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A low-energy total diet replacement program demonstrates a favorable safety profile and improves liver disease severity in nonalcoholic steatohepatitis

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Abstract

Objective: Low-energy diets are used to treat obesity and diabetes, but there are fears that they may worsen liver disease in patients with nonalcoholic steatohepatitis (NASH) and significant-to-advanced fibrosis.

Methods: In this 24-week single-arm trial, 16 adults with NASH, fibrosis, and obesity received one-to-one remote dietetic support to follow a low-energy (880 kcal/d) total diet replacement program for 12 weeks and stepped food reintroduction for another 12 weeks. Liver disease severity was blindly evaluated (magnetic resonance imaging proton density fat fraction [MRI-PDFF], iron-corrected T1 [cT1], liver stiffness on magnetic resonance elastography [MRE], and liver stiffness on vibration-controlled transient elastography [VCTE]). Safety signals included liver biochemical markers and adverse events.

Results: A total of 14 participants (87.5%) completed the intervention. Weight loss was 15% (95% CI: 11.2%–18.6%) at 24 weeks. Compared with baseline, MRI-PDFF reduced by 13.1% (95% CI: 8.9%–16.7%), cT1 by 159 milliseconds (95% CI: 108–216.5), MRE liver stiffness by 0.4 kPa (95% CI: 0.1–0.8), and VCTE liver stiffness by 3.9 kPa (95% CI: 2.6–7.2) at 24 weeks. The proportions with clinically relevant reductions in MRI-PDFF (≥30%), cT1 (≥88 milliseconds), MRE liver stiffness (≥19%), and VCTE liver stiffness (≥19%) were 93%, 77%, 57%, and 93%, respectively. Liver biochemical markers improved. There were no serious intervention-related adverse events.

Conclusions: The intervention demonstrates high adherence, favorable safety profile, and promising efficacy as a treatment for NASH.

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) with significant-to-advanced fibrosis is a severe form of nonalcoholic fatty liver disease (NAFLD). It can lead to cirrhosis and liver cancer. It is estimated to affect up to 2% of adults worldwide, with its prevalence projected to increase by 50% between 2016 and 2030 [1]. Compared with patients with early-stage NAFLD, patients with NASH and fibrosis stage F2 to F3 have a tenfold risk of liver-related events, a threefold risk of cardiovascular disease, and a twofold risk of all-cause mortality. This

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increases the burden on both patients and health care systems [2, 3].

Treatments aim to improve fibrosis without the worsening of NASH and vice versa, but no pharmacological agent is currently licensed. Up to 90% of patients have obesity, and weight gain is independently linked with disease progression [4]. However, clinical guidelines suggest general weight loss advice but rarely recommend offering formal weight loss programs [5]. In current care, general weight loss advice varies greatly and leads to only 3 kg of mean weight loss [6], which is unlikely to meaningfully affect the disease trajectory. Qualitative data suggest that this lack of support to lose weight frustrates patients [7].

Systematic reviews with meta-analysis of trials show that 7% to 10% weight loss can resolve NASH but with no evidence of impacting fibrosis stage [8, 9]. Weight loss of 15% to 20% is associated with improvements in fibrosis in most, but not all, studies [4, 10, 11]. This is typically a result of bariatric surgery, but surgery cannot be offered at scale for a disease as prevalent as NASH. Pharmacotherapy in development for NASH is projected to be expensive; therefore, dietary approaches leading to substantial weight loss at scale would fill this gap but they have not been tested in patients with NASH and liver fibrosis.

Randomized controlled trials of a low-energy, nutritionally replete total diet replacement (TDR) program with behavioral support show 10% mean weight loss at 1 year and 6% at 3 years [12]. It leads to clinically significant reductions in cardiovascular disease risk and liver fat in early-stage NAFLD and to type 2 diabetes remission [13]. It is estimated to be cost-effective for the treatment of obesity and it is currently being rolled out to 10,000 patients with type 2 diabetes within the UK National Health Service (NHS) for diabetes remission [14]. However, there are some safety concerns that the rapid weight loss achieved by the program might worsen existing liver disease. This is based on evidence that NASH or fibrosis may worsen after bariatric surgery in 10% of patients [15], that alanine aminotransferase (ALT) increases transiently during TDR [16], and that fibrosis may develop in patients losing at least 1.6 kg/wk over 4 to 6 months [17].

Therefore, the aim of this study was to assess the safety signals and potential efficacy of the intervention in people with NASH and significant-to-advanced liver fibrosis using noninvasive markers of liver disease severity.

Study Importance

What is already known?

- In the absence of licensed pharmacotherapy for nonalcoholic steatohepatitis (NASH) with fibrosis, weight loss advice is the mainstay of treatment, but, in the vast majority of cases, this leads only to modest weight loss.
- The benefits of a low-energy total diet replacement program have been demonstrated in patients with type 2 diabetes, but there are safety concerns of using this approach in patients with significant-to-advanced liver disease.

What does this study add?

- In this prospectively registered trial in patients with NASH and fibrosis, a low-energy, nutritionally replete total diet replacement program over 24 weeks demonstrated the following: 15% body weight loss; safety and tolerability with no deterioration in liver chemistry or function; significant and persistent improvement in noninvasive assessments of disease severity; and significant and persistent improvement in cardiometabolic markers.

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

- These findings need to be evaluated in a definitive trial.
- The intervention has the potential to reverse the disease trajectory in patients with NASH and moderate-to-advanced fibrosis.
- The intervention has the potential to be implemented in routine care in a cost-effective manner.

METHODS

Design

This was a prospectively registered (ISRCTN12900952), single-arm trial conducted in a tertiary metabolic hepatology clinic at the Oxford University Hospitals NHS Foundation Trust, Oxford, UK. The study was approved by the London-Surrey Borders Research Ethics Committee (reference: 19/LO/1856), and all participants provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Participants

Adults with body mass index (BMI) ≥ 30 kg/m^2 who had 1) histologic evidence of NASH on liver biopsy within the last 36 months defined by presence of all key histological features of NASH according to NASH Clinical Research Network criteria and 2) histologic evidence of Kleiner fibrosis stages 2 to 3 were recruited. The main exclusion criteria were weight loss ≥ 5% since the diagnostic biopsy, evidence of other known forms of chronic liver disease, high alcohol consumption (>14 units in the last week and/or a score >8 on the alcohol screening tool [AUDIT-C]), current insulin use, hemoglobin A1c (HbA1c) > 9%, and unstable medication for type 2 diabetes. Detailed criteria are presented in the online Supporting Information.

Intervention

The 24-week intervention was a low-energy, nutritionally replete TDR program with behavioral support. During the first 12 weeks, participants replaced all food with a package of four soups, shakes, and bars per day, providing approximately 880 kcal/d (Optifast, Nestle Health Science). In the next 12 weeks, participants gradually reduced the meal replacement products while reintroducing food-based meals in line with healthy eating recommendations. Throughout the intervention, participants had one-to-one regular (weekly to biweekly in the first 16 weeks and monthly thereafter) behavioral support delivered over the phone or via a mobile app by a registered dietitian (Oviva) and had their medication for type 2 diabetes and hypertension adjusted, as detailed in the online Supporting Information.

Procedures and measures

Blood pressure, weight, fat-free mass, and fat mass (using bioelectrical impedance) were measured with a standardized protocol. Alcohol intake was based on a 7-day recall interview. Blood samples were analyzed for ALT, aspartate aminotransaminase (AST), alkaline phosphatase, total bilirubin, and HbA1c using standard protocols in the hospital laboratory. Trained operators conducted magnetic resonance imaging and elastography (MRI and MRE) and vibration-controlled transient elastography (VCTE) at 0, 12, and 24 weeks. Participants fasted for at least 4 hours before scans. MRI scans were performed on a Siemens Prisma 3-T scanner (Siemens Healthineers, Erlangen, Germany). MRI-proton density fat fraction (PDFF) and T2* maps were determined using two multiple-echo gradient recalled echo sequences, whereas T1 maps were acquired using a standard shortened modified Look-Locker (shMOLLI) sequence. Values for iron-corrected T1 (cT1) were provided by Perspectum, based on the aforementioned sequences [18]. A difference in cT1 of 81 and 88 milliseconds has been correlated with a one-unit change in ballooning and two-point change in the NAFLD activity score, respectively, and a value of 800 milliseconds has been shown to have good sensitivity and specificity in separating NAFLD from NASH [19, 20]. MRE liver stiffness was determined using a gradient echo sequence. A change of at least 19% in MRE liver stiffness was considered to indicate true change with 95% confidence as per the Quantitative Imaging Biomarkers Alliance guidance and it reflects a one-stage change in fibrosis [21, 22]. Changes in fibrosis-4 (FIB-4), FibroScan-AST (FAST), and MRI-AST (MAST) scores were calculated [23, 24]. Weight loss was used as a marker for intervention adherence in line with previous trials of TDR [25, 26], and participants evaluated the intervention with a feedback questionnaire. Details are available in the online Supporting Information.

Sample size

We took a pragmatic decision to recruit 16 participants. The sample size was in line with other phase II pharmacotherapy trials in NASH evaluating safety and potential efficacy [27, 28]. With this sample size and lack of randomization, we could estimate the precision of the proportion of people with worsening disease in the population with 95% confidence at 0% to 19% if we were to observe no concerning safety signals in our study [29]. If these concerning safety signals were to appear in one, two, or three people in the study, the proportion of people with worsening disease in the population would be 1% to 28%, 3% to 36%, or 7% to 43%, respectively, with 95% confidence.

Blinding

Because of the nature of the intervention, participants could not be blinded. Assessors of the blood samples, VCTE, MRI, and MRE were blinded to intervention adherence and other measurements (e.g., weight change). Assessors of MRI and MRE were also blinded to the time point of the scan. Weight and blood pressure measurements were unblinded.

Statistical methods

All enrolled participants were included in the analysis on an intention-to-treat basis. Missing data were not imputed. Continuous data are reported as medians with interquartile ranges (IQR) and categorical data as counts and percentages. Differences between time points were assessed with the two-sided Wilcoxon signed rank test and they are presented as pseudo-medians with 95% confidence intervals (CI). All p values are nominative and descriptive. In figures, red lines indicate cut-offs for normalized values, and blue lines indicate median change. Statistical analysis was conducted in RStudio version 2022.02.3.

RESULTS

Recruitment and characteristics

Between March 2020 and December 2021 (with recruitment paused between March 24, 2020, and October 26, 2020, because of COVID-19-related restrictions), 36 potentially eligible patients were identified. Of those, 16 participants (44%) were enrolled, and 20 (56%) were not. The reasons for exclusion are in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1).

All participants had histologically proven NASH with fibrosis stage F2 to F3 (Figure 2). The median NAFLD activity score was five (range four to six), with scores ranging between two and three for steatosis, one and two for ballooning, and one for inflammation. The liver fibrosis stage was F2 and F3 in 10 and 6 participants, respectively. Supporting Information Table S1 shows participant characteristics, and Table 1 shows baseline values of outcome measures.

Weight and body composition

During the periods of 0 to 4, 5 to 12, and 13 to 24 weeks, the rate of weight change was −1.9 kg/wk (IQR: −2.5 to −1.3), −1.1 kg/wk

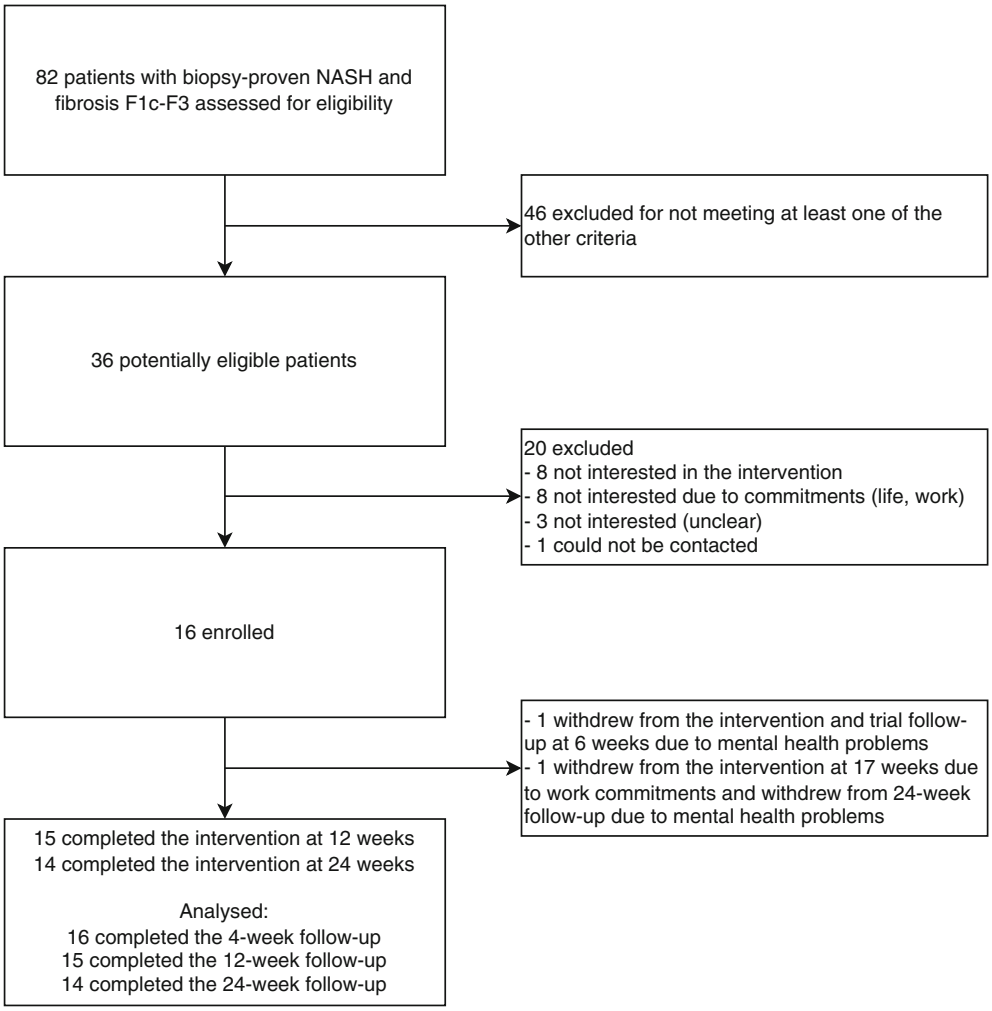

FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) diagram. NASH, nonalcoholic steatohepatitis

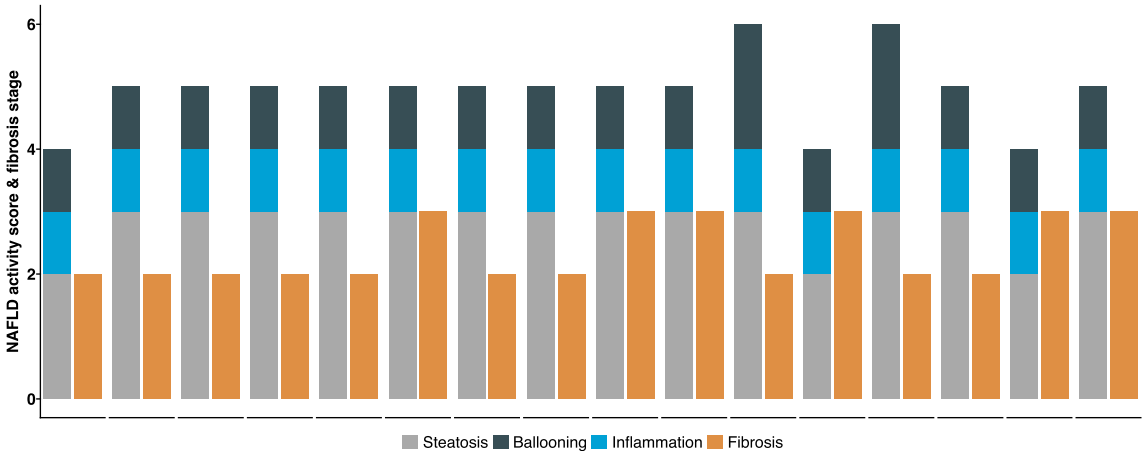

FIGURE 2 Histological NAFLD activity score and fibrosis stage of individual participants at baseline. NAFLD, nonalcoholic fatty liver disease [Color figure can be viewed at wileyonlinelibrary.com]

(IQR: −1.5 to −0.6), and −0.1 kg/wk (IQR:−0.3 to 0.3), respectively. Relative to the median (IQR) weight of 116.6 (93.2 to 123.4) kg at baseline, participants lost 6.6% (95% CI: 5.8% to 8.0%), 14.5% (95% CI: 11.8% to 17.6%), and 15.0% (95% CI: 11.2% to 18.6%) of their weight at 4, 12, and 24 weeks, respectively (Figure 3A). The proportion of people losing 5%, 10%, 15%, and 20% of their weight at 24 weeks

TABLE 1 Changes from baseline in the anthropometric, liver, and cardiometabolic markers

	0 Weeks ($n = 16$)	4 Weeks ($n = 16$)	12 Weeks ($n = 15$)	24 Weeks ($n = 14$)	Change: 0–4 weeks	Change: 0–12 weeks	Change: 0–24 weeks
BMI (kg/m^2)	36.2 (4.9)	33.5 (4.2)	29.8 (3.6)	30.2 (5)	−2.4 (−2.9 to −2)	−5.4 (−6.7 to −4.2)	−5.5 (−6.7 to −4)
Weight (kg at each time point and % change)	116.6 (30.3)	106.6 (25.7)	92.2 (24)	89.2 (26.3)	−6.6 (−8 to −5.8)	−14.5 (−17.6 to −11.8)	−15 (−18.6 to −11.2)
Body fat (kg)	43.3 (10.8)		28.2 (7.5)	29.4 (8.8)	−5.2 (−7.2 to −3.6)	−14 (−17.6 to −9.9)	−12.2 (−16.2 to −9.5)
MRI-PDFF (%)	18.6 (8.5)		3.6 (2)	3 (3.6)		−13.2 (−17.5 to −9.8)	−13.1 (−16.7 to −8.9)
Controlled attenuation parameter (dB/m)	348 (80)		242 (55.5)	221 (73.2)		−91 (−132.5 to −55.5)	−96 (−140.5 to −66.5)
cT1 (ms)[a]	973 (168.5)		765 (109.5)	771.5 (67.8)		−173.5 (−227 to −113)	−159 (−216.5 to −108)
MRE liver stiffness (kPa)[b]	2.8 (0.7)		2.6 (0.7)	2.5 (0.6)		−0.3 (−0.6 to −0.1)	−0.4 (−0.8 to −0.1)
VCTE liver stiffness (kPa)[b]	9.3 (4.9)		5.6 (2)	5.8 (1.1)		−3.8 (−5.7 to −2.8)	−3.9 (−7.2 to −2.6)
ALT (IU/L)	52.5 (39.8)	58 (27.8)	28 (12.5)	22 (10.2)	−3.1 (−18 to 8)	−30 (−53 to −7.5)	−28.5 (−47.5 to −11)
AST (IU/L)	38 (19.2)	37.5 (9)	25 (8.5)	21.5 (9.5)	−1.5 (−8 to 7)	−10.5 (−20 to −1)	−12 (−21 to −3)
Bilirubin (μmol/L)	8.5 (7)	13.5 (5)	10 (9.5)	10 (8.8)	3.5 (1.5 to 5)	4 (0.5 to 6.5)	2 (−0.5 to 4.5)
ALP (IU/L)	97.5 (43)	84.5 (28.2)	77 (42.5)	91.5 (40.2)	−13 (−21 to −7)	−17 (−28 to −6)	−12 (−23 to −4)
FIB-4	1 (0.3)	1.3 (0.8)	1.2 (0.7)	1.1 (0.6)	0.1 (0 to 0.2)	0.1 (−0.1 to 0.2)	0 (−0.1 to 0.2)
HbA1c (%)	6 (1.5)		5.4 (0.7)	5.3 (0.6)		−1 (−1.5 to −0.5)	−0.7 (−1.4 to −0.5)
Systolic blood pressure (mm Hg)	127 (16.6)	116.8 (12)	115.5 (14.5)	122.8 (18.6)	−8.7 (−13.5 to −4.5)	−12.5 (−19.2 to −6)	−8.5 (−14.5 to −4.2)
Diastolic blood pressure (mm Hg)	71.8 (10.2)	69.8 (9.6)	69.5 (6.5)	70.2 (10.4)	−3.2 (−7.3 to 0.2)	−5.2 (−8.3 to −1.7)	−1.7 (−5.7 to 2)

Note: Data are presented as medians with IQR at each time point and Wilcoxon-calculated medians with 95% CI for change in each period.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; cT1, iron-corrected T1; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; VCTE, vibration-controlled transient elastography.

[a]Baseline data available for $n = 15$, as measurement for 1 participant was not quantifiable.

[b]12-week data available for $n = 14$, as measurement of 1 participant was not quantifiable/valid.

was 93%, 71%, 57%, and 21%, respectively. The loss of body fat followed a similar pattern at 5.2 kg (95% CI: 3.6 to 7.2), 14.0 kg (95% CI: 9.9 to 17.6), and 12.2 kg (95% CI: 9.5 to 16.2), respectively. Figure 3B shows the changes in body composition at 24 weeks (individuals and median), indicating that 79% of weight lost was fat mass.

Radiological markers of liver disease severity

The median (IQR) MRI-PDFF at baseline (measured on a 0% to 100% scale) was 18.6% (13.3% to 21.9%). At follow-up, MRI-PDFF worsened in no one, and the significant reduction at 12 weeks was largely maintained at 24 weeks (absolute change from baseline: −13.1% [95% CI: −16.7% to −8.9%] and relative change from baseline: −75.4% [95% CI: −82.5% to −55.6%]). At 12 and 24 weeks, 87% ($n = 13$) and 71% ($n = 10$) of participants, respectively, had less than 5.6% fat in their liver, indicating resolution of steatosis (Figure 4A). The data on the controlled attenuation parameter followed a similar pattern (Figure 4B).

The median (IQR) MRE liver stiffness at baseline was 2.8 (2.6 to 3.3) kPa and it was significantly changed at 12 and 24 weeks compared with baseline by −0.3 (95% CI: −0.6 to −0.1) kPa and −0.4 (95% CI: −0.8 to −0.1) kPa. MRE liver stiffness increased by at least 19% in 14% ($n = 2$) of participants but it was reduced by at least 19% in 57% ($n = 8$) of participants (Figure 4C). The reductions in VCTE liver stiffness were more pronounced, with no one having worsening in their measurement, and 78% ($n = 11$) of participants had normalized stiffness (<6.5 kPa) at 24 weeks (Figure 4D).

cT1, which was elevated at baseline, worsened in no one and it was significantly reduced at follow-up (reduction from baseline at 24 weeks by 159 [95% CI: 108–216.5] milliseconds), with 12 participants having values below 800 milliseconds at 24 weeks (Figure 4E).

Blood-based and combination markers of liver disease severity

By 24 weeks, ALT and AST significantly decreased. No participant showed an increase in ALT or AST values that exceeded the values regarded as the upper limit of the normal reference range used by the laboratory (45 U/L and 42 U/L for ALT and AST, respectively) by more than four times. There was evidence of small but statistically significant increases in total bilirubin levels at 4 and 12 weeks that remained within the normal range and returned to baseline levels by 24 weeks. There were small reductions in alkaline phosphatase and no evidence of changes in the FIB-4 score (Figure 5 and Supporting Information Figure S1). Both the MAST and FAST scores were significantly reduced (Supporting Information Figure S2).

Cardiometabolic markers

HbA1c significantly changed at 12 and 24 weeks compared with baseline (−1% [95% CI: −1.5% to −0.5%] and −0.7% [95% CI: −1.4% to −0.5%], respectively). Systolic blood pressure markedly decreased at 4 and 12 weeks, and the changes were largely maintained at 24 weeks compared with baseline (−8.5 mm Hg [95% CI: −14.5 to −4.2]). Changes in diastolic blood pressure were less pronounced, with no significant difference between baseline and 24 weeks (−1.7 mm Hg [95% CI: −5.7 to 2]). These improvements were observed despite reduction and/or withdrawal of medication for type 2 diabetes and hypertension (Figure 6 and online Supporting Information).

Adverse events

A safety overview is presented in Supporting Information Table S2, with detailed description of adverse events. The majority were judged as mild or moderate by the participants and were transient.

Intervention engagement and evaluation

Of the 14 participants completing the intervention, 4 were offered the reset option of repeating up to 4 weeks of TDR because of >2 kg weight regain between 12 and 24 weeks. One of them followed the reset option at week 22 for 2 weeks, and another did so at week

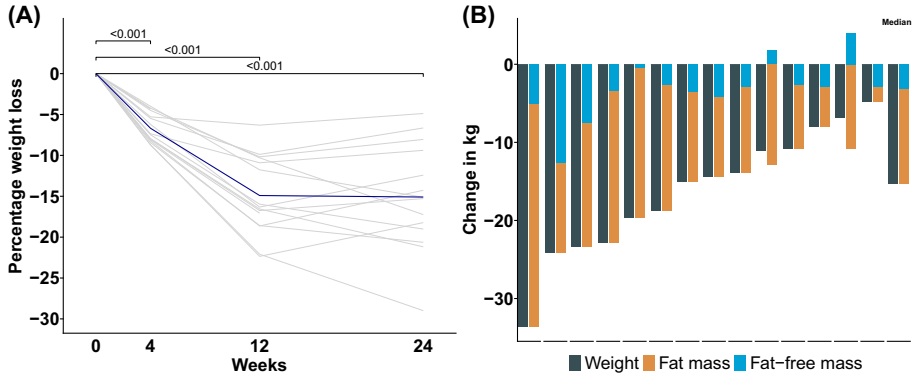

FIGURE 3 (A) Individual weight trajectories of percentage weight loss, with the blue line indicating the median change. (B) Absolute changes in weight, fat, and fat-free mass at 24 weeks in each individual and median (last column) [Color figure can be viewed at wileyonlinelibrary.com]

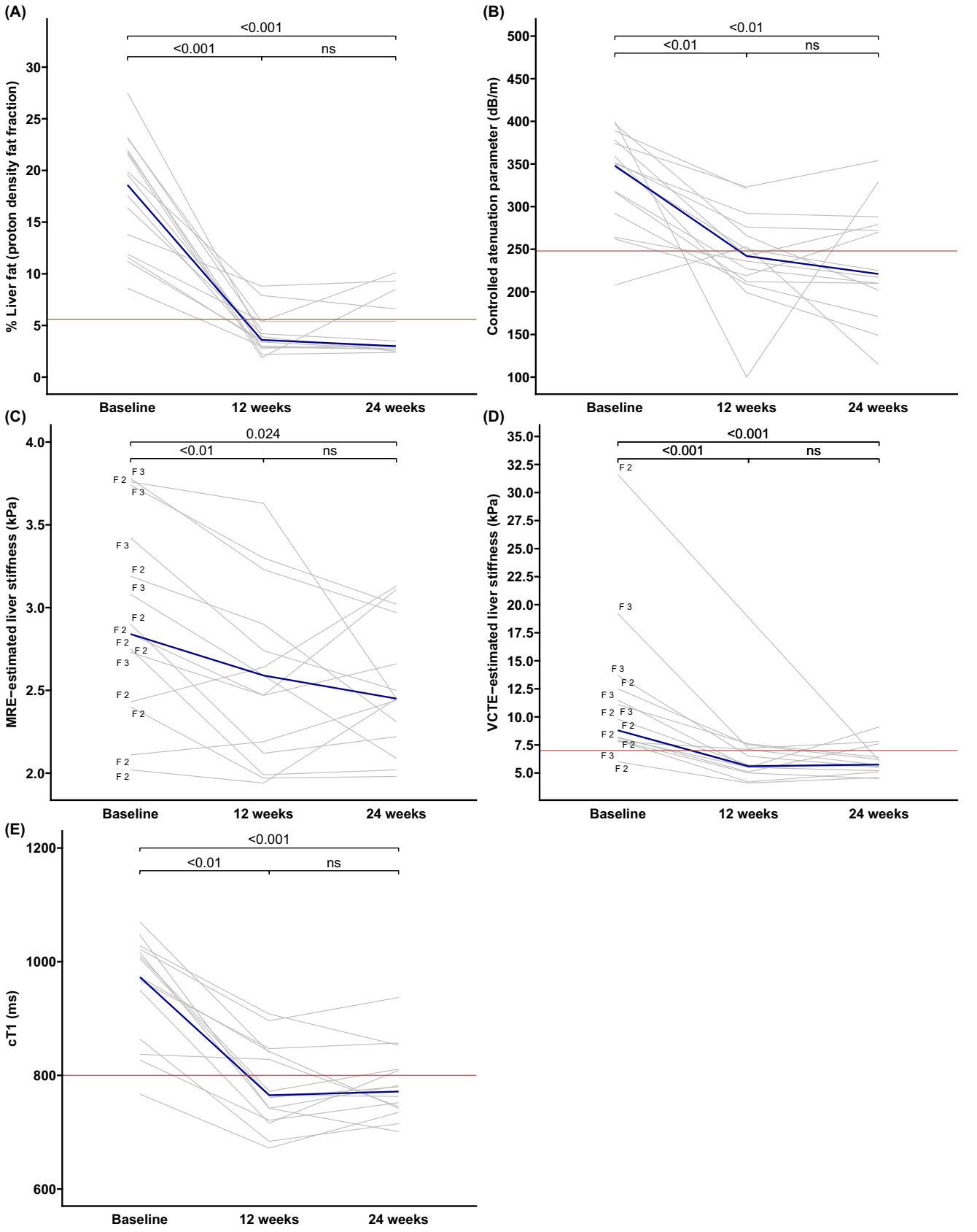

FIGURE 4 (A) Absolute changes in MRI-proton density fat fraction, (B) controlled attenuation parameter, (C) MRE liver stiffness, (D) VCTE liver stiffness, and (E) cT1. cT1, iron-corrected T1; MRE, magnetic resonance elastography; VCTE, vibration-controlled transient elastography [Color figure can be viewed at wileyonlinelibrary.com]

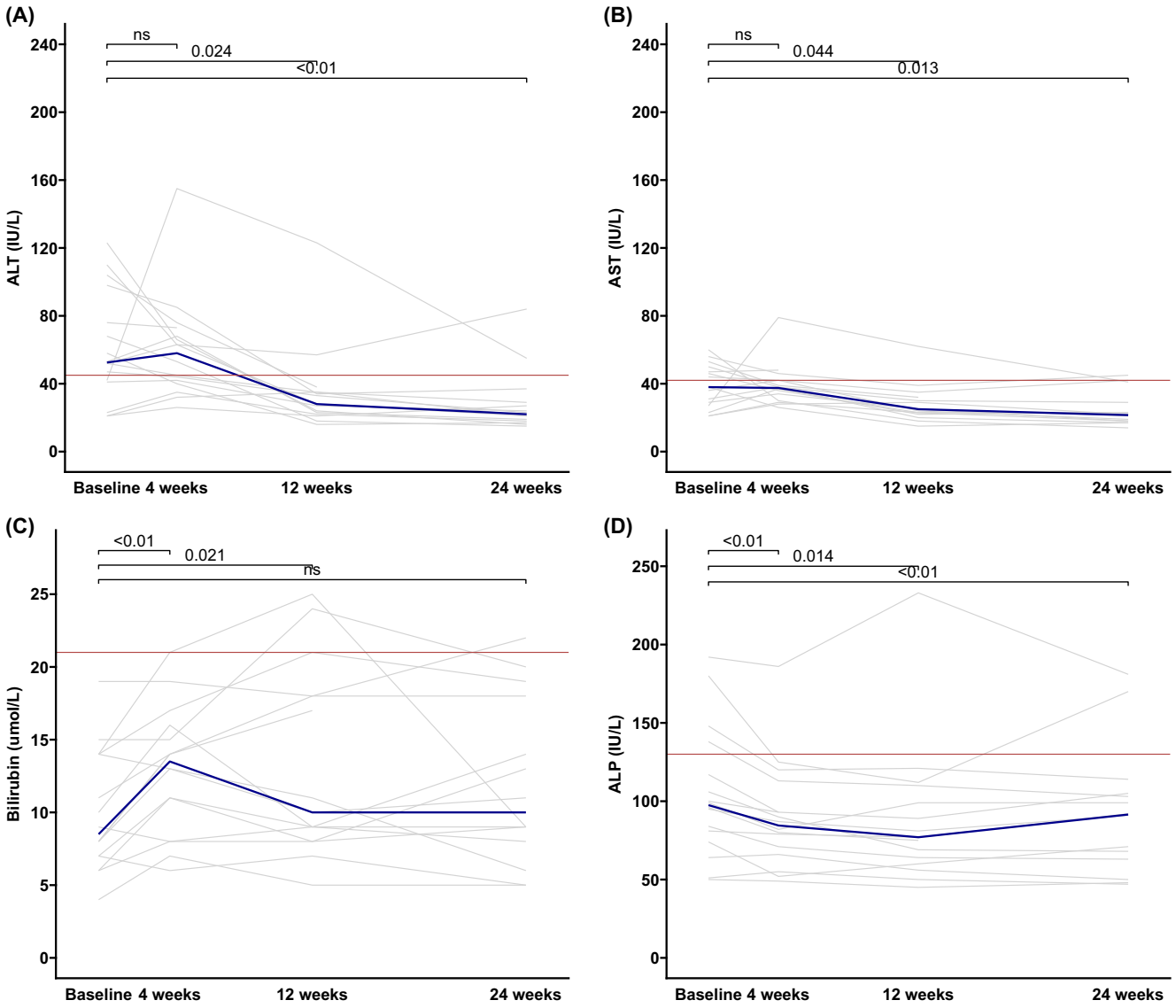

FIGURE 5 Absolute changes in liver function tests. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransaminase [Color figure can be viewed at wileyonlinelibrary.com]

19 for 4 weeks. Intervention engagement was high among the 14 participants, with 9 participants fully engaging with the whole program, 2 participants not engaging with the phone call at week 24, and 2 participants not engaging with the phone calls at weeks 20 and 24 (engagement data missing for 1 participant). The 2 participants who withdrew fully engaged with the program up to their withdrawal (Figure 1). The median weight change among those who fully engaged and among those who partially engaged with the program was −19.6 kg (IQR: −23.4 to −11.1) and −13.9 kg (IQR: −14.4 to −8). Of the 14 participants returning evaluation questionnaires, 12 and 2 participants said that the intervention exceeded and met their expectations, respectively. Their feedback is presented in the online Supporting Information.

DISCUSSION

Patients with NASH and significant-to-advanced fibrosis achieved substantial weight loss following a TDR program, which was associated with sustained clinically meaningful reductions in all measured noninvasive markers of liver disease severity without serious intervention-related adverse events. This provides reassurance regarding the safety of intensive weight loss and evidence of potential efficacy to treat liver fat, inflammation, and fibrosis.

We did not observe any consistent worsening of noninvasive markers of liver disease severity in any participant. No participant had worsening of liver fat or a clinically significant increase in cT1 [19]. Two participants (who lost 15% and 20% of their weight at 24 weeks) with previous histological fibrosis F2 and low baseline MRE liver stiffness had an increase (≥19%) in MRE liver stiffness deemed clinically meaningful [21, 30], but this increase was not corroborated with any of the other markers. No participant met the Food and Drug Administration (FDA) criteria of signals of potential hepatotoxicity [31]. The transient mild elevations in ALT and AST in a minority are in line with data in early-stage NAFLD [32]. This may relate to the rapid release and transport of fatty acids to the liver in the early weeks of the diet and potential transient increase in liver fat [33]. The transient mild

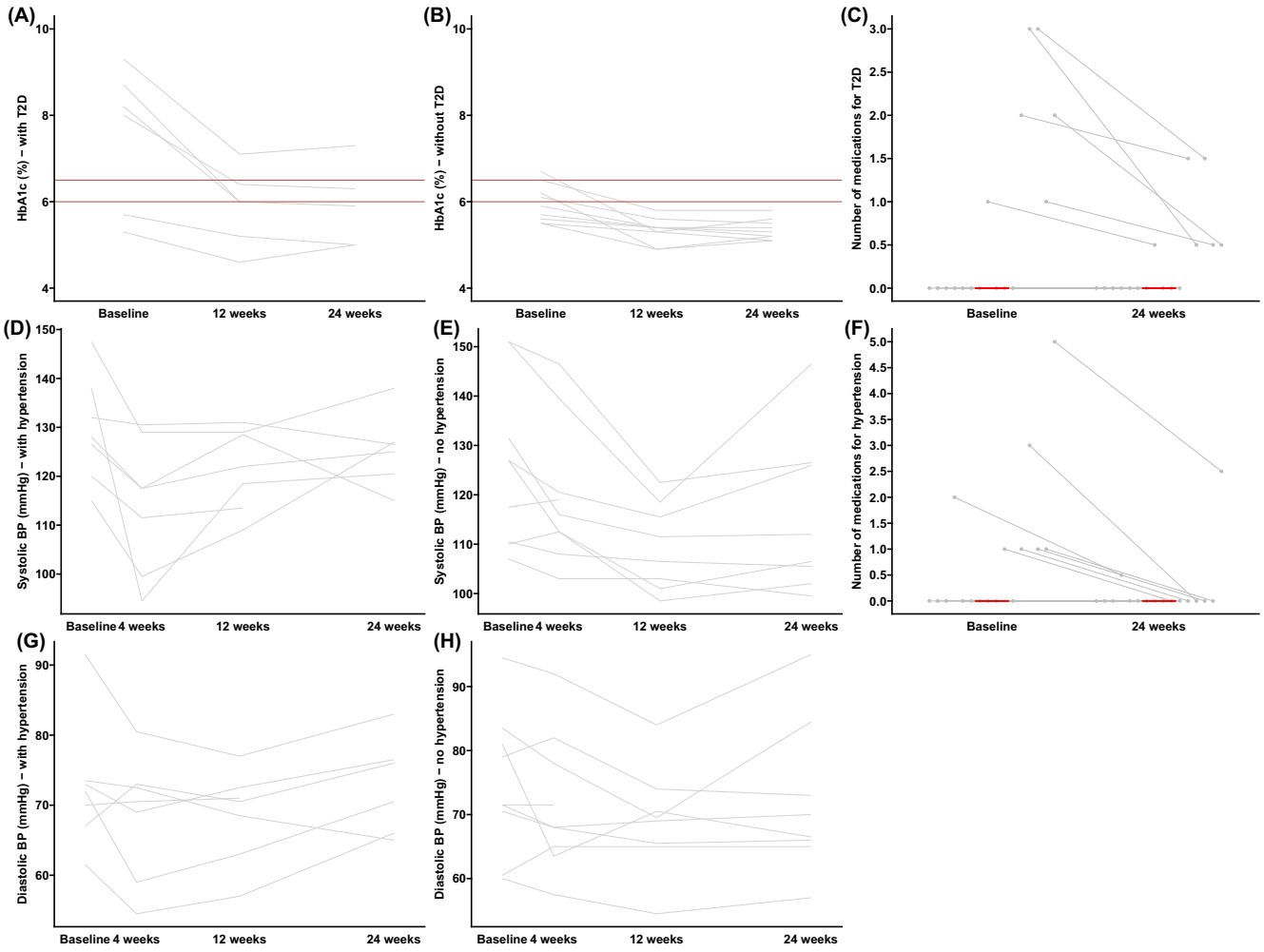

FIGURE 6 Absolute changes in HbA1c, systolic BP, and diastolic BP by baseline medication for T2D and hypertension (panels A,B,D,E,G,H) and number of medication changes (panels C,F). A reduction of 0.5 in the number of medications indicates a 50% dose reduction. The red lines in panels C and F indicate median number of medication at each time point. BP, blood pressure; HbA1c, hemoglobin A1c; T2D, type 2 diabetes [Color figure can be viewed at wileyonlinelibrary.com]

elevations in bilirubin have previously been associated with positive outcomes [34].

The magnitude of observed improvements is among the largest reported in the literature, approaching that seen after bariatric surgery in NASH [10], and is associated with high probability of histological NASH resolution and fibrosis improvement [22, 35, 36]. Based on the combination of clinically meaningful changes in noninvasive markers of liver disease severity, 46% of patients would be predicted to have had improvements in both NASH and fibrosis at 6 months. This suggests that such improvements would be seen with 95% confidence in 23% to 71% of the general population with NASH and fibrosis (based on the Wilson score) [29]. Liver fibrosis is the key driver of morbidity and mortality in this population. The significant reductions in the MRE liver stiffness and other markers of fibrosis suggest possible early improvements in liver fibrosis, although improvements in liver stiffness and other markers of fibrosis may be seen in the context of changes in body habitus and improvement in hepatic steatosis and inflammation. The rapid substantial weight loss, if sustained, is likely to drive fibrosis regression. Our estimates of MRE changes are in line with reductions in MRE liver stiffness 6 months after 14 kg weight loss with bariatric surgery, and an analysis of 421 patients showing that the probability of histological fibrosis improvement with no NASH worsening was 35% (23%–50%) after 15 kg weight loss [4, 37]. However, they contrast with three trials of semaglutide achieving slightly lower weight losses (8%, 11%, and 13% over 24–72 weeks) that showed no changes in MRE liver stiffness, small or no improvement in VCTE liver stiffness, and no changes in histological fibrosis [11, 27, 38].

Long-term data on weight loss maintenance and liver markers are needed to allow for confident predictions on long-term morbidity outcomes. Additional interventions need to be developed to reduce the extent of long-term weight regain. Without intervention, a modest amount of weight regain is expected, with trials suggesting a 6% weight loss from baseline at 3 years, respectively [12]. The impact of this weight regain on the liver in this population requires investigation, as a trial of a 6-month dietary weight loss showed no increase in liver fat at 2 years despite modest weight regain [39], and most trials of

weight loss interventions show strong legacy benefits despite weight regain on type 2 diabetes and cardiovascular risk [40].

The observed weight loss through remote delivery mirrors the weight loss in trials with face-to-face delivery in other populations [12, 13]. Programs of similar duration and intensity have been costed between £796 and £1223 per participant (UK 2017 prices) [14, 41]. The meaningful improvements in cardiometabolic markers are crucial given that cardiovascular disease is the leading cause of mortality [42]. So far, no medication has shown both antifibrotic and cardioprotective properties in NASH and fibrosis stage F2 to F3. Taken together, these data suggest the need for a definitive trial.

Strengths of the trial include a well-characterized population with NASH and significant-to-advanced fibrosis testing of a scalable intervention, blinded outcome assessment, and prospective trial registration. The small sample and lack of a control group are limitations, but the magnitude of changes was large, providing confidence that the changes observed were likely due to the intervention. The ethnic diversity reflected the local population, but studies with more diverse populations are needed. Detailed longitudinal assessments with an array of the most promising markers of liver disease severity minimized risk to patients and allowed serial measurements to determine the changes to measures of liver disease severity over the course of the study, but the lack of paired biopsies means that expected histological changes are extrapolated from other studies that assess histological changes with weight loss. Given that histology was not an outcome measure in this study, we took the pragmatic decision to include patients with histological NASH and fibrosis up to 36 months before screening. However, we excluded patients with more than 5% weight loss since their diagnostic biopsy. This ensured that the stage of the disease at baseline was not underestimated because weight loss is independently associated with disease regression [4].

In conclusion, a low-energy TDR program with behavioral support to achieve weight loss appears safe and efficacious in the treatment of NASH with significant-to-advanced fibrosis. This has the potential to reverse the disease trajectory and it needs to be evaluated in a definitive trial.O

AUTHOR CONTRIBUTIONS

Concept: Susan A. Jebb and Paul Aveyard. Design: Dimitrios A. Koutoukidis, Jeremy F. Cobbold, Susan A. Jebb, Paul Aveyard, Jeremy W. Tomlinson, and Michael Pavlides. Acquisition of data: Dimitrios A. Koutoukidis, Jeremy F. Cobbold, Ferenc E. Mozes, Michael Pavlides, and Francesca Saffioti. Delivery of the intervention: Rosemary Huntriss. Analysis: Dimitrios A. Koutoukidis and Ferenc E Mozes. Interpretation of data: All authors. Funding: Susan A. Jebb and Paul Aveyard. Drafting of the manuscript: Dimitrios A. Koutoukidis. Critical revision and approval of the manuscript: All authors. Supervision: Jeremy F. Cobbold, Jeremy W. Tomlinson, Susan A. Jebb, and Paul Aveyard. Dimitrios A. Koutoukidis is the guarantor of the article.

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CONFLICT OF INTEREST STATEMENT

Dimitrios A. Koutoukidis, Susan A Jebb, Jeremy W. Tomlinson, Michael Pavlides, Paul Aveyard, and Jeremy F. Cobbold are investigators in an investigator-led, publicly funded National Institute of Health Research (NIHR) trial in which the weight loss intervention was donated by Nestle Health Sciences and Oviva to the University of Oxford outside the submitted work. None of these associations led to payments to these authors. Paul Aveyard spoke at a symposium at the Royal College of General Practitioners conference that was funded by Novo Nordisk A/S. Jeremy W. Tomlinson has been part of the scientific advisory boards for Pfizer, Novo Nordisk A/S, and Poxel SA. Michael Pavlides is a shareholder in Perspectum, a University of Oxford spinout company, and has applied for a patent for medical imaging. Rosemary Huntriss was employed by Oviva during the trial. Rosemary Huntriss was an employee of Oviva at the time of the study. Jeremy F. Cobbold has served on advisory boards and consulted for Intercept Pharmaceuticals, Inc., Novo Nordisk A/S, and Alnylam Pharmaceuticals, Inc. The other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ISRCTN12900952.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data are available from the corresponding author on reasonable request. All proposals requesting data access will need to complete a data request form with details of the research question and analysis plan.

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SUPPORTING INFORMATION

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

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