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Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake

Kevin D. Hall[1]✉, Juen Guo[1], Amber B. Courville[1], James Boring[2], Robert Brychta[1], Kong Y. Chen[1], Valerie Darcey[1], Ciaran G. Forde[3], Ahmed M. Gharib[1], Isabelle Gallagher[1], Rebecca Howard[1], Paule V. Joseph[4,5], Lauren Milley[1], Ronald Ouwerkerk[1], Klaudia Raisinger[2], Irene Rozga[1], Alex Schick[1], Michael Stagliano[1], Stephan Torres[2], Mary Walter[1], Peter Walter[1], Shanna Yang[2] and Stephanie T. Chung[1]

The carbohydrate–insulin model of obesity posits that high-carbohydrate diets lead to excess insulin secretion, thereby promoting fat accumulation and increasing energy intake. Thus, low-carbohydrate diets are predicted to reduce ad libitum energy intake as compared to low-fat, high-carbohydrate diets. To test this hypothesis, 20 adults aged 29.9 ± 1.4 (mean ± s.e.m.) years with body mass index of 27.8 ± 1.3 kg m^{-2} were admitted as inpatients to the National Institutes of Health Clinical Center and randomized to consume ad libitum either a minimally processed, plant-based, low-fat diet (10.3% fat, 75.2% carbohydrate) with high glycemic load (85 g 1,000 kcal^{-1}) or a minimally processed, animal-based, ketogenic, low-carbohydrate diet (75.8% fat, 10.0% carbohydrate) with low glycemic load (6 g 1,000 kcal^{-1}) for 2 weeks followed immediately by the alternate diet for 2 weeks. One participant withdrew due to hypoglycemia during the low-carbohydrate diet. The primary outcomes compared mean daily ad libitum energy intake between each 2-week diet period as well as between the final week of each diet. We found that the low-fat diet led to 689 ± 73 kcal d^{-1} less energy intake than the low-carbohydrate diet over 2 weeks (P < 0.0001) and 544 ± 68 kcal d^{-1} less over the final week (P < 0.0001). Therefore, the predictions of the carbohydrate–insulin model were inconsistent with our observations. This study was registered on ClinicalTrials.gov as NCT03878108.

Increasing obesity prevalence is thought to have been caused by increased availability, convenience and marketing of food whose quality, quantity and composition have changed over time to promote excess energy intake[1]. Two competing models of obesity and its treatment contrast the relative roles of dietary fat versus carbohydrate. According to the carbohydrate–insulin model of obesity, intake of high-glycemic carbohydrates results in elevated postprandial insulin, which is believed to promote body fat accumulation and thereby increase hunger and energy intake[2,3]. Alternatively, high-fat foods may promote passive overconsumption of energy due to their high energy density, their weak effect on satiation and satiety[4–7], as well as modifying food hedonics in a way that supports increased intake[4,6–8].

Whether consumption of low-carbohydrate (LC) or low-fat (LF) diets offer benefits for appetite control has been the subject of long-standing debate. Outpatient diet studies have repeatedly failed to observe meaningful differences in long-term weight loss when participants are randomized to follow LC versus LF diet prescriptions[9]. However, free-living people do not often adhere to prescribed diets, even when all study food is provided[10–12]. Inpatient studies ensure diet adherence, but few inpatient studies lasting more than a few days have measured ad libitum intake differences between diets varying in carbohydrate and fat[13–15] and none has investigated LC versus LF diets that were both sufficiently low in their targeted macronutrients to potentially reveal the benefits of one diet over another. For example, substantial restriction of dietary carbohydrate is required to induce a state of ketosis, which is thought to suppress appetite[16,17].

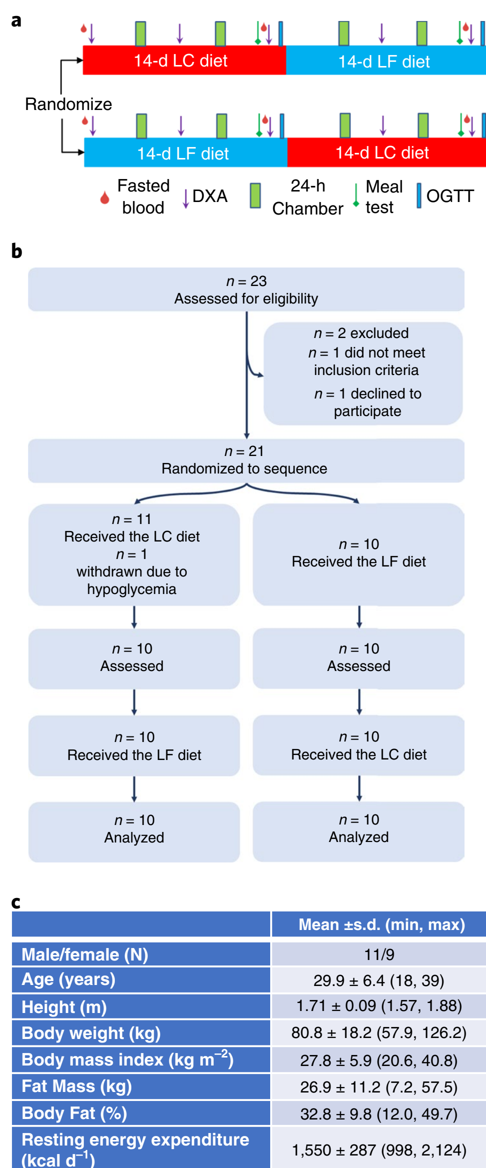
Advocates of LC, ketogenic diets often recommend consumption of nonstarchy vegetables and a variety of animal products, while avoiding foods high in sugar and starch. In contrast, advocates of LF diets often recommend 'whole food' plant-based diets that also include nonstarchy vegetables, but with added whole grains, legumes and starchy vegetables, while avoiding oils, cooking fats and spreads.

We conducted an inpatient crossover study in 20 adults without diabetes who were exposed for 2 weeks each in random order to an animal-based, ketogenic, LC diet with ~10% of energy from carbohydrates, ~75% from fat and high energy density (~2 kcal g^{-1}) compared to a plant-based, LF diet with ~10% of energy from fat, ~75% from carbohydrate and low energy density (~1 kcal g^{-1}) (Fig. 1a). Both diets were low in ultra-processed food and were matched for nonstarchy vegetables. The first primary outcome compared mean ad libitum energy intake between each 2-week diet period. The second primary outcome compared mean ad libitum energy intake on the second week of each diet period to allow for physiological adaptations to the diets and dissipation of carryover effects.

Results

Volunteers were recruited through the National Institutes of Health (NIH) Office of Patient Recruitment beginning 28 February 2019.

[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA. [2]National Institutes of Health Clinical Center, Bethesda, MD, USA. [3]Singapore Institute for Food and Biotechnology Innovation, Singapore, Singapore. [4]National Institute of Nursing Research, Bethesda, MD, USA. [5]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA. ✉e-mail: kevinh@niddk.nih.gov



	Mean ±s.d. (min, max)
Male/female (N)	11/9
Age (years)	29.9 ± 6.4 (18, 39)
Height (m)	1.71 ± 0.09 (1.57, 1.88)
Body weight (kg)	80.8 ± 18.2 (57.9, 126.2)
Body mass index (kg m^{-2})	27.8 ± 5.9 (20.6, 40.8)
Fat Mass (kg)	26.9 ± 11.2 (7.2, 57.5)
Body Fat (%)	32.8 ± 9.8 (12.0, 49.7)
Resting energy expenditure (kcal d^{-1})	1,550 ± 287 (998, 2,124)

Fig. 1 | Overview of the study design, participant flow and baseline information. a, Adult participants were confined to a metabolic ward where they were randomized to consume either an animal-based, ketogenic, LC diet or a plant-based, LF diet for 2 consecutive weeks followed immediately by the alternate diet. Body weight, vital signs and capillary β-hydroxybutyrate were measured daily in the overnight fasted state. Accelerometers and CGMs were worn throughout. Every week, participants spent 1 d residing in a respiratory chamber to measure energy expenditure. Body composition was measured by DXA as indicated. Meal tests and OGTTs were performed at the end of the second week on each diet. **b**, Participant flow diagram. **c**, Baseline information about the study participants.

Screening and enrollment began 15 April 2019 and the last participant was discharged on 4 March 2020. One volunteer who was enrolled in the study was removed during their first week due to a hypoglycemia episode during the LC diet (Fig. 1b). Data from this participant were excluded. We admitted 11 male and 9 female adults with stable weight (Fig. 1c) aged 29.9 ± 1.4 y (mean ± s.e.) with body mass index of 27.8 ± 1.3 kg m^{-2} as inpatients to the Metabolic Clinical Research Unit at the NIH Clinical Center, where they resided for a continuous 28-d period. Full participant inclusion and exclusion criteria are available in the Methods. Participants were randomly assigned to either the LC or LF diet for 2 weeks immediately followed by the alternate diet for the final 2 weeks (Fig. 1; Methods). We did not include a washout period between test diets to reduce the likelihood of dropouts. Participants were not informed of the primary aims of the study but were told that its purpose was to learn about how diets varying in carbohydrate and fat affect the body. The volunteers were told that this was not a weight loss study and that they should not be trying to change their weight. They wore loose fitting clothing throughout the study and were blinded to daily weight, ketone and continuous glucose measurements.

During each diet phase, participants were presented with three daily meals at standardized times and a continuous supply of snacks and bottled water. Daily food and beverages were provided at twice each participant's estimated baseline energy requirements (calculated as 1.6 × resting energy expenditure measured at screening) and they were instructed to consume as much or as little as desired. Up to 60 min was allotted to consume each meal. Menus rotated on a 7-d schedule and meals were designed to be well matched across diets for total energy, protein and nonstarchy vegetables. However, the diets differed widely in energy density and the percentage of energy derived from carbohydrate versus fat such that the LC diet contained 10.0% of total energy from carbohydrate, 75.8% fat, 14.2% protein and had a nonbeverage energy density of 2.2 kcal g^{-1}, while the LF diet contained 10.3% of total energy from fat, 75.2% carbohydrate, 14.5% protein and had a nonbeverage energy density of 1.1 kcal g^{-1} (Table 1). The LC meals derived 82% of energy from animal products, whereas the LF meals contained only plant-based products. Details of the foods and beverages provided are in Supplementary Materials.

Ad libitum energy intake. Fig. 2a shows the time course of the mean daily ad libitum energy intake during the LF and LC diet periods. Mean energy intake during the LF diet was 689 ± 73 kcal d^{-1} lower than the LC diet over the 2-week test periods ($P < 0.0001$) which was the first primary aim of the study. There were no significant effects of diet order ($P = 0.32$) or sex ($P = 0.13$). The second primary aim was to compare ad libitum energy intake during the second week of each diet period, which was 544 ± 68 kcal d^{-1} lower during the LF diet compared to the LC diet ($P < 0.0001$). While energy intake was not significantly different between the first and second week of the LF diet (14 ± 46 kcal d^{-1}; $P = 0.77$), during the second week of the LC diet, energy intake was 312 ± 46 kcal d^{-1} lower than the first week ($P < 0.0001$).

Fig. 2b shows the 2-week average energy intake values for each individual participant, showing that all participants consumed less energy during the LF diet compared with the LC diet. Similar results were found comparing the final week on each diet (not shown).

Fig. 2c shows that the macronutrient composition of the consumed foods and beverages was similar to those presented (Table 2), with LC consumption being 9.9 ± 0.3% carbohydrate, 74.6 ± 0.2% fat and 15.5 ± 0.2% protein and LF consumption being 10.5 ± 0.2% fat, 75.5 ± 0.3% carbohydrate and 14.0 ± 0.2% protein. Carbohydrate and fat intake substantially differed between the diets by design ($P < 0.0001$), but despite matching the dietary protein in the presented LC and LF diets, protein intake was lower during the LF diet, both in absolute terms (−135 ± 14 kcal d^{-1}; $P < 0.0001$) as well as when expressed as a fraction of the energy consumed (−1.5 ± 0.3%; $P < 0.0001$).

We also undertook post hoc analyses of differences in energy intake in meals and snacks and found that the LF diet resulted in lower intake than the LC diet at breakfast (624 ± 27 kcal d^{-1} with LF versus 865 ± 27 kcal d^{-1} with LC; $P < 0.0001$), lunch (625 ± 25 kcal d^{-1} with LF versus 768 ± 25 kcal d^{-1} with LC; $P = 0.0008$), dinner (632 ± 26 kcal d^{-1} with LF versus 827 ± 26 kcal d^{-1} with LC; $P < 0.0001$) and snacks (171 ± 25 kcal d^{-1} with LF versus 299 ± 25 kcal d^{-1} with LC; $P = 0.002$). Energy density of consumed

Table 1 | Diet composition of the average 7-d rotating menu presented to the participants during the animal-based, ketogenic, LC diet and plant-based, LF diet

	LC diet	LF diet
Three daily meals		
Energy (kcal d^{-1})	3,875	3,869
Carbohydrate (%)	9.9	75.2
Fat (%)	74.4	10.6
Protein (%)	15.7	14.2
Energy density (kcal g^{-1})	1.72	0.92
Nonbeverage energy density (kcal g^{-1})	1.80	0.92
Sodium (mg 1,000 kcal^{-1})	2,362	2,013
Fiber (g 1,000 kcal^{-1})	6.8	29.9
Sugars (g 1,000 kcal^{-1})	10.1	50.9
Saturated fat (g 1,000 kcal^{-1})	29.7	1.9
Monounsaturated fat (g 1,000 kcal^{-1})	25.9	2.7
Polyunsaturated fat (g 1,000 kcal^{-1})	18.7	4.2
Omega-3 fatty acids (g 1,000 kcal^{-1})	2.2	0.5
Omega-6 fatty acids (g 1,000 kcal^{-1})	16.5	3.1
Glycemic index	43	55
Glycemic load (g 1,000 kcal^{-1})	8	90
Animal products (energy %)	82	0
Ultra-processed foods (energy %)	43	34
Nonstarchy vegetables (g)	1,000	953
Snacks (available all day)		
Energy (kcal d^{-1})	1,291	1,288
Carbohydrate (%)	10.3	75.0
Fat (%)	80.2	9.4
Protein (%)	9.5	15.6
Energy density (kcal g^{-1})	6.39	3.04
Sodium (mg 1,000 kcal^{-1})	589	219
Fiber (g 1,000 kcal^{-1})	13.8	35.9
Sugars (g 1,000 kcal^{-1})	6.4	145.6
Saturated fat (g 1,000 kcal^{-1})	10.2	2.7
Monounsaturated fat (g 1,000 kcal^{-1})	51.5	2.4
Polyunsaturated fat (g 1,000 kcal^{-1})	29.3	5.8
Omega-3 fatty acids (g 1,000 kcal^{-1})	0.8	0.7
Omega-6 fatty acids (g 1,000 kcal^{-1})	28.5	5.1
Glycemic index	14	42
Glycemic load (g 1,000 kcal^{-1})	2	70
Animal products (energy %)	0	0
Ultra-processed foods (energy %)	0	0
Nonstarchy vegetables (g)	0	0
Daily meals + snacks		
Energy (kcal d^{-1})	5,166	5,157
Carbohydrate (%)	10.0	75.2
Fat (%)	75.8	10.3
Protein (%)	14.2	14.5
Energy density (kcal g^{-1})	2.10	1.11
Nonbeverage energy density (kcal g^{-1})	2.20	1.11
Sodium (mg 1,000 kcal^{-1})	1,919	1,565
Fiber (g 1,000 kcal^{-1})	8.5	31.4

Continued

Table 1 | Diet composition of the average 7-d rotating menu presented to the participants during the animal-based, ketogenic, LC diet and plant-based, LF diet (continued)

	LC diet	LF diet
Sugars (g 1,000 kcal^{-1})	9.2	74.6
Saturated fat (g 1,000 kcal^{-1})	24.8	2.1
Monounsaturated fat (g 1,000 kcal^{-1})	32.3	2.6
Polyunsaturated fat (g 1,000 kcal^{-1})	21.4	4.6
Omega-3 fatty acids (g 1,000 kcal^{-1})	1.8	0.5
Omega-6 fatty acids (g 1,000 kcal^{-1})	19.5	3.6
Glycemic index	38	52
Glycemic load (g 1,000 kcal^{-1})	6	85
Animal products (energy %)	61	0
Ultra-processed foods (energy %)	32	26
Nonstarchy vegetables (g)	1,000	953

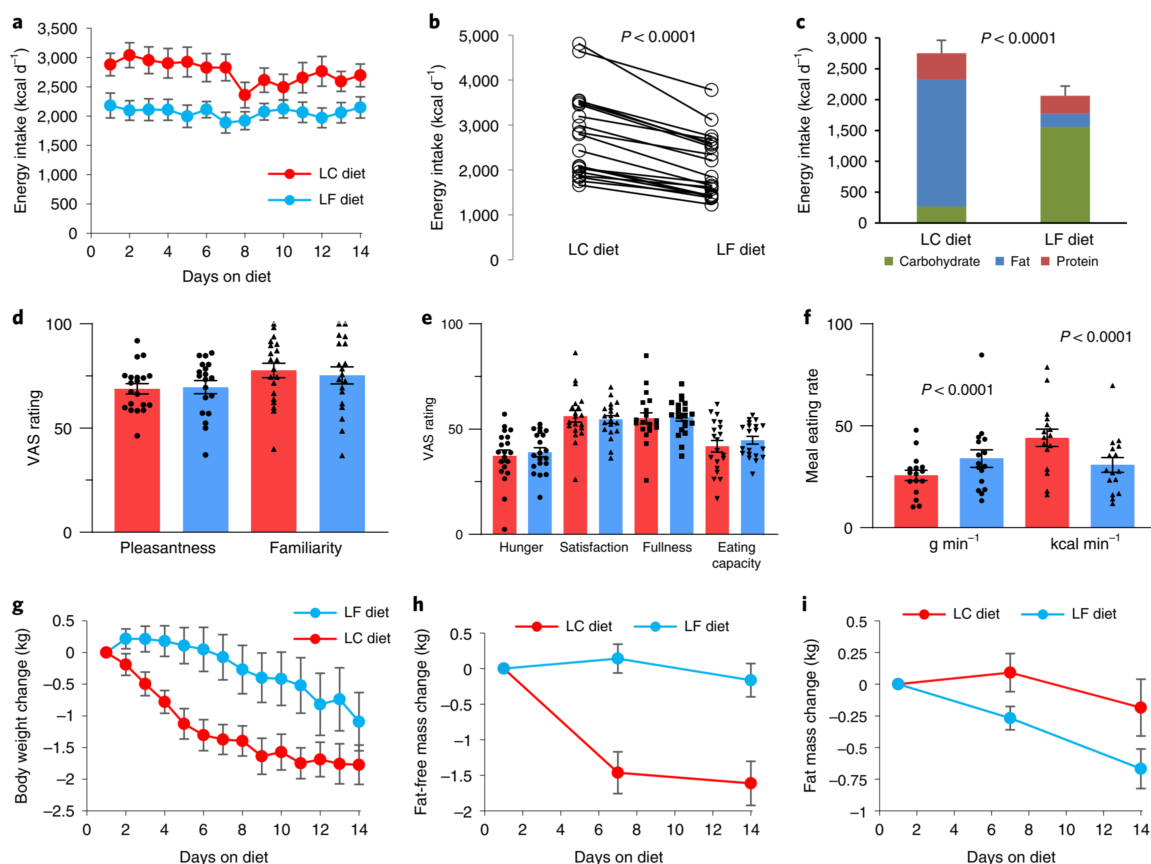


Fig. 2 | Ad libitum food intake and body composition change. a, Time course of the mean daily ad libitum energy intake during 2 weeks of consuming the plant-based, LF diet as compared to the animal-based, ketogenic LC diet ($n = 20$). Each participant's energy intake for all meals and snacks was calculated each day and the data points indicate the mean daily energy intake across participants. **b**, Individual daily average energy intake over 2 weeks consuming the LF diet and the LC diet. **c**, Average macronutrient intake during the 2-week LC and LF diet periods ($n = 20$). Error bars indicate s.e.m. energy intake. **d**, VAS ratings of meal pleasantness and familiarity of foods during the LC ($n = 20$) and LF ($n = 19$) diet periods were completed as part of sensory and palatability assessments. **e**, Hunger and satiety assessments were completed over 3 consecutive days during the second week of the LC and LF diet periods ($n = 20$). **f**, Meal eating rate was determined for 552 LC diet meals and 552 LF diet meals and was expressed in terms of kcals min^{-1} and g min^{-1} ($n = 16$). **g**, Body weight changes over time during the LC and LF diets ($n = 20$). **h**, Fat-free mass changes during the LC and LF diet periods ($n = 20$). **i**, Body fat mass changes during the LC and LF diet periods ($n = 20$). Data are presented as mean ± s.e.m. and were analyzed by analysis of variance (ANOVA) with individual participants as blocking factors and two-sided Student's *t*-tests were used to compare the diet groups. *P* values were not adjusted for multiple comparisons.

Table 2 | Fasting blood measurements at baseline and at the end of the animal-based, ketogenic, LC and plant-based, LF diet periods

	Baseline (*n*)	Baseline	LC diet (*n*)	LC diet	*P* value LC diet versus baseline	LF diet (*n*)	LF diet	*P* value LF diet versus baseline	*P* value LC versus LF diet
HbA1c (%)	20	5.2 ± 0.2	20	5.0 ± 0.2	<0.0001	19	5.1 ± 0.2	0.001	0.28
Glucose (mg dl^{-1})	20	91.4 ± 1.4	20	84.1 ± 1.4	0.0007	20	85.4 ± 1.4	0.004	0.55
Glucagon (pmol l^{-1})	20	16.9 ± 2.1	20	13.8 ± 0.6	0.15	20	12.4 ± 0.6	0.04	0.12
Insulin (μU ml^{-1})	20	11.3 ± 0.5	20	7.4 ± 0.5	<0.0001	19	8.3 ± 0.5	0.0002	0.22
C-peptide (ng ml^{-1})	20	2.18 ± 0.06	20	1.57 ± 0.06	<0.0001	20	1.93 ± 0.06	0.003	<0.0001
Acetoacetate (mM)	20	0.035 ± 0.04	19	0.431 ± 0.04	<0.0001	18	0.054 ± 0.04	0.73	<0.0001
Acetone (mM)	20	0.023 ± 0.07	19	0.567 ± 0.07	<0.0001	18	0.029 ± 0.07	0.95	<0.0001
β-hydroxybutyrate (mM)	20	0.089 ± 0.2	19	2.01 ± 0.2	<0.0001	18	0.125 ± 0.2	0.91	<0.0001
Ketones (mM)	20	0.147 ± 0.3	19	3.01 ± 0.3	<0.0001	18	0.209 ± 0.3	0.89	<0.0001
Free fatty acids (μmol l^{-1})	20	328 ± 48	20	760 ± 48	<0.0001	20	508 ± 48	0.01	0.0006
Triglycerides (mg dl^{-1})	20	75.5 ± 4.5	20	63.4 ± 4.5	0.066	20	93.3 ± 4.5	0.008	<0.0001
VLDL particle number (nmol l^{-1})	20	39.8 ± 3.5	19	18.9 ± 3.8	0.0003	20	46.8 ± 3.7	0.18	<0.0001
VLDL size (nm)	20	44.1 ± 1.4	15	45.6 ± 1.8	0.53	19	47.2 ± 1.6	0.16	0.50
Total cholesterol (mg dl^{-1})	20	162.5 ± 3.9	20	161.2 ± 3.9	0.8	20	120.7 ± 3.9	<0.0001	<0.0001
Calc LDL cholesterol (mg dl^{-1})	20	93.2 ± 4.0	20	101.6 ± 4.0	0.14	20	64.5 ± 4.0	<0.0001	<0.0001
LDL cholesterol (mg dl^{-1})	20	87.9 ± 3.4	19	92.4 ± 3.6	0.38	18	64.7 ± 3.7	<0.0001	<0.0001
LDL particle number (nmol l^{-1})	20	1,072 ± 53	20	1,224 ± 53	0.055	19	781 ± 53	0.0006	<0.0001
LDL particle size (nm)	20	20.9 ± 0.09	20	20.5 ± 0.09	0.002	19	20.6 ± 0.09	0.023	0.38
Large LDL (nmol l^{-1})	20	162 ± 19	19	55 ± 20	0.0004	18	147 ± 21	0.60	0.0024
Medium LDL (nmol l^{-1})	20	328 ± 46	19	334 ± 47	0.93	18	158 ± 50	0.016	0.013
Small LDL (nmol l^{-1})	20	855 ± 68	19	1,130 ± 71	0.008	18	692 ± 74	0.11	0.0001
HDL cholesterol (mg dl^{-1})	20	54.4 ± 1.3	20	47.1 ± 1.3	0.0002	20	37.5 ± 1.3	<0.0001	<0.0001
HDL particle number (nmol l^{-1})	20	32.9 ± 0.6	20	27.9 ± 0.6	<0.0001	20	24.4 ± 0.6	<0.0001	0.0003
HDL size (nm)	20	9.31 ± 0.06	20	9.28 ± 0.06	0.67	20	9.28 ± 0.06	0.72	0.95
Large HDL (nmol l^{-1})	20	2.6 ± 0.2	19	2.5 ± 0.2	0.50	18	1.5 ± 0.2	<0.0001	0.0002
Medium HDL (nmol l^{-1})	20	4.1 ± 0.2	19	2.2 ± 0.3	<0.0001	18	3.0 ± 0.3	0.002	0.05
Small HDL (nmol l^{-1})	20	13.5 ± 0.5	19	14.0 ± 0.5	0.44	18	10.2 ± 0.5	<0.0001	<0.0001
Apolipoprotein-A-1 (mg dl^{-1})	20	130.5 ± 2.4	19	117.5 ± 2.5	0.0005	18	94.5 ± 2.6	<0.0001	<0.0001
Apolipoprotein-B (mg dl^{-1})	20	73.5 ± 2.8	19	77.1 ± 3.0	0.39	18	57.5 ± 3.1	0.0005	<0.0001
Lipoprotein (a) (U l^{-1})	20	401 ± 38	20	286 ± 38	0.04	20	411 ± 38	0.86	0.025
Branched-chain amino acids (μmol l^{-1})	20	456 ± 17	19	635 ± 17	<0.0001	18	353 ± 18	0.0002	<0.0001
Valine (μmol l^{-1})	20	233 ± 8	19	332 ± 8	<0.0001	18	176 ± 9	<0.0001	<0.0001
Leucine (μmol l^{-1})	20	162 ± 7	19	201 ± 7	0.0002	18	125 ± 7	0.0006	<0.0001
Isoleucine (μmol l^{-1})	20	61 ± 4	19	102 ± 4	<0.0001	18	52 ± 4	0.094	<0.0001
Alanine (μmol l^{-1})	20	325 ± 12	19	194 ± 13	<0.0001	18	310 ± 13	0.38	<0.0001
Uric acid (mg dl^{-1})	20	5.3 ± 0.2	20	7.2 ± 0.2	<0.0001	20	4.8 ± 0.2	0.17	<0.0001
Thyroid-stimulating hormone (μIU ml^{-1})	20	2.26 ± 0.12	20	2.34 ± 0.12	0.64	20	1.86 ± 0.12	0.03	0.009
Free triiodothyronine (pg ml^{-1})	20	3.30 ± 0.07	20	2.61 ± 0.07	<0.0001	20	3.13 ± 0.07	0.08	<0.0001
Free thyroxine (ng dl^{-1})	20	1.26 ± 0.02	20	1.35 ± 0.02	0.002	20	1.27 ± 0.02	0.73	0.006
Triiodothyronine (ng dl^{-1})	20	119.9 ± 2.8	20	88.3 ± 2.8	<0.0001	20	113.6 ± 2.8	0.12	<0.0001
Thyroxine (μg dl^{-1})	20	7.23 ± 0.13	20	6.93 ± 0.13	0.11	20	6.96 ± 0.13	0.15	0.89
hsCRP (mg l^{-1})	16	2.1 ± 0.2	20	2.1 ± 0.2	0.82	17	1.2 ± 0.2	0.008	0.003
GlycA (μmol l^{-1})	20	349 ± 5.7	19	301 ± 6.0	<0.0001	18	331 ± 6.2	0.038	0.0014

Least squares mean ± s.e.m. Reported *P* values are not adjusted for multiple comparisons. HbA1c, glycated hemoglobin; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; GlycA, glycoprotein N-acetyl methyl group signature.

foods was significantly lower with the LF diet compared to the LC diet (0.96 ± 0.03 kcal g^{-1} with LF versus 1.9 ± 0.03 kcal g^{-1} with LC; $P < 0.0001$). A significantly greater mass of food was consumed during the LF diet compared to the LC diet (2,140 ± 43 g d^{-1} with LF versus 1,473 ± 43 g d^{-1} with LC; $P < 0.0001$). Dietary fiber intake was significantly greater during the LF diet (60.8 ± 2.2 g d^{-1} with LF versus 20.5 ± 2.2 g d^{-1} with LC; $P < 0.0001$), whereas sodium intake was significantly greater during the LC diet (3,725 ± 187 mg d^{-1} with LF versus 5,938 ± 187 mg d^{-1} with LC; $P < 0.0001$).

Appetitive measurements and eating rate. Fig. 2d shows that there were no significant differences in the reported pleasantness (0.21 ± 2.7; $P = 0.94$) or familiarity (−3.4 ± 3.0; $P = 0.26$) between the LF and LC meals rated on a continuous 100-point visual analog scale (VAS). Furthermore, Fig. 2e shows that participants reported no significant differences in hunger (1.5 ± 1.4; $P = 0.3$), satisfaction (−1.5 ± 1.4; $P = 0.31$), fullness (0.74 ± 1.5; $P = 0.6$) or eating capacity (2.3 ± 1.6; $P = 0.16$) between the LF and LC diets despite large differences in energy intake.

We performed exploratory post hoc analyses of meal eating rates by recording start and stop times of 552 meals for each diet in 16 participants. Figure 2f shows that LF meals were eaten more quickly in terms of g min^{-1} compared to LC meals (33.8 ± 0.90 g min^{-1}with LF versus 25.7 ± 0.90 g min^{-1} with LC; $P < 0.0001$) but the higher energy density of LC meals resulted in a faster energy intake rate compared to LF meals (30.9 ± 0.99 kcal min^{-1} with LF versus 44.2 ± 0.99 kcal min^{-1} with LC; $P < 0.0001$). Average meal duration was slightly longer with the LF diet compared to the LC diet (22.9 ± 0.6 min with LF versus 20.8 ± 0.6 min with LC; $P = 0.007$).

Energy expenditure and respiratory quotient. Participants' daily energy expenditure in the respiratory chamber was 153 ± 24 kcal d^{-1} lower while consuming the LF diet compared to the LC diet (2,141 ± 17 kcal d^{-1} with LF versus 2,294 ± 17 kcal d^{-1} with LC; $P < 0.0001$), which partially compensated for the reduced ad libitum energy intake with the LF diet with respect to overall energy balance. The LF diet resulted in lower sedentary expenditure (1,731 ± 21 kcal d^{-1} with LF versus 1,891 ± 21 kcal d^{-1} with LC; $P < 0.0001$) and sleeping energy expenditure (1,392 ± 14 kcal d^{-1} with LF versus 1,568 ± 14 kcal d^{-1} with LC; $P < 0.0001$), whereas physical activity expenditure was not significantly different (393 ± 21 kcal d^{-1} with LF versus 397 ± 21 kcal d^{-1} with LC; $P = 0.88$) in the respiratory chamber. Accelerometry measurements revealed no significant physical activity differences between the 2-week diet periods (average daily metabolic equivalents 1.502 ± 0.0017 with LF versus 1.503 ± 0.0017 with LC; $P = 0.82$).

Daily respiratory quotient was significantly greater with the LF diet (0.885 ± 0.005 with LF versus 0.753 ± 0.005 with LC; $P < 0.0001$), indicating significantly greater carbohydrate oxidation (306 ± 15 g d^{-1} with LF versus 24 ± 15 g d^{-1} with LC; $P < 0.0001$) and lower fat oxidation (49 ± 6 g d^{-1} with LF versus 142 ± 6 g d^{-1} with LC; $P < 0.0001$).

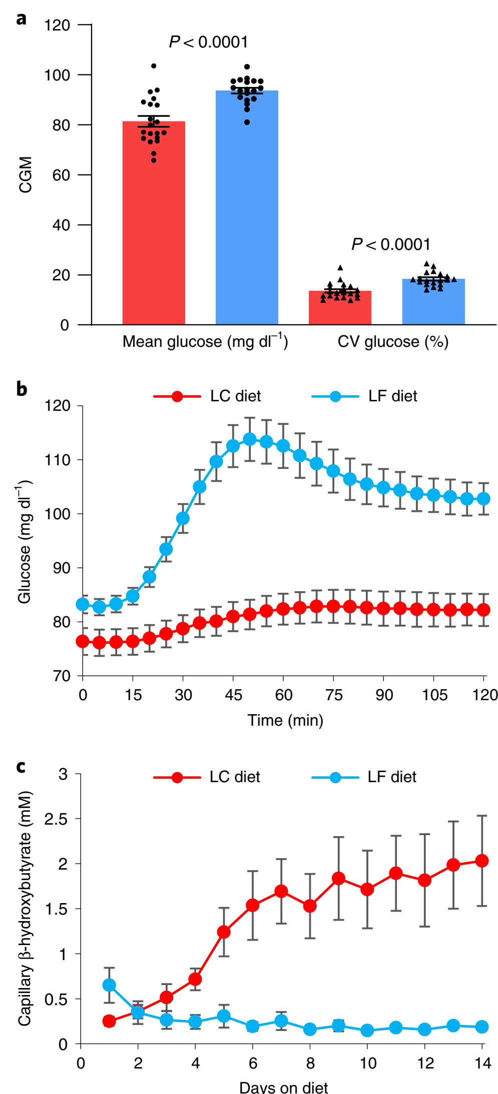


Fig. 3 | Continuous glucose monitoring and daily capillary β-hydroxybutyrate. a, Mean interstitial glucose levels and coefficients of variation (CV) of interstitial glucose measured using CGMs during the LC ($n = 20$) and LF ($n = 19$) diet periods. **b**, Mean postprandial interstitial glucose following ad libitum consumption of 394 LF meals and 368 LC meals ($n = 15$). **c**, Time course of mean fasting capillary β-hydroxybutyrate during LC and LF diet periods ($n = 15$). Data are presented as mean ± s.e.m. and were analyzed by ANOVA with individual participants as blocking factors and two-sided Student's t-tests were used to compare the diet groups. P values were not adjusted for multiple comparisons.

Body weight and composition. Body weight decreased during both diets as illustrated in Fig. 2g. The LC diet resulted in rapid weight loss during the first week and total weight loss after 2 weeks was 1.77 ± 0.32 kg ($P < 0.0001$). The LF diet led to slower initial weight loss, but after 2 weeks weight loss amounted to 1.09 ± 0.32 kg ($P = 0.003$) which was not significantly different from the LC diet ($P = 0.15$). Figure 2h indicates that most of the of the weight changes with the LC diet were due to changes in fat-free mass measured by dual-energy X-ray absorptiometry (DXA) (−1.61 ± 0.27 kg; $P < 0.0001$), whereas the LF diet did not result in a significant change in fat-free mass (−0.16 ± 0.27 kg; $P = 0.56$). Figure 2i shows that the LC diet did not result in a significant change in body fat after the first week (0.09 ± 0.12 kg; $P = 0.47$), but fat mass seemed to decrease during the second week of the LC diet as energy intake decreased compared to the first week. Nevertheless, body fat mass was not significantly changed at the end of the LC diet (−0.18 ± 0.19 kg; $P = 0.35$). In contrast, the LF diet resulted in significant changes in fat mass after both the first week (−0.27 ± 0.12 kg; $P = 0.038$) and the second week (−0.67 ± 0.19 kg; $P = 0.001$). While there was no statistically significant difference in the amount of body fat lost at the end of the LF and LC diet periods (0.48 ± 0.27 kg; $P = 0.085$), the rate of body fat loss was 35 ± 14 g d^{-1} ($P = 0.019$) greater with the LF diet with an average fat loss rate of 51 ± 10 g d^{-1} ($P < 0.0001$) versus 16 ± 9.7 g d^{-1} ($P = 0.12$) with the LC diet.

Liver fat was measured by magnetic resonance spectroscopy (MRS) in 16 participants whose baseline liver fat was 3.4 ± 0.5% and was not significantly different after either the LF diet (3.4 ± 0.5%; $P = 0.99$) or LC diet (2.8 ± 0.5%; $P = 0.36$).

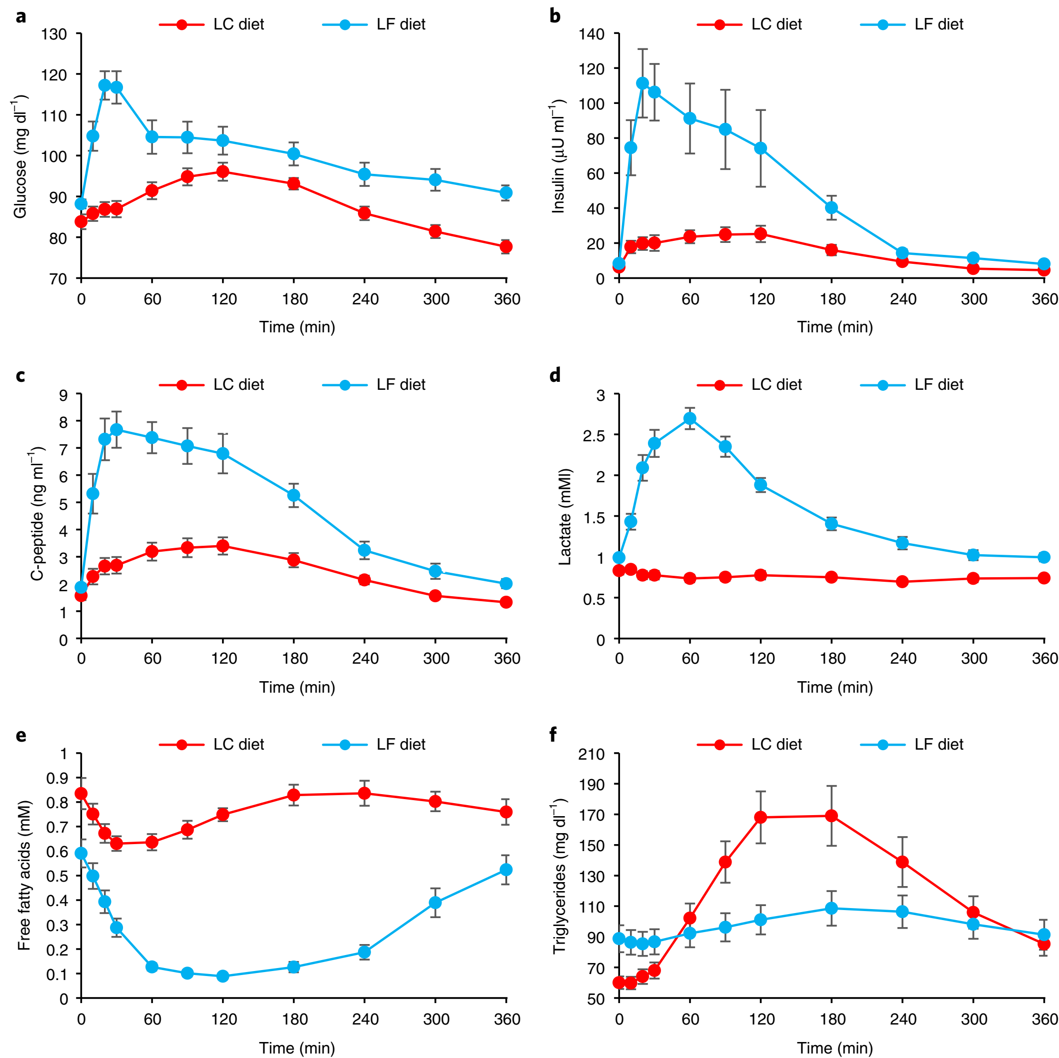


Fig. 4 | LC and LF meal tests. a–f, Mean postprandial glucose (**a**), insulin (**b**), C-peptide (**c**), lactate (**d**), free fatty acids (**e**) and triglycerides (**f**) following isocaloric LC and LF meal tests conducted during the second week of the respective LC and LF diet periods ($n=20$). Data are presented as mean ± s.e.m.

24-h urinary excretion. During the LF diet, 24-h urinary excretion of C-peptide was ~60% higher (16.2 ± 0.9 nmol d^{-1} with LF versus 6.1 ± 0.9 nmol d^{-1} with LC; $P<0.0001$), indicating substantially increased daily insulin secretion compared to the LC diet. Daily urinary excretion of ketones was 1.44 ± 0.06 g d^{-1} during the LC diet ($P<0.0001$), whereas the LF diet had no detectable ketone excretion (0.007 ± 0.06 g d^{-1}; $P=0.91$). Daily excretion of urea was lower during the LF diet (6.8 ± 0.2 g d^{-1} with LF versus 12.9 ± 0.2 g d^{-1} with LC; $P<0.0001$) as was excretion of ammonia (0.16 ± 0.02 g d^{-1} with LF versus 0.98 ± 0.02 g d^{-1} with LC; $P<0.0001$) and creatinine (1.24 ± 0.03 g d^{-1} with LF versus 1.38 ± 0.03 g d^{-1} with LC; $P=0.002$). Total daily urinary nitrogen excretion was lower during the LF diet (14.1 ± 0.9 g d^{-1} with LF versus 24.5 ± 0.9 g d^{-1} with LC; $P<0.0001$) and the difference between dietary nitrogen intake and urinary excretion was significantly lower with the LC diet (−1.8 ± 0.9 g d^{-1} with LF versus −7.8 ± 0.9 g d^{-1} with LC; $P<0.0001$), indicating that the LC diet resulted in a greater net loss of body protein despite consumption of more dietary protein than the LF diet.

Circulating metabolites and hormones. Table 2 shows that the LC and LF diets led to widespread differences in fasting blood concentrations measured at the end of each diet period. All participants wore continuous glucose monitors (CGMs) throughout the study. Figure 3a illustrates that the LF diet resulted in greater mean concentrations of interstitial glucose (94.3 ± 1.6 mg dl^{-1} with LF versus 81.3 ± 1.6 mg dl^{-1} with LC; $P<0.0001$) and its coefficient of variation (18.4 ± 0.5 % with LF versus 13.5 ± 0.5 % with LC; $P<0.0001$). Figure 3b shows that postprandial glucose was significantly higher following LF meals, with mean glucose in the 2 h following LF meals of 102.5 ± 0.7 mg dl^{-1} as compared to 80.5 ± 0.8 mg dl^{-1} following LC meals ($P<0.0001$).

In 15 volunteers, we measured daily capillary β-hydroxybutyrate in the overnight fasted state. Figure 3c shows that the LC diet led to an increase in capillary β-hydroxybutyrate that quickly surpassed the 0.5 mM threshold defining a state of nutritional ketosis. During the second week of the LC diet, capillary β-hydroxybutyrate did not significantly change over time (rate of change was 0.06 ± 0.04 mM d^{-1}; $P=0.18$) and had an average concentration of 1.8 ± 0.1 mM. In contrast, the LF diet resulted in a low concentration of capillary β-hydroxybutyrate averaging 0.2 ± 0.1 mM during the second week, which was significantly lower than that during the LC diet ($P<0.0001$).

Mixed-meal tests. During the second week of each diet phase, a liquid meal test was performed in the overnight fasted state. The macronutrient composition of each test meal matched the prevail-

ing diet composition and provided 30% of each participant's calculated energy requirements. Figure 4 illustrates that the LF meal compared to the LC meal led to significant increases in average postprandial glucose ($101 \pm 2\,mg\,dl^{-1}$ with LF versus $88 \pm 2\,mg\,dl^{-1}$ with LC; $P < 0.0001$), insulin ($47.6 \pm 5.2\,\mu U\,ml^{-1}$ with LF versus $14.9 \pm 5.0\,\mu U\,ml^{-1}$ with LC; $P = 0.0003$), C-peptide ($4.9 \pm 0.2\,ng\,ml^{-1}$ with LF versus $2.5 \pm 0.2\,ng\,ml^{-1}$ with LC; $P < 0.0001$) and lactate ($1.59 \pm 0.04\,mmol\,l^{-1}$ with LF versus $0.75 \pm 0.04\,mmol\,l^{-1}$ with LC; $P < 0.0001$). Postprandial free fatty acids were substantially lower following the LF meal compared to the LC meal ($233 \pm 21\,\mu mol\,l^{-1}$ with LF versus $764 \pm 20\,\mu mol\,l^{-1}$ with LC; $P < 0.0001$). Notably, the LC diet resulted in fasting triglycerides that were lower compared to the LF diet, but the peak triglyceride concentration was much higher following the LC meal such that the average postprandial triglyceride was significantly higher following the LC meal compared to the LF meal ($96.1 \pm 7.4\,mg\,dl^{-1}$ with LF versus $125.2 \pm 7.4\,mg\,dl^{-1}$ with LC; $P = 0.014$).

Oral glucose tolerance. At the end of each diet phase, an oral glucose tolerance test (OGTT) was performed. The LC diet resulted in a relative impairment of glucose tolerance compared to the LF diet (Extended Data Fig. 1). Mean glucose during the OGTT was $115.6 \pm 2.9\,mg\,dl^{-1}$ with the LF diet compared to $143.3 \pm 2.9\,mg\,dl^{-1}$ with the LC diet ($P < 0.0001$). Glucose measured at 2 h was $108.5 \pm 4.3\,mg\,dl^{-1}$ with the LF diet compared to $142.6 \pm 4.3\,mg\,dl^{-1}$ with the LC diet ($P < 0.0001$). The 2-h glucose measurement exceeded the $\geq 140\,mg\,dl^{-1}$ threshold, defining impaired glucose tolerance in nine participants during the LC diet compared to only three of these same volunteers during the LF diet.

During the OGTT, there were no significant diet differences in mean insulin ($85.5 \pm 6.6\,\mu U\,ml^{-1}$ with LF versus $97.8 \pm 6.6\,\mu U\,ml^{-1}$ with LC; $P = 0.21$) or C-peptide ($8.8 \pm 0.3\,ng\,ml^{-1}$ with LF versus $9.1 \pm 0.3\,ng\,ml^{-1}$ with LC; $P = 0.47$). Mean lactate was significantly higher after the LF diet ($1.35 \pm 0.05\,mmol\,l^{-1}$ with LF versus $1.09 \pm 0.05\,mmol\,l^{-1}$ with LC; $P = 0.0007$), whereas mean free fatty acids were significantly lower following the LF diet ($174.8 \pm 21\,\mu mol\,l^{-1}$ with LF versus $346.5 \pm 21\,\mu mol\,l^{-1}$ with LC; $P < 0.0001$).

The Matsuda index, a measure of insulin sensitivity derived from the OGTT data, was not significantly different between the diets (4.53 ± 0.28 with LF versus 4.44 ± 0.28 with LC; $P = 0.82$). However, the insulinogenic index tended to be higher with the LF diet (53.3 ± 8.9 with LF versus 27.5 ± 8.9 with LC; $P = 0.054$), indicating relatively greater insulin secretion during the OGTT compared to the LC diet.

Blood pressure and pulse rate. Blood pressure and pulse rate were measured daily throughout the month-long inpatient stay. The LF diet resulted in significantly lower systolic blood pressure ($112.2 \pm 0.4\,mm\,Hg$ with LF versus $115.8 \pm 0.4\,mm\,Hg$ with LC; $P < 0.0001$), diastolic blood pressure ($66.9 \pm 0.4\,mm\,Hg$ with LF versus $68.5 \pm 0.4\,mm\,Hg$ with LC; $P = 0.0012$) and pulse rate (72.6 ± 0.5 b.p.m. with LF versus 76.9 ± 0.5 b.p.m. with LC; $P < 0.0001$) compared to the LC diet.

Discussion

Our study was designed to measure ad libitum energy intake when inpatient participants were exposed to food environments corresponding to either a plant-based, LF diet versus an animal-based, ketogenic, LC diet. The LF diet had higher glycemic load and resulted in greater postprandial glucose and insulin levels compared to the LC diet that was higher in energy density. Energy intake during the LF diet was spontaneously reduced by ~550–700 $kcal\,d^{-1}$ compared to the LC diet, with participants losing weight and body fat while reporting no significant differences in hunger, fullness, satisfaction or pleasantness of the meals. These data suggest that while the LC diet had benefits for reducing glucose and insulin levels, the LF diet had benefits for appetite control.

Two previous inpatient studies found that LF diets (15–20% of total energy from fat) resulted in ~630–880 $kcal\,d^{-1}$ less energy intake over 14 d compared to diets higher in fat[14,18]. However, the high-fat diets contained 29–42% of total energy from carbohydrate, which may have been too high to sufficiently decrease insulin or increase ketones, which may mediate the appetite-suppressing benefits of LC diets[16,17]. An inpatient study of participants with obesity and type 2 diabetes found that a very-low-carbohydrate diet (~4% of energy from carbohydrates) decreased ad libitum energy intake by ~950 $kcal\,d^{-1}$ over 14 d following a 'usual diet' that was not low in fat (44% of total energy from fat)[13] and included a variety of ultra-processed foods that may promote excess energy intake[19]. An outpatient study of participants with obesity found that a very-low-fat diet (~7% fat, ~78% carbohydrate, ~15% protein) resulted in ~1,000 $kcal\,d^{-1}$ decrease in ad libitum energy intake over 21 d as compared to a self-reported baseline diet that was ~32% fat, ~51% carbohydrate and ~17% protein[20]. Finally, a controlled feeding study of men with obesity found that a high-protein ketogenic diet (5% carbohydrates, 65% fat and 30% protein) resulted in a modest ~170 $kcal\,d^{-1}$ lower ad libitum energy intake compared to a moderate carbohydrate diet with matched protein and energy density (36% carbohydrate, 34% fat and 30% protein)[21].

Energy intake on the LF diet was stable over both weeks and was persistently lower than the LC diet. Energy intake during the LC diet was significantly decreased during the second week compared to the first week and coincided with increased capillary β-hydroxybutyrate during the second week of the LC diet. It is intriguing to speculate that the observed ~300 $kcal\,d^{-1}$ reduction in energy intake from the first to second week of the LC diet corresponds to the magnitude of the appetite-suppressive effect of ketones. Whether long-term adaptations to the diets would eventually eliminate or reverse the energy intake differences is unknown. A recent study found that after 10–15 weeks of adaptation to a LC diet (~20% carbohydrate, ~60% fat), participants reported significantly reduced satiety as compared to a LF diet (~60% carbohydrate, ~20% fat),[22] which supports our shorter-term observation of greater energy intake during the LC diet.

The physiological process of adapting to a ketogenic diet is multifaceted, involving multiple organ systems and plays out over a variety of time scales[23]. Inpatient feeding of the LC diet for 2 weeks resulted in a substantial degree of physiological adaptation by several metrics. First, we observed impaired glucose tolerance at the end of the second week of the LC diet that likely indicates a substantial degree of physiological adaptation to the diet. Second, daily respiratory quotient was ~0.75 during the LC diet, indicating a substantial increase in fat and ketone oxidation, which has previously been shown to occur within the first week of adaptation to a ketogenic diet with no further changes over the following few weeks[24]. Third, nutritional ketosis was established within several days of instituting the LC diet and capillary β-hydroxybutyrate was stable during the second week of the diet. Stable fasting blood ketones have been observed at weeks two, three and four of an isocaloric ketogenic diet in a previous inpatient controlled feeding study,[24] suggesting that it is unlikely that further increases in ketones would be expected with prolonged exposure to the LC diet. Finally, plasma uric acid approximately doubles at the onset of a ketogenic diet but returns to ~20–50% greater than baseline after 4–8 weeks of adaptation in an outpatient setting[25–27]. This was similar to the ~35% greater than baseline uric acid levels that we observed after 2 weeks of inpatient LC feeding (Table 2) and suggests that outpatient studies may require longer adaptation periods to ketogenic diets, perhaps due to reduced diet adherence compared to our inpatient study that had greater control over the food environment.

Despite the substantial differences in energy intake between LF and LC diets, total weight loss after 2 weeks was similar. Greater weight loss during the first week of the LC diet compared to the LF diet was likely primarily due to differences in body water, glycogen, protein and gastrointestinal contents. While fat-free mass was relatively preserved with the LF diet, fat-free mass was decreased with the LC diet, which also resulted in a state of of negative nitrogen balance, indicating net loss of body protein despite consumption of more dietary protein than during the LF diet. Only the LF diet led to significant body fat loss. The DXA method used to measure body composition changes in our study has been demonstrated to accurately detect acute body fluid shifts as changes in fat-free mass without affecting body fat mass measurements[28–31].

Unlike the LF diet that resulted in significant loss of body fat, the LC diet had no significant body fat changes, suggesting that energy intake during the LC diet was approximately equivalent to the total amount of energy that was expended. The rate of body fat loss during the LF diet was ~35 g d^{-1} greater compared to the LC diet, which corresponds to a difference in energy balance of ~330 kcal d^{-1} between the diets, which was somewhat smaller than the observed differences in energy intake between the LF and LC diets. Indeed, energy expenditure as measured in the respiratory chambers was ~150 kcal d^{-1} lower during the LF diet compared to the LC diet and therefore partially compensated for the ~690 kcal d^{-1} reduction in energy intake during the LF diet. That leaves ~210 kcal d^{-1} unaccounted by our measurements, but the uncertainty of this estimate is ~150 kcal d^{-1} as calculated by the quadratic sum of the s.e. of the energy intake, energy expenditure and rates of change in body fat differences between the diets[32]. So, it is possible that these energy accounting calculations are simply at the limits of energy balance measurement precision in our short-term study. Alternatively, it is possible that unmeasured diet differences in fecal energy excretion or energy expenditure differences that were undetected during the days spent in the respiratory chambers could have contributed to the unaccounted energy imbalance.

In accordance with previous studies[24,33], the approximately eucaloric LC diet with ~15% protein likely led to very little changes in energy expenditure compared with baseline. By contrast, the ~700 kcal d^{-1} decrease in energy intake during the LF diet resulted in decreased energy expenditure. We previously observed that a controlled ~800 kcal d^{-1} selective reduction of dietary fat from an energy balanced baseline diet, without reductions in dietary carbohydrate or protein, led to a nonsignificant ~50 kcal d^{-1} decrease in 24-h energy expenditure[34]. However, the diet used in the previous study was composed of ~8% fat, 71% carbohydrate and 21% protein and was therefore significantly higher in protein compared to the 14% protein consumed during the LF diet. Because dietary protein is more thermogenic than carbohydrate or fat[35], the comparatively higher protein intake in our previous study might have been responsible for the relative maintenance of 24-h energy expenditure compared to the LF diet in the present study, which resulted in a ~150 kcal d^{-1} decrease in 24-h energy expenditure.

Both fasting and postprandial triglycerides are thought to increase risk for cardiovascular disease[36]. The LC diet resulted in decreased fasting triglycerides compared to baseline, whereas the LF diet increased fasting triglycerides. Notably, despite lower fasting triglycerides during the LC diet, postprandial triglycerides were higher following the LC test meal compared to the isocaloric LF test meal likely due to the very high fat content of the LC meal. In contrast, the LF meal led to higher postprandial glucose and insulin levels. The CGM measurements of interstitial glucose concentrations demonstrated that both mean and postprandial glucose excursions were much larger throughout the LF diet period compared to the LC diet. This is of potential concern because high glucose variability is thought to be a risk factor for coronary artery disease[37]. Interestingly, postprandial lactate concentrations were much higher following the LF meal compared to the LC meal, likely due to increased glucose uptake and glycolysis after the LF meal. High lactate levels might have widespread implications for immune modulation as well as oncogenesis[38].

What was the mechanism for the reduced ad libitum energy intake in the LF diet compared to the LC diet? The LC and LF diets had similar protein presented to the participants, but protein intake during the LC diet was increased compared to the LF diet. Higher protein consumption during the LC diet would be expected to increase satiety and decrease energy intake compared to the LF diet[35,39], but the observed differences in energy intake were in the opposite direction.

Perhaps the greater dietary fiber and substantially lower nonbeverage energy density of the LF diet promoted a reduction in energy intake compared to the LC diet[40–43]. Indeed, the LC diet was at the 75th percentile for US population nonbeverage energy density, whereas the LF diet was below the 25th percentile[44]. However, the determinants of ad libitum energy intake and overall energy balance are likely to be quite complex and unlikely to be explained by dietary fiber and energy density alone. Previous ad libitum feeding studies employing high-fat diets with somewhat lower energy densities than our LC diet (but higher in carbohydrate and lower in fat and protein) resulted in positive energy balance and weight gain[14,15], whereas our LC diet led to weight loss. Our previous ad libitum feeding study used an ultra-processed diet that closely matched the nonbeverage energy density of the LC diet and had more dietary fiber, but only the ultra-processed diet led to gain of weight and body fat[19]. The LF diet and the unprocessed diet also had matching nonbeverage energy densities and both contained high amounts of fiber, but more body fat was lost with the LF diet, indicating a greater degree of negative energy balance despite the higher glycemic load of the LF diet compared with the unprocessed diet. Both the LC and LF diets contained few ultra-processed foods, with both diets having a percentage of total calories from ultra-processed food that was within the lowest 20% of the population distribution[45,46]. Although such cross-study comparisons are obviously imperfect, they suggest that the determinants of energy intake and body fat change cannot be adequately explained by individual factors such as glycemic load, protein intake, dietary fiber or energy density. A more comprehensive model incorporating multiple factors, including eating rate[47,48], is likely required.

The main limitation of our study is that the inpatient environment makes it difficult to generalize our results to real-world settings. The participants were told that this was not a weight-loss study, were instructed not to attempt to change their weight and were blinded to their body weight measurements as well as the primary purpose of the study. Whether our results would have been different in free-living people actively trying to lose weight is unknown.

The passive overconsumption model of obesity predicts that consuming a diet with high energy density results in excess energy intake and weight gain. The carbohydrate–insulin model predicts that consuming a diet with high-glycemic carbohydrates results in increased postprandial insulin that drives body fat accumulation, thereby increasing energy intake. While our LF diet contained foods with high glycemic load that substantially increased postprandial glucose and insulin levels compared to the LC diet, the LF diet led to less energy intake compared to the LC diet, which contradicts the predictions of the carbohydrate–insulin model. While the LC diet was high in energy density, it did not result in body fat gain, which challenges the validity of the passive overconsumption model. Our results suggest that regulation of energy intake is more complex than these and other simple models propose.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-01209-1.

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Methods

Participants. The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes & Digestive & Kidney Diseases (NCT03878108) and is available on the Open Science Framework website (https://osf.io/fjykq/). Participants were fully informed of the risks of the study and signed consent forms before any study procedures.

Inclusion criteria. Inclusion criteria were as follows: male and female adults age 18–50 years; weight stable (<±5% over past 6 months); body mass index $\geq$20 kg m^{-2}; body weight $\geq$53 kg; able to complete daily bouts of stationary cycling at a moderate rate and intensity with a heart rate (HR) equal to or greater than $0.3 \times (220 - \text{age} - HR_{rest}) + HR_{rest}$ but not exceeding $0.4 \times (220 - \text{age} - HR_{rest}) + HR_{rest}$ and no signs of arrhythmia.

Exclusion criteria. Exclusion criteria were as follows: evidence of metabolic or cardiovascular disease or disease that may influence metabolism (for example cancer, diabetes, thyroid disease); taking any prescription medication or other drug that may influence metabolism (for example diet/weight-loss medication, asthma medication, blood pressure medication, psychiatric medications, corticosteroids or other medications at the discretion of the study team); positive pregnancy test or lactation as determined by volunteer report (women only); participating in a regular exercise program (>2 h week^{-1} of vigorous activity); hematocrit <37% for women and <40% for men; habitual caffeine consumption >300 mg d^{-1}; regular use of alcohol (>2 drinks per day), tobacco (smoking or chewing), amphetamines, cocaine, heroin or marijuana over past 6 months; psychological conditions such as (but not limited to) eating disorders, claustrophobia, clinical depression, bipolar disorders, as determined by investigators after reviewing the results of the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure; past or present history of claustrophobia; implants, devices or foreign objects implanted in the body that interfere with the magnetic resonance procedures; strict dietary concerns (for example vegetarian or kosher diet, food allergies) as determined by investigators after reviewing the results of the Food Frequency Questionnaire; volunteers unwilling or unable to give informed consent; and non-English speakers owing to unavailability of required questionnaires in other languages.

Research setting and diets. Study participants were admitted as inpatients to the Metabolic Clinical Research Unit at the NIH Clinical Center where they resided in individual rooms. Visitors could meet with study participants in a common area under observation of the nursing and/or research staff to avoid the exchange of food or beverages. Up to four simultaneous participants were investigated, often with staggered start dates and each was randomly assigned to receive either the LF or the LC diet for the first 14 d, immediately followed by the alternate diet for 14 d. Except for the respiratory chamber days, volunteers consumed all food and beverages in their rooms with the doors open.

Randomization of diet order was conducted by the NIH Clinical Center Nutrition Department using an online randomization program (https://www.sealedenvelope.com/simple-randomiser/v1/lists), which randomized diets in blocks of ten (five participants × two treatments) and participants were assigned according to date of inpatient admission. The randomization scheme was not revealed to participants or study investigators or staff; however, blinding to the diet assignment was not possible once the food was delivered.

All meals and snacks for the diets were designed and analyzed using ProNutra software (v.3.4, Viocare) with nutrient values derived from the USDA National Nutrient Database for Standard Reference, Release 26 and the USDA Food and Nutrient Database for Dietary Studies, 4.0. The meals were provided on 7-d rotating menus (the Supplementary Information contains detailed menu information) and were provided in the same order for both weeks on each diet. Foods and beverages were categorized according to the NOVA system[49] and glycemic index was calculated relative to 50 g of oral glucose[50]. Both diets had a common foundation of nonstarchy vegetables with low amounts of digestible carbohydrates. The LC diet added animal-based products including meat, poultry, fish, eggs, dairy and nuts. The LF diet added legumes, rice, root vegetables, soy products, corn, lentils, peas, whole grains, bread and fruit.

Bottled water and snacks representative of the prevailing diet were provided ad libitum throughout the day in snack boxes located in the inpatient rooms. Meals were presented to the participants (plated approximately as shown in the photographs included in the Supplementary Information) with instructions to eat as much or as little as desired. Volunteers were given up to 60 min to eat their meals. When meals were finished, the time was documented by the participants, but these data were incomplete with meal start and stop times available for 552 of the 840 meals provided on each diet.

Remaining food and beverages from each meal were identified and weighed by nutrition staff to calculate the amount of each food consumed and the nutrient and energy intake were calculated using the nutrition software described above. This was completed for all 1,680 meals, as well as for the daily snacks and bottled water. Two participants had errors in their food weights while on the LF diet and therefore, the intake data for the days with these errors (3 d total) was removed from the final dataset. There were also four participants who did not receive the entire 7-d rotation of the menus and had a day repeated in the sequence. This had minimal impact on the macronutrient composition of the diets because each day was targeted to closely match the prespecified targets. Meal eating rate was calculated by dividing the measured food intake for each meal by its duration.

Subjective assessment of appetite and meal palatability. During the second week of each diet period, volunteers were asked to complete hunger and satiety assessments over the course of 3 separate days implemented using Research Electronic Data Capture tools[51]. The surveys comprised VAS in response to four questions: (1) “How hungry do you feel right now?”; (2) “How full do you feel right now?”; (3) “How much do you want to eat right now?”; and (4) “How much do you think you can eat right now?”. Participants answered the questions using a 100-point VAS line scale anchored at 0 and 100 by descriptors such as ‘not at all’ and ‘extremely’. The questions were answered immediately before each meal and at least every 30–60 min over the 2–3 h following the consumption of each meal.

On the last 2 d of the first diet period and the first 2 d of the second diet period, participants were asked to complete sensory and palatability assessments to assess the palatability and familiarity of the meals provided. Questions were embedded among distracter ‘mood’ ratings (for example, alert, happy and clear-headed). Survey items were completed after the first bite of the meal.

Body weight and composition. Daily body weight measurements were performed at 06:00 each morning after the first void (Welch Allyn Scale-Tronix 5702). Volunteers wore hospital-issued top and bottom pajamas, which were pre-weighed and deducted from scale weight. Body composition measurements were performed at baseline and weekly using DXA (General Electric Lunar iDXA). The resulting percentage body fat measurements were applied to the scale measurements on the day of the scan to calculate fat mass and fat-free mass. Because the scan days were not always conducted precisely on days 1, 7 and 14 of each diet period, the sum of the body fat and fat-free masses at the beginning, middle and end of the diet periods do not precisely match the scale weights on days 1, 7 and 14 of the diets. The rate of body fat change during each 14-d diet period was calculated by linear regression. Liver fat measurements were performed using T1- and T2-corrected proton MRS with a breath-holding technique in a 3T scanner (MAGNETOM Verio; Siemens)[52].

Physical activity monitoring. Overall physical activity was quantified by calculating average daily metabolic equivalents using small, portable, pager-type accelerometers (Actigraph) sampled at 80 Hz and worn on the hip[53].

Energy expenditure via respiratory chamber. All chamber measurement periods were >23 h and we extrapolated data to represent 24-h periods by assuming that the mean of the measured periods was representative of the 24-h period. Energy expenditure was calculated as follows:

$$EE_{chamber}(\text{kcal}) = 3.88 \times [VO_2(\text{L}) - 0.32(\text{L/g}) \times K_{excr}(\text{g})] + 1.08 \times VCO_2(\text{L}) - 1.57 \times N(\text{g}) + 1.39 \times K_{excr}(\text{g})$$

where VO_2 and VCO_2 were the volumes of oxygen consumed and carbon dioxide produced, respectively, K_{excr} was the 24-h urinary ketone excretion and N was the 24-h urinary nitrogen excretion.

Sleeping energy expenditure was determined by the lowest energy expenditure over a continuous 180-min period between the hours of 00:00 and 06:00 (ref. [54]). Sedentary energy expenditure includes the thermic effect of food as previously described[24] and physical activity expenditure was the difference between 24-h energy expenditure and sedentary energy expenditure.

24-h urinary excretion. For 5 consecutive days during the second week of each diet period, including each 24-h respiratory chamber stay, all urine was collected. C-peptide was measured by ELISA (Mercodia). Acetoacetate and ammonia were measured by colorimetric assay from BioVision, β-hydroxybutyrate and urea were measured by fluorometric assay (Cayman Chemical Co.), creatinine was measured by an enzymatic method (Abbott ARCHITECT) and total nitrogen was measured by chemiluminescence (Antek MultiTek Analyzer).

Mixed-meal tests. After an overnight fast and during the second week of the LC and LF diet periods, a liquid meal was provided, matching the macronutrient content of the prevailing diet and amounting to 30% of the estimated daily calorie requirements as determined by multiplying the resting energy expenditure measured at screening by a factor of 1.6. Blood samples were obtained at 0, 10, 20, 30, 60, 90, 120, 180, 240, 300 and 360 min to measure glucose, lactate, free fatty acid, triglyceride, C-peptide and insulin concentrations.

Oral glucose tolerance tests. After an overnight fast at the end of the LC and LF diet periods, 75 g of oral glucose were administered. Blood samples were obtained at 0, 10, 20, 30, 60, 90, 120 and 180 min to measure glucose, insulin, C-peptide, free fatty acid and lactate concentrations.

Circulating metabolites and hormones. Participants wore the Dexcom G4 Platinum (Dexcom) CGM daily during the inpatient stay. The device consisted of a small sensor, a transmitter and a hand-held receiver. The sensor was inserted subcutaneously in the lower abdomen to measure interstitial glucose

concentrations every 5 min, which were transmitted to the receiver. Finger-stick calibrations were required at insertion as well as each morning and night. The sensor was changed every 7 d. Volunteers were blinded to their glucose readings. The CGM was removed during magnetic resonance imaging/MRS procedures and DXA scans. All data were downloaded at the end of the inpatient stay. Of the 552 meals on each diet with recorded meal times, postprandial CGM data analysis was limited to 368 LC diet meals and 394 LF diet meals with CGM measurements of at least 105 min after the meal with a minimum of 20 data points during the 120 min after starting each meal.

Capillary β-hydroxybutyrate was measured in the overnight fasted state using the Abbott Precision Xtra blood glucose and ketone monitoring system (Abbott Diabetes Care) in daily finger-prick blood samples obtained from 15 participants.

Fasting measurements of blood acetoacetate, acetone, β-hydroxybutyrate, VLDL particle number, VLDL size, LDL cholesterol, LDL particle number, LDL particle size, large LDL, medium LDL, small LDL, HDL particle number, HDL size, large HDL, medium HDL, small HDL, apolipoprotein-A-1, apolipoprotein-B, branched-chain amino acids (valine, leucine, isoleucine, alanine) and GlycA were performed using LP4 NMR MetaboProfile Analysis (LipoScience/LabCorp Global Research Services).

Glucagon, C-peptide and Lp(a) were measured by ELISA (Mercodia). HbA1c was measured by high-performance liquid chromatography and glucose was measured by the hexokinase method (Abbott ARCHITECT). Insulin was measured by electrochemiluminescence immunoassay and free fatty acids were measured by colorimetric assay (Roche Cobas analyzer), Triglycerides were measured by the glycerol phosphate oxidase method, total cholesterol was measured by the enzymatic method, HDL cholesterol was measured by the accelerator selective detergent method and uric acid was measured by the uricase method (Abbott ARCHITECT). Thyroid-stimulating hormone, triiodothyronine, free triiodothyronine, thyroxine and free thyroxine were measured by two-step Chemiluminescent Microparticle Immunoassay (Abbott ARCHITECT). hsCRP was measured by the immunoturbidometric method (Abbott ARCHITECT). Data on other inflammatory markers, proteins and metabolites will be reported elsewhere.

Unreported questionnaires and tasks. We performed a variety of exploratory measurements involving questionnaires (Profile of Mood States, Three-Factor Eating Questionnaire, MacArthur Socioeconomic Status Questionnaire, Self-Reported Habit Index, Satisfaction with life, Happiness and Well Being scales, UPPS-P Impulsive Behavior Scale, Liking Survey, Barrett's Impulsiveness Scale, Yale Food Addiction Scale 2.0) and tasks (Psychophysical Taste Tasks, Slips of Action Paradigm, Reward Prediction Error, Liking and Wanting, Delay Discounting), the results of which will be reported elsewhere.

Quantification and statistical analyses. The primary outcomes of this study were to measure differences in mean daily ad libitum energy intake between the LC and LF diets over the entire 14 d on each diet and over the final 7 d on each diet. Each participant's cumulative intake over 14 d and the final 7 d was calculated for each diet and the individual daily energy intake was calculated by dividing the cumulative energy intake by the number of days.

The study power calculations were informed by what we considered to be a minimal meaningful effect size (~150–200 kcal d^{-1}) along with previous studies measuring day-to-day variability of ad libitum energy intake having an s.d. of about 500–600 kcal d^{-1} (refs. [55–57]). Using the conservative assumption that within-subject energy intake correlations are zero, over a 14-d diet period each participant would have a mean energy intake with an s.e. of about 130–160 kcal d^{-1} and the mean energy intake difference between the study diets would have an s.e. of about 190–230 kcal d^{-1}. Using this range of s.e., we calculated that 20 study completers would allow for detecting a difference in mean ad libitum energy intake of 125–150 kcal d^{-1} over the 14-d test diet period with probability (power) of 0.8 with a Type I error probability of 0.05. For the final 7-d period on each diet, we estimated that each participant would have a mean energy intake with an s.e. of about 190–230 kcal d^{-1} and the mean energy intake difference between the study diets would have an s.e. of about 270–320 kcal d^{-1}. Therefore, 20 completers would allow for detecting a difference in mean ad libitum energy intake of 175–210 kcal d^{-1} over the final 7 d of each diet period probability (power) of 0.8 with a Type I error probability of 0.05. Power calculations were performed using PROC POWER (SAS v.9.4; SAS Institute).

Statistical analyses were performed using SAS (v.9.4; SAS Institute). The baseline data and figures are presented as mean ± s.e. Data were analyzed by ANOVA with individual participants as blocking factors (PROC GLM, SAS). Normality of the data was evaluated with Shapiro–Wilk and Kolmogorov–Smirnov tests and visually inspected with QQ plots. The data in the text and tables are presented as least squares mean ± s.e. and two-sided Student's t-tests were used to compare diet groups. Diet order effects for primary outcomes were analyzed as carryover effects. As reported in the main text, the carryover effect was not significant and was therefore excluded from the final statistical model. Because nonprimary measurements in this study were exploratory in nature, reported P values were not adjusted for multiple comparisons and therefore any apparent significance of these results should be confirmed in future experiments.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The study protocol, de-identified individual data, and statistical analysis code for the results reported in this manuscript will be posted on the Open Science Framework website (https://osf.io/fjykq/) and is freely available without restrictions.

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Author contributions

K.D.H. designed the study. K.D.H. and J.G. analyzed the data. A.C. and S.Y. designed the diets and measured food and beverage intake with the assistance of J.B. and S.T. R.B. and K.Y.C. performed the indirect calorimetry measurements. C.G.F. assisted with the appetitive and eating rate measurements and their interpretation. A.M.G. and R.O. performed the liver fat measurements. M.W. and P.W. analyzed the blood and urine samples. S.T.C., I.R. and M.S. were responsible for the clinical care of the research participants and supervised the day-to-day operation and coordination of the study by V.D., I.G., R.H., L.M., P.V.J., K.R. and A.S. K.D.H. wrote the manuscript and is the guarantor of this work and has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the draft and approved the final manuscript.

Competing interests

C.G. Forde has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, serves on the scientific advisory council for Kerry Taste and Nutrition and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-020-01209-1.

Supplementary information is available for this paper at https://doi.org/10.1038/s41591-020-01209-1.

Correspondence and requests for materials should be addressed to K.D.H.

Peer review information Jennifer Sargent was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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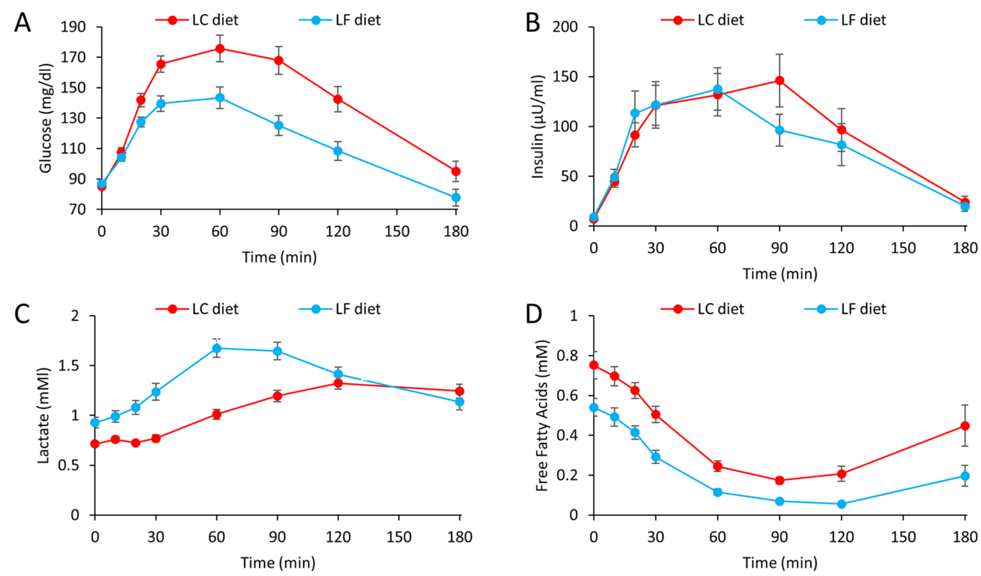

Extended Data Fig. 1 | Oral glucose tolerance. Mean blood concentrations in response to 75g oral glucose tolerance tests conducted at the end of the LC and LF diet periods (n=20) with respect to **a**) glucose, **b**) insulin, **c**) lactate, and **d**) free fatty acids. Data are presented as mean ± SEM.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The study protocol, de-identified individual data, and statistical analysis code for the results reported in this manuscript will be posted on the Open Science Framework website (https://osf.io/) upon publication.
Data analysis	All meals and snacks for the diets were designed and analyzed using ProNutra software (version 3.4, Viocare, Inc., Princeton, NJ) with nutrient values derived from the USDA National Nutrient Database for Standard Reference, Release 26 and the USDA Food and Nutrient Database for Dietary Studies, 4.0. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA). The baseline data and figures are presented as mean ± SE. Data were analyzed by analysis of variance with individual participants as blocking factors (PROC GLM, SAS). Normality of the data was evaluated with Shapiro-Wilk and Kolmogorov-Smirnov tests, and visually inspected with QQ plots. The data tables present least squares mean ± SE and two-sided t-tests were used to compare the diet groups. Diet order effects for the primary outcomes were analyzed as carry-over effects. As reported in the main text, the carryover effect was not significant and was therefore excluded from the final statistical model. Because the non-primary measurements in this study were exploratory in nature, the reported p-values were not adjusted for multiple comparisons and therefore any apparent significance of these results should be confirmed in future experiments.

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Life sciences study design

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Sample size	The study power calculations were informed by what we considered to be a minimal meaningful effect size (~150-200 kcal/d) along with previous studies measuring day to day variability of ad libitum energy intake having a standard deviation of about 500-600 kcal/d. Using the conservative assumption that within-subject energy intake correlations are zero, over a 14-day diet period each participant would have a mean energy intake with a standard error of about 130-160 kcal/d and the mean energy intake difference between the study diets would have a standard error of about 190-230 kcal/d. Using this range of standard errors, we calculated that 20 study completers would allow for detecting a difference in mean ad libitum energy intake of 125-150 kcal/d over the 14-day test diet period with probability (power) of 0.8 with a Type I error probability of 0.05. For the final 7-day period on each diet, we estimated that each participant would have a mean energy intake with a standard error of about 190-230 kcal/d and the mean energy intake difference between the study diets would have a standard error of about 270-320 kcal/d. Therefore, 20 completers would allow for detecting a difference in mean ad libitum energy intake of 175-210 kcal/d over the final 7 days of each diet period probability (power) of 0.8 with a Type I error probability of 0.05. Power calculations were performed using PROC POWER (SAS version 9.4; SAS Institute Inc, Cary, NC, USA).
Data exclusions	One subject who was enrolled in the study was removed during their first week due to a hypoglycemia episode during the LC diet. All other subjects who enrolled in the study completed the four-week inpatient stay and no other data were excluded from the analyses.
Replication	Our results have not yet been replicated.
Randomization	Randomization of diet order was conducted by the NIH Clinical Center Nutrition Department using an online randomization program (https://www.sealedenvelope.com/simple-randomiser/v1/lists) which randomized diets in blocks of 10 (5 subjects x 2 treatments) and subjects were assigned according to date of inpatient admission. The randomization scheme was not revealed to participants or study investigators or staff.
Blinding	Due to the nature of the diet interventions, once the food was delivered blinding of the subjects, investigators, or staff was not possible. However, all subjects were blinded to the primary aim of the study and were blinded to their data, including daily weight, glucose, and ketone measurements.

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Materials & experimental systems

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Methods

n/a	Involved in the study	
☒	☐	ChIP-seq
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Human research participants

Policy information about studies involving human research participants

Population characteristics	11 male and 9 female weight-stable adults aged (mean±SE) 29.9±1.4 y with BMI=27.8±1.3 kg/m2
Recruitment	Volunteers through the NIH Office of Patient Recruitment beginning in February of 2019. Screening and enrollment began April 15, 2019 and the last participant was discharged on March 4, 2020. Volunteers with strict dietary concerns, including food allergies or adherence to particular diets (e.g., vegetarian, vegan, kosher, etc.) were excluded. Subjects were not informed of the primary aims of the study but were told that the purpose of the study was to learn about how diets varying in carbohydrate and fat affect the body. The subjects were told that this was not a weight loss study and that they should not be trying to change their weight. They wore loose fitting clothing throughout the study and were blinded to daily weight, ketone, and continuous glucose measurements.
Ethics oversight	The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes & Digestive & Kidney Diseases (NCT03407053).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

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Clinical trial registration	ClinicalTrials.gov Identifier NCT03878108
Study protocol	The full protocol will be made available at the Open Science Framework website (https://osf.io/) upon publication
Data collection	The study was conducted from April of 2019 to March of 2020 at the Metabolic Clinical Research Unit of the NIH Clinical Center.
Outcomes	The first primary outcome compared the mean energy intake between each two-week diet period. The second primary outcome compared the mean energy intake on the second week of each diet period to allow for physiological adaptations to the diets and dissipation of any carryover effects.