Fast track to health — Intermittent energy restriction in adolescents with obesity. A randomised controlled trial study protocol

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 A B S T R A C T

Background: Intermittent energy restriction (IER) has shown early success in adolescents with obesity, however efficacy trials are needed. This study aims to determine if IER results in lower body mass index (BMI) z-score after 52 weeks in metabolically unhealthy adolescents with obesity compared with continuous energy restriction (CER).

Methods/design: This is a prospective, randomised, multi-centre trial conducted in tertiary care settings, with three phases: jumpstart (weeks 0–4); intensive intervention (weeks 5–16); continued intervention and/or maintenance (weeks 17–52). During the jumpstart phase, all participants follow a very low energy diet (~800 kcal/3350kJ/day), then transition to their allocated intervention: IER or CER. IER involves three energy-restricted days/week, consuming one-third of daily energy requirements (~600–700 kcal/2500–2950kJ/day), and four days/week of a healthy meal plan. The CER, which is current standard care, has individually tailored energy prescription based on age and sex (13–14 years, 1430–1670 kcal/6000–7000kJ/day; 15–17 years, 1670–1900 kcal/7000–8000kJ/day). The study will recruit 186 (93 per arm) treatment-seeking adolescents aged 13–17 years with obesity and at least one metabolic co-morbidity. The primary outcome is change in BMI z-score at 52 weeks. Secondary outcomes are changes at 4, 16 and 52 weeks in: body composition; diet quality, food choices and food patterns; cardio-metabolic risk factors; physical activity and sedentary behaviour; sleep and psycho-behavioural measures.

Discussion: This study challenges existing clinical paradigms that CER is the only method for weight management in metabolically unhealthy adolescents. If successful, IER may offer an alternate medical nutrition therapy approach for those seeking treatment in tertiary settings.

Clinical trial registration number: ACTRN12617001630303.

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Introduction

Context

Global trends indicate the prevalence of obesity in adolescents is the highest it has ever been in history [1–3] with emerging evidence that severity of obesity in this age group is also increasing [4–6]. Obesity in adolescence may be complicated by psychosocial distress [7] and associated with a range of other health problems, including insulin resistance, orthopaedic disorders, high blood pressure, non-alcoholic fatty liver disease, dyslipidemia and type 2 diabetes [8,9]. If untreated, obesity in adolescence is highly likely (relative risk 5.21 [95%CI: 4.50, 6.02]) to persist into adulthood [10], with many attendant complications and co-morbidities [11,12].

Management of obesity in adolescence

Although obesity prevention is important, effective treatment of those who actively seek weight loss is equally important [13]. Published systematic reviews of treatment programs for adolescents with obesity conclude that lifestyle interventions, including diet, lead to mild-to-moderate weight loss [14–16], and improvements in cardio-metabolic outcomes [15]. There are also substantial gains in quality of life, improvements in eating behaviours and increased self-esteem that accompany weight loss [17–20] which are maintained in longer term follow-up [18,20]. Reviews also report weight loss is achieved regardless of the macronutrient composition of the interventions [21], indicating that the primary goal of interventions focused on diet for weight loss in adolescents should be reducing energy without compromising micro-nutrient intake. However, the optimal way to achieve long term adherence to such a dietary pattern has not been identified. Despite evidence for some improvements in weight status with dietary management, many adolescents do not achieve a clinically important weight loss. Long term success appears to be related to an early reduction in body mass index (BMI) [22,23]. Contemporary interventions should be suited to adolescent lifestyles and focused on their needs. New approaches that provide the relevant support for behaviour change, and are easy for an adolescent to incorporate into their lifestyle, are needed for adolescents seeking weight loss advice.

Very low energy diet (VLED)

More intensive dietary interventions may induce greater weight loss and facilitate longer term weight maintenance compared to standard dietary interventions. VLEDs typically aim for <800 kcal/3350 kJ and <50 g carbohydrate per day, often achieved using meal replacements such as shakes and bars, which are fortified with micronutrients. In adolescents with obesity, VLEDs can produce short term improvements in body weight and metabolic parameters [24–27], and reverse newly diagnosed type 2 diabetes [28]. Several studies have shown that achieving early BMI reduction is predictive of longer term weight outcomes in both adults [29–31] and adolescents [23,32]. Thus, VLEDs can be useful as an initial ‘rapid’ weight loss phase which is then followed by prolonged dietary interventions for continued ‘slower’ weight loss or longer term maintenance of weight loss [33], but should only be utilised under medical and dietetic supervision.

Interval energy restriction interventions (IER)

IER has been shown to improve body composition and cardio-metabolic profiles in adult intervention studies [34–36]. There are a number of IER approaches in the literature, but typical protocols involve intense energy restriction (<600 kcal/2500 kJ) for 2–6 days per week [36]. These ‘intermittent fasting’ diets have gained public popularity due to media coverage and books published in the lay press. Compared to other dietary interventions in adults with obesity, IER achieves a lower average energy intake by substantially reducing intake on 2–4 days per week, which is not usually compensated for on the remaining days [37]. Theoretically, dietary adherence improves due to individuals feeling less restricted by including ‘days off’, and impacts on regulation of appetite following energy restriction [38]. A pilot study on the use of IER in 30 adolescents with obesity conducted by our team [39] found IER involving 3 days per week of energy restriction and 4 days per week of healthy eating to be feasible, effective and acceptable. Following 26 weeks of intervention, IER resulted in a reduction in BMI and triglycerides and improved emotional eating, quality of life and vascular function and structure. When given the choice, adolescents chose to continue with IER, reporting that the relative flexibility provided by that dietary pattern (enabling flexibility in their food choices to suit social and school events) suited their lifestyle [39]. We propose that long term adherence to this dietary approach in young people is therefore increased, warranting its further investigation in a larger sample and as a potential alternative to standard care.

Study aims

To determine whether IER results in lower BMI z-score after 52 weeks of intervention in treatment seeking adolescents with metabolic complications associated with obesity compared with continuous energy restriction (CER).

Materials and methods

Ethics approval and trial registration

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). This study has been reviewed and approved by the Sydney Children’s Hospitals Network Human Research Ethics Committee (HREC/17/SCHN/164). Governance authorisation has been granted at The Children’s Hospital at Westmead (SSA/17/SCHN/396) and Monash Health (SSA/17/MonH454). An independently chaired Data Safety Monitoring Committee will oversee study safety, and adverse events will be assessed and managed by the participant’s physician, or general practitioner, with the event documented and followed to resolution. Written informed consent from parents and assent from adolescents will be sought prior to their enrolment in the study. The protocol for this study is registered with the Australian New Zealand Clinical Trial Registry (ACTRN12617001630303).

Study design

This is a prospective, randomised, multi-centre trial, with recruitment at two tertiary children’s hospitals in Australia: The Children’s Hospital at Westmead, Sydney, and Monash Children’s Hospital, Melbourne. The study consists of three phases:

- Phase I (0–4 weeks): jumpstart
- Phase II (5–16 weeks): intensive intervention
- Phase III (17–52 weeks): continued intervention and/or maintenance

Fig. 1 shows the study design. At the commencement of the study all adolescents will be randomised to one of two dietary patterns (CER or IER). All participants will undergo a 4 week VLED...
then transition to their allocated dietary intervention. Intervention intensity and support will be the same for the two intervention arms, the only difference being the dietary pattern prescribed.

Outcomes

The primary outcome is change in BMI z-score at 52 weeks. The secondary outcome measures are changes at 4, 16 and 52 weeks in: body composition; diet quality, food choices and food patterns; cardio-metabolic risk factors; physical activity, and sedentary behaviour; sleep and psycho-behavioural measures. These measures are described below and Table 1 shows the measurement timeline.

Participants and recruitment

This study will recruit 186 (93 in each treatment arm) treatment-seeking adolescents aged 13–17 years with obesity and at least one metabolic complication (defined below) through doctor-, health professional- or self-referral. Self-referral will mainly occur through completion of an expression-of-interest online form on the study website. Doctor referral will be through weight management and endocrinology clinics at The Children’s Hospital at Westmead, Sydney, and Monash Children’s Hospital, Melbourne, as well as local general practitioners (primary care physicians) and paediatricians. To aid recruitment, a range of established strategies [40,41] will be implemented including: regularly updated social media accounts, with redirection to the study website; information for patients on waiting lists at the participating clinics; a variety of communications to health professionals; youth focussed and parent focussed local media campaigns; and study branding.

Selection criteria

Inclusion criteria: 13–17 years with obesity as defined by the International Obesity Task Force criteria [42] (i.e. BMI equivalent to adult BMI > 30 kg/m²) and at least one of the following:

- Pre-diabetes: impaired fasting glucose 5.6–6.9 mmol/L and/or impaired glucose tolerance with 2h post load glucose 7.8–11.1 mmol/L
- Insulin resistance (defined as fasting insulin (pmol/L)/glucose (mmol/L) ratio > 20 [43])
- Presence of acanthosis nigricans
- Hypertension (defined as systolic and/or diastolic blood pressure above the 90th percentile for sex, age and height)
- Low HDL-cholesterol (defined as < 1.03 mmol/L)
- High triglycerides (defined as ≥ 1.7 mmol/L)
- Elevated alanine transaminase (ALT) or gamma-glutamyl transferase (GGT) (defined as ALT or GGT > 45 U/L) [44]
- Diagnosis of polycystic ovary syndrome

Exclusion criteria: secondary obesity; significant intellectual disability as documented by the referring doctor; significant medical or psychiatric illness; diagnosis of type 2 diabetes mellitus; undergoing treatment for a clinical eating disorder; pregnancy or planning to become pregnant within the next 18 months; taking medications that have an effect on weight in the short term (excluding metformin); adolescent or parent with sub-optimal level of spoken English; current enrolment in a weight loss program; and a BMI in excess of 45 kg/m². Individuals with a BMI above 45 kg/m² will not be eligible to participate due to the higher risk of comorbidities requiring additional specialist multidisciplinary care during the course of the trial.

Screening

After the adolescent is identified as meeting the selection criteria, the young person and their parent/carer will be informed about the study by the study physician or dietitian. If interested in participating, the adolescent and parent/carer will be provided with written information detailing the study researchers, interventions, the potential risks and benefits, required commitment and consent form. Participants will undergo a medical assessment to determine eligibility (including a review of fasting glucose, insulin, lipid profile and liver function), and screening for clinical depression and eating disorders prior to recruitment into the study. The Eating Disorder Examination Questionnaire (EDE-Q) [45] and Centre for Epidemiologic Studies Depression Scale- revised 10-item version for adolescents (CESDR-10) [46] will be used as screening tools to identify participants at risk of having an undiagnosed eating disorder or clinical depression respectively. Screening questionnaires will be reviewed by a study psychologist based on pre-determined cut-points. CESDR-10 cut-points (Fig. 2) have been set based on the scoring criteria described by Haroz et al. [46]. Adolescents who report any purging behaviour on the EDE-Q, have a global score greater than or equal to 2.7 [47] or report two or more episodes of binge eating, loss of control or binge eating with loss of control in the previous 28 days, will be identified during screening (Fig. 3). These adolescents will be assessed by, or in consultation with, the study psychologist and/or specialist paediatrician prior to enrolment based on questionnaire responses and input from the study dietitian. These adolescents may subsequently enrol in the study following medical clearance, be referred for treatment, or be excluded due to significant medical or psychiatric illness.
on a case-by-case basis. Repeat screening for eating disorders signs or symptoms and clinical depression will occur at 4, 16 and 52 weeks.

Once written consent is obtained, the participant will be randomised to one of the two intervention arms and informed of the dietary intervention group to which they have been allocated.

### Randomisation

Participants will be randomly allocated to a dietary intervention group using a computer-generated randomisation schedule (1:1) from the NHMRC Clinical Trials Centre (University of Sydney). Random allocation will occur via a process of minimisation with allocations concealed, and stratified by intervention site, age (13–14 years; 15–17 years), sex and BMI (equivalent to 30 to <35 kg/m²; 35–45 kg/m²).

### Sample size

The sample size is based on the primary outcome, change in BMI z-score between dietary intervention groups at 52 weeks. Assuming a difference in the change in BMI z-score at 52 weeks of 0.12 and a SD 0.24 (based on our previous RCT which also recruited adolescents with obesity [48]), 80% power, and a two-sided significance level of 0.05, a sample size of 65 adolescents per group, 130 in total, is required. Assuming a 30% attrition rate, which is consistent with attrition rates of 23% at 52 weeks for our RESIST study [48] and 30% for our Loozit study [49], we will recruit 186 adolescents.

### Interventions

#### VLED

The product used for Phase 1 is a micronutrient complete VLED (Optifast® VLCD™, Nestlé Health Science, Nestlé Australia Ltd), provided at no cost to the participant, who will choose to either consume:

1. Four Optifast® formulated meal replacement products per day (shakes and/or soups, and/or bars, and/or desserts), with low carbohydrate vegetables and 1 teaspoon of vegetable oil or
2. Three Optifast® formulated meal replacements and one meal consisting of 100–150 g lean, cooked meat, low carbohydrate vegetables and 1 teaspoon vegetable oil.

These combinations provide ~800 kcal/3350 kJ per day, consisting of less than 40% of energy from carbohydrate (~50 g/d), 40–55% of energy as protein, and less than 20% of energy as fat. The reduced carbohydrate prescription during the VLED is designed to induce ketosis, which is monitored at the weekly dietitian visits using Freestyle Optium Neo Blood Glucose and Ketone Monitoring System. Participants can also eat ad libitum from a list of “low-energy” fruits and vegetables. Participants will be encouraged to consume at least 2 L of water or other low energy beverages daily. At 4–5 weeks, participants will transition to either IER or CER.

#### IER

IER involves three energy restricted days each week, consuming approximately one third of daily energy requirements (~600–700 kcal/2500–2950 kJ), and following a healthy meal plan for the four non-restricted days. Participants receive a meal plan containing detailed information on a wide variety of food choices.
that are appropriate for energy restricted and non-restricted days. Participants are provided with a written resource listing servings in approximately 100 kcal portions to support food choices on energy restricted days, but are not encouraged to calorie count. On energy restricted days participants can also eat ad libitum from a list of “low-energy” fruits and vegetables in addition to the energy prescription. Non-restricted days do not have a prescriptive energy level but participants are given a flexible healthy eating plan that includes the recommended number of daily servings of fruit, vegetables and dairy foods, and a variety of meal options to guide food choices [50]. These guidelines assist in maximising micronutrient provision, given the challenges in meeting micronutrient requirements for this age group with an energy restricted diet [51]. In addition, energy-dense, nutrient-poor foods are encouraged to be limited to one standard serve per week (~145 kcal/600 kcal), and participants have one ‘meal off’ per week incorporated into their plan to account for eating out and social gatherings. Given the high nutrient requirements for this age group and length of intervention, a commercial multivitamin (containing essential fatty acids) is provided to ensure micronutrient adequacy.

CER

The CER intervention is high in fibre (>30 g/d), with 40–50% of energy obtained from carbohydrate and 20–25% of energy from protein. The plan has a daily prescriptive energy level based on age:

1430–1670 kcal/6000–7000 kcal/day for those aged 13–14 years, or 
1670–1900 kcal/7000–8000 kcal/day for those aged 15–17 years.

These energy targets are used as a guide and further tailored based on the dietitian’s clinical judgement including participant weight, sex, diet tolerance, preferences and progress. Participants receive a detailed meal plan with a variety of food choices and are encouraged to monitor intake using a calorie counting smartphone application of their choice. This eating plan has been used previously in clinical trials [52] and is nutritionally adequate for the target age group. As above, participants are provided a commercial multivitamin (containing essential fatty acids) to ensure micronutrient adequacy.

Phase 1 — Jumpstart

Given the relationship between early weight loss and long term success [23,53], Phase 1 has been designed to induce rapid weight loss. Participants, usually accompanied by a parent/guardian, will have weekly contact with the study dietitian, who delivers the VLED intervention, reviews dietary intake and eating behaviours and supports the family during this initial phase. Contact will be face-to-face at weeks 0, 1 and 4. At weeks 2 and 3, face-to-face visits are encouraged. However, dependent on participant preference/commitments and discretion of the dietitian, verbal support may be given via phone or video call consultation. To address
anticipated challenges in commencing the VLED, additional phone support is provided by the dietitian during week 1.

Phase 1 is based on current clinical practice in the weight management clinic at The Children’s Hospital at Westmead and the successful pilot ‘SHAKE-IT’ study of adolescents with obesity and type 2 diabetes [26].

**Phase 2 — intensive intervention**

Participants meet with the study dietitian at weeks 6, 9 and 12. Contact will be face-to-face, or by voice or video call, with at least one visit being face-to-face. Additional support via text message, phone or email will be provided by the dietitian at weeks 8, 11 and 14. At each visit the dietitian reviews dietary intake, eating behaviours, weight loss, discusses and modifies goals as necessary, and encourages adherence to the intervention. The dietitian will provide a prescribed meal plan and participants choose and pay for their own food for the remainder of the intervention. The meal plans, titled ‘My Meal Plan’, take into consideration individual food preferences with the aim of weight loss.

Calculated goal weights are determined by the dietitian and will equate to an adult BMI of 25 kg/m² using the International Obesity Task Force age and sex adjusted BMI cut offs. Personal goal weight is the target weight determined by discussion between the participant and dietitian: this is not compulsory and not all participants may choose to define a specific goal weight. If maintenance occurs during the intervention period, plans will be individualised according to allocated dietary patterns. IER participants may transition from three energy restricted days to two, one or no days per week. CER will transition onto a modified plan based on The Australian Guide to Healthy Eating [50]. At each visit the dietitian reviews dietary intake, eating behaviours, weight loss, modifies goals as necessary, and encourages adherence to the intervention. During this phase, participants will have less contact with the dietitian than in previous phases. At weeks 20, 26 and 36 the contact will be face-to-face, voice or video call. A minimum of two contacts during this time will be face-to-face. Additional dietitian support will be provided via text message, phone or email at weeks 18, 24, 28, 42 and 48. Participants meet with the dietitian at week 52 (end of intervention).

**Phase 3 — continued intervention and/or maintenance**

Participants allocated to either the IER or CER groups will continue with the prescribed intervention during this phase unless their personal or calculated healthy weight goal has been reached.

**Study completion**

At the week 52 appointment, during the final review with the study dietitian, an individualised plan for ongoing monitoring will be discussed and developed in collaboration with the participant.

and their family. All participants will be referred for ongoing care and follow-up to their referring physician, general practitioner, a local dietitian, or may remain within the weight management service provided by the hospital. Strategies for weight maintenance will be discussed and may include focusing on mealtime behaviours, increasing activity and self-monitoring (e.g. keeping a food and activity diary). Locally available services will be utilised where possible, e.g. phone coaching.

Intervention delivery

All interventions will be delivered by trained dietitians. Dietitians will be provided with specific training to deliver the interventions via a standardised training manual and will complete a 6-week part-time course on motivational interviewing and behaviour change techniques. Dietitians will also undergo training on the psychological complexities associated with adolescent obesity and in the recognition of eating disorders. Dietitians will undertake regular review of practice together via clinical supervision sessions at least three times during the study period. Individual dietitians will receive clinical supervision at approximately six weekly intervals, as per hospital standard practice.

A motivational ‘coaching’ model will be used during consultations, which provides a theoretical basis for several psychological variables which are important in achieving dietary compliance, lifestyle change and sustainable weight loss, such as self-efficacy, stage of change intervention, autonomy, assuming responsibility, self-monitoring, goal setting, accountability and self-directed behaviour change [54]. Techniques from cognitive behaviour therapy will be applied on an individual basis in the context of cognitive restructuring to guide and support alternative thoughts and behaviours when they are identified as disrupters of health supporting behaviours.

The aims and outline of each participant encounter will follow a pre-specified pathway based on Michie et al.‘s [55] behaviour change taxonomy, all of which are documented in the intervention standard operating procedure framework. Due to the multi-component and interactive nature of dietetic and behaviour counselling, components that are of relevance in weight management will be integrated into participant consultations, for example, agreeing to goals that are specific, measurable, attainable, relevant and timely (SMART) and review of attainment of goals will occur at each encounter, making tailored individual action plans, problem solving and self-monitoring of behaviours. Social support strategies will include encouraging parental involvement in the weight loss process, stimulus control and engagement with siblings and peers, if appropriate, in supporting goals such as increasing activity and improving self-esteem. Between appointments, participants can opt in to receive standardised motivational texts delivered weekly via SMS to their mobile phone. As suggested by Goldschmidt et al. [56], participants will be monitored by the dietitian for development of disordered eating behaviours at every visit (Fig. 4). The monitoring procedure is in addition to the screening measures taken at baseline, weeks 4, 16 and 52 (Fig. 3). The procedure has been developed to guide dietary review by the study dietitian, and to allow the identification of binge eating and compensatory behaviours (e.g. purging, or laxative use), excessive dietary restriction or excessive weight loss (Fig. 4). Participants identified during routine monitoring will be referred for further assessment by the study psychologist and/or specialist paediatrician.

24. month follow up

Participants will be followed up by the study team at 24 months. Consent to contact participants and their families will be obtained at the week 52 appointment. Contact will be maintained with families between 12 and 24 months via text messages and to confirm referral services have been engaged.

Intervention fidelity

The framework proposed by Carroll et al. will be used to evaluate intervention fidelity, considering overall adherence of the study implementation to the original protocol and factors that may impact or moderate overall adherence to the protocol [57]. Table 2 outlines the intervention fidelity measures.

Blinding

Assessors of the main outcome measures will be blinded to treatment allocation. These include the trial nurses and research assistants responsible for undertaking the anthropometric measures and blood sampling, the technician who performs the dual energy X-ray absorptiometry (DXA) measurements, and laboratory assistants.

Psychological support

A study psychologist will review all participant screening questionnaire data, complete screening assessments when necessary and review enrolled participants identified as requiring further assessment by the study physician or dietitian.

Measurements

Details of measurement timeline are outlined in Table 1.

Anthropometry

Weight and height will be measured using standard free standing procedures and BMI and z-scores calculated [58]. For weight, a single measurement to the nearest 0.1 kg is measured with calibrated electronic scales (Sydney site: Tanita MC780 MA, Tanita Corporation, Tokyo, Japan; Melbourne site: Seca® mBCA 515, Seca®, Hamburg, Germany). Height will be measured with a stadiometer (Sydney site: custom built and calibrated by The Children’s Hospital at Westmead Biomedical Department; Melbourne site: Holtain Ltd, Crosswell, Wales) to the nearest 0.1 cm, and the average of two measures will be used for data analysis. Waist circumference will be measured to the nearest 0.1 cm using a flexible steel tape. The waist is defined as the horizontal distance around the umbilicus using the left hand under technique [52]. The average of three measurements will be used for data analyses. Waist-to-height ratio will be used as a measure of central adiposity and metabolic risk [8,59].

Blood pressure

Blood pressure will be measured three times using an automated blood pressure monitor (Sydney site: CareScape™ Dinamap V100, GE Healthcare, Milwaukee, WI, USA; Melbourne site: Welch Allyn 3400 series NIBP, Welch Allyn, Skaneateles Falls, USA), according to standard procedures [8], and the average of the final two measures used for data analysis. Age-, sex- and height-specific percentiles will be used to calculate individual z-scores.

Dual energy X-ray absorptiometry (DXA)

DXA will be used to measure body composition at baseline, 16 and 52 weeks. At The Children’s Hospital at Westmead the Prodigy Lunar–GE DXA (Madison, WI USA) will be used [52]. At Monash, the GE Lunar iDXA (GE Medical, Software Lunar DPX enCORE 2012 version 14.0, Madison, WI, USA) will be used. The manufacturer recommended scan mode (as determined by height and weight) will be used for total body mass measurements.

Monitoring of weight and binge eating at each visit by the study dietitian
(This is to be used as a guide, professional judgement should be applied.)

Reported binge eating
Assess: quantity, frequency, triggers, loss of control, compensatory behaviours
Additional weekly support calls until resolved
If frequency of more than 1/14, discuss with medical investigator and study psychologist

Consistent excess weight loss
>2-3kg/week in Phase 1
>1-2kg/week in Phase 2/3

Discuss excess weight loss with participant:
Check for possible explanations, excessive exercise or obsessive behaviours

No compensatory behaviours identified
Address triggers
Behaviour diary for 1-2 weeks to assess/monitor frequency

Identified compensatory behaviours

If Bulimia Nervosa suspected:
Assessment by Specialist Paediatrician and/or Study Psychologist and referral/withdrawal from study if necessary

If Anorexia Nervosa suspected:
Assessment by Specialist Paediatrician and/or Study Psychologist and referral/withdrawal from study if necessary

Continued binge eating with loss of control for >4 weeks

If Binge Eating Disorder suspected:
Assessment by Specialist Paediatrician and/or Study Psychologist and referral/withdrawal from study if necessary

Fig. 4. A protocol for the monitoring of eating disorder risk during visits with the study dietitian.

Bioelectrical impedance analysis (BIA)
At baseline, weeks 4, 16 and 52, BIA will be used to assess body composition using a multi-frequency stand on body composition analyser (Sydney site: Tanita MC780MA, Tanita Corporation, Tokyo, Japan; Melbourne site: Seca mBCA515 Seca®, Hamburg, Germany). Standard positioning will be used as described in the instruction manual in all measurements and skin-to-skin contact avoided. In brief, participants are asked to stand with bare feet on the electrode panel and hold electrodes in both hands; with the electrodes in contact with thumb and palm during the measurements [60]. Raw measures of reactance and impedance will be used to determine total body water and body fat.

Psychological outcome questionnaires
At baseline, weeks 4, 16, and 52 a range of psychological outcomes will be assessed using validated tools: EDE-Q [45]; Body Appreciation Scale [61]; Weight Bias Internalisation scale [62]; Binge Eating Scale [63]; Rosenberg Self-Esteem Scale [64]; CES-D-R10 [46]; Depression Anxiety Stress Scale 21-items (DASS-21) [65]; Quality of Life using Impact of Weight on Quality of Life – Kids [66]; and Dutch Eating Behaviour Questionnaire (DEBQ) [67].

Dietary assessment
Diet quality, food choices and food patterns will be assessed using the online version of Australian Child and Adolescent Eating Survey (AACES) [68,69], a validated self-administered, semi-quantitative food frequency questionnaire, at baseline, week 16 and week 52. The AACES is a 120-item semi-quantitative Food Frequency Questionnaire which assesses usual consumption frequency of 120 food items over the previous three or six months. The AACES demonstrate reliability and relative validity for ranking nutrient intakes in Australian children and adolescent as described previously [68–71].

Differences between mean group dietary intake and adherence in past 24 h will be assessed using the Automated Self-Administered 24 h Dietary Assessment Tool (ASA24-Australia) at baseline and weeks 12 and 36.

Sedentary behaviour, physical activity and sleep quality
The Godin Leisure-time Questionnaire and the Pittsburgh Sleep Quality Index [72] will be used at baseline, weeks 4, 16 and 52. Participants will be given a Fitbit® Flex 2 wristband (Fitbit, Inc. CA, USA) at week 16 to increase motivation and assess physical activity and sleep patterns. These data will be used by the dietitian to discuss
Table 2

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sleep and physical activity goals, providing motivation and engagement while the contact with the dietitian decreases during the final phase of the study. The Fitbit® Flex 2 uses a 3 axis accelerometer which identifies the intensity of the activity being performed. Fitbit® devices have been shown to adequately measure both sleep and activity when compared to gold standard methods, however the accuracy and reliability of these measures is under examination [73,74]. Participants’ physical activity and sleep data will be accessed and downloaded by the study team during week 16 and week 52.

Acceptability

Parent and adolescent views relating to acceptability of the diet intervention, program satisfaction and feedback will be collected in questionnaires at weeks 4, 16 and 52. Participants and their parents or carer will be invited to participate in a semi-structured interview upon completion of the study.

Biochemistry

A fasting blood sample will be collected to measure high-sensitivity CRP, lipids (total triglycerides and high-density and low-density cholesterol), glucose and insulin levels, and liver function. All blood samples will be collected by trained personnel using standard operating procedures. As poor renal function is a contraindication for initiating a VLED plan, urea and electrolytes will be measured at baseline. The Monash cohort will measure a range of inflammatory markers (adiponectin, IL-1β, IL-6, leptin, resistin, TNF-α). Blood ketones will be measured to assess adherence to the VLED protocol and IER plan. They will be measured weekly during Phase 1, using the Freestyle Optium Neo Blood Glucose and Ketone Monitoring System. Ketones will also be measured using the Freestyle Optium Neo for the IER group only at week 16 and 52.

Resting energy expenditure

Resting energy expenditure (REE) will be measured at Monash only. REE will be measured using indirect calorimetry using a Vantage CPX with canopy option (Care Fusion, Hoenberg, Germany). Participants will be measured in the morning after an overnight fast at baseline, weeks 4, 16 and 52 and will be rested in the supine position for a minimum of 15 min before measurement for 30 min (discarding the first 5 min) [75].

Data analysis

Data analyses will be carried out according to a pre-established plan, with the primary analysis based on intention-to-treat and with statistical support from the biostatistician in the Office of Research, The Children’s Hospital at Westmead. Analysis will be undertaken blinded to treatment allocation. The difference in BMI z-score between groups at 52 (±4) weeks will be assessed using a t-test. Mixed models will also be used to investigate changes over time. The mixed models procedure will take into account within-participant correlations and missing data points. A time by group interaction will be included to investigate whether rates of change of weight loss were significantly different between the two intervention groups or intervention sites.

Post hoc analysis will compare protocol adherers to non-adherers. An adherer will be defined by a range of measures including weight change, blood ketones, attendance, and dietary pattern.

Discussion

For effective management of obesity in adolescents with weight-related co-morbidities seeking treatment via tertiary care paediatric hospitals, there is a need for more high quality evidence of efficacious interventions, which serve both to reduce cardiovascular risk factors and support self-esteem and psychological health. A range of different dietary interventions from which adolescents can choose, may enable improvement in weight-related health, weight status and maintenance of weight loss over time. We speculate that IER will result in greater weight loss compared to CER. As the prescribed energy intake is not matched to the CER intervention group, we expect that participants allocated to the IER intervention group will achieve average lower energy intakes, and therefore greater weight loss. In addition, IER eating plans tend to fit in well with youth lifestyles, allowing adolescents to attend social activities on ‘days off’ [39]. We propose that long-term adherence...
to this dietary pattern in adolescents will be increased. The combination of lower energy intake, the avoidance of every day calorie restriction and the flexibility of IER may make it more appealing and acceptable to adolescents with obesity.

Authors’ contributions

NBL, HT, SPG, KV, CTC, CEC, SJP, MLG, JB, SA, LAB contributed to all aspects of the conception, design and funding of the study, and drafting and review of the manuscript. HJ contributed to the design of the study, drafting and review of the manuscript. KA, KC, AMG, KD, SL and MI contributed to the intervention design and reviewed the manuscript. All authors have read and approved the final manuscript.

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Ethics approval and trial registration

This study has been reviewed and approved by The Sydney Children’s Hospitals Network Human Research Ethics Committee (HREC/17/SCHN/164), Governance authorisation has been granted at The Children’s Hospital at Westmead (SSA/17/SCHN/396) and Monash Health (SSA/17/MonH/454). Written informed consent from parents and assent from adolescents will be sought prior to their enrolment in the study. The protocol for this study is registered with the Australian New Zealand Clinical Trial Registry (ACTRN12617001630303).

Declaration of interest

Krista Varady has received author fees from Hachette Book Group for the book, The Every Other Day Diet.

References