PROTOCOL: The INKA trial
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Generalizability of overweight patients with knee osteoarthritis awaiting knee surgery accepting to join a weight loss randomized trial: *Protocol for a cross-sectional study comparing baseline characteristics and propensity of patients accepting/declining enrolment*

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Disclaimers

The views expressed in the submitted protocol are the authors' own and not an official position of the institution or funder.

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Conflict of interest declaration

None declared.

SUMMARY

Background: Overweight is a main and modifiable risk factor for developing knee osteoarthritis (OA). Studies indicates a beneficial effect of weight loss on the symptoms of knee OA. The INtensive diet vs Knee Arthroplasty (INKA) trial is a RCT, which aims to assess weight loss as a non-inferior intervention and/or an alternative to surgical knee arthroplasty in overweight and obese patients suffering from knee OA. As RCTs carry a risk for selection bias and thereby risk for low external validity, comparison of the recruited trial participants and the invited participants, who decline trial participation will enable assessment of the external clinical validity and generalizability of the INKA trial

Objective: The objective of this study is to compare baseline characteristics of overweight knee OA patients accepting vs. declining enrolment in the INKA trial to explore if enrolled patients differ systematically from the declining participants with respect to both measured as well as unmeasured baseline characteristics.

Design: Cross-sectional study collecting baseline characteristics of patients with Knee OA eligible for enrolment in the INKA trial, whether accepting or declining enrolment.

Setting: Potential trial participants will be identified during their routine visits in the orthopaedic outpatient clinics at Copenhagen University Hospital Bispebjerg-Frederiksberg and Copenhagen University Hospital Amager-Hvidovre.

Participants: Adults ≥ 18 years old, obese (BMI≥30 kg/m^2), with an indication for primary knee arthroplasty (unicondylar or total arthroplasty) due to knee OA are included either with consent or refusal to participation in the INKA trial. We will recruit 400 patients in total, 200 in each group.

Measurements: Baseline characteristics for the 2 groups are obtained extracting data from the participants medical records including questionnaires answered by all patients, of which the main is The Oxford Knee Score (the primary outcome for INKA participants).

Data synthesis: We will use standardized difference of the mean (or medians) of continuous variables or the prevalence of dichotomous baseline covariates between INKA and nINKA participants a standardized difference of ≥0.2 to indicate that there might be a meaningful imbalance in the baseline covariate, whereas a standardized difference ≥0.8 will be considered as definitive incomparability. We will also apply the PROC NPAR1WAY procedure (using SAS software) to compute empirical distribution function (EDF) statistics. Finally, we will do a logistic regression to calculate propensity scores to represent the probability that a consent participation based on observed covariates.

Registration: This protocol will be registered with ClinicalTrials.gov before recruiting the participants. Data management (storage, analysis, backup and deletion) will be consistent with standard procedures of Region Hovedstaden.

1.0 INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the world, with a prevalence of around 16% for individuals aged ≥ 15 years, and around 23% for individuals older than 39 years old worldwide. It is found as a leading cause for disability and loss of function with huge costs to the society through lost workdays, early retirement and direct treatment costs (1,2). Knee OA stands for 83% of all OA localizations, with 250 million cases worldwide (3) Many risk factors, like increasing age, acute joint injury, joint deformity and overweight have been identified, where overweight is considered to be a main risk factor for developing knee OA (1,4). The treatment of knee OA is a multi-step process, that starts with physiotherapy, weight loss, non-pharmacological treatment and simple medical treatment as step one, advanced pharmacological treatment as step 2, a last pharmacological attempt on the third step, and ends with joint replacement for the end stage disease if not contra-indicated (5). Given the fact that the obesity is a modifiable risk factor, weight loss is an important part of the treatment strategy of knee OA (5,6). A weight reduction of over 5.1% bodyweight within 20-weeks period is found to significantly improve disability in a systematic review and meta-analysis from 2007 (7). A more recent randomized, 2-phase, parallel-group trial found that a mean 10% weight reduction with a 1-year weight maintenance program improves symptoms in patients with knee OA and a subsequent long term follow-up showed that the use of daily meal replacements or intermittent low-energy diet maintained weight reduction for 3 years (8,9). In the pursuit of reducing the incidence of joint replacement surgery, a cohort study from Australia suggests that the risk of total knee replacement (TKR) can be reduced with weight loss of >7.5% of body weight in adults with overweight or obesity, but no such correlation could be found for total hip replacement (THR) (10). Furthermore, a weight reduction of 10% before TKR surgery is found to improve the general health-related outcomes one year after TKR (11).

The INtensive diet vs Knee Arthroplasty (INKA) trial is a RCT, which aims to assess weight loss as a non-inferior intervention and/or an alternative to surgical knee arthroplasty in overweight and obese patients suffering from knee OA. The INKA study carries by the nature design of a RCT a high internal validity. The external validity of the trial is important to know to convince professionals to change the treatment strategy, as it reflects the generalizability of the trial results.

2.0 RATIONALE

Many systematic reviews of published articles have found a tendency of poor representativeness of external validity (12–15). To interpret the generalizability of a RCT, evaluation of excluded and declining patients is of importance. In the INKA trial, we may speculate that those declining inclusion have a more severe knee problem whereas those who are included may be more concerned about having knee surgery. A comparison of the recruited trial participants and the invited participants, who decline trial participation on a range of clinical, para-clinical, and phenotypical variables will enable assessment of the external clinical validity and generalizability of the INKA trial, which will strengthen the usefulness and relevance of the INKA trial results.

3.0 OBJECTIVE(S)

The objective of this study is to compare baseline characteristics of overweight knee OA patients accepting vs. declining enrolment in the INKA trial, in order to explore if the enrolled patients differ systematically from the declining participants in both measured as well as unmeasured baseline characteristics.

4.0 METHODS

4.1 Study design

The INKA trial is designed as a pragmatic, randomized, parallel-group trial. The trial is designed to compare the effectiveness of a supervised weight loss program to surgical knee arthroplasty in obese individuals with knee OA.

We will use a cross-sectional study design collecting baseline characteristics of patients with knee OA eligible for enrolment in the INKA trial, accepting or declining enrolment in the clinical trial, while recruiting patients for the trial. Data collection starts on the 01.01.2022 and ends with the inclusion of the last patient in INKA study (i.e. anticipated: 01-06-2023) Figure 1.

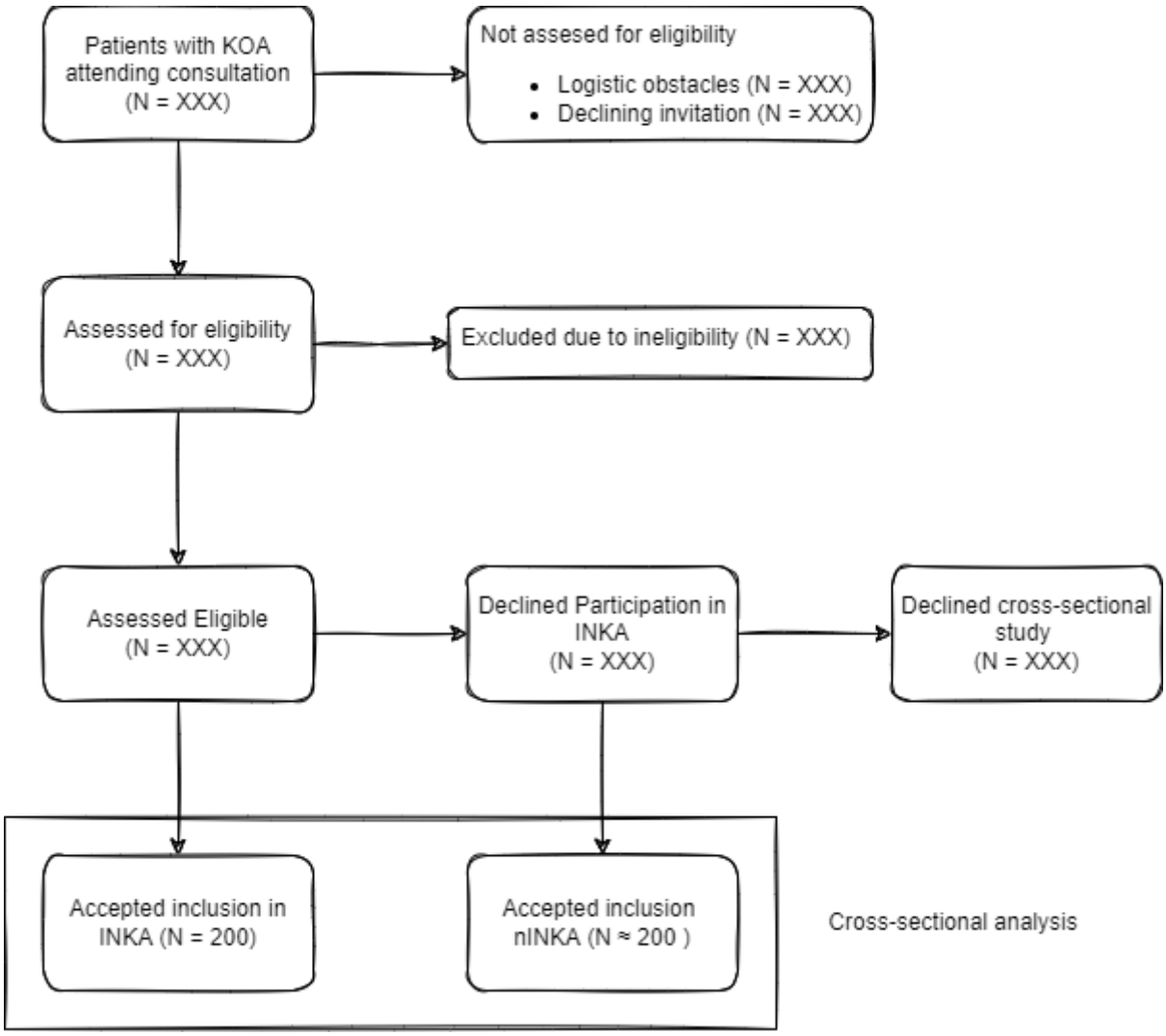

Figure 1- study flow chart

4.2 Setting

Potential trial participants will be identified by an investigator or his/her delegate in the orthopaedic outpatient clinics at Copenhagen University Hospital Bispebjerg-Frederiksberg and Copenhagen University Hospital Amager-Hvidovre. The identification of potential participants may occur during regular clinical visits.

4.3 Participants

All patients found eligible in INKA study (inclusion criteria for INKA) and accepting and declining enrolment in the INKA study are invited to participate in our study. We report the number of patients assessed for eligibility and reasons of exclusion. Study participants will be adults (i.e. at

least 18 years old), have a diagnosis of knee osteoarthritis with an indication for primary knee arthroplasty (unicondylar or total arthroplasty), and be obese (BMI≥30 kg/m^2). An individual will be eligible for study participation if he/she meets the following criteria:

1. Age 18 or more
2. A clinical and radiological diagnosis of knee OA
3. BMI ≥ 30 kg/m^2
4. Motivated for weight loss as by the provided program
5. Signed informed consent.

A possible participant will, however, be excluded from the study if he/she meets any of the following criteria:

1. The scheduled surgery is for revision of an existing prosthesis
2. Planned surgery for more than one knee within the observation period
3. KA indication due to sequelae of fracture(s)
4. Injection of medication or substances in the target knee within 3 months prior to participation
5. Immuno-inflammatory arthritis as cause of the knee OA
6. Current systemic treatment with glucocorticoids equivalent to > 7.5 mg of prednisolone/day
7. Previous or planned obesity surgery
8. Inability to understand or read Danish incl. instructions and questionnaires
9. Any other condition or impairment that, in the opinion of the investigator (or his/her delegate), makes a potential participant unsuitable for participation or which obstruct participation.

4.4 Variables

The following variables will be assessed at baseline independent of their acceptance to participate in the INKA Trial

1. Age
2. Sex
3. Disease duration

4. Height (meters)
5. Body weight (kg)
6. Type of scheduled arthroplasty (Total vs Unicondylar prosthesis)
7. The Oxford Knee Score (OKS)
8. Health outcome and quality of life survey (EuroQoL questionnaire)
9. Use of analgesics
10. The Knee injury and Osteoarthritis Outcome Score (KOOS) – 12 item short form
11. Patient's global assessment of impact of the knee in daily life (PGA)
12. Illness perception questionnaire

Table 1: *Collected baseline characteristics*

Characteristics	Patients accepting INKA group	Patients declining nINKA group	Standardised Difference
Total, no. (%)			
Age, year			
Gender:			
Females, no. (%)			
Males, no. (%)			
Disease duration, years			
Height, meters			
Weight, kg			
Type of scheduled arthroplasty:			
Total knee arthroplasty, no. (%)			
Unicondylar knee arthroplasty, no. (%)			
The Oxford Knee Score (OKS)			
EuroQoL Index			
EuroQoL VAS			
Regular use of analgesics no. (%)			
Paracetamol/acetaminophen			
NSAIDs			
Acetylic acids			
Opiods			
The Knee injury and Osteoarthritis Outcome Score (KOOS) – 12 item short form:			

Pain score			
Function score			
QoL score			
Patient's global assessment of impact of the knee in daily life (PGA)			
Illness perception questionnaire:			
Item 1, score			
Item 2, score			
Item 3, score			
Item 4, score			
Item 5, score			
Item 6, score			
Item 7, score			
Item 8, score			

4.5 Data sources/measurements

4.5.1 The Oxford Knee Score (Primary Outcome)

The Oxford Knee Score (OKS) is a 12-item Patient Reported Outcome questionnaire developed specifically to assess the patient's perspective on the outcomes of knee arthroplasty (KA) with respect to combined pain and physical function. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. Thus, a total score is calculated that ranges from 0 and 48, with 48 indicating the best outcome. The OKS is short, practical, reliable, valid, and sensitive to clinically important changes over time (16).

4.5.2 Health outcome and quality of life survey (EQ-5D-5L)

EQ-5D-5L is a standardized patient-reported instrument for use as a measure of health outcome and quality of life. EQ-5D-5L is designed for self-completion by respondents and is ideally suited for use in surveys.

The EQ-5D-5L consists of a descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Standardized answer options are given (5 Likert boxes) and each question

is assigned a score from 1 to 3. It is simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

The EQ-5D VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled '*the best health you can imagine*' and '*the worst health you can imagine*'. This information can be used as a quantitative measure of health as judged by the individual respondents.

4.5.3 Analgesic use

At clinical outcome assessment visit, the participants will be interviewed by an investigator about their use of analgesics since last visit. The interview will be focused on intake of

1. Paracetamol/acetaminophen
2. NSAIDS
3. Acetylic acids
4. Opioids

The use of these analgesics will be recorded as a 0-3 points Likert scale (0, never; 1, rarely; 2, 2-3 times per week; 3, daily o almost daily).

4.6 The Knee Injury and Osteoarthritis Outcome Score – 12 item short form (KOOS-12)

KOOS-12 is a 12-item measure derived from the original 42-item Knee injury and Osteoarthritis Outcome Score (KOOS) (17,18). KOOS-12 contains 4 KOOS Pain items, 4 KOOS Function (Activities of Daily Living and Sport/Recreation) items, and 4 KOOS Quality of Life (QOL) items (19). KOOS-12 provides scale scores for knee-specific Pain, Function and QOL, along with a summary measure of overall knee impact. KOOS-12 is intended to elicit people's opinions about the difficulties they experience due to problems with their knee and covers aspects of pain, functional limitations and knee-related quality of life.

Reliability, validity and responsiveness of the KOOS-12 scales have been shown to be acceptable (19) and there is evidence that supports the use of KOOS-12 for evaluating joint replacement outcomes (20).

Each item is scored from 0 to 4, left to right, with 0 representing no knee problems and 4 representing extreme knee problems. The separate KOOS-12 Pain, Function and QOL scale scores are calculated using the method of summated ratings, in which item responses in a scale are simply summed. KOOS-12 scale scores are transformed so 0 is the worst possible and 100 is the best possible score.

The KOOS-12 Summary knee impact score is calculated as the average of the KOOS-12 Pain, KOOS-12 Function and KOOS-12 QOL scale scores. A Summary impact score is not calculated if any of the three scale scores are missing. The KOOS-12 Summary impact score also ranges from 0 to 100, where 0 is the worst possible and 100 is the best possible score.

4.6.1 Patient's global assessment of impact of the knee in daily life (PGA)

The participant's assessment of the impact of their knee on everyday life is measured as the response to the question "*Taking into account all the activities you have during your daily life, your level of pain, and your functional impairment, how much does your [left/right] knee impact your daily life*?". A 100 mm visual analogue scale (VAS) will be used as assessment instrument with anchors: 0 = "*No impact*" and 100 = "*Worst imaginable impact*". The actual question asked will be in Danish.

4.6.2 Body weight

The participants body weight is transferred from the medical records of their visit in the orthopaedic outpatient clinic.

4.6.3 Brief Illness perception questionnaire (B-IPQ)

B-IPQ is a generic 9-item questionnaire developed to rapidly assess the cognitive and emotional representations in a variety of illnesses. B-IPQ is a short version of the 84-item revised illness perception questionnaire (IPQ-R) (21). B-IPQ assesses perceptions on the following five

dimensions: Identity, Cause, Timeline, Consequences and Cure-Control. Five of the items assess cognitive illness representations; two of the items assess emotional representations; and one item assesses illness comprehensibility. The ninth item is a free text field in which the respondent can formulate their beliefs about their condition (cause). We will not use this field in our study.

The first 8 items are scored on a 0-3 Likert scale with descriptors (none or extreme) at either end. The B-IPQ scores have shown good test-retest reliability and adequate concurrent, discriminative, and predictive validity amongst patient samples with musculoskeletal disorders and other chronic disorders (22,23).

4.7 Sample size and power considerations

As illustrated below, since the INKA trial will include 200 patients in total (approximately 100 individuals in each group), we anticipate that the present study (comparing INKA vs non-INKA participants) will enrol around 400 patients in total; i.e. the enrolment of the "non-INKA participants" (nINKA) will be recruiting individuals during the exact same time period as the INKA trial is enrolling eligible patients, which is estimated to be:

First Patient First Visit (FPFV): 01-02-2022

Last Patient First Visit (LPFV): 01-07-2023

The present study will be focusing on whether the treated (INKA) and untreated (nINKA) subjects have similar distributions of observed baseline covariates. We will assess whether the propensity score model has been correctly specified: comparing mean's and prevalence's of baseline characteristics using standardized differences.

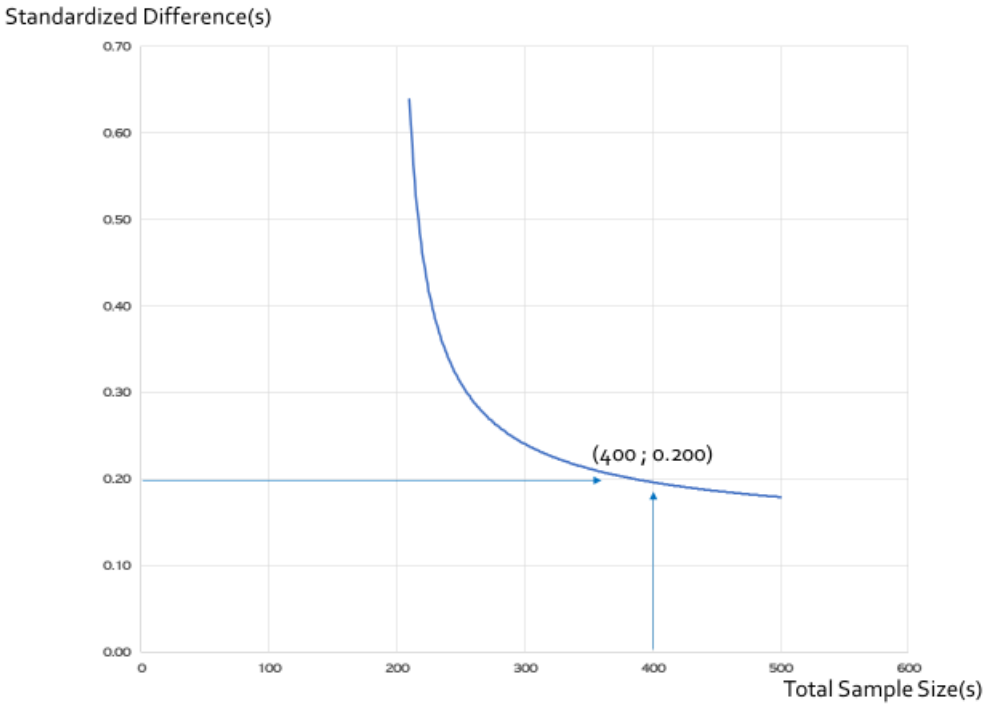

Figure 2 sample size and power considerations

As illustrated in figure 2, we will tentatively assume that a standardized difference between groups could be indicative of a "significant" difference between the groups.

NOTE: In the INKA trial the primary outcome is the OKS at week 38. For the intensive diet intervention strategy to be worthwhile it needs to demonstrate non-inferiority in the OKS score after 38 weeks compared to KA: The minimally important difference estimate applicable for group comparisons in RCTs has been suggested to be 4.84 OKS points. Therefore, we will consider a difference in group mean OKS scores smaller than or equal to 4 OKS points as showing non-inferiority. Based on a recent observational study on 960 KA patients in our region, a standard deviation of 8 OKS points after 38 weeks is expected. Thus, if the true difference between groups is 0 OKS points in a balanced design (1:1 randomization), a one-sided t-test with a significance level of 0.025 will have a power of 90.3% to reject the null hypothesis that the intensive diet intervention is inferior to KA, with a sample size of 86 patients per group (172 in total). To account for attrition (incl. possible "cross-over") in the ITT population it is decided to aim for, and randomize, 200 patients in total, which correspond to - based on the above assumptions - a statistical power of 94% to reject the null-hypothesis that intensive diet is inferior to KA. Power and sample size analyses were conducted using 'proc power' in SAS (SAS Institute Inc., Cary, 968 North Carolina).

4.8 Bias and confounding variables

Confounding is an important concept in epidemiology, because, if presents, it can cause an over- or underestimate of the observed association between exposure and health outcome. The distortion introduced by a confounding factor can be large, and it can even change the apparent direction of an effect. However, unlike selection and information bias, it can be adjusted for in the analysis.

The challenge with observational data (like the proposed comparison) is that the groups (INKA vs nINKA) are not applied randomly, leading to selection bias and thus potentially confounding variables. For example, when we study the impact entering a "promising weight loss trial" before having direct access to a KA, and we compare the outcome among those (who accept the invitation to join the INKA trial) versus all of those who declined, we would potentially have some selection bias, as those who decline are different per definition. The difference can range from baseline characteristics that would influence the outcome; i.e., an advanced disease stage that make any potential delay of the surgery intolerable, or failure/ineffectiveness of previous weight loss trials. Or it can be a characteristic with neglectable effect on the outcome, ie., not having the time or the desire to be included in a clinical trial. Improved confounding variable balance (i.e. de-confounding) between INKA and nINKA groups can be achieved by matching observations from each group based on the propensity score, which in this case would be the probability that a patient accept participation in INKA given the observed covariates.

4.9 Statistical methods

We will use the term balance diagnostics to describe the methods we use to assess whether the distribution of baseline covariates is similar between the two groups (INKA and nINKA, respectively). We designed the study to compare the mean (or medians) of continuous variables or the prevalence of dichotomous baseline covariates between INKA and nINKA participants. We will report the means and/or medians of continuous variables and the distribution of categorical variables for each of the two groups. These crude comparisons (between INKA=treatment and nINKA=control, respectively) will enable an assessment of the comparability of the two groups which will be indicative of the generalizability of the INKA trial (24).

Standardized differences for comparing means and prevalences between groups: For continuous variables, the standardized difference is defined as

$$d = \frac{(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

where *x*'s denote the sample means of the covariate in treated (INKA) and control (nINKA) participants, respectively, while the s^2's denote the sample variance of the covariate in the groups. For dichotomous variables, the standardized difference will be defined as

$$d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1 - \hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1 - \hat{p}_{\text{control}})}{2}}}$$

where *p*'s denote the prevalence or mean of the dichotomous variable in treated (INKA) and control (nINKA) participants, respectively.

By using the standardised differences, it allows for the comparison of the relative balance of variables measured in different units (e.g. age in years with a 'Timed Up and Go'). Unlike t-tests and other statistical tests of hypothesis, the standardized difference is not influenced by sample size. Thus, the use of the standard difference will be used to compare balance in measured variables between treated and untreated subjects. Standardized differences are increasingly being used to compare balance in baseline covariates between groups in the propensity-score matched samples. A limitation to their use is lack of consensus as to what value of a standardized difference denotes important residual imbalance between treated and untreated subjects in the matched sample. While there is no clear consensus on this issue (24), as illustrated in the figure above, we will apply a standardized difference of ≥0.2 to indicate that there might be a meaningful imbalance in the baseline covariate (i.e. possibly poor generalizability); whereas a standardized difference ≥0.8 will be considered as definitive incomparability.

We will also apply the PROC NPAR1WAY procedure (using SAS software) to compute empirical distribution function (EDF) statistics, to statistically test the distribution of the baseline variables. PROC NPAR1WAY provides a summary of the Wilcoxon scores for the analysis baseline variable by class level (INKA and nINKA, respectively). It also displays the one-way ANOVA statistic, which for Wilcoxon scores corresponds to the Kruskal-Wallis test: If the statistical test indicates that there might be difference between groups <0.05 this (P<0.05) leads to rejection of the null hypothesis that the groups are similar.

The propensity score is the conditional probability that a participant accepts the invitation to participate in the INKA (weight loss vs direct surgery) trial given the participant's observed covariates (i.e. baseline measures). The goal of the propensity scoring will be to evaluate whether the data is comparable between the datasets by enabling a balancing observed covariate between individuals in INKA and nINKA, respectively. We will organise our data into a single dataset with all the baseline (potential confounding) variables that we collect in this study, along with the column that indicates whether the patient accepted participation in INKA (i.e. 1='yes' and 0='No', respectively). From this data matrix, logistic regression will be used to develop propensity scores, represent the probability that a patient accept participation in INKA based on the participant's observed covariates. Thus, we will create a logistic regression model in which the baseline variables are used to balance between our groups are used as our predictors of group, our dependent variable (y=1, INKA participation; while y=0, nINKA) in the logistic regression model.

5.0 HEALTH RESEARCH ETHICS

5.1 General considerations

This study only involves questionnaire and medical records and is hence exempt from approval from The Health Research Ethics Committee and can be implemented without permission from the Ethics Committee according to Danish legislation (heath Research Ethics Committee Act § 1, paragraph 1).

Nevertheless, we will conduct this study obeying high health research ethical standards. Prior to screening, all potential trial participants are informed, both orally and in writing, about the purpose of this study, its process, and costs and benefits of participation. All participants are informed of their rights to withdraw from the study at any time without this impacting on any

future investigations and/or treatments at any site or by any of the members of the study group. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing a consent form before trial participation can take place.

5.2 Written information and informed consent

A written consent to participation in the study is given after verbal explanation and consent.

A written information material and informed consent form (ICF) have been prepared (both attached as appendices, files in Danish). By signing the ICF the participant accepts to be contacted by an investigator (or his/her delegate) and authorise him/her to collect relevant information from the participant's hospital record according to Danish legislation (Act on Processing of Personal Data).

The ICF must be signed and dated by the participants prior to participation in the study. A copy of the form is provided to the participants. A note will be made in the patients' hospital records about participation in the study and signed authorisation to collect relevant data from the records.

6.0 REGULATORY STANDARDS

6.1 Notification to the Danish Data Protection Agency

Because the study is carried out at hospital departments, it is regarded as "public" in accordance with the Data Protection Agency guidance. The study will be notified to the Data Protection Agency.

6.2 Participant confidentiality

Participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

With the participant's permission, medical information may be collected for scientific use and shared with his or her personal physician or with other medical personnel responsible for the participant's welfare.

When the data from this study are published, the presentation format will not include names, recognizable photos, personal information or other data which compromises the anonymity of participating participants.

6.3 Quality assurance

All data will be entered into a study database for analysis and reporting. Any data captured electronically will be stored electronically in a separate database according to standard procedures of Region Hovedstaden. Upon completion of data entry, the databases will be checked to ensure acceptable accuracy and completeness. System backups and record retention for the study data will be consistent with Region Hovedstadens standard procedures.

Individuals involved in study evaluations will be trained to perform the efficacy evaluations and activity measurements described in the protocol.

6.4 Financing and insurance information

The study has not received any specific funding. If funding is obtained, the amount and donor will be disclosed on the written information material.

The participants are insured by the Danish Patient Insurance Association. Financing and insurance issues are addressed in the written information material.

7.0 LIST OF APPENDICES

- Questionnaires
- Written information material (In Danish)
- Informed consent form (In Danish)
- Screening log (In Danish)

8.0 REFERENCE LIST

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