Prevention of diabetes through lifestyle intervention and population studies in Europe and around the world

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1) To determine the preventive effect of a higher protein-low GI vs. medium protein higher-GI diet in combination with either moderate or high intensity physical activity on the incidence of type 2 diabetes in predisposed, pre-diabetic children,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON45201

Source
ToetsingOnline

Brief title
Preview

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
overweight, pre-diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: European Committee. Substudies are part of the funding and were applied for together with the main intervention study.

Intervention

Keyword: food-reward related brain signaling, hormones, physical activity, protein-diet, sleep, sleep quality

Outcome measures

Primary outcome

For adults:

Incidence of type 2 diabetes, in a combination of protein and physical activity

combinations, measured during 3 years after baseline and based on WHO/IDF

criteria:

* Fasting plasma glucose (FPG) > 7.0 mmol/l (126 mg/dl) or,

* 75 g oral glucose tolerance test (OGTT) with FPG > 7.0 mmol/l (126 mg/dl)

and/or 2 hour plasma glucose > 11.1 mmol/l (200 mg/dl) or,

Sub study parameter/endpoint

* Fat distribution by MRS (TWO study arms)

* Physical fitness (VO2 max) (TWO study arms)

* Brain reward activity by fMRI (TWO study arms)

* Substrate metabolism with respiration chamber (TWO study arms)

For children and adolescents:

Change in insulin resistance at 2 years after randomization to a combination of

protein diet and physical activity, measured by the homeostatic model

(HOMA-IR).

Secondary outcome

For adults:

* The effects of vigorous vs. moderate intensity physical activity on incidence of type 2 diabetes, based on WHO/IDF criteria (adjusted for diet);

* Change in HbA1c, a measure of average blood glucose levels;

* Change in body weight and waist, hip and thigh circumference;

* Change in body fat mass (kg measured by BodPod, proportion of body weight);

* Proportion of subjects maintaining at least 0, 5 or 10% weight loss (relative to initial body weight);

* Insulin sensitivity (e.g. Matsuda Index based on the OGTT, glucose and insulin area under the curve (AUC) during OGTT, beta-cell disposition index)

* Risk factors for cardiovascular disease, with at least the following measures: blood pressure, lipids (triglycerides, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol), C-reactive protein, and liver enzymes;

* Changes in perceived quality of life and workability, habitual well-being, and chronic stress, subjective appetite sensations, and habitual physical activity.

* Effect of circadian rhythm on weight maintenance.

For children and adolescents:

* Change in body fat mass (kg, proportion of body weight)

* Sleep architecture

Study description

Background summary

Type II diabetes, is one of the fastest growing chronic diseases worldwide. This is primarily due to increasing prevalence of obesity, caused by a sedentary and inactive lifestyle and general food abundance. It is estimated that in year 2000 there were approximately 150 million individuals with type II diabetes and that this number is likely to double by 2025.The relative risk of getting type II diabetes rises exponentially with increasing body mass index (BMI) and already at a BMI above 23 kg/m2 the risk of getting type II diabetes doubles. During the past 20 y, the US has experienced a surge in overweight and obesity, and the increase in incidence of type II diabetes has paralleled these conditions. Persons with diabetes have a 2-4 times higher risk of dying from heart diseases compared with persons without diabetes and overall, the health and economic costs related to the increased numbers in both young, adults and the ageing population are huge.
The global increase in the prevalence of obesity is most likely driven by a simultaneous increase in global food abundance incl. food of reduced nutritional quality, together with increased sedentariness and decreased physical activity during work and leisure time. Recent studies have also indicated that a deviation of normal sleeping pattern (7-8 h sleep per night), particularly short sleep, increases appetite and promotes obesity and its related diseases (e.g. type II diabetes and cardiovascular diseases).

It is recognized now that many of the adult morbidities associated with metabolic disease originate in childhood. An increasing number of Dutch and children around the world are laying the foundations for metabolic disease by being overweight, a well known predisposing factor for co-morbidities such as type 2 diabetes, liver disease and cardiovascular disease. This increasing prevalence of obesity in children poses a tremendous threat for future generations and an enormous economic burden, especially considering the fact, that childhood obesity is one of the biggest risk factors for adult obesity.

There are generally two ways to prevent type II diabetes:
1) By preventing weight gain and type II diabetes in the general population (population-approach)
2) By preventing type II diabetes in at-risk individuals (pre-diabetics) by weight loss and maintenance.

Main drivers in both situations are changes in dietary and physical activity patterns, but also sleep and stress may be important factors. Unfortunately,

despite convincing evidence from clinical trials that type II diabetes can be prevented or delayed through intensive lifestyle interventions resulting in weight loss, the reality is that weight regain and incremental weight *creep* are very common and jeopardise diabetes prevention. The recent FP6 DiOGenes Study (Diet, Obesity and Genes) identified two dietary factors that were associated with shorter-term prevention of weight regain after prior weight loss: higher protein intake and lower glycemic index (GI). The findings showed that overweight and obese participants assigned to the combination of modestly higher protein and lower GI ad libitum had significantly better completion rates and weight maintenance after 6 months as compared with the official dietary guidelines. Indeed, those consuming the high protein-low GI combination diet continued to lose weight during the weight maintenance phase and were twice as likely to have maintained a 5% weight loss compared to the other groups. On this basis, we hypothesize that the same diet may be superior to conventional diets (i.e. those currently recommended by public authorities) for both diabetes prevention and the reduction of its complications.

Although the positive role of physical activity in prevention of type II diabetes has been well established, especially the role of exercise intensity is unclear. Moreover, the data on physical activity use in connection with lowered carbohydrate intake is very limited.

There are a few important mediating variables, which are understudied when assessing the relationship of diet, exercise and risk for type 2 diabetes:

1. Age
An important lack in the literature is insight into potential interaction between age and prevention of type II diabetes. It is not known whether the proposed strategies are equally effective in young, adult and ageing individuals. Obesity tends to *track* from childhood to adulthood. It was shown that measures of childhood and adolescent body composition were good predictors for body composition throughout the lifespan. Therefore, early intervention was suggested as a key factor in tackling the obesity epidemic.

2. Sleep
Based on the literature we can assume an interaction between obesity, diabetes and sleeping pattern. Especially sleeping behaviour in children has changed tremendously in the last decade with more TV*s and computers available in bedrooms and less physical activity. Both, short sleep duration and a lack of sleep quality are associated with appetite. Only one night of sleep fragmentation, resulting in reduced REM sleep causes an unfavorable shift in insulin concentrations, while GLP-1 (a satiety hormone) levels and fullness scores are reduced and ghrelin (a hunger hormone) concentrations are elevated. These results show how reduced sleep and sleep quality may contribute to increased food intake and insulin resistance.

3. The brain

In human research, the existence of brain insulin resistance along with peripheral insulin resistance was suggested after the observation of a reduction in insulin-induced changes in the global cerebral metabolic rate for glucose in insulin resistant research participants compared to insulin sensitive participants. Given that insulin is an important satiety signal not only in the homeostatic system but also in the brain reward center, insulin resistance was associated with un-inhibited activity in those centers, leading to overeating and increased hunger perception.

The primary goal of PREVIEW is to identify the most efficient lifestyle pattern for the prevention of type-2 diabetes in a population of pre-diabetic overweight or obese individuals. This will be done by conducting a multi-centre, multinational, clinical randomized intervention trial of 3 year duration with a total of 2200 pre-diabetic participants, including children and adolescents, adults and elderly, 315 of which will be investigated at the Maastricht University.

The study will consist of a main study (RCT), investigating the interaction of protein intake and physical activity on incidence type 2 diabetes and several substudies, examining the role of the mediating variables for the outcome of the main study. Maastricht University will take part in the multicenter mainstudy, conduct four site-specific subsidies (all n = 40), and take part in one multicenter substudy. More specifically, one substudy will investigate children (n = 40) to identify the mediating role of sleeping patterns (sleep quality and duration) for the main study outcome. One substudy will investigate adults to identify the role of the brain, one other sub-study the role of liver-fat, for the outcome variable *incidence of type 2 diabetes*, and one substudy will assess the study conditions in a controlled manner in a respiration chamber setting with regard to substrate metabolism, sleep, hunger, satiety and cardiovascular markers . Participants in the substudies will differ in only one condition. For brain plasticiy as well as liver fat 40 participants in the moderate physical activity condition will be compared based on medium vs. higher protein intake. In a 36 hour respiration chamber study a total of 40 participants (20 from each protein intervention) the effect of protein will be assessed with regard to substrate metabolism, sleep, cardiovascular risk, and hunger and satiety hormones.
The substudy in children will compare the moderate vs. higher protein condition in a group with moderate physical activity intensity. For the multi-center substudy on VO2 max 40 adults with moderate protein will be compared based on moderate vs. high intensity physical activity.
Children and adults will be treated differently for the purpose of the main study. This will be further specified below.

Study objective

1) To determine the preventive effect of a higher protein-low GI vs. medium protein higher-GI diet in combination with either moderate or high intensity

physical activity on the incidence of type 2 diabetes in predisposed, pre-diabetic children, young, and older adults (both genders). This will be done by conducting a randomized, controlled, multicentre trial (RCT) among participants at high risk of developing diabetes (i.e. overweight with BMI > 25 kg/m2 and increased diabetes risk factors). The trial will be performed worldwide including 6 EU nations: Bulgaria, Denmark, Finland, Spain, the Netherlands, United Kingdom, and in Australia and New Zealand.
* Our hypothesis is, that the interaction of the higher-protein/ high intensity physical activity condition will be superior to other combinations of protein intake and physical activity intensities regarding the prevention of type 2 diabetes.

Objective of the sub study in children:

2. To evaluate the role of sleeping pattern for the effect of the moderate vs. higher protein diet on insulin sensitivity in children with moderate intensity physical activity
* Our hypothesis is that the higher protein diet may improve the sleeping architecture, sleep quality, and sleep duration, leading to improved levels of insulin sensitivity.

Objective of the sub studies in adults:

3. To evaluate the role of the brain, and liver fat for the effect of moderate vs. higher protein diet on incidence of type 2 diabetes in adults with moderate physical activity.
* Our hypothesis is that the higher protein diet decreases the activity of brain reward pathways in response to visual food/ non-food cues and thus reduce overeating in the absence of hunger.
* Our hypothesis is that the higher protein diet will reduce liver fat and thereby decrease the incidence of type 2 diabetes.

4. To evaluate the role moderate vs higher intensity physical activity on VO2max in adults with moderate protein intake.
* Our hypothesis is that the higher intensity physical activity will improve VO2max and thereby decrease the incidence of type 2 diabetes.

5. To evaluate the role of moderate vs high protein intake on substrate metabolism, sleep, cardiovascular risk and hunger and satiety participants will stay in the respiration chamber for 36 hours.
* Our hypothesis is that the higher protein intake will affect all aspects in a stronger way than the medium protein intervention.

Study design

1. Design Main study adults
The study will be carried out as a 3-year (156 weeks) multi-center, randomized,

clinical intervention trial in 8 sites in different countries. The study consists of two distinct parts, namely an 8-wk weight-reduction period (same for all adult participants regardless of intervention group assignment), followed by a 148-wk randomized weight-maintenance intervention. The first part is preceded by screening and randomization of eligible participants. Subjects are randomized into four groups and a total of 2,500 eligible participants are included (with an approx. screening of 5000 people) in two age-cohorts: 1) younger adults (25 * 54 y, n=800), and 3) and older adults (55 * 70 y, n=1500). Furthermore, 200 children (10 * 18 y) will be recruited (for child-specific study design see 3.3) It is the plan to recruit an equal number of participants (n = 310-15) from each of the 8 study sites. The MUMC+ will contribute 135 children and 215 adults to the PREVIEW study. Adults will be recruited from all 8 sites. Adult participants with successful weight reduction (at least 8% of initial body weight, estimated 75% of the number of recruited particpants) will continue into the weight maintenance phase of the study.
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The main assessment points after the screening visit (clinical investigation days, CID) are at the following weeks:
* Week 0 (CID1, baseline, start of weight reduction with LCD)
* Week 8 (CID2, end of weight reduction/start of randomized intervention)
* Week 26 (CID3, 6 months from baseline and 4 months after randomization)
* Week 52 (CID4, 12 months from baseline and 10 months after randomization)
* Week 78 (CID5, 18 months from baseline and 16 months after randomisation; lightened protocol)
* Week 104 (CID6, 24 months from baseline and 22 months after randomization)
* Week 156 (CID7, 36 months from baseline and 34 months after randomization / End of Trial, (EOT))

The 8-week run-in weight loss phase on a low calorie diet (LCD) providing 800-1000 kcal/d will precede randomization. LCD will be provided by Cambridge Weight Plan ®. Those who achieve the target weight loss of equal or more than 8% of initial body weight will be included in the second phase (75% from the recruited subjects, as being estimated).
The second phase will consist of 148 weeks of weight maintenance. The weight maintenance period participants will be centrally cluster randomized for both, the dietary and physical activity arms. Participants will be instructed to maintain their weight loss, though further weight reduction will be allowed. After the trial participants can follow the advise on their own terms but do not get any supervision anymore, since the project is over.
The four study groups include:
1. Higher protein (25 E%), Moderate carbohydrate (45 E%), Low GI (<50) diet
2. Moderate protein (15 E%), High carbohydrate (55 E%), Medium GI (>56) diet
3. High-intensity physical activity (> 6 MET) Group 1: HP-HI Group 3: MP-HI
4. Moderate-intensity physical activity (3-6 MET) Group 2: HP-MI Group 4: MP-MI

The abbreviations refer to the dietary regimen (HP/MP) and to the intensity of

physical activity (HI/MI).
MET = Metabolic equivalent of task (energy expenditure compared to resting energy expenditure). Note that the MET*s may vary on individual basis because of variation in fitness (intensity is always relative to a participant*s maximal fitness). Participants will be approached up to three years after the study via email to inquire about their diabetes status, by means of a little questionnaire. Participation is voluntary. The purpose of this approach is to assess the long term effects of the intervention and increase statistical power with regard to the primary endpoint of the study, type 2 diabetes.

2. Design Sub-studies adults (brain imaging, physical fitness, body fat distribution, and respiration chamber)
Subgroup of n = 50 adults will participate in a repeated measures design for functional imaging (fMRI), a subgroup of n=50 for determination of fitness (VO2max) and a subgroup of n=50 for body fat distribution, especially liverfat (MRS). A subgroep of 50 participants is needed to determine substrate metabolism in the respiration chamber. Participants will come for a total of three times (except for the respiration chamber study which requires only one appointment) throughout the main study period (baseline, after weight loss at week 26, and after weight maintenance at week 104) to assess changes in brain reward response to visual food cues, have their physical fitness assessed or their liver fat content. For specification of methodology see study procedures. Inclusion of participants will be based on treatment groups: all participants from the main study will be asked if they are willing to participate. Those who are interested will be stratified based on age and gender (for fMRI and for MRS) comparing moderate vs. higher protein, both in the presence of moderate intensity physical activity. For the comparison regarding VO2 max, participants will be stratified based on age and gender. Only participants with moderate protein intake will be compared with respect to moderate vs. high intensity physical activity.

3. Design Main study children
The study in children and adolescents (10 - 18 y, n=200) will be carried out as a randomized clinical intervention trial, where children will be recruited from 4 sites (Maastricht University n=135, University of Copenhagen n=50, University of Nottingham n=25, and University of Navarra n=25). Children and adolescents will be randomized by the same principle as adults, but without any requirements for weight loss during the weight reduction period. The goal for children and adolescents is to maintain weight (while gaining length) during the initial 8 weeks, thus resulting in a BMI reduction during those 8 weeks. For the duration of those 8 weeks, participants will be advised and guided by a trained dietician to follow a diet that is based on individually calculated needs. All children participating at the Maastricht University will come from the COACH program, a standard care treatment program in the MUMC+, a previous study (the MIKADO study) conducted by the department of Paediatrics of the MUMC+, distributing flyers at the paediatric outpatient clinic of the MUMC+, or

the childhood obesity programs of Atrium MC Heerlen or Orbis MC Sittard. After the study children will stay part of the childhood obesity program at their local hospital.

4. Design Sub-Study children
In a sub-group of 40 children and adolescents, age 10-18 years, sleep architecture will be assessed for one night in the PICU (pediatric intensive care unit), a standard measure of COACH. Changes in total sleeping time, sleep latency, REM sleep and SWS will be related to the intervention related effects on insulin sensitivity, respectively body-composition, waist circumference, body-weight maintenance. Sleep architecture will be assessed with poly-somnography. Inclusion of participants will be based on treatment groups: all participants from the main study moderate intensity physical activity condition will be asked if they are willing to participate. In case the PICU does not provide enough space and polysomnography devises, the children will spend a night in an S1 chamber of the MRUM (metabolic research unit, NOT a respiration chamber). Then their polysomnography will be measured by an experienced researcher, similarly to the measurement in the PICU. The researcher will stay overnight with the children. In addition, at CID4 and CID6 children will be asked to wear an iButton for 7 days after admission to the hospital to assess circadian rhythm.
Those who are interested will be stratified based on age and gender comparing moderate vs. higher protein diet regarding sleep related outcomes. Measurements of the sub-study do not exceed the measurements that are part of the standard COACH program.

Intervention

1. Dietary intervention

A. The energy restricted LCD diet (for adults only) consists of 800-1000 kcal/d and the target macronutrient composition of the diet will be 15-20% of total energy from fat, 35-40% from protein and 45-50% from carbohydrate. During this period, subjects will attend five group meetings at the site-centre where their body weight, adverse events (AE) and concomitant medication will be registered and dietary and behavioural instructions will be given. No specific instructions on physical activity are given during the weight-reduction phase. All adult participants should follow their LCD until they are measured at wk 8 visit.
The weight reduction period is reinforced during group meetings led by a dietician/weight loss counsellor. There is also a meeting on week 8, following the CID2 (clinical investigation day 2), at which participants will be introduced to the intervention to which they have been randomized.

B. Adult participants with at least an 8% weight loss at the CID2 visit are allowed to start the randomized intervention phase. After the screening visit,

participants have already been randomized to one of the dietary interventions, HP = Higher protein (25 E%), moderate carbohydrate (45 E%), starchy food items with low GI, or MP = Moderate protein (15 E%), high carbohydrate (55 E%), starchy food items with moderate GI.
The diets are to be consumed ad libitum with respect to energy, i.e. the participants are not asked to count the energy content, and they are not provided with an individual target for energy intake. However, they will be instructed about the importance of controlling portion size of particular food types in order to achieve the macronutrient / GI prescription, and in self-monitoring and adjustment of portion sizes in general, in order to maintain weight loss. They will also be advised to have a regular meal pattern. They will be repeatedly reminded, at the group meetings, about the importance of maintaining weight at the level achieved after the weight-reduction phase. Additional weight reduction is allowed, but without any other means than the study diet and physical activity regimens (e.g. LCD*s using commercial products and/or weight-reducing drugs are not allowed in the weight maintenance period). The idea of the food-based dietary guidelines is that both diets are planned to be healthy and supportive for weight maintenance. This implies that the food items with increased use have at least suggestive scientific evidence on prevention of weight gain and/or type 2 diabetes. Respectively, foods with decreased use have at least suggestive evidence on increasing weight gain and/or type 2 diabetes.

The participants have group-meetings counselled by a dietician (or another qualified experienced health-care professional) on study weeks 8 (end LCD/ beginning of the randomized intervention), 10, 12, 16, 20, 26, 32, 44, 52, 64, 78, 104, 130 and 156.

A typical group-meeting will take up to 60 minutes. The participants will be in small groups (6-12 participants per group). Participants of the two dietary interventions (HP and MP) will not be mixed in the group meetings. The first part of each meeting is devoted to dietary supervision. The second part of the meeting is devoted to physical activity. Like for diet, the two physical activity programmes (HI and MI) are not mixed. Moreover, participants are also encouraged to contact the site-staff if they have any questions related to diet, physical activity programme or any other items of the study.

Dietary intake is recorded by 4-d dietary records and compliance of protein intake by analysing nitrogen in urine.

C. All participants will be randomized to one of the two physical activity interventions, HI = high-intensity (vigorous) or MI = moderate-intensity. Measured heart-rate (by heart-rate monitor or palpitation) is the principle way of determining MET-levels.
Physical activity is in general unsupervised. Hence, the participants can choose from several options with similar level of metabolic turnover (energy expenditure divided by resting metabolic rate, i.e., MET values). The two

physical activity interventions will have roughly similar target energy expenditure (1000 kcal/wk), but the specific advice is based on the Centre for Disease Control (CDC) recommendations on 75 min vigorous or 150 min moderate-intensity physical activity weekly.
In the beginning of the weight maintenance phase (week 8), the participants, assisted by an exercise instructor (or another experienced health-care professional), plan their personal physical activity programme. In the group sessions, the participants are also instructed on basic principles of increasing physical activity. Moreover, they are taught problem-solving techniques, that is, how to overcome urges to refrain from planned physical activities. All physical activity sessions are planned to be at the same visit with the dietary supervision at the site-centre.
The first month of the interventions (study weeks 9*12) is used to increase the weekly physical activity volume to 75 min. The intensity is kept moderate in all participants.
The next month (study weeks 13*16) is used to reach the intended prescribed program. For the HI-groups, this means that the volume (weekly duration, i.e., 75 min) is kept constant while the intensity is gradually increased so that in the end of this period all physical activity sessions should have an intensity of at least 6 METs. There will be no intensity change for the MI-group, but the volume is gradually increased from 75 min to 150 minutes per week during this 4-week period.

Study burden and risks

For adults: The research is beneficial to the participant, given that everyone receives treatment with the aim to loose weight and improve metabolic health through increased physical activity. The total of 8 laboratory visits is a tolerable amount over the time of 156 weeks. For those participating in one of the sub-studies investigating the role of neural activity, physical fitness or liver fat for the incidence of type 2 diabetes the burden will be somewhat bigger, since they have 3 additional study visits. Those however will be compensated accordingly. Blood sampling will happen on every visit for the main study. The total amount of blood taken is minimal over the time period and there are no extra risks associated with blood drawing other than the risk for minor bruising.
FMRI is a non-invasive standard method to determine blood oxygenation in areas of the brain without any significant risks (see also tandardized and approved methods for conducting fMRI experiments involving human subjects). Brain structures and function are visualized through the utilization of a magnetic field.
Studies in the respiratory chamber will be conducted using standard operating procedures. A pair of subjects will always participate in the study at the same time and therefore they will never be alone. The subjects will be able to contact the investigators during the entire night. In addition, they will be able to get out of the chamber at any time they feel uncomfortable.

Vascular measurements are routine and are not expected to lead to physical side effects.
The LCD will bear no extra risks for the participant as the macronutrient composition and vitamins/ minerals content meet the Dutch allowance of daily recommendation. Due to extensive experience with LCD*s in our laboratory and support of group meetings we believe that adherence to the diet is possible, mostly due to motivation to loose weight.
For children: All participating children are part of the COACH program at the MUMC+ or the childhood obesity programs at Atrium MC Heerlen or Orbis MC Sittard, or are recruited through advertisements, flyers distributed at the paediatric outpatient clinic of the MUMC+ or via a previous study (the MIKADO study) of the department of paediatrics of the MUMC+. The intervention program integrates care and prevention and offers the possibility to evaluate physical and psychological co-morbidities in children and adolescents with overweight or obesity and long term tailored care. The aim is to improve the health of children with overweight and to prevent passing on an unhealthy lifestyle to the next generation. These programs are standard care treatment programs in the participating hospitals. Children and adolescents with overweight and obesity are predisposed to significant health problems. It is known that childhood obesity can adversely affect almost every organ system, and if left untreated, the major impact of childhood overweight is likely to be felt in the next generation of adults. Therefore it is of great importance to study whether intensive (life-style based) intervention programs should start as young as possible, or if obesity-related pathology can even be reversed to *normal* when the program starts at young adulthood.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Adults: age between 25 and 70;
BMI > 25kg/ m2;
The criteria from IDF (International Diabetes Foundation) for assessing pre-diabetes will be used as the formal inclusion criteria, i.e. having Impaired Fasting Glucose (IFG): Fasting venous
plasma glucose concentration 5.6-6.9 mmol/l or
Impaired Glucose Tolerance (IGT): Venous Plasma glucose concentration of 7.8 * 11.0 mmol/l at
2 h after oral administration of 75 g glucose (oral glucose tolerance
test, OGTT).
Children:
age 10-18
HOMA-IR has to be ><=2.

Exclusion criteria

1) Diabetes mellitus
2) Significant cardiovascular disease including current angina; myocardial infarction or stroke within the past 6 months; heart failure; symptomatic peripheral vascular disease
3) Systolic blood pressure above 160 mmHg and/or diastolic blood pressure above 100 mmHg whether on or off treatment for hypertension. If being treated, no change in drug treatment within last 3 months;
4) Advanced chronic renal impairment;
5) Significant liver disease e.g. cirrhosis (fatty liver disease allowed);

6) Malignancy which is currently active or in remission for less than five years after last treatment (local basal and squamous cell skin cancer allowed);
7) Active inflammatory bowel disease, celiac disease, chronic pancreatitis or other disorder potentially causing malabsoption;
8) Previous bariatric surgery;
9) Chronic respiratory, neurological, musculoskeletal or other disorders where, in the judgement of the investigator, participants would have unacceptable risk or difficulty in complying with the protocol (e.g. physical activity program);
10) A recent surgical procedure until after full convalescence (investigators judgement);
11) Transmissible blood-borne diseases e.g. hepatitis B, HIV;
12) Psychiatric illness (e.g. major depression, bipolar disorder).;Medication:
13) Use currently or within the previous 3 months of prescription medication that has the potential of affecting body weight or glucose metabolism such as glucocorticoids (but excluding inhaled and topical steroids; bronchodilators are allowed), psychoactive medication, epileptic medication, or weight loss medications (either prescription, over the counter or herbal). Low dose antidepressants are allowed if they, in the judgement of the investigator, do not affect weight or participation to the study protocol. Levothyroxine for treatment of hypothyroidism is allowed if the participant has been on a stable dose for at least 3 months. ;Personal/Other:
14) Engagement in competitive sports;
15) Self-reported weight change of >5 % (increase or decrease) within 2 months prior to screening;
16) Special diets (e.g. vegan, Atkins) within 2 months prior to study start. A lacto-vegetarian diet is allowed;
17) Severe food intolerance expected to interfere with the study;
18) Regularly drinking > 21 alcoholic units/week (men), or > 14 alcoholic units/week (women); children under 16 more than 0 glasses per week and children older than 16 more than 10 glasses per week.
19) Use of drugs of abuse within the previous 12 months;
20) Blood donation or transfusion within the past 1 month before baseline or CID*s;
21) Self-reported eating disorders;
22) Pregnancy or lactation, including plans to become pregnant within the next 36 months.
23) No access to either phone or Internet (this is necessary when being contacted by the instructor*s during the maintenance phase);
24) Inadequate understanding of national language;
Psychological or behavioural problems, which, in the judgement of the investigator, would lead to difficulty in complying with the protocol.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-11-2013
Enrollment:	530
Type:	Actual

Ethics review

Approved WMO Date:	04-09-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-05-2016
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01777893
CCMO	NL43054.068.13

Study results

Date completed:	08-03-2018
Actual enrolment:	203

Summary results
Trial is onging in other countries