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The Efficacy of Mobile Applications for Weight Loss

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Abstract

Purpose of Review A variety of mobile-based applications aimed at weight loss have become popular in recent years. This review describes the features and effectiveness of mobile weight loss apps.

Recent Findings Overall, mobile apps can help patients lose weight either as well as or better than traditional paper-and-pencil weight loss interventions and often better than minimal intervention control groups. Mobile apps promote multiple strategies, including self-monitoring of diet, exercise, and weight, as well as social support and educational content. Significant variation exists in app types, which makes it difficult to conclude which features drive program effectiveness. Intervention success varies based on patients' level of engagement with the app. There is a deficit of apps and app-based studies of older, less tech-savvy adults, ethnic/racial minorities, and low-income individuals, as well as longer-term studies.

Summary Mobile apps can successfully help patients lose weight and represent a cost-effective, accessible alternative to intensive in-person weight loss programs. More research is needed into their long-term potential, especially for hard-to-reach populations.

Keywords Weight loss · Mobile apps · mHealth · Weight monitoring · Patient engagement

Introduction

Many successful weight loss programs teach overweight individuals important fundamentals of nutrition, exercise, self-monitoring, and weight loss relapse prevention. However, many of these interventions are time-consuming and costly, both for providers and patients. These barriers lead to high attrition and hinder the long-term involvement needed for successful weight loss and weight loss maintenance. Weight loss interventions delivered on a mobile app represent a more accessible, alternative. Mobile apps are defined as software applications designed to run on a mobile phone [1]. This provides the app with greater accessibility than other computer programs designed for laptops or desktop computers. Approximately, 97% of Americans own a mobile phone and 85% own a smartphone [2]. Much like telemedicine, the COVID-19 pandemic has highlighted the need for remote interventions which allow patients to access services more easily.

Methods

The purpose of this review was to describe the effectiveness of mobile phone applications ("apps") for weight loss. To be included, manuscripts needed to focus on adults with obesity (BMI > 30 kg/m^2) or overweight (BMI > 25 kg/m^2 or > 23 kg/m^2 for Asian populations). Because the focus was on the effectiveness of weight loss apps, manuscripts needed to include outcomes related to weight loss, such as weight loss, BMI, and body fat loss, rather than simply changes in diet and physical activity (PA). Manuscripts without data, such as commentaries and protocols, were excluded. We also excluded pregnancy-related samples (post-partum or excessive gestational weight gain), patients recovering from

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Table 1 Summary characteristics of interventions utilizing weight loss apps

Author	Date	Intervention duration	Mobile app	Target population	Study type	Functionalities	Outcomes
Ahn et al	2020	6 weeks	Well-D	Young adults (age 18–39), South Korea	RCT with paper diary control	Food diaries with immediate feedback, self-monitoring, food & recipe database	Weight$^{\&}$, BMI$^{\&}$, waist$^{\&}$, body fat$^{\&}$, energy$^{\&}$ App: skeletal muscle$^{\#}$; waist$^{\#}$, body fat$^{\#}$; energy intake$^{\#}$ Paper control: bodyweight$^{\#}$, BMI$^{\#}$, waist$^{\#}$, body fat$^{\#}$, energy intake$^{\#}$,
Apinaniz et al	2019	6 months	AKTDIET, created for this study	Patients in Basque public health network in contemplation stage	RCT with health advice only control	Diet & exercise recommendations, instructional videos, exercise program, text messages	Weight$^{\&}$, cholesterol$^{\&}$, blood pressure$^{\&}$, diet$^{\&}$, Hba1c*
Bender et al	2017	6 months	Fitbit Zip accelerometer and mobile app	Filipino-American adults with type 2 diabetes	RCT with wait-list control	Culturally tailored program with real-time self-monitoring of steps/PA, daily self-monitoring of food, weekly weight self-monitoring; private Facebook group for coaching, social support & educational content	Weight loss*$^{\#}$, BMI*$^{\#}$, waist*$^{\#}$, fasting glucose*$^{\#}$, HbA1c$^{\#}$, step counts*
Duncan et al	2020	6 and 12 months	Balanced app, CalorieKing app, & Fitbit activity tracker	18–65 year olds	3 arm-RCT. traditional arm (diet & PA) vs enhanced (diet, PA, sleep) v wait-list control	Handbook, text messages, email with educational content, goal setting, self-monitoring, feedback; sleep quality & hygiene content	Weight$^{\&}$ Resistance training* Energy intake* Insomnia symptoms* Waist Circumference* Sedentary time*
Haas et al	2019	12 months	Oviva	German-speaking Swiss adults	Pre-posttest pilot study	Photo-based food log, group chat, personalized feedback text messages & video chats, activity & weight tracking, goal setting, database of educational content	Weight$^{\&}$ BMI$^{\&}$ Waist$^{\&}$ Body fat$^{\&}$
Hernández-Reyes et al	2020	6 months	Accupedo, created for this study	Adult Caucasian women (Andalusia, Spain); 32% body fat or higher	RCT. App with push notifications vs app without push notifications	Exercise program (randomly assigned intensity), push notifications with personalized messages; weight tracking; hypocaloric diet with 500 kca/day deficit	Body fat*, muscle mass maintenance*,

Table 1 (continued)

Author	Date	Intervention duration	Mobile app	Target population	Study type	Functionalities	Outcomes
Patel et al	2019	12 weeks	MyFitnessPal	Adults	RCT of weight & diet tracked simultaneously feedback v. weight & diet tracked sequentially feedback v app-only diet tracking only	Weekly personalized feedback & tips email; skill training materials; log food & beverages with database of nutritional information	Weight$^{\&}$
Toro-Ramos et al	2020	6 and 12 months	Noom-based diabetes prevention program	Adults with prediabetes	RCT with usual care + paper-based DPP curriculum control group	Real-time, daily coaching with motivational interviewing; DPP program; food, PA & weight logging; group messaging; daily challenges; SMART goals, positive reinforcement, accountability	Weight at 12 and 6 months*, BMI at 12 and 6 months*, HbA1c$^{\#}$

$^{*}p<.05$ difference vs control group
$^{\&}p>.05$ difference vs control group
$^{\#}p<.05$ difference pre vs post-intervention

eating disorders, or bariatric surgery patients. Articles must be published from 2017 onward. Search strategies including the terms “obesity, weight loss, weight loss maintenance, mobile app, phone app, computer app, and weight loss app” were completed in PubMed, Web of Science, Ovid, Scopus, and Cochrane (see summary in Table 1).

Results

Below, we summarize key findings from our review of studies of mobile apps.

Can Mobile Apps Help with Weight Loss?

A meta-analysis by Islam and colleagues [3] describes 12 RCTs or case–control weight loss app studies, published from January 2000 to April 2019. Eleven involved adults, and in one, the average age was twelve. Compared to no mobile app applications, interventions using mobile apps showed significant decreases in body weight (– 1.07 kg, 95% CI – 1.92 to – 0.21 kg, $p=0.01$) and BMI (– 0.45 kg/m^2, 95% CI – 0.78 to – 0.12 kg/m^2, $p=0.008$). A similar meta-analysis by Cai and colleagues describes 14 studies of mobile apps for weight loss in persons with type 2 diabetes [4]. While participants had a mean BMI of 30.0 kg/m^2, the authors acknowledge that not all participants were initially overweight. Pooled results showed a weight reduction of 0.84 kg (95% CI 1.51 to 0.17 kg), with greater results among those with a BMI > 30 kg/m^2 ($p=0.001$). There was also a decrease in waist circumference (1.35 cm 95% CI 2.16 to 0.55). Collectively, these meta-analyses provide evidence that mobile apps can help patients to lose weight.

Mobile App Characteristics

Successful weight loss apps include components common to traditional weight loss programs. For example, Well-D was designed to expand upon paper food diaries [5]. Ahn et al. describe an RCT in which patients received either Well-D or paper diaries [6]. Participants were encouraged to log their meals, including supplements, and aim for a 500 kcal/day energy deficit. Following the 6-week intervention, no significant differences between the Well-D app and paper diary were found in terms of weight changes ($p=0.33$), BMI ($p=0.34$), waist circumference ($p=0.70$), body fat mass ($p=0.71$), and skeletal muscle mass ($p=0.054$) [6]. When pre- and post-intervention biometrics were compared, significant decreases in weight were found with the paper diary group losing about 1 kg more weight. This may be explained by the concurrent finding that the app group significantly increased skeletal muscle mass while the paper diary group did not. Both groups showed similar, significant losses in body fat (app mean − 1.2 kg (SD 1.8) $p = 0.004$ vs paper mean − 1.3 kg (SD 2.4) $p = 0.01$. This suggests that the lack of overall weight loss in the app group may have resulted by a gain in muscle [6].

Oviva [7••] was designed to remotely deliver what would be received from an in-person dietician. This app featured regular personalized contact with a dietician via either text messages or video calls to help patients to set goals, receive feedback and positive reinforcement, problem-solving, etc. Participants also used the app to record their food, PA, and weight, as well as to access educational materials and a group chat. The 12-month pre-posttest intervention was designed for weight loss in the 1st 3 months, stabilization in months 4–6, and maintenance in months 7–12, similar to other weight loss programs such as the Diabetes Prevention Program (DPP). Participants lost a significant amount of weight during the 1st 3 months (− 3.8 kg, $p < 0.001$) and maintained the loss at 12 months (median − 4.9 kg or 6% body weight, $p < 0.001$), also losing a small amount of additional weight in months 3–12 (median − 1.1 kg, $p = 0.08$). Similar significant changes were seen in BMI (median 1.8 kg/m^2, $p < 0.001$), waist circumference (median − 3.8 cm, $p < 0.001$), and body fat percentage (median − 2.5%, $p < 0.001$), with the majority of the change taking place during the initial 3 months. Improvements, although not significant ones, were noted in Hba1c%, blood glucose, triglycerides, and high-density lipoprotein.

Personalization is a Key Feature of Mobile Apps

Successful interventions allow patients to make healthier dietary and exercise choices. Because food and leisure-time physical activity are closely tied to patients' cultural and social contexts, successful interventions personalize recommendations and activities. An example may be found in the PilAm Go4Health program [8], an intervention of Filipino-American adults with overweight/obesity (BMI > 23 kg/m^2, mean BMI = 30.1 kg/m^2, SD = 4.6) and type 2 diabetes. Cultural tailoring was achieved by translating educational pamphlets into Tagalog, incorporating common Filipino foods and activities, highlighting the higher prevalence of T2D and obesity among Filipinos, encouraging family members to join in-person office visits, and input from community stakeholders during study design. During the intervention, participants received a Fitbit Zip accelerometer and accompanying Fitbit mobile app to track their steps, physical activity, food, and weight. Participants were also invited to join a private Facebook group for virtual social support, weekly educational topics from the research staff, and additional coaching. During the first 3 months, participants were randomized to the intervention or to an active wait-list control that only received the Fitbit Zip accelerometer. After 3 months, participants randomized to the intervention entered a maintenance phase, while those randomized to the wait-list began the intervention. Groups receiving the intervention lost significantly more weight than the control group, both during phase 1 (− 2.6% body weight, 95% CI − 3.9 to − 1.4, $d = 0.53$) and during phase 2 (wait-list group) (− 3.3% body weight, 95% CI − 1.8 to − 4.8, $d = 0.37$).

Advantages of Mobile Apps

The widespread availability of smartphones allows for immediate recording of meals and PA, as well as real-time feedback and support. Mobile apps allow providers and researchers to easily deliver intervention content to a large number of people and allow patients to access the intervention throughout their day, without traveling to a specific location at a certain time. In this way, mobile apps share many of the same conveniences as telemedicine [9]. Educational content may be found on-demand through an online database or scheduled with a provider. Mobile apps may include social support and accountability from either a virtual peer group, such as a group text or social media site, or directly from a healthcare provider. The frequency of provider contact varies both by study and sometimes within the study, with more frequent contact during an acute weight-loss phase and decreased contact during maintenance.

Successful weight loss programs invariably teach patients to self-monitor their weight and diet. Diet may be tracked by scanning barcodes of prepackaged foods, inputting recipes and amounts, or through photos of meals. Well-D, for example, includes a database of 20,000 foods and recipes, into which patients may add new recipes to be evaluated by a dietician [6], something not possible in a non-digital context. Furthermore, comparisons of nutrient intake levels showed strong correlations, ranging from $r = 0.47$, $p = 0.02$ (cholesterol) to $r = 0.71$, $p < 0.001$ (iron), between Well-D scores and 24-h recall dietary records, suggesting the Well-D records nutrient intake accurately. This may address a perennial problem with many weight loss programs—the difficulty of accurately tracking dietary intake and portion size. Access to accurate information and feedback helps patients to make healthier dietary choices. A post-intervention analysis of dietary intake from patients using Oviva found that patients improved their diets with increased intake of fruits and vegetables, lower intake of sweets, fats, and alcohol, and increased time spent in leisure-time physical activities [7••], which leads to post-intervention weight loss.

Weight loss interventions may pair weight and dietary apps with other behaviors, including sleep, stress management, and most commonly, physical activity (PA). PA may be tracked by entering activity type and duration into the app's records or through a wearable accelerometer that links to the mobile app. Some weight loss interventions try to achieve greater lifestyle changes via multiple apps. One example is the move, eat, and sleep study [10], a three-arm RCT which compared a traditional diet and exercise intervention with a diet, exercise, and sleep intervention, and a wait-list control group. A Fitbit accelerometer to track PA was paired with CalorieKing, a calorie-tracking app, and Balanced, a sleep and meditation app. Participants (BMI 25–40 kg/m^2) also received support and educational materials via text messages, emails, a printed handbook, and in-person dietary counseling sessions. Contrary to the hypothesis that the diet-sleep-exercise intervention would show greater weight loss, the three groups showed little difference in body weight at 6 months (between-group difference − 0.92, 95% CI − 3.33 to 1.48) and 12 months (0.00, 95% CI − 2.62 to 2.62). Compared to the control group, a pooled intervention group showed improvements in resistance training at 6 months (OR = 7.83, 95% CI 1.08 to 56.63), energy intake at 6 months (− 1037.03, 95% CI − 2028.24 to − 45.22) and insomnia symptoms at 12 months (− 2.59, 95% − 4.79 to − 0.39). The authors speculate that the wait-list control group may have been motivated to lose weight, regardless of their group assignment, because all three groups, including the wait-list control group, lost weight during the study. Nonetheless, this study raises interesting questions about whether apps may improve health even in the absence of weight loss, such as via increased lean body mass or improved sleep.

Functionalities of Mobile Apps

Just as in-person weight loss interventions often include multiple strategies, such as self-monitoring, educational content, and social support, most mobile apps incorporate multiple functionalities. Accountability and motivation are some of the most effective and common functions. For example, Toro-Ramos and colleagues [11] studied the impact of Noom, a commercially available app featuring health coaches trained to deliver the CDC's Diabetes Prevention Program (DPP) on adults with prediabetes (HbA1c% 5.7–6.4%) [12]. Most participants also had obesity or overweight, (mean BMI (Noom group) = 31.25 kg/m^2, SD = 6.43), mean BMI (control group) = 30.94 kg/m^2, SD = 7.23), although a few had BMI > 25 kg/^{2}. Participants were randomized to either receive paper DDP educational materials or to receive these materials on Noom. Support was provided via daily messaging with a health coach, social support via group messaging, and self-monitoring via logs of weight, food, and PA. Coaches encouraged participants to set SMART goals and problem-solving through difficult scenarios. The intervention group lost more weight (− 2.64 kg, SE 0.71, $p < 0.001$) and had a lower BMI (− 0.99 kg/m^2, SE 0.29, $p = 0.001$) at 6 months and 12 months (− 1.80 kg, SE 0.81, $p = 0.01$) (− 0.58 kg/m2 SE 0.24, $p = 0.01$). The groups did not differ in HbA1c at 6 months (mean difference 0.004%, SE = 0.05, $p = 0.94$) or 12 months (mean difference 0.006% SE 0.07, $p = 93$) [11].

The meta-analyses described by Islam et al. [3] and Cai et al. [4] noted that mobile apps rarely limit themselves to one functionality and many have 4–5. The authors found significant heterogeneity in functionalities, including motivating text messages, self-monitoring with food diaries, social support via groups, and setting reminders. The delivery mode varied and included email, online trackers, blogs, exercise planners, podcasts, food recall diaries/planners, and seminars. The impact of individual functions may consequently be difficult to determine. It is also possible that the variety rather than any specific functionality drives the intervention. There may also be synergistic effects among different functions. Cai et al. noted a trend towards greater weight loss when the mobile app was part of a multidisciplinary study, including elements such as health coaching or diabetes care management ($p = 0.08$) [4] but that specific functionalities (glucose monitoring, weight tracking, etc.) within the app did not influence outcomes ($p > 0.5$).

Participant Engagement

Apps are not useful without sustained usage. For example, Toro-Ramos and colleagues [11] noted that results of the Noom vs written DPP study varied not just by condition but by whether patients actively engaged with the intervention. Participants assigned to the Noom intervention who did not start the program or who started but did not engage meaningfully with the program, (for example, read fewer than one educational article over 4 weeks), showed results similar to the control group. Participants who completed the program lost a significant amount of weight, (5.6% body weight (SE 0.81, $p < 0.001$) at 6 months and maintained a 4.7% weight loss (SE 0.88, $p < 0.001$) at 12 months. Successful weight loss at 12 months was predicted by more frequent weight recording ($\beta = -0.30$, $p = 0.01$), logging more steps ($\beta = -0.21$, $p = 0.08$), and more frequently logging meals ($\beta = -0.41$, $p = 0.001$) [11], further highlighting that greater engagement with the app results in more weight loss. While this provides some evidence that engagement itself promotes success, it is important to remember that patients who are not engaged with apps may have other characteristics (e.g. beliefs, personality, and comfort with digital technology) that may make them naturally more resistant to weight loss.

In contrast, patients tend to lose less weight if mobile apps fail to engage patients or patients are not yet ready to fully engage in an intensive weight loss intervention. Apinaniz and colleagues [13] describe a randomized trial of patients in the contemplation stage of change, defined as considering behavior change within the next 6 months but not ready to make an immediate change.

The intervention group received diet and exercise guidelines on the AKTDIET app, such as videos of correct exercise forms and guidelines on recording food intake. The AKTDIET group also received text messages on the importance of a healthy lifestyle. The control group received only written diet and exercise recommendations. After 6 months, the groups did not differ in weight loss (mean difference 1.9 kg, 95% CI − 9.8 to 6.1 kg, $p = 0.637$), blood cholesterol levels ($p = 0.897$), and systolic blood pressure ($p = 0.68$). HbA1c% showed better results in the control group (5.5% app vs 5.45% control group, mean difference − 0.095%, $p = 0.046$) [13]. The authors speculate that patients in the contemplation stage of change required further behavioral support, as they may not have been truly ready to undertake weight loss.

A larger variety of available functionalities may lead to greater patient engagement only up to a point. The sleep, eat, exercise study utilized three apps. Study authors found that even though the sleep-enhanced group had an additional behavior to track and an app to use, the total number of self-monitoring entries did not differ between the two intervention groups (diet and PA intervention = 156.5 + / − 102.8 entries vs diet, PA, and sleep intervention = 140.4 + / − 83.3 entries) [10]. They also note that engagement was lower for entries which participants had to enter manually, such as diet than for entries which were automatically recorded, such as Fitbit's PA record. This highlights that simplicity and ease of use are essential for long-term engagement.

Facilitating Greater Patient Engagement

Participants who may not initially be ready for weight loss may benefit from a longer run-in or trial period. Interestingly, during phase 1 of the PiAm Go4Health study, 18% of the intervention group lost 5% body weight, while during phase 2, 30% of formerly wait-listed participants lost 5% body weight. The authors theorize that 3 months of familiarity with the Fitbit wearable and mental preparation to begin a serious weight loss program may have primed them for better intervention success [8].

Unique features of mobile apps allow for greater real-time interaction between providers and patients, which may in turn facilitate greater engagement and greater weight loss. For example, Hernández-Reyes and colleagues [14••] compared weight loss outcomes among women who received a simple pedometer app, which records physical activity and steps, with those who received the same app with additional push notifications, a system in which participants receive an app-based alert which informs them of an incoming message and invites them to interact with it. Participants who received push notifications then received personalized motivational messages on topics such as PA, self-monitoring, and nutrition tips. Women who received push notifications lost more body fat (mean − 12.9% SD 6.7% vs mean − 7.0% SD 5.7, $p < 0.001$) and maintained more muscle mass (mean − 0.8% SD 4.5 vs − 3.2% SD 2.8, $p < 0.018$). The push-notification group lost more weight than the group that did not receive push notifications, although not a statistically significant amount (mean − 7.9 kg, SD 3.9 vs − 7.1 kg SD 3.4, $p = 0.39$), possibly because the push-notification group maintained greater muscle mass [14••].

Patel and colleagues investigated if differing self-monitoring practices would lead to greater engagement with the app MyFitnessPal [15]. Participants (BMI 25–45 kg/m^2) were randomized to either track both weight and diet for 12 weeks (simultaneous condition) or track only weight for the first 4 weeks and then add dietary tracking (sequential condition). Participants in the simultaneous or sequential conditions received weekly feedback emails with support for tracking diet and/or diet and weight. Participants could also be randomized to a control condition which tracked diet but received no additional support ("off the shelf" condition). Contrary to the hypothesis that a slower build-up in the sequential condition would result in greater engagement and weight change, at 12 weeks the 3 conditions did not significantly differ in weight loss (sequential − 2.7 kg, 95% CI − 3.9 to − 1.5; simultaneous -2.8 kg, 95% CI − 4.0 to − 1.5; Control − 2.4 kg, 95% CI − 3.7 to − 1.2 kg). Engagement, defined as the number of days that diet/weight was self-monitored, significantly correlated with 12-week weight change but did not differ across conditions, once again highlighting the relationship between patient engagement and weight loss.

Patient and Provider Perceptions

A survey of diabetes clinicians found that 53% recommended mobile apps to their patients. The most commonly recommended apps were MyFitnessPal (59%), CalorieKing (49.5%), and Fitbit, the app which pairs with the Fitbit tracker device (43%) [16]. Clinicians recommended mobile weight loss apps to patients rather than traditional paper and pen tracking because they believed that apps helped track diet better, were more portable than paper and pens, provide immediate feedback, could also track PA, and help patients make healthier food options. Providers appreciated that most apps were free and had features such as barcode scanners which made counting carbohydrates easier. Providers perceived that patients may be more likely to use an app because mobile phones are more likely to be on hand, and apps tend to incorporate easy tracking methods, such as photographing meals.

A review of qualitative mobile health (mHealth) studies found that participants' preferences largely coincided with the most effective features of mobile apps [17]. Participants wanted messages that were personally relevant, such as suggesting local exercise classes or activities relevant to their age group. Messages were best received when they were simple, without technical jargon, supportive and upbeat, and did not induce feelings of guilt or failure during difficult periods. There was no consensus on preferred message timing, but participants did indicate that too many messages could lead to overload and disengagement. Participants also expressed a preference for easy-to-use, entertaining, visually pleasing apps that included all content in one place. Barriers included technical difficulties, internet connectivity in rural areas, having to use multiple apps for all functionalities, and monotony if the same message was repeated too often.

Limits and Future Directions

As Karduck and colleagues found when soliciting qualitative responses from clinicians who recommend mobile apps for diabetes treatment, there were drawbacks related to both the apps themselves and how patients interacted with them. The apps are not always user-friendly, especially for older, low-income, or Spanish-speaking patients. Entering accurate information into apps can be time-consuming, causing patients to become frustrated and stop using them. Some apps were less accurate, for example in their estimates of calories burned during exercise, or needed better features for counting carbohydrates and/or measuring blood glucose. The authors also note that not all populations have smartphones capable of running mobile apps. This may be especially true of older, low-income adults who only use a limited number of programs on their smartphones [18].

Mobile apps' greatest strength is their broad reach and ability to be available long-term. Yet, most studies tended to be of short duration (6 ≥ months) and lacked racial/ethnic diversity, serious issues given the higher rates of obesity in racial/ethnic minorities and the need for a long-term lifestyle change to maintain weight loss [3]. For example, even the PilAm Go4 Health program, in which most of the participants were Filipino immigrants, largely featured highly acculturated participants who had lived in the USA for > 5–10 years, were well-educated and spoke English [8]. More trials are needed with less acculturated individuals.

Conclusions

Overall results indicate that mobile apps represent a novel and useful platform for weight loss. Multiple studies indicate that many of the same strategies used during in-person weight loss interventions are replicated by mobile apps. Mobile apps also have the additional advantages of accessibility, portability, and may be easy to use. However, mobile apps require user engagement to be effective and may be best suited for motivated, tech-savvy patients. More research is necessary to make apps more user-friendly for older patients with less familiarity with technology and to sustain patient engagement long-term.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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