INTERMITTENT ENERGY RESTRICTION / INTERMITTENT FASTING
Sponsor

Nestlé Health Science Optifast® VLCD™
Overview

› What is intermittent energy restriction (IER)

› Rationale for IER

› Variations of IER

› Systematic Reviews and Meta-analyses of IER

› Severe Energy Restriction / Very Low Energy Diets (VLEDs)

› Discussion / Questions
What is intermittent fasting / intermittent energy restriction (IER)?

Cycle between:

Periods of feeding / energy balance ('Feed day')

and

Periods of total fasting / severe energy restriction (~2000 - 2500 kJ/day) ('Fast day')
Daily energy restriction or continuous energy restriction (CER)
Adaptive Response to Energy Restriction

- Weight gain
- Adaptive response
  - Decreased hunger
  - CNS response to circulating hormones
  - Energy dissipation
    - Increased thermogenesis
    - Increased metabolic rate

- Increased energy intake

- Decreased energy intake

- Adaptive response
  - Increased hunger
  - CNS response to circulating hormones
  - Energy conservation
    - Decreased thermogenesis
    - Decreased metabolic rate
    - Reduced fat oxidisation

- Weight loss

Obesity Clinical Gate 2015
Rationale for intermittent energy restriction

› Can periods of energy balance during energy restriction attenuate / deactivate adaptive responses?

› More acceptable and easier to follow than daily restriction / continuous energy restriction (CER)?
Variations of intermittent energy restriction

 › **Time-Restricted Feeding (TRF):**
   8/6/4 hours feeding, 16/18/20 hours fasting

 › **Alternate Day “Fasting” (ADF):**
   75% energy restriction on ‘fast’ day alternated with a ‘feed’ day

 › **5:2 Diet:**
   ‘Fast’ on 2 consecutive or non-consecutive days/week

 › **Warrior Diet:**
   Fast during the day and have one large meal at night

 › **Eat Stop Eat:**
   ‘Fast’ for 24 hours 1-2 days/week
Variations of intermittent energy restriction

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  ‘Fast’ for 24 hours 1-2 days/week
5:2 DIETS
Effects of 5:2 (non-consecutive days) vs CER in adults during a 12-month period

- N = 112, 30-45 kg/m²
- Randomized to IER or CER (6-month weight-loss) then 6-month maintenance

Sundfør, Nutr Metab Cardiovasc, 2018
Effects of 5:2 (non-consecutive days) vs CER in adults during a 12-month period

- Randomized to IER or CER
  - CER: reduce energy intake evenly 7 days / week
  - 5:2: 400/600 kcal (female/male) on two non-consecutive, usual diet for 5 days
Both IER and CER resulted in similar weight loss and improvements in cardiovascular risk factors after 1 year

- Weight loss similar in IER and CER groups (8 - 9 kg)
- Improvements in both groups with no difference between groups:
  - Waist circumference,
  - Blood pressure,
  - Triglycerides and HDL-cholesterol
- Weight regain was minimal and similar between IER and CER
- IER reported higher hunger scores than CER
Effects of 5:2 (consecutive days) vs CER in adults
5:2 (consecutive days) as effective as CER in weight loss, insulin sensitivity and health biomarkers

› IER and CER equally effective for weight loss
› Both groups experienced comparable reductions in:
   › Leptin
   › Free androgen index
   › High sensitivity C-reactive protein
   › Total and LDL cholesterol, triglycerides
   › Blood pressure
› ↑ Sex hormone binding globulin, IGF binding proteins 1 and 2
› ↓ Fasting insulin, insulin resistance, greater with IER than CER
› ← time to attain 5% weight loss between groups

Harvie IJO 2011, Antoni British J nutr 2018
IER (consecutive/non-consecutive) vs CER in adults with overweight / obese during 12- and 24- months

\[ N = 332 \]

- Randomised to 3 groups:
  - **CER**: Women: 4200 kJ/d; Men: 5040 kJ/d
  - Week-on-week-off: alternating between same energy restriction as CER and habitual diet
  - **5:2**: Women: 2100 kJ/d; Men: 2520 kJ/d on 2 days of energy restriction, consecutive or non-consecutive

Headland ML R IJO 2018, Headland ML R IJO 2020
IER not different for weight loss, cardiometabolic risk factors vs CER after 12 months in adults with overweight/obesity

- Similar dropout rate
- No difference between groups in body fat, HDL-cholesterol and triglycerides at 12 months
- No changes in fasting glucose or LDL-cholesterol
# 24-months follow-up

<table>
<thead>
<tr>
<th></th>
<th>Time (weeks)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>0</td>
<td>8/16</td>
<td>52</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>109</td>
<td>90.3 ± 15.3</td>
<td>84.5 ± 14.8</td>
<td>84.4 ± 15.5</td>
<td>86.7 ± 15.8</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>109</td>
<td>33.0 ± 4.5</td>
<td>30.9 ± 4.4</td>
<td>30.9 ± 4.7</td>
<td>31.7 ± 4.9</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>91</td>
<td>40.3 ± 10.5</td>
<td>36.3 ± 11.1</td>
<td>35.3 ± 11.1</td>
<td>37.2 ± 11.5</td>
<td>&lt;0.001</td>
<td>0.09</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>91</td>
<td>47.9 ± 9.7</td>
<td>46.3 ± 9.6</td>
<td>47.0 ± 9.6</td>
<td>47.2 ± 9.2</td>
<td>&lt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Glucose</td>
<td>109</td>
<td>5.6 ± 0.5</td>
<td>5.5 ± 0.6</td>
<td>5.5 ± 0.6</td>
<td>5.5 ± 1.2</td>
<td>0.51</td>
<td>0.41</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>109</td>
<td>6.0 ± 1.1</td>
<td>5.7 ± 1.1</td>
<td>6.0 ± 1.1</td>
<td>5.9 ± 0.9</td>
<td>0.02</td>
<td>0.65</td>
</tr>
<tr>
<td>HDL</td>
<td>109</td>
<td>1.5 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>0.50</td>
<td>0.86</td>
</tr>
<tr>
<td>LDL</td>
<td>109</td>
<td>4.1 ± 1.1</td>
<td>4.0 ± 1.1</td>
<td>4.2 ± 1.1</td>
<td>4.0 ± 1.0</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>109</td>
<td>1.4 ± 0.7</td>
<td>1.1 ± 0.5</td>
<td>1.2 ± 0.6</td>
<td>1.4 ± 0.7</td>
<td>0.90</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*a* P value between WOWO and CER at 104 weeks

*b* P value between 5:2 and CER at 104 weeks time by diet effect
Spontaneous reduction in energy intake on unrestricted days

Table 2: Energy intake at baseline and on the different unrestricted days of intermittent energy restriction in Study 1 (n = 44) and Study 2 (n = 67) in (kJ/day)

<table>
<thead>
<tr>
<th></th>
<th>Baseline reported intake</th>
<th>Recommended intake on unrestricted day, 93% of estimated energy requirements</th>
<th>Day immediately before restricted day</th>
<th>Other unrestricted day</th>
<th>Mean (95% CI) difference between days immediately before and other unrestricted day</th>
<th>p value Day immediately before and other unrestricted day</th>
<th>Day immediately after restricted day</th>
<th>Other unrestricted day</th>
<th>Mean (95% CI) difference between days immediately after and other unrestricted day</th>
<th>p value Day immediately after and other unrestricted day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 energy intake (kJ/day) n = 44</td>
<td>7,928 (7,397, 8,458)</td>
<td>7,728 (7,536–7,921)</td>
<td>6,226 (5,799–6,648) (59 days)</td>
<td>6,230 (5,866, 6,594) (177 days)</td>
<td>~4 (-381, 368)</td>
<td>.98</td>
<td>6,427 (5,966–6,883) (59 days)</td>
<td>6,226 (5,841, 6,607) (177 days)</td>
<td>261 (-335, 736)</td>
<td>.46</td>
</tr>
<tr>
<td>Study 2 energy intake (kJ/day) n = 67</td>
<td>8,484 (8,049, 8,923)</td>
<td>7,546 (7,399–7,691)</td>
<td>5,925 (5,535–6,318) (73 days)</td>
<td>6,117 (5,807, 6,427) (632 days)</td>
<td>~192 (-506, 121)</td>
<td>.23</td>
<td>6,042 (5,665–6,418) (166 days)</td>
<td>6,134 (5,820, 6,443) (632 days)</td>
<td>~92 (-393, 209)</td>
<td>.55</td>
</tr>
</tbody>
</table>

› Study 1: IER (2 consecutive days ~70% ER, 5 unrestricted days /week) for 6 months
   Study 2: 2 forms of IER (2 consecutive days ER, 5 unrestricted days /week) for 4 months

› Reduction in EI below baseline EI (by 21% and 29%) and prescribed EI (by 19%) during unrestricted days including the days immediately before and after restricted days may contribute to the weight loss success

Harvey J, Food Science and Nutrition, 2017
Summary 5:2

› Clear benefits to 5:2 diet

› IER is as effective as CER with regard to weight (fat) loss, insulin sensitivity and other health biomarkers and cardiovascular benefits

› Consecutive or non-consecutive days?
5:2 DIETS AND TYPE 2 DIABETES
Effects of 5:2 vs CER on glycemic control and weight loss in patients with T2D during a 12-month period

Adults with type 2 diabetes with overweight/obese: N = 137

Randomised to 2 groups:

- CER: 1200-1500 kcal/d for 7 days/week for 12 months
- 5:2: 500-600 kcal/d on 2 nonconsecutive days/week and usual diet for the other 5 days

Medication management protocol - medications likely to cause hypoglycemia were reduced at baseline.

Carter S JAMA 2018
IER is an effective alternative diet strategy for the reduction of HbA1c and is comparable with CER in adults with T2D

Figure 2. Mean Between-Group Difference in Change in Hemoglobin A1c Level, Weight, and Body Composition for the Intermittent vs Continuous Groups (Intention-to-Treat Analysis)

To convert hemoglobin A1c to proportion of total hemoglobin, multiply by 0.01. Error bars indicate 2-sided 90% confidence intervals. Tinted area indicates zone of equivalence.
Glucose monitoring for safe use of a 2-day IER in patients with type 2 diabetes

› Is adjusted medication protocol superior to fixed protocol at reducing hypoglycaemic events during a 2 week 5:2 diet?

› 60% participants on adjusted protocol had no hypoglycaemic events.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Fixed medication protocol</th>
<th>Adjusted medication protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7% (≤3 mmol/mol)</td>
<td>Discontinue at baseline</td>
<td>Discontinue at baseline</td>
</tr>
<tr>
<td>&gt;7-8% (≥53-64 mmol/mol)</td>
<td>Discontinue on IER days only</td>
<td>Long and intermediate-acting insulin discontinued the night before the IER. All insulin discontinued on the day of the IER. Insulin will not be resumed until a full day's caloric intake is planned (if taken in the morning) or achieved (if taken in the evening).</td>
</tr>
<tr>
<td>&gt;8-10% (≥64-86 mmol/mol)</td>
<td>Discontinue on IER days only</td>
<td>All insulin discontinued on the day of the IER. Insulin will not be resumed until a full day's caloric intake is planned (if taken in the morning) or achieved (if taken in the evening).</td>
</tr>
<tr>
<td>&gt;10-12% (≥86-108 mmol/mol)</td>
<td>Continues</td>
<td>Short-acting insulin is discontinued, intermediate-acting is halved and long-acting insulin is reduced by 10 units or 10% whichever is greater, on IER days only.</td>
</tr>
<tr>
<td>&gt;12% (≥108 mmol/mol)</td>
<td>Continues</td>
<td>Short-acting insulin is discontinued and long-acting insulin continued.</td>
</tr>
</tbody>
</table>

One or more events (<3.9 mmol/L for >15 min) over 2 weeks then follow protocol 1 level greater than appropriate. E.g: if HbA1c is >7-8% then the participant should follow the <7% protocol.

Carter S, Diabetes Res Clin Pract, 2019
ALTERNATE DAY FASTING
Alternate day fasting (ADF)

- Alternating ‘feed’ and ‘fast’ days

- Feed days: usually no restrictions on types / quantities of foods over 24 hrs

- Fast days: ~500 kcal over 24 hrs. ADF for weight loss, recommended to consume at least 50 g of protein to decrease hunger.

- Calories can be consumed all at once, or spread through day, without affecting rate of weight loss.  

  Hoddy Obesity, 2014

- Another ADF strategy involves 0 kcal on the fast day, also known as zero-calorie ADF.
Compensatory responses induced by weight loss following IER (3 non-consecutive days) and CER

Start of weight loss intervention

18 randomly assigned to an IER diet (12 weeks):
- 3 non-consecutive days of a commercial VLCD + a diet matching energy needs on the other days

4 withdrew:
- 1 pregnancy
- 2 personal reasons
- 1 difficult to adhere to the diet

14 participants tested at the end of weight loss (week 13):
- same tests as at baseline

17 randomly assigned to a CER diet (12 weeks):
- a low calorie diet every day.

3 withdrew:
- 1 was excluded (lack of compliance)
- 1 personal reasons
- 1 difficult to adhere to the diet

14 participants tested at the end of weight loss (week 13):
- same tests as at baseline

Weight loss: ~12.5%

Coutinho S, Clin Nutr, 2018
IER or CER does not appear to modulate the compensatory mechanisms activated by weight loss

Changes in anthropometric measurements, RMR, fasting RQ, and exercise efficiency in the IER and CER groups.

<table>
<thead>
<tr>
<th></th>
<th>IER group</th>
<th></th>
<th></th>
<th></th>
<th>CER group</th>
<th></th>
<th></th>
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<th></th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of WL</td>
<td>P-value*</td>
<td>Baseline</td>
<td>End of WL</td>
<td>P-value*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>107.2 ± 3.4</td>
<td>93.3 ± 3.4</td>
<td>&lt;0.001</td>
<td>97.5 ± 3.4</td>
<td>85.7 ± 3.4</td>
<td>&lt;0.001</td>
<td>0.089</td>
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<tr>
<td>FM (kg)</td>
<td>47.0 ± 2.0</td>
<td>35.7 ± 2.0</td>
<td>&lt;0.001</td>
<td>43.0 ± 2.0</td>
<td>33.4 ± 2.0</td>
<td>&lt;0.001</td>
<td>0.141</td>
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<tr>
<td>FM (%)</td>
<td>43.9 ± 1.6</td>
<td>38.5 ± 1.6</td>
<td>&lt;0.001</td>
<td>44.1 ± 1.6</td>
<td>38.9 ± 1.6</td>
<td>&lt;0.001</td>
<td>0.706</td>
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<tr>
<td>FFM (kg)</td>
<td>60.4 ± 2.7</td>
<td>57.6 ± 2.7</td>
<td>&lt;0.001</td>
<td>54.5 ± 2.7</td>
<td>52.6 ± 2.7</td>
<td>&lt;0.001</td>
<td>0.262</td>
<td></td>
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<tr>
<td>FFM (%)</td>
<td>56.1 ± 1.6</td>
<td>61.5 ± 1.6</td>
<td>&lt;0.001</td>
<td>55.9 ± 1.6</td>
<td>61.1 ± 1.6</td>
<td>&lt;0.001</td>
<td>0.741</td>
<td></td>
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<tr>
<td>RMR (kcal/day)</td>
<td>1488 ± 55</td>
<td>1368 ± 55</td>
<td>&lt;0.001</td>
<td>1342 ± 55</td>
<td>1302 ± 55</td>
<td>0.193</td>
<td>0.151</td>
<td></td>
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</table>

No difference between groups in:
Subjective appetite ratings (hunger, fullness, desire to eat), or Appetite-regulating hormones (CCK, PYY, GLP-1)

Coutinho S, Clin Nutr, 2018
Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults
A Randomized Clinical Trial

John F. Trepanowski, PhD; Cynthia M. Kroeger, PhD; Adrienne Barnosky, MD; Monica C. Klempel, PhD; Surabhi Bhutani, PhD; Kristin K. Hoddy, PhD, RD; Kelsey Gabel, MS, RD; Sally Freels, PhD; Joseph Rigdon, PhD; Jennifer Rood, PhD; Eric Ravussin, PhD; Krista A. Varady, PhD

**IMPORTANCE** Alternate-day fasting has become increasingly popular, yet, to date, no long-term randomized clinical trials have evaluated its efficacy.

**OBJECTIVE** To compare the effects of alternate-day fasting vs daily calorie restriction on weight loss, weight maintenance, and risk indicators for cardiovascular disease.

**DESIGN, SETTING, AND PARTICIPANTS** A single-center randomized clinical trial of obese adults (18 to 64 years of age; mean body mass index, 34) was conducted between October 1, 2011, and January 15, 2015, at an academic institution in Chicago, Illinois.

**INTERVENTIONS** Participants were randomized to 1 of 3 groups for 1 year: alternate-day fasting (25% of energy needs on fast days; 125% of energy needs on alternating "feast days"). calorie restriction (75% of energy needs every day), or a no-intervention control. The trial involved a 6-month weight-loss phase followed by a 6-month weight-maintenance phase.

**MAIN OUTCOMES AND MEASURES** The primary outcome was change in body weight. Secondary outcomes were adherence to the dietary intervention and risk indicators for cardiovascular disease.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00960505

Published online May 1, 2017.
ADF did not produce superior adherence, weight loss or weight maintenance vs CER

- Weight loss phase:
  - ADF: 25% fast days, 125% feed days
  - DCR: 75% daily

- Weight maintenance phase:
  - ADF: 50% fast days, 150% feed days
  - DCR: 100% daily

- ADF: n=34, DCR: n=35, 44 years, 34 kg/m²
- Food provided for first 3 months to ADF and DCR
- Weight loss ADF: 6%, DCR: 5.3% at 12 months

Trepanowski J, JAMA 2017
ADF did not produce superior cardioprotection vs CER

No significant differences between groups at 6 or 12 months:

- Blood pressure
- Heart rate
- Triglycerides
- Fasting glucose
- Fasting insulin
- Insulin resistance
- C-reactive protein
Prescribed vs Actual Energy Intake in the ADF and CER Groups

Dropout rate: ADF: 38% and DCR: 29%

Trepanowski J, JAMA 2017
INTERMITTENT ENERGY RESTRICTION AS A WEIGHT MAINTENANCE DIET
Use of TMRD as weight maintenance

› Patients with knee osteoarthritis previously completed a lifestyle intervention trial and achieved 10% loss of initial body weight.

› Participants were randomly assigned to:
  › IF with meal replacement products for 5 wk every 4 mo for 3 year
  › Daily meal replacements of 1–2 meals for 3 year

Christensen, AJCN 2017
SYSTEMATIC REVIEWS AND META-ANALYSES
Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials

Radhika V. Seimon a, Jessica A. Roekenes a, Jessica Zibellini a, Benjamin Zhu a, Alice A. Gibson a, Andrew P. Hills b, Rachel E. Wood c, Neil A. King d, Nuala M. Byrne c, Amanda Sainsbury a, *

a The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, Sydney Medical School, Charles Perkins Centre, The University of Sydney, Camperdown NSW 2006, Australia
b Centre for Nutrition and Exercise, Mater Research Institute, The University of Queensland, South Brisbane QLD, 4101, Australia
c Bond Institute of Health and Sport, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia
d Queensland University of Technology (QUT), Institute of Health and Biomedical Innovation and School of Exercise and Nutrition Sciences, Brisbane, QLD 4059, Australia

ABSTRACT

Energy restriction induces physiological effects that hinder further weight loss. Thus, deliberate periods of energy balance during weight loss interventions may attenuate these adaptive responses to energy restriction and thereby increase the efficiency of weight loss (i.e. the amount of weight or fat lost per unit of energy deficit). To address this possibility, we systematically searched MEDLINE, PreMEDLINE, PubMed and Cinahl and reviewed adaptive responses to energy restriction in 40 publications involving humans of any age or body mass index that had undergone a diet involving intermittent energy restriction, 12 with direct comparison to continuous energy restriction. Included publications needed to measure one or more of body weight, body mass index, or body composition before and at the end of energy restriction. 31 of the 40 publications involved ‘intermittent fasting’ of 1–7-day periods of severe energy restriction. While intermittent fasting appears to produce similar effects to continuous energy restriction to reduce body weight, fat mass, fat-free mass and improve glucose homeostasis, and may reduce appetite, it does not appear to attenuate other adaptive responses to energy restriction or improve weight loss efficiency. Albeit most of the reviewed publications were not powered to assess these outcomes. Intermittent fasting thus represents a valid – albeit apparently not superior – option to continuous energy restriction for weight loss.

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IER appears equivalent to conventional diets for multiple health outcomes…

› Weight loss (3–5 kg after ~10 weeks)
› Waist and hip circumference
› Fat loss (including visceral adipose tissue)
› Loss of fat free mass
› Improvements in glucose homeostasis
› Dropout rates - no clear evidence that easier to adhere/follow

Seimon R Mol Cell Endocrinol 2015
Review

Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Intermittent Energy Restriction Trials Lasting a Minimum of 6 Months

Michelle Headland, Peter M. Clifton *, Sharayah Carter and Jennifer B. Keogh

School of Pharmacy and Medical Sciences, University of South Australia, Adelaide 5000, Australia; michelle.headland@mymail.unisa.edu.au (M.H.); sharayah.carter@mymail.unisa.edu.au (S.C.); Jennifer.Keogh@unisa.edu.au (J.B.K.)
* Correspondence: peter.clifton@unisa.edu.au; Tel.: +61-8-8302-1357

Received: 15 March 2016; Accepted: 2 June 2016; Published: 8 June 2016

Abstract: The aim of this systematic review and meta-analysis is to summarise the effects of intermittent energy restriction on weight and biological markers in long term intervention studies of >6 months duration. An electronic search was performed using the MEDLINE, EMBASE and the Cochrane Library databases for intervention trials lasting 6 months or longer investigating the effects of intermittent energy restriction. A total of nine studies were identified as meeting the pre-specified criteria. All studies included an intermittent energy restriction arm, with six being directly compared to continuous energy restriction. A total of 981 subjects were enrolled and randomised, with weight loss observed in all intermittent energy restriction arms regardless of study duration or follow up length. Eight interventions in six trials were used for the meta-analyses, with results indicating neither intermittent or continuous energy restriction being superior with respect to weight loss, $0.084 \pm 0.114$ (overall mean difference between groups ± standard error; $p = 0.458$). The effects of intermittent energy restriction in the long term remain unclear. The number of long term studies conducted is very limited, and participant numbers typically small (less than 50 completers), indicating the need for larger long term trials of 12 months or more, to be conducted in order to understand the impact of intermittent energy restriction on weight loss and long term weight management. Blood lipid concentrations, glucose, and insulin were not altered by intermittent energy expenditure in values greater than those seen with continuous energy restriction.
Effect of IER on weight loss in the long-term (> 6 months)

- Weight loss difference between groups: \(0.084 \pm 0.114\) kg
- Similar improvements in circulating lipid profile
- Similar improvements in glucose homeostasis
- Similar dropout rate
Summary

› Valid option for weight loss

› Some individuals may prefer IER to daily restriction

› Provides another tool for the management of overweight/obesity

› Benefits for many health conditions, diabetes mellitus, CVD

› No studies report serious adverse events, no evidence of disordered eating/unhealthy diets - no long-term evidence
Clinical consideration

People may experience hunger, irritability, and a reduced ability to concentrate during fast days but disappear.
SEVERE ENERGY RESTRICTION
Effect of Weight Loss via Severe vs Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity: The TEMPO Diet Randomized Clinical Trial

Radhika V. Seimon, PhD; Anthony L. Wild-Taylor, BSc (Hons); Shelley E. Keating, PhD; Sally McClintock, MSc; Claudia Harper, BSc (Hons); Alice A. Gibson, PhD; Nathan A. Johnson, PhD; Hamish A. Fernando, PhD; Tania P. Markovic, MD; Jacqueline R. Center, MD; Janet Franklin, PhD; Peter Y. Liu, MD; Stuart M. Grieve, MD; Jim Lagopoulos, PhD; Ian D. Caterson, MD; Nuala M. Byrne, PhD; Amanda Sainsbury, PhD

Abstract

IMPORTANCE Severely energy-restricted diets are the most effective dietary obesity treatment. However, there are concerns regarding potential adverse effects on body composition.

OBJECTIVE To compare the long-term effects of weight loss via severe vs moderate energy restriction on lean mass and other aspects of body composition.

DESIGN, SETTING, AND PARTICIPANTS The Type of Energy Manipulation for Promoting Optimum Metabolism: Health and Body Composition in Obesity (TEMPO) Diet Trial was a 12-month, single-center, randomized clinical trial. A total of 101 postmenopausal women, aged 45 to 65 years with body mass index (calculated as weight in kilograms divided by height in meters squared) from 30 to 40, who were at least 5 years after menopause, had fewer than 3 hours of structured physical activity per week, and lived in the Sydney metropolitan area of New South Wales, Australia, were recruited between March 2013 and July 2016. Data analysis was conducted between October 2018 and August 2019.

INTERVENTION Participants were randomized to either 12 months of moderate (25%-35%) energy restriction with a food-based diet (moderate intervention) or 4 months of severe (65%-75%) energy restriction with a total meal replacement diet followed by moderate energy restriction for an additional 8 months (severe intervention). Both interventions had a prescribed protein intake of 1.0 g/kg of actual body weight per day, and physical activity was encouraged but not supervised.

MAIN OUTCOMES AND MEASURES The primary outcome was whole-body lean mass at 12 months after commencement of intervention. Secondary outcomes were body weight, thigh muscle area and muscle function (strength), bone mineral density, and fat mass and distribution, measured at 0, 4, 6, and 12 months.

Key Points

Question What are the long-term effects of severe vs moderate energy restriction on lean mass and other aspects of body composition?

Findings This randomized clinical trial included 101 postmenopausal women with obesity. At 12 months, participants who had undergone severe energy restriction experienced approximately 2-fold greater weight and fat loss, approximately 1.5 times as much loss of whole-body lean mass (proportional to total weight lost), and approximately 2.5 times as much loss of total hip bone mineral density compared with participants who had undergone moderate energy restriction.

Meaning Although severe energy restriction is an effective obesity treatment, caution is necessary when implementing it in postmenopausal women, especially those with osteopenia or osteoporosis.
Study Protocol

“MODERATE” Intervention

“SEVERE” Intervention

Time (months)

Seimon, JAMA, 2019
Moderate (~30%) energy restriction from baseline requirements

Number of serves from 5 ‘core’ food groups serves to meet energy target and ~1g protein per kg body weight

- Grain (cereals)
- Vegetables
- Fruit
- Reduced fat dairy
- Lean meat/alternatives
Severe (~70%) energy restriction from baseline requirements

3-4 commercial meal replacement products + Whey protein isolate to meet ~1g protein per kg body weight + 2 cups low energy vegetables & 1 teaspoon oil
Study Protocol

- Prescribed protein intake of 1g/kg of actual body weight per day
- Physical activity was encouraged but not supervised

Seimon R, Healthcare, 2018
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>SEVERE ((n = 50))</th>
<th>MODERATE ((n = 51))</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.0 ± 4.4</td>
<td>58.0 ± 4.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90.1 ± 9.4</td>
<td>92.4 ± 8.3</td>
</tr>
<tr>
<td>Body Mass Index (kg/m(^2))</td>
<td>34.3 ± 2.5</td>
<td>34.3 ± 2.5</td>
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Data: Mean ± SD
Flow of participants throughout the 12-month trial

101 Underwent randomization

50 Randomized to the SEVERE intervention

4 Discontinued the trial
   2 Discontinued during 4-month SEVERE intervention
      1 Felt unwell on testing day
      1 Health reasons unrelated to trial
   2 Discontinued after 4-month SEVERE intervention
      1 Dissatisfied with diet
      1 Lost to follow-up

46 Completed 12-month SEVERE intervention

51 Randomized to the MODERATE intervention

12 Discontinued the trial
   5 No longer able to commit
   5 Dissatisfied with diet/weight loss
   1 Lost to follow-up
   1 No reason provided

39 Completed 12-month MODERATE intervention

46 Completed 12-month SEVERE intervention

39 Completed 12-month MODERATE intervention
Change in body weight (kg)

Data: Mean ± SEM
* vs 0 months, P < 0.05; # vs MODERATE, P < 0.05

Seimon, JAMA, 2019
Change in body weight (%) at 12 months

Seimon, JAMA, 2019
Fat Mass and Distribution

Data: Mean ± SEM
* vs 0 months, P < 0.05; # vs MODERATE, P < 0.05

Seimon, JAMA, 2019
Abdominal Fat Mass

Abdominal Subcutaneous Adipose Tissue (cm³)

Abdominal Visceral Adipose Tissue (cm³)

Data: Mean ± SEM

* vs 0 months, P < 0.05; # vs MODERATE, P < 0.05

Seimon, JAMA, 2019
Lean Tissue

Data: Mean ± SEM

* vs 0 months, P < 0.05; # vs MODERATE, P < 0.05

Seimon, JAMA, 2019
Summary

Compared to moderate energy restriction over a 12-month period, severe energy restriction resulted in:

- ~2 times more weight loss (2.5-3 times more likely to lose 10% body weight)
- ~2 times more fat loss, abdominal adipose tissue volume
- ~1.5 times more loss of lean mass (albeit proportional to total weight lost)
- More likely to remain in the trial