Childhood Obesity – Prevention of diabetes through changed Eating Patterns (The **COPE**-study): A non-randomized trial investigating the efficacy of dietary changes in protein

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Clinical trial registration
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NB: As a result of the COVID-19 pandemic (impacting the study from December 2020 to February 2021), the study arms have been renamed in the protocol to enhance the clarity and interpretation of the study design and results.

Background

Globally, the prevalence of childhood obesity has increased by ~50% from 1980 to 2013(1). In children and adolescents overweight and obesity are classified by an age-and- sex adjusted BMI. The World Health Organization (WHO) defines overweight by a BMI-SDS greater than 1 standard deviation (SD) and obesity by a BMI-SDS greater than 2 SD(2). This is equivalent to an ISO-BMI (ISO-BMI = the weight in kilograms divided by the height in meters squared) greater than or equal to 25 kg/m^2 and greater than or equal to 30 kg/m^2(3). The most marked increase in childhood obesity has been observed in high-income countries, however, in the last part of the time-period a substantial increase has also been observed in middle- as well as low-income countries(1, 4). The Danish trends for childhood obesity are comparable to other high-income countries and in 2018, the Danish Health Authorities reported that 2.7% of children at age 7-13 years, 3.2% at age 14-15 years, and 3.9% at age 16-18 years were considered to be obese. For comparison, 16.8% of the adult Danish population is considered obese(5).

The development of childhood obesity is both complex and multifactorial depending on a combination of genetic/maternal, psychosocial, and environmental factors(6). Obesity in childhood and adolescence is highly predictive of continuous obesity into adulthood(7) and furthermore, associated with an increased risk of developing diseases such as type 2 diabetes (T2D), cardiac arrhythmias, premature stroke (age <55 years) and coronary heart disease (both non-fatal and fatal events) in adulthood as compared to never obese children(8-11). In addition, compared to their lean peers, children with obesity have in general lower self-esteem, more loneliness and a decreased quality of life (QoL), which is comparable to that of children with chronic diseases such as diabetes and cancer(12, 13).

Treatment or attenuation of obesity in children and adolescents can be obtained in various ways such as lifestyle interventions (i.e. changes in diet and physical activity), pharmacotherapy and bariatric surgery. As an adjunct to lifestyle intervention, pharmacotherapy could be an option, but only a few short-term (<6 months) studies have been performed. Recently, Liraglutide 3.0mg treatment for 7-13 weeks was found to significantly reduce BMI Z-score by –0.28 in a population of 7-11 years old children with obesity (isoBMI >30 kg/m^2)(14). However, in the same study 37.5% *vs.* 12.5% in the placebo group experienced gastrointestinal side effects. Taking the possible adverse effects and the modest weight loss effects into account, these studies have had somewhat discouraging results and more long-term studies are needed(14, 15). Bariatric surgery is well-established as an obesity treatment in adults leading to weight loss and weight loss maintenance(16). Bariatric surgery is rarely performed in children and adolescents. In a study in adolescents with up to 5 years of follow-up, bariatric surgery was found to induce a weight reduction of 26%, comparable to the 29% found in adults(17). Despite comparable weight change 5 years after bariatric surgery, adolescents were significantly more likely to obtain remission of diabetes and hypertension as compared to adults, although both groups were still severely obese (BMI ~37kg/m^2) at that time point(17). However, in the same study, the rate of reoperations and nutritional problems were significantly higher in the adolescents, a finding that is comparable to another study in which ~25% of the included young subjects (13-18 years of age) underwent additional abdominal surgery due to complications and ~70% displayed nutritional deficiencies(17, 18). Due to the invasive and somewhat discouraging results of pharmacotherapy and surgery in children and adolescents with obesity, lifestyle interventions seem to be a preferable and safe treatment option.

The literature on dietary intake and differences in macronutrient composition primarily comes from studies in adults. In adults, comprehensive studies in large cohorts have found that high intake of carbohydrates was associated with higher risk of total mortality and inversely, that higher intake of fruit, vegetable, legume, and dairy products was associated with a lower risk of total mortality(19-21). In line with the latter findings, total intake of fat as well as subtypes of fat (including saturated fat) was associated with lower risk of total mortality(19). In relation to carbohydrate intake it was recently suggested that the carbohydrate quality is of significant importance in relation to development of disease and there seem to be a dose-response relationship between the intake of dietary fiber, whole grain, and all-cause mortality as well as the development of non-communicable disease such as T2D, cardiovascular disease, and certain cancers (e.g. colorectal and breast cancer)(22, 23). In addition, intake of whole grain, fruit, and legume was reported to be inversely associated with the development of overweight and obesity in adults, and sugar-sweetened beverages to be the opposite, although the quality of evidence was low(24). In relation to weight loss and especially weight loss maintenance, protein, including dairy protein, seems at least in adults to be of importance(25). In children and adolescents, a recent systematic review found that caloric restriction down to a 50% reduction in estimated daily energy requirement resulted in a mean weight loss of ~10kg with a sustained weight loss of ~5kg after 5-14 months, with the most pronounced effect in adolescents (10-18 years)(26). Only two of the 24 studies included in this review reported on psychological well-being and found improvement in QoL. Only one of these reported on changes in eating behavior and found no effect on eating behavior(26). Few studies have investigated the effects of macronutrient composition in diets designed for weight loss in children and adolescents. Some report similar results on weight loss whether low carbohydrate or low fat was applied (27). Some report a beneficial effect of a high-protein/low carbohydrate diet compared to a low-fat diet on weight loss in severely obese children (28) and one recent meta-analysis found dairy products to be associated with a decreased risk of developing obesity in children(29). Other studies in children have reported conflicting results on supplementation with increased dietary protein as a way to obtain weight loss and/or reduce hunger when exposed to caloric restriction(30-32).

Dietary studies in children and adolescents on weight loss or weight loss maintenance combined with measures of QoL, including eating behavior and eating habits, are scarce. Therefore, the purpose of the present study is to perform a 10-week dietary intervention study with a follow-up after 52 weeks in children from 7-14 years of age with overweight or obesity in a multi-component overnight camp setting. In a caloric restricted and increased physical activity setting, the control group will consume a low-moderate protein diet (15 energy percent (E%)/day) whereas the intervention group will consume a higher protein diet (25E%/day).

Aims

1. To test whether a diet with higher consumption of protein-containing foods is more favorable than the current weight-loss diet served to children and adolescents in the setting of a multi-component overnight camp (Julemærkehjem) on:
    a. Anthropometry (BMI-SDS, fat-mass, fat-free masse)
    b. Metabolic, inflammatory and liver markers.
    c. QoL, eating behavior, eating habits and overeating/loss of control eating episodes.

Hypotheses

Compared to the current weight-loss diet, we hypothesize that a diet with higher consumption of protein-containing foods will more effectively induce weight loss (a reduction in BMI-SDS) or weight maintenance in children with overweight or obesity, and improve risk factors for type 2 diabetes. Furthermore, we hypothesize that QoL will improve during the intervention and in relation to weight loss.

Study setup

The COPE-study is a non-randomized trial and a collaboration with the staff of the multi-component-overnight camps (Julemærkehjem) in Denmark. The multi-component-overnight camps are well-established intensive weight loss camps to which Danish schoolchildren, from 7-14 years of age, are referred to for 10-weeks intervention focusing on a healthy lifestyle, healthy eating, new habits and increased physical activity.

Participants

A total of 350 children attending a multi-component overnight camp in Hobro and Fjordmark for 10 weeks will be invited to participate in the study. The capacity is 48 children in camp Hobro and 30 children at camp Fjordmark, and every 2nd or 3rd week new children start camp in groups of 8-12 children. Annually, 240 children attend camp Hobro and 150 children attend camp Fjordmark.

Parent/guardian will be co-participants and help their child answer questionnaires. One time, in the initial period of the study, parent/guardian will be asked to report their weight (kg) and height (m) and parents will be asked health-related and family-related questions. Furthermore, at least one parent/guardian will participate in the nutrition education class at the multi-component-overnight camp with their child.

Recruitment/consent

The camp staff manage the visitation of the children. At the first visit (pre-visit), which is an individual meeting at camp held behind closed doors with one of the camp staff, the parent/guardian will be asked to sign one written consent to participate themselves and one written consent for their child to participate. Furthermore, they will give oral consent if both parties want to participate in the trial.

We want to invite all the participating children and parents/guardians to a follow-up meeting 3 years, 5 years, 7 years and 10 years after the intervention to measure anthropometry and to answer questionnaires. Also a blood test will be collected from all participating children who voluntarily agrees to a blood test. When the children turn 18 years old, we will provide written and oral information to the adolescents and collect independent written and oral consent from the adolescent to continue to participate in the study.

Participants can be included if:

- The child start camp in Hobro or Fjordmark between October 2020 and March 2022.
- The child is between 7 and 14 years of age (inclusive) while attending camp.
- At least one parent/guardian submit written and oral consent to participate with his/her child.

- Parent/guardian has submitted oral and written consent to participation of their child. In case of shared custody both parents must submit oral and written consent to participation of their child. If one parent is not present at the first visit at camp, this parent must send a power of attorney with the other parent.

Participants will be excluded if:

- The child has a disease, diagnose or eating disorder that requires a special diet.
- The child or parent/guardian participate in another clinical trial or plan to do so in the near future.
- The parent/guardian do not understand the written informed consent.
- The child or parent/guardian are unwilling to or unable to comply with the study protocol and instruction given by the study staff.

Methods

The camp staff will assign the participating children to one of three different groups (see specifications below). The assignment of children to the various groups will therefore be blinded for the research group.

- SARS CoV-group: The children attending camp Hobro from October 2020 to April 2021 were affected by a COVID19 lockdown of the camps and sent home for 5 weeks with no control of diet and physical activity.
- Control group: The children attending camp Fjordmark from May 2021 to June 2022 will receive the current weight-loss diet (low to moderate protein diet equal to ~15E%/day) for the 10 weeks they attend camp. After leaving the camp, the children and their families will be contacted once every month within the first 6 months and one time halfway between 6 months and 52-weeks follow-up (7 times total). The families will be contacted by phone, face-time, skype as they prefer (see specifications below).
- Protein group (PG): The children attending camp Hobro from May 2021 to March 2022 will be served a higher protein diet equal to ~25E%/day for the 10 weeks they attend camp. After leaving camp they will receive written guidelines and be instructed how to continue a higher consumption of protein-containing foods at home until 52-weeks follow-up. After leaving camp, the children and their families will be contacted once every month within the first 6 months and one time halfway between 6 months and 52-weeks follow-up (7 times total). The families will be contacted by phone, face-time, skype as they prefer (see specifications below).

The trial design is shown in Figure 1, below.

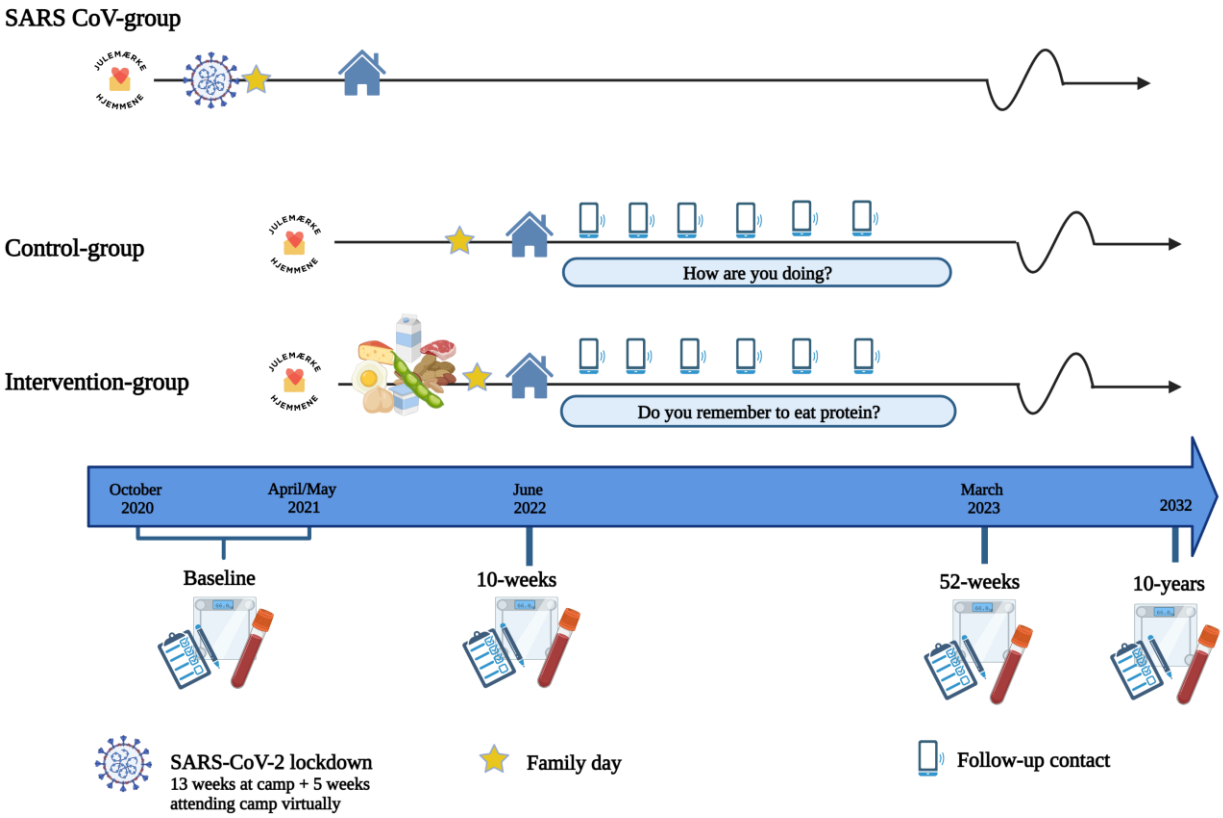

Figure 1: Trial design

The COPE-Study intervention components

Dietary intervention

The dietary intervention at the multi-component overnight camp uses the official Danish dietary guidelines as basis (33, 34). In all three groups the daily energy intake will be between 1200-1800 kilocalories (kcal) depending on age and gender and a number of foods are limited and restricted for the children during the 10 weeks they attend camp. In the CG and the SARS CoV-group, the protein intake will be ~15E%/day and in the PG the protein intake will be aiming at ~25E%/day. In the PG carbohydrates-rich foods at breakfast and two in between-meals will be replaced by protein containing foods (e.g. dairy products) to make the intervention isocaloric.

The kitchen staff serving meals to the CG will be instructed to continue their usual fixed weight-lost diet plan. Likewise, the kitchen staff serving meals to the SARS CoV-group will be instructed to continue their usual fixed weight-loss diet plan.
The kitchen staff serving meals to the PG will be instructed how to replace some meals by protein containing foods and be responsible for including the predetermined amount of protein foods in the diet plan. After leaving camp the children in the PG will be instructed how to consume protein containing foods as part of their diet until the 52-week follow-up.

Nutritional education class

All children and their parents will three times total (3-5 weeks before camp; 4-6 weeks into camp; 4-8 weeks after camp) be invited to camp in groups of 8-12 families. All three days they will learn about healthy eating and nutrition.

The CG will be introduced to the official Danish dietary guidelines (33, 34) and be introduced to different foods and recipes to promote healthy eating. The nutritional education class will be an oral presentation performed by the kitchen staff at camp and each session will last 10-15 minutes.

The PG will also be introduced to the Danish dietary guidelines (33, 34) and be introduced to different foods and recipes to promote healthy eating before and after camp. During camp the PG will learn about protein relative to weight loss, satiety and physical activity and furthermore, they will learn how to identify macronutrients, especially protein, in foods. Knowledge of protein and macronutrients will be communicated through story-telling, games and by showing examples of protein containing foods and meals. This session will be held by the primary investigator and last 20-30 minutes.

Follow-up intervention

Children and their families attending the PG and the CG will be contacted once every month within the first 6 months' after camp and one time halfway between 6 months and 52-weeks follow-up (7 times total) by the primary investigator.

The conversation with the CG will be about successes and challenges (e.g. concerning healthy eating and physical activity) after camp and the child and their parent/guardian will choose 1-3 issues which they feel is challenging after camp. Those issues will be the main focus at the next follow-up conversation. Likewise, the following follow-up conversations will be based on issues reported as challenging at the last conversation.

The conversation with the PG will primarily focus on protein consumption and before the conversation they will be asked to answer a food frequency questionnaire on protein foods. The primary investigator will motivate the children in the PG to continue eating protein until 52-weeks follow-up.

All children and their families will be contacted by phone, face-time or skype, as they prefer, within a predetermined and known timeframe, and the follow-up conversation will last approximately 10 minutes.

In case of none response the children and their families will receive an SMS reminding them to be in contact with the primary investigator within the week.

Outcome measurements

The primary outcome measure is BMI-SDS (35) which will be compared between the CG and the PG. BMI will be calculated (kg/m^2) and weight categories defined using age- and sex-specific BMI-cut-offs from 2007 WHO references (35). Body weight (kg) and fat-free mass/fat-mass will be measured according to standard procedures by using a Bioelectric impedance (InBody model 270). Height (m) will be measured using a fixed wall measuring tape.

Teachers at the multicomponent overnight camps will be instructed how to measure anthropometrics and be responsible for measuring children. Children will be measure three times total; at baseline, 10-weeks and 52-weeks.

One participating parent/guardian will self-report their height and weight at baseline. All measurements are recorded to the nearest 0.1 kg and 0.1 cm.

Additionally, after resting in a chair, all children will have their blood pressure measured at baseline, 10-weeks and 52-weeks. Blood pressure will be measured with the right arm placed at heart level using an automatic non-invasive blood pressure monitor (Omron M3 model). Camp

staff will be instructed how to measure blood pressure correctly and note three measurements at each event from which an average will be calculated.

A blood test will be collected three times total; at baseline, 10 weeks and 52 weeks, from all participating children who voluntarily agrees to a blood test. The blood test will be collected to measure relevant metabolic-, inflammatory- and liver markers.

Questionnaires

Background characteristics will be assessed by a self-developed parent-reported questionnaire with questions concerning parental education, household income, diseases in the family (T2D, hypertension, lipid disorders, ischemic heart disease, thyroid disease), child and parent participation in physical activity (leisure time, sports), ethnicity etc.

Quality of Life will be measured using the Children PedsQL4.0 (36) questionnaire, which is a child-reported questionnaire containing 23 questions.

Children's eating habits will be measured using the Children's Eating Habits Questionnaire-FFQ (CEHQ-FFQ), which is a parent/child-reported questionnaire containing 36 questions (37). Parent and child are encouraged to answer this questionnaire together because it is difficult for the parent/guardian to know exactly which foods their child eat during school and leisure.

Children's eating behaviour will be measured using the Child Eating Behaviour Questionnaire (CEBQ), which is a parent-reported questionnaire containing 35 questions (38).

Children will be asked two questions (see below) from the Eating Disorder examination questionnaire (EDE-Q 6.0) (39) to investigate overeating/loss of control eating episodes and the risk of developing binge eating disorder (BED).

- *No. 13: Over the past 28 days, how many times have you eaten what other people would regard as an unusually large amount of food (in relation to your size and age)?*
- *No. 14: … On how many of these times did you have a sense of having lost control over your eating (at the time you were eating)?*

Details on the distribution of questionnaires are outlined in Figure 2, below.

Questionnaires will be delivered to the participants using REDcap.

	Aim	- 8 weeks (before camp)	- 4 weeks (before camp)	Baseline (first day)	+10 weeks (end of camp)	+14 weeks	+18 weeks	+ 22 weeks	+ 52 weeks (end of study)
Parent-reported	Background information	X							
Parent-reported	Eating behavior (CEBQ)		X		X			X	X
Parent/child reported	Food habits (CEHQ-FFQ)		X		X			X	X
Parent/child reported	Physical activity								X
Child reported	Disturbed eating/BED (EDE-Q)	X	X	X	X	X	X		X
Child reported	Quality of life (PedsQL 4.0)		X		X				X

Figure 2: Distribution of questionnaires

Patient health records

We do not need to access patient health records to complete this study.

Compensation scheme/Insurance

Within the whole study period the participants will be covered by the Act on Complaints and Compensation Access within Health Care (cf. legislation number: 1113 07/11/2011 www.retsinformation.dk). The participants in the trial are covered by the patient compensation scheme.

Publication of results

Positive, negative and inconclusive results from the **COPE**-study will be submitted for publication in peer-review journals with Dorthe Dalstrup Jakobsen as first author and presented at scientific conferences from the beginning of year 2023, when some parts of the data are analysed. All analysis and the trial are expected to be finished in 2032. This study is registered and published at clinicaltrials.gov with ID: NCT04522921. All participants will be anonymized in the publication of results.

Ethics

All parts of the **COPE**-study will be performed in accordance with good clinical practice and conforming to the Declaration of Helsinki. The protocol is approved by the local Committee of Ethics (journal number: 1-10-72-73-20) and the data entering the project will be safeguarded using REDCap database at Aarhus University securing the General Data Protection Regulation. The Data Protection regulation and the Data Protection Act will be complied by all involved parties, researchers and camp staff, when handling trial data. Furthermore, the trial is registered internally at Aarhus University.

Before participation, the nature, purpose and potential risks of the study will be carefully explained to all children and their parents/guardians. All participating children will be invited to follow-up 3 years, 5 years, 7 years and 10 years after the intervention to measure anthropometry

and to answer questionnaires. Also a blood test will be collected from all participating children who voluntarily agrees to a blood test 3 years, 5 years, 7 years and 10 years after the intervention. When the children turn 18 years old, we will provide written and oral information to the adolescents and collect independent written and oral consent from the adolescent. Participants may at any time withdraw from the study without any reason given. All information obtained in the study will be treated as confidential and national authorities will have access to the data if requested.

Significance of the project

The results on weight loss/weight maintenance, biomarkers, QoL, eating habits, eating behaviour and overeating/loss of control eating episodes will provide important information for future weight-loss programmes and report on the effects of increased consumption of protein-containing foods as part of an overall weight-management setting. The access to prospectively follow the cohort and compare the participating children to the other Danish children using a register-based approach will provide invaluable information on the long-term development of disease (e.g. T2D) and various psychosocial factors.

Power calculation and statistics

The power calculation was based on a previous study investigating the effect of a higher protein intake (21E% vs. 32E%) on childhood obesity (28). In this study, 22 and 24 children were allocated to the standard and high protein diet, respectively. Both groups had a reduction in BMI z-score during the 13-week intervention (from 2.48 ± 0.06 BMI-z to 2.10 ± 0.10 BMI-Z in the high protein group, and from 2.51 ± 0.05 BMI-Z to 2.40 ± 0.10 BMI-Z in the standard protein group), with a greater reduction in the high protein group ($p = 0.03$). The number of participants needed to detect a between-group difference of − 0.27 SD with a power of 80% and a significance level of 5% was calculated to be ~ 55 children in each group. Preferably, unadjusted mixed effects models will be performed to investigate differences in change between the groups.

Economic/funding

The multi-component-overnight camps are financed with the revenue from public sale of Christmas stamps, funding from investors and private companies. The organization behind the camps will provide facilities and staff to help implement and manage the intervention.

The project is funded by an unrestricted grant from Arla Foods Amba on 970,593 Danish kroner (130.000 EUR). Tests, test-instruments, other test-personnel such as bioanalysts, project materials for information, education e.g. and the salary of the primary investigator will be funded by the grant, and payments will continuously be paid as costs arise.

The research team declare no financial interest or affiliation with Arla Foods Amba.

Project group

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