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Randomized Control Trials

Diets differing in carbohydrate cellularity and amount similarly reduced visceral fat in people with obesity - a randomized controlled trial (CARBFUNC)

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SUMMARY

Background & aims: Visceral adipose tissue (VAT) volume is associated with common lifestyle diseases. Dietary quality, including food matrix and degree of carbohydrate cellularity, as well as the carbohydrate/fat ratio, may influence VAT volume. We aimed to determine the effects of isocaloric diets differing in either "cellularity", a novel marker of dietary carbohydrate quality, or carbohydrate amount on visceral fat volume and anthropometric measures in adults with obesity.

Methods: In a randomized controlled trial of 193 people with obesity/central adiposity, we compared changes in VAT volume after 6 and 12 months, measured by abdominal computed tomography, on three isocaloric eating patterns based on "acellular" carbohydrate sources (e.g., flour-based whole-grain products; comparator arm), "cellular" carbohydrate sources (minimally processed foods with intact cellular structures such as fruits, potatoes/tubers, and rice), or low-carbohydrate high-fat (LCHF) principles. Outcomes were compared by an intention-to-treat (ITT) analysis using constrained linear mixed-effects modelling (cLMM) providing baseline-adjusted change scores and proper missing data handling without imputation.

Results: 78 and 57 participants completed 6 and 12 months, respectively, with similar intakes of energy (females: 1820–2060 kcal, males: 2480–2550 kcal) and protein (16–17 energy percent, E%) throughout the intervention, and only modest reductions in energy from baseline. Reported dietary intakes were 42–44, 41–42, and 11–15 E% carbohydrate and 36–38, 37–38, and 66–70 E% fat in the acellular, cellular and LCHF groups, respectively. There were no significant between-group differences in VAT volume after 6 months (cellular vs. acellular [95% CI]: −55 cm^3 [−545, 436]; LCHF vs. acellular [95% CI]: −225 cm^3 [−703, 253]) or after 12 months (cellular vs. acellular [95% CI]: −122 cm^3 [−757, 514]; LCHF vs. acellular [95% CI]: −317 cm^3 [−943, 309]). VAT volume decreased significantly within all groups by 14–18% and 12–17% after 6 and 12 months, respectively. Waist circumference was reduced to a significantly greater

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degree in the LCHF vs. acellular group at 6 months (LCHF vs. acellular [95% CI]: −2.78 cm [−5.54, −0.017]).
Conclusions: Despite modest energy restriction, the three isocaloric eating patterns, differing in carbohydrate cellularity and amount, decreased visceral fat volume significantly and to a similar clinically relevant degree.
Clinical trials identifier: NCT03401970. https://clinicaltrials.gov/ct2/show/NCT03401970.

Abbreviations

A-HCLF	acellular high-carbohydrate low-fat diet
BMI	body mass index
C-HCLF	cellular high-carbohydrate low-fat diet
cLMM	constrained linear mixed-effects model
CT	computed tomography
E%	energy percent
GI	glycemic index
GL	glycemic load
HU	Hounsfield units
ITT	intention-to-treat
LCHF	low-carbohydrate high-fat diet
PAL	physical activity level
RCT	randomized controlled trial
SAT	subcutaneous fat tissue
VAT	visceral adipose tissue
WC	waist circumference
WHtR	waist-to-height ratio

Introduction

Excess intra-abdominal visceral adipose tissue (VAT) is associated with metabolic syndrome components and fat accumulation in the liver [1,2], and through its unique metabolic properties is thought to promote metabolic and cardiovascular disease [3–5]. Dietary management combined with behavior modification are key elements of obesity treatment [6–8] and longer-term studies have shown similar overall weight loss with different dietary approaches [9,10]. However, it remains debated whether certain dietary approaches are more effective than others for reducing visceral and hepatic fat volume specifically. For example, while low-carbohydrate high-fat (LCHF) diets have shown rapid reductions in hepatic fat in humans, despite relatively high energy intake and minimal total weight loss [11], few randomized trials, comparing either carbohydrate quantity or quality (lasting up to 6 months), have included precise quantification of VAT volume [12–15].

Parallel with the major increase in obesity prevalence over the last few decades, there has been extensive globalization of the food system and increased availability of processed foods high in added sugar and other refined carbohydrates [16,17]. Traditional markers of carbohydrate quality include the glycemic index (GI), dietary fiber, and sugar content [18], but do not adequately account for the possible metabolic impact of the food matrix [19], and there could be adverse metabolic effects of carbohydrate refining aside from added sugar (e.g., flour-based products, even whole-grain versions). An alternative marker of carbohydrate quality has therefore been proposed, "cellularity", based on the degree of food matrix breakdown and intactness of the cellular structures in plant-based foods [20]. The cellularity of the diet may affect oral processing, the composition, and function of the microbiota, and the degree of bioavailability and absorption of carbohydrates, also irrespective of GI [20].

Although the beneficial effects on weight loss appear similar between low-carbohydrate and low-fat diets in previous studies [12,21–23], the degrees of energy restriction and definitions of the diets may differ greatly [24]. In most studies, a substantial energy restriction may have masked diet-specific effects, and important questions remain regarding the impact of the carbohydrate restriction and the types of foods and carbohydrate sources consumed, especially on long-term effects. Indeed, many studies comparing low-carbohydrate and low-fat diets did not report the specific types of carbohydrate sources and carbohydrate quality of their diets [18]. Furthermore, regardless of high completion rates, the conclusions of many long-term diet comparisons may be challenged due to decreasing diet adherence resulting in too similar diets over time [25–27]. Additionally, no previous long-term studies have directly assessed the relative importance of altering carbohydrate quality, compared to strongly reducing carbohydrate intake overall, which requires a three-arm design.

We here report results from a three-armed randomized controlled trial (RCT) designed to compare the effect of dietary carbohydrates, both quality (cellularity as a possible marker) and quantity, on changes in internal abdominal fat in people with obesity. We used multi-slice computed tomography (CT) imaging, a gold standard approach [28], to directly quantify abdominal fat volume at baseline, 6-, and 12-month follow-up, with changes in the VAT depot (cm^3) as the primary outcome measure. We primarily sought to assess the efficacy of strict diets as opposed to effectiveness.

Materials and methods

Participants and study design

The present study was an RCT conducted from January 2018 through March 2021 in accordance with the guidelines in the Declaration of Helsinki and was approved by the Regional Ethics Committee in Western Norway (2017/621/REC West). We registered the study protocol at ClinicalTrials.gov (NCT03401970) and collected written informed consent from all participants before enrollment. Participants were recruited through local newspaper advertisements, radio broadcasts, and social media (including advertisements on Facebook), in Bergen, Norway, and the surrounding area.

Inclusion criteria were obesity defined as BMI $\geq$ 30 (kg/m^2) and/or waist circumference (WC) $\geq$102 cm for males and $\geq$88 cm for females, age 20–55 years, and <5% change in body weight within the last 2 months. Exclusion criteria included smoking, known food allergies, habitual alcohol consumption of >2 alcohol units per day, recent surgical or antibiotics treatment during the past 2 months,

use of statins and/or diabetes medication, severe diseases, including chronic inflammatory bowel disease, and for female subjects: pregnancy, breastfeeding, and post-menopause. Participants who fulfilled the initial inclusion criteria were asked by study staff to demonstrate the ability to complete online dietary recordings as a prerequisite for enrollment.

Randomization and blinding

Research personnel not otherwise involved in the study randomly allocated participants to one of the three diets after baseline data collection, using block randomization with block sizes of 6–9 and stratification by sex (R package *blockrand*, version 1.5, RStudio, Inc., Boston, MA, USA). Participants taking part in the study together with a partner, family member, or friend were allocated to the same intervention group to facilitate adherence and prevent disclosure of the diets across groups. Due to the nature of the intervention, participants and staff were not blinded after randomization, with exception of the statistician who was blinded to the group identities until all measures reported herein had been analyzed.

Study visits

Data collection took place at the Research Unit for Health Surveys at the University of Bergen at six time points: baseline, 3, 6, and 9 months, 1 and 2 years. CT scans were performed at baseline, 6 months, and 1 year. The participants arrived in the morning at the research unit after fasting for ≥12 h, abstaining from alcohol consumption for 24 h, and avoiding any strenuous physical activity for the past 48 h.

All participants underwent individual counseling/motivational interviewing with a member of staff between baseline and 3 months and were given a choice of individual counseling or group sessions between the remaining study visits. The group sessions covered content appropriate for their respective diets, including food preparation, maintaining the assigned diet while traveling or dining at restaurants, and strategies for adherence throughout the intervention.

Study intervention

The three study diets were planned as isocaloric diets with 2000 and 2500 kcal per day for females and males, respectively. The quality of dietary carbohydrate sources was defined based on the degree of cellularity as a guiding principle [20], as illustrated by high-resolution microscopic images (Supplementary Fig. 1), resulting in the following study arms: 1) an acellular high-carbohydrate low-fat diet (A-HCLF), 2) a cellular high-carbohydrate low-fat diet (C-HCLF), and 3) a low-carbohydrate very-high-fat diet (LCHF). The planned macronutrient profiles of the A-HCLF and C-HCLF diets were 17 energy percent (E%) protein, 45 E% carbohydrate, and 38 E% fat, differing only in the quality of dietary carbohydrates, and 17 E% protein, 8 E% carbohydrate, and 75 E% fat for the LCHF diet. The planned contribution of saturated fatty acids to total energy intake was 10–12 E% for the A-HCLF and C-HCLF diets, and 30 E% for the LCHF diet. In addition, to limit negative perceptions/bias associated with added sugar and primarily compare other aspects of carbohydrate quality, planned intake of added sugar was low for all groups (<5 E% for A-HCLF and <1 E% for C-HCLF and LCHF diets).

The acellular carbohydrate sources included refined carbohydrate products, such as bread, bakery products, pasta, and quick oats, while cellular carbohydrate sources included minimally refined carbohydrate foods, such as whole (unground) grains, unpolished rice, potatoes, bananas, and rolled oats as depicted in commonly chosen example meals for the respective groups (Supplementary Fig. 2). Of note, rolled oats were previously shown to have more intact cell structures than quick oats [29].

For each study diet, an extensive recipe booklet including diet-specific recipes was provided to all participants. The booklets were developed with the application FileMaker Pro 18 Advanced (Claris International Inc., Santa Clara, CA, USA), which also enabled the linking of recipes and ingredients to a comprehensive database of nutritional content compiled from national and international food composition tables, as described previously [30]. The participants were asked to choose two recipes from the breakfast/lunch recipes (50% of total daily energy intake) and one dinner recipe (50% of total daily energy intake) per day. Of note, the study diets were not eucaloric as tailoring of the recipe booklets to individual energy requirements rather than standardized according to sex (planned with 2000 kcal/d for females and 2500 kcal/d for males) was not feasible. All recipes were given a unique identifier, included accurate amounts of each ingredient and food item, and preparation instructions. The nutrient content of each recipe was pre-calculated so that all diet-specific recipes complied with the macronutrient profiles (both in grams and percentage of energy) and food profiles of the study diets. Over 175 recipes were provided for each diet, allowing the participants to choose from a variety of recipes, both simple and more advanced. Participants also received digital scales for weighing foods/ingredients.

On all three diets, the participants were encouraged to adhere to principles of a varied and nutritious diet by choosing recipes that included 2–3 dinners of fish per week, 2–3 portions of dairy products per day, and ≥500 g of fruits, berries, and/or vegetables per day. Sugary drinks were not included in any of the study diets, and avoidance of artificial sweeteners was encouraged.

Dietary recordings/adherence and physical activity level

During the intervention, we asked participants to record dietary intake for three days every second week including two weekdays and one weekend day. An expanded description of the procedures for nutrient calculation, as well as collection of 6 consecutive day dietary intake data at baseline, is available elsewhere [30]. The participants used an online dietary recording system (www.diett.no; operated by Dietika AS, Slemmestad, Norway) and recorded the unique identifier of the predefined recipes of choice. Alternatively, modifications of the recipes or own compositions of meals were recorded as at baseline. The participants were also asked to answer a questionnaire at every 3-month study visit rating their dietary adherence from “no adherence” (0%) to “complete adherence” (100%) in 20% increments.

A similar physical activity level during the intervention was encouraged, and participants recorded the frequency, duration, and intensity of all daily life activities and sports for 3 days, using the same online system as for dietary recordings. Physical activity level (PAL) was estimated for each participant based on the sum of estimated energy expenditure for each recorded activity and associated metabolic equivalents (METs) divided by 24 h [31].

CT scans

In non-contrasted abdominal CT scan images, we quantified VAT volume (cm^3), SAT volume (cm^3), total abdominal fat volume (VAT + SAT, cm^3), liver density (in Hounsfield units, HU), and liver-to-spleen density ratio (calculated as liver/spleen attenuation index using Hounsfield units; mean hepatic HU/mean splenic HU) in the upper abdomen (from the upper right diaphragm to vertebral corpus L5/S1). The participants underwent CT scanning at baseline,

6 months, and 12 months in a supine position using a 384-slice multidetector CT scanner (SOMATOM Force, Siemens; Siemens CARE Dose 4D automatic exposure control system; 120 peak kilovoltage; 20 mA). The abdominal CT scans were acquired with single-breath-hold technique, and participants were in a fed state having consumed a light meal 2–3 h prior to imaging.

Each single radiation dose was <10 millisievert (mSv), regarded as low-dose radiation without any direct epidemiological data supporting increased cancer risk [32]. Participants who underwent three CT scans from baseline to 1-year follow-up received on average a total radiation dose of 23.2 (SD 8.6) mSv, equivalent to 5 times the estimated natural yearly background exposure in Norway (approximately 4.5 mSv per year) [33]. Overall, the mean dose length product (DLP) was 489 (SD 204) milligray cm (mGy-cm), 383 (SD 154) mGy-cm, and 385 (SD 136) mGy-cm, at baseline, 6 months, and 12 months, respectively. The total radiation exposure in our study is considered to afflict a low risk of adverse effects compared to individual lifetime exposure.

VAT, SAT and total abdominal fat volumes were quantified in iNtuition software (TeraRecon Inc., San Mateo, CA, USA) using a semi-automated method based on segmentation of pixels with values for HU corresponding to fat tissue (−195 to −45 HU) [34]. The segmentations were conducted on a contiguous series of 5 mm thick cross-sectional CT scan images from the participant's upper right diaphragm to the L5/S1 level. After the initial automatic segmentation of VAT and SAT, all segmented volumes were visually verified and manually adjusted if necessary (tracing the abdominal muscular wall separating the two compartments).

Liver and spleen HU densities were measured on single-slice CT images from the central liver and spleen, respectively. Trained personnel performed manual tracing of 15 mm^2 regions of interest (ROIs), three for each organ, and were instructed to avoid vessels and hepatic/splenic pathology when feasible. The average HU score of each ROI was used to calculate liver and spleen density. Finally, the liver-to-spleen density ratio was calculated.

Anthropometry

Height was measured in the upright position with the Frankfort plane horizontal, using a portable stadiometer (Seca 217, Seca, Hamburg, Germany). Body weight was measured with a Class III approved calibrated scale (Seca 877, Seca, Hamburg, Germany) to the nearest 100 g in light clothing without shoes. WC was measured with a non-elastic tape halfway between the point of the lowest rib and the iliac crest and was repeated three times. The average of the last two measurements was recorded.

Statistical analyses

The primary outcome reported in this study is the between-group differences in absolute change scores in VAT volume (cm^3) measured by CT imaging. Secondary outcomes are change scores in subcutaneous fat volume (cm^3), the total volume of abdominal fat (VAT + SAT, cm^3), liver density, liver-to-spleen density ratio, body weight (kg), WC (cm), BMI (kg/m^2), and waist-to-height ratio (WHtR). The results presented are derived from an intention-to-treat (ITT) analysis including all randomized participants (n = 192). The statistical analyses were conducted with R v3.6.1 (https://www.r-project.org), data transformation and exploration were performed with the tidyverse packages (https://tidyverse.tidyverse.org), and plots were made by the ggplot2 package v3.3.5. The distribution of data points from different measurements is shown by violin plots in Supplementary Fig. 3. All inferential tests were two-tailed with a nominal alpha level of 0.05.

The sample size calculation for the primary analysis was based on previous research reporting the effects of different weight-loss diets on visceral fat loss [12,35]. To detect a significant group difference in the study's primary outcome, expected to be around −1300 (500) cm^3 in one group and −1800 (700) cm^3 in the other, our power calculation suggested that n = 18 in each group would be sufficient if the alpha level (type I error rate) was 0.05 and the beta level (type II error rate) was 0.2 (i.e., statistical power of 80%). A higher number of participants were recruited to account for dropouts, which we expected to be high given the strict and long-term dietary program.

Continuous study outcomes were analyzed by baseline-adjusted constrained linear mixed-effects models (cLMMs), a constrained longitudinal data analysis technique [36–40], with "subjects" as the random factor to account for repeated measurements. Sex was used as a stratum in the randomization of the participants and thus included in the model to give valid inference [41]. In addition to 'sex', another stratum used in the randomization process and included in the model was the binary variable indicating whether a participant was randomized as part of a couple or not ('rac'). cLMMs were performed by using the *lme* function in the *nlme* package v3.1–140. The cLMM inherently adjusts for baseline differences when the main term "group" is excluded, thereby constraining the baseline values to be equal across diet arms, a reasonable assumption in RCTs [37,39,40]. See further details in the **Details on statistical analyses** in the Supplementary materials.

The categorical main terms in the models were defined by orthogonal sum coding in planned comparisons showing absolute or relative within- and between-group differences. In the between-group comparisons, the A-HCLF diet was defined as the reference group (comparator arm). Values were transformed by the natural logarithm before analyses of responses in relative terms.

The model validation involved using the Shapiro–Wilk test for normality, the D'Agostino test for skewness, and graphical tools (boxplots, quantile-quantile plots, histograms), to evaluate the distribution of standardized residuals. The Supplementary materials provide further details on the model validation (see **Details on statistical analyses**).

As linear mixed-effects modelling efficiently deals with data sets containing missing outcome values and may serve as an optimal estimator in trials of repeated outcome measures with a large portion of missing data [42–45], we did not pre-specify any other strategy for dealing with potential intermittent missing data or missing data resulting from dropouts. For example, we did not conduct multiple imputation before mixed modelling, as this has shown to add no obvious benefits compared to a standard mixed model approach without imputed values [42–45].

When no outcome data are missing, the test for group difference over time in the cLMM is essentially equivalent to a test for group difference in an ANCOVA mixed model (AMM) [36,37,39,40], which is often regarded as the most robust and powerful method [46–48]. However, the cLMM is at least as efficient and powerful as the AMM [37–40]. Yet, the results of cLMM slightly differ from the results of AMM because of the random part of the models [37,40]. Additionally, when outcome data are missing, the two analyses are based on different populations because participants with missing baseline or follow-up measurements are deleted in the AMM, while the cLMM uses all available data [36,37,39,40]. We therefore conducted a sensitivity analysis of baseline-adjusted follow-up scores at 6 and 12 months to assess how completers contributed to the observations at these time points. This AMM included the fixed terms 'group', 'baseline', 'age', 'sex', and 'rac' (randomized as a couple), a random effects structure with random intercepts-only, a general unstructured correlation structure, and a data-driven variance structure. Here, missing data were not replaced by imputed values before the mixed modeling.

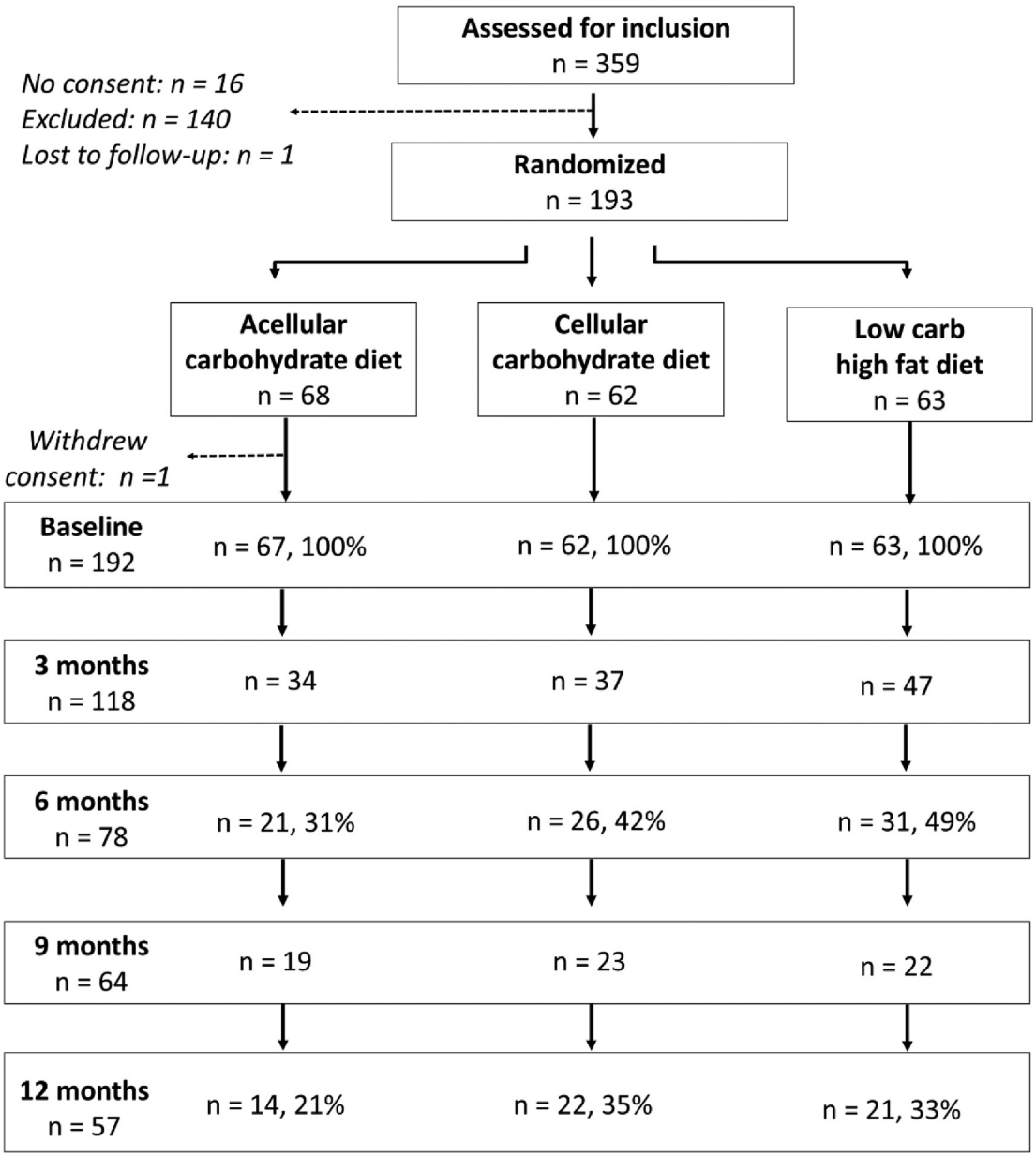

Fig. 1. Flow diagram of the study.

Table 1
Baseline characteristics of participants included in the ITT analysis and the 12-month completers.[a]

	All randomly assigned participants[b]			Only participants who completed 12 months[c]		
	All (n = 192)	Female (n = 101)	Male (n = 91)	All (n = 57)	Female (n = 24)	Male (n = 33)
Age, y	41.6 ± 8.8	40.1 ± 9.1	43.3 ± 8.1	43.4 ± 8.0	43.3 ± 8.4	43.5 ± 7.8
Body weight, kg	111 ± 19	104 ± 16	119 ± 18	105 ± 17	106 ± 17	118 ± 19
Height, m	1.74 ± 0.09	1.68 ± 0.06	1.81 ± 0.06	1.76 ± 0.09	1.69 ± 0.07	1.81 ± 0.07
BMI, kg/m^2	36.7 ± 4.8	36.8 ± 4.7	36.5 ± 4.9	36.6 ± 5.2	37.2 ± 5.6	36.2 ± 5.0
WC, cm	117 ± 12	113 ± 12	121 ± 11	112 ± 13	114 ± 14	121 ± 11
BMR[d], kcal	1913 ± 277	1736 ± 196	2113 ± 213	1944 ± 280	1732 ± 213	2099 ± 215
PAL[e]	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.6 ± 0.3

Abbreviations: BMR, basal metabolic rate; PAL, physical activity level; WC, waist circumference.
[a] Values are means ± SDs.
[b] Baseline characteristics for all randomized participants, excluding one participant who withdrew consent, (n = 192).
[c] Baseline characteristics for all participants who completed 12-month follow-up (n = 57).
[d] Estimated BMR calculated with the Mifflin-St Jeor equation.
[e] Estimated PAL calculated based on estimated energy expenditure for self-reported activity and their associated metabolic equivalent values divided by 24 h.

Results

We included 203 participants, of which 193 participants (102 females) were randomly assigned to one of three study diets. Ten participants were lost to follow-up between baseline assessment and random assignment (Fig. 1). One participant withdrew consent, resulting in available data from 192 participants (101 females) at baseline with a mean age of 42 (SD 8.8) years and mean BMI of 36.6 (4.8). Six of the participants had a MBI below 30 but fulfilled the criteria for waist circumference (≥102 cm for males and ≥88 cm for females). Baseline characteristics for all participants and stratified by sex are presented in Table 1.

78 (41%) and 57 participants (30%) completed the 6 months and 1-year follow-up with 14 (7 females) in the A-HCLF group, 22 (7 females) in the C-HCLF group, and 21 (6 females) in the LCHF group after 12 months (Fig. 1). We were not able to retrieve the CT images from one of the participants in the C-HCLF group at 12 months, resulting in a total of 56 participants with complete data from the CT scans at 12 months.

Sex-specific plots and plots for completers vs. dropouts for primary and secondary outcome measures showed overall similar trajectories (Supplementary Figs. 4 and 5).

Dietary intake, energy, and macronutrients

The most frequently chosen diet-specific recipes/menus, the total food volume, and the frequency of food groups consumed are shown in Supplementary Tables 1 and 2. Overall, the reported mean daily energy intake and the macronutrient profiles remained relatively unchanged throughout the intervention for all three diets. As planned, total energy intake did not differ significantly between groups at any time point during the intervention, except for a significant between-group difference in change scores after 12 months when comparing the HCLF diets (C-HCLF vs. A-HCLF [95% CI]: −290 kcal [−562, −18.8]) (Supplementary Table 3). The reported energy intake did not significantly change from baseline in the A-HCLF or LCHF diets, while in the C-HCLF diet there was a significant modest reduction at all four time points (−11% at both 6 and 12 months) (Supplementary Table 3).

Throughout the intervention, the percentage of energy from carbohydrates and fat was 41–43 E% and 36–38 E% for the A-HCLF and C-HCLF diets (Fig. 2). In the LCHF group, carbohydrate intake was reduced to 11 E% after 3 months, gradually increasing to 15 E% after 12 months. Conversely, the percentage of energy from the fat intake on the LCHF diet increased to 70 E% after 3 months, gradually declining to 66 E% after 12 months (Fig. 2). After a small reduction from baseline to 3 months, protein intake remained stable at 16–17 E% on all three diets and did not differ between groups at any time point (Supplementary Table 3).

Added sugar intake was low on all three diets throughout the study, contributing with 1–2 E% on the A-HCLF diet and <1 E% on the C-HCLF and LCHF diets (Supplementary Table 3). The intake of fiber increased from 20 g/d at baseline to 32–33 and 38–43 g/d on the A-HCLF and C-HCLF diets, respectively (Fig. 2). Although the LCHF group substantially decreased the overall carbohydrate intake, the reduction in fiber was marginal with a mean consumption of 17–19 g/d throughout the intervention.

The estimated contribution of saturated fatty acids to total energy intake was 13 E% and 11–12 E% throughout the intervention for the A-HCLF and C-HCLF diets, and 30–31 E% for the LCHF diet. Polyunsaturated fatty acid intake was 7–8 E% on the LCHF diet and 5–6 E% on the A-HCLF and C-HCLF diets (Supplementary Table 3).

Changes in internal and subcutaneous fat volume

In the primary analysis using cLMM we found no statistically significant between-group differences in change scores for VAT volume (the primary outcome measure) from baseline to 6 or 12 months (Fig. 3, Table 2). There were no significant between-group differences in change scores for SAT volume or total fat volume (VAT + SAT) at any time point (Fig. 3, Table 2). On the LCHF diet, there was a significantly greater increase from baseline in VAT/SAT ratio and VAT% of total fat volume compared to the A-HCLF diet after 6 months (Table 2), reflecting greater loss of SAT volume on the LCHF diet (Supplementary Table 4). There was a significant reduction in VAT volume after 6 months by 14%, 18% and 17% on the A-HCLF, C-HCLF, and LCHF diets, respectively (Fig. 3, Supplementary Table 4). These reductions were largely maintained after 12 months (12–17%). In addition, the total volume of abdominal fat, as well as SAT, significantly decreased from baseline to 6 and 12 months in all three groups (Supplementary Table 4). Finally, the diets produced similar increases in liver-to-spleen density ratio, reflecting reduced hepatic fat content (Table 2). In a sensitivity analysis we also analyzed the CT data by ANCOVA mixed models, which showed a significantly greater reduction in percent VAT at 6 months and in VAT mass at 12 months for the LCHF compared to the A-HCLF diet (Supplementary Table 5). As with cLMM, ANCOVA mixed showed

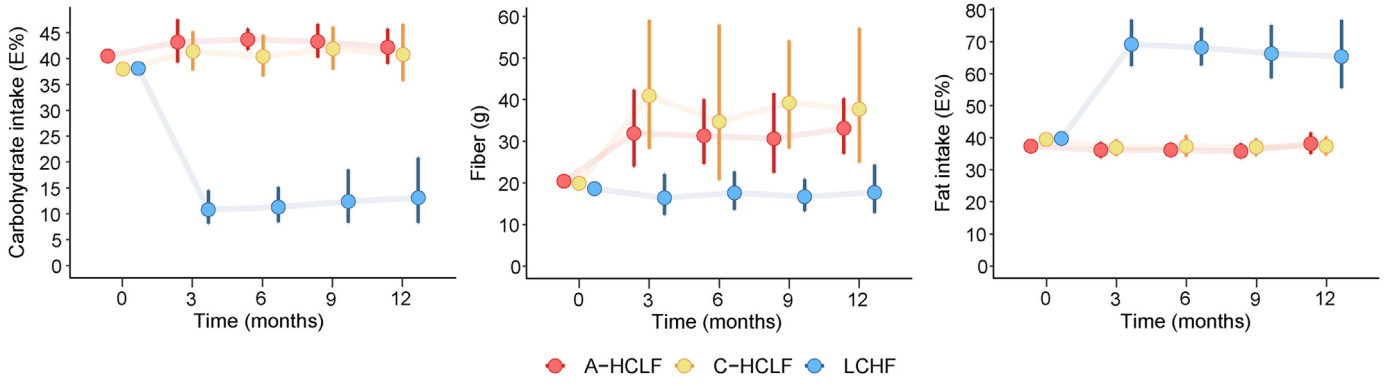

Fig. 2. Dietary intake of carbohydrate (E%), fat (E%), and fiber (g) from baseline to 12 months on the three study diets. Intakes are estimated from three-day dietary records every second week during the intervention. Abbreviations: A-HCLF, acellular high-carbohydrate low-fat diet; C-HCLF, cellular high-carbohydrate low-fat diet; E%, energy percent; LCHF, low-carbohydrate high-fat diet.

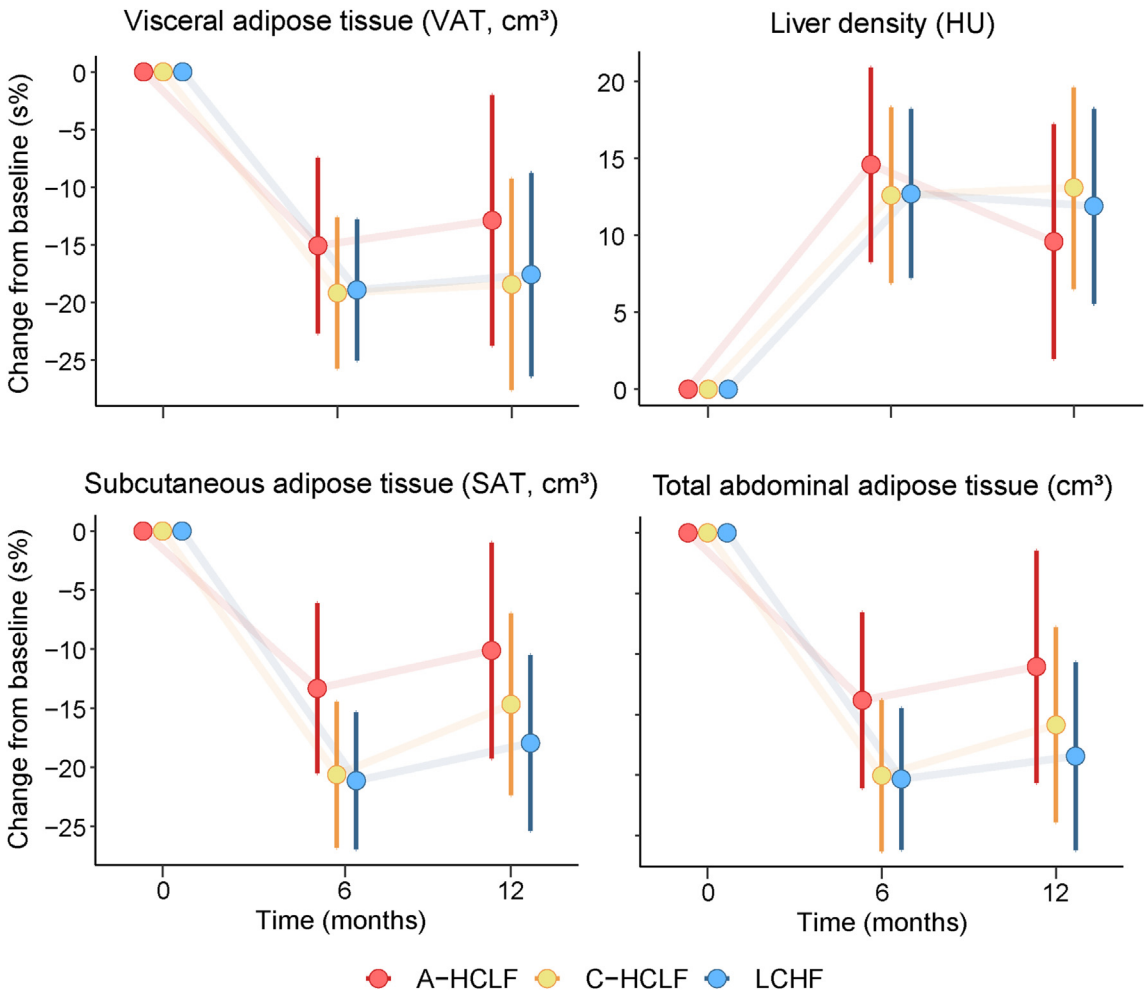

Fig. 3. Changes from baseline in abdominal and hepatic fat volume measured with computed tomography for the three study diets (ITT). Changes are shown in sympercents (95% CIs). Sympercents are additive and symmetric percentage differences on the 100 $\log_e$ scale, calculated as the difference between the natural logs of two numbers multiplied by 100, i.e., 100 × ln(a) − 100 × ln(b) [61]. Abbreviations: A-HCLF, acellular high-carbohydrate low-fat diet; C-HCLF, cellular high-carbohydrate low-fat diet; LCHF, low-carbohydrate high-fat diet; s%, sympercent.

no significant between-group differences in the other CT measures (Supplementary Table 5).

Changes in other anthropometric measures

No significant between-group differences were observed in change scores for mean body weight at any of the follow-up time points (Fig. 4, Supplementary Table 6). Within groups, total body weight decreased significantly on all three diets from baseline to 12 months, with mean reductions of 5.8, 6.7, and 8.2 kg on the A-HCLF, C-HCLF, and LCHF diets, respectively, resulting in an average 5–7% weight loss (Supplementary Table 4). Also, weight loss was significant at all other time points throughout the intervention compared to baseline. In total, 66% of the participants who completed 12 months lost >5% of their initial body weight, and over half of them lost >10%. There was a significantly greater reduction in WC on the LCHF compared to the A-HCLF diet after 6 months (Fig. 4, Supplementary Table 6). No significant between-group differences were observed for WC, WHtR, or BMI after 6 and 12 months (Supplementary Table 6). However, all three diets resulted in significant reductions of 5–8% and 5–7% in WC, WHtR, and BMI after 6 and 12 months, respectively. Analysis by ANCOVA mixed showed a significantly greater reduction on the LCHF compared to the A-HCLF diet at 6 months in body weight, WC, body fat mass and WHtR but no differences at 12 months (Supplementary Table 5).

Adherence to the study diets and maintenance of physical activity level (PAL)

Reported adherence did not differ significantly between the study diets, with an exception after 3 months between the LCHF (80% [SD 23]) and A-HCLF diets (71% [21]) (Supplementary Table 7). The highest (80% [23]) and the lowest (63% [26]) adherence scores were reported in the LCHF diet after 3 and 12 months, respectively. There were no significant differences in PAL between groups after 12 months. PAL was similar at 1.5–1.6 throughout the intervention in all three diet groups (Supplementary Table 6).

Discussion

In this three-armed RCT of adults with obesity, there were no significant differences in the reduction of visceral adipose tissue volume after 6 or 12 months on diets with different carbohydrate cellularity or content. In addition, there were overall no significant between-group differences in subcutaneous adipose tissue volume or liver fat content, nor in anthropometric measures including body

Table 2
Abdominal and hepatic fat volume during the intervention showing between-group differences in absolute change scores[a].

Variable	Baseline[b]	6 months[b]	12 months[b]	Change score 6 mo[c]	p-value[c]	Change score 12 mo[d]	p-value[d]
VAT, cm^3							
A-HCLF	5186 (2410)	4402 (1978)	4855 (2351)				
C-HCLF	5428 (2626)	4647 (2570)	4592 (2609)	−54.9 (−545, 436)	0.825	−122 (−757, 514)	0.706
LCHF	4801 (2344)	4205 (2037)	4299 (1530)	−225 (−703, 253)	0.353	−317 (−943, 309)	0.318
SAT, cm^3							
A-HCLF	9827 (3420)	8360 (3171)	9287 (3172)				
C-HCLF	11,080 (3541)	9674 (3595)	9695 (3716)	−476 (−1211, 259)	0.203	−148 (−1118, 823)	0.764
LCHF	9782 (3523)	7252 (3292)	7341 (3054)	−489 (−1205, 227)	0.179	−542 (−1498, 414)	0.264
Total abdominal fat, cm^3							
A-HCLF	15,013 (4634)	12,762 (3699)	14,142 (3927)				
C-HCLF	16,508 (4792)	14,321 (4812)	14,287 (4904)	−547 (−1695, 602)	0.348	−250 (−1770, 1270)	0.745
LCHF	14,582 (4546)	11,456 (4297)	11,640 (3408)	−704 (−1823, 416)	0.216	−925 (−2423, 572)	0.224
VAT, %							
A-HCLF	34.3 (11.7)	34.8 (12.4)	34.1 (12.7)				
Variable	Baseline[b]	6 months[b]	12 months[b]	Change score 6 mo[c]	p-value[c]	Change score 12 mo[d]	p-value[d]
C-HCLF	32.4 (11.4)	32.2 (12.3)	31.6 (13.1)	1.06 (−1.27, 3.44)	0.373	−1.32 (−4.18, 1.61)	0.370
LCHF	32.7 (12.4)	37.0 (13.9)	37.9 (13.0)	0.99 (0.29, 1.69)	0.006	−0.031 (−0.92, 0.85)	0.944
VAT/SAT ratio							
A-HCLF	0.58 (0.33)	0.59 (0.33)	0.57 (0.32)				
C-HCLF	0.53 (0.32)	0.54 (0.36)	0.53 (0.38)	0.015 (−0.006, 0.036)	0.172	0.000 (−0.024, 0.023)	0.971
LCHF	0.55 (0.37)	0.68 (0.45)	0.70 (0.44)	0.028 (0.007, 0.049)	0.010	−0.009 (−0.034, 0.016)	0.481
Liver density, HU							
A-HCLF	54.0 (14.7)	63.3 (6.58)	59.2 (11.1)				
C-HCLF	55.7 (12.7)	60.5 (8.86)	59.3 (10.4)	−0.79 (−4.03, 2.46)	0.631	1.19 (−3.04, 5.42)	0.579
LCHF	56.7 (14.2)	59.8 (9.80)	61.0 (9.90)	−0.75 (−3.92, 2.42)	0.639	1.15 (−3.04, 5.33)	0.588
Spleen density, HU							
A-HCLF	52.9 (2.78)	53.5 (2.31)	52.9 (3.42)				
C-HCLF	52.1 (2.28)	52.2 (2.58)	52.0 (2.48)	−0.15 (−1.14, 0.84)	0.764	0.096 (−1.27, 1.46)	0.890
LCHF	53.0 (2.62)	54.0 (2.30)	53.6 (2.14)	0.48 (−0.49, 1.45)	0.328	0.31 (−1.05, 1.66)	0.653
Liver/spleen ratio							
A-HCLF	1.02 (0.29)	1.19 (0.14)	1.13 (0.23)				
C-HCLF	1.07 (0.24)	1.16 (0.18)	1.14 (0.22)	−0.008 (−0.070, 0.054)	0.789	0.012 (−0.074, 0.098)	0.783
LCHF	1.08 (0.28)	1.11 (0.20)	1.14 (0.19)	−0.026 (−0.086, 0.035)	0.398	0.042 (−0.029, 0.11)	0.242

Abbreviations: A-HCLF, acellular high-carbohydrate low-fat diet; C-HCLF, cellular high-carbohydrate low-fat diet; cLMMs, constrained linear mixed-effects models; HU; Hounsfield unit; LCHF, low-carbohydrate high-fat diet; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

[a] Data from measurements of body composition with computed tomography imaging were analyzed with cLMMs (ITT). In the between-group comparisons, the A-HCLF intervention was defined as the reference group.

[b] Values are arithmetic means (SDs) of anthropometric measurements at baseline and after 6 and 12 months of follow-up.

[c] Absolute model-adjusted mean change scores (95% CIs) from baseline to 6 months and p-values from the cLMMs.

[d] Absolute model-adjusted mean change scores (95% CIs) from baseline to 12 months and p-values from the cLMMs.

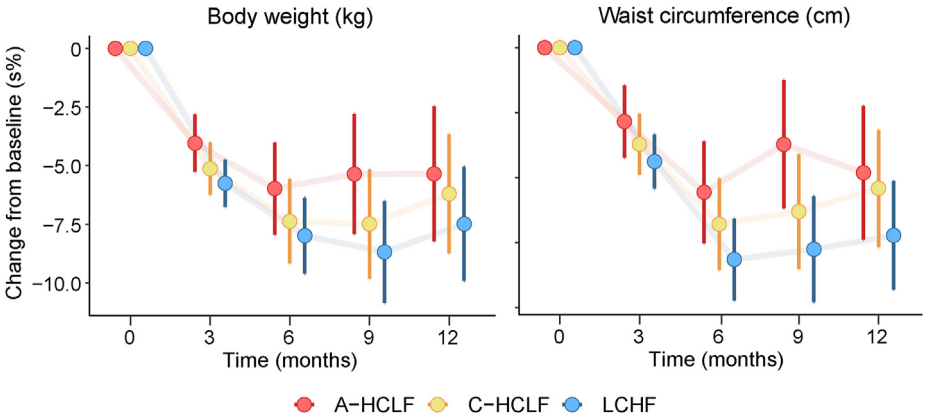

Fig. 4. Changes from baseline in body weight and waist circumference for the three study diets (ITT). Changes are shown in sympercents (95% CIs). Sympercents are additive and symmetric percentage differences on the 100 $\log_e$ scale, calculated as the difference between the natural logs of two numbers multiplied by 100, i.e., $100 \times \ln(a) - 100 \times \ln(b)$ [61]. Abbreviations: A-HCLF, acellular high-carbohydrate low-fat diet; C-HCLF, cellular high-carbohydrate low-fat diet; LCHF, low-carbohydrate high-fat diet; s%, sympercent.

weight, WC, and BMI, except for WC at 6 months with a greater reduction in the LCHF compared to the A-HCLF diet. Despite only modest changes in energy intake from baseline, all three study diets were successful in reducing VAT volume and resulted in a clinically significant body weight loss, as well as improvements in all additional anthropometric outcomes measured both in the shorter and longer-term.

A common challenge in long-term diet studies is to maintain sufficient differences in macronutrient composition and other dietary factors over time [25–27]. Furthermore, many previous long-

term diet comparisons that focus on specific dietary elements may be confounded by differences in overall food profiles and differential intakes of energy, protein, carbohydrates, added sugar, and fiber. A unique characteristic of the present trial is the similar intakes of all or most of these constituents on the three diets while maintaining a long-term intake of carbohydrate types and amounts over 12 months (11–15 vs. 41–44 E% on the LCHF vs. HCLF diets). Importantly, insufficient maintenance of carbohydrate restriction on an LCHF diet may lessen the metabolic benefits [49,50]. A notable difference in carbohydrate cellularity over time was also achieved, even with limited amounts of added sugar, allowing for direct comparison of the long-term impact of carbohydrate sources of different quality as well as amount.

An important finding of our study is the significant reduction of VAT volume after 6 months (14–18%) on all three dietary interventions, largely maintained after 12 months (12–17%), despite a relatively high energy intake and a moderate weight loss (5–8% and 5–7% after 6 and 12 months, respectively). Importantly, the VAT volume reduction after 6 months (14–18%) was largely maintained after 12 months. Overall, our findings of similar VAT loss on the LCHF and HCLF diets are in line with our previous 3-month RCT (FATFUNC) [12], comparing the effect of a largely unprocessed HCLF diet (2200 kcal) and an LCHF diet (2100 kcal) in males with obesity, and with a 6-month randomized comparison of participants with overweight or obesity when following hypocaloric diets (−30% of baseline energy intake) with either moderately reduced carbohydrate or fat intakes [51]. In the latter study, both diets resulted in similar VAT loss of 21% and 22% after 6 months, slightly greater than at 12 months in the present study. Interestingly, despite substantially higher energy intake compared to other studies, and no changes in physical activity level, the present study showed equal or greater reductions of VAT volume after 12 months compared to several dietary and/or exercise interventions, where weight loss was comparable (5–7%) but the duration was shorter [52]. Notably, in the present study we found a significantly greater reduction in waist circumference after 6 months on the LCHF compared to the acellular carbohydrate diet. Additionally, the sensitivity analysis using ANCOVA mixed supports that the LCHF diet was more efficacious for fat loss than the acellular diet, with significant differences in percent visceral fat, body weight, waist circumference and waist-height ratio at 6 months and in visceral fat mass at 12 months.

Corresponding with VAT changes, improvements in liver fat content are expected with weight loss in people with obesity [53], and a body weight reduction of 5–10% has been proposed as a recommended target to improve hepatic steatoses [54]. In our study, the mean baseline liver density values (54–56 HU) were not below 40 HU, which is a common diagnostic criterion for liver steatosis corresponding to ~30% liver fat. However, the baseline ratio of liver-to-spleen was ~1, indicating borderline mild hepatic steatosis with a threshold of liver-to-spleen HU < 1.0 [55,56]. Nonetheless, liver density increased on all three study diets from baseline to 6 months (13–16%) and 12 months (10–14%), indicating a reduction of liver fat content, likely to be metabolically beneficial.

To our knowledge, no previous studies have used cellularity as a measure of carbohydrate quality to compare the effects of dietary interventions on VAT volume. The role of other markers of carbohydrate quality on VAT volume has been studied, indicating a protective effect of higher fiber intake (2-year cohort study) [57], a negative effect of sugar intake exemplified through consumption of sugar-sweetened beverages (6-month RCT) [14], and a beneficial effect of low-GL diets, especially in females (4-month randomized trial) [15]. Specifically, the trial using GL as a marker of carbohydrate quality found an 11% reduction in VAT volume on an 8-week hypocaloric diet in the low-GL group compared to an increase of 1% in the high-GL group [15]. However, these diets differed not only in GL but also in macronutrient composition (low-GL: 43 E% carbohydrates; high-GL: 59% carbohydrates), preventing attribution of the VAT reduction to carbohydrate quality alone. In a recent review by Reynolds et al. [58], total dietary fiber and whole grains were reported as clinically relevant markers of carbohydrate quality, while GI and GL were deemed less useful markers of carbohydrate quality. When evaluating several markers for carbohydrate quality in the A-HCLF and C-HCLF diets in our study, both groups achieved significant reductions in added sugar intake and increases in fiber intake, in line with the Nordic Nutrition Recommendations of added sugar intakes <10 E% and above dietary fiber intakes of 25–35 g/d [59]. Also, fruit and vegetable intakes on both HCLF diets were above estimated average intakes in the Norwegian adult population [60]. The cellularity of carbohydrate foods, or more precisely the increased consumption of acellular forms of carbohydrate foods due to modern processing techniques, was proposed to contribute to obesity [20]. Although the present study did not find significant differences between the acellular and cellular carbohydrate diets in the reported outcomes, diets with greater differences in carbohydrate refining (e.g., including added sugar and flour) might yield different results.

An important methodological aspect of our study is the accurate quantification of adipose tissue using volumetric analysis for reliable measures of VAT and SAT volumes from CT imaging. The multi-slice analysis is superior to the single-slice analysis for repeated scans over time as the movement of soft-tissue structures may alter the location of VAT in a specific single-slice, thus decreasing the reliability of visceral fat measurements. Other whole-body imaging methods, such as dual-energy X-ray and air displacement plethysmography, cannot distinguish between VAT and SAT. Only CT and magnetic resonance imaging can offer direct volumetric measures of VAT [3].

Strengths of the present study include recruiting comparable proportions of male and female participants, collecting extensive high-quality data at repeated time points using robust measures to determine the fat distribution and body composition, and blinding during statistical analyses. These aspects strengthen the confidence in our findings. In addition, detailed information on macronutrient intake was obtained by repeated dietary recordings and pre-planned diet-specific meal recipes, increasing the reliability of the nutrient intake estimates. The diets were matched for energy and protein intakes, and both planned and recorded daily energy intakes were higher than in most comparable dietary interventions. Moreover, physical activity level was recorded throughout the study to increase confidence in the comparison of our outcome measures. Finally, to obtain baseline-adjusted effect estimates of change scores, we used cLMMs, a data analysis technique that increases power compared to ANCOVA mixed modelling when missing data are present.

Our study also has limitations. While substantial efforts were made to maintain adherence, including access to a variety of diet-specific recipes and accessible staff offering support to attain dietary adherence, dropout likely introduced selection bias and/or biased/imprecise effect estimates, potentially limiting the generalizability of the study. However, we used linear mixed-effects modelling without prior imputation, which is more powerful than other options for an ITT analysis in studies with a high proportion of missing data [45], and robust for data sets with up to 60% missing values under different missing value mechanisms [43], supporting our analyses. Notably, no ad hoc strategy was implemented for dealing with missing repeated outcome measurements, as multiple imputations of missing values are not necessary before analyzing longitudinal data with a mixed model approach, regardless of the missing data mechanism [42–44]. Nonetheless, according to the power calculation which estimated a need for 18

participants per diet, the analysis may have been underpowered with 14 completers in the A-HCLF comparator arm. Moreover, while CT provides unique measures of fat distributions, segmenting fat based on fixed CT density thresholds may to some degree under-/overestimate the fat components, especially within the complex visceral fat. Diffuse or microscopic fatty infiltration around visceral vessels and intestines may not reach the fatty threshold defined by CT density (−195 to −45 HU) due to partial volume effects. Thus, it is possible that the absolute CT quantification of visceral fat volumes may be slightly underestimated, particularly in patients with pronounced visceral obesity, which may have contributed to some of the individual variation before and after intervention. Furthermore, the inclusion of relatively healthy non-smoking individuals with obesity further limits the generalizability of our findings. Finally, we cannot rule out that the significant fat loss occurred due to greater energy deficit on the interventions than captured by the dietary records (which showed no or only modest changes in energy intake), particularly if underreporting was more pronounced at baseline.

Conclusion

In conclusion, we found similar changes in visceral adipose tissue volume after diets based on acellular or cellular carbohydrate sources or low carbohydrate intake altogether, all relatively high in total energy but very low in added sugar. The VAT volume reduction at 6 months (14–18%) was largely maintained at 12 months (12–17%). Our study supports recommending the different dietary profiles for people with intra-abdominal obesity based on personal preferences, without the need for strict energy restriction, to achieve clinically relevant long-term fat loss.

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Author contributions

Cathrine Horn Sommersten: Writing - original draft preparation, Project administration, Investigation, Data curation, Methodology. Johnny Laupsa-Borge: Formal analysis, Software, Data curation, Validation, Writing - review & editing. Amanda I. O. Andersen: Investigation, Data curation, Resources, Writing - review & editing. Kristine Eldevik Fasmer: Methodology, Writing - review & editing. Mari-Anna Holmefjord: Investigation, Data curation, Writing - review & editing. Ingrid Revheim: Investigation, Resources, Writing - review & editing. Kristine Kjerpeseth Johannessen: Investigation, Resources, Writing - review & editing. Nicole T. Næsheim: Investigation, Resources, Writing - review & editing. Inghild Storås: Investigation, Resources, Writing - review & editing. Trine Leikanger: Investigation, Resources, Writing - review & editing. Kristin Amundsen: Investigation, Writing - review & editing. Karoline Lyngstad Skjerve: Visualization, Writing - review & editing. Laurence Lawrence-Archer: Visualization, Writing - review & editing. Camilla Spjelkavik: Investigation, Writing - review & editing. Ingfrid Haldorsen: Methodology, Writing - review & editing. Inge Lindseth: Conceptualization, Methodology, Writing - review & editing. Jutta Dierkes: Resources, Funding acquisition, Writing - review & editing. Gunnar Mellgren: Resources, Funding acquisition, Writing - review & editing. Simon N. Dankel: Conceptualization, Investigation, Supervision, Project administration, Methodology, Resources, Funding acquisition, Writing - review & editing.

Data statement

Data described in the manuscript will be made available upon request pending application and approval.

Conflict of Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

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