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Statistical analysis plan

Title (preliminary):

"Impact of multifactorial lifestyle interventions on psychosocial well-being for children living with obesity."

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Purpose:

To provide an overview of the study design, context, and objectives, as well as to describe how the data management and data analyses will be performed. The statistical analysis plan will be attached as a supplementary document upon submission.

Introduction:

The continuous rise in overweight and obesity among children has become a critical public health issue, due to the associated risks of continuous obesity and development of metabolic disorders in adulthood (1-4). While these consequences may not be apparent until later in life, the obesity-related complications typically seen in childhood are related to attenuated psychosocial well-being (5). Childhood obesity has been shown associated with reduced self-image, poor self-esteem, bullying and stigmatization (2, 3). Furthermore, children and adolescents with obesity have a higher risk of impaired health-related quality of life (QoL) compared with children not characterized as obese (6-8). QoL in children with obesity has shown to be inversely related to the degree of obesity and the physical, social, and school functioning is significantly lower for children with obesity (8-10). In addition, children with obesity have been reported more likely to suffer from depression and anxiety (11-13). Therefore, there is consensus that increasing levels of obesity is a potential risk factor for reduced psychosocial well-being in children and adolescents (14).

While there is agreement that obesity is associated with reduced psychosocial well-being in children and adolescents, studies evaluating how a lifestyle intervention affects psychosocial well-being remain

scarce. Hence, little is known about the long-term impact of obesity treatment on the psychosocial well-being in children with obesity (15).
Considering the high prevalence of impaired well-being in children with obesity, it is necessary to identify effective lifestyle interventions that can handle and improve this issue (16-18).

Objective:

To investigate the long-term changes in psychosocial well-being in children living with obesity after participation in one of two multifactorial family-centered lifestyle interventions. Furthermore, to compare this alteration in psychosocial well-being between the intervention groups and with a reference group of children who were never invited to participate in the interventions. Also, we aim to investigate the effect that is not caused by the weight change by adjusting for this.

Methods:

Design:

This observational cohort study includes children living with obesity in two municipalities in Denmark between August 1st, 2014, and June 30th, 2020. The children were followed until February 1st, 2023, with questions from the Danish National Well-being Questionnaire (DNWQ) obtained from the Danish agency for IT and Learning (STIL), The ministry of Education (19).

Participants:

Children in the intervention groups were 5 to 10 years of age and participated in one of two different family-centered intervention: a one-year intervention and a three-year intervention. Children with obesity living in one of the municipalities and who were never invited to participate in the interventions will act as a reference group for this study.
Obesity is defined by the International Obesity Task Force (IOTF) guideline as a BMI ≥ 30 kg/m^2 adjusted for age and sex (20). If a child's BMI (adjusted for age and sex) was above this cut-off, the parents were notified, and the family invited to participate in the intervention. After acceptance from the parents, the child was referred to the intervention.

Inclusion criteria:

- Inclusion visit between August 1st, 2014, and June 30th, 2020 (figure 1).
- Obesity at time of referral as defined by the IOTF guideline (20).
- Age between 5 and 10 years at inclusion visit.

- A completed DNWQ within a timeframe of 10 months prior to 2 months after inclusion.
- A completed DNWQ at follow-up (1 to 3 years after inclusion visit).

Exclusion criteria:

- Children declining participation in a community-based lifestyle intervention.

The groups

- Two intervention groups:
  - Children with obesity attending the one-year intervention.
  - Children with obesity attending the three-year intervention.
- Non-intervention group/reference group: children with obesity who were not invited to the interventions.

Outcome:

The outcome of the study will be the children's answers to specific questions from the DNWQ regarding the psychosocial well-being related to school. The DNWQ is a national questionnaire used to examine how primary school-children perceive their well-being and learning environment in school. For the children in 0th to 3rd grade, the questionnaire consists of 20 questions where the children express their level of agreement with each question using a three-point Likert scale, ranging from 1 to 3. For children and adolescents in 4th to 9th grade, the questionnaire consists of 40 questions where the level of agreement with each question is rated on a five-point Likert scale, ranging from 1 to 5. The DNWQ is completed annually from January 20th to March 20th and is an integrated part of the teaching for all school children in public primary schools, including special schools and treatment centers. The DNWQ was introduced in 2015.

We selected four primary and three secondary questions as representative of psychosocial well-being. Our focus will be on the four primary questions. The answers at time of inclusion and follow-up will be included in the analyses. At follow-up the answers of the questionnaire completed closest to two years from the time of inclusion, will be prioritized.

All the questions will be dichotomized into: High well-being / Low well-being. Responses 1 and 2 for grades 0-3 and response 1-3 for grades 4-9 will be characterized as low well-being.

Primary outcomes:

The following four questions have been selected as our primary outcomes

1. <u>Question:</u>

   Are you happy with your school?

2. Questions:
   Do you feel lonely at school? (0-3 grade)
   Do you feel lonely? (4-9 grade)

3. Question:
   Is anyone teasing you so that you feel sad? (0-3 grade)
   Have you been bullied this school year? (4-9 grade)

4. Question:
   Does your stomach ache when you are at school? (0-3 grade)
   How often does your stomach ache? (4-9 grade)

Secondary outcomes:

The following three questions has been selected as our secondary outcome

A. Question:
   Are you good at solving your problems? (0-3 grade)
   How often can you find a solution to problems, just by trying hard enough? (4-9 grade)

B. Question:
   Can you concentrate during class?

C. Question:
   Are you good at helping each other in class? (0-3 grade)
   Most students in my class are friendly and helpful. (4-9 grade)

Data sources and study variables:

Data sources:

1. Children who participated in one of the two interventions will be identified by using data from TM-Sund and NOVAX. Data recorded at obligatory health check-ups at the school containing height and weight can also be extracted from TM-Sund and NOVAX. TM-Sund and NOVAX are data capturing tools used by the community health care nurses employed at the two municipalities, respectively. The reference group will be identified in TM-Sund.
2. The DNWQ data will be obtained from the Danish agency for IT and Learning (STIL), The ministry of Education (19).

3. Data on socioeconomic status (SES), immigration, family structure, and psychiatric diagnoses will be obtained from the national Danish registries through Statistics Denmark (21-23).

We wish to include the following co-variables:

- Inclusion outcome (High well-being / Low well-being)
- Age at inclusion (e.g. 5.8 years)
- BMI z-score (24).
- Sex (girl/boy)
- Highest completed Household Education (HHE)
    - "Short": Primary school (UNESCO's International Standard Classification of Education (ISCED) level 1-2).
    - "Middle": Highschool, vocational education, and similar shorter education (ISCED level 3-5).
    - "Long": Tertiary education at bachelor level or higher (ISCED level 6-8)
- Immigration status (Danish origin / Immigrants)
- Disposition for mental illness (lifetime) (yes / no)
- Mental illness, child (lifetime) (yes / no)
- Family structure (single caretakers / non-single caretaker)

Statistics:

All statistical analyses will be performed using Stata/SE 15 (StataCorp LP, College Station, Texas, USA). All statistical tests will be two-sided with a significance level of 0.05.

For the characteristics at time of inclusion:

- Normally distributed data will be analyzed using a one-way ANOVA (several means) and a t-test (two means).
- Non-normally distributed data will be compared using a Kruskal-Wallis test (>2 groups) and a Mann-Whitney U test (2 groups).
- Categorical variables will be analyzed using a Fisher's exact test.

For missing data (education, immigration status, and family-type), a multiple imputation (MI) with chained equations will be utilized to replace missing values with imputed values. Rubin's rule will be applied to obtain overall estimates of 100 imputed datasets.

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We will perform the analyses in several steps:
Firstly, the McNemar test will be used to investigate potential change in psychosocial well-being from time of inclusion to follow-up for each of the dichotomized Questions 1-4 (primary outcome) and Questions A-C (secondary outcomes) in both intervention groups. All questions will be dichotomized into: high well-being/low well-being.
Secondly, a crude and an adjusted logistic regression analysis will be conducted to compare the change in psychosocial well-being between children in the intervention group and the non-intervention group and between the two intervention groups.

The multivariable model will be adjusted for no more than 1 co-variate per 10 observations of the least common outcome.
The co-variates are listed in prioritized order: 1) Inclusion outcome, 2) BMI z-score, 3) age at inclusion 4) sex, 5) highest completed household education, 6) immigration status, 7) disposition for mental illness, 8) mental illness, and 9) family structure.

As an explorative outcome, a logistic regression model adjusted for change in BMI z-score (from inclusion to follow-up) will be performed to remove the potential effect of weight change on the association between exposure and change in psychosocial well-being based on the primary outcomes (Questions 1-4). The BMI z-score observed closest to the included DNWQ at follow-up will be used.

We wish to investigate the stratified effect of BMI z-score, parental level of education, immigration status and disposition for mental illness before we examine their potential for effect modification for the change in psychosocial well-being for each of the primary questions. These analyses will be conducted across comparisons of each intervention group with the non-intervention group and between the two intervention groups.

Figure 1: Lexi diagram for time of inclusion (x-axis), inclusion age of the participants (y-axis), and time points for the DNWQ.

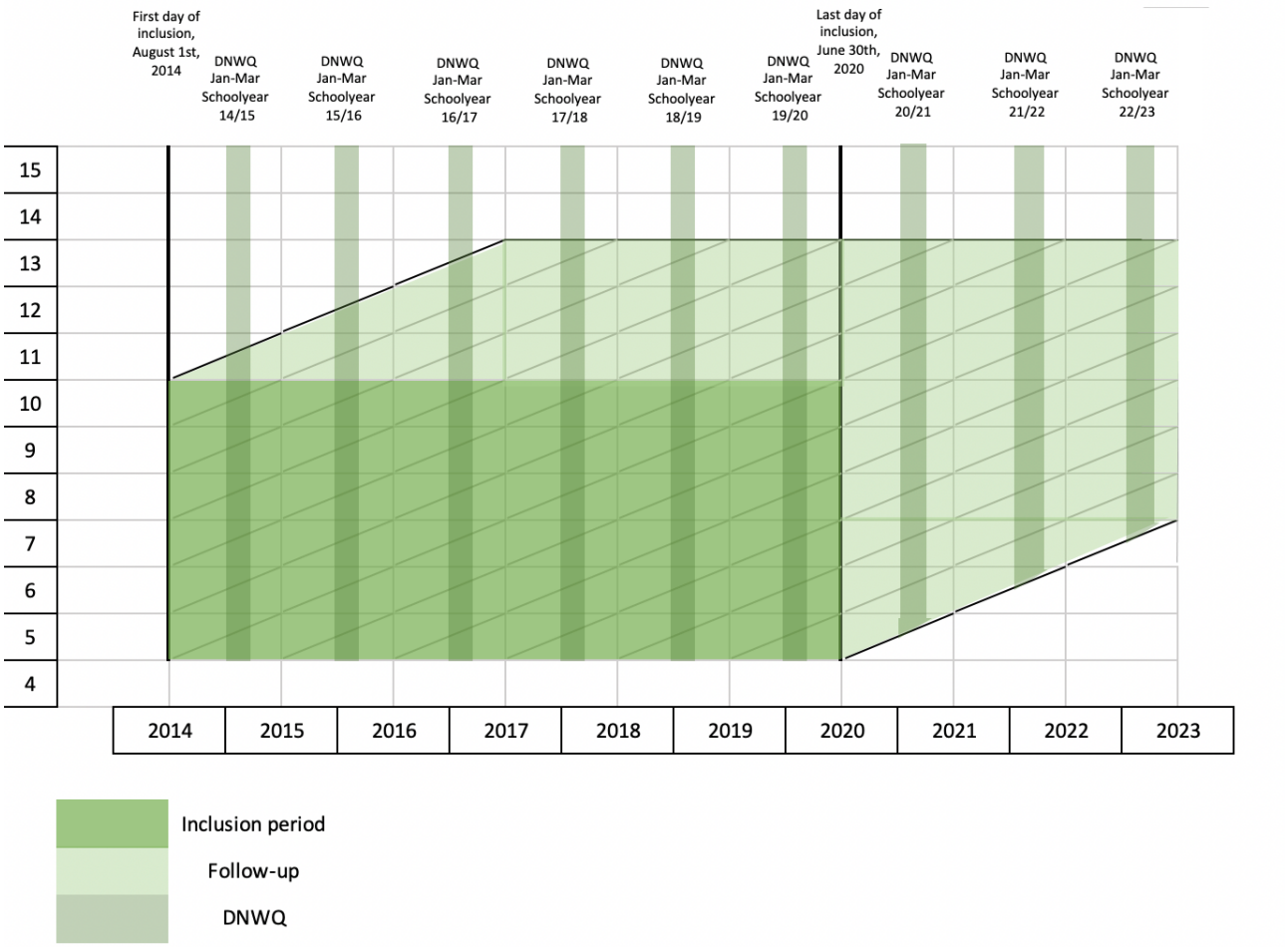

Table 1: Characteristics at time of inclusion, divided by groups:

	One- year Intervention (n =)	Three-year Intervention (n =)	Non-Intervention (n =)
Age (year) at inclusion			
Sex, n (%)			
Boys			
Girls			
BMI z-score			
Highest completed household education, n (%)			
Short			
Middle			
Long			
Family type, n (%)			
Single caretaker			
Non-single caretaker			
Immigration status, n (%)			
Danish origin			
Immigrants			
Parental mental illness (yes), n (%)			
Psychiatric diagnosis, child (yes), n (%)			

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Table 2: The distribution of answers to each of the questions on psychosocial well-being at inclusion and follow-up, divided by groups.

n (%)	One-year intervention		Three-year intervention		Non-intervention	
	Inclusion	Follow-up	Inclusion	Follow-up	Inclusion	Follow-up
Question 1: Are you happy with your school?						
High well-being (yes)						
Low well-being (no)						
Question 2: Do you feel lonely at school? (0-3 grade) Do you feel lonely? (4-9 grade)						
High well-being (no)						
Low well-being (yes)						
Question 3: Is anyone teasing you so that you feel sad? (0-3 grade) Have you been bullied this school year? ? (4-9 grade)						
High well-being (no)						
Low well-being (yes)						
Question 4: Does your stomach ache when you are at school? (0-3 grade) How often does your stomach ache? (4-9 grade)						
High well-being (no/rarely)						
Low well-being (yes/often)						
Question A: Are you good at solving your problems? (0-3 grade) How often can you find a solution to problems, just by trying hard enough? (4-9 grade)						
High well-being (yes/often)						
Low well-being (no/rarely)						
Question B: Can you concentrate during class?						
High well-being (yes)						
Low well-being (no)						
Question C: Are you good at helping each other in class? (0-3 grade) Most students in my class are friendly and helpful? (4-9 grade)						
High well-being (yes)						
Low well-being (no)						

Table 3: McNemar's test and logistic regression analyses for the primary outcomes comparing the change in psychosocial well-being between intervention and non-intervention group:

	Question 1	Question 2	Question 3	Question 4
	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value
McNemar's				
One-year intervention				
Three-year intervention				
Logistic regression model 1[a]				
One-year vs Non-intervention				
Three-year vs Non-intervention				
Three-year vs. one-year intervention				
Logistic regression model 2[b]				
One-year vs Non-intervention				
Three-year vs Non-intervention				
Three-year vs. one-year intervention				

[a]Logistic regression model with the groups as the independent variable, the follow-up outcome as the dependent variable, and adjusted for the co-variable: inclusion outcome.
[b]Logistic regression model with the groups as the independent variable, the follow-up outcome as the dependent variable, and the following covariables: inclusion outcome, age, BMI z-score, sex, highest completed household education, immigration status, disposition for mental illness, mental illness (child), and family structure.
OR: odds ratio; CI: confidence interval.

Table 4: McNemar's test and logistic regression analyses for the secondary outcomes comparing the change in psychosocial well-being between intervention and non-intervention group:

	Question A	Question B	Question C
	OR (95% CI), p-value	OR (95% CI), p-value	OR (95% CI), p-value
McNemar's			
One-year intervention			
Three-year intervention			
Logistic regression model 1[a]			
One-year vs Non-intervention			
Three-year vs Non-intervention			
Three-year vs. one-year intervention			
Logistic regression model 2[b]			
One-year vs Non-intervention			
Three-year vs Non-intervention			
Three-year vs. one-year intervention			

[a]Logistic regression model with the groups as the independent variable, the follow-up outcome as the dependent variable, and adjusted for the co-variable: inclusion outcome.
[b]Logistic regression model with the groups as the independent variable, the follow-up outcome as the dependent variable, and the following covariables: inclusion outcome, age, BMI z-score, sex, highest completed household education, immigration status, disposition for mental illness, mental illness (child), and family structure.
OR: odds ratio; CI: confidence interval.

Table 5: Effect modification analyses of the primary outcomes comparing the change in psychosocial well-being between the one-year intervention and non-intervention groups.

Subgroup	Number of children			aOR (95% CI for the primary outcomes)				P-value for interaction
	Total	Non-intervention	One-year intervention	Q1	Q2	Q3	Q4	
BMI z-score								
< 3								
> 3								
Highest completed household education								
Shorter								
Longer								
Parental mental illness								
Yes								
No								
Immigration status								
Danish origin								
Immigrants								
Full population								

The adjusted odds ratios and 95% intervals (CI) for the primary outcome (Q1-4 at follow-up) displayed, comparing the intervention group to the non-intervention group after adjusting for the following co-variables (excluding the one stratified for): inclusion outcome, age, BMI z-score, sex, highest completed household education, immigration status, disposition for mental illness, mental illness (child), and family structure.
OR: odds ratio; CI: confidence interval.

Table 6: Effect modification analyses of the primary outcomes comparing the change in psychosocial well-being between the three-year intervention and non-intervention groups.

Subgroup	Number of children			aOR (95% CI for the primary outcomes)				P-value for interaction
	Total	Non-intervention	Three-year intervention	Q1	Q2	Q3	Q4	
BMI z-score								
< 3								
> 3								
Highest completed household education								
Shorter								
Longer								
Parental mental illness								
Yes								
No								
Immigration status								
Danish origin								
Immigrants								
Full population								

The adjusted odds ratios and 95% intervals (CI) for the primary outcome (Q1-4 at follow-up) displayed, comparing the intervention group to the non-intervention group after adjusting for the following co-variables (excluding the one stratified for): inclusion outcome, age, BMI z-score, sex, highest completed household education, immigration status, disposition for mental illness, mental illness (child), and family structure.
OR: odds ratio; CI: confidence interval.

Table 7: Effect modification analyses of the primary outcomes comparing the change in psychosocial well-being between the three-year intervention and one-year-intervention groups.

Subgroup	Number of children			aOR (95% CI for the primary outcomes)				P-value for interaction
	Total	One-year intervention	Three-year intervention	Q1	Q2	Q3	Q4	
BMI z-score								
< 3								
> 3								
Highest completed household education								
Shorter								
Longer								
Parental mental illness								
Yes								
No								
Immigration status								
Danish origin								
Immigrants								
Full population								

The adjusted odds ratios and 95% intervals (CI) for the primary outcome (Q1-4 at follow-up) displayed, comparing the two intervention groups after adjusting for the following co-variables (excluding the one stratified for): inclusion outcome, age, BMI z-score, sex, highest completed household education, immigration status, disposition for mental illness, mental illness (child), and family structure.
OR: odds ratio; CI: confidence interval.

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