Regulation of Energy Balance during Long-Term Physical Inactivity Induced by Bed Rest with and without Exercise Training

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Background: Short-term physical inactivity affects energy balance and is considered conducive to weigh gain. Long-term effects are unknown.

Objective: The objective of the study was to use a bed-rest model to determine the long-term effects of physical inactivity on energy balance regulation and test the effect of exercise training on energy balance adjustment to physical inactivity.

Design: Sixteen lean women were divided into two groups (n = 8 each): a control group subjected to a strict 60-d bed rest and an exercise group subjected to a combined aerobic/resistive exercise training concomitantly to bed rest. Body composition, spontaneous energy intake, hunger, total energy expenditure (TEE), and fasting gut hormones were measured.

Results: Based on bed-rest-induced body composition changes, the control group were in slight negative energy balance (−0.4 ± 0.4 MJ/d; P = 0.01 vs. zero), essentially due to muscle atrophy (P < 0.001 vs. zero). The stable fat mass (P = 0.19 vs. zero), and the matching between spontaneous energy intake and TEE indicated, however, a stable energy balance. Hunger and gut hormones remained unchanged during the bed rest. In the exercise group, TEE was 24% higher than in the control group (P = 0.004). Unexpectedly, desire to consume food (P = 0.025) decreased and spontaneous energy intake (P = NS) was not stimulated, promoting a negative energy balance (−1.1 ± 0.5 MJ/d, P = 0.0003 vs. zero).

Conclusions: Energy balance is regulated during 2 months of physical inactivity, contrasting with short-term experiments. Conversely, exercise-induced energy expenditure in bed-resting subjects who have no spontaneous physical activity did not induce hunger and promoted a negative energy balance, suggesting a potential role of nonexercise physical activities in energy balance regulation. (J Clin Endocrinol Metab 95: 1045–1053, 2010)
Epidemiological data suggest that during the last decades, energy intake and fat consumption increased (1) and physical activity decreased (2). These changes were considered to act synergistically in the direction of encouraging obesity and diabetes. The complex interplay between physical activity and hence energy expenditure and the food environment and hence energy intake in weight regulation, however, remains incomplete.

Some studies (3–5) suggested that energy intake poorly tracks changes in total energy expenditure (TEE) and results in positive energy balance during conditions of reduced physical activity. These observations have been used as proof of a defect in the mechanisms of energy balance regulation conducive to weight gain among individuals with a sedentary lifestyle. This hypothesis was supported by a thorough review of cross-sectional data from doubly labeled water (DLW) studies in men but not women (6). Surprisingly few intervention studies investigated the effect of physical inactivity on appetite and energy balance. Murgatroyd et al. (3) noted that on a given diet, either high- or low-fat diets, active and sedentary subjects consumed the same level of energy, regardless of the level of TEE. Similarly, the decrease in activity associated with the sedentary environment induced by 1 (4) or 7 d (5) spent in a calorimeter room generated a positive energy balance in both lean and obese subjects. Thus, a decrease in activity has considerable ability to decrease energy balance in both lean and obese subjects. Therefore, it may take at least 2–4 wk for energy intake to adjust to a decreased TEE versus daily energy intake and TEE, body composition, spontaneous feeding behavior, hunger, and related hormonal determinants, allowed us to investigate the effects of long-term physical inactivity on energy balance regulation and tested the buffering effect of exercise training performed concomitantly to the bed rest.

The thorough nutritional and metabolic monitoring performed during the WISE study, i.e., daily energy intake and TEE, body composition, spontaneous feeding behavior, hunger, and related hormonal determinants, allowed us to investigate the effects of long-term physical inactivity on energy balance regulation and tested the buffering effect of exercise training performed concomitantly to the bed rest.

### Subjects and Methods

#### Study design

Sixteen healthy women volunteered for a 60-d bed rest. Table 1 shows their baseline characteristics. The protocol was approved by the Midi-Pyrénées I Institutional Review Board (France). The study was divided into a 20-d ambulatory control period, 60 d of bed rest in head-down tilt position (−6°), and a 20-d recovery period. During the in-patient control period, the

| TABLE 1. Characteristics of the participants in ambulatory period at baseline, during bed rest and 1 yr after the end of the experiment |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Baseline        | 60 d after bed rest | After 1 yr      |
|                 | Control         | Exercise         | Control         | Exercise         | Control         | Exercise         |
| n               | 8               | 8                | 6               | 8                | 6               | 8                |
| Age (yr)        | 34 ± 4          | 33 ± 4           | 34 ± 4          | 33 ± 4           | 35 ± 3          | 34 ± 4           |
| Height (m)      | 1.63 ± 0.06     | 1.65 ± 0.07      | 1.62 ± 0.06     | 1.65 ± 0.07      | 1.62 ± 0.06     | 1.65 ± 0.07      |
| Body mass (kg)  | 55.6 ± 3.8      | 58.4 ± 6.5       | 52.3 ± 3.8a     | 54.9 ± 6.1a      | 54.8 ± 4.8      | 58.7 ± 6.3       |
| BMI (kg/m²)     | 21.3 ± 1.4      | 21.7 ± 1.4       | 19.7 ± 1.2      | 20.2 ± 1.5a      | 21.3 ± 0.9      | 21.3 ± 1.5       |
| Fat-free mass (kg) | 40.8 ± 3.1     | 43.8 ± 5.8       | 38.0 ± 3.0a     | 42.5 ± 5.7a      | 40.6 ± 3.4      | 44.0 ± 6.0       |
| Fat mass (kg)   | 14.8 ± 3.7      | 14.5 ± 3.2       | 14.3 ± 3.5      | 12.4 ± 3.6a      | 14.2 ± 4.1      | 14.7 ± 2.6       |
| VO₂peak (liters/min) | 1.9 ± 0.4     | 2.1 ± 0.4        | 27.1 ± 5.5%     | 22.6 ± 6.2%a     | 25.7 ± 5.8%     | 25.1 ± 4.5%      |
|                 | 34.5 ± 7.7 ml/kg·min | 35.1 ± 4.4 ml/kg·min |

Values are mean ± sd. No between-group differences were noted. Inclusion criteria included age between 25 and 45 yr, nonsmokers, no regular consumption of alcohol, and participation in at least 30 min of moderate activity per day achieved with either structured exercise or activities of daily living. Exclusion criteria included familial history of clinical or biomedical diseases, regular high-volume physical activities, acute diseases requiring medications 3 months prior to the study, sleep disorders, chronic back pain, history of thrombophlebitis, special food diets, and tendon or bone fracture. Participants stopped birth control pills 3 months before the study. BMI, Body mass index; VO₂peak, Peak O₂ consumption.

a Paired t test with Bonferroni correction; P < 0.013 vs. baseline period.
exercise was controlled and baseline data collection was performed. During the bed rest, the subjects were randomized into two groups (n = 8, each): a control group that with no added activity and an exercise group subjected to a supine resistance and aerobic exercise training protocol.

One year after the end of the study (R + 360), the participants came back to complete postintervention tests (n = 16).

**Exercise training protocol**

The resistance exercise training program was performed on a flywheel ergometer (14), allowing subjects to perform maximal concentric and eccentric actions in the supine squat and calf press. A total of 19 sessions were scheduled for each subject approximately every third day and lasted 35 min after a 10-min warm-up (15, 16).

The aerobic training protocol was performed three to four times per week using a specially designed vertical treadmill (17). Subjects performed 29 exercise sessions lasting 50 ± 2 min at intensities ranging between 40 and 80% VO₂peak (25% at high intensity and 75% at moderate intensity), as previously described (22, 23).

**Energy intake**

The diet had a macronutrient composition of 30% fat, 15% proteins, and 55% carbohydrates. Food intake was provided as a base diet and snacks and was calculated to match requirements during bed rest (8, 20). The approach differed from previous studies (3–5) that aimed to investigate individual energy intake adaptation from offered meal sizes equivalent to the active conditions. Our paradigm discouraged the initial well-described passive overeating by adjusting meals size to bed rest and bed rest plus exercise energy needs. The subjects were not required to finish their meal and could also request larger portions when hungry. Additional facultative snacks were offered. Thus, energy intake was allowed to fluctuate around theoretical base diet that met energy requirements to measure spontaneous changes in energy intake and ingestive behaviors associated with the physical inactivity.

During the control period, energy requirements were calculated as resting metabolic rate (RMR), measured by indirect calorimetry, times a physical activity level of 1.4 (21). A physical activity level of 1.2 was selected for the bed-rest period (20). RMR was measured twice in each period. Fat mass was assessed by dual-energy x-ray absorptiometry every 15 d and subjects were weighted daily. Those parameters were used to adjust the base energy prescription.

Diet, supplied by the hospital kitchen and controlled by three dietitians, consisted of a Western diet after a 7-d rotating menu, with two daily choices. Meals were provided at breakfast (0800–0900 h), lunch (1200–1300 h), and dinner (0700–0800 h). Snacks were offered in the afternoon around 1600 h. Ingredients for each recipe were entered in the Geni Software (Frana, Nancy, France). All food and leftovers were weighted individually.

**Perceived hunger profile**

One hundred-millimeter visual analog scales were used to assess perceived hunger, satiety, fullness, desired food consumption, and desire to eat something fatty or sweet as previously described (22, 23). Visual analog scales, distributed every week, were administered 15 min before and after each meal and at 1000 and 1600 h.

**TEE**

TEE was determined at the end of the bed-rest period (d 46–56) and 1 yr after the bed rest by the DLW method over a 10 d period (24). The subjects ingested a premixed 2 g/kg estimated total body water dose of DLW composed of 0.2 and 0.15 g/kg estimated total body water of 10% H₂¹⁸O and 99% ²H₂O, respectively (Cambridge Isotope Laboratories, Andover, MA).

Equilibration and end point urines were cleaned as previously described (25). Deuterium and 18-oxygen isotopic abundances were analyzed by pyrolysis on an elemental analyzer (Flash HT; ThermoFisher) connected to a continuous flow isotope ratio mass spectrometer (Delta V; ThermoFisher, Scwerle, Germany). The results were scaled using two laboratory standards. Analyses were performed in quadruplicate and repeated if the SD exceeded 2% for deuterium and 0.5% for 18-oxygen.

The total body water and TEE were calculated as previously described (10, 26) using a food quotient of 0.86.

**RMR, diet-induced thermogenesis, and activity-related energy expenditure**

RMR was measured fasting by indirect calorimetry (Deltatrac II; General Electric, Indianapolis, IN) for 1 h before and during the bed rest. Diet-induced thermogenesis (DIT) was calculated as the increment of RMR during the 4-h postbreakfast period (50% of RMR in energy). TEE minus RMR minus DIT was computed as an estimate of activity energy expenditure. One year after the end of the bed rest, RMR, but not DIT, was measured for 1 h in fasting state.

**Body mass and composition**

Body mass was measured daily. Fat mass and fat-free mass were measured twice during the ambulatory period, every 15 d during the bed-rest period and 1 year after the end of the experiment by dual-energy x-ray absorptiometry on QDR 4500 W scanner using the version software 11.2 (Hologic, Roissy Charles-de-Gaulle, France).

**Energy balance**

Energy balance during the whole bed-rest period was calculated based on the changes in body composition (27).

**Hormone measurements**

Fasting blood samples were collected at baseline and after 30 and 60 d of bed rest. Fasting glucagon like-peptide (GLP)-1, leptin, and ghrelin were measured in duplicate using the Bioplex Diabetes (Bio-Rad, Marnes-la-Coquette, France). Total peptide YY (PYY) was measured in duplicate by the Millipore single Plex (Millipore, Molsheim, France).

**Data and statistical analysis**

Longitudinal variables were averaged to a 15-d time frame. Data were analyzed by a repeated-measure ANOVA with time as the repeated measure and group (control vs. exercise) as main effects. When the repeated measure involve more than two time points (measurements every 15 d), we focused on main effects and no post hoc tests were performed. When the repeated measure involved only two time points (before and during bed rest), post hoc tests were performed using the Bonferroni-Dunn test. To compare subjects characteristics during and 1 yr after the bed rest to baseline values, unpaired and paired t tests were per-
formed using a Bonferroni correction ($P < 0.0125$ considered statistically significant) to adjust for the multiple testing. All statistics were performed using Statistica version 7.1.515.0 (Statsoft, Paris, France), and reported values are means $\pm$ SD (unless otherwise stated), with $P < 0.05$ considered statistically significant.

**Results**

**Body composition changes during the bed rest**

Body mass decreased similarly in both groups ($-3.3 \pm 0.3$ kg; $P < 0.0001$, Fig. 1, left panel). Fat mass was maintained in the control group (bed rest by group interaction: $P = 0.005$) and the loss in body mass was essentially due to a reduction of $-2.9 \pm 0.1$ kg in fat-free mass ($P < 0.0001$). On the contrary, the exercise training partially counteracted the physical inactivity-induced muscle atrophy (bed rest by group interaction: $P = 0.0006$), and the body mass reduction was mainly explained by a decrease in fat mass ($-1.9 \pm 0.3$ kg; $P = 0.001$) in the exercise group.

**Base diet and spontaneous energy intake during the bed rest**

The differences in the prescribed energy intake during the bed-rest period between the two groups correspond to the estimated cost of the exercise training (Supplemental Table 1, published as supplemental data on The Endocrine Society’s Journals Online web site at http://jem.endojournals.org). During the bed rest, the volunteers spontaneously reduced their energy intake below the prescription. This is represented by the increase in leftovers (Fig. 1, right panel). The volunteers in the control group consumed almost the total quantity of provided meals during all the period of the bed rest (99 and 97% during the ambulatory control period and the first 45 d of bed rest, respectively), but they ate 95% of the prescribed energy intake during the last 15 d of the bed rest. The leftovers of the exercise group already represented 6% of energy intake from the 30th to the last day of the bed rest.

**Energy expenditure during the bed rest**

The exercise group had a significant higher TEE than the control group during the bed rest ($7.12 \pm 0.78$ vs. $8.85 \pm 1.14$ MJ/d, $P = 0.004$, Fig. 2A). RMR did not differ between the control ($4.98 \pm 0.43$ MJ/d) and the exercise ($5.30 \pm 0.40$ MJ/d) groups, even after adjustment for fat-free mass. No between-group difference was noted in DIT (control: $0.43 \pm 0.13$ MJ/d; exercise: $0.52 \pm 0.17$ MJ/d). Consequently, although it was not statistically significant, the difference in TEE between the two groups was mainly accounted for by a greater activity energy expenditure in the exercise group than the control group ($3.02 \pm 1.09$ vs. $1.71 \pm 1.09$ MJ/d, respectively). Activity energy expenditure was, however, statistically different after normalization for body mass between the exercise and control groups ($53.74 \pm 17.71$ vs. $33.07 \pm 22.59$ MJ/d·kg, respectively; $P = 0.0002$).

**Energy balance after 60 d of bed rest**

Energy balance was negative in the exercise group ($-1.1 \pm 0.5$ MJ/d; $P = 0.0003$ vs. zero, Fig. 2B). A small but significant negative energy balance was noted in the control group ($-0.4 \pm 0.4$ MJ/d, $P = 0.01$ vs. zero). The negative energy balance in the control group was essentially due to the loss of fat-free mass during the bed rest ($P < 0.001$ vs. zero) because fat mass remained stable ($P = 0.19$ vs. zero; Fig. 2B).

The difference between TEE and prescribed energy intake during the DLW period was $-0.2 \pm 1.0$ and $-0.9 \pm 0.8$ MJ/d in the control and exercise groups, respectively. This gap was only significantly different from zero ($P = 0.01$) in the exercise group. During this period, the difference between the base and actual energy intake was similar.
between the control and exercise groups (−0.4 ± 0.2 and −0.4 ± 0.2 MJ/d, respectively) and not different from zero in both groups. These results suggest that appetite was not stimulated in the exercise group promoting a negative energy balance.

**Subjective hunger changes during the bed rest**

Desired food consumption decreased significantly by 25% gradually during the bed rest in both groups (P = 0.025; Supplemental Table 2). Hunger, fullness, and preferences toward fatty or sweet food were not affected by the bed rest in both groups. No group effect was noted.

The variation in prospective food consumption positively correlated with the differences between base and actual energy intake during the last 15 d of bed rest in the exercise group (r² = 0.76; y = 0.028 × −0.014; P = 0.005; Fig. 3A) but not in the control group (r² = 0.33, P = 0.13).

**Hormonal pattern changes during the bed rest**

Fasting plasma ghrelin, PYY, and leptin did not vary during the bed rest period in both groups and no group effect was observed (Fig. 4A).

At all time points, leptin concentrations were strongly associated with fat mass (Fig. 4A). Given the between group difference in fat mass changes during the bed rest, the lack of significant change in leptin was unexpected. The fasting leptin concentrations on d 60 adjusted for fat mass negatively correlated with the spontaneous energy intake (r² = 0.49, P = 0.006, Fig. 4B).

GLP-1 concentration increased in the two groups (P = 0.0076), but the increase was higher in the exercise group (bed rest by group interaction: P = 0.048, group effect: P = 0.014, Fig. 4A). In both groups, GLP-1 during the bed-rest period positively correlated with desired food consumption (r² = 0.29; P = 0.04, Fig. 3B).

**Characteristics of the volunteers after 1 yr of follow-up**

All the volunteers recovered their initial body mass and composition 1 yr after the end of the intervention (Table 1). In ambulatory conditions, TEE was not statistically different between the control and exercise groups (9.82 ± 1.24 vs. 11.36 ± 0.93 MJ/d, respectively; Fig. 2A). In both groups free-living TEE was higher than during the bed-rest conditions (control group: +22%, P = 0.0001 and exercise group: +27%, P = 0.0004). RMR did not differ between the control (5.20 ± 0.30 MJ/d) and the exercise groups (5.58 ± 0.58 MJ/d). Activity energy expenditure in daily life was not different between the exercise group and the control group (4.70 ± 0.82 vs. 3.53 ± 1.52 MJ/d), even after normalization for body mass.

**Discussion**

The female volunteers in the control group had a physical activity level of 1.45 during the 2-month bed rest due to a 51% decrease in activity energy expenditure. This physical activity level values is lower than the average ambulatory
physical activity level of 1.80 but not as low as the generally accepted minimal physical activity level of 1.3 that is the requirement for total inactivity (28). Interestingly, rather than responding with positive energy balance as have been reported in short-term studies (3–5), the volunteers maintained a 16% lower energy intake during the bed rest compared with the ambulatory period. Based on the body composition changes, energy balance was even moderately negative. However, the loss of fat-free mass repeatedly reported during bed-rest studies is due to muscle disuse regardless of energy balance (29). In fact, muscle atrophy is even more pronounced when energy balance is positive (29). Therefore, it has been previously established that changes in fat mass rather than changes in body mass are representative of energy balance during bed-rest studies (30). In the present study, fat mass did not vary significantly in the control group, confirming that they reached a stable energy balance during the bed-rest period. Similar results were observed in a previous 42-d bed rest (8) during which healthy men were provided excess amounts at meals in a more traditional ad libitum manner. To complete these observations, we reanalyzed data from a 90-d bed rest conducted in men (15). Energy prescription was based on a 35 kcal/kg·d food allotment reduced arbitrarily by 200 kcal/d at the beginning of the bed rest. However, the volunteers were free to ask bigger size portions or not finish their meals. Energy intake and leftovers remained quite stable over the 90-d study, resulting in a global stable fat mass (overall change of 0.3 ± 0.6 kg; Supplemental Fig. 1). Taken together, these results suggest that the volunteers subjected to long-term physical inactivity adjusted their energy intake to TEE and to maintain energy balance.

The volunteers in the exercise group had a physical activity level of 1.68 during the bed rest, which places them slightly above the average activity of the general population (31, 32). Interestingly, the exercise group was in negative energy balance, which was due to a larger decrease in spontaneous energy intake compared with the drop in TEE during the bed rest. It is possible that this reduced energy intake may be influenced by our experimental design coupled with an underestimation of the energy cost of the exercise. This was, however, unlikely the case because the subjects were allowed to request more food. Yet the volunteers increased leftovers. This voluntary reduction in energy intake is well highlighted by the relationship between the subjective desired food consumption and the differences between the prescribed and actual energy intake.

These results complete the studies performed by the team of Stubbs et al. (33, 34). During a 7-d study conducted in men (33), a graded increase in TEE due to medium (about 1.6 MJ/d) or high exercise regimens (about 3.2 MJ/d) markedly elevated TEE, which was not compensated for by any increase in energy intake, generating a negative energy balance. Later Whybrow et al. (35) assumed that accurate adjustments of energy intake to acute increases in TEE are likely to take weeks rather than days. However, our results suggest that the lack of compensatory effect on energy intake was fully engaged at d 15 and was evident in daily energy intake as soon as 3 d after the rest started (data not shown). In fact, Whybrow et al. (35) reported a partial compensation (~30%) for the exercise-induced energy deficit on a longer time scale through a decrease in TEE in both treatments because of a gradual drop in nonexercise activity energy expenditure (NEAEE), i.e. nonexercise activity thermogenesis. If we hypothesized that NEAEE is a stronger buffer of energy deficit than spontaneous energy intake, the exercise-training program that significantly impacts on TEE induced a negative energy balance because no regulation could be achieved through the removed NEAEE during bed rest (Fig. 5). The combined resistive and aerobic exercises significantly increased TEE by about 8% and results in reduced fat mass. Conversely, during the 90-d bed rest in men (15), the resistive exercise program performed every 3 d for 35 min had only an estimated impact on TEE of 2%, and fat mass remained stable with rather a light tendency to increase (Supplemental Fig. 1). The estimated energy balance was calculated at only 0.4 MJ over the 90-d period.
These results may appear to contrast to many long-term, outpatient studies (up to 12 wk) showing that exercise training induced a loss of weight no larger than 1 kg on average (36). In fact, these studies are complementary because compensation was shown to occur by either increases in energy intake or decreases in NEAEE (33–35). The decrease in NEAEE in other studies is an interesting hypothesis to explain the difference between our study (in nonexercise-deficient subjects in whom compensation can occur only through modulation of energy intake) and the long-term outpatients studies (in subjects with large modulation possible through NEAEE).

Although the palatability reported by the volunteers remained unchanged during all the duration of the bed rest (data not shown), a limitation of our study and any human study into the compensatory changes in energy intake is that there is little control over cognitive influences on energy intake. These may differ between study cohorts, especially when cohort sizes are on the order of 4–16 as is the case in most complex human studies like these.

Although the subjects desired eating less during the bed rest and decreased their energy intake, long-term physical inactivity did not significantly affect the fasting plasma concentrations of the gut hormones. Although no variation in fasting leptin concentration was noted (despite a negative energy balance), fasting leptin adjusted for fat mass was higher during the bed rest in the control group, as was previously observed in a 7-d bed rest (37). Except for a putative relationship with the increase in circulatory inflammatory markers observed during bed rest (12), we do not know how to explain a higher fat mass-adjusted fasting leptin levels in this context. It is also interesting to note that fat mass-adjusted fasting leptin levels can represent a potentially good biomarker of energy intake. Further studies are clearly needed to support that observation.

The exercise training increased the fasting concentration of GLP-1 that was weakly, but negatively, related to the subjective desired food consumption in the exercise group. A rise in GLP-1 was previously reported during an acute exercise at 65% of the maximal heart rate and associated with a relative decrease energy intake compared with exercise-induced TEE in both normal-weight males and females (38). Taking these results together, the weak coupling between energy intake and TEE at high levels of TEE induced by acute or chronic exercise may be mediated, at least in part, through the action of GLP-1.

In conclusion, whereas energy balance is well regulated under long-term physical inactivity, no such adjustment in response to exercise-induced energy expenditure was observed in NEAEE-deficient females. The role of the low levels in NEAEE induced by bed rest warrants further investigations, especially in males and overweight individuals but do complement the numerous publications in which added exercise does not promote weight loss in fully efficient nonexercise activity outpatients. These results suggest that the regulation of energy balance in response...
to an energy deficit induced by exercise training rather involves, at least in lean individuals, a reduction in non-exercise physical activities and removed by design during bed-rest, than an increase in spontaneous energy intake.

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Disclosure Summary: A.B. collected and analyzed the data, conducted the statistical analysis, and drafted the manuscript. I.M. participated in the writing of the manuscript and gave relevant advices in the interpretation of the results. B.S. designed the study; helped with the collection, statistical analysis, and interpretation of the data; corrected the first draft of the manuscript; and got funding. C.S. assisted with the statistical analysis and data interpretation. D.A.S. helped with the interpretation of the results with special reference to the energetics and corrected the English of the manuscript. S.N. strongly helped with the study organization and the collection of the data. A.Z. performed all the doubly labeled water analyses. B.L. analyzed the gut hormones. None of the authors had any personal or financial conflicts of interest with regard to the study.

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