Intermittent Energy Restriction Is a Feasible, Effective, and Acceptable Intervention to Treat Adolescents with Obesity

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ABSTRACT

Background: Intermittent energy restriction (IER) is an effective obesity management strategy in adults.

Objective: The aim of this study was to investigate the feasibility, effectiveness, and acceptability of IER in adolescents (aged 12–17 y) with obesity [adult equivalent body mass index (BMI; kg/m²) ≥30].

Methods: During weeks 1–12 participants followed an IER dietary plan consisting of a very-low-energy diet (VLED) 3 d/wk (500–600 kcal/d) and an eating plan consistent with national dietary guidelines 4 d/wk. For weeks 13–26 participants chose to continue with 1–3 VLED d/wk or follow a prescriptive eating plan. Primary outcomes were feasibility and change in BMI expressed as a percentage of the 95th percentile (BMI %95th percentile) at 12 wk. Secondary outcomes were diet acceptability, body composition, cardiometabolic risk, vascular structure and function, quality of life (Pediatric Quality of Life Inventory), and eating behaviors (Dutch Eating Behavior Questionnaire (DEBQ-C)). Linear mixed models were used to assess change in outcome measures.

Results: Of 45 adolescents invited to participate, 30 adolescents (mean ± SD age: 14.5 ± 1.4 y, female n = 25) with a median BMI of 34.9 (range: 27.7–52.4) were recruited. At 12 wk, 23 participants chose to continue with the VLED 2–3 d/wk, and 21 completed the study, indicating the feasibility of IER. Consistent with intention-to-treat analysis, BMI %95th percentile was reduced at 12 wk (difference in estimated marginal means ± SEMs: −5.6 ± 1.1, P < 0.001) and 26 wk (−5.1 ± 1.9, P = 0.013) compared with baseline. Plasma triglycerides were reduced at 26 wk from baseline (−0.33 ± 0.12 mmol/L, P = 0.03). Body fat percentage reduced between 12 and 26 wk (−1.57% ± 0.76%, P = 0.05). Carotid intima-media thickness (CIMT) (−0.06 ± 0.01 mm, P < 0.001) and flow-mediated dilation (absolute increase 0.44% ± 0.11%, P = 0.001) improved between baseline and 12 wk, with reduced CIMT maintained at 26 wk (P < 0.001). DEBQ-C and Pediatric Quality of Life Inventory scores improved throughout the intervention. Nineteen adolescents completed an acceptability interview, rating IER as easy and pleasant to follow (mean ± SD: +2.1 ± 1.2; +1.9 ± 1.2, respectively) on a Likert scale from −4 to +4.

Conclusion: IER is a feasible, effective, and acceptable intervention in adolescents with obesity achieving reductions in BMI and cardiovascular disease risk. This trial was registered at www.anzctr.org.au as ACTRN12618000200280. J Nutr 2019;149:1189–1197.

Keywords: adolescent obesity, diet intervention, intermittent fasting, weight management, energy restriction, lifestyle intervention, weight loss

Introduction

Over the past 40 y, the worldwide prevalence of adolescent obesity has increased (1). Effective treatment is essential to prevent associated health complications and have a positive impact on future generations. First-line treatment of obesity involves weight management through lifestyle intervention, including a combination of dietary energy restriction, physical activity, and/or behavior modification. Dietary change, alone and in combination with lifestyle interventions, is effective at reducing body mass (2, 3) and improving cardiometabolic outcomes (3) in adolescents ≤1 y from baseline. To date, most dietary interventions have involved continuous energy restriction (3); however, weight loss outcomes are modest (−0.8 to −2.7 kg/m² over 6 mo) (3), with the best dietary intervention largely unknown (4). Adolescence is a period of human development associated with marked physical, neurodevelopmental, psychological, and social changes (5),...
which may affect patients’ ability to adhere to a dietary intervention. Intervention success is dependent upon dietary adherence (6), with individual preference, family environment, and available support contributing to the selection of an appropriate strategy. Given this, novel interventions are required to expand the evidence base for a range of treatment options.

One option yet to be explored in adolescents is intermittent energy restriction (IER). IER is a regimen that includes periods of complete fast or severely reduced energy intake, with alternating periods of a prescribed energy restriction or ad libitum feeding (7). IER is as effective as continuous energy restriction in adult populations, achieving weight loss and reduced adiposity (8–11). In addition, IER may enable higher levels of dietary adherence for adults with obesity (12), providing a viable alternative for those unable to follow conventional treatment. With shorter periods of energy restriction and greater flexibility, IER may be more acceptable to adolescents.

The aim of this study was to investigate the feasibility, effectiveness, and acceptability of IER, involving a very-low-energy diet (VLED) 3 d/wk and 4 d/wk of a prescribed healthy eating plan, to reduce body mass and fatness and improve cardiometabolic risk factors in adolescents with obesity. We hypothesized that IER would be feasible to deliver to adolescents with obesity; would result in reduced BMI, adiposity, and cardiometabolic risk; and would be an acceptable dietary intervention.

**Methods**

**Study design**

Eligible adolescents were aged 12–17 y with obesity, defined as an age- and sex-adjusted BMI equivalent to an adult BMI ≥30 (in kg/m²) (13). Exclusion criteria included type 1 diabetes or type 2 diabetes requiring insulin; secondary causes of obesity; psychiatric disturbance that would hinder the adolescent’s ability to comply with the study protocol; receiving weight-altering medications; and inability of the adolescent and/or parent/carer to speak English. A target sample size of 30 adolescents was thought to be sufficient to inform the practicalities of delivering an IER dietary pattern (14). This 26-wk duration noncontrolled trial (ACTRN12618000200280) was conducted at The Children’s Hospital at Westmead, Sydney, NSW, Australia, and was approved by the Sydney Children’s Hospital Network Human Research Ethics Committee (HREC/14/SCHN/189). Agreement to participate was sought from the adolescent, with written informed consent obtained from their parent/carer. Participants were recruited via referral from clinicians working in the Endocrinology, Weight Management, and Nutrition and Dietetics services at the hospital from February, 2015 to February, 2017.

The intervention consisted of 2 phases (Figure 1).

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Abbreviations used: BMI %95th percentile, BMI expressed as a percentage of the 95th percentile; CIMT, carotid intima-media thickness; DEBO-C, Dutch Eating Behavior Questionnaire for Children; EMM, estimated marginal mean; FMD, flow-mediated dilation; HRQOL, health-related quality of life; IER, intermittent energy restriction; MD, mean difference; PWA, pulse wave analysis; PWV, pulse wave velocity; VLED, very-low-energy diet.

**Phase 1: 0–8 wk**

- VLED 2500–2900 kJ/d (600–700 kcal/d) 3 d/wk—all food provided for VLED
- Prescribed healthy eating plan 4 d/wk
- Face-to-face visits at 2, 4, and 8 wk
- Phone/email/SMS support at 1, 3, and 6 wk

**Phase 1: 9–12 wk**

- Continue with VLED 2500–2900 kJ/d (600–700 kcal/d) 3 d/wk and provide own food
- Prescribed healthy eating plan 4 d/wk
- Face-to-face visit at 12 wk
- Phone/email/SMS support at 9 and 11 wk

**Phase 2: 13–26 wk**

- Participants choose 1 of the following plans:
  1) 3 d/wk VLED + 4 d/wk prescribed healthy eating plan OR
  2) 2 d/wk VLED + 5 d/wk prescribed healthy eating plan OR
  3) 1 d/wk VLED + 6 d/wk prescribed healthy eating plan OR
  4) 7 d/wk prescribed healthy eating plan
- Face-to-face visits at 16, 20, and 26 wk
- Phone/email/SMS support at 13, 18, and 23 wk

**FIGURE 1** Intermittent energy restriction, consisting of 3 d/wk of a VLED and 4 d/wk of a prescribed healthy eating plan, for adolescents aged 12–17 y with obesity: intervention design. Prescribed healthy eating refers to an individualized plan developed by the study dietitian in consultation with the participant, based on recommended food group serve sizes within the Australian Guide to Healthy Eating, SMS, short message service; VLED, very-low-energy diet.

Phase 1 (0–12 wk): at baseline, participants commenced an IER diet comprised of a VLED 3 d/wk and 4 d/wk of healthy eating. All food for the VLED 3 d/wk was provided to participants free of charge up to week 8 of the study, and included prepackaged readily available meals and snacks including frozen meals, frozen and tinned fish, yogurt, and cheese. From 9 wk, participants paid for their own food. No food was provided for the 4 d/wk of healthy eating. Participants were supported by a study dietitian during 20- to 40-min individual face-to-face consultations and via their choice of electronic mail, short message service, or telephone calls between visits. Dietitian contact was used to encourage adherence, identify and address any problems following the diet, and set goals with the participant.

Phase 2 (13–26 wk): at the week 12 visit, participants were given the choice to continue with the VLED 3 d/wk, or reduce to 2, 1, or 0 VLED d/wk in the context of a healthy eating plan for the next 14 wk. They then continued to be provided with regular face-to-face consultations and support between visits by the study dietitian.
Dietary intervention  
**VLED.**

On VLED days (Figure 1) participants consumed 3 nutritionally complete meal replacements (Optifast VLCD, Nestlé Health Science), a combination of meal replacements and food, or food alone, providing a total of 2500–2900 kJ/d (600–700 kcal/d). Participants were provided with a structured meal plan that was revised at each visit. A nutrition resource containing detailed information on a wide variety of food choices in 420-kJ (100-kcal) portion sizes was provided to assist with food choices on VLED days and with appropriate alternatives for foods included on their meal plan. Participants were provided with a list of “free” foods including low-carbohydrate vegetables, condiments, and diet beverages, which they could consume ad libitum to help reduce hunger and encourage dietary adherence. Participants were encouraged to drink 2–3 L/d of water.

**Healthy eating plan.**

An individualized prescribed healthy eating plan was developed by the study dietician in consultation with the participant, based on recommended food group serve sizes within the Australian Guide to Healthy Eating (15). A prescriptive energy target was not provided for healthy eating days. The plan aimed to account for individual preferences and accommodate for daily routine, e.g., after-school activities. Meal plans aimed to optimize micronutrient intake while following an IER diet (16) by including 4 serves/d of dairy products or fortified alternatives, iron-rich foods, and encouraging vegetable intake with every meal. Participants were advised to eat until full and to not aim for an energy intake deficit on these days.

Throughout the intervention participants were able to have a “meal off” 1 d/wk, where they could eat out with family or friends, and a 600-kJ (140-kcal) portion-controlled serve of a discretionary food 1 d/wk on a healthy eating day.

**Physical activity and screen time**

There was no formal physical activity component to the intervention. Participants were encouraged to increase physical activity and reduce recreational screen time, consistent with the Australian Physical Activity Guidelines (17). At week 2, participants were given an activity tracker (Fitbit One; Fitbit) to encourage physical activity.

**Measurements**

The primary outcomes were feasibility of the intervention and weight loss, measured as change in BMI expressed as a percentage of the 95th percentile (BMI %95th percentile) at 12 wk. Secondary outcomes were BMI %95th percentile at 26 wk; BMI %95th percentile (BMI %95th percentile) at 12 wk. Secondary outcomes were body composition (fat mass [kg], fat-free mass [kg], body fat percentage) was measured by bioelectric impedance (MC-180, Tanita Australia) (21); fat mass index [fat mass (kg)/height (m)^2] and fat-free mass index [fat-free mass (kg)/height (m)^2] were calculated (22).

**Cardiometabolic risk factors.**

Fasting blood samples were collected in the Endocrinology Testing Unit at the hospital by trained endocrine nurses using standard hospital procedures. Samples were centrifuged (Centrifuge 5702R, Eppendorf AG) in the Testing Unit for 5 min at a maximum of 1288 × g at 4°C, with analysis conducted in the hospital laboratory. Plasma glucose (YSI 2300 STAT Plus Analyser, YSI Life Sciences), plasma insulin (plasma fraction stored frozen at −20°C; Mercodia Ultra Sensitive Insulin ELISA, Mercodia AB), plasma lipids (total cholesterol, HDL cholesterol, and TGs; VITROS Chemistry system, Ortho Clinical Diagnostics), and plasma hepatic transaminases (alanine aminotransferase, γ-glutamyl transferase; VITROS Chemistry system, Ortho Clinical Diagnostics) were measured. LDL cholesterol was calculated using the equation by Friedewald et al. (23). Blood pressure was measured by the study nurse using an automated monitor (Dinamap 1846 SX, GE Healthcare) after participants had spent 5 min at rest in a seated position. Three measures were taken, with the mean of the second and third measurements used in analysis. Insulin resistance was defined as a ratio of fasting insulin (picomoles per liter) to glucose (millimoles per liter) >20 (24).

**Vascular structure and function.**

Noninvasive tests were used to assess cardiovascular structure and function. Flow-mediated dilation (FMD) of the right brachial artery was used as a measure of endothelial function, carotid-femoral pulse wave velocity (PWV) and brachial pulse wave analysis (PWA) as measures of arterial stiffness, and carotid intima-media thickness (CIMT) to assess structural changes in the arterial wall. All tests were conducted and analyzed by a trained research assistant blinded to study outcomes, in the morning after participants had fasted overnight, with participants in the supine position after 10 min at rest.

FMD. Brachial FMD was documented with the use of ultrasound (Philips, iE33) with a high-resolution 5-MHz transducer (imaging frequency: 7.5 MHz). Vasodilation in response to reactive hyperemia was measured by the technique described by Celermajer et al. (25) and the method described by Haghighi and Ayer (26), with higher values indicating better endothelial function. All images were stored offline and later analyzed using the automated edge detection software, Brachial Analyzer for Research (Medical Imaging Applications LLC). Brachial FMD was computed as: FMD (%) = [(post peak diameter – baseline diameter) / baseline diameter] × 100, as previously described (27). Measurements taken after a VLED day were not analyzed separately, because such variation in energy intake has been shown to not influence FMD (28).

CIMT. High-resolution B-mode ultrasonography of the right and left carotid arteries was performed. Mean CIMT was measured along the far walls of the right and left common carotid arteries, as previously described (29). Images were analyzed with Carotid Analyzer (Medical Imaging Applications LLC). Mean CIMT was determined for 3 separate images of each of the right and left common carotid arteries, with CIMT calculated as the average of these values (29).

PWA and PWV. PWA and PWV were measured in a subsample of 18 participants. A standard brachial cuff (SphygmoCor XCEL) was used to capture a right brachial waveform for measuring PWA, as recently described (26). In brief, augmentation pressure and augmentation index [(augmentation pressure/pulse pressure) × 100] were determined from 3 separate recordings and averaged. Carotid-femoral PWV was assessed by applanation tonometry of the right carotid artery and a femoral cuff transducer placed around the participant’s upper thigh (SphygmoCor XCEL). The transit time of the pulse waveform between the right carotid and femoral arteries and the transit distance were used to calculate PWV. An mean of 3 representative measurements was calculated.
Questionnaires.

At baseline, questionnaires on demographic, medical, and family history were completed by the parent/carer. Participants completed questionnaires on psychological dimensions of eating behaviors and health-related quality of life (HRQOL), using the Dutch Eating Behavior Questionnaire for Children (DEBQ-C) (30) and Pediatric Quality of Life Inventory 4.0 Generic Core Scale (31), respectively.

The DEBQ-C is a 20-item self-report questionnaire, adapted from the adult DEBQ, and validated in children aged 7–12 y (30). The DEBQ-C measures dietary restraint (7 items), emotional eating (7 items), and external eating (6 items) using a 3-choice response scale: no (1), sometimes (2), and yes (3). Scores range from 1 to 3 for each subscale, where higher scores equate to a greater presence of the behavior (30).

The Pediatric Quality of Life Inventory is a 23-item self-report questionnaire encompassing physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Items were linearly transformed to a 0–100 scale and reverse-scored (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Scores for each scale or for total HRQOL range from 0 to 100, where higher scores indicate better HRQOL. Emotional, social, and school functioning subscales were combined to provide a Psychosocial Health Summary Score (31).

Adherence.

Participants were given a food diary to record all food consumed on the 3 VLED d/wk during weeks 0–12, as used in previous studies (32). The dietitian demonstrated how to record food consumed (including brand names and recipes), portion size consumed using household measures, and timing. An example was provided. Food diaries completed within 2 wk of the measurement visit were included in the analysis, with the most recent 3 records being used. Entries without recorded portion size data were excluded (n = 3 records). Analysis was conducted in Foodworks 8 Professional (version 8.0.3553, Xyris Software Australia Pty Ltd) using the AusFoods 2015 and AusBrands 2015 databases, to measure energy intake on VLED days.

Qualitative aspects of the intervention.

We sought participants’ views on the intervention through a structured interview with the study dietitian at 12 and 26 wk. Participants were asked to comment on strategies for adhering to IER, the impact on their lifestyle, and difficulties faced, and to rate how easy/difficult and pleasant/unpleasant the intervention was on a Likert scale from −4 to +4. A questionnaire was completed by the parent/carer at 12 and 26 wk to determine the effect of the intervention on family life including perception of cost, compliance, and support provided to the participant (33).

Statistics

IBM SPSS Statistical Software, version 22 (IBM), was used for data analysis. Data were assessed for normality and nonparametric tests were used as appropriate. Group differences were tested using independent-sample t tests for normally distributed data, or Mann–Whitney U tests for nonparametric data. All participant data were retained, consistent with intention-to-treat analysis. Linear mixed models, with an unstructured covariance and restricted maximum likelihood, were used to estimate the change in outcomes between baseline, 12, and 26 wk. Results are presented as the difference in estimated marginal means (EMMs) ± SEMs. Completer analysis was conducted to estimate the mean difference ± SD between baseline and 26 wk using a paired t test for normally distributed data, or Wilcoxon’s Signed Rank test for nonparametric data. Completer analysis was reported when results were different to those from linear mixed models. Correlations for normally distributed and nonparametric data were assessed using Pearson correlation coefficients and Spearman’s ρ, respectively. All analyses were independently conducted in duplicate (by HJ and MLG). Differences of P ≤ 0.05 were considered statistically significant.

Results

In total, 45 patients were invited to participate in the study of whom 30 adolescents aged 12–17 y (mean ± SD: 13.1 ± 1.4 y, 25 females) were enrolled, at a recruitment rate of 67%. Participants lived with 1 (n = 13) or both (n = 17) parents. Most participants were born in Australia (n = 24), including 3 Aboriginal or Torres Strait Islander participants; 3 were born in the Middle East, 2 in Asia, and 1 in Sub-Saharan Africa. Most participants reported a family history of overweight or obesity (n = 26) including 8 with affected siblings. Two-thirds reported a family history of stroke or heart disease (n = 20), hypertension (n = 24), or type 2 diabetes (n = 23) including 14 parents and 1 sibling, and 10 had an aunt or mother with polycystic ovary syndrome. At baseline, participants (n = 30) had a mean ± SD BMI of 37.0 ± 6.8, equivalent to 132 ± 22 BMI %95th percentile (Table 1). Of the 30 adolescents recruited, 20 were classified as having morbid obesity and 28 had insulin resistance.

Study retention was 70%, with 21 participants completing the study (Figure 2). Seven participants withdrew from the study before the week 8 visit, 1 withdrew at 16 wk (did not want to continue with the study), and 1 at 19 wk (after unrelated surgery). Noncompleters were all female and tended to be older [mean difference (MD) ± SEM: 1.3 ± 0.50 y, P = 0.012] and heavier (7 ± 9 percentage points, BMI %95th percentile, P = 0.45). Most (19 of the 21) participants who completed the study attended all study visits. The remaining 2 attended 7 of 8 scheduled visits.

Anthropometry

After 12 wk of intervention, BMI %95th percentile and BMI z score decreased from baseline (difference in EMM ± SEM: −5.6 ± 1.1 percentage points, P < 0.001; −0.10 ± 0.02, P < 0.001, respectively) with reductions maintained at 26 wk (−5.1 ± 1.9 percentage points, P = 0.013; −0.12 ± 0.04, P = 0.007, respectively). Figure 3 highlights the individual change in BMI %95th percentile for study completers. Waist-to-height ratio was reduced at 12 wk (−0.02 ± 0.008, P = 0.018). Body fat percentage reduced between 12 and 26 wk (−1.57% ± 0.76%, P = 0.05).

Cardiometabolic risk

Plasma TGs were reduced at 26 wk from baseline (−0.33 ± 0.12 mmol/L, P = 0.03) and fasting plasma glucose concentrations increased (0.20 ± 0.08 mmol/L, P = 0.023). Overall mean fasting plasma insulin concentrations did not change during the intervention; however, reduced insulin was associated with reduced BMI %95th percentile at 26 wk (r = 0.56, P = 0.009) in study completers. No significant changes in total cholesterol, HDL cholesterol, LDL cholesterol, hepatic transaminases, or blood pressure were seen.

Vascular structure and function

Arterial wall thickness (CIMT: −0.06 ± 0.01 mm, P < 0.001) and endothelial function (FMD: absolute increase 0.44% ± 0.11%, P = 0.001) improved between baseline and 12 wk (Table 1), with reductions in CIMT maintained at 26 wk (P < 0.001). Increased FMD remained significant in 16 study completers who had both baseline and week 26 measures recorded (MD ± SD: 0.5% ± 0.75%, P = 0.017). Changes in FMD, but not CIMT, were inversely associated with a reduced BMI %95th percentile at 26 wk (r = −0.896, P < 0.001). No mean changes were seen in PWV and...
augmentation index; however, an association between improved PWV and reduced BMI %95th percentile was seen at 26 wk ($\rho = 0.63, P = 0.022$).

**Eating behaviors and quality of life**

At baseline, most participants reported occasional or frequent (score ≥2) restrained eating (89%) and eating in response to external cues (69%), with a lower prevalence of emotional eating (32%). There were no differences in baseline eating behaviors between study completers and noncompleters. Those who withdrew from the study had significantly lower baseline general wellbeing (MD ± SEM: $-28.3 ± 7.3, P = 0.001$) than study completers.

Dietary restraint increased (difference in EMM $0.09, \rho = 0.024$) at 26 wk compared with baseline study completers.

**TABLE 1** Anthropometry, body composition, and biochemistry at baseline, 12, and 26 wk in adolescents (aged 12–17 y) with obesity following intermittent energy restriction, consisting of 3 d/wk of a very-low-energy diet and 4 d/wk of a prescribed healthy eating plan

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 wk</th>
<th>26 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight z score</td>
<td>2.42 ± 0.08</td>
<td>2.32 ± 0.08*</td>
<td>2.29 ± 0.08*</td>
</tr>
<tr>
<td>Height z score</td>
<td>0.55 ± 0.19</td>
<td>0.59 ± 0.18</td>
<td>0.51 ± 0.18</td>
</tr>
<tr>
<td>BMI z score</td>
<td>2.29 ± 0.05</td>
<td>2.19 ± 0.06*</td>
<td>2.17 ± 0.07*</td>
</tr>
<tr>
<td>BMI %95th percentile</td>
<td>132 ± 4</td>
<td>127 ± 4*</td>
<td>127 ± 4*</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>0.69 ± 0.02</td>
<td>0.67 ± 0.01*</td>
<td>0.67 ± 0.02</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>119 ± 2</td>
<td>117 ± 3</td>
<td>120 ± 2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62 ± 1</td>
<td>63 ± 2</td>
<td>63 ± 2</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat, %</td>
<td>47.6 ± 1.6</td>
<td>47.3 ± 1.8</td>
<td>45.8 ± 1.7</td>
</tr>
<tr>
<td>Fat mass index, kg/m²</td>
<td>17.9 ± 1.2</td>
<td>17.5 ± 1.2</td>
<td>17.0 ± 1.2</td>
</tr>
<tr>
<td>Fat-free mass index, kg/m²</td>
<td>19.0 ± 0.4</td>
<td>18.3 ± 0.4*</td>
<td>18.9 ± 0.5</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>4.9 ± 0.07</td>
<td>5.1 ± 0.07</td>
<td>5.1 ± 0.06*</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>197 ± 15</td>
<td>196 ± 18</td>
<td>201 ± 23</td>
</tr>
<tr>
<td>Plasma ALT, U/L</td>
<td>35 ± 3.6</td>
<td>37 ± 4.8</td>
<td>37 ± 4.2</td>
</tr>
<tr>
<td>Plasma GGT, U/L</td>
<td>28 ± 3.2</td>
<td>25 ± 3.3</td>
<td>28 ± 3.4</td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L</td>
<td>4.4 ± 0.12</td>
<td>4.4 ± 0.14</td>
<td>4.3 ± 0.12</td>
</tr>
<tr>
<td>Plasma TGs, mmol/L</td>
<td>1.6 ± 0.26</td>
<td>1.3 ± 0.09</td>
<td>1.3 ± 0.10*</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mmol/L</td>
<td>1.0 ± 0.03</td>
<td>1.1 ± 0.04</td>
<td>1.0 ± 0.04</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mmol/L</td>
<td>2.7 ± 0.11</td>
<td>2.7 ± 0.11</td>
<td>2.7 ± 0.11</td>
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<tr>
<td><strong>Vascular testing</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>6.44 ± 0.22</td>
<td>6.78 ± 0.24</td>
<td>6.81 ± 0.26</td>
</tr>
<tr>
<td>Central aortic systolic pressure, mm Hg</td>
<td>105 ± 2.3</td>
<td>105 ± 3.0</td>
<td>98 ± 4.1</td>
</tr>
<tr>
<td>Central aortic diastolic pressure, mm Hg</td>
<td>69 ± 3</td>
<td>67 ± 2</td>
<td>66 ± 2</td>
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<tr>
<td>Mean central pressure, mm Hg</td>
<td>81 ± 2</td>
<td>81 ± 3</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68 ± 2</td>
<td>67 ± 2</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>39 ± 2</td>
<td>38 ± 2</td>
<td>37 ± 1</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>9.72 ± 2.17</td>
<td>11.62 ± 2.40</td>
<td>11.30 ± 2.19</td>
</tr>
<tr>
<td>Carotid intima-media thickness, mm</td>
<td>0.53 ± 0.01</td>
<td>0.46 ± 0.01*</td>
<td>0.46 ± 0.01*</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>5.56 ± 0.25</td>
<td>6.0 ± 0.22*</td>
<td>5.92 ± 0.26</td>
</tr>
<tr>
<td><strong>Eating behavior score (DEBQ-C)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrained eating</td>
<td>2.30 ± 0.07</td>
<td>2.52 ± 0.08*</td>
<td>2.57 ± 0.07*</td>
</tr>
<tr>
<td>Emotional eating</td>
<td>1.70 ± 0.11</td>
<td>1.56 ± 0.11</td>
<td>1.47 ± 0.09*</td>
</tr>
<tr>
<td>External eating</td>
<td>2.10 ± 0.07</td>
<td>2.05 ± 0.12</td>
<td>2.00 ± 0.09</td>
</tr>
<tr>
<td><strong>Quality of life score (PedsQL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical²</td>
<td>76.8 ± 3.7</td>
<td>76.3 ± 3.3</td>
<td>77.5 ± 3.1</td>
</tr>
<tr>
<td>Emotional²</td>
<td>64.6 ± 4.2</td>
<td>70.2 ± 4.2</td>
<td>72.3 ± 3.9*</td>
</tr>
<tr>
<td>Social²</td>
<td>73.0 ± 4.4</td>
<td>74.9 ± 3.6</td>
<td>79.4 ± 3.1</td>
</tr>
<tr>
<td>School²</td>
<td>64.4 ± 4.7</td>
<td>63.5 ± 3.7</td>
<td>65.7 ± 4.2</td>
</tr>
<tr>
<td>Psychosocial health²</td>
<td>67.5 ± 3.9</td>
<td>68.5 ± 3.4</td>
<td>71.3 ± 3.7</td>
</tr>
<tr>
<td>Total HRQOL²</td>
<td>70.4 ± 3.6</td>
<td>71.2 ± 3.0</td>
<td>73.3 ± 3.4</td>
</tr>
<tr>
<td>General wellbeing²</td>
<td>59.3 ± 4.2</td>
<td>64.0 ± 2.7</td>
<td>67.3 ± 3.2*</td>
</tr>
</tbody>
</table>

1Values are estimated marginal means ± SEMs, n = 30 unless otherwise specified. *Different from baseline, P ≤ 0.05. Different from 12 wk, P ≤ 0.05. ALT, alanine aminotransferase; BMI %95th percentile, BMI expressed as a percentage of the 95th percentile; DEBQ-C, Dutch Eating Behavior Questionnaire for Children (scores range from 1 to 3, higher score reflects a greater presence of the eating behavior); GGT, \(\gamma\)-glutamyl transferase; HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory 4.0 Generic Core Scale (scores range from 0 to 100, high scores indicate better quality of life).

2n = 29, missing data for 1 participant.

3n = 18, specified measures of vascular structure were conducted in a subsample of participants.
(4.58 ± 2.08, P = 0.041, between 12 and 26 wk) subscales, and general wellbeing (7.93 ± 3.73, P = 0.049). Study completers who maintained a reduced BMI %95th percentile at 26 wk had greater improvements in psychosocial (P = 0.039) and total HRQOL (P = 0.028) than those who did not reduce their weight.

Dietary adherence
Food diaries were completed during VLED days at 1 (15 participants, 45 d of food records), 8 (10 participants, 28 d), 12 (8 participants, 22 d), and 26 wk (5 participants, 15 d). Mean reported energy intake ranged from 2650 to 2850 kJ/d (633–681 kcal/d) at each time point, which was not significantly different from the energy prescription (2500 kJ/d). Reported energy intake did not differ between the food provision period (weeks 0–8) and when participants purchased their own food for VLED days (weeks 9–12).

Acceptability to participants and families
At 12 wk, 23 participants chose to continue with IER, including either 2 d/wk (n = 11), 3 d/wk (n = 10), or 5 d/fortnight (n = 2) of the VLED. By 26 wk 5 participants had ceased the VLED days. The main challenge highlighted by participants at 12 wk was going out with friends while on the diet (n = 10); however, by 26 wk only 2 participants still identified this as a challenge. Between 12 and 26 wk study completers reported swapping VLED days to accommodate social or family events, and at 26 wk rated the plan as easy (n = 19, mean ± SD: +2.1 ± 1.2) and pleasant (n = 19, +1.8 ± 1.2) to follow. All participants would recommend this diet to other young people and thought that their child was happy and well supported while following the dietary plan and could follow the diet long term. The cost of food while on the study was perceived to be less than, or the same as, usual intake (86%).

Discussion
To our knowledge, this is the first study to investigate the feasibility, effectiveness, and acceptability of IER on change in BMI in adolescents with obesity. Thirty participants were recruited into the study with 21 completing the 26-wk intervention. Findings from this study support our hypothesis that IER is an effective dietary intervention which can lead to reductions in BMI and cardiometabolic risk. Adolescents also reported that the dietary plan was acceptable, appreciating the relative flexibility that IER provides. Together these results add to the adult literature on the use of IER, indicating that it may be an alternative eating plan for adolescents with obesity.

FIGURE 2  Intermittent energy restriction, consisting of 3 d/wk of a very-low-energy diet and 4 d/wk of a prescribed healthy eating plan, for adolescents (aged 12–17 y) with obesity: recruitment and retention. CIMT, carotid intima-media thickness; F, female; FMD, flow-mediated dilation; M, male; PWV, pulse wave velocity.
is greater than has been reported in other short-term multidisciplinary weight management interventions conducted in adolescents. For example, the 2017 Cochrane review reported a pooled BMI z score reduction of \(-0.02\) units in 12 short-term (\(\leq 6\) mo) multidisciplinary lifestyle intervention studies, compared with controls receiving no treatment or usual care (2). Our results highlight that the use of an IER dietary plan may be more effective at achieving BMI reduction in the short term, warranting investigation in a larger sample. Furthermore, the reduction in both waist-to-height ratio and body fat percentage indicates a potential improvement in cardiometabolic risk. This builds on the literature in adults demonstrating that IER achieves reductions in BMI, waist circumference, and fat mass in adults with overweight or obesity (8).

Adolescents found IER to be an acceptable dietary intervention, reporting adherence to the energy prescription and rating the dietary pattern as being both pleasant and easy to follow. All study completers attended \(\geq 7\) of the 8 scheduled visits, indicating high engagement with the intervention. This builds on previous work demonstrating that structured dietary interventions are preferred by adolescents (34). Adolescents also appreciated the flexibility IER provided, reporting moving VLED days around during the week to accommodate school or social functions. This may have contributed to BMI reduction being maintained at 26 wk. Nevertheless, adolescents who withdrew from the study were of a higher BMI %95th percentile and reported reduced general wellbeing compared with those who completed the intervention. Thus, IER may not be appropriate for all adolescents.

Adolescents following IER reported improvements in quality of life and a reduction in emotional eating. These findings are consistent with our previous study in adolescents with type 2 diabetes which demonstrated that a 34-wk intervention, including an 8-wk VLED component, did not worsen eating behaviors and improved quality of life (35). Similarly, decreased depression and binge eating have been reported after alternate-day fasting in adults with obesity (36). Our results suggest that IER does not have adverse effects on psychosocial wellbeing in adolescents with obesity, at least in the short term, and may provide the structure required to improve wellbeing. Together with the demonstrated effectiveness of IER, these outcomes support the feasibility of using an IER dietary plan with an adolescent cohort.

Participants had reduced cardiovascular disease risk, with both structural and functional changes in vasculature, and reduced TGs after 26 wk of IER. Endothelial function improved after 12 wk of IER, supporting the adult literature, with improved FMD reported after a similar 12-wk IER regimen of alternate-day fasting in 25 adults with obesity (37). Given its sensitivity to change, interventions tend to have a more rapid effect on endothelial function than on arterial wall thickness. For example, improved FMD has been seen after a 6-wk lifestyle intervention including continuous energy restriction and weekly exercise classes in 35 adolescents with obesity (38). Woo et al. (39) also reported improved FMD after a 6-wk lifestyle intervention in children (9–12 y) with overweight or obesity, maintained to 12 mo with continued intervention adherence. This suggests that although rapid improvement is possible, long-term adherence is required to maintain changes in endothelial function. Given our changes in FMD were maintained to 26 wk in study completers, IER may provide a feasible option to promote improved vascular function.

Our study showed a reduction in CIMT after 12 and 26 wk of IER, with mean values returning to the normal range as defined by Meyer et al. (40). This is a more rapid reduction than previously demonstrated in other weight management interventions. To our knowledge, only 2 studies have measured CIMT after dietary change in adolescents with obesity. Kelishadi et al. (38) reported no change in CIMT after a 6-wk lifestyle intervention. Masquio et al. (41) conducted a
12-mo multicomponent lifestyle intervention in 132 adolescents with obesity, reporting reduced CIMT of the same magnitude as we have found (−0.06 mm) at 12 mo, although only in those who completed the intervention with substantial weight loss (41). Interestingly, the change in CIMT in adolescents with obesity after IER is similar to that reported 12 mo after bariatric surgery in young adults, with no change reported at 6 mo (42). Our results suggest that dietary change, rather than weight loss alone, may induce earlier improvements in vascular structure and function in the young, reinforcing the need for early treatment of obesity to reverse early atherosclerotic changes and preserve cardiovascular health.

In our sample, TGs reduced by 0.33 mmol/L, more than has previously been reported in pediatric lifestyle interventions of 6–6 mo duration (−0.20 mmol/L) (43). This may be attributable to the IER dietary pattern, with reductions in TGs reported in adult trials with a similar IER regimen (12, 44). We speculate that this may be due to a reduced carbohydrate intake on VLED days, highlighting a potential increased benefit of IER for adolescents with insulin resistance or at increased cardiovascular disease risk.

This study had a number of strengths. Vascular structure and function, as novel markers of cardiovascular disease risk, to our knowledge have not previously been measured in adolescents with obesity following IER. Participants were well supported by the study dietitian with frequent visits and contact. Participants were provided with the prescribed food for VLED days (during weeks 0–8) to assist with education on food selection and portion sizes, and to improve adherence. There were also a number of limitations. The study delivered a short-term intervention without long-term follow-up or a control group. The participant population was drawn from tertiary-level services and, therefore, may not be generalizable to the general population with obesity. The menstrual cycle was not accounted for with measures of FMD and PWV and results should be interpreted with caution. Participant acceptability interviews were conducted by the study dietitian and were susceptible to response bias.

The range of evidence-based dietary interventions available for the treatment of adolescent obesity remains limited. Our study shows that IER was feasible, effective at reducing BMI and cardiometabolic risk, and an acceptable intervention in adolescents with obesity. The dietary intervention from this study has informed a randomized controlled trial (AC-TRN12617001630303), which commenced in March, 2018. Our results suggest that IER is a suitable option for adolescents with obesity and that it may be considered within the suite of treatment options available for adolescent weight management.

**Acknowledgments**

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