

# **The AFTER Study: Assessing Future Trajectories of hEalth and well-being among childhood obesity treatment Recipients**

**Short title: The AFTER Study**

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### List of abbreviations

|        |                                                                                                     |
|--------|-----------------------------------------------------------------------------------------------------|
| AFTER  | Assessing Future Trajectories of hEalth and well-being among childhood obesity treatment Recipients |
| BMI    | Body Mass Index                                                                                     |
| CI     | Confidence Interval                                                                                 |
| EDE-QS | Eating Disorder Examination Questionnaire - Short                                                   |
| FMI    | Fat Mass Index                                                                                      |
| FFMI   | Fat Free Mass Index                                                                                 |
| HM     | Holbæk Model                                                                                        |
| HRQoL  | Health-related quality of life                                                                      |
| PedsQL | Pediatric Quality of Life Inventory                                                                 |
| SDQ    | Strengths and Difficulties Questionnaire                                                            |
| SF-12  | Short-Form Health Survey                                                                            |
| WHO-5  | WHO-5 Well-Being Index                                                                              |
| WHR    | Waist-to-Hip Ratio                                                                                  |
| WHtR   | Waist circumference-to-height ratio                                                                 |

# 1. Background

Pediatric obesity is a global public health concern associated with a variety of complications, reduced psychosocial well-being, and adult obesity and related morbidities (1–4). Most patients can be treated with a reasonable short-term effect on weight-related outcomes (5–7). However, relapse after treatment remains common (8,9), and only very few studies have investigated the long-term physical and mental health outcomes following childhood obesity treatment (10–13). Consequently, there is currently limited evidence of the long-term health implications of pediatric obesity treatment.

## **The Holbæk Model for pediatric obesity treatment**

The Children's Obesity Clinic's Treatment Protocol (also known as the "Holbæk Model" (HM)) is a treatment approach for pediatric obesity developed and implemented since 2008 at the Department of Pediatrics at Holbæk Hospital in Denmark (14). The approach is based on the understanding that obesity is a chronic disease, and fat mass is considered a neuro-endocrinologically regulated feature that is influenced by genetic susceptibilities and an obesogenic environment (14).

The treatment protocol is family-centered, and the treatment is designed to individually balance and mitigate obesity-related risk factors in the child's life by providing individually tailored life-style advice in a detailed plan (14). The treatment is provided by pediatricians, pediatric nurses, dieticians, and, if needed, a social worker or psychologist (15). Patients aged <20 years with age- and sex-specific body mass index (BMI) above the 99<sup>th</sup> percentile are eligible for treatment, and they are usually referred by their general practitioner or school nurse (14,16). The children often have related physical or mental comorbidities, and the treatment protocol has no exclusions, e.g., due to psychiatric comorbidity (14). Visit frequency is highly variable, depending on the individual patient's needs. The treatment has no time limit, but patients can remain in treatment only until age 24 (14,16).

## **Previous studies of the Holbæk Model**

Short-term studies of the HM have demonstrated improvements in the degree of obesity and a range of complications (14,17,18), and psychosocial well-being (15) among treated children. These results were found to be independent of socioeconomic position, degree of obesity, disturbed eating behaviors, and a genetic risk score for obesity (19,20). Based on these results, the treatment protocol has been adopted by other hospital-based treatment clinics (21) and community care settings (22) in Denmark. The method is currently implemented at several pediatric departments in Denmark and abroad, and in up to 80 Danish municipalities (23).

However, past studies of the HM did not include post-treatment effects, had no control groups, and/or were performed on smaller sub-populations to investigate specific research aims (14,15,17,18). The existing studies had a maximum follow-up of seven years from treatment initiation, with most patients followed for no more than two years (15,18). Therefore, the long-term developments in BMI, degree of overweight or obesity, body composition, psychosocial well-being, and disordered eating patterns among individuals treated with HM during childhood remain unclear. Given that the HM is widely implemented in pediatric obesity treatment in Denmark and abroad, evidence on long-term health outcomes in individuals treated according to the model is urgently needed.

## 2. Study aims

### 2.1. Overall aim of the AFTER Study

The **overall aim** of the AFTER Study is to investigate the long-term development in physical health and psychosocial well-being among children and young adults treated for overweight and obesity using the HM during a follow-up period of up to 20 years after treatment initiation. The study will examine the risk of multiple physical and mental health outcomes in a large cohort of children and young adults treated for childhood obesity according to the HM, and will compare these risks with relevant reference cohorts where feasible.

The HLFU study consists of two sub-studies:

- 1) An active follow-up study, and
- 2) A register-based follow-up study

This protocol primarily describes the active follow-up study, because the register-based study is not considered notifiable to the Scientific Ethics Committee under Danish Law. The register-based follow-up study is briefly described in **Section 4**.

### 2.2. Aims and hypotheses of the active follow-up study

The **aim** of the active follow-up study is to investigate long-term developments in anthropometric indicators, body composition, indicators of psychosocial well-being, and mental health among children and young adults, as well as disordered eating patterns among young adults, who received childhood obesity treatment according to the HM, during a follow-up period of up to 20 years since treatment initiation. Where feasible, the outcomes will be compared with outcomes in a previously established population-based reference cohort from the same catchment area.

The **specific research aims** are:

#### 1) In children aged 7–17 years at follow-up:

- a. To investigate the distribution of BMI z-score, waist circumference, waist circumference-to-height ratio (WHtR), fat mass index (FMI), fat free mass index (FFMI), height, and the prevalence of underweight, normal weight, overweight, and obesity at follow-up.
  - b. To investigate self- and/or parental-reported health-related quality of life (HRQoL), emotional symptoms, conduct problems, hyperactivity/inattention problems, peer relationship problems, and prosocial behavior at follow-up.
  - c. To investigate changes in the mentioned outcomes over time from treatment initiation to last treatment contact, and to the time of follow-up.
- 2) To investigate how the outcomes differ according to selected child-, family-, and treatment-related factors.

## 2) In young adults aged 18–29 years:

- a. To investigate the distribution of BMI, waist circumference, waist-to-hip ratio (WHR), FMI, FFMI, height, and the prevalence of underweight, normal weight, overweight, and obesity at follow-up.
- b. To investigate self-reported HRQoL, physical, mental, and social well-being, and disordered eating patterns at follow-up.
- c. To investigate changes in the mentioned outcomes over time from treatment initiation to last treatment contact, and to the time of follow-up.
- d. To investigate how the outcomes differ according to selected participant-, family-, and treatment-related factors.
- e. To compare the distribution and prevalence of the mentioned outcomes among young adults treated for childhood obesity to a population-based reference cohort of comparable age recruited from the same catchment area.

The specific **research hypotheses** of the active follow-up study are provided in **Appendix 1**. A protocol resumé is available in **Appendix 2**.

## 3. Methods

### 3.1. Study design

The active follow-up study is designed as an observational cohort study using two cohorts:

1. **A treatment cohort** including children and young adults treated for childhood obesity at Holbæk Hospital, and
2. **A population-based reference cohort** previously recruited from the same catchment area.

Further details on participants, inclusion/exclusion criteria, and recruitment procedures are provided in sections 3.2.1, 3.2.2, and 3.4.

Since the study aims to perform a long-term follow-up of patients treated according to the HM since 2008, a randomized controlled trial is not feasible. Due to the observational design, the study will not conclude on the efficacy of the HM compared with alternative treatment methods or no treatment. Instead, the study will provide a comprehensive description of long-term health and well-being outcomes among individuals treated for pediatric obesity and will investigate the potential influence of factors such as treatment duration and treatment response on these outcomes.

The study will be conducted in two phases:

1. **Phase 1: Internal pilot study (1½ years)**
2. **Phase 2: Main study (approx. 3 years)**

Figure 1 provides an overview of the study design, and the pilot study and main study are further described in sections 3.1.2 and 3.1.3, respectively.

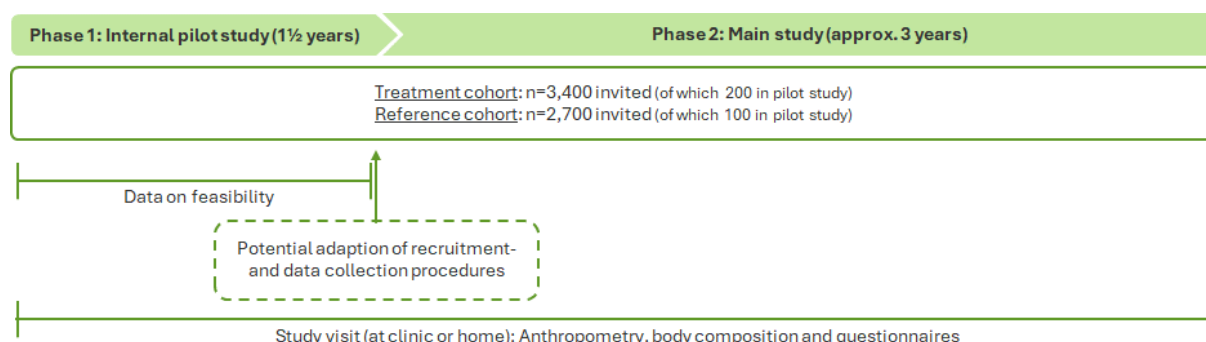


Figure 1: Overview of study design

### 3.1.1. Cohorts

Participants in the study will be recruited from two cohorts previously established by researchers at Holbæk Hospital.

- **Treatment cohort:** Holbæk Hospital has established a research cohort of all children, adolescents, and young adults who were enrolled in pediatric obesity treatment at the Holbæk Hospital Children's Obesity Clinic from March 2007 and onwards. As of December 2024, the cohort included a total of 4,115 patients (14,24). The present study will include the subset of this cohort who initiated treatment from 1.1.2008–31.12.2025, were aged 5–17 years at treatment start, and are aged ≤30 years at follow-up (**expected n≈3,400**) (Figure 1).
- **Reference cohort:** As the reference cohort, we will use a subset of a previously established cohort recruited from the general population in the Capital and Zealand Regions during 2010–2016 (25–27). In the original cohort, 3,811 children and adolescents aged 2–19 years were recruited from schools and municipal dental clinics in 11 municipalities. Data collection took place on school property in a mobile laboratory by trained healthcare staff (25,27) or at scheduled visits to the dental clinic or the school nurse (26). Participation rates varied from 23% to 29% (25–27). Since the reference cohort was established 10–15 years ago, due to their age at follow-up, they will only contribute as a reference group for the young adults in the treatment cohort (aged 18–29 years at follow-up) to ensure comparability with respect to age. For the present study, we will invite the subset of the reference cohort who were aged 5–17 years at enrolment and are aged 18–30 years at follow-up (**expected n≈2,700**) (Figure 1).

### 3.1.2. Phase 1: Pilot study

An initial pilot study will be conducted to test the feasibility and acceptability of the planned recruitment procedures and study logistics, and to assess expected participation rates and resource use in the main study.

The pilot study will be conducted as an internal pilot, meaning it is considered an integrated part of the main study (28). This type of pilot study is preferred when the focus is on estimating expected recruitment rates and resource use, and when only minor adjustments to recruitment- and data collection procedures are expected (28). The pilot will promote the efficiency of the main study, as increasingly requested by methodological experts (28).

For the pilot study, we will invite 200 members of the treatment cohort and 100 members of the reference cohort for an active follow-up visit. At the visit, data will be collected on anthropometry, body composition, HRQoL, psychosocial well-being, and (for individuals aged >18 years) disordered eating patterns. Further details on recruitment and data collection are provided in sections 3.4 and 3.5.

### **3.1.3. Phase 2: Main study**

The main study will be conducted in direct continuation of the pilot using similar procedures and measurement methods. The treatment and reference cohorts will be invited to an active follow-up visit for data collection on anthropometry and body composition, assessment of HRQoL, psychosocial well-being, and (for individuals aged >18 years) disordered eating patterns using validated questionnaires.

Since the outcomes and measurement methods are expected to be the same in the pilot and main phases, data from both phases will be pooled for the final data analysis. Thus, cohort members who participated in the pilot phase will not be re-invited for the main phase. This is in accordance with standard practice for internal pilot studies (28) and will enable efficient use of data, time, and resources for both participants and researchers.

However, based on learnings from the pilot phase, the recruitment procedures and study logistics in the main phase may be slightly adjusted. In this case, an amendment protocol will be submitted to the Scientific Ethics Committee for evaluation.

### **3.1.4. User panel**

Prior to study start, a user panel will be established to provide input to the project, e.g., on how to improve recruitment rates and avoid stigma related to invitation and data collection. The user panel will be invited to provide input and feedback on invitation materials, recruitment procedures, and measurement protocols. Furthermore, after the study is completed, we will ask the user panel for input on how to disseminate the study results to lay audiences. The user panel will consist of approx. 5–7 members of the treatment cohort, and we will seek to include both families with children and young adults.

If changes to invitation materials are implemented based on user panel input, these changes will be described in an amendment protocol submitted to the Scientific Ethics Committee.

## **3.2. Participants**

### **3.2.1. Inclusion and exclusion criteria**

Table 1 provides an overview of inclusion and exclusion criteria (covering both the pilot and main study).

**Table 1. Overview of inclusion and exclusion procedures**

|                    | <b>Treatment cohort<br/>(expected n≈3,400 invited)</b>                                                                                                                                                                                                                                                | <b>Reference cohort<br/>(expected n≈2,700 invited)</b>                                                                                                                                                                                                |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Inclusion criteria | <ul style="list-style-type: none"> <li>• At least one treatment contact for childhood overweight or obesity at the Children's Obesity Clinic at Holbæk Hospital during 1.1.2008–31.12.2025</li> <li>• Age 5–17 at treatment initiation</li> <li>• Age ≤30 years at invitation to follow-up</li> </ul> | <ul style="list-style-type: none"> <li>• Participated in the reference cohort previously established by Holbæk Hospital (25–27)</li> <li>• Age 5–17 at inclusion in reference cohort</li> <li>• Age 18–30 years at invitation to follow-up</li> </ul> |
| Exclusion criteria | <ul style="list-style-type: none"> <li>• Died</li> <li>• Living abroad</li> <li>• Previously declined to be contacted for future research purposes</li> </ul>                                                                                                                                         | <ul style="list-style-type: none"> <li>• Died</li> <li>• Living abroad</li> <li>• Previously declined to be contacted for future research purposes</li> </ul>                                                                                         |

### 3.2.2. Participants in pilot and main study

For the pilot study, we will invite a sample of 100 children (aged 7–17 years) and 100 young adults (aged 18–29 years) from the treatment cohort, and 100 adults (aged 18–29 years) from the reference cohort. This sample size is selected based on sample size calculations showing that it yields a margin of error of maximum ±10 percentage points around the observed response rate in each group (using a 95% confidence interval (CI)) (29). We consider this sufficiently precise to estimate the response rate in the main study, thereby allowing us to plan time and resources in the main study. To ensure that the pilot sample resembles the total cohort, sampling for the pilot study will be stratified by age at follow-up, sex, region of residence, and parental ethnicity and educational level at inclusion. The pilot sample (n=300) corresponds to approx. five percent of the available total sample for the study (n=6,100).

For the main study, we will invite all eligible members of the treatment- and reference cohorts, except those who already participated in the pilot study. Cohort members who were invited to the pilot study but did not participate will be re-invited to the main study unless they have actively declined participation.

### 3.2.3. Withdrawal criteria

Participants will be informed that they may withdraw from the study at any time without providing an explanation. In the event of withdrawal, participants will be asked whether they are willing to explain the reason for their withdrawal, but their response is entirely voluntary. Data provided until the time of withdrawal will be included in the study.

The Primary Investigator has the right and obligation to terminate participation of any child at any time if it is deemed to be in the child's best interest, e.g.:

- If a child's safety or well-being is compromised by further participation
- If the investigator judges that the child does not want to continue his/her participation.

### 3.3. Overview of study procedures

Table 2 provides an overview of the planned study procedures, including recruitment- and data collection. More details on recruitment and consent procedures are provided in section 3.4, and on data collection in section 3.5.

**Table 2: Overview of recruitment procedures and data collection**

| Activity        | Procedures                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recruitment     | <ul style="list-style-type: none"> <li>• Invitation letter in E-boks</li> <li>• If no response within 7 days: Reminder letter in E-boks</li> <li>• If no response within 7 days from reminder: Follow-up phone call and text message</li> <li>• Oral and written participant information</li> <li>• Consent to participate (RedCap (standard) or physical letter)</li> <li>• Registration of non-participation</li> </ul> |
| Booking         | <ul style="list-style-type: none"> <li>• Scheduled individual oral participant information face-to-face before study visit or on telephone</li> <li>• Booking of visit date and time</li> <li>• Reminders via text messages/phone calls</li> </ul>                                                                                                                                                                        |
| Measurement day | <ul style="list-style-type: none"> <li>• Welcome, questions, and registration of informed consent</li> <li>• Physical measurements (anthropometry and body composition)</li> <li>• Questionnaires</li> <li>• Closing questions (e.g., health concerns, future contacts)</li> <li>• Remuneration and thank you for participation</li> </ul>                                                                                |

### 3.4. Recruitment and informed consent

The recruitment and consent procedures are described below.

#### 3.4.1 Identification of participants

The participants in the treatment cohort will be identified through patient records at Holbæk Hospital, and participants in the reference cohort will be identified through data from the Holbæk Study. SDCC will receive a list of CPR numbers of cohort members from Holbæk Hospital, as further described in sections 3.6.1. and 3.6.2.

Via the Central Person Register, SDCC will obtain up-to-date information on participants' full names, address, vital status, and (for participants aged <18 years) information on the CPR numbers and names of custody holders. This information will be used to invite the participants as described below.

#### 3.4.2 Invitations

Participants will be invited via secure digital mail (E-boks), with a follow-up reminder sent one week later. For participants younger than 15 years, the invitation will be sent to the legal guardians; for participants 15–17 years, the invitation will be sent to the E-boks of the adolescent and the legal guardians; and for participants aged 18 years or above, it will be sent to the E-boks of the young adult only (overview in **Table 3**). The invitation letters (**Appendix 3A–3D**) and reminders (**Appendix 4A–4D**) will inform potential participants about the study purpose and what participation involves. Contact details will be provided, allowing potential participants to call or email the

project team for further information, to schedule an appointment, or to decline participation. The invitation letter and reminder will include a link and QR-code to a webpage describing the project (**Appendix 10**), including a brief video presentation (**Appendix 11**), and a contact formula to request further information. The invitation letter will also include a statement that the project team will follow up by telephone if we do not hear from the participant/legal guardians within 14 days of the first invitation.

If we have not heard from the participant/legal guardians within 14 days of the first invitation (seven days from the reminder), we will attempt to reach them by telephone. If there is no answer to the call, a short text message will be sent with information about who called, why, and how to receive more information about the study or decline participation (**Appendix 5A–5B**). If we fail to reach participants/legal guardians after two calls, we will send a physical letter identical to the E-boks reminder (**Appendix 4A–4D**).

Participants are considered lost to contact if none of the abovementioned channels are successful.

The first contact aims to briefly inform potential participants about the project and, if interested, to schedule a time for an oral participant information session at a time and setting that allows for an undisturbed conversation. It will also be possible to book an appointment straight away. If the potential participant does not wish to be contacted, this will be recorded.

### **3.4.3 Participant information and informed consent process**

When initial contact has been established, appointments will be confirmed by a letter in E-boks with written participant information about the study (**Appendix 6A–6D**), including the pamphlet ‘Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt’, released and revised by the Ethical Committee. As a supplementary material, a link to a video presenting the participant information will be provided (**Appendix 12**). The video cannot substitute the written participant information, but can be regarded as an extra service to those that prefer visual presentation. The letter will also include consent forms for participants and/or their legal guardians (**Appendix 7A–7B**) (**Table 3**). For participants aged <18 years, the legal guardians will also receive a power of attorney for one guardian to provide informed consent on behalf of both guardians (**Appendix 8**).

If the adolescent participants aged 15–17 years wish, they will also receive written information about the study in a language and content tailored for their age (**Appendix 6B**).

Prior to enrolment, participants (and their legal guardians for participants aged <18 years) will receive oral information about the study. The provision of oral participant information will be delegated by the Principal Investigator to appropriately trained scientific staff with the required knowledge and communication skills. Oral participant information will be provided during a scheduled face-to-face conversation, by telephone, or via an online meeting by trained study staff experienced in communicating with different target groups. The staff will receive specific training in communicating with children (aged <15 years) and adolescents (aged 15–17 years) and will possess the necessary pedagogical skills to communicate with these age groups appropriately. Information to children (age <15 years) and adolescents (age 15–17 years) will be provided in a language and at a level appropriate to their age and comprehension. Participants will be informed that they have the right to invite a companion or legal guardian to participate in the conversation.

Adequate time will be allowed for participants and legal guardians to ask questions and to discuss any concerns related to study participation. It will be clearly emphasized that participation is entirely voluntary, that participants are entitled to a consideration period of at least 24 hours, and that consent may be withdrawn at any time without justification and without any consequences for the participant. Furthermore, participants/legal guardians with limited proficiency in Danish will be offered adequate support to fully understand the study information.

For children under 15 years, consent will be obtained from their legal guardians (parents or custody holders); for participants aged 15–17 years, consent will be obtained from both the participant and their guardians. For minors with two legal guardians, consent will be obtained from both guardians, and alternatively, one legal guardian can empower the other to decide whether the child should participate (**Appendix 6**) (**Table 3**). It will be possible to fill out the consent forms electronically with digital signature (in REDCap) or on physical paper.

Children will receive oral participant information in a language and at a level suitable for the child's age and comprehension. Parents will be encouraged to discuss the study and implications of participation with their child. The views and expressions of the child will be duly considered. If the project staff judges that the child does not want to participate in the study, the child will not be included.

It is possible to give immediate consent after the oral participant information; however, participants will be informed that they have a right to a minimum reflection period of 24 hours between receiving the information and signing the consent form (**Appendix 7A–7B**).

Recruitment materials will be available in Danish and English to enable recruitment of diverse population groups and ensure inclusivity.

**Table 3** provides an overview of the recruitment and consent procedures and materials for each age group of participants.

**Table 3. Overview of recruitment- and consent materials for each age group of participants**

| Procedure                              | Cohort and age of participants                                                    |                                                                                                                                                                    |                                                                                |                                                                                |
|----------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                        | Treatment cohort                                                                  |                                                                                                                                                                    |                                                                                | Reference cohort                                                               |
|                                        | Children<br>aged 7–14 years                                                       | Adolescents<br>aged 15–17 years                                                                                                                                    | Young adults<br>aged 18–29 years                                               | Young adults<br>aged 18–29 years                                               |
| <b>Invitation letter</b>               | Appendix 3A sent to legal guardians                                               | Appendix 3B sent to adolescents<br>Appendix 3A sent to legal guardians                                                                                             | Appendix 3C sent to young adults                                               | Appendix 3D sent to young adults                                               |
| <b>Reminder letter</b>                 | Appendix 4A sent to legal guardians                                               | Appendix 4B sent to adolescents<br>Appendix 4A sent to legal guardians                                                                                             | Appendix 4C sent to young adults                                               | Appendix 4D sent to young adults                                               |
| <b>Telephone call and text message</b> | Call to legal guardians<br>Appendix 5A sent to legal guardians                    | Call to legal guardians<br>Appendix 5A sent to legal guardians                                                                                                     | Call to young adults<br>Appendix 5B sent to young adults                       | Call to young adults<br>Appendix 5B sent to young adults                       |
| <b>Written participant information</b> | Appendix 6A to legal guardians<br>(6A_pilot: Pilot study;<br>6A_main: Main study) | Appendix 6B to adolescents<br>(6B_pilot: Pilot study;<br>6B_main: Main study)<br>Appendix 6A to legal guardians<br>(6A_pilot: Pilot study;<br>6A_main: Main study) | Appendix 6C to young adults<br>(6C_pilot: Pilot study;<br>6C_main: Main study) | Appendix 6D to young adults<br>(6D_pilot: Pilot study;<br>6D_main: Main study) |

| Oral participant information                           | Provided to children and legal guardians                                                                                                                                                         | Provided to adolescents and legal guardians                                                                                                                                                                                                                | Provided to young adults                         | Provided to young adults                         |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Written informed consent (Electronic or physical form) | Informed consent from both legal guardians (Appendix 7A)<br>or<br>Informed consent from one legal guardian (Appendix 7A) and power of attorney from one legal guardian to the other (Appendix 8) | Informed consent from adolescents (Appendix 7A)<br>and<br>Informed consent from both legal guardians (Appendix 7A)<br>or<br>Informed consent from one legal guardian (Appendix 7A) and power of attorney from one legal guardian to the other (Appendix 8) | Informed consent from young adults (Appendix 7B) | Informed consent from young adults (Appendix 7B) |

### 3.4.4 Advertisement of the study by posters, flyers and social media posts

To increase public awareness about the study and inform potential participants that the study is ongoing, we will advertise the study by posters and flyers (**Appendix 13**) which will be placed in public places, for example supermarkets, shopping centers, education facilities, libraries etc., in areas where a large proportion of the cohort lives (e.g. in Holbæk). Furthermore, the study will be advertised in social media posts encouraging patients previously participating in the Holbæk Study to visit the webpage in order request further information (**Appendix 14**).

## 3.5. Data collection at the study visit

Data collection for the pilot and main study includes anthropometrics, bioimpedance to assess body composition, and questionnaires to assess self-reported psychosocial well-being and disordered eating patterns. The data collection will be described in detail in the ‘Data on health and well-being’ section (**3.5.2**). Measures will be collected during a face-to-face visit at a location as close as possible to the participants’ home. Measurement stations will be established at Steno Diabetes Center Copenhagen, Steno Diabetes Center Zealand at several locations in Zealand, and if needed at suitable municipal sites close to participants' homes, e.g. the community health center. Participants who live far from measurement locations or who prefer this option will be offered a home visit. During the pilot phase, quantitative and qualitative data will be collected to assess feasibility and acceptability of the recruitment- and data collection procedures, as described below in the ‘Pilot data’ section (**3.5.1**).

### 3.5.1 Pilot data

The following data will be collected in the pilot study to investigate the feasibility and acceptability of recruitment and data collection logistics:

- *Semi-structured interviews (minimum n=10)* will be conducted with individuals accepting participation (face-to-face interviews, preferably conducted immediately after the study visit) and individuals declining participation (telephone interviews, conducted at a time of the participant’s preference). We will strive to achieve variation across age, sex, and sociodemographic characteristics.
- *Observations and field notes* will be collected during at least 20 study visits by a staff member not conducting measurements on that day.
- Participants declining participation by phone or text message will be asked for their *reason for declining*. It will, however, be stressed that providing a reason is optional.
- We will *systematically document* the following indicators: number of invited participants, contact attempts to invited participants (letter, phone, text message), cancelled or rescheduled

visits, no-shows, on-site visits vs. home visits, participants providing informed consent, completing measurements and questionnaires, staff time expenditure, and direct costs.

### 3.5.2 Data on health and well-being

Physical measurements at the study visit include height, weight, waist circumference, and hip circumference (30), and bioimpedance analysis (BIA) to assess body composition (31,32). Standing height will be measured three times to the nearest millimeter with a stadiometer. Sitting height will be measured three times to the nearest millimeter with a stadiometer (33,34). Waist circumference will be measured three times to the nearest millimeter by a non-elastic measuring tape at the level of the umbilicus. Hip circumference will only be measured in participants aged  $\geq 18$  years. It will be measured three times to the nearest millimeter by a non-elastic measuring tape at the largest circumference around the buttocks. Weight and body composition will be measured twice using the Tanita BC-420MA body composition analyzer, with the participant standing barefoot on the scale for approximately 30 seconds each time. A very low electrical current passes through the body, which is safe and imperceptible. The device estimates body composition from the current resistance. Females will be asked about the possibility of pregnancy prior to measurements and those who are planning pregnancy or who are pregnant will be excluded from measurement of body composition and anthropometry. The information will be stored in RED-Cap.

Measurements will be performed by trained personnel, taking age, potential discomfort, and potential language barriers into account. All measurements will be performed in a private undisturbed setting, without interruptions. Participants will be wearing light clothing during measurements. Participants can choose whether they wish to be informed of their results.

BMI z-scores will be calculated using national reference data covering the age groups 0–45 years (35), and weight categories will be determined using the extended international (IOTF) BMI cut-offs for children (36) and BMI cut-offs defined by WHO for adults (37).

At the face-to-face visit, self-administered questionnaires for measuring psychosocial well-being and (for participants aged  $\geq 18$  years) disordered eating will be distributed. Time will be allocated to completing the questionnaire on tablets, with potential support from staff. If participants prefer, it can also be completed at home. The measures will include validated questionnaires suited for the specific age groups, which are comparable to Danish norms and/or other large Danish surveys:

For children (aged 7–17 years):

- The *Strengths and Difficulties Questionnaire* (SDQ) (38) measures socio-emotional skills in five domains, a total score for overall difficulties based on four domains, and an impact score. The SDQ will be completed by parents for children aged 7–11 years, and by children themselves for ages 12–17 years (39).
- The *Pediatric Quality of Life Inventory* (PedsQL) measures health-related quality of life (40). Children and/or their parents have previously completed this questionnaire during treatment (for the treatment cohort) or at baseline (for the reference cohort) (41,42). The PedsQL will be used in the parent-report version for children aged 7–12 years, and in the self-report version for participants aged 13–17 years (43).

For adults (aged 18–29 years):

- The *Short-Form Health Survey* (SF-12), a 12-item questionnaire measuring physical and mental health across eight domains (41).
- The *WHO-5 Well-Being Index* assesses subjective psychological well-being (42).
- The *PedsQL* for young adults and adults (18-25 years) (44).
- The *Eating Disorder Examination Questionnaire - Short* (EDE-QS), a questionnaire on disturbed eating (45).

Copies of questionnaires are available in **Appendix 9**.

In addition to the abovementioned validated scales, the questionnaire will contain questions on background information (**Appendix 9**), including:

- Participation in other obesity treatments
- Use of weight loss medication (for adolescents and adults)
- Reasons for discontinuing obesity treatment(s)
- Experience of participating in obesity treatment(s)
- Pubertal stage (for children and adolescents)

To avoid re-inviting participants and collecting redundant data, we expect that data collected in the pilot phase can be included in the final dataset for the main study. If substantial changes are made to study procedures or measurement methods based on the pilot phase, we will carefully consider which data can be validly included in the final dataset, and all decisions will be transparently disclosed in study publications, in line with recommendations for internal pilot studies (28).

At the end of the study visit, participants will be offered an invitation letter for a separate research project conducted by Holbæk Hospital with more extensive clinical, biochemical and physiological examinations. This project is not a part of the present protocol but is approved separately by the Regional Scientific Ethics Committee of Region Zealand (project no. SJ-104). It will be clearly emphasized to participants that receiving the invitation letter is entirely voluntary, and that participation in the separate research project is likewise completely voluntary.

### 3.6. Data from other sources

#### 3.6.1. Research data from the “Holbæk Study”

The present study will utilize data on the treatment- and reference cohorts which have previously been collected by the Children’s Obesity Clinic at Holbæk Hospital as part of the research study the “Holbæk Study” (24). The Holbæk Study is approved by the Regional Ethics Committee of Zealand (SJ-104) and is registered at Clinical Trials.gov (NCT009928473) (24).

For cohort members who participated in the Holbæk study, we will use the following data: Dates on background (such as contact, birth date, sex, parental educational level and employment, ethnicity), physiology and anthropometry (e.g. pubertal stage, height, weight, BMI, waist circumference, hip circumference, body composition assessed by bioimpedance), health-related quality of life (assessed by PedsQL), parental BMI, receipt of pharmacological obesity treatments and other obesity treatments, and lifestyle variables (e.g. diet and physical activity). These

data are necessary to fulfill our research aim of investigating how the outcomes in the treatment- and reference cohorts depend on prior child-, family-, and treatment-related characteristics.

From the Holbæk Study, we will also receive the CPR-numbers of participants in the treatment- and reference cohorts who participated in the Holbæk Study, their full names and latest recorded postal address and telephone number. These data are necessary to invite the participants to the present study via E-boks and conduct register linkages (further information on registry linkages below, section 3.6.3).

The abovementioned data will be transferred from Holbæk Hospital to Steno Diabetes Center Copenhagen pursuant to Section 10 of the Danish Data Protection Act. The data transfer will be governed by a data transfer agreement, and data will be transferred using a secure FTP-server. All data will be handled and stored in accordance with the General Data Protection Regulation and the Danish Data Protection Act.

### **3.6.2. Patient record data on the treatment cohort**

For the full treatment cohort (n=4,115 individuals), we request to receive patient record data from the patient records at Holbæk Hospital. The patient records cover the time period from the patient's first contact at the Children's Obesity Clinic (earliest date: 1 Jan 2008) to the last treatment contact (latest date: 31 Dec 2025).

The following data from patient records are requested:

- CPR-number
- Full name of participant and (if aged <18) his/her parents
- Last recorded postal address and telephone number
- Whether the patient or (if aged <18 years) his/her parents have requested not to be contacted for research purposes
- Dates of contact at Holbæk Hospital
- Background information, such as sex, birthdate, parental education and employment, ethnicity
- Information on anthropometry and body composition, such as height, weight, BMI, hip- and waist circumference, body composition results, pubertal stage
- Assessments of health-related quality of life.

These data are necessary to:

- Identify the subset of the treatment cohort fulfilling the inclusion criteria for the present study (cf. Table 1, Inclusion criteria)
- Ensure that we do not contact patients who have requested not to be contacted for research purposes (cf. Table 1, Exclusion criteria)
- Invite the potential participants for the present study following the procedure described in section 3.4.1. and 3.4.2.
- Identify the sub-sample to be invited for the pilot study (enabling selection of a sub-sample stratified for age, parental education, and ethnicity, as described in section 3.2.2.)
- Compare characteristics of those who agree to participate in the study with those who are invited but do not participate, with respect to demographic and socioeconomic characteristics, anthropometry, body composition, and health-related quality of life (non-response analysis).

To fulfil these purposes, it is necessary to receive information on the full treatment cohort, (n=4,115), and not only for those who provide informed consent for the present study. We therefore request to receive these patient record data without informed consent, pursuant to the Danish Health Act section 46(1).

The data will be transferred from Holbæk Hospital to Steno Diabetes Center Copenhagen. The transfer will be governed by a data transfer agreement, and data will be transferred using a secure FTP-server.

For patients who provide consent to participate in the study, the informed consent authorizes the Principal Investigator, the sponsor, the sponsor's representatives, and any relevant regulatory authorities to obtain direct access to the participant's medical records, including electronic health records, to access health-related information necessary for conduct of the research project, quality control, monitoring, audit and inspection purposes.

### **3.6.3. Register data for the active follow-up study**

The data collected in the active follow-up study will be supplemented with data from national health- and population registers. The register data will be used to minimize respondent burden and will also be used to compare socioeconomic and demographic characteristics of participants and eligible non-participants, i.e. analysis of non-response bias.

Register data will be obtained on the following covariates: socioeconomic characteristics, family type, country of origin, child psychiatric and somatic comorbidity, receipt of pharmacological obesity treatments and other medications, and relevant parental disease history. These variables will be derived from the National Patient Register, the National Prescription Register, the Medical Birth Register, and several socioeconomic databases in Statistics Denmark (including BEF, UDDA, INDH, AKM and FALK).

To enable analysis of non-response bias, these register data will be obtained on all eligible participants in the treatment- and reference cohorts, regardless of informed consent for the active follow-up study. To ensure patient confidentiality, all linkages of data to national register data will be done on pseudonymized data at a secure server at Statistics Denmark where identification of individual participants is not possible.

## **3.8. Collection and storage of materials in a biobank**

There will be no collection or storage of materials in a biobank. The sampled data consists solely of non-biological materials.

## **3.9. Statistics**

### **3.9.1 Sample size calculations**

We have conducted sample size calculations to assess the recruitment rates required in the main study, focusing on BMI z-score (children) and BMI (adults) as outcomes. Two calculations were conducted:

- 1) Change in BMI z-score within the treatment cohort

- Research question: What is the change in BMI z-score from last treatment contact to follow-up, and how does this vary by sex, age, socioeconomic status, and treatment response?
- Calculation: To detect a 0.25-point change in BMI z-score (minimally clinically relevant difference) with 90% power (paired t-test), assuming SD = 0.88 and correlation = 0.7, 81 participants are needed. For stratified analyses across  $\geq 3$  subgroups, 243 participants are required ( $\approx 7\%$  participation among 3,400 invited).

## 2) Difference in BMI at follow-up between treatment and reference cohorts (young adults)

- Research question: How does BMI differ between the treatment- and reference cohorts, and how does this vary by sex, age, socioeconomic status, and baseline BMI z-score?
- Calculation: To detect a 1.3-point difference in BMI (considered clinically relevant, 5% of BMI=26.5) with 90% power (independent t-test), assuming SD=4.6, a sample size of 265 in each group would be required. For stratified analyses across  $\geq 3$  subgroups, 795 participants in each group are required, corresponding to a response rate of  $795/2700 = 29\%$  in the treatment cohort and  $795/2500 = 32\%$  in the reference cohort.

### 3.9.2 Statistical analyses

The long-term outcomes of BMI, BMI z-scores, weight categories, waist circumference, waist circumference-to-height ratio (for children), waist-to-hip ratio (for adults), and psychosocial well-being will be analyzed using descriptive statistics and multivariable regression models suited for observational cohort studies. Most statistical analyses will be performed separately for children and adults.

For children (7–17 years), within-person changes will compare first and last treatment visits to outcomes at follow-up. Multivariable regression will examine the influence on potential predictors, such as treatment duration, treatment response and age at treatment initiation, on study outcomes. For adults (18–29 years), analyses will include treatment- vs. reference cohort comparisons, addressing selection bias via enrollment pattern analysis and inverse probability weighting (43). Descriptive statistics will be used to describe and compare the distributions and prevalences of relevant covariates (e.g. socioeconomic status, country of origin, somatic and psychiatric comorbidities, and receipt of pharmacological obesity treatments) in the treatment cohort and the reference cohort. Within-person changes for adults will be assessed by comparing outcome measures from baseline to the outcome measures at the follow-up visit. To account for differences in covariates between cohorts, we will employ multivariable regression models and propensity score techniques. We will report standardized outcomes which will be standardized to the observed distribution of the covariates in the treatment cohort e.g. treatment duration. All analyses will account for the time since baseline (for treatment cohort: treatment initiation; for reference cohort: date of inclusion).

Subgroup analyses will target patients who have not been seen at the Holbæk Hospital clinic within defined time intervals to evaluate long-term outcomes post-treatment, acknowledging individualized visit intervals and treatment duration.

The conduction of statistical analyses will be supervised by a senior statistician at SDCC. The analysis plan will be uploaded to ClinicalTrials.gov before data closure, i.e., the last patient visit.

## 4. The register-based follow-up study (brief description)

In addition to the active follow-up study, a register-based follow-up study will be conducted as part of the overall HLFU study.

The aims of the register-based study are:

- 1) To investigate the risk of selected somatic and psychiatric diagnoses, patterns of health care and medication utilization, body mass index (BMI) at end of compulsory school, school-related wellbeing and absence, and educational achievements in a cohort of children and young adults treated for pediatric overweight and obesity using the HM, compared to a reference cohort from the general population, and compared to a matched register-based population of children with obesity.
- 2) To investigate how the mentioned outcomes differ according to selected child-, family-, and treatment-related factors.

The study populations for the register study include: A) The treatment cohort of children and young adults treated for childhood obesity at Holbæk Hospital (n=4,115); B) A population-based reference cohort sampled from the Danish Population Register, matched to the treatment cohort on age and sex; and C) A reference cohort of children with obesity sampled from the National Child Health Register (46).

To investigate the abovementioned research aims, these study populations will be linked with multiple national registers, including the National Patient Register, the Psychiatric Central Research Register, the National Health Services Register, the National Prescription Register, the Population Education Register, the Academic Achievement Register, the Student Register, and the Employment Classification Module. Information on school-related well-being will be obtained from the National Survey of Well-being, and data on school absence will be obtained from the Board of IT and Learning.

All register linkages will be performed on the secure research server of Statistics Denmark. All analyses are performed on pseudonymized data.

## 5. Ethical conduct of the study

### 5.1. Ethical approval and study registration

The study will be conducted in accordance with the ethical principles set out in the Declaration of Helsinki. Ethical approval will be obtained from the Scientific Ethics Committee of the Capital Region. The study will be registered in ClinicalTrials.gov as an observational study before enrolment of the first participant.

### 5.2. Underage study participants – justification and precautions

The justification for including children in the study is in line with the Committee Act (Komitéloven §19, stk. 3), which concerns studies not involving medicine, as the project can only be conducted in the described age group to answer the study objectives. Also, as further elaborated above in section 4.3., the study poses minimal risk of harm to participants, as all measurements are non-

invasive and associated with minimal discomfort or risk. The study addresses an important evidence gap regarding the long-term implications of treatment for childhood obesity, and the results of the project are expected to substantially benefit future treatment of children and adolescents with obesity. Therefore, we assess that the benefits outweigh the potential harms.

### 5.3. Participant discomforts and risks

Measuring anthropometry and body composition involves a risk of weight stigmatization and negative body focus. We will therefore take great care to minimize potential discomfort and stigmatization for participants. Written communication will be prepared carefully and with guidance from the user panel to ensure a respectful and non-stigmatizing tone, and personnel will be carefully trained in the communication of weight-related issues (47). We will use a people-first language and the Danish word for overweight (“personer med overvægt”). Participants may choose whether to receive their anthropometry and body composition results. Participants may wear light clothing during the examination.

Bioelectrical impedance analysis (BIA) is a standard measurement tool for assessing body composition. BIA is a non-invasive and radiation-free method that estimates body composition by applying a very low-level alternating electrical current. The procedure is considered safe for healthy individuals and poses no known health risks. No ionizing or non-ionizing radiation is involved. Potential contraindications include individuals with implanted electronic devices (e.g., pacemakers) and, as a precautionary measure, pregnant participants. These groups will be excluded from this measurement. The measurement is painless, and participants will be informed about the nature of the procedure and its safety profile in the consent form.

The clinically responsible physician, Peter Rossing, will review anthropometry and body composition measures for potential abnormal values. In accordance with Danish guidelines (48), participants with severe overweight (BMI>30) or severe underweight (BMI<16) will be advised to contact their general practitioner (GP) for further diagnostic evaluation. Since the questionnaires for measuring psychosocial well-being and disordered eating are population-based risk assessment tools, not diagnostic tools, and they are completed confidentially by participants, scores on SDQ, PedsQL, SF-12, and EDE-QS will not be used for referral. However, in accordance with recommendations from the World Health Organization, adult participants with a raw score of <13 on WHO-5, indicating a high likelihood of depression, will be advised by staff onsite to contact their general practitioner (49). If, during the follow-up visit or at any other point during the study, participants display concerning behavior or symptoms, such as suicidal thoughts or self-harm, they will be advised to contact their general practitioner or, in case of acute concern, will be referred to a psychiatric emergency service.

### 5.4. Benefits of the study and risk-benefit evaluation

The potential benefits of this study significantly outweigh the minimal risks involved. Participants face minimal risks, mainly minor discomfort during measurements and potential feelings of weight-related stigma. These potential risks will be mitigated through respectful communication, trained staff, private, undisturbed measurement settings, and the exclusion of individuals with contraindications for BIA.

The study addresses a critical knowledge gap on long-term outcomes of pediatric obesity treatment. Findings will inform clinical practice and health policy, benefiting future patients and society. The data collected in this study will also enable future cohort or clinical studies to supplement and extend the knowledge gained. Given the negligible physical risk and substantial expected benefits, we judge the study to be fully ethically justified.

## 6. Handling of personal data

Data from the study visit, including clinical measurements and questionnaire data, will be collected and stored directly using RedCap (a secure application for building and managing online surveys and databases). This mode of storage is in accordance with the General Data Protection Regulation for data handling.

Documents that identify the participant (such as the signed informed consent document) will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing and/or monitoring by the appropriate regulatory authority. All information obtained during the study will be handled in accordance with local regulations and the General Data Protection Regulation. The study is registered in Privacy, the research register of the Capital Region.

Transfer of personal data from Holbæk Hospital to SDCC for research purposes will take place pursuant to the Danish Data Protection Act Section 10 (for research data), and the Danish Health Act section 46(1) for patient record data (see section 3.6.1 and 3.6.2 for more details). A detailed data transfer agreement governing SDCC's use of data will be signed between the parties. In addition, a collaboration agreement will be executed. All analyses will be performed on de-identified data.

There are no plans to transfer personal data outside Denmark for the purposes of the present study.

## 7. Financing

The HLFU study was initiated by SDCC, Head of Department for Prevention, Health Promotion and Community Care, Professor Ulla Toft, and the Center for Childhood Health, Head of Programmes and Development Nina Geiker. The study purpose, design, and methods were determined by investigators at SDCC. Funding for the register-based follow-up study (April 2026 – March 2029) and the pilot phase of the active follow-up study (April 2026 – September 2027) has been obtained from the Center for Childhood Health. The grant amounts to DKK 12,038,060, of which DKK 9,947,577 is awarded to SDCC, and DKK 2,090,482 is awarded to the Children's Obesity Clinic, Holbæk Hospital. Funding for the main phase of the active follow-up study will be applied from the Center for Childhood Health in Summer 2027, based on the learnings from the pilot phase.

The study funds will be transferred to a research account at SDCC, which is subject to public audit. The funding will cover the salaries of project staff, project materials, and the project's general execution. The researchers declare that they have no financial interests in the study's results or any economic affiliation with any of the project partners.

## 8. Remuneration

Participants will be offered a remuneration of 300 DKK (40 EUR) as a flat fee to compensate for inconvenience, time, and potential travel costs. Given the modest amount of this remuneration, it is unlikely to influence the decision to provide informed consent and is therefore deemed ethically appropriate.

## 9. Publications

Results from the study, whether positive, negative, or inconclusive, will be summarized and published in peer-reviewed scientific journals and presented at scientific conferences, e.g., the European Childhood Obesity Group Congress. Authorship of publications will be decided in line with the Vancouver guidelines. The AFTER Study, including reporting, authorship, and subsequent use of data, will be carried out in full compliance with the [Danish Code of Conduct for Research Integrity — Ministry of Higher Education and Science](#).

## 10. Insurance

The participants are insured in accordance with the Law: “Lov om arbejdsskadeforsikring” (cf. LBK nr 376 af 31. marts 2020) by the current insurance at Steno Diabetes Center Copenhagen. During the study, the participants will be covered by law: “Lov om klage- og erstatningsadgang inden for sundhedsvæsenet” (cf. LBK no. 995 14/06/2018 [www.retsinformation.dk](http://www.retsinformation.dk)).

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