Pilot and Feasibility Studies

RESEARCH

Open Access

A pilot sequential multiple assignment randomized trial for developing a biobehavioral adaptive intervention to improve insulin sensitivity in patients with stage 1 obesity

Aseel El Zein[1], Katie M. Ellison[1], Julianne G. Clina[3], Chelsi Reynolds[1], Caroline W. Cohen[1], James O. Hill[2], Gareth R. Dutton[4], Tapan S. Mehta[1] and R. Drew Sayer[1*]

Abstract

Background Intervention packages targeting obesity-related conditions often include multiple behavioral and pharmacological components, yet the independent and synergistic effects of these strategies on disease progression remain largely unexplored. Adaptive interventions offer a structured approach to tailoring treatments based on individual responses, but feasibility data in primary care settings are limited. The objective of this pilot Sequential Multiple Assignment Randomized Trial (SMART) was to investigate the feasibility of a 25-week adaptive biobehavioral intervention designed to improve insulin sensitivity among patients with stage 1 obesity.

Methods Forty participants were initially randomized to either nutrition counseling (NC) or exercise counseling (EC), both employing a weight-neutral approach. At week 8, insulin sensitivity was reassessed using the Quantitative Insulin Sensitivity Check Index (QUICKI). Participants with a > 5% improvement were classified as responders, while non-responders were re-randomized to either augment their first-stage intervention with metformin or switch to weight loss counseling (WLC). Feasibility outcomes included recruitment and retention, adherence to intervention components, and preliminary treatment effect estimates.

Results Findings support the overall feasibility of the SMART design, with high adherence to virtual counseling sessions and favorable participant retention. The study effectively differentiated responders from non-responders at week 8, with responders showing greater improvements in insulin sensitivity. Among non-responders, WLC and metformin provided a potential rescue effect, but overall insulin sensitivity remained lower than at of responders. While NC and WLC were preferred over EC and metformin, adherence to counseling sessions remained high across all interventions, regardless of preference. Metformin adherence posed challenges due to frequent gastrointestinal side effects and difficulties tracking usage.

Conclusions This pilot study supports the feasibility of an adaptive biobehavioral intervention for improving insulin sensitivity among adults with obesity in a primary care setting. However, further refinement is needed to enhance clinical integration, optimize intervention messaging, and improve medication tracking. Findings from this study will inform a second pilot SMART, laying the foundation for a full-scale primary-care embedded intervention delivering personalized, adaptive strategies for improving cardiometabolic health.

*Correspondence:
R. Drew Sayer
sayerd@uab.edu
Full list of author information is available at the end of the article

Trial registration NCT04392283 on April 19th, 2020.

Keywords Obesity, Insulin sensitivity, Adaptive intervention, Biobehavioral intervention, Nutrition counseling, Exercise counseling, Metformin, Primary care, Sequential Multiple Assignment Randomized Trial (SMART), Personalized treatment, Cardiometabolic Health

Key messages regarding feasibility

- What uncertainties existed regarding the feasibility?

This pilot Sequential Multiple Assignment Randomized Trial (SMART) assessed key feasibility parameters to inform the design of a larger trial. Specifically, it examined the suitability of the recruitment strategies in achieving adequate enrollment within the study timeline, the appropriateness of conducting the SMART within a family medicine clinic, and the adherence to intervention components including attendance at counseling sessions and medication adherence. Additionally, there were uncertainties regarding the acceptability and feasibility of weight-neutral nutrition and exercise counseling as first-stage interventions, and behavioral weight loss counseling and metformin use as second-stage interventions for early non-responders. Another key uncertainty was whether the study's predefined response criterion > 5% improvement in the Quantitative Insulin Sensitivity Check Index (QUICKI) after 8 weeks, would effectively differentiate responders from non-responders. Addressing these uncertainties provided critical insights into the practicality of study design and procedures, informing necessary modifications for a future trial.

- What are the key feasibility findings?

The findings suggest that the SMART design is feasible for adults with stage 1 obesity, with several key strengths while highlighting areas for improvement. Participant adherence to counseling sessions was high, and retention rates exceeded feasibility benchmarks, reflecting strong overall engagement. However, metformin adherence presented some challenges with over half of participants reporting gastrointestinal discomfort. The study successfully differentiated responders from non-responders using QUICKI as an early indicator of insulin sensitivity improvements. Despite the effectiveness of weight-neutral strategies for some participants, they did not resonate as well with those who strongly preferred interventions explicitly focused on weight loss, underscoring the need for clearer intervention messaging. Additionally, the study highlighted the importance of better integration of the intervention within the clinical workflow of primary care settings, suggesting that more streamlined protocols could enhance implementation, scalability, and long-term clinical applicability.

- What are the implications of the feasibility findings for the design of the main study?

Findings from this pilot study highlighted the need for additional pilot and feasibility work before proceeding with a full-scale SMART. Insights informed key modifications, which will be tested in the next pilot SMART. To enhance clinical integration, the next trial will align research visits with clinical appointments, and train clinic staff to assist with study procedures. Messaging will be refined to clearly differentiate weight-focused and weight-neutral interventions. Alternative methods will be explored to improve medication adherence tracking, and a qualitative specialist will assess participant experiences with weight loss vs. weight-neutral approaches. These refinements will strengthen feasibility and scalability in broader clinical settings and advance the development of adaptive, personalized strategies for managing insulin resistance in patients with obesity.

Background

Behavioral weight loss interventions have long been the cornerstone of obesity treatment, despite consistent evidence that most individuals successful with initial weight loss will regain the majority of it within 3 years [1]. These intervention packages typically encompass multiple components —such as improving diet quality, reducing energy intake, and increasing physical activity—yet little is known about how lifestyle changes interact with medications commonly prescribed to treat obesity-related chronic conditions. For example, while some evidence suggests that metformin, a first-line treatment for type 2 diabetes, may blunt expected exercise-induced improvements in glycemic control [2–4], other studies report additive benefits when combined with long-term physical activity [5, 6]. Meanwhile, the recent—and conflicting—prominence of both pharmacological treatments for obesity [7] alongside weight-neutral approaches to improve health and well-being [8], further challenges the

nearly exclusive reliance on traditional behavioral interventions. Collectively, these factors, along with the limited long-term success of behavioral approaches and the complex interplay between lifestyle and medication, represent a potential inflection point for behavioral weight loss strategies.

Improving diet quality [9], engaging in regular physical activity [10], reducing weight [11], and initiating metformin therapy [12], are each independently associated with improved glycemic control. However, recommendations to "eat healthy", "eat less", and "exercise more" are often oversimplified and commonly conflated under the notion of "going on a diet." Patients with obesity and related conditions are regularly encouraged to engage in these health behaviors concurrent with medication usage. This results in the clinical use of complex biobehavioral intervention strategies without a complete understanding of interactions among behavioral and pharmacological components of the intervention package. Moreover, there is limited evidence to guide individual treatment tailoring or inform the criteria for adapting interventions based on patient-level treatment response. In the context of biobehavioral interventions, adaptations for patients with suboptimal treatment outcomes could include adding or intensifying behavioral strategies, increasing medication dosages, or adding pharmacotherapies. More and higher-quality evidence is needed to inform clinical decision-making regarding the initiation and adaptation of integrated biobehavioral intervention strategies to improve the health and well-being of individuals with obesity and related conditions.

The Sequential Multiple Assignment Randomized Trial (SMART) provides a promising framework to address these gaps and inform the development of personalized, adaptive interventions [13]. Unlike traditional randomized controlled trials, SMART designs allow for dynamic, data-driven intervention adjustments. Participants are initially randomized to one of two first-stage intervention strategies, with their responses assessed at a predetermined time point based on a predefined threshold. Responders—whose responses meet or exceed the threshold—continue with the first-stage intervention for the remainder of the study period. Non-responders—whose responses fall below the threshold—are re-randomized to a second-stage intervention which may involve intensifying the existing approach, augmenting with additional strategies, or transitioning to a different approach. This design enables investigating both initial and adaptive intervention strategies, comparing different adaptive treatment sequences (i.e., embedded adaptive interventions), and predicting optimal treatment sequences based on individual characteristics and early response patterns [13].

This study presents a pilot SMART designed to provide essential feasibility and pilot data in support of a future, full-scale SMART to develop an adaptive biobehavioral intervention for improving insulin sensitivity in adults with stage 1 obesity (i.e., overweight or obesity with at least one mild to moderate weight-related condition) [14]. The study tested two weight-neutral lifestyle interventions targeting diet quality and physical activity, with adaptive modifications based on individual treatment responses. The primary objectives of this pilot SMART were to (1) assess feasibility by documenting the recruitment, retention, and adherence rates, (2) evaluate intervention preferences and acceptability, and (3) obtain preliminary estimates of treatment effects and their variances.

Methods

Study design

In this 25-week pilot SMART (Fig. 1), participants were randomized at baseline with equal probability to receive one of two first-stage treatments: nutrition counseling (NC) with a registered dietitian or exercise counseling (EC) with an exercise specialist. Both interventions were designed to be weight-neutral, with NC focusing on improving overall diet quality per the Dietary Guidelines for Americans [15], while EC aiming to increase physical activity engagement per the Physical Activity Guidelines for Americans [16].

At week 8, participants' responses to the first-stage interventions were re-assessed by using the Quantitative Insulin Sensitivity Check Index (QUICKI) [17]. Change in insulin sensitivity was selected as the response criterion for this trial, as insulin resistance is a key factor in cardiometabolic conditions associated with stage 1 obesity and metabolic syndrome [18]. An increase in QUICKI of > 5% was the threshold for distinguishing early responders and non-responders. This level of improvement in insulin sensitivity is consistent with observed mean improvements in QUICKI following behavioral weight loss in individuals with obesity and metabolic syndrome [19] which is similar to the AACE/ACE definition of stage 1 obesity, that was used to guide the study's eligibility criteria [14].

Participants identified as responders at the week 8 assessment continued with their first-stage intervention until week 25. In contrast, non-responders were re-randomized to one of two second-stage intervention options: (1) *augmenting* their first-stage intervention with metformin or (2) *switching* to behavioral weight loss counseling (WLC). This SMART design resulted in four embedded adaptive interventions (EAI), as summarized in Table 1.

The study was reviewed and approved by the Institutional Review Board at the University of Alabama at Birmingham and is registered at ClinicalTrials.gov (NCT04392284).

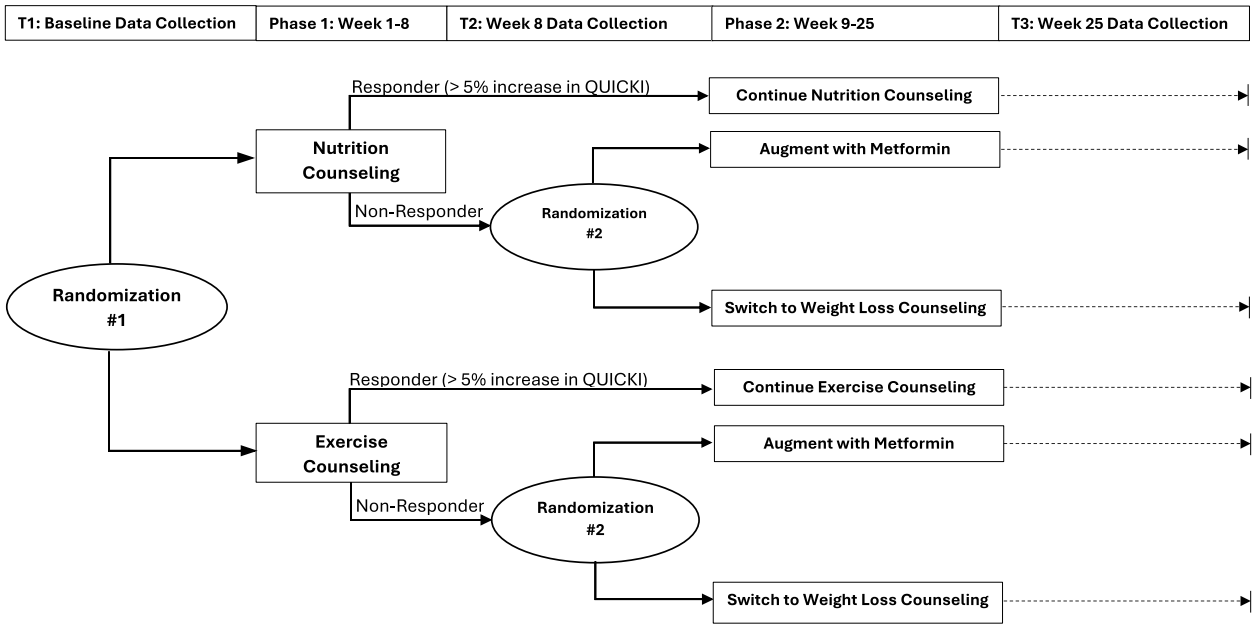

Fig. 1 Sequential Multiple Assignment Randomized Trial (SMART) design flowchart

Table 1 Embedded adaptive interventions in the pilot SMART

Embedded Adaptive Intervention	First-stage intervention	Status	Second-stage intervention
#1	Nutrition counseling	Responder	Continue nutrition counseling
		Non-responder	Augment with metformin
#2	Nutrition counseling	Responder	Continue nutrition counseling
		Non-responder	Weight loss counseling
#3	Exercise counseling	Responder	Continue exercise counseling
		Non-responder	Augment with metformin
#4	Exercise counseling	Responder	Continue exercise counseling
		Non-responder	Weight loss counseling

Sample size justification

The primary objective of the pilot SMART was to obtain clinical trial feasibility data in support of a future full-scale SMART. Consistent with accepted guidelines for the design, conduct, and analysis of pilot studies in general [20] and pilot SMARTs in particular [21], the study was not intended to statistically test for differences in clinical outcomes across intervention conditions. For SMARTs, a primary interest for study feasibility is ensuring that a sufficient number of participants are identified as non-responders to first-stage interventions for re-randomization to second-stage interventions. Using power calculations provided by Almirall et al. [21], the probability that a minimum number of participants will be re-randomized to each non-responder subgroup can be calculated based on an expected non-response rate to first-stage interventions in the pilot SMART. According to these power calculations, a sample size of $n=40$ and an expected 65% non-response rate provides >80% probability that at least five participants will be re-randomized into each of the four non-responder subgroups (i.e., $n=20$ total non-responders). The anticipated 65% non-response rate was based on a previous behavioral weight-loss trial with a mean 5% increase in QUICKI [19]. The non-response rate to the first-stage interventions was expected to exceed 50%, as these interventions were designed to be weight-neutral rather than focused on promoting weight loss.

Study participants

Inclusion

Participants were enrolled between June 2021 and May 2022**.** Inclusion criteria were as follows: (1) age between 18 and 65 years; (2) a BMI of ≥ 27 kg/m^2; (3) presence

of at least one mild-to-moderate obesity-related condition (e.g., prediabetes, type 2 diabetes, metabolic syndrome, dyslipidemia, hypertension, or non-alcoholic fatty liver disease). These BMI and comorbidity criteria were designed to align with stage 1 obesity as defined by the AACE/ACE obesity practice guidelines [14], except that the BMI requirement was adjusted from 25 to 27 kg/m^2 for study eligibility. Additional eligibility criteria included (4) stable medication type and dosage for at least 3 months for medications known to affect body weight/appetite (e.g., steroids, type 2 diabetes medications, antidepressants, or antipsychotics, as determined by the study physician); (5) non-smoker or stable smoking behavior for at least 3 months if currently smoking; (6) ability and willingness to comply with study procedures; and (7) provision of informed consent to participate in the study.

Exclusion

Participants were excluded if they met any of the following criteria: (1) currently pregnant, planning to become pregnant within the next 3 months, or breastfeeding; (2) use of weight loss medications within the previous 3 months; (3) presence of severe obesity-related complications requiring immediate and more intensive clinical intervention (e.g., pharmacotherapy or bariatric surgery) as determined by study physician and/or referring practitioner, (4) history of kidney disease with an estimated glomerular rate (eGFR) below 45 mL/min/1.73 m^2, due to an increased risk of lactic acidosis with metformin, (5) current prescription medications such as acetazolamide (Diamox), dichlorphenamide (Keveyis), methazolamide, topiramate (Topamax, in Qsymia), or zonisamide (Zonegran), which may elevate the risk of lactic acidosis when combined with metformin; (6) presence of a life-sustaining medical implant (e.g., pacemaker); (7) current or recent (within 3 months) prescription of metformin; (8) an HbA1c level exceeding 12%; (9) current exogenous insulin treatment; or (10) self-reported alcohol or drug abuse/dependence.

Recruitment

Participants were recruited through multiple channels. First, potential participants were referred by primary care physicians and registered dietitians from the University of Alabama at Birmingham (UAB) family medicine clinic, where study visits were conducted. Healthcare providers identified individuals meeting the study's general eligibility criteria and provided them with a patient letter containing a brief study overview and a contact number for study personnel. Patients who expressed interest could then initiate contact with the study team for further screening.

Second, the study team utilized the Integrating Biology & the Bedside (i2b2) web-based tool, a clinical research data warehouse, to identify potential participants from electronic health records. Using predefined eligibility criteria, the system generated a list of patients who met key inclusion parameters. Study personnel then conducted outreach to these patients, explaining the study and assessing their interest in participation.

Third, a digital recruitment strategy was implemented through an online eligibility screener hosted by BUMP Digital Marketing. This platform allowed individuals to self-screen for eligibility and provide their contact information if they were interested in learning more about the study. Study personnel followed up with potentially eligible individuals via phone to complete a more detailed screening assessment and determine final eligibility for enrollment.

Initial screening

The SMART study flow is depicted in Fig. 1. Potential participants identified through family medicine clinic referrals, i2b2 queries, or the web-based survey were contacted via telephone to determine their preliminary eligibility screening. The brief phone screen collected contact information, demographics, medical history, and key inclusion/exclusion criteria related to the study. Individuals meeting preliminary eligibility were invited to attend an in-person screening visit, where written informed consent was obtained and eligibility was confirmed.

Baseline assessment and randomization procedures

Eligible participants underwent a baseline assessment within 2 weeks prior to the intervention start date. Trained staff collected anthropometric measurements, including weight, height, waist circumference, and body composition analysis. A fasting blood draw was also conducted. Clinical measures are described in greater detail in later sections.

Following the baseline visit, participants underwent first-stage randomization (R1) using a computer-generated random allocation process with permuted block randomization (block sizes of 4 and 8) and equal allocation. Participants were randomized to receive either NC with a or EC. Assessors and participants were not blinded to group assignments, and participants were informed of their randomization results immediately after the baseline visit.

At week 8, the intervention response was assessed using the QUICKI score. Non-responders underwent a second randomization (R2) to either augment their first-stage intervention with metformin or switch to behavioral weight loss counseling (WLC).

Study interventions

First-stage interventions: nutrition counseling (NC) or exercise counseling (EC)

Nutrition counseling (weight-neutral approach)

Nutrition counseling (NC) sessions consisted of one-on-one virtual sessions utilizing motivational interviewing techniques [22], led by a registered dietitian. The initial session consisted of a 60-min nutrition assessment, while subsequent sessions lasted 20–30 min each. Participants met with the dietitian weekly during the first month (weeks 1–4) and then biweekly for the remainder of the study (weeks 5–25), resulting in a total of 15 individual counseling sessions over the study period.

During phase 1 (weeks 1–8), the primary objective of NC was to assess if improvements in insulin sensitivity could occur without explicitly focusing on weight loss. Therefore, a weight-neutral approach was adopted, wherein weight loss was not discussed as a specific goal. Instead, the sessions focused on enhancing overall well-being and improving diet quality and variety. Counseling emphasized replacing simple carbohydrates with fiber-rich alternatives, reducing sodium intake, substituting saturated fats with unsaturated fats, limiting alcohol consumption, and incorporating more fruits, vegetables, nuts, seeds, and whole grains.

Counseling sessions were designed to be personalized and practical, accommodating participants' individual needs and interests. Rather than following a rigid structure, they explored strategies that aligned with their preferences, needs, and lifestyles. Examples included budget-friendly grocery shopping, interpreting nutrition labels, smart snacking, and exploring new recipes to enhance flavor and variety. Participants also determined how they wanted to approach moderation with less nutrient-dense foods, such as packaged desserts, fast food, and sugar-sweetened beverages, allowing them to make informed choices that felt realistic and sustainable. If patients felt ready, they could choose to set a dietary goal that aligned with their preferences and readiness for change, supporting gradual behavior modification.

To facilitate informed food choices, participants selected one of three meal plan patterns based on the 2020–2025 Dietary Guidelines for Americans: the Healthy U.S. Dietary Pattern, Healthy Vegetarian Dietary Pattern (lacto-ovo-vegetarian), or the Healthy Mediterranean Dietary Pattern [15]. Using their chosen plan as a foundation, the study dietitian collaborated with participants to develop five personalized sample meal plans tailored based on individual energy needs, derived from the Institute of Medicine (IOM) equations for weight maintenance [23].

Exercise counseling (weight-neutral approach)

Participants assigned to EC followed the same schedule of intervention contacts as the NC condition, meeting with an exercise specialist for a total of 15 sessions. These sessions occurred weekly during the first month and biweekly meetings for the remainder of the study (weeks 9–25). The intervention was designed to empower participants to develop sustainable physical activity habits in alignment with the established 2018 Physical Activity Guidelines for Americans [16]. EC focused on enhancing overall well-being and promoting long-term physical activity engagement rather than weight loss.

Central to the approach was the customization of EC to suit individual preferences, needs, and capabilities. The exercise specialist worked as a collaborative guide, helping participants define personalized activity goals progressively built toward 150 to 300 min of physical activity per week. During counseling sessions, participants engaged in collaborative discussions to assess their current fitness levels, health aspirations, and potential barriers to consistent physical activity.

Using motivational interviewing techniques [22], participants co-created short-term and long-term goals that integrated activities they enjoyed and could fit into their daily routines. Individualized recommendations helped them choose suitable exercise modalities, adjust intensity levels, and gradually duration and frequency. To enhance self-monitoring and accountability, participants were asked to maintain daily physical activity logs.

Second-stage interventions: metformin or weight loss counseling

Metformin

Non-responders who were re-randomized to augment their first-stage intervention with metformin continued with their initial NC or EC intervention for the remainder of the study. Metformin was prescribed and monitored under the guidance of the study physician, following a structured dosage progression plan to optimize tolerability.

Participants initially received 850 mg of metformin once daily, taken with a meal, for the first 2 weeks. After this period, they were instructed to increase their dosage to 850 mg twice daily, also taken with meals, for the remainder of the study. However, if participants reported gastrointestinal distress, progression to the higher dosage was delayed until symptoms improved.

For participants experiencing persistent gastrointestinal symptoms for more than 6 weeks at the initial dosage of 850 mg once-daily dose, an extended-release

(XR) formulation of metformin was introduced. In these instances, participants started with 500 mg of metformin XR at the evening meal for 1 week and then gradually increased the dosage by 500 mg per week, up to a maximum of 1500 mg taken once per daily at the evening meal.

Weight loss counseling (weight-loss focused approach)

Weight loss counseling (WLC) was one of two potential second-stage interventions for participants who did not respond to the initial NC or EC interventions. Non-responders who were re-randomized to WLC engaged in virtual one-on-one sessions with a registered dietitian every other week during phase 2 of the study (weeks 9–25). The initial WLC session included a 60-min nutrition assessment, while the remaining sessions were 20–30 min each, resulting in a total of eight sessions over the intervention period.

During WLC, the emphasis shifted explicitly to weight loss as a means to enhance insulin sensitivity. Participants received personalized meal plans and recommendations to reduce caloric density, with a targeted daily caloric deficit of 25–35% based on energy prescriptions derived from the IOM equations [23]. Meal plans were designed based on the 2020–2025 Dietary Guidelines for Americans, with options including the Healthy U.S. Dietary Pattern, Healthy Vegetarian Dietary Pattern (lacto-ovo-vegetarian), and the Healthy Mediterranean Dietary pattern [15].

To monitor their food and energy intake, participants were encouraged to use either a provided food log template or a preferred mobile application like MyFitnessPal or Lose It. The study dietitian reviewed the food logs throughout the intervention period to provide feedback and support.

Counseling sessions focused on self-management strategies to support sustainable weight loss. These strategies included monitoring hunger cues, identifying patterns in dietary intake, reading nutrition labels, effective problem-solving for dietary challenges, and practicing portion control. Additionally, participants were asked to record their weight on a weekly basis.

Outcome measures

Feasibility

Feasibility of the study was assessed through several key measures, including recruitment, retention, response rate, adherence to intervention components, intervention preference, and adverse events. These measures were evaluated to determine the practicality and acceptability of the intervention and to identify potential barriers to future implementation.

Recruitment and retention Recruitment feasibility was assessed by tracking the number of individuals screened via phone and in-person, as well as the final enrollment numbers. Retention was measured based on the proportion of participants completing assessments at weeks 8 and 25, with pre-specified retention targets set at $\geq 85\%$ at week 8 and $\geq 80\%$ at week 25. Additional retention metrics included the number of withdrawals and participants lost to follow-up.

Response rate The response rate was determined by classifying participants as responders or non-responders based on the predefined criterion of a QUICKI score improvement of $> 5\%$. The pre-specified feasibility target for response to initial interventions was set at $\geq 33\%$, inclusive of withdrawals.

Adherence Adherence to virtual counseling sessions (NC, EC, and WLC) was measured as the percentage of attended sessions relative to scheduled sessions with registered dietitians or exercise specialists. The feasibility benchmark for adherence was set at $\geq 80\%$ attendance. Adherence to metformin in the second-stage intervention was assessed using pill counts from returned pill bottles and the percentage of pills consumed relative to the prescribed dosage.

Intervention preference To assess the acceptability and participant engagement with the interventions, participants' preferences were recorded at two time points: baseline for first-stage interventions (NC vs. EC) and week 8 for second-stage interventions (metformin vs. WLC) before randomization. Although the intervention assignment was randomized, participants were asked about their hypothetical preferences using a 5-point Likert scale. Strong preferences were represented at the scale's endpoints (1 and 5), moderate preferences at 2 and 4, and a neutral response (3) indicated no preference. For analysis, participants expressing a strong or moderate preference for one option were categorized as "preferred" for that intervention. Participants who were randomized to their preferred intervention were classified as "matched", while those assigned to a non-preferred intervention were categorized as "mismatched."

Adverse events and feasibility-related barriers Adverse events were monitored throughout the study, with documentation of any reported side effects, discomfort, or unexpected health issues arising from the interventions. No pre-specified feasibility criteria were developed for adverse events; rather, these data were collected to identify potential safety concerns and guide future protocol modifications.

Additionally, feasibility-related challenges, such as participant burden, logistical barriers, and adherence difficulties, were documented to assess their modifiability for future confirmatory trials.

Clinical measures

Data collection was conducted at baseline, week 8, and week 25 for all participants. All measurements were performed on the same day following an overnight fast of at least 8 h.

Insulin sensitivity Insulin sensitivity, the primary clinical outcome of this study, was assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI). QUICKI is calculated as the reciprocal of the fasting glucose-insulin product and has been shown to have a significantly stronger linear correlation with glucose-clamp-derived insulin sensitivity than other minimal-model estimates, particularly in individuals with obesity and diabetes [24]. Higher QUICKI values indicate greater insulin sensitivity, whereas lower values suggest reduced insulin sensitivity [25]. An increase in QUICKI exceeding 5% at the week 8 assessment served as the criterion to differentiate early responders from non-responders [19].

Anthropometrics and body composition Anthropometric measurements, including weight, height, and waist circumference, as well as body composition assessments were conducted by trained research staff following standardized protocols using calibrated equipment. Participants were asked to void prior to measurement and remove shoes and heavy clothing.

Body weight was measured using a calibrated digital platform scale (Health O Meter Professional Scales, McCook, IL, USA) with an accuracy of ± 0.1 kg. Waist circumference was measured using a Gulick tape at the midpoint between the lowest palpable rib and the superior of the iliac crest in accordance with the CARDIA protocol [26]. Measurements were recorded to the nearest 0.1 cm and averaged.

Standing height was measured using a stadiometer to the nearest 0.1 cm. Participants stood barefoot with their feet together, and their heads were positioned level with a horizontal Frankfurt plane, which is an imaginary line from the lower border of the eye orbit to the auditory meatus [27].

All measurements were taken twice, and if they fell within a pre-specified margin of error, they were averaged. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared (kg/m^2).

Body composition, including fat mass (FM) and lean body mass (LBM), was assessed using a multi-frequency bioelectrical impedance analysis (BIA) tool (InBody® S10, Cerritos, CA, USA). Participants were asked to lie supine for 10–15 min prior to the test to ensure fluid stabilization. Electrodes on the fingers, thumbs, and ankles, according to the manufacturer's guidelines. To minimize interference, participants were instructed to remove jewelry and wear clothing free of zippers, wires, or metal accessories.

Blood samples Fasting blood samples were collected at baseline, week 8, and week 25 to assess glucose metabolism and lipid profiles. Biomarkers included fasting glucose, fasting insulin, HbA1c, and a comprehensive metabolic panel, along with lipid profile components: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol. Blood draws were obtained by clinical phlebotomists at the family medicine clinic, and the samples were processed and analyzed at the UAB Hospital Laboratory.

Blood pressure Blood pressure was measured in the left upper arm using a calibrated mercury sphygmomanometer (Omron 3 Series Upper Arm Blood Pressure Monitor, BP7100, Omron Healthcare, Inc., Lake Forest, IL, USA). Measurements were taken after the participant had rested quietly for at least 5 min in a seated position. A properly sized blood pressure cuff was selected [28], and testing was performed in a quiet environment. Participants were seated with their backs supported, feet flat on the floor, and legs uncrossed. Participants were instructed to sit quietly until the measurement was completed.

Statistical analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure web-based application hosted at UAB. REDCap is designed to support research data collection by providing a user-friendly interface for structured data entry, audit trails for tracking data modifications, automated export procedures to statistical software, and integration capabilities for external data sources [29].

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24. Descriptive statistics were used to summarize participant demographics, retention rates, response rates (responder vs. non-responder), adherence to intervention components, and intervention preferences. Descriptive data

were presented as means with standard deviations medians with interquartile ranges (IQR) for continuous variables, where appropriate. Categorical variables were reported as frequencies with percentages.

Changes in clinical and intervention-related outcomes were analyzed within and between groups at week 8 and week 25, relative to baseline, for participants assigned to both first-stage and second-stage interventions. For the effects of the first-stage interventions, we included all participants originally assigned to EC and NC, regardless of their response status or subsequent second-stage intervention assignment. In contrast, second-stage intervention effects (WLC vs. metformin) were evaluated only among non-responders, averaging across first-stage intervention assignments. Between-group differences at each intervention stage were quantitatively assessed using *t*-tests to calculate mean changes, with results reported alongside 95% confidence intervals and effect sizes, measured as Cohen's *d*. *P*-values were not reported as this study was not designed to test confirmatory hypotheses.

Results

Participant characteristics

Table 2 presents the characteristics of the study participants. The mean age of the sample was 53 ± 12 years, with the majority being female (81%) and non-Hispanic Black (72.5%). More than half of the participants were married or in a committed relationship (55%), and most (66.7%) had completed at least a 4-year university degree.

The mean BMI was 37.6 ± 8.0 kg/m^2, with a mean percent body fat of 53.1 ± 12.2%. Most participants (82.5%) had obesity, categorized as class 1 (30%; BMI 30–34.9 kg/m^2), class 2 (20%; BMI 35–39.9 kg/m^2), or class 3 (32.5%; BMI ≥ 40 kg/m^2).

At baseline, the mean HbA1c level was 5.7 ± 0.5%, with 51.3% of participants HbA1c levels in the normal range (< 5.7%), 43% in the prediabetes range (5.7–6.4%), and 5.1% with HbA1c levels ≥ 6.5%. The mean QUICKI score at baseline was 0.31 ± 0.03, indicating reduced insulin sensitivity.

Lipid profiles, including total cholesterol, LDL-cholesterol, and HDL-cholesterol, were within the normal range at baseline. However, the mean baseline blood pressure met the criteria for stage 2 hypertension, with systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

Table 2 Baseline characteristics of study participants ($n = 40$)

Characteristic	Mean or n	% or ± SD
Demographics		
Age (years)	53.10	± 12.17
Female	33	82.5%
Race/ethnicity		
Non-Hispanic White	10	25.0%
Non-Hispanic Black	29	72.5%
Asian	1	2.5%
Income bracket		
< $45	11	30.6%
$45 k–$70 K	12	33.3%
> $70 K	13	36.1%
Educational level		
< 4-year degree	11	33.3%
4-year degree	13	39.4%
> 4-year degree	9	27.3%
Marital status		
Single	18	45.0%
Married or in a relationship	22	55.0%
Clinical characteristics		
Weight (kg)	105.98	± 28.20
BMI (kg/m^2)	37.57	± 8.04
% Body Fat	53.10	± 12.17
HbA1c (%)	5.73	± 0.48
FBG (mg/dL)	95.85	± 10.79
QUICKI	0.31	± 0.03
Cholesterol (mg/dl)	186.85	± 36.07
LDL (mg/dL))	115.43	± 33.97
HDL (mg/dL))	52.37	± 12.55
Triglycerides (mg/dL))	104.55	± 45.61
Systolic BP (mm Hg)	141.38	± 20.14
Diastolic BP (mm Hg)	84.62	± 11.75
BMI (kg/m^2)	37.57	± 8.04

All data are presented as mean (SD) for continuous variables and % (frequency) for categorical variables. *Abbreviations*: *HbA1c* hemoglobin A1c, *FBG* fasting blood glucose, *QUICKI* Quantitative Insulin Sensitivity Check Index, *LDL* Low-density lipoprotein cholesterol, *HDL* High-density lipoprotein cholesterol, *BP* Blood pressure, *BMI* Body mass index

Feasibility outcomes

Recruitment and retention

Figure 2 illustrates the participant flow throughout the study, following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. A total of 112 individuals underwent initial phone screening, of whom 52 were ineligible or declined participation resulting in a 53.6% conversion rate from initial contact to scheduling an in-person screening visit. Among the 60 individuals eligible for in-person screening, 16 declined participation before their screening visit, and 4 patients were determined to be ineligible after screening. Ultimately, 40 participants were enrolled, yielding an overall recruitment rate of 35.7% (40/112 contacted) and a 66.7% screen pass rate (40/60 eligible for screening).

Recruitment spanned approximately eight months, starting with the initial telephone screening in March 2021, followed by the first in-person screenings and enrollments in April 2021, concluding with the final enrollment in November 2021.

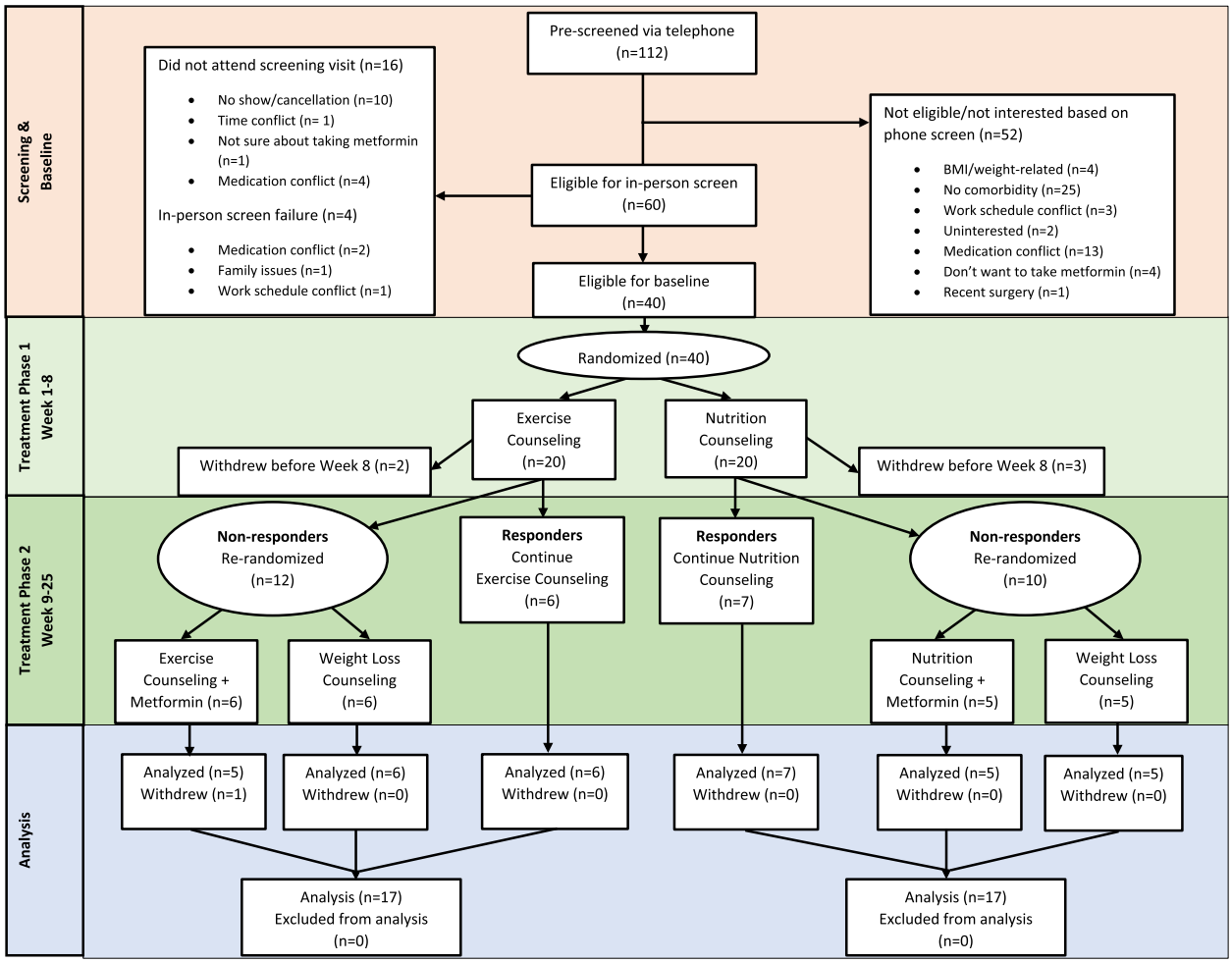

Fig. 2 CONSORT diagram of study flow and participant allocation

Study retention exceeded the pre-specified feasibility benchmarks of ≥ 85% at week 8 and ≥ 80% at week 25. Five participants withdrew before reaching the week 8 assessment, resulting in a retention rate of 87.5% at week 8. An additional participant withdrew after week 8, leaving a final sample size of 34 study completers, and an overall retention rate of 85%.

Participants who discontinued the intervention were younger (mean age: 43.50 ± 8.45 years), had higher income levels (50% reporting income > $70,000), and were more likely to be single (55%) compared to study completers, who had a mean age of 53.79 ± 12.02 years, with 33.3% reporting an income > $70,000, 55.9% being married or in a relationship.

Response rate

At week 8, 35 participants were assessed for their response to first-stage interventions, defined as > 5% increase in QUICKI score. Among them, 37.1% ($n = 13$, 95% CI 23.2–53.7%) were categorized as responders, while 62.9% ($n = 22$, 95% CI: 46.3–76.8%) were classified as non-responders and subsequently re-randomized (R2) to second-stage interventions. When accounting for all 40 enrolled participants, including the five who withdrew before the week 8 assessment, the overall response rate was 32.5% (95% CI 20.1–48.0%), aligning with the pre-specified feasibility benchmark of 33%.

Among week 8 completers, 41.2% ($n = 7$, 95% CI 21.6–64.0%) in the NC group were classified as responders, compared to 33.3% ($n = 6$, 95% CI 16.3–56.3%) in the EC group. Conversely, 58.8% ($n = 10$, 95% CI 36.0–78.4%) of NC participants and 66.7% ($n = 12$, 95% CI 43.7–83.7%) of EC participants were classified as non-responders.

At baseline, glycemic status varied between responders and non-responders. A greater proportion of responders (58.3%, $n = 7$) had normoglycemic HbA1c values (< 5.7%) compared to non-responders (45.5%, $n = 10$). Similarly, fewer responders had HbA1c values in the prediabetes

range (41.7%, $n=5$) had HbA1c values in the prediabetes range compared to non-responders (45.5%, $n=10$). Notably, none of the responders had HbA1c values ≥ 6.5% at baseline, whereas 9.1% ($n=2$) of non-responders had HbA1c levels in this range.

Adherence

Counseling sessions

Adherence to counseling sessions was evaluated based on the total number of sessions attended (Table 3). During phase 1 (weeks 1–8), mean adherence was 90.00% ± 15.67% for EC and 80.00% ± 32.71% for NC, with corresponding median adherence of 100% (IQR 17%) and 100% (IQR 33.3%), respectively. When excluding two NC participants who did not attend any phase 1 sessions, the mean NC adherence increased to 88.89% ± 18.96%, aligning more closely with EC adherence.

Across the study, adherence generally met or exceeded the ≥ 80% feasibility benchmark, with EC demonstrating the most consistent engagement across both phases. The exception was NC in Phase 2, where mean adherence was 75.93% ± 30.27% (median 88.89% [IQR 36%]). However, after excluding one patient who attended only one session, mean NC adherence increased to 80.80% ± 26.3%, reaching the feasibility threshold. Additionally, adherence to WLC in phase 2 was 81.11% ± 20.98% (median 88.89% [IQR 33.3%]), comparable to NC adherence in the same phase.

Metformin

To assess metformin adherence, participants were asked to return their pill bottles with any unused pills each month using a pre-paid mailer. The number of pills consumed was determined by calculating the difference between the prescribed amount and the number of pills remaining. At week 8, 11 participants were re-randomized to metformin; however, one participant withdrew after randomization, and another declined to receive metformin bottles. As a result, adherence data were available for nine participants.

Between weeks 9 and 25, a total of 36 metformin pill bottles were mailed to participants, with each participant receiving one bottle per patient every 4 weeks. Of these, 35 bottles were successfully received, while one was lost in the mail. Approximately 65.7% (23 bottles) were returned using prepaid mailers, while the remaining bottles were not returned and assumed to be unused. Among the returned bottles, the percentage of pills presumably taken was 51.68 ± 25.21%.

Side effects were formally reported at study visits and included gastrointestinal upset (3 participants) and vaginal infection with itching (1 participant). However, based on the exit interview, 54.5% (6 participants) assigned to receive metformin reported experiencing gastrointestinal discomfort.

Intervention preference

Intervention preference data were available from 37 participants, as three participants did not complete the survey. Among those who responded, 54.1% (20 participants) preferred NC, 24.3% (9 participants) preferred EC, and 21.6% (8 participants) had no preference. Of the 29 participants who expressed preference, 58.6% matched with their preferred first-stage intervention, while 41.4% did not receive their preferred assignment.

During phase 1 (weeks 1–8), participants who were randomized to NC and matched with their preferred intervention exhibited modestly higher adherence to counseling sessions compared to those who were mismatched (89.4 ± 21.4% vs. 83.3 ± 16.7%, respectively). In contrast, participants randomized to EC demonstrated similar session attendance regardless of preference matching (88.9 ± 17.2% for matched vs. 90.7 ± 16.9% for mismatched).

Table 3 Adherence to virtual counseling sessions by intervention type and phase

Intervention type	Phase	Sample size (*n*)	Mean adherence (%) ± SD	Median adherence (IQR) (%)
First-stage interventions				
Exercise counseling	Phase 1	20	90.00 ± 15.67	100.00 (17.00)
	Phase 2	11	87.88 ± 10.48	88.89 (22.00)
Nutrition counseling	Phase 1	20	80.00 ± 32.71	100.00 (33.33)
	Phase 2	12	75.93 ± 30.27	88.89 (36.00)
Second-stage interventions				
Weight loss counseling	Phase 1	–	–	–
	Phase 2	10	81.11 ± 20.98	88.89 (IQR 33.3)

Phase 1 (weeks 1–8): includes nutrition counseling (NC) and exercise counseling (EC)

Phase 2 (weeks 9–25): includes NC and EC for responders, and weight loss counseling (WLC) for non-responders

Among non-responders who completed the intervention preference questions for the second randomization at week 8 (21), 52.4% (11 participants) preferred switching to WLC, 38.1% (8 participants) preferred augmenting their first-stage intervention with metformin, and 9.5% (2 participants) had no preference. Of the 19 non-responders who expressed a preference, 52.6% were re-randomized to a second-stage intervention matching their preference, while 47.4% did not receive their preferred assignment. Similar to phase 1, adherence to WLC sessions was higher among participants who were matched with their preferred second-stage intervention compared to those who were mismatched (88.9 ± 7.8% vs. 75.0 ± 31.9%).

Participant feedback

A total of 33 out of 40 participants completed exit interviews, providing insights into their experiences within the study. Overall, participants reported positive interactions with the study dietitian, exercise specialist, research staff, and clinical staff. Common feedback highlighted the supportive and individualized nature of counseling, with representative comments such as, "It held me accountable, which is what I needed," "The counseling was individualized", and "It caused a change in mindset", were representative of the general sentiment related to the interventionists. Research and clinical staff were commonly described as "very helpful, very reliable, and friendly."

Participants were asked hypothetically whether they would have preferred group-based intervention or in-person sessions, even though they have received on-on-one virtual counseling throughout the study. Most participants indicated a preference for one-on-one counseling sessions, and the virtual format was generally favored over in-persons sessions. However, this study was conducted during a period of high COVID-19 infection rates, which may have influenced these responses. At least two participants explicitly referenced concerns about COVID-19 when considering in-person participation. One participant noted, "The convenience of me doing it online and in the house was wonderful. I don't know what in-person would be like with COVID."

Some participants expressed confusion regarding the weight-neutral approach used in the initial 4 weeks of the study. Several participants not assigned to WLC mentioned a desire for weight loss or referenced weight changes in their interviews, suggesting that expectations around weight-related outcomes may not have been fully aligned with intervention goals. Most participants were satisfied with their initial assignments to NC or EC, though two participants assigned to EC reported in their exit interviews that they would have preferred nutrition counseling in their exit interviews.

Among the non-responders, assignment to the WLC was more favorably received compared to metformin. Participants who received metformin reported more negative feedback, primarily related to gastrointestinal effects. Six participants were assigned to receive metformin specifically experiencing nausea and upset stomach.

Adverse events

During the study period, a total of 15 adverse events (AEs) were reported among 12 participants. Based on severity, five were categorized as mild, nine as moderate, and one as severe.

Two events met the criteria for serious adverse events (SAEs), as they required hospitalization. However, both were determined by the study physician to be unrelated to the study interventions. One participant, assigned to WLC, was hospitalized due to a COVID-19 infection, while another participant, assigned to EC, required spinal surgery for pre-existing hip and back pain.

Among the 15 total reported AEs, four were determined to be related to the study intervention, all occurring in participants randomized to metformin. These moderate AEs included gastrointestinal symptoms (nausea, diarrhea, and cramping) and metformin-related vaginal odor, itch, and yeast infection.

The remaining 11 non-serious AEs were distributed as follows: four events in the EC group, six in the NC group, and five in the metformin group.

Clinical outcomes and preliminary efficacy

QUICKI changes by response status

Figure 3 presents changes in QUICKI score throughout different phases of the study: between baseline and week 8 (phase 1), week 8 and week 25 (phase 2), and the overall period from week 1 and 25. At week 8, participants classified as responders showed an increase in QUICKI score of 11.4 ± 6.5%, whereas non-responders experienced a decrease in QUICKI score of 2.0 ± 6.2%. This resulted in a mean percent change difference of 13.4 (95% CI 8.9, 17.4) and a large effect size ($d = 2.1$).

Between weeks 8 and 25, when responders remained on their initial intervention while non-responders received their second-stage intervention (augmented with metformin or switched to WLC), responders experienced minimal changes in QUICKI score (0.38 ± 9.7%), whereas non-responders showed an average increase of 4.4 ± 9.7%. The mean percent change difference between the two groups was 4.0 (95% CI − 3.2, 11.2), with a small effect size ($d = 0.42$).

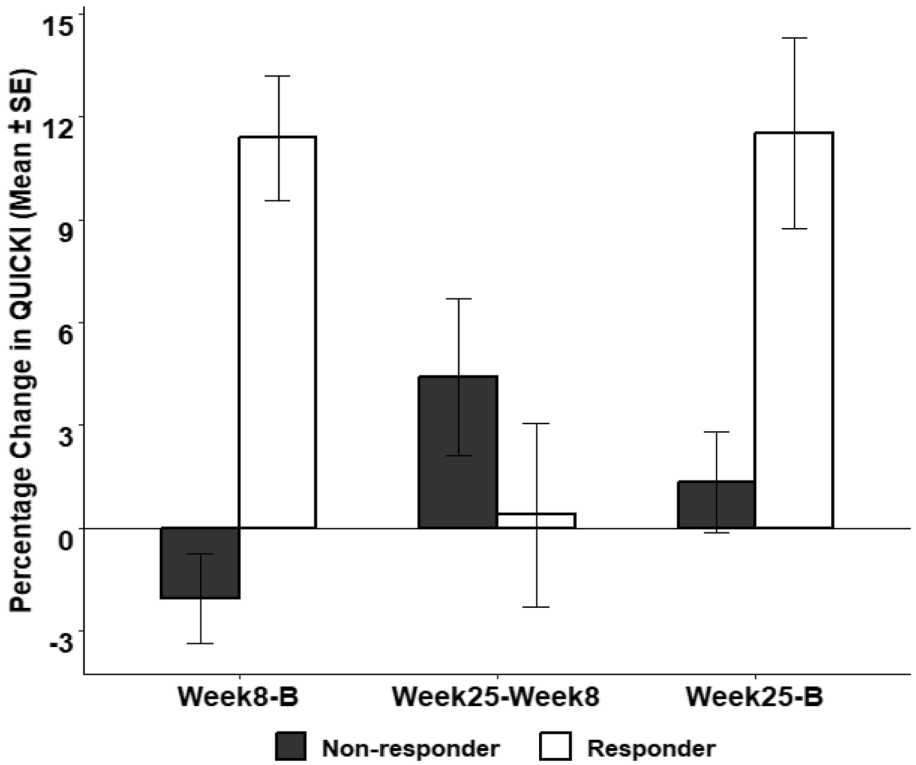

Fig. 3 Percentage change in QUICKI Score by Response Status Across Assessment Timepoints. B (Baseline) represents the pre-intervention assessment; week 8 reflects the response to first-stage interventions; week 25 indicates the post-intervention assessment; non-responders (black bars) and responders (white bars) are classified based on response to the initial intervention at week 8, and data are presented as mean ± standard error (SE)

Over the entire study duration (baseline to week 25), responders demonstrated an 11.5 ± 10.0% increase in QUICKI score, primarily driven by changes during phase 1 and their maintenance during phase 2. Conversely, non-responders experienced a smaller overall increase of 1.3 ± 10.0% in QUICKI score, resulting in a mean percent change difference of 10.7 (95% CI 4.3, 16.0) and a large effect size ($d = 1.26$).

QUICKI changes by intervention components

First-stage interventions: nutrition counseling vs. exercise counseling

Table 4 summarizes the mean QUICKI score at baseline and week 25 for participants randomized to NC or EC as their first-stage intervention. At baseline, the mean QUICKI scores were 0.32 ± 0.041 for NC and 0.31 ± 0.027 for EC. By week 25, the mean QUICKI scores increased to 0.34 ± 0.042 for NC and 0.33 ± 0.044 for EC. Both groups showed an improvement in QUICKI score from baseline, with NC showing a change of 6.0 ± 7.8% increase in QUICKI and EC showing a 4.6 ± 11.1% increase. The between-group mean difference in percent change was − 1.4% (95% CI − 8.2, 5.4), indicating a small between-group effect ($d = -0.27$).

Second-stage interventions: weight loss counseling vs. metformin

Among non-responders who were re-randomized to second-stage interventions, baseline QUICKI scores were 0.32 ± 0.039 for WLC and 0.32 ± 0.046 for metformin. By week 25, non-responders in the WLC showed an average increase of 3.7 ± 7.6% in QUICKI, whereas those assigned to the metformin group experienced a decrease of 0.97 ± 4.6%. The between-group difference in QUICKI change between WLC and metformin groups was 4.63 (95% CI − 1.27, 10.55), with a moderate effect size ($d = 0.73$).

Secondary outcome measures

Body weight, waist circumference, and body composition (body fat percentage and lean body mass) were secondary clinical outcome measures. Given the weight-neutral approach of NC and EC, weight changes between baseline and week 8 were also evaluated as a feasibility outcome. Mean weight change during this period was − 0.48% ± 2.20 with individual participant weight changes ranging from 5.94% weight loss to 3.43% weight gain. Two participants in the NC condition experienced weight loss of ≥ 5% during the first 8 weeks.

Table 4 Change in Quantitative Insulin Sensitivity Check Index (QUICKI) from baseline to week 25 by first- and second-stage interventions

Treatment	Baseline (M ± SD)	Week 25 (M ± SD)	Mean change (M ± SD)	% Change (± SD)	95% CI	Cohen's *d*
All	0.319 ± 0.034	0.333 ± 0.043	0.016 ± 0.030	5.35	2.07, 8.55	–
First-stage interventions						
NC	0.324 ± 0.041	0.339 ± 0.042	0.018 ± 0.024	6.04 ± 7.81	–	–
EC	0.314 ± 0.027	0.327 ± 0.044	0.014 ± 0.035	4.63 ± 11.08	–	–
Between-group difference	–	–	–	−1.41	−8.18, 5.36	−0.27
Response to first-stage interventions						
All responders	0.308 ± 0.026	0.344 ± 0.044	0.035 ± 0.032	11.52 ± 9.99	6.30, 17.29	–
NC Responder	0.311 ± 0.031	0.336 ± 0.037	0.026 ± 0.028	8.59 ± 9.25	–	–
EC Responder	0.306 ± 0.022	0.353 ± 0.054	0.047 ± 0.357	14.94 ± 10.53	–	–
Between-group difference	–	–	–	6.35	−5.71, 18.42	−0.17
Second-stage interventions						
All non-responders	0.323 ± 0.039	0.326 ± 0.041	0.003 ± 0.021	1.34 ± 6.57	4.57, 7.83	–
WLC	0.320 ± 0.034	0.333 ± 0.029	0.010 ± 0.024	3.67 ± 7.61	–	–
Metformin	0.325 ± 0.046	0.319 ± 0.051	−0.002 ± 0.014	−0.97 ± 4.61	–	–
Between-group difference	–	–	–	4.63	−1.27, 10.55	0.73

QUICKI Quantitative Insulin Sensitivity Check Index, *NC* Nutrition counseling, *EC* Exercise counseling, *WLC* Weight loss counseling, *M ± SD* mean ± standard deviation, *95% CI* 95% confidence interval. The between-group difference represents the mean change between groups

Baseline to week 25 changes in body weight, waist circumference, and body composition were modeled as the main effects of first and second-stage interventions [13]. For first-stage intervention effects, all participants initially assigned to EC and NC were included in the analysis, regardless of response status or second-stage intervention assignment. Among applicable second-stage intervention assignments. Among first-stage interventions, the NC mean weight change at week 25 versus baseline in the NC group was −2.67 ± 3.49 kg and 0.87 ± 3.24 kg in the EC group (Table 5). The mean change at week 25 versus the baseline difference between the two groups was 3.55 kg (95% CI 1.47, 5.82), with a large effect size ($d = 1.05$). Changes in waist circumference, body fat percentage, and lean body mass between NC and EC showed small to trivial effect sizes.

For second-stage interventions, only non-responders to initial intervention assignments were included in the analysis (Table 6). Weight change at week 25 was −1.14 ± 4.83 kg for WLC and −1.23 ± 3.79 kg for metformin, with a negligible between-group difference (0.08 kg, 95% CI −3.91, 4.08, $d = 0.01$). Changes in waist circumference, BMI, body fat percentage, and lean body mass were small to trivial between groups.

Discussion

The present study evaluated the feasibility of a biobehavioral adaptive intervention designed to improve insulin sensitivity among adults with obesity and at least one mild-to-moderate weight-related cardiometabolic condition (i.e., stage 1 obesity). Using a SMART design, the study aimed to assess recruitment, retention, adherence, response rates, and preliminary intervention effects within a primary care setting. Findings demonstrated that recruitment was achievable within a defined timeframe, retention exceeded feasibility benchmarks, adherence to counseling interventions was generally high, and the study successfully distinguished responders from non-responders based on insulin sensitivity changes. While adherence to counseling sessions was high, metformin-related side effects were common, with some participants discontinuing due to gastrointestinal discomfort. No serious study-related adverse events were reported. These feasibility indicators suggest that a full-scale SMART is viable with minor design modifications to enhance implementation and clinical integration.

Recruitment and retention outcomes were strong, demonstrating that participant engagement strategies were effective. Over an eight-month period, 40 participants were successfully enrolled, and by the 25-week mark, reached 85%, exceeding the pre-specified feasibility threshold of 80%. These outcomes likely reflect the structured multi-pronged recruitment strategy, which included direct engagement, personalized follow-ups, and patient-centered retention efforts. When a decline in attendance was observed, targeted follow-up efforts were made to identify barriers and collaboratively seek resolutions. Virtual counseling helped in improving adherence, as participants reported that remote sessions reduced transportation burdens and

Table 5 Secondary post-treatment outcomes by first-stage interventions

Outcome	*n*	Baseline	*n*	Week 25	Mean change	95% CI	Cohen's *d*
Weight, kg	20						
NC	20	100.08 (26.48)	17	97.91 (28.22)	−2.67 (3.49)		
EC	20	111.89 (29.28)	17	115.57 (32.54)	0.877 (3.24)		
Between-group difference					3.55	1.47, 5.82	1.05
BMI, kg/m^2							
NC	20	36.04 (7.68)	17	35.27 (7.99)	−0.98 (1.20)		
EC	20	39.09 (8.30)		40.61 (9.10)	0.28 (1.17)		
Between-group difference					1.27	0.47, 2.06	1.07
Waist circumference, cm							
NC	20	108.98 (16.06)	17	109.26 (16.38)	−1.28 (5.46)		
EC	20	119.71 (20.13)	17	119.33 (25.80)	−1.70 (12.15)		
Between-group difference					−0.71	−9.79, 5.52	−0.06
Body fat, %							
NC	20	44.87 (11.56)	17	43.00 (7.05)	−0.92 (2.76)		
EC	20	43.12 (9.23)	17	43.78 (9.88)	−0.80 (3.40)		
Between-group difference					0.12	−2.04, 2.28	0.04
Lean body mass, %							
NC	20	57.04 (8.31)	17	57.15 (6.82)	1.11 (2.96)		
EC	20	54.57 (12.20)	17	55.80 (9.52)	3.10 (7.97)		
FBG, mg/dL							
NC	20	97.10 (12.14)	17	93.24 (11.44)	−5.52 (9.74)		
EC	20	94.60 (9.39)	17	93.41 (12.35)	−0.94 (13.58)		
Between-group difference					4.58	−3.66, 12.84	0.38
Cholesterol, mg/dL							
NC	20	186.60 (43.37)	17	187.10 (28.11)	−7.35 (38.96)		
EC	20	187.10 (28.11)	17	195.00 (50.83)	9.52 (34.21)		
Between-group difference					16.88	−8.73, 42.49	0.46
LDL, mg/dL							
NC	20	113.10 (40.98)	17	113.82 (32.88)	−7.17 (34.25)		
EC	20	117.75 (26.03)	17	129.41 (42.96)	13.17 (30.22)		
Between-group difference					20.35	−2.21, 42.92	0.63
HDL, mg/dL							
NC	20	56.10 (12.90)	17	52.35 (12.70)	−2.23 (5.84)		
EC	20	48.65 (11.29)	17	47.12 (9.74)	−2.17 (8.87)		
Between-group difference					0.05	−5.19, 5.30	0.008
Triglycerides, mg/dL							
NC	20	93.15 (47.95)	17	96.71 (51.80)	−4.00 (30.28)		
EC	20	115.95 (41.21)	17	109.65 (60.63)	2.05 (33.32)		
Between-group difference					6.05	−16.18, 28.30	0.20
Systolic BP mm Hg							
NC	20	137.60 (17.87)	17	138.98 (19.20)	−7.74 (18.55)		
EC	20	145.17 (21.97)	17	137.10 (15.71)	−2.78 (11.48)		
Between-group difference					4.95	−5.82, 15.74	0.32
Diastolic BP, mm Hg							
NC	20	84.36 (13.97)	17	85.84 (8.55)	2.28 (10.45)		
EC	20	84.87 (9.39)	17	84.14 (10.51)	−1.64 (8.29)	−10.42, 2.65	−0.41
Between-group difference							

All data are presented as mean (SD)

Abbreviations: EC Exercise counseling, *NC* Nutrition counseling, *FBG* Fasting blood glucose, *LDL* Low-density lipoprotein cholesterol, *HDL* High-density lipoprotein cholesterol, *BP* Blood pressure, *HbA1c* Hemoglobin A1c, *BMI* Body mass index

Table 6 Secondary post-treatment outcomes by second-stage interventions

Outcome	*n*	Baseline	*n*	Week 25	Mean change	95% CI	Cohen's *d*
Weight, kg							
WLC	11	104.21 (23.30)	11	103.07 (25.01)	−1.14 (4.83)		
Metformin	11	118.18 (32.73)	10	119.12 (34.68)	−1.23 (3.79)		
Between-group difference					0.08	−3.91, 4.08	0.01
BMI, kg/m^2							
WLC	11	35.64 (5.60)	11	35.22 (6.31)	−0.41 (1.67)		
Metformin	11	42.33 (9.65)	10	42.86 (10.24)	−0.42 (1.32)		
Between-group difference					0.009	−1.38, 1.39	0.006
Waist circumference, cm							
WLC	11	111.80 (15.13)	11	111.25 (15.65)	−0.54 (5.22)		
Metformin	11	123.32 (19.65)	10	124.43 (23.14)	−0.72 (5.14)		
Between-group difference					0.17	−4.56, 4.92	0.03
Body fat, %							
WLC	11	42.17 (7.24)	11	42.18 (6.35)	0.009 (3.16)		
Metformin	11	48.30 (6.49)	10	48.52 (5.68)	−0.59 (3.17)		
Between-group difference					0.59	−2.29, 3.49	0.18
Lean body mass, %							
WLC	11	55.80 (8.13)	11	57.79 (6.34)	1.99 (5.77)		
Metformin	11	51.69 (6.52)	10	51.45 (5.67)	0.56 (3.17)		
Between-group difference					1.43	−2.89, 5.75	
FBG, mg/dL							
WLC	11	96.00 (12.13)	10	94.18 (9.16)	−1.81 (11.27)		
Metformin	11	95.18 (13.12)	11	97.60 (16.93)	2.10 (14.17)		
Between-group difference					−3.91	15.56, 7.72	−0.30
Cholesterol, mg/dL							
WLC	11	172.82 (21.94)	11	175.09 (31.84)	2.27 (26.03)		
Metformin	11	193.73 (34.89)	10	197.20 (49.48)	3.50 (22.95)		
Between-group difference					−1.22	−23.74, 21.29	−0.05
LDL, mg/dL							
WLC	11	110.18 (20.09)	11	114.36 (29.97)	4.18 (26.37)		
Metformin	11	120.55 (35.59)	10	126.00 (43.24)	6.40 (16.89)		
Between-group difference					−2.21	−22.69, 18.25	−0.07
HDL, mg/dL							
WLC	11	47.00 (13.97)	11	43.55 (11.26)	−3.45 (5.73)		
Metformin	11	52.18 (8.61)	10	49.70 (7.52)	−2.80 (4.49)		
Between-group difference					−0.65	−5.39, 4.08	−0.12
Triglycerides, mg/dL							
WLC	11	120.91 (55.26)	11	118.36 (71.23)	−2.54 (31.79)		
Metformin	11	107.55 (31.37)	10	119.80 (52.43)	16.30 (32.47)		
Between-group difference					−18.84	−48.21, 10.52	−0.58
Systolic BP, mm Hg							
WLC	11	134.80 (15.09)	11	133.09 (14.45)	−1.70 (9.98)		
Metformin	11	151.50 (25.40)	10	141.30 (20.89)	−13.15 (19.70)		
Between-group difference					11.44	−2.62, 25.51	0.74
Diastolic BP, mm Hg							
WLC	11	88.86 (9.56)	11	8.65 (2.60)	−3.22 (9.49)		
Metformin	11	85.01 (12.54)	10	10.90 (3.44)	−0.67 (10.09)		
Between-group difference					−2.55	−11.50, 6.38	−0.26

All data are reported in mean (SD)

WLC Weight loss counseling, *FBG* Fasting blood glucose, *LDL* Low-density lipoprotein cholesterol, *HDL* High-density lipoprotein cholesterol, *BP* Blood pressure, *HbA1c Hemoglobin A1c, BMI* Body mass index

made participation more convenient. The ability to maintain high retention rates suggests that such strategies should be maintained in future trials.

With regard to the feasibility of the SMART specifically, the response rate to initial interventions closely matched the a priori target of 33% responders. The ability to successfully differentiate between responders and non-responders supports the feasibility of using QUICKI as an early indicator for tailoring second-stage interventions in a full-scale trial. Improvements in QUICKI scores among responders during the initial 8 weeks were maintained throughout the study, reinforcing the durability of early metabolic changes. Notably, the observed increases in QUICKI scores of over 10% among responders exceeded previously reported improvements previously observed from behavioral weight loss interventions [17, 19], suggesting that NC and EC interventions may have contributed meaningfully to insulin sensitivity improvements.

It is notable that the initial NC and EC interventions were delivered in a weight-neutral approach, emphasizing focusing not on weight loss but rather on improving lifestyle habits. While two NC participants had > 5% weight loss, considered the minimal clinically important difference [30], during the initial eight weeks of the study, the overall mean weight change at week 8 was minimal. This finding underscores that improvements in insulin sensitivity could occur in the absence of weight loss, using weight-neutral counseling techniques to improve diet quality and engage in regular exercise. Among non-responders, insulin sensitivity slightly declined on average by week 8, suggesting that first-stage interventions alone may not be sufficient for all individuals. The second-stage interventions, WLC and metformin, appeared to exert a potential rescue effect, with a 4.4% increase in QUICKI scores between weeks 8 and 25. However, non-responders still exhibited lower overall insulin sensitivity improvements compared to responders at the end of the intervention, highlighting the need for more intensive or alternative intervention strategies for this subgroup.

Intervention preferences and adherence patterns provided additional insights into participant engagement. At baseline, the majority of participants expressed moderate or strong preferences for certain intervention components, with NC and WLC being favored over EC and metformin. While some trends suggested that participants who were matched with their preferred intervention had slightly higher adherence, attendance rates remained high (≥ 75%) across all intervention groups regardless of preference alignment. These findings are consistent with previous randomized trials, which suggest that while personal preference can enhance motivation, it does not significantly impact engagement in interventions or subsequent weight loss when compared to random assignment [31, 32]. The ability to maintain high adherence across different intervention components supports the feasibility of delivering structured virtual behavioral interventions within a primary care setting.

Participant feedback further reinforced the acceptability of the interventions while highlighting areas for refinement. Exit interviews revealed that participants were highly satisfied with their engagement in the study and appreciated the support provided by interventionists and study coordinators. However, some participants expressed confusion about the distinction between NC (which followed a weight-neutral approach) with WLC (which explicitly targeted weight loss), underscoring the need for clearer communication regarding intervention goals. Despite a growing and vocal interest in concepts related to body positivity and weight-neutral interventions, these preliminary qualitative findings highlight a prevalent association among many individuals with obesity between "nutrition counseling" and weight loss. This underscores the importance of explicitly clarifying intervention goals to ensure participants fully understand the intended focus of each approach. To further explore perceptions of weight-neutral interventions, future studies should incorporate more rigorous qualitative methods to better capture participant expectations and refine intervention messaging.

Beyond intervention clarity, the format in which counseling sessions were delivered also influenced engagement. Exit interviews indicated that the virtual format not only enhanced accessibility but also reduced transportation and scheduling burdens. These findings align with prior research demonstrating the benefits of telehealth in behavioral interventions [33] and suggest that future trials should continue to leverage remote delivery as a means of enhancing participation and adherence. Ensuring flexibility in session formats may also help accommodate diverse participant needs, particularly in populations with limited access to in-person clinical visits.

Despite the overall feasibility of the intervention model, adherence to metformin presented some challenges. Over half of the participants assigned to metformin reported gastrointestinal discomfort during exit interviews. Additionally, tracking medication adherence using mailed pill returns proved challenging as some participants did not return their bottles, leading to uncertainty in adherence assessments. These findings suggest that alternative medication strategies or improved adherence tracking methods, such as electronic pill monitoring [34], may be needed in future trials.

Building on these insights, the long-term vision for this line of research is to develop adaptive biobehavioral

interventions that can be effectively integrated into primary care settings. The study was successfully conducted within a family medicine clinic and proceeded without major issues, aside from occasional scheduling conflicts between clinical and research assessments. While the study effectively utilized clinic space and resources, it was conducted by research-based staff and interventionists rather than clinic personnel, and not all participants were active patients of the clinic. To enhance the integration of research into routine clinical practice and facilitate the eventual translation of these interventions into primary care, future studies should adopt a more pragmatic approach that aligns more closely with existing healthcare workflows.

Following established frameworks such as the ORBIT Model [35] and the NIH Stage Model [36], future efforts will focus on refining and enhancing the implementation of adaptive intervention packages under investigation to ensure greater alignment with clinical practice. Key strategies will include prioritizing the recruitment of existing clinic patients, scheduling research study visits within the clinic's master calendar to minimize logistical conflicts, and designing study procedures that align with standard clinical workflows. Additionally incorporating clinic-based staff, such as certified medical assistants (CMAs), to conduct study visits and document study outcomes via the electronic health record could further streamline implementation. These modifications will enhance the integration of research into clinical settings, ultimately improving the feasibility, scalability, and long-term impact of the interventions.

Future directions

Building on the findings from the current study, the research team will conduct a second pilot SMART (NCT06284681), incorporating many of the same intervention strategies while implementing key modifications to enhance feasibility. First, participants will be initially randomized to either weight-focused or weight-neutral health coaching led by a registered dietitian for eight weeks. In the weight-focused approach, health coaches will recommend an energy-restricted diet, emphasize weight loss as an important mediator of health improvements, and monitor body weight during health coaching sessions. Conversely, in the weight-neutral approach, health coaches will emphasize the inherent health benefits of consuming a healthy eating pattern and engaging in consistent exercise, independent of changes in weight, with no measurements of body weight taken during the health coaching sessions.

For the second-stage interventions, participants will either receive (1) an intensification of lifestyle-based strategies through a no-cost 4-months YMCA membership, including enrollment in at least two group fitness classes per week, or (2) an augmentation of lifestyle-based interventions by primary care-led medical or pharmaceutical management of obesity and related cardiometabolic risk factors. Importantly, enrollment in the new study will be focused on existing patients of the UAB family medicine clinic where the research will be conducted. This approach aligns visits with clinic appointments, leading to a more pragmatic design that integrates research with routine clinical care. Study visits will be structured to align with the workflow of UAB's established lifestyle medicine clinic. Additionally, a qualitative researcher has been added to the research team to conduct more rigorous qualitative assessments of participant experiences and perceptions of weight-focused and weight-neutral approaches. These refinements will provide deeper insights into intervention acceptability and effectiveness while enhancing the potential for long-term clinical translation.

Conclusions

The findings of this study support the feasibility of conducting a full-scale SMART; however, the research team determined that additional protocol refinements and further feasibility testing through a second pilot SMART were necessary before advancing to a larger trial. The planned modifications aim to enhance intervention delivery, improve integration within clinical settings, and address key implementation challenges identified in this study. Collectively, the results from these two pilot and feasibility trials are expected to provide a strong support foundation for designing a full-scale SMART that will compare weight-focused and weight-neutral adaptive biobehavioral interventions delivered within primary care settings. By targeting improvements in cardiometabolic health among adults with obesity and weight-related chronic conditions, this research will contribute valuable insights into optimizing tailored and adaptive intervention strategies for long-term clinical impact.

Abbreviations

AE	Adverse events
BMI	Body mass index
BP	Blood Pressure
EC	Exercise counseling
FBG	Fasting blood glucose
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
NC	Nutrition counseling
QUICKI	Quantitative Insulin Sensitivity Check Index
SAE	Serious adverse events
WLC	Weight loss counseling

Acknowledgements

The authors extend their gratitude to the clinical staff, nurses, and primary care providers at the University of Alabama at Birmingham, Highlands family medicine clinics, for their invaluable collaboration. Additionally, the authors would like to thank the participants of this study for their contribution.

Authors contribution
RDS, TSM, GRD, and JOH conceived the research design; RDS supervised the study conduct; AE, KME, CNR, and JGC conducted study visits; AE and CWC were study interventionists; AE completed the statistical analyses with support from TSM; AE and RDS drafted the manuscript. JOH is the Principal Investigator of the UAB Nutrition Obesity Research Center and a supplemental grant, which provided support for this study. All authors reviewed, contributed to, and approved the final manuscript.

Funding
This project received support from the National Institute of Diabetes and Digestive and Kidney Diseases, under Award Number P30DK056336, from the UAB Nutrition Obesity Research Center–Chronic Disease and Health Disparities Revision, under Award Number 3P30DK056336-18S1, from the National Institutes of Minority Health and Health Disparities, under award number (5P50MD017338-03, Sub-Project ID 9180), and as part of a competitive revision to the Forge AHEAD Center (P50MD017338-03S1).

Availability of data and materials
The datasets utilized and analyzed in this study are available for access upon a reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study has attained ethical approval from the University of Alabama at Birmingham Institutional Review Board IRB-300005391. The study is also registered at clinicaltrials.gov at (NCT04392284).

Consent for publication
Not applicable.

Competing interests
TSM has received consulting fees from The Obesity Society, Novo Nordisk, New Balance Foundation Obesity Prevention Center, and Heart Rhythm Clinical Research Solutions. The remaining authors declare that they have no competing interests relevant to this work.

Author details
[1]Department of Family and Community Medicine, University of Alabama at Birmingham, Birmingham, AL 35233, USA. [2]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL 35233, USA. [3]Division of Physical Activity and Weight Management, Department of Internal Medicine, Medical Center, University of Kansas, Kansas City, KS 66160, USA. [4]Department of General Internal Medicine and Population Science, University of Alabama at Birmingham, Birmingham, AL 35233, USA.

Received: 19 April 2024 Accepted: 11 March 2025
Published online: 05 April 2025

References

1. MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: Innovative research to improve maintenance of weight loss. Obesity (Silver Spring). 2015;23(1):7–15.
2. Malin SK, Gerber R, Chipkin SR, Braun B. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. Diabetes Care. 2012;35(1):131–6.
3. Sharoff CG, Hagobian TA, Malin SK, Chipkin SR, Yu H, Hirshman MF, et al. Combining short-term metformin treatment and one bout of exercise does not increase insulin action in insulin-resistant individuals. Am J Physiol Endocrinol Metab. 2010;298(4):E815–23.
4. Konopka AR, Laurin JL, Schoenberg HM, Reid JJ, Castor WM, Wolff CA, et al. Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. Aging Cell. 2019;18(1): e12880.
5. Ortega JF, Morales-Palomo F, Ramirez-Jimenez M, Moreno-Cabanas A, Mora-Rodriguez R. Exercise improves metformin 72-h glucose control by reducing the frequency of hyperglycemic peaks. Acta Diabetol. 2020;57(6):715–23.
6. Moreno-Cabanas A, Morales-Palomo F, Alvarez-Jimenez L, Mora-Gonzalez D, Ortega JF, Mora-Rodriguez R. Metformin and exercise effects on postprandial insulin sensitivity and glucose kinetics in pre-diabetic and diabetic adults. Am J Physiol Endocrinol Metab. 2023;325(4):E310–24.
7. Wilding JPH, Calanna S, Kushner RF. Once-weekly semaglutide in adults with overweight or obesity. Reply N Engl J Med. 2021;385(1): e4.
8. Penney TL, Kirk SF. The Health at Every Size paradigm and obesity: missing empirical evidence may help push the reframing obesity debate forward. Am J Public Health. 2015;105(5):e38-42.
9. Nansel TR, Lipsky LM, Liu A. Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. Am J Clin Nutr. 2016;104(1):81–7.
10. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537–44.
11. Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374–83.
12. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes Care. 2012;35(2):446–54.
13. Almirall D, Nahum-Shani I, Sherwood NE, Murphy SA. Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. Transl Behav Med. 2014;4(3):260–74.
14. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016;22(Suppl 3):1–203.
15. U.S. Department of Agriculture & U.S. Department of Health and Human Services. (2020). Dietary guidelines for Americans, 2020–2025. https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials.
16. Stamatakis E, Straker L, Hamer M, Gebel K. The 2018 physical activity guidelines for Americans: what's new? Implications for clinicians and the public. J Orthop Sports Phys Ther. 2019;49(7):487–90.
17. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes. 2005;54(7):1914–25.
18. Gallagher EJ, Leroith D, Karnieli E. Insulin resistance in obesity as the underlying cause for the metabolic syndrome. Mt Sinai J Med. 2010;77(5):511–23.
19. Rector RS, Warner SO, Liu Y, Hinton PS, Sun GY, Cox RH, et al. Exercise and diet-induced weight loss improves measures of oxidative stress and insulin sensitivity in adults with characteristics of the metabolic syndrome. Am J Physiol Endocrinol Metab. 2007;293(2):E500–6.
20. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1.
21. Almirall D, Compton SN, Gunlicks-Stoessel M, Duan N, Murphy SA. Designing a pilot sequential multiple assignment randomized trial for developing an adaptive treatment strategy. Stat Med. 2012;31(17):1887–902.
22. Miller WR, Rollnick S. Motivational interviewing: helping people change. New York: Guilford Press; 2013.
23. Food and Nutrition Board, Institute of Medicine. (2005). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (Macronutrients). The National Academies Press. https://doi.org/10.17226/10490.
24. Hui Chen GS, Lilly Q, Yue, Katz A, Quon MJ. QUICKI is a useful index of insulin sensitivity in subjects with hypertension. Am J Physiol Endocrinol Metab. 2003;284(4):E804–12.
25. Katsuki A, Sumida Y, Gabazza EC, Murashima S, Urakawa H, Morioka K, et al. QUICKI is useful for following improvements in insulin sensitivity after therapy in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2002;87(6):2906–8.
26. Smith D. The CARDia trial protocol. Heart. 2003;89(10):1125–6.
27. Bouchard, C., & Katzmarzyk, P. T. (Eds.). (2013). Weight management: A practitioner's guide. Wiley-Blackwell. https://www.wiley.com/en-us/Weight+Management%3A+A+Practitioner's+Guide-p-9781118343326.
28. Association for the Advancement of Medical Instrumentation. American National Standard. Electronic or automated sphygmomanometers. Arlington (VA): AAMI; 2006.

29. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
30. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? Obesity (Silver Spring). 2015;23(12):2319–20.
31. Yancy WS Jr, McVay MA, Voils CI. Effect of allowing choice of diet on weight loss–in response. Ann Intern Med. 2015;163(10):805–6.
32. Burke LE, Warziski M, Styn MA, Music E, Hudson AG, Sereika SM. A randomized clinical trial of a standard versus vegetarian diet for weight loss: the impact of treatment preference. Int J Obes (Lond). 2008;32(1):166–76.
33. Pande RL, Morris M, Peters A, Spettell CM, Feifer R, Gillis W. Leveraging remote behavioral health interventions to improve medical outcomes and reduce costs. Am J Manag Care. 2015;21(2):e141–51.
34. Chan AHY, Foot H, Pearce CJ, Horne R, Foster JM, Harrison J. Effect of electronic adherence monitoring on adherence and outcomes in chronic conditions: a systematic review and meta-analysis. PLoS ONE. 2022;17(3):e0265715.
35. Czajkowski SM, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. Health Psychol. 2015;34(10):971–82.
36. National Institute on Aging. NIH Stage Model for Behavioral Intervention Development [Internet]. 2021. Available from: https://www.nia.nih.gov/research/dbsr/nih-stage-model-behavioral-intervention-development.

Publisher's Note