.008
rs17782313	Anthropometric	Weight	0.003
		BMI	0.001
		Fat Percent	0.014
	Biological	Leptin	0.018
	Psychological	K-BDI-II	0.048
rs1799724	Anthropometric	Weight	0.014
		BMI	0.006
		Fat Percent	0.006
		LBM	0.007
	Biological	Leptin	0.01
	Psychological	BSQ-8C	0.005
rs1800588	Anthropometric	LBM	0.008
	Psychological	BSQ-8C	0.036
		RSES	0.019
rs1815739	Anthropometric	BMI	0.048
		Fat Percent	0.041
	Biological	Leptin	0.046
	Psychological	BSQ-8C	0.003
rs1942880	Anthropometric	Weight	0.014
		BMI	0.009

		Fat Percent	0.012
	Biological	Leptin	0.041
rs2025804	Anthropometric	LBM	0.034
	Psychological	BSQ-8C	0.007
rs2229094	Anthropometric	LBM	0.014
	Psychological	BSQ-8C	0.011
rs2568958	Anthropometric	Weight	0.023
		BMI	0.02
		Fat Percent	0.02
rs3093664	Anthropometric	Weight	0.007
		BMI	0.01
rs328	Psychological	RSES	0.017
rs34872471	Psychological	BSQ-8C	0.014
rs4818	Anthropometric	BMI	0.047
rs4961	Anthropometric	Weight	0.019
		BMI	0.03
rs737865	Psychological	K-BDI-II	0.024
rs7481311	Psychological	TAI	0.028
rs7673908	Anthropometric	Fat Mass	0.018
	Psychological	BSQ-8C	0.037
rs780094	Psychological	K-BDI-II	0.044
rs822393	Anthropometric	BMI	0.034
	Psychological	K-BDI-II	0.035
		TAI	0.007

BMI = Body Mass Index; LBM = Lean Body Mass; BSQ-8C = Body Shape Questionnaire; K-BDI-II = Beck Depression Inventory-II in Korean; TAI = Trait-Anxiety Inventory; RSES = Rosenberg Self Esteem Scale.

Chapter 4. Discussion

Part I. *Validating the treatment efficacy and finding its predictive markers*

I successfully examined the efficacy of a newly developed multi-factorial and daily-based personalized CBT model conducted by a psychologist via a digital platform for managing body weight, BMI, and body fat mass and showed a legacy effect even after the intervention terminated. This was performed by comparing this group to the active comparators using only the app as the control group. Furthermore, this study successfully explored the predictors for the efficacy of the dCBT-O from the baseline characteristics and recommended them as precision medicine biomarkers, namely, depression, anxiety, self-esteem, and motivation. Comparing the result from this study to previous mHealth RCTs, it is comparable to other mHealth RCTs. The mean percentage weight loss of dCBT-O was 4% of initial body weight, and previous mHealth RCTs reported a mean percentage weight loss ranging from 1% to 3% (16, 18, 90, 91). Moreover, this study successfully showed weight maintenance. Most interventions for obesity have shown a tendency to weight regain after discontinuing the treatment (18, 28, 83, 90-94), but the dCBT-O showed a sustained trend of further decrease even up to 16 weeks after cessation of the 8 week-intervention. This affords solid support for the assumption that digital CBT promotes an overall healthy lifestyle.

The threshold for "good response" of dCBT-O

With regard to the appropriate threshold, previous behavioral weight loss studies often reported 5% weight loss in the majority of participants (83, 95, 96). Conventionally, several studies adopted a 5% threshold as a clinically significant threshold (18, 83, 95, 97). However, in contrast to the conventional 5% threshold, we adopted a tempered 3% weight loss

threshold as the “good response” threshold for two main reasons. First, the duration of the active intervention period in this study was shorter than in other studies and only persisted transiently for the initial 2 months. The majority of previous behavioral studies had a full 6-month active intervention design (83, 98, 99). However, the duration of the active intervention period in this study was only 8 weeks (2 months). There was no intervention delivered after 8 weeks (2 months) until the 6-month time point. Thus, the subjects did not receive the intervention during the remaining 4 months after the initial 2-month active intervention. Second, the components of the intervention in this study did not include extreme restrictions/requirements in either the diet or exercise. The main goal of dCBT-O was to implement sustainable weight management skills by learning an appropriate behavioral process as well as establishing new cognitive processes. Therefore, the weight loss per se could be weaker than with the stringent diet restrictions and exercise requirements of a behavioral program during the intervention.

Predictive markers for clinical efficacy

This study can be considered a practical one because it explored clinical markers that predict the effect of digital CBT and suggested plausible criteria that can be applied to clinical settings. The follow-up results at 24 weeks in this study showed that the levels of motivation, depression, anxiety, and self-esteem were the predictive markers of weight loss based on the dCBT-O. Some of the results regarding the predictors of weight control conflict with the findings of previous research (100), but they are consistent with recent findings that the level of motivation is the strongest predictive trait for weight control (101, 102). We defined people who lost less than 3% of their baseline weight as poor responders to the treatment. Thus, people with a SIMS score lower than 76.5 are recommended to find and pursue their own way of enhancing their motivation to lose weight before they undertake the dCBT-O. Furthermore, a person whose score is higher than

7.5 on K-BDI, 41.5 on TAI, or 24.5 on RSES is encouraged to handle the relevant issue before or at the same time as the dCBT-O. This will prevent further distress from repeated failure to control weight, save limited resources, and allow better concentration in individuals with a higher chance of success in weight control.

The characteristics of the comparator

Considering the comparator of this study as the best active comparator without human coaching, dCBT-O is a competent intervention for obesity in the current situation in the digital healthcare industry. I provided education on how to log meals and exercise as well as how to use the InBody dials and mobile app not only to the dCBT-O group but also to the control group during the orientation. Thus, the control group in this study can be defined as an active group as in previous studies (97, 103, 104). Moreover, since the participants in dCBT-O group received an intense intervention, they could be more likely to experience a pause in response that follows the delivery of the intervention, like 'post-reinforcement pause', than those in the control group. This can be one of the interpretations to the result that there was no significant difference in primary outcomes between the two groups at 24 weeks. In addition, there was no significant difference in the level of motivation to lose weight between the dCBT-O group and the control group at the baseline. This was reflected in the result showing the constant decreased pattern in the primary outcome of the control group practicing digital-based self-care provided as an active comparator. Therefore, the results of this study are notable since I compared dCBT-O group to active control group, yet they still show the significant difference in primary outcome at 8 weeks.

Limitations

While the results are highly promising, the study is not without limitations. First, the participants were limited to those in their 20s and 30s, resulting in limited generalizability. However, since these ages have shown the highest

prevalence of overweight and obesity among the other age groups (105), the participants of this study can be considered as a relevant sample to validate the clinical efficacy of dCBT-O. Second, since this is not a blinded study, an observer bias could have been generated. Moreover, there can be some bias since the participants could behave differently while they know they are being watched, called a Hawthorne effect (106). In effort to overcome this effect, an additional control group - a treatment as usual (TAU) group without using digital modalities - could be used. Thus, three-arm study design is recommended for future research. Third, the sample size was relatively small (n = 70). Therefore, most of the results did not pass the strict multiple-comparison-corrected P-threshold. In addition, although I intended to make imbalanced allocation ratio between the randomized groups, this could lead to a statistical bias while interpreting the results. To resolve this issue, ensuring a balance in sample size across groups using, for example, block randomization is recommended for the future research. Fifth, the follow-up period needs to be extended to increase the reliability and validity of my results. Sixth, the total amount of food calories in the app might have been underestimated because the amount per serving for diverse types of food was not precise and people may have miscalculated their food intake. The primary reason for errors in food records is that most people have difficulties in estimating food portions (107). The discrepancy in food choice between the food diary and actual meals (i.e., recording similar but not exact menus, skipping reports of foods eaten, or logging foods not offered) could explain the remainder of the total miscalculation (108). In addition, it should be noted that it is necessary to involve dietitians on multidisciplinary healthcare teams for obesity CBT, as their evaluations of dietary assessment and nutritional advice would greatly strengthen the efficacy of the intervention. Next, the automatic thoughts of depression were not statistically promoted, though the anthropometrics had significantly improved after the dCBT-O. This implies that the effect of cognitive

restructuring of dCBT-O is limited to obesity-related cognition. Lastly, there is a feasibility issue regarding the dCBT-O since it is intensive and costly, requiring daily intervention by therapists trained in both physical and mental healthcare. Thus, some restrictions such as scalability issues, quality control of coaches' competency (standardization of human coaches), and cost-effective concerns are expected to apply this intervention in the real-world setting. More research involving human factors in technology-based treatments should be conducted to collect enough data to create automatic functions, decreasing the burdens of therapists in the future.

<u>Part II.</u> Eating behavioral analysis using buffet test-meal and food diary app

This study successfully demonstrated the function of psychological features and IR concerning changes in healthy diet eating behaviors. Food intake and diversity were promoted after the lifestyle modification intervention. Baseline psychological characteristics effectively predicted these changes in eating behaviors. In addition, changes in both psychological conditions and IR could explain the changes in eating behavior. This study also demonstrated for the first time the usefulness of implementing two different assessment methods for eating behaviors: the buffet test-meal and food diary in the app.

To my knowledge, this is the first study to investigate changes in food intake, proportion, and diversity obtained through dCBT-O in an RCT design. These changes were implemented by comparing the dCBT-O group to the active comparators applied in the control group. Previous systematic reviews and meta-analysis have also shown the impact and validity of mobile interventions on nutrition behaviors or nutrition-related health outcomes (109, 110). However, they have only reported a single dimension among the clinical outcomes such as anthropometrics or self-reported measures of eating behavior. To reduce the potential bias from interpreting

unidimensional and self-reported measures, this study has examined the eating behavior with multi-dimensional phenotypes in two different settings: buffet test-meal (experimental setting) and a food diary in app (real-world setting). Regarding the experimental setting measures, FIB-H and FDB-H significantly improved in the dCBT-O group compared to the control group. In addition, according to the measures in the real-world setting, the change in FID-B significantly increased in the dCBT-O group compared to the control group. Thus, dCBT-O successfully improved both food intake and diversity in healthy diets and encouraged people to eat breakfast.

Methodology: multi-dimensional eating behavior

For the first time, this study assessed eating behavior with multi-dimensional (intake, proportion, diversity, healthy vs. unhealthy diet foods, nutrients) phenotypes in a prospective study design. Several previous studies have used cross-sectional research designs or a 24-h food recall method (50) with only a unidimensional index to assess eating behavior (111, 112). For this reason, they cannot provide correlational and comprehensive explanations of changes in eating behaviors. In contrast, this study observed behavioral changes in multiple aspects of eating behavior, such as food intake, food proportion, and food diversity. Specifically, the food diversity index is applicable when there are more than four different dietary categories (50). The study developed the most effective design to assess food diversity behavior by applying the most diverse numbers of food items within the 24 food items. Moreover, it provides evidence of causal relationships among eating behaviors, psychological features, and physiological factors due to the prospective design. Thus, this study investigates the multiple dimensions and mechanisms of eating behavior, dissecting its inherent complexities.

Methodology: buffet test-meal and food diary in app

This is also the first study to assess eating behavior with two different procedures: a buffet test-meal (experimental setting) and a food diary using

a mobile app (real-world setting). Previous studies assessed eating behavior by applying only a single method, either an experimental test meal (113) or a food diary app (114). Studies assessing eating behavior with laboratory meals showed higher reliability and validity, but insufficiently reflected real-world eating behaviors. In contrast, those using food diary apps were more likely to reflect the real-world setting. However, they showed underreporting of the measures related to the smartphone app's ability, the level of engagement in the app, and either overestimated or underestimated records provided by self-report assessment (114, 115). Based on the results of the study, the behavioral eating patterns detected by the two assessment methods showed differences in performance. The CV of the buffet test-meal was greater than that of the food diary app. This result could be interpreted to indicate that the buffet test-meal effectively demonstrates the actual heterogeneity of individuals' eating behavior characteristics.

Compared to the app's food diary (12 indices), the buffet test-meal (17 indices) provided a higher eating behavior index. In addition, buffet-test meals defined the nutritional components and identified healthy or unhealthy foods. I successfully detected changes in eating behavior related to healthy diets, but did not find a significant change among the nutritional factors. This may be because the main goal of dCBT-O was to promote a healthy diet rather than control nutritional factors. The food diary app could specify each diet and the daily meals, such as breakfast, lunch, dinner, and snacks, differently from the buffet test-meal. This study successfully detected a significant change in breakfast intake that provides further evidence to support the idea that the main result of the dCBT-O intervention was to enhance a healthy diet change.

Taken together, these results support the idea that the buffet test meal is more relevant to quantifying the eating behavior changes after the intervention, while the food diary app has the advantage of identifying breakfast, lunch, and dinner meals separately.

Psychological features predicting healthy eating behavior improvement

Although several previous studies examined the predictors of weight loss (116, 117), this study is the first to identify predictors for changes in eating behaviors during a lifestyle modification intervention. I found that a restrained eating behavior style was the most favorable predictive marker of healthy eating behavior among individuals in the dCBT-O program. This result provides new evidence that the dCBT-O program could be most beneficial to improving the diversity in a healthy diet for people who have a restrained eating behavior style.

Indeed, restrained eating behavior is a barrier to successful weight loss due to loss of control of eating in response to certain events such as emotional stress, alcohol, or palatable foods (118). In fact, restrained eating behavior refers to the intention to restrict food intake, which is more likely to be under cognitive control than under internal or other physiological controls. When restrained eating habits break down, individuals tend to be disrupted or disinhibited by stimuli. Since people with greater restrained eating behavior showed larger increases in healthy food diversity, the dCBT-O program successfully restructured their cognitive frame, leading to healthier eating behavior.

In a previous study using dietary intervention, in contrast to the dCBT-O program, dietary restraint was a predictor of unfavorable weight loss (117). This also illustrates the importance of targeting cognitive components to improve healthy eating behavior during lifestyle interventions, especially for people with severe dietary restraint.

Psychological features as mechanisms and IR as a consequence of improved healthy eating behavior

This study is also the first to provide comprehensive insight combining psychological and physiological features into changes in healthy eating behavior. The results confirmed that individuals with a greater decrease in body shape dissatisfaction showed greater increases in healthy food intake

and diversity. Previous studies have concluded that body shape satisfaction is closely linked to lifestyle-related behaviors and changes in body weight (119). There is a higher risk of engaging in health-damaging eating behaviors, such as excessive dietary restriction, for people with high levels of body shape dissatisfaction (120). The results suggest that improvements in body shape satisfaction could be a mediator of improved healthy eating behavior.

In addition, the study reports that people with a greater decrease in IR presented greater increases in healthy food intake and diversity. It is obvious that IR is one of the major issues for many chronic diseases that require healthy lifestyle modification as a treatment (121, 122). As a part of lifestyle behavior, unhealthy eating behavior induces IR. Thus, there is no doubt that as eating behavior becomes healthier, IR improves. Based on these results, IR improvement can be seen as a consequence of healthy eating behavior. Healthy eating behavior also leads to weight loss (116). These results also indicate that weight loss improves IR, suggesting that healthy IR may be the outcome of improved healthy eating behavior.

Limitations

Notwithstanding these strengths, this study also has limitations. First, the participants were in their 20s and 30s, limiting generalizability. Second, although eating behavior is a comprehensive behavior, the indices I used to measure it were limited to calorie intake, food proportion, and diversity. In future studies, it is recommended that other dimensional measures of behavior be included, such as latency to initiate eating behavior or inter-response time. Third, to reduce the possibility of a type 1 error, I applied the false discovery rate method for multiple comparisons which balances the beta and alpha error. After this correction, there was no significant difference between randomized groups. However, the comparisons among eating behavioral phenotypes were not completely independent of each other. This may increase the risk of type II error, where there is a real treatment

effect, but failed to detect it. Thus, the larger sample size is required to adjust the results from this study. Lastly, missing data is a known limitation, and mean imputation methods could lead to underestimation of the variance. However, since there were only a few missing values, the single imputation method would positively and efficiently present this numerical dataset, providing further insight into the mechanisms underlying the association between eating behavior and both psychological and biological conditions.

Part III. *Digital phenotyping using machine-learning analysis*

Using a machine-learning approach based on elastic net regression, I successfully demonstrated the conceptual paradigm's applicability with complex dimensions of how in-app engagement is formed and affects health outcomes. This study showed that mobile applications' engagement was significantly associated with health outcomes, even four months after the cessation of digital interventions. I also found that both conventional motivation (before the intervention) and in-app motivation (during the intervention) were closely related to both engagement and clinical outcomes. Multiple aspects of motivation before and during the intervention could be used to predict engagement and health outcomes. Furthermore, both engagement and health outcomes are associated with multivariate psychological indices patterns, such as behavioral, cognitive, emotional, and motivational components, driven by regularized multivariate profiles obtained with the machine learning approach. From the results, I conclude that individuals' psychological states are the primary elements that influence engagement and health outcomes.

The relationships between engagement in app and clinical outcomes

This study makes a clear implication on how engagement with apps influences clinical outcomes. The finding that a higher frequency of logging into an app drives more significant improvements in health outcomes during the active intervention period is consistent with previous studies (123, 124).

A notable finding in this study, however, is that those who logged into the app more frequently also showed more favorable health outcomes after the cessation of the active intervention period. These results indicate that engagement is paramount to the app's potential effectiveness for behavior change, leading to a change in symptomatology. Thus, it is feasible for clinicians and users to predict their health outcomes according to the intensity of their participation in apps.

The effect of human factor on the engagement

Digital interventions via apps are not the only realm in which engagement is an issue. Both face-to-face and digital interfaces encounter difficult problems in maintaining adherence and engagement with monitoring, medications, and psychotherapies (125). Since digital therapeutics are beneficial to monitor and analyze real-time data and reach out to users without barriers in space and time; however, they are more applicable to offer immediate feedback and prevent attrition than face-to-face clinics. From this perspective, a previous meta-analysis has claimed that integrating a human factor into the treatment is an actionable strategy to alleviate the dropout rates in the digital intervention (126). The result from this study is also supportive in that the number of messages (interaction frequency between the user and therapist) showed the highest positive standardized coefficient with the engagement with the app. Taken together, I suggest that human feedback is involved in the development of digital therapeutics to strengthen the engagement rate, leading to greater clinical efficacy.

Assessing multiple dimensions of motivation

For the first time, this study evaluated the multiple dimensions of motivation at two different periods: before (conventional motivation) and during the intervention (in-app motivation). (127, 128). Previous studies assessed the motivation at several time points, but only one dimension (i.e., usability or satisfaction of digital intervention) (129, 130). Furthermore, other studies measured multiple dimensions of motivation (i.e., satisfaction,

acceptability, and usability) but only assessed at one period (i.e., after the digital intervention) (131, 132). These previous designs have limitations to reflect the users' true motivation and predict both engagement and clinical outcomes. According to my results, the common predictors of both engagement rate and health outcomes were in-app motivational phenotypes, referred to as satisfaction with the intervention, desire to improve health outcomes, and self-confidence. The level of self-esteem at baseline was also a common predictor of both engagement and health outcomes. Moreover, before implementing the intervention, the level of motivation was strongly related to health outcomes in both the short- and long-term courses. Altogether, these results suggest that motivation is the main component that determines engagement and health outcomes.

Previously, pragmatic qualities, systematic flow, satisfaction, usability, and aesthetics were known as the major contributors to digital therapeutics engagement (56, 123, 125). These prior results only serve as a basis for preliminary hypotheses on what may force engagement with apps. Few studies have examined engagement based on individuals' interactions with various intervention elements such as frequency of access, an average of steps, article views, message views, and so on (124, 133, 134). However, it is still challenging to establish a standardized approach to assess these phenotypes' engagement because of various factors such as diverse technological aspects, different intervention exposure times, and individual characteristics. Thus, I suggest measuring the multiple aspects of motivation directly before and during the intervention to predict dropout and give each participant individualized attention.

Categorizing diverse phenotypes into representative psychological constructs

This is the first study to categorize diverse digital phenotypes into four different constructs: behavior, cognition, emotion, and motivation. This allows a comprehensive understanding of the nature of behavior change,

which is closely related to the engagement and clinical outcomes of digital interventions. I suggest that the behavioral phenotypes (calorie density of food, snack time of the day, amount of food intake per meal, and frequency of message interactions with the therapists), emotional phenotypes (irritated, bored, and depressed), and motivational phenotypes (satisfaction, will, and confidence) are the favorable phenotypes for predicting the engagement in app and health outcomes. However, none of the cognitive phenotypes was capable of the engagement rate in the app. This can be inferred that the machine learning approach could not detect the sufficient explanatory and predictive power among cognitive phenotypes since they were the only dimension assessed in binary scale (i.e., 0 = No, 1 = Yes). The phenotypes predicting the health outcomes were similar but not identical to the engagement because the amount of nutritional intake was included instead of the amount of food intake per meal for the behavioral phenotypes, and depressive moods were excluded from the emotional phenotypes. These findings imply that not only users' physical participation in a specific target behavior (e.g., logging food diary, number of steps) and behavior in digital spaces (e.g., number of accesses) but also the user's psychological conditions (e.g., emotion and motivation) are relevant to engagement and clinical outcomes.

Identifying the predictive model by applying machine-learning approach

To the best of my knowledge, this is the first study to apply a machine-learning approach to provide relevant insights into improving both the adherence and clinical outcomes of digital interventions. Although previous mHealth intervention studies have shown that user engagement is critical to clinical outcomes, little effort has been made to conceptualize and estimate it. The major reason is that only a few mHealth programs predominantly use the applicable data to investigate participants' engagement or to examine its correlation with primary outcomes. However, I demonstrated the whole

framework of how different types of phenotypes at baseline and during the intervention, carry out in-app engagement and health outcomes. I used machine-learning strategies with digital phenotypes to find an applicable model to predict intervention adherence for the first time. This is also the first study to examine the determinants of significant weight changes from digital interventions. Additionally, this first attempt to explore the phenotypes in two different periods (at baseline and during the intervention) and categorized them into four distinctive dimensions (behavior, cognition, emotion, and motivation) present more comprehensive perceptions of engagement mechanisms clinical outcomes. Finally, this study applied two specific methods, in-app and an online survey, for the first time, to collect sufficient data, which led us to explore various components attaining favorable solutions for the issue of engagement and clinical efficacy in digital therapeutics. Utilizing digital phenotypes and enhancing my insight into them to promote management will involve refined approaches for choosing and investigating diverse digital health data streams in a definite manner.

Limitations

This study had several limitations. First, all participants received cognitive behavioral therapy, so it lacked a control group that did not receive any intervention. Second, the number of participants was relatively small, which might not be sufficient for reliable interpretation. However, as I extracted multivariate profiles to predict engagement and health outcomes, I remedied the shortage by using a machine learning approach. Furthermore, as this study explores the challenging concept of digital interventions, a small number of participants are still tolerable to apply the machine learning analysis (135). Third, considering the relatively small sample size, the LOOCV may be sensitive to outliers in the dataset. Moreover, assessing in the binary scale (i.e., digital cognitive phenotypes of this dCBT-O intervention) may not be applicable to be analyzed using LOOCV method.

Lastly, the experiment did not track longitudinal changes in health outcomes in the app.

Part IV. *Genetic analysis for predicting the clinical responses*

This is the first study to integrate multi-dimensional components, including psychological elements, eating behavior phenotypes, and anthropometric measures, to determine the response to dCBT-O. The findings suggest that the CETP rs9939224 SNP could predict "super-responders" which will exhibit greater BMI reduction after lifestyle modification, while APOA2 rs5082 could predict "poor-responders" which will exhibit a small BMI reduction after dCBT-O. Moreover, these SNPs may play a role in modulating changes in healthy eating behavior and psychological behavior during the intervention period. I also found that classification using gene-gene interaction between CETP rs9939224 and APOA2 rs5082 predicts the best response associated with a greater decrease in BMI after dCBT-O.

Association between CETP and other obesity-related phenotypes

CETP, which is a hydrophobic glycoprotein, plays a key role in transporting cholesterol from the peripheral tissues to the liver and is highly expressed in adipose tissue with low lipid contents (136, 137). According to previous studies, the CETP SNP rs3764261 was primarily associated with plasma high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and the risk of coronary atherosclerosis (137, 138). On the other hand, genetic variants of the CETP gene are also associated with alcohol consumption (139, 140) and dietary fat intake (141). Furthermore, it has been reported that the CETP SNP rs3764261 is highly associated with HDL-C change after lifestyle modification intervention (i.e., Look AHEAD, Weight Gain Prevention; SNAP) (142, 143). The rs3764261 SNP is linked with the rs9939224 SNP evaluated in the present study with a linkage disequilibrium of D'=0.863 (144). In addition, this study revealed that the CEPT SNP rs9939224 modulates changes in BMI, healthy eating behavior, and

psychological behavior after dCBT-O. Accordingly, the group considered super-responders based on this CETP SNP can be preferentially recommended to receive dCBT-O. These results emphasize how this specific SNP significantly influences the behavioral and psychological mechanisms associated with the efficacy of obesity treatments.

Association between APOA2 and other obesity-related phenotypes

APOA2 is a protein involved in TG, fatty acid, and glucose metabolism (145). Previous studies have reported that it is closely associated with insulin resistance, obesity, and hypertriglyceridemia. Moreover, the G genetic variants within the APOA2 promoter (rs5082) are associated with higher food consumption and lower polyunsaturated fatty acid (PUFA) intake (146, 147). The G allele in the APOA2 promoter, which is generally associated with lower APOA2 expression, would give rise to lower plasma concentrations of APOA2 (145, 147). Thus, since APOA2 also acts as a satiety signal, lower plasma APOA2 concentrations lead to a greater appetite (146, 147). The effect of the G allele on appetite could be the underlying biological mechanism linking this genotype to poor treatment response after lifestyle modification. Notably, this is the first study to show that the APOA2 rs5082 SNP can be used as a precision medicine biomarker to predict the efficacy of an intervention. These novel findings have shown that the APOA2 rs5082 SNP modulates BMI and healthy eating behavior changes after dCBT-O. Thus, those who exhibit this SNP and would become poor responders to dCBT-O can be recommended to receive other treatments, such as pharmacotherapy or surgical therapy.

Implications on Gene × Gene Interactions

Gene–gene interactions are essential to maximize the clinical efficacy of precision medicine, especially when single gene predictions have limited efficacy (148). Thus, I also investigated combinations between CETP and APOA2 SNPs to determine potential associations which may influence the response to interventions. The interactions between CEPT and APOA2

SNPs showed augmented predictive power among the groups (-11.45% mean BMI change for the best response group vs. +2.62% mean BMI change for the worst response group), which were associated with changes in obesity-related phenotypes after dCBT-O. Therefore, these results suggest that gene-gene interactions between CETP and APOA2 SNPs could be significant determinants of the clinical efficacy of dCBT-O.

Limitations

This study also has several limitations. Firstly, I limited the sample size by restricting this study to the dCBT-O arm. Secondly, the risk of false positives should be considered due to the multiple comparison issues. Since the p-values from this part of the study are unadjusted p-values, they should be adjusted for multiple testing (e.g., FDR method which balances the beta and alpha error) and be confirmed within the replicated research. Finally, since the study population was limited to women with a BMI > 24 kg/m^2, aged between 19 and 39 years, and with relatively high motivation levels, this limits the extrapolation of the results of this study to the general population.

Perspectives A. Main issues related to DTx for obesity and eating behavior problems

Based on the current status of the field, I suggest seven major constructive issues that should be addressed in order to make progress in DTx for obesity and eating-related problems (Figure 22).

Perspectives A-1. Comprehensiveness of an individual's multifactorial health condition

As mentioned earlier, obesity and eating behavior problems have complicated contexts (9). Therefore, multifactorial domains—behavioral (e.g., late-night meals, snacks), cognitive (e.g., arbitrary inference, selective abstraction), emotional (e.g., irritation, loneliness), motivational (i.e., willingness to change, self-confidence), and anthropometric—are suggested

to be addressed to comprehensively understand and monitor the progress of weight control and eating behavioral patterns (116). Since cognitive structuring and emotional regulation significantly affect behavior styles and engagement with DTx, an integrated approach concerned with all these components will ultimately solve problems related to obesity.

Perspectives A-2. Efficacy of DTx in RCTs

The aim of RCTs is to test the effectiveness of new treatments while minimizing biases (e.g., the placebo effect). RCTs prove both efficacy and safety, which are decisive components related to FDA approval. Although numerous studies have tested digital interventions for weight loss, not all of them were designed as RCTs (149). To reliably prove the efficacy of novel DTx, RCTs are a prerequisite.

A critical and challenging aspect of RCT design for DTx is designing an adequate control group. Digital modalities have a variety of features (e.g., self-monitoring, CBT, UI/UX, human coaching, etc.), which results in ambiguity regarding which features are effective, and which specific features should be compared (150). Thus, it is challenging to select the main active ingredient of DTx and devise a specific active sham control group (identical DTx platform without the main active ingredient). It is also difficult to establish a completely blinded condition, as in placebo-controlled trials of medications. Therefore, new RCT frameworks tailored to DTx have been developed, such as the multiphase optimization strategy (MOST), sequential multiple assignment randomized trials (SMART), micro-randomized trials, clustered randomized control trials, unequal-allocation randomized controlled trials, and control optimization trials (151-154). Each design aims to answer different research questions and thereby to provide the gold standard for proof in clinical medicine. In addition, due to the nature of digital technologies, RCTs of DTx could adopt fully digital online innovative designs, including digital enrollment, digital intervention, and digital outcome phenotyping, potentially avoiding the requirement for

on-site visits.

Perspectives A-3. Tailoring the individual feedback in DTx

Personalized DTx can deliver tailored feedback based on personal data from multifactorial domains, as mentioned above in the discussion of the first issue. I have shown that this is critical since personalization is closely related to engagement in digital intervention and the potential for lifestyle change in the long-term (116). However, most app-based interventions use non-tailored behavioral strategies (e.g., prompts for monitoring, appointment reminders, and health education), uniformly produced common content, or limitedly customized algorithms based on a few domains such as diet, physical activity, and body weight (17, 20). These strategies have shown limitations regarding engagement in the intervention and the maintenance of treatment efficacy. Thus, based on baseline and/or real-time multifactorial measures (e.g., behavior, emotion, cognition, and motivation), tailored feedback and adaptive intervention can increase the engagement and the effectiveness of DTx. Furthermore, other characteristics such as, genetic, social, and economic factors, as well as comorbidities, could be utilized for the development of tailored DTx.

Perspectives A-4. The role of a health coach

A health coach is a person who delivers an evidence-based intervention to users. Embedding a human factor, such as healthcare providers or peers, may enhance the engagement and efficacy of DTx. Recently, I have shown better clinical outcomes from interventions with a human coach compared to those with self-guided conditions (17, 18, 116). The major role of a health coach is to provide practical solutions to problems, emotional support, motivational interviews, and informative knowledge to support effective behavioral changes. The function of human coaching can be automated by virtual conversational agents, such as chatbots. Natural language processing studies could help develop augmented text coaching platforms for both human coaches and chatbots.

Perspectives A-5. Temporal strategies for intervention frequency

Temporal strategies for intervention frequency are an important factor influencing the engagement rate in DTx. Broadly, there are three types of time points for an intervention: daily, weekly, and monthly. Previous studies applying either weekly or monthly interventions showed high attrition rates (155). In contrast, I recently showed that more intensive daily coaching could produce a high adherence rate, with 80% of participants remaining active users until the last session of the treatment. A reason for this high adherence rate is that I delivered more intensive daily personalized feedback by facilitating real-time access to a human coach. Since the engagement rate in DTx influences the clinical outcomes, considering the intensity of interaction between providers and users is necessary. More intensive daily interventions could stimulate higher engagement. However, an extremely frequent intervention could be fatiguing or burdensome to both users and coaches. This can be alleviated by implementing advanced digital technologies such as artificial intelligence or machine-learning approaches to replace repetitive tasks by automated services (156).

Perspectives A-6. Evidence-based psychological theory for intervention strategies

Although digital health modalities have become very well-designed, the extent to which they involve evidence-based behavior change strategies or clinical protocols should be examined. Evidence-based interventions are defined as intervention strategies with empirical support for their efficacy and accountability. There are several representative psychological interventions; CBT, dialectical behavior therapy, acceptance and commitment therapy, and mindfulness-based cognitive therapy. CBT is widely applied to various types of mental health conditions. Thus, many researchers are exploring possibilities to expand its applicability, especially using digital modalities. Adopting these scientifically proven intervention strategies for behavioral change will produce more efficacious DTx.

Furthermore, it is recommended to involve health professionals (i.e., doctors, nurses, psychologists, and trainers) in the development process of DTx for interventions to be reliable.

Perspectives A-7: Target populations

Most DTx related to lifestyle modifications or eating-related problems have focused on the adult population. Although the epidemic of childhood/adolescent obesity is responsible for the prevalence of metabolic diseases in adults, studies of DTx for lifestyle modifications targeting youth are scarce. To treat children or young adults, it is more efficient to employ their caregivers/guardians in the intervention to achieve efficacious clinical outcomes. A similar point holds for older adults, who are more likely to already have metabolic or psychiatric diseases. It is recommended to include their families in the intervention to obtain successful outcomes via DTx. Furthermore, clinicians may consider implementing applicable strategies according to the target symptoms, such as major depressive disorder, eating disorders, diabetes, or hypertension.

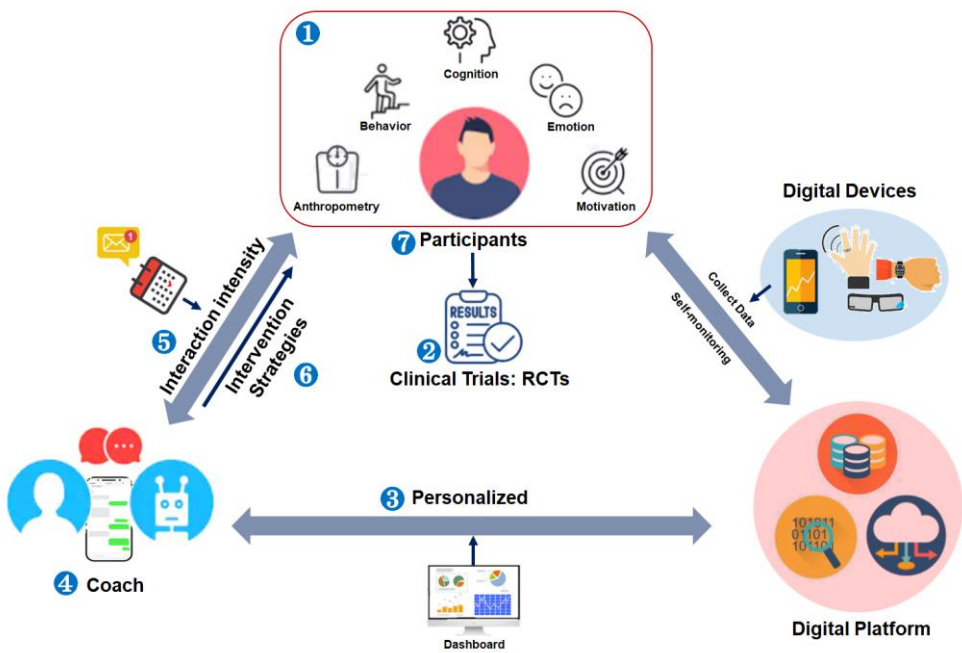


Figure 22. Major considerations and main issues for digital therapeutics.

Perspectives B. Limitations of DTx being applied in the clinics

To date, many efforts have been made to develop various types of DTx, but still they remain unsettled in the clinical settings due to following limitations. Currently, low engagement and low efficacy of DTx are two major concerns in understanding the full scalability and competency of it (155). Next, similar to traditional pharmaceuticals, DTx must undergo RCTs for the approval procedure to verify safety and efficacy in the premarket (1). However, DTx software is capable of being frequently updated and adjusted to FDA guidance at any moment, unlike other pharmaceuticals. Lastly, cybersecurity and data rights are other bottlenecks of the mass adoption of DTx. One of the solutions can be the partnerships between the industries and academics, which the companies behind successful DTx collaborate with academic groups to address scientific rigor as expected of traditional pharmaceutical drugs.

Perspectives C. Future perspectives and recommendations

As the field of behavioral medicine is leveraging digital technologies to heighten the scalability and effectiveness of interventions, I would like to make the following recommendations for future DTx researchers and industries (see Figure 23).

Different phenotyping methods with multi-dimensional phenotypes

Applying various phenotyping methods to gather individual information is required to optimize DTx (116). Phenotypes can be classified as digital or conventional. The digital phenotype refers to both passively and actively gathered data using digital modalities, such as smartphones and wearables (157). It can be acquired by wearable sensors, smartphones, and other digital devices. The conventional phenotype refers to measures that are assessed by traditional methods (i.e., blood samples, self-reported questionnaires,

electronic medical records, and buffet test-meals). These collected phenotypes are then classified into multi-dimensional phenotypes (physical health, behavioral, cognitive, emotional, and motivational). In other words, each of these dimensions can be assessed by either (or both) of these two phenotyping methods. A comprehensive integration of conventional and digital phenotypes is a key component for developing and delivering personalized interventions within DTx (116).

Devising analytical methods and developing dashboards for administrators

Regarding analytical methods, I suggest applying artificial intelligence technologies and machine-learning analyses to extract clinically meaningful features from immense and intricate data to obtain useful insights for clinical decision-making. It is then important to create insightful visualizations displayed on dashboards for administrators including coaches, caregivers, school teachers, and health professionals, as well as the users themselves (158). Here, the term “administrators” refers to the people who monitor individuals’ performance and instruct them about relevant skills to promote lifestyle modifications. Developing different versions of dashboards for each administrator may generate a better user environment since administrators could then support users in diverse aspects. This will improve individuals’ performance, leading to better clinical outcomes.

Integrating DTx with online-to-offline (O2O) services

When DTx is delivered to individuals from administrators, its efficacy can be expanded by combining O2O services with the DTx intervention. For example, providing discounted passes to work out in a gym would be beneficial for people who need to reduce their body fat and build muscle strength. Another possibility would be enabling people to purchase fitness equipment (e.g., a treadmill or barbell) on sale by bundling these services with DTx. Moreover, delivering fresh salads every day would be applicable for people who find it challenging to prepare healthy meals. Expanding

these systems may allow us to establish a ubiquitous environment (i.e., smart homes or smart schools) that adapt advanced digital technologies in daily life. Hospitals, workplaces, schools, homes and healthcare-related markets will be seamlessly connected via DTx (159, 160). All administrators will be able to prescribe home-care, work-care, school-care, and medical-care–related products through DTx. As boundaries between different sectors are fading away, new policies are required for stakeholders including health professions, patients, and guardians. This will enable sustainable ecosystems and business models that serve the public's interest.

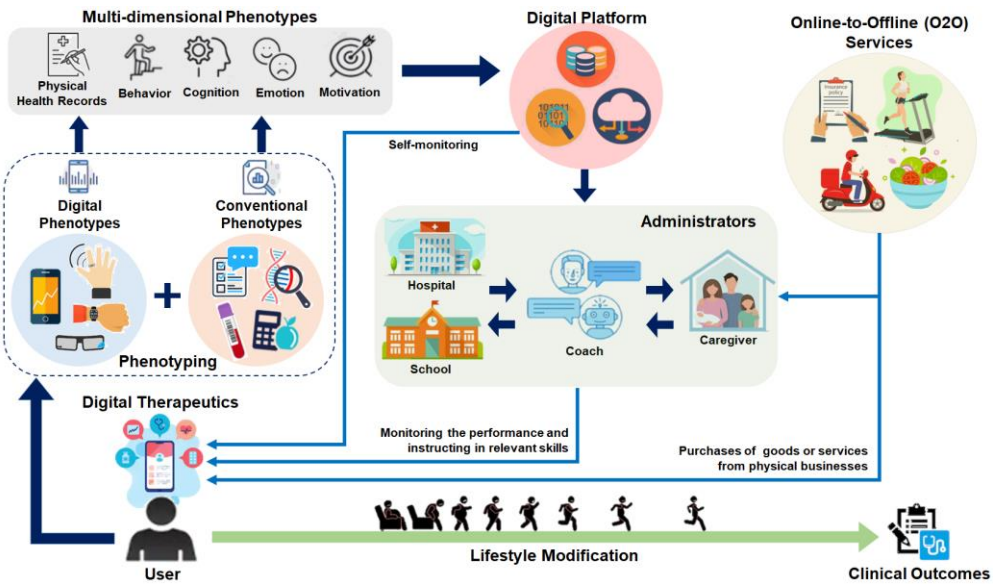


Figure 23. Future perspectives for the ecological environment of digital therapeutics

Chapter 5. Conclusion

Advanced digital technologies have been leveraged to behavioral medicine, establishing “digital therapeutics (DTx).” We are living in the digital era where digital transformation is inevitable. For the first time, I examined that human-based dCBT-O is capable of treating obesity using digital tools. Also, I found predictable psychological markers to estimate the efficacy of the dCBT-O. The proof-of-concept study using a machine learning approach demonstrated that it is possible to develop an interpretable digital phenotype model that predicts digital engagement in a mobile app and a digital intervention's clinical efficacy. Moreover, I examined, for the first time, the role of psychological conditions and IR in eating behavior changes analyzed by two different behavioral assessments: buffet test-meal (laboratory setting) and food diary in app (real-world setting) during lifestyle modification intervention. Lastly, I found that CETP and APOA2 SNPs are key elements for genotype-based precision medicine for obesity. I expect that these results will play a significant role in establishing the most practical and effective precision digital medicine. Furthermore, new policy actions are necessary in the community, city, government, and industry to adapt to this forthcoming flow.

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국문 초록

비만 디지털 치료제 효과 검증 및 다차원적인 메커니즘 분석: 무작위배정 임상시험 연구

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비만은 대표적인 생활습관 질병으로 알려져 있다. 따라서, 효과적인 비만 치료를 위해서는 다차원적인 치료적 접근이 중요시되는데, 디지털 치료제(Digital Therapeutics; DTx)는 이러한 접근에 최적화 되어있다. 본 연구의 목적은 새로 개발한 비만 디지털 치료제의 효과를 임상적 지표들과 섭식 행동 표현형들의 변화를 기반으로 검증하며, 치료적 순응도와 효과성을 예측할 수 있는 디지털 표현형들과 유전형들을 탐색하는 것이다.

본 연구에서는 BMI 24 이상, 기타 임상적인 증상을 보이지 않는 70명의 2-30대 여성들을 대상으로 대조군 대비 비만 디지털 치료제군(Digital Therapeutic for Obesity; dCBT-O군)에 1:2 비율의 무작위배정 임상시험을 시행하였다. dCBT-O군의 비만 치료는 임상심리학 전공 및 디지털 헬스케어 전문가가 8주 동안 진행하였으며, 24주차에는 치료 후 경과에 대한 평가를 실시하였다. 비만 디지털 치료제 효과 검증의 주요 지표는 체중을 비롯한 다양한 신체 계측 지표들의 변화이다. 이차 지표는 뷔페실험과 모바일 어플리케이션 내 식단기록에서 수집된 섭식행동 표현형들을 기반으로 건강한 섭식행동 변화이다. 치료 순응도 및 효과 예측 인자들을 발굴하기 위해서는 다차원적인 시계열 디지털 표현형들을 머신러닝 기법으로 분석하였다. 그리고, 치료 반응 수준을 예측하는 유

전형들을 찾기 위해 단일염기다형(Single Nucleotide Polymorphisms; SNP) 분석을 시행하였다.

본 연구의 주요 결과로 첫째, 8주간 치료 직후 dCBT-O군의 체중 변화가 대조군의 체중 변화에 비해 유의미하게 감량하였으며, 치료 종료 후 24주차도 체중이 감량 및 유지되었다. 둘째, dCBT-O군의 섭식행동이 대조군의 섭식행동에 비해 유의미하게 건강한 섭식행동으로 증진되었다. 셋째, 머신러닝 분석의 결과 16가지 디지털 표현형들이 치료적 순응도를 예측하고, 13가지 디지털 표현형들이 단기적인 치료효과를 예측하며, 8가지 디지털 표현형들이 장기적인 치료효과를 예측하였다. 마지막으로, CETP와 APOA2 SNP 유전형들이 신체계측 변화와 섭식행동변화와 유의미한 상관을 보였다.

본 연구는 디지털 기술을 활용한 다학제적인 접근이 비만 디지털 치료제의 임상 효과를 향상시킨다는 것을 보여준다. 또한 다차원적인 분석을 통해 체중 조절과 관련된 인간의 섭식 행동의 메커니즘을 더 잘 이해하는 데 기여한다. 본 연구는 첨단 예방의학과 정밀의학을 위한 디지털 치료제 개발에 중요한 패러다임을 제시할 것이다.

주 요 어: 디지털 치료제, 비만, 섭식행동, 디지털 표현형, 유전형 분석
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“Have I not commanded you? Be strong and courageous. Do not be afraid; do not be discouraged, for the Lord your God will be with you wherever you go” (The Holy Bible, Joshua 1:9)