Sweeteners and sweetness enhancers: Prolonged effects on health, obesity and safety

Published: 29-01-2020
Last updated: 10-04-2024

The overall objective of this study is to investigate both the efficacy as well as the safety of combined and prolonged use of S&SEs - as part of a healthy diet - in a population of overweight/obese adults and children.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON54914

Source
ToetsingOnline

Brief title
SWEET

Condition

- Diabetic complications
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, obesity, overweight, Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: University of Copenhagen
Source(s) of monetary or material Support: EU

Intervention

Keyword: Gut microbiota, Insulin sensitivity, Obesity, Sweeteners

Outcome measures

Primary outcome

The two co-primary endpoints are change in the body weight (i.e. efficacy) and change in gut microbiota (i.e. safety) both measured in adults from baseline to year 1.

Secondary outcome

Other secondary endpoints are changes in; anthropometry, risk factors for cardiovascular disease (blood pressure, lipidemia) and type 2 diabetes (glycemia), adverse events (AE), concomitant medication, appetite sensation, and allergenicity.

Study description

Background summary

Dietary overconsumption of energy is suggested to be a main factor driving the obesity epidemic. Sugar is a key nutritional component contributing to the overall energy density of diets, and may therefore promote a positive energy balance. Dietary sugars can be replaced by non-caloric sweeteners and sweetness enhancers (S&SE), however, the long term effects of S&SE intake on metabolic health and safety outcomes are currently unclear. The multicentre SWEET-project has been initiated with the overall objective to examine the likely risks and benefits of using S&SE to replace sugar in the diet in the context of health, obesity, safety. We hypothesize that the prolonged consumption of S&SEs products as part of a healthy diet improves body weight control compared to a healthy diet without consumption of S&SEs products. We also hypothesize that there will be no safety concerns using S&SEs in the long term.

Study objective

The overall objective of this study is to investigate both the efficacy as well

as the safety of combined and prolonged use of S&SEs - as part of a healthy diet - in a population of overweight/obese adults and children.

Study design

To determine if prolonged use of S&SEs in a whole diet approach (foods and drinks) improves dietary health and obesity related risk factors in both adults and children on the long term, a 1 year, randomized, controlled, multicentre trial (RCT) will be conducted. Families where at least one adult (both gender) and one child (both gender) are overweight/obese will be recruited. All adult participants are first treated by a low energy diet (LED) for 2 months with an aim to reduce body weight (minimum 5% weight loss (WL)), whereas children are treated separately with a conventional weight maintenance (WM) diet, without a specific aim for absolute WL. The families are randomized into two different diet interventions for 10 months with or without inclusion of S&SEs products (foods and drinks). The adult participants are weighed (min. 3 times: months 0, 0.5 and 1, and if needed at month 1.5) and supervised during the WL period (min. 2 times: months 0 and 1, and if needed at months 0.5 and 1.5) and throughout the WM period (5 times: months 2, 4, 6, 9, 12). Meeting frequency is reduced towards the end of the study. Children will follow a similar, but less strict time schedule (their participation is preferred but not required for all dietitian meetings). Maastricht university is one of the four institutes where the initial intervention study will take place. The study will also be performed in Denmark, Greece and Spain. In Maastricht, we will also focus on the effects of S&SE intake on: the glycaemic response, adipose tissue function, liver fat accumulation, the satiety response and the gut-microbial composition of children. Furthermore, physical activity levels will be measured in all participants at UM.

Intervention

All participants, (with the exception of the fMRI-substudy control group,) independent of randomization will receive dietary advice based on existing recommendations for a healthy diet, importantly to reduce their consumption of added sugar <10 E%. The families are randomized into two different diet interventions for 10 months and will follow this healthy diet with or without inclusion of S&SEs products (foods and drinks).

Study burden and risks

The study consists of a total of minimum 12 visits (including information meeting and screening) for adults and minimum 6 visits (including information meeting and screening) for children. During the first year, the participants (both adults and children) will have 4 clinical investigation days (CID) and they will be supervised by dietitian-investigators at least every 3rd month (Months: 0, 0.5, 1, 2, 4, 6, 9 and 12). After inclusion, the total duration of

the study for each participant will be 1 year. For adults, at screening a maximum of 10 ml blood is drawn. During CIDs this will be a maximum of 85 ml (study total = maximal 325 ml). For children, no blood samples will be taken during screening. During CIDs, children will donate 20 ml of blood, which is less than 1 ml blood/kg body weight (study total = maximal 60 ml). Participants of the fMRI control group will donate less blood, namely 3 times 30 ml at timepoints 0, 2 months and 12 months. They will also perform dexa scans, hand in feces and complete a 4-day food diary at the beginning and end of the study period.

The benefit of participating in the study for the adult participant is weight loss and the inclusion of obese and overweight children in the intervention is expected to produce a health benefit in terms of weight stability or reduced weight gain during growth. Furthermore, all participants will obtain knowledge about their health status for example blood parameters and support for BMI/BMI-for-age management which may reduce their future susceptibility to diseases associated with overweight/obesity. Potential risks include: bruise formation the days after blood sampling and exposure to minor doses of radiation during body composition analysis (adults only). Adults might experience headaches, dizziness, tiredness and nausea might occur due to the reduced energy and particularly carbohydrate intake (particularly in the first few days) during the weight loss period. The risks of this study on part of the individual participant are evaluated as minimal and offset by the potential gain in knowledge and benefits of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adults:
- Age: 18-65 years.
- BMI: *25.0 kg/m2 (no upper limit).
- For women: Use of contraceptive methods and not wishing/planning to become pregnant the 2 years of the intervention study.
- Regular consumption of sugar-containing/sugar-sweetened products.
- Motivation and willingness to be randomized to any of the two groups and to do the best to follow the given protocol.

Children:
- Age: 6 up to and including 12 years.
- BMI-for-age: >85th percentile (no upper limit).
- Able to participate in CID*s and the dietitian-investigator meeting (month 18) during normal working hours.
- Motivation and willingness to be randomized to any of the two groups and to do the best to follow the given protocol.

fMRI sub-study: control group
- Age: 18 up to and including 65 years.
- BMI: *25.0 kg/m2 (no upper limit).
- For women: Use of contraceptive methods and not wishing/planning to become pregnant the 2 years of the intervention study.
- Regular consumption of sugar-containing/sugar-sweetened products.

Exclusion criteria

Adults:
Based on interview and/or questions, adults with the following issues will be excluded:

- Weight change (increase or decrease) >5% during the past 2 months prior to the study.
- Surgical treatment of obesity.
- Blood donation < 3 month prior to study.
- Change in smoking habits during the last month. Smoking is allowed provided subjects have not recently changed habits. However, smoking status is monitored throughout the study and used as a confounding variable.
- Regularly drinking > 21 alcoholic units/week (men), or > 14 alcoholic units/week (women).
- Intensive physical training (>10 hours of per week).
- Self-reported eating disorders.
- Intolerance and allergies expected to interfere with the study.
- Self-reported use of drugs of abuse within previous 12 months.
- Night- or shift work.
- For women: Pregnancy, lactation.
- Persons who do not have access to either (mobile) phone or internet
- Insufficient communication with national language.
- Regular use of pro-/prebiotics
- Inability, physically or mentally, to comply with the procedures required by the study protocol as evaluated by the daily study manager, site-PI, PI or clinical responsible.
- Subject*s general condition contraindicates continuing the as evaluated by the daily study manager, site-PI, PI or clinical responsible.
- Simultaneous participation in other clinical intervention studies.

Medical conditions as known by the persons:
- Diagnosed diabetes mellitus.
- Medical history of CVD
- Systolic BP above 160 mmHg and/or diastolic BP above 100 mmHg (measured at screening) whether on or off treatment for hypertension.
- Significant liver disease, e.g. cirrhosis (fatty liver disease allowed).
- Malignancy which is currently active or in remission for less than five years after last treatment (local basal and squamous cell skin cancer allowed).
- Active inflammatory bowel disease, celiac disease, chronic pancreatitis or other disorder potentially causing malabsorption.
- Thyroid diseases, except those on Levothyroxine treatment of hypothyroidism if the person has been on a stable dose for at least 3 months.
- Psychiatric illness (e.g. major depression, bipolar disorders).

Medication:
- Use currently or within the previous 3 months of prescription or over the counter medication that has the potential of affecting body weight incl. food supplements.
- Use of antibiotics during the 3 months prior to the start of the study
- Cholesterol or BP lowering medication, if the dose has changed during the last 3 months

Laboratory screening:
If all of the above criteria are satisfied, the adult participant is eligible for a laboratory screening. A blood sample is collected and immediately analyzed for the following exclusion criteria:
- Prevalence of type 2 diabetes (Fasting Glucose * 7.0 mmol/L)
- Low haemoglobin levels (to predict anemia etc.)
- Kidney malfunction (Creatinine)
- Liver malfunction (ALT, AST, Gamma-GT)

Children:
Based on interview and/or questions with the child and the representative adult, children with the following issues will be excluded:
- Intensive physical training (>10 hours of per week).
- Self-reported eating disorders.
- Intolerance and allergies expected to interfere with the study.
- Insufficient communication with national language.
- Inability, physically or mentally, to comply with the procedures required by the study protocol as evaluated by the daily study manager, site-PI, PI or clinical responsible.
- Subject*s general condition contraindicates continuing the study as evaluated by the daily study manager, principal investigator or clinical responsible.
- Simultaneous participation in other clinical intervention studies.

Medical conditions as known by the child and the representative adult:
- Diagnosed diabetes mellitus.
- Other diseases that may influence the study outcomes as evaluated by the daily study manager, site-PI, PI or clinical responsible.

Medication:
- Use currently or within the previous 3 months of prescription or over the counter medication that has the potential of affecting body weight.

fMRI sub-study (all participants):

Based on interview and/or questions, adults with the following issues will be excluded:
- Weight change (increase or decrease) >5% during the past 2 months prior to the study.
- Surgical treatment of obesity.
- Blood donation < 3 month prior to study.
- Smoking
- Regularly drinking > 21 alcoholic units/week (men), or > 14 alcoholic units/week (women).
- Intensive physical training (>10 hours of per week).
- Self-reported eating disorders.
- Intolerance and allergies expected to interfere with the study.
- Self-reported use of drugs of abuse within previous 12 months.

- Night- or shift work.
- For women: Pregnancy, lactation.
- Persons who do not have access to either (mobile) phone or internet
- Insufficient communication with national language.
- Regular use of pro-/prebiotics
- Inability, physically or mentally, to comply with the procedures required by the study protocol as evaluated by the daily study manager, site-PI, PI or clinical responsible.
- Subject*s general condition contraindicates continuing the as evaluated by the daily study manager, site-PI, PI or clinical responsible.
- Simultaneous participation in other clinical intervention studies.

Medical conditions as known by the persons:
- Diagnosed diabetes mellitus.
- Medical history of CVD
- Systolic BP above 160 mmHg and/or diastolic BP above 100 mmHg (measured at screening) whether on or off treatment for hypertension.
- Significant liver disease, e.g. cirrhosis (fatty liver disease allowed).
- Malignancy which is currently active or in remission for less than five years after last treatment (local basal and squamous cell skin cancer allowed).
- Active inflammatory bowel disease, celiac disease, chronic pancreatitis or other disorder potentially causing malabsorption.
- Thyroid diseases, except those on Levothyroxine treatment of hypothyroidism if the person has been on a stable dose for at least 3 months.
- Psychiatric illness (e.g. major depression, bipolar disorders).

Medication:
- Use currently or within the previous 3 months of prescription or over the counter medication that has the potential of affecting body weight incl. food supplements.
- Use of antibiotics during the 3 months prior to the start of the study
- Cholesterol or BP lowering medication, if the dose has changed during the last 3 months

fMRI related exclusion criteria:
- Metal objects such as implants present in the body (e.g. electronic implants, pacemakers, metal fragments in the eyes, skin or body)
- The use of permanent make-up (eyeliners, eyebrows)
- Tattoos on the head, shoulders, breast or neck
- Subjects who do not want to be informed about accidental findings
- Claustrophobia
- Able to taste the difference between sugar-sweetened and sweetener-sweetened beverages during the taste-test at the fMRI specific screening

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-08-2020
Enrollment:	108
Type:	Actual

Ethics review

Approved WMO Date:	29-01-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-02-2022
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
CCMO	NL70977.068.19