Received: 21 October 2022 | Revised: 9 January 2023 | Accepted: 24 January 2023

DOI: 10.1002/oby.23744

ORIGINAL ARTICLE

Clinical Trials and Investigations

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

A randomized-controlled trial to evaluate the app-based multimodal weight loss program *zanadio* for patients with obesity

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Abstract

Objective: This study aimed to evaluate the effectiveness of the app-based, multimodal weight loss program *zanadio*.

Methods: A randomized-controlled trial was conducted from January 2021 to March 2022. A total of 150 adults with obesity were randomized into an intervention group and used *zanadio* for 1 year or into a wait list control group. The primary end point, weight change, and the secondary end points, quality of life, well-being, and waist to height ratio, were assessed every 3 months for up to 1 year via telephone interviews and online questionnaires.

Results: After 12 months, participants of the intervention group lost, on average, −7.75% (95% CI: −9.66% to −5.84%) of their initial weight, achieving a clinically relevant and statistically stronger weight reduction than the control group (mean = 0.00% [95% CI: −1.98% to 1.99%]). All secondary end points improved significantly in the intervention group, with significantly greater improvements in well-being and waist to height ratio than in the control group.

Conclusions: This study showed that adults with obesity who have used *zanadio* achieved a significant and clinically relevant weight loss within 12 months and improved further obesity-related health variables compared with a control group. Because of its effectiveness and flexible applicability, the app-based multimodal treatment *zanadio* might alleviate the present care gap for patients with obesity in Germany.

INTRODUCTION

According to current estimates, 23% of adults in the WHO European region are living with obesity (body mass index [BMI] ≥ 30 kg/m^2). Obesity is defined as an excess accumulation of body fat that can affect health at various levels [1]. It is a major risk factor for physical and mental comorbidities, including type 2 diabetes, hypertension, coronary heart disease, anxiety disorders, and depression [2-4]. In conjunction with these factors, obesity negatively impacts well-being and quality of life (QoL) [5-7]. A timely treatment of obesity is therefore indicated. Studies have shown that a weight reduction of 5% can already reduce the risk of obesity-associated health problems and

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improve well-being and QoL and, therefore, is of clinical relevance [8-10].

According to current international and national guidelines [8,11] conservative obesity treatments should include gradual weight reduction through nutritional, behavioral, and exercise therapeutic interventions. The combination of these domains has been shown to be more effective than treatments comprising only one domain [8,12,13]. Unfortunately, multimodal treatment options are not available for a large number of patients because of a lack of local availability of treatment centers, high and inflexible time expenditure, and insufficient cost coverage by patients' health insurance companies [14]. Digital treatments offer a chance to lower these access barriers because they can be used independent of time and patients' residence. Superior treatment effects of multimodal digital programs have been confirmed, just as for analog programs [12-14].

In Germany, digital health applications with proven positive health effects that are certified as medical devices and approved by the German Federal Institute for Drugs and Medical Devices (BfArM) are fully covered by health insurers. *zanadio* (certified medical device; aidhere GmbH, Hamburg, Germany) is an app-based, multimodal treatment program for patients with obesity. The program follows current national guidelines for conservative obesity treatment, focusing on evidence-based interventions from the areas of nutrition, exercise, and behavioral therapy [8]. It aims to empower patients in self-management and lifestyle change to achieve a clinically relevant weight loss (>5% of initial body weight) within 12 months and to reduce the negative health impacts of obesity [15].

This study aimed to evaluate *zanadio* and to quantify the medical benefits of the program in order to achieve approval by the BfArM. A two-arm, randomized-controlled trial was conducted, in which half of the participants used *zanadio* for 12 months (intervention group [IG]), whereas the other half did not receive access to the app (control group [CG]). We hypothesized that the IG would show a clinically relevant and significantly higher weight loss after 12 months than the CG. Additionally, it was hypothesized that the IG, in contrast to the CG, would demonstrate a significant reduction of visceral body fat (i.e., reduction in waist to height ratio [WHtR]) and significant improvements in well-being and QoL.

Study Importance

What is already known ?

- A weight loss of 5% can reduce adverse health impacts of obesity.
- Conservative treatments that combine nutritional, physical, and psychological interventions are most effective for the treatment of obesity.
- Affordable or free of charge treatment options for individuals with obesity are still scarce.

What does this study add?

- The app-based, multimodal treatment for patients with obesity *zanadio* led to a significant and clinically relevant weight loss (>5%) within 12 months.
- Moreover, *zanadio* helped participants to significantly improve their well-being, quality of life, and waist to height ratio.
- Overall, this study shows that digital treatments such as *zanadio* can be an effective tool for weight management with low-access barriers to treat obesity.

How might these results change the direction of research or the focus of clinical practice?

- The results of the study suggest that digital multimodal interventions for weight loss could help alleviate the care situation for patients with obesity.
- Further work should focus on identifying which parts of digital interventions drive weight loss and how these elements can be individualized and weighted to achieve the best possible outcome for different individuals.

METHODS

Study design and participants

The study is a prospective, parallel-group, randomized-controlled clinical trial. The research protocol was approved by the Ethics Committee of the University of Leipzig (511/20-ek; Leipzig, Germany). The trial was conducted in accordance with the Declaration of Helsinki and was registered at the German Clinical Trials Register (DRKS00024415). All participants gave written informed consent to participate in the study.

Participants were recruited between January and March 2021 via a study website, which was part of the official, publicly accessible *zanadio* website, hosted by the manufacturer. Individuals interested in the *zanadio* program specifically or digital weight loss programs in general were likely to find the website, where the study was advertised. Patients interested in participating were redirected to a brief survey on the platform SoSci, implemented by the University of Leipzig. This survey included questions about patients' gender, age, weight, and height. Before final enrollment, individuals fulfilling the key inclusion criteria (age: 18-65 years, BMI: 30-40) were interviewed by trained study personnel via telephone and screened for eligibility (inclusion and exclusion criteria in Table 1). The study period (i.e., 12 months) varied depending on the date of randomization. The date of the first patient in was January 22, 2021, and the date of the last patient out was March 5, 2022.

Randomization

Eligible participants were randomly assigned by a trained study coordinator to the IG or CG using a sequential, stratified randomization approach

to ensure equal distribution of potentially moderating variables, i.e., BMI (strata: obesity class I and II) and age (strata: 18-34, 35-49, and 50-65 years) across both groups. Study participants were not blinded because of the nature of the intervention. Similarly, study personnel were unblinded because they provided all relevant information to IG participants and, if necessary, assisted with account activation.

Intervention

The treatment program *zanadio* is a smartphone application that has been developed to treat patients with obesity (*International Classification of Diseases, Tenth Revision* [ICD-10] code E66). The recommended treatment duration is 12 months. At the time of data collection, the app was preliminarily approved by the BfArM to be used by individuals with BMI of 30 to 40 [15].

TABLE 1 Inclusion and exclusion criteria for participating in the *zanadio* trial

Inclusion criteria	Exclusion criteria
• Individuals with obesity (all genders; BMI: 30-40 kg/m^2, age: 18-65 years), ICD-10 diagnosis E66.00 and E66.01; classification according to EOSS level 0-2 • Ownership of a mobile device • Fluency in written and spoken German	• Patients in preparation for bariatric surgery or after bariatric surgery (gastric bypass, gastric reduction, gastric banding, or similar; past 3 years) • Advanced concomitant physical diseases (corresponding to EOSS level 3) • Acute untreated or unstable mental disorders • Current pregnancy or pregnancy planned within next 12 months • Presence of secondary forms of obesity (Cushing syndrome, Prader-Willi syndrome, hypogonadism, etc.) • Hypothyroidism if not treated with medication in advance • Lack of change resources • Physical limitations that do not allow moderate independent physical activity

Abbreviations: EOSS, Edmonton Obesity Staging System; ICD, International Classification of Diseases.

In line with present guidelines for treating obesity [8], *zanadio* aims to support individuals with obesity to develop a healthy lifestyle that supports a sustainable weight loss. The multimodal approach includes validated methods from behavioral science, exercise therapy, and nutrition, which are implemented in different features of the health application and which can be categorized into the following subareas: 1) knowledge transfer; 2) change; and 3) motivation and support. Further information regarding the methods implemented in the app have been recently reported [15], as summarized in the online Supporting Information Methods.

Experimental procedure

After randomization, participants were invited for the baseline assessment. Following that, participants in the IG received full access to the *zanadio* app over a period of 12 months, whereas participants in the CG did not. The latter were instructed to continue their lives as usual, which could include self-initiated or externally initiated weight loss attempts. Information about such weight loss attempts was assessed via online questionnaires. This design was chosen to represent the current health care situation in Germany, where patients with obesity have to find and choose accessible weight loss offers themselves. The CG was offered to use *zanadio* for 12 months after the active trial phase. All participants received a compensation of €50.

Primary and secondary outcomes were collected at five time points (Figure 1) via a structured telephone interview that was conducted by trained study personnel at baseline and 3, 6, 9, and 12 months after baseline assessment (+/− 1 week). Demographic data and psychological measures (well-being and QoL) were assessed via online surveys administered using SoSci (https://www.soscisurvey.de/en/index). A personalized link to access the online questionnaires was sent after the telephone interview. Participants were instructed to fill out the questionnaires as soon as possible.

Outcomes

The primary end point was defined as the percentage weight change from baseline (T0) to 12 months (T4). Participants were instructed to measure their body weight in the morning before breakfast with light clothing and by using the same scale throughout the study.

FIGURE 1 Study design of the *zanadio* trial. End points were assessed at baseline (T0) and after every 3 months (T1-T4) for up to 12 months.

To further quantify the beneficial effects of *zanadio*, the following secondary variables were defined: changes in 1) body fat distribution; 2) well-being; and 3) QoL from baseline (T0) to 12 months (T4).

Body fat distribution is an indicator of metabolic and cardiovascular health risks. Visceral fat mass correlates particularly high with obesity-associated diseases such as cardiovascular events, diabetes, or hypertension [16-18] and, therefore, was evaluated using WHtR (waist circumference in centimeters divided by body height in centimeters). Participants were instructed to measure their waist circumference at navel height while standing and with or without light clothing. To ensure reliability of the assessment, participants were provided with standardized and detailed information on how to measure their waist circumference in advance and again during data collection. Well-being was assessed using the WHO-5 Well-Being Index (WHO-5) [19]. The questionnaire contains five items requiring participants to rate their opinion on a scale from 0 to 5. The sum score of the items (range 0-25) was calculated. A value above 13 indicates good well-being, whereas a value below 13 suggests impaired well-being [20].

To measure general, disease-independent QoL, we used the WHOQOL-BREF questionnaire [21], which is a 26-item questionnaire in which each item can be rated on a Likert scale (1 to 5 points). Overall QoL is assessed using a global score based on two generic questions. The questionnaire further addresses four QoL domains: "physical health," "psychological health," "social relations," and "environment." For each domain, as well as overall QoL, a score was calculated (sum of item scores divided by the number of domain items, multiplied by 4) [22]. Subsequently, each of the five scores were converted into a scale from 0 to 100, in which 0 points indicates the worst and 100 points indicates the best possible state regarding the respective domain or overall QoL (i.e., global score) [23]. In this study, the global score was used in the main analysis. The results of the four QoL domains are shown in Supporting Information Figure S1 in order to explain changes in overall QoL.

Sample size calculation

To determine the sample size, a power analysis was carried out using G × Power [24]. Based on effect sizes reported in a meta-analysis of randomized-controlled trials of digital weight loss programs [13] and the evaluation of a multimodal, on-site treatment program [10], an effect size of Cohen $f = 0.15$ was expected for the *time* × *group* interaction. Using the parameters $\alpha = 0.05$, 1-ß = 0.95, and $f = 0.15$, a total of 116 participants ($n = 58$ per group) was estimated. Longitudinal trials in general and weight reduction trials in particular face relatively high dropout rates [10,25,26]. To allow for up to 30% attrition, the total sample size was increased to 150 ($n = 75$ per group).

Statistical analyses

Statistical analyses were performed using R version 4.1.0 within Rstudio version 2021.09.1. Along with descriptive statistics of baseline data, intention-to-treat (ITT) analyses as well as per-protocol (PP) analyses were conducted for all end points. The PP sample excluded participants who did not comply with the study protocol, e.g., participants who did not use the app at least once a month. The primary confirmatory analysis was performed based on the ITT principle, which included all participants who were randomized regardless of protocol compliance. Missing data due to noncompliance or dropout were imputed using multiple imputation using the copy reference method [27], with $n = 100$ imputations [28]. The R package *RefBasedMI* version 0.0.23 was used to build separate imputation models to each end point variable (including the factors time and group and all covariates as predictors, i.e., age, gender, education level, and BMI at T0) [29, 30] and to generate imputed data. Under the assumption that, after dropout, participants of the IG no longer receive treatment and are thus comparable with the CG, monotone missing values of the IG were imputed with data based on parameters of the CG. Interim missing data were assumed to be missing completely at random and were therefore imputed based on estimates from the IG itself. For the CG, all missing data were replaced based on parameters of the CG itself. In general, imputation was performed using raw values of the respective end points (e.g., weight in kilograms). The transformation into percent weight change for the primary end point and the change from baseline for all secondary end points, respectively, was performed later. A linear mixed model was fitted to each of the resulting imputed data sets and subsequently pooled using a multivariate Wald test [29, 31]. Each linear mixed model included the fixed factors *time* (T1 to T4) and *group* (IG, CG), a *group* × *time* interaction term, and a random intercept for *subject*. In addition, age, gender, education level, and BMI at T0 were entered as covariates of no interest. Note that BMI at baseline was not included when analyzing WHtR because of significant correlations between both variables ($r = -0.70$, $p < 0.001$). For each secondary end point, the model further comprised the baseline value of the respective end point. All results will be reported as mean, standard deviation [SD] and 95% confidence interval [CI] (adjusted for the previously mentioned covariates). Hypotheses testing was performed using the function *emmeans* version 1.7.2. Contrasts were used to statistically compare groups. Changes in primary and secondary end points within the IG were tested using one-sided one-sample *t* tests with the parameters mu = 5 for the primary end point and mu = 0 for each secondary end point using *emmeans::test*. Multiplicity adjustment (false discovery rate [FDR]) [32] was applied separately for the primary and secondary end points. Cohen *d* and 95% CI will be reported as effect sizes, calculated based on the *t* values from contrasts and one-sample *t* tests.

RESULTS

Participant characteristics and participant flow

After assessment of eligibility, $N = 150$ patients were enrolled in the study and randomized into the IG or CG. One participant immediately withdrew consent to study participation and to use any data obtained

so far. Therefore, the final sample comprised 76 IG participants and 73 CG participants. Figure 2 shows the participant flowchart, including reasons for exclusions. The difference among the sample size for the PP analysis and missing data is due to protocol deviation, as described earlier. One participant of the CG used *zanadio* and thereby deviated from the protocol.

At baseline, study participants had an average age of 43.4 years (SD = 10.9). The average baseline weight was 102.5 kg (SD = 13.4),

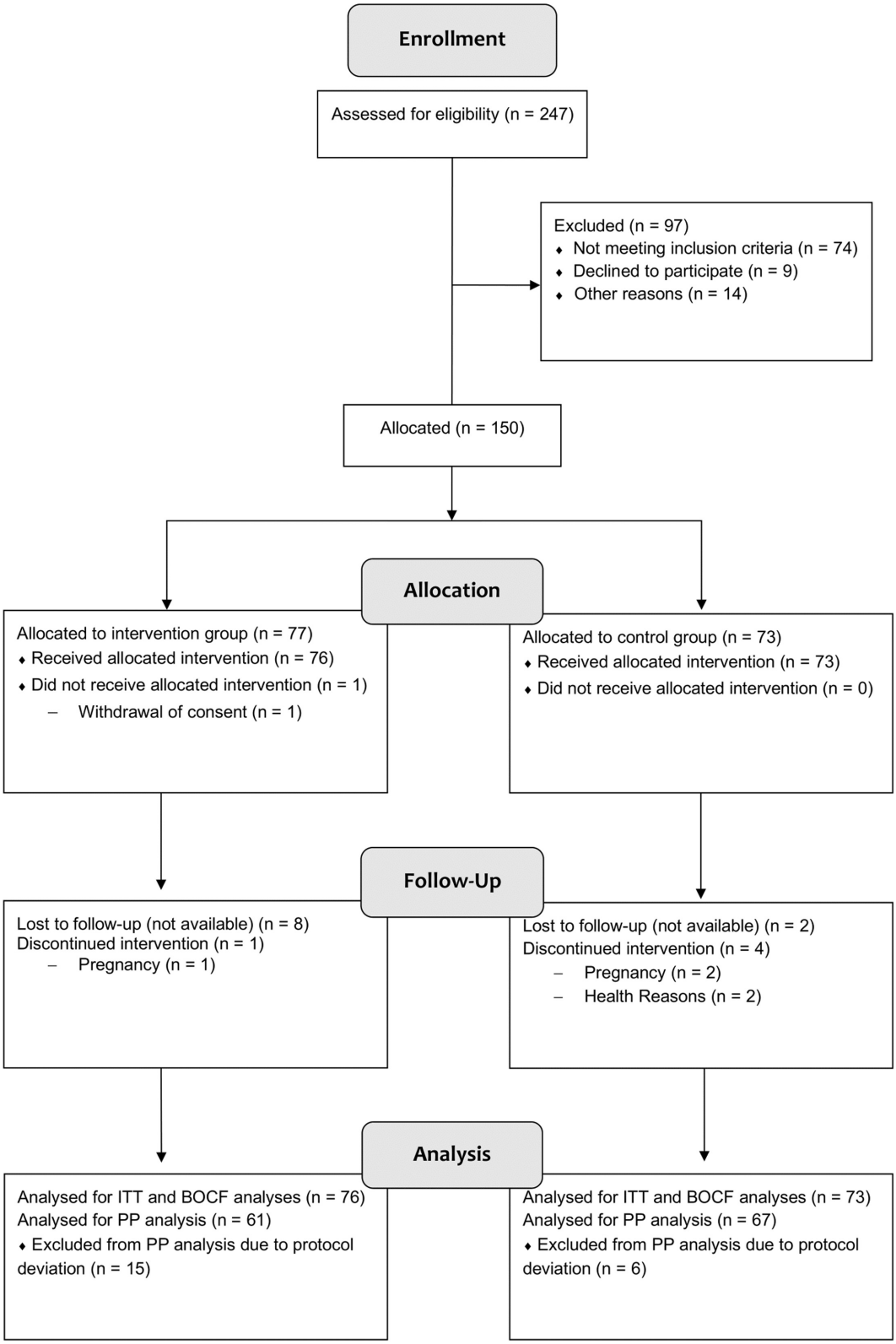

FIGURE 2 Participant flowchart. BOCF, baseline observation carried forward; ITT, intention-to-treat; PP, per-protocol

and the average baseline BMI was 35.8 (SD = 3.2). A total of 91.3% of the sample were female. Overall, both groups were comparable regarding demographic data and initial values of end points (Tables 2 and 3).

Primary end point

At T4, data from 135 patients were obtained (IG: 88.2%; CG: 93.2%). The PP analysis includes $n = 129$ patients (IG: 80.3%, CG: 91.8%).

TABLE 2 Demographic characteristics of the randomized sample at T0

	IG ($n = 76$)	CG ($n = 73$)
Gender		
Female	69 (90.7)	67 (91.8)
Male	7 (9.2)	6 (8.2)
Age (y) /BMI (kg/m^2)		
18-34/30-34.99	4 (5.3)	7 (9.6)
18-34/35-40	11 (14.5)	13 (17.8)
35-49/30-34.99	14 (18.4)	14 (19.2)
35-49/35-40	22 (28.9)	20 (27.4)
50-65/30-34.99	13 (17.1)	11 (15.1)
50-65/35-40	12 (15.8)	8 (11.0)
Educational level		
Lower secondary	5 (6.5)	1 (1.4)
Secondary	25 (32.9)	21 (28.8)
Higher secondary	12 (15.8)	19 (26.0)
Degree course	27 (35.5)	23 (31.5)
Other	7 (9.2)	9 (12.3)
Shift work		
Yes	14 (18.4)	9 (12.3)
No	62 (81.6)	62 (84.9)
NA	0	2 (2.7)
Marital status		
Married/in partnership	54 (71.1)	56 (76.7)
Divorced/widowed	6 (7.9)	6 (8.2)
Single	16 (21.1)	9 (12.3)
NA	0	2 (2.7)
Children		
Yes	48 (63.2)	43 (58.9)
No	28 (36.8)	28 (38.4)
NA	0	2 (2.7)

Note: Data given as *n* (%). At the time of participant screening, i.e., at study inclusion, all study participants fell within the intended BMI range (30-40 kg/m^2). Because screening and baseline measurements (T0) could be several weeks apart, few study participants fell below or exceeded the intended BMI range at T0 (BMI range: IG = 27.2-42.6, CG = 27.1-41.2). This did not lead to the exclusion of participants.
Abbreviations: CG, control group; IG, intervention group; NA, missing values.

ITT analysis

Based on the ITT sample, the IG participants lost, on average, −7.75% (95% CI: −9.66% to −5.84%) of their initial body weight after 12 months, whereas the weight of the CG did not change (mean = 0.00% [95% CI: −1.98% to 1.99%]). The statistical analysis yielded significant main effects and interactions of the factors group and time and a significant effect of the covariate gender (Supporting Information Table S1). As hypothesized, the IG showed a weight reduction of more than 5% ($t[168] = -2.846$, $p_{FDR} = 0.003$, $d = -0.44$ [95% CI: −0.74 to −0.13]), which was significantly higher compared with the CG (mean difference = −7.75 [95% CI: −9.61 to −5.89]; $t[216] = -8.156$, $p_{FDR} < 0.001$, $d = -1.11$ [95% CI: −1.40 to −0.82]; Figure 3). Information on participants achieving a clinically relevant weight loss of at least 5% and 10% is given in Figure 4 and Supporting Information Table S2.

PP analysis

Based on the PP sample, participants in the IG lost, on average, −7.95% (95% CI: −9.89% to −6.01%) of their initial body weight, whereas the weight of the CG only slightly changed (−0.17% [95% CI: −2.14% to 1.80%]; Figure 3). The PP analysis showed a significant main effect of group and a significant interaction among the factors group and time and of the covariate gender (Supporting Information Table S1). A one-sample *t* test showed that the IG participants had lost significantly more than 5% of their initial body weight ($t[148] = -3.002$, $p_{FDR} = 0.002$, $d = -0.49$ [95% CI: −0.82 to −0.17]) and significantly more than the CG ($t[184] = -8.182$, $p_{FDR} < 0.001$, $d = -1.21$ [95% CI: −1.52 to −0.89]).

Secondary end points

ITT analysis

The ITT analysis for WHtR showed a significant main effect of the factor group (Supporting Information Table S3). All other main effects and interactions of the secondary end points did not reach significance. The covariate age as well as the respective baseline values for each secondary end point was significant (Supporting Information Table S3). Planned contrasts confirmed significant improvements for all secondary end points in the IG from baseline to 12 months, which were significantly stronger in the IG than the CG for the end points well-being and WHtR (Table 4).

PP analysis

For the PP analysis of the secondary end points, further participants were excluded when secondary end point data were not available at 12 months. Therefore, the PP sample included 116 patients (IG:

TABLE 3 Further demographic and outcome characteristics of the randomized sample at T0

	IG ($n = 76$), *n* (NA)	CG ($n = 73$), *n* (NA)	IG			CG		
			M (SD)	Var	Min-Max	M (SD)	Var	Min-Max
Age	76 (0)	73 (0)	43.8 (10.6)	117.8	20-64	42.9 (11.1)	117.8	22-65
BMI (kg/m^2)	76 (0)	73 (0)	36.0 (3.1)	9.6	27.2-42.6	35.6 (3.4)	11.3	27.1-41.2
Primary end point								
Body weight (kg)	76 (0)	73 (0)	102.2 (12.3)	150.8	80-135	103.0 (14.6)	212.1	74.6-139.6
Secondary end point								
WHtR	75 (1)	72 (1)	0.93 (0.1)	0.0	0.8-1.1	0.9 (0.1)	0.01	0.7-1.2
QoL	76 (0)	71 (2)	55.6 (18.0)	322.5	12.5-100	54.6 (16.7)	277.9	25.0-100
Well-being	76 (0)	71 (2)	12.2 (5.1)	25.7	1-25	11.7 (4.6)	20.8	3-21

Note: As the primary end point of weight development cannot be calculated at T0, body weight at T0 is reported instead.
Abbreviations: CG, control group; IG, intervention group; M, mean; Max, maximum; Min, minimum; NA, missing values; QoL, quality of life; Var, variance; WHtR, waist to height ratio.

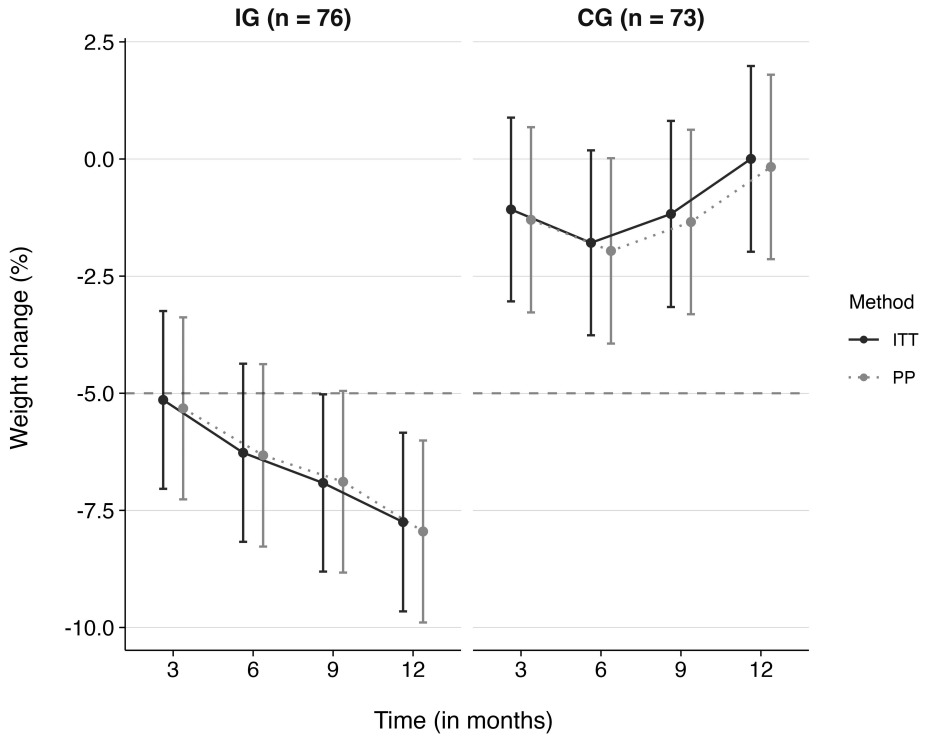

FIGURE 3 Percentage weight change in the IG and CG during the study phase. Adjusted mean values and 95% CI are given for the per-protocol and intention-to-treat analyses for the IG and the CG and each measurement point (T1 to T4, i.e., month 3, 6, 9, and 12). The area below the dashed line indicates a clinically relevant weight loss of 5%. CG, control group; IG, intervention group

$n = 55$; CG: $n = 61$) for well-being and QoL and 121 patients (IG: $n = 58$; CG: $n = 63$) for WHtR.

PP analyses revealed significant main effects for the factor group on WHtR and the factor time on QoL (Supporting Information Table S4). Again, the covariates age and the respective baseline values for each end point were significant. Planned contrasts confirmed significant improvements for the IG in all secondary end points within 12 months. However, compared with the CG only, the WHtR decrease was significantly stronger in the IG (Table 4).

DISCUSSION

This study investigated the care effects of *zanadio*, an app-based, multimodal program for the treatment of obesity. The primary goal of the treatment program is a weight reduction of at least 5% from baseline weight within 12 months.

The study demonstrated that participants using *zanadio* lost, on average, 7.75% of their initial body weight, confirming that the digital treatment program successfully supported patients with obesity in reducing their excess body weight. More than half of the patients

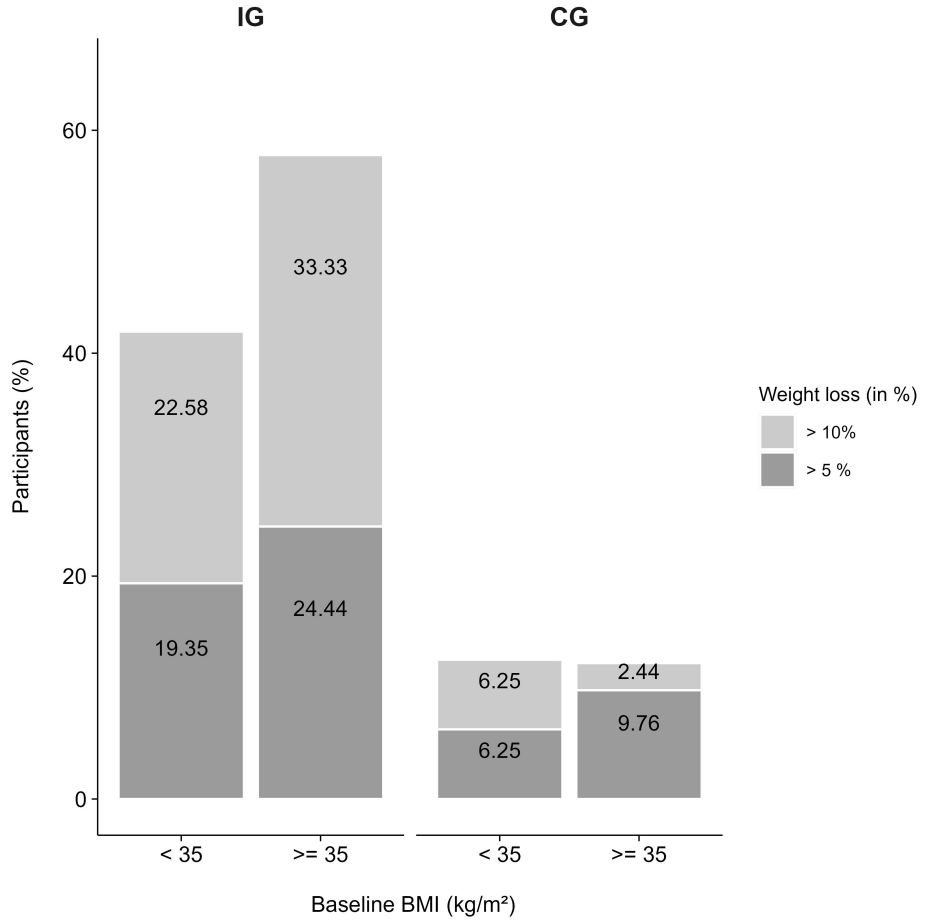

FIGURE 4 Percentage of participants showing at least 5% and 10% weight loss after 12 months. Percentages are given by group (IG, CG) and baseline obesity grade (grade I: baseline BMI < 35 kg/m^2 and grade II: baseline BMI > 35 kg/m^2). Percentages are based on the intention-to-treat analysis and adjusted for covariates. CG, control group; IG, intervention group

who have used *zanadio* for 12 months achieved a clinically relevant weight reduction of at least 5%, assumed to be associated with further health improvements [8-10]. This was achieved by only 12% of the CG participants, who were also free to start weight loss attempts during the study phase. Consistent with previous studies, self-initiated weight reduction attempts led to an initial weight loss in the CG, which, however, was not maintained over the course of the study [33]. In fact, a large proportion of the CG participants showed an increase in weight during the study period, and some even progressed to obesity grade III (BMI = 40-45 kg/m^2; Supporting Information Figure S2).

The effects on weight change observed in this study are similar or even stronger than those of comparable multimodal analog treatment programs. Randomized-controlled trials and observational studies for in-person treatments have demonstrated weight reductions of 3.8% to 6.0% within 12 months [10, 34, 35]. The average weight reduction of 7.75% lies well within the range of other effects reported for digital treatments (e.g., Noom: −0.2% [36]; ABC: −11.4% [37]). However, direct comparisons among different digital treatment programs are of limited validity because these interventions are heterogeneous with respect to treatment duration, additional on-site treatments, low-caloric diets, and intended users (e.g., BMI range, comorbidities). Furthermore, existing studies vary methodologically, and evidence is often based on prospective observational studies only, whereas randomized-controlled trials are lacking.

All other additional end points demonstrated positive health effects of *zanadio*. WHtR, an approximate measure of accumulated visceral body fat, was significantly reduced in the IG. Future studies should aim at collecting objective parameters to gather detailed information about changes in body composition (i.e., loss of fat [-free] mass), using, for instance, bioelectrical impedance analysis. The IG further showed significant improvements in the psychological factors well-being and QoL. Although well-being improvements were significantly stronger in the IG compared with the CG (ITT analysis), improvements in overall QoL did not significantly differ between groups. Several reasons might account for this, such as the use of a generic but commonly used QoL questionnaire. Using a questionnaire assessing obesity-specific QoL might capture treatment-related improvements more accurately. The repeated changes among COVID-19-related lockdowns and more relaxed phases during the study phase are an extraordinary external influence that might have superimposed treatment effects. In fact, COVID-19-related lockdowns seemed to have negatively affected well-being of patients with obesity also because they were more likely to engage in negative

TABLE 4 Results of the planned contrasts of the secondary end points well-being, QoL, and WHtR after 12 months for the intention-to-treat and the per-protocol sample

		Statistic				
Variable	**Hypothesis**	**Estimate (95% CI)**	***t***	**df**	***p*FDR**	***d* (95% CI)**
Intention-to-treat						
Well-being	IG: T0 < T4	1.57 (0.05 to 3.08)	2.040	203	0.026*	0.29 (0.01 to 0.56)
	IG > CG	1.77 (0.31 to 3.23)	2.380	309	0.026*	0.27 (0.05 to 0.49)
QoL	IG: T0 < T4	7.93 (5.20 to 10.66)	3.074	253	0.002**	0.39 (0.14 to 0.63)
	IG > CG	1.60 (−3.55 to 6.75)	0.609	421	0.543	0.06 (−0.13 to 0.25)
WHtR	IG: T0 < T4	−0.04 (−0.05 to 0.02)	−5.040	198	<0.001***	−0.72 (−1.00 to −0.43)
	IG < CG	−0.03 (−0.04 to −0.01)	−3.768	296	0.001**	−0.44 (−0.67 to −0.21)
Per-protocol						
Well-being	IG: T0 < T4	1.51 (−0.10 to 3.13)	1.848	162	0.050.	0.30 (−0.02 to 0.61)
	IG > CG	0.93 (−0.66 to 2.52)	1.144	234	0.304	0.15 (−0.11 to 0.41)
QoL	IG: T0 < T4	8.49 (2.96 to 14.01)	3.016	174	0.006**	0.46 (0.16 to 0.76)
	IG > CG	2.29 (−3.32 to 7.90)	0.799	276	0.424	0.10 (−0.14 to 0.33)
WHtR	IG: T0 < T4	−0.04 (−0.05 to −0.05)	−5.126	161	<0.001***	−0.82 (−1.14 to −0.50)
	IG < CG	−0.03 (−0.05 to −0.02)	−3.974	264	<0.001***	−0.52 (−0.78 to −0.26)

Abbreviations: CG, control group; df, degrees of freedom; IG, intervention group; FDR, false discovery rate; QoL, quality of life; T0, baseline value; T4, final assessment value after 12 months; WHtR, waist to height ratio.
Significance codes: ***< 0.001, **< 0.01, *< 0.1.

health-related behaviors such as unhealthier eating, less exercise, and impaired sleep [38]. The QoL subdomains in the current study (Supporting Information Figure S1), mental health in particular, showed a more favorable progression for the IG than the CG.

Although obesity prevalence in Germany does not differ significantly between genders [1], the present study sample included mainly women. An overrepresentation of women is common in weight reduction studies [25, 26], and it might be explained by men perceiving obesity as a problem later than women, the latter being more aware of their own body weight and more likely to seek treatment [39, 40]. In line with this, digital health applications, regardless of their indication, but also *zanadio* itself, are used mainly by women [15, 41]. In the current study, the effect of the covariate gender was significant, indicating overall higher weight loss for male participants. Because of the small male sample, whether this effect was driven by the IG cannot be statistically investigated. Despite the unequal gender distribution in the present study, the validity and transferability of the results to male patients can be assumed because studies have reported either no gender differences in weight loss or marginally stronger effects in male patients [42]. This is also reflected in the present German guidelines, which emphasize patient-centered treatments rather than gender-specific treatments [8].

Long-term weight loss studies often face high dropout rates [10, 26], making it hard to estimate realistic effects of an intervention. Digitalized treatments might be a tool to increase adherence because they can be used in a way that best suits the patients' needs and schedules. In fact, the dropout rate in the IG, 19.7% after 12 months, was considerably lower than the expected dropout rate of 30% and dropout rates reported in other weight loss studies, ranging from 26.8% to 39% [26] in the IGs. The most frequent reasons for dropout in the present study were, apart from unexplained inaccessibility at the scheduled measurement times, pregnancies in both study groups. Reasons for protocol deviations included highly time-consuming or challenging events in private or professional life (e.g., own or significant others' illness, stress due to the COVID-19 pandemic). Only in a few cases, dropout was justified by the amount of time required for the program, thereby indicating good acceptance of the digital treatment. A long-term treatment using digital tools seems feasible to successfully implement new behaviors and pursue health-related goals.

This study had some limitations. It lacks an alternative active treatment for the CG; however, this design allows a comparison between *zanadio* and care-as-usual in the German health care system, in which most patients with obesity do not have access to structured treatment programs. Furthermore, we cannot exclude some kind of selection bias because patients might have already been interested in using digital weight loss interventions before they self-registered for study participation. Consequently, this sample might have been particularly motivated and digitally savvy compared with the general patient with obesity. Participants of the CG were granted access to *zanadio* after 1 year, which might have diminished their motivation to lose weight within the first study year. As assessed retrospectively in the final online questionnaires, most of the CG participants ($n = 50$; 68.5%) tried to change their diets and increase their physical activity, partly using alternative (online) programs. Structured information on whether participants of the IG used additional programs is lacking and will be assessed in future studies. Anthropometric measures were assessed and reported by patients. Although studies have shown that

women especially tend to over- or underreport their weight and waist or hip circumferences, high correlations among measurements taken by study personnel and self-reported values were reported [43]. To overcome this potential source of bias, participants could be equipped with Bluetooth scales to automatically track their weight or attend study visits in person.

CONCLUSION

The app-based, multimodal obesity treatment *zanadio* has been shown to help patients with obesity achieve a significant and clinically relevant weight loss within 12 months and significant improvements in body fat distribution, well-being, and QoL. Being a certified digital treatment program, it represents a low-threshold and widely accessible treatment offer for patients with obesity in Germany that might alleviate the present care gap for this patient group. A study including male and female patients with BMI values of 30 to 45 kg/m^2 is currently being carried out (German Clinical Trials Register DRKS00029070) to replicate and extend the previous clinical trial. Further studies should assess treatment effects on physiological values (i.e., blood pressure, body fat percentage) and identify app- and patient-related drivers of treatment success. This knowledge will help us to better understand the chronic disease obesity and to improve its treatment by providing individually tailored treatments.O

AUTHOR CONTRIBUTIONS

Annette Horstmann and Nora Mehl planned and conceptualized the study. Annette Horstmann and Madeleine Ordnung wrote the statistical analysis plan. Madeleine Ordnung and Lena Roth acquired and analyzed data according to the statistical analysis plan. Annette Horstmann supervised the work. Lena Roth and Katarina Forkmann drafted the manuscript. Lena Roth and Madeleine Ordnung designed the figures. All authors discussed and interpreted the results, edited the manuscript, and approved the final version.

ACKNOWLEDGMENTS

We would like to thank Jenny Schalk for study support. Deidentified data, the study protocol, and the statistical analysis plan will be available upon request to the primary investigator. Please contact the primary investigator to complete a use agreement for access to these resources. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This study was supported by aidhere GmbH. The funders (aidhere GmbH) had no role in the design of the clinical trial, the data collection, or analyses of clinical trial data. Annette Horstmann and Madeleine Ordnung received payment from the University of Leipzig.

CONFLICT OF INTEREST STATEMENT

Katarina Forkmann and Lena Roth are employees of aidhere GmbH. Nora Mehl is an employee and founder of aidhere GmbH. The other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

German Clinical Trials Register DRKS00024415.

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SUPPORTING INFORMATION

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

How to cite this article: Roth L, Ordnung M, Forkmann K, Mehl N, Horstmann A. A randomized-controlled trial to evaluate the app-based multimodal weight loss program *zanadio* for patients with obesity. *Obesity (Silver Spring)*. 2023; 31(5):1300-1310. doi:10.1002/oby.23744