BMJ Open

Intensive Dietary and Activity Counselling (IDAC) study: a randomised trial following infants genetically susceptible to type 1 diabetes to prevent β-cell dysfunction and islet autoimmunity – a study protocol

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To cite: Aronsson CA, Hummel S, Eriksson Hallström E, *et al*. Intensive Dietary and Activity Counselling (IDAC) study: a randomised trial following infants genetically susceptible to type 1 diabetes to prevent β-cell dysfunction and islet autoimmunity – a study protocol. *BMJ Open* 2026;**16**:e112056. doi:10.1136/bmjopen-2025-112056

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-112056).

Received 07 October 2025
Accepted 28 April 2026

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ABSTRACT

Introduction Type 1 diabetes is a chronic autoimmune disease, preceded by the presence of islet autoantibodies, a preclinical state defined as islet autoimmunity. Several environmental exposures have been associated with the initiation of islet autoimmunity but the triggers remain largely unknown. Rapid growth and weight gain during childhood are some of the exposures that have been proposed to promote islet autoimmunity. A high intake of protein and animal milks in early childhood is consistently associated with increased later obesity. Growth during early childhood is directly related to dietary intake and especially protein intake and this association has been linked to increased risk of islet autoimmunity and type 1 diabetes. The Intensive Dietary and Activity Counselling (IDAC) study aims to determine whether a healthy lifestyle counselling from age 3 months to age 2 years improves β-cell health in children with increased risk for islet autoimmunity.

Methods and analysis The IDAC study is a randomised trial (1:1 allocation) with two parallel groups, aiming to enrol 1244 children at increased genetic risk of type 1 diabetes before the age of 4 months. Participants will be randomised to either the control or intervention group based on the child's current breastfeeding status (currently breastfeeding or no longer breastfeeding). The intervention group will receive regular dietary and physical activity counselling. The primary outcome is β-cell health at 36 months, assessed by fasting and stimulated proinsulin-to-C-peptide ratio. Secondary outcomes include accelerated growth during infancy, overweight at 36 months, and time to development of persistent confirmed islet autoantibodies or type 1 diabetes. Growth measures, blood samples for serological markers, stool samples, dietary intake (nutrients and food group data) and questionnaire data will be collected regularly throughout the study period. Regression models will be used to estimate the effects of the intervention on the primary outcome.

Ethics and dissemination The research protocol was approved by the Swedish Ethical Review Authority (dnr 2024-05217-01, 2024-08622-02, 2025-01759-02). Study findings will be presented at national and international conferences, submitted for publication in peer-reviewed journals, shared on social media and disseminated through patient-education materials.

Trial registration number NCT06670625.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised clinical trial in a genetically high-risk paediatric population.
⇒ Comprehensive longitudinal data collection, including growth, dietary intake, physical activity level and metabolic biomarkers, will allow investigation of potential mechanisms linking early-life exposures to β-cell health.
⇒ Randomisation stratified on breastfeeding status, ensuring equal numbers of breastfed infants in the intervention and control arms.
⇒ The exploratory nature of the primary endpoint.
⇒ Challenges in dietary compliance monitoring, participants' adherence issues, the control group may change their diet and the potential for biases.

INTRODUCTION

Type 1 diabetes is a chronic autoimmune disease, preceded by the appearance of autoantibodies against β-cell antigens such as insulin autoantibody (IAA), glutamic acid decarboxylase autoantibody (GADA), insulinoma antigen-2 (IA-2A) or Zink transporter (ZnT8A), indicating the onset of an autoimmune process against the insulin-producing β-cells in the pancreas.[1 2]

Type 1 diabetes susceptibility is primarily defined by genetic factors within the human leucocyte antigen (HLA) complex on chromosome 6 and it is estimated that the genetic contribution via certain genotypes accounts for between 40% and 50% of the contribution to the disease risk.[3 4] Individuals with these specific HLA DR-DQ genotypes confer markedly elevated risk for type 1 diabetes, which can be further refined by adding 45 risk SNPs.[5] In addition, several environmental exposures (toxicants, pathogens, diet and psychosocial factors) have all been correlated with the initiation of islet autoimmunity, but the triggers remain largely unknown.[6]

Rapid growth and weight gain during childhood are some of the exposures that have been proposed to promote islet autoimmunity by creating an increased demand of insulin from the β-cells, leading to greater stress on the β-cells and making them more susceptible to an autoimmune attack due to other triggering factors.[7] Adipokines and inflammatory cytokines secreted from the adipose tissue as well as the metabolic overload induced by circulating nutrients have been discussed to play a role in the pathogenesis of autoimmune disorders by their impact on immune-cell function and activation.[8 9]

There is a consistent association between childhood overweight and obesity and subsequent increased risk of islet autoimmunity and progression to type 1 diabetes.[10–13] In addition, specific growth patterns during early childhood have been associated with islet autoimmunity and progression to type 1 diabetes in genetically at-risk children.[14]

It was stated in a systemic review that higher protein intake, especially of animal origin, in children younger than 18 months of age is linked to higher body mass index (BMI).[15] Growth during infancy and early childhood is directly related to dietary intake and especially dietary protein intake. Animal protein, especially from sources like cow's milk, has been associated with an increased risk of type 1 diabetes.[16] Higher protein intake in infancy may lead to increased insulin-like growth factor 1 (IGF-1) concentrations, which can contribute to accelerated growth and potentially increase the risk of type 1 diabetes.[17]

A growing body of evidence supports a beneficial role of physical activity and muscle strengthening during the first year of life on improved health development during later life, including prevention of overweight and obesity.[18 19] In a multinational clinical trial, differences in BMI and risk for being overweight were seen in the study population followed during the COVID-19 pandemic.[20] Children who were followed during the pandemic had a higher risk of increased BMI and being overweight compared with children who were followed before the pandemic. These findings indicate the importance of changes in physical activity and dietary behaviour in response to the containment policies implemented during this specific period and its impact on early BMI development. This finding was strengthened by observations of lower rates of exclusive breastfeeding, more time spent on restrictive devices, and less access to toys during the pandemic.[18 21] In addition, higher levels of physical activity have also been linked to improved glucose homeostasis and reduced risk of progression to type 1 diabetes in young children.[22 23]

AIMS AND HYPOTHESES

Study hypothesis

Lifestyle influences the susceptibility to islet autoimmunity by increasing β-cell vulnerability. If this holds, training in a 'healthy β-cell' lifestyle from infancy will reduce β-cell vulnerability and the likelihood of islet autoimmunity.

Study aims

The primary objective is to determine whether an Intensive Diet and Activity Counselling (IDAC) from age 3 months to age 2 years improves ß-cell health in children with increased risk for islet autoimmunity.

Secondary objectives are to determine whether IDAC is associated with infant and early childhood growth and body composition and to determine whether IDAC reduces the cumulative incidence of islet autoantibodies or type 1 diabetes in childhood.

METHODS AND ANALYSIS

Study design

The IDAC study is a randomised study (1:1 allocation) with two parallel groups enrolling children at moderate increased (7%–10%) genetic risk of type 1 diabetes (figure 1). The duration of study participation will be from 3 months of age until 3 years of age. There will be general dietary and activity counselling at baseline visit (age 13–17 weeks) for all enrolled children. Children randomised to the intervention arm (IDAC+) will receive additional counselling at the 6, 12 and 24 months clinic visits.

Study setting

The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) is a European platform that identifies infants with an elevated genetic risk of developing type 1 diabetes via newborn screening with the intention to establish an infrastructure for primary prevention trials. A total of five countries are members of the platform (Germany, Sweden, Belgium, Poland and the UK). Mothers are informed about genetic screening for type 1 diabetes within the GPPAD-02 (ASTR1D) study.[3] If the custodial parent(s) sign the informed consent, a blood sample for analysis of genetic risk is taken either as cord blood or a venous sample after birth.

In Sweden, the ASTR1D screening is done in all five maternity clinics at the academic hospitals in Skåne, located in the most southern part of Sweden. Up to date, more than 40 000 newborn children have been screened since start of the programme. The region of Skåne has a relatively high population density with 121 people per km^2 and a total of 1.4 million inhabitants, with a higher

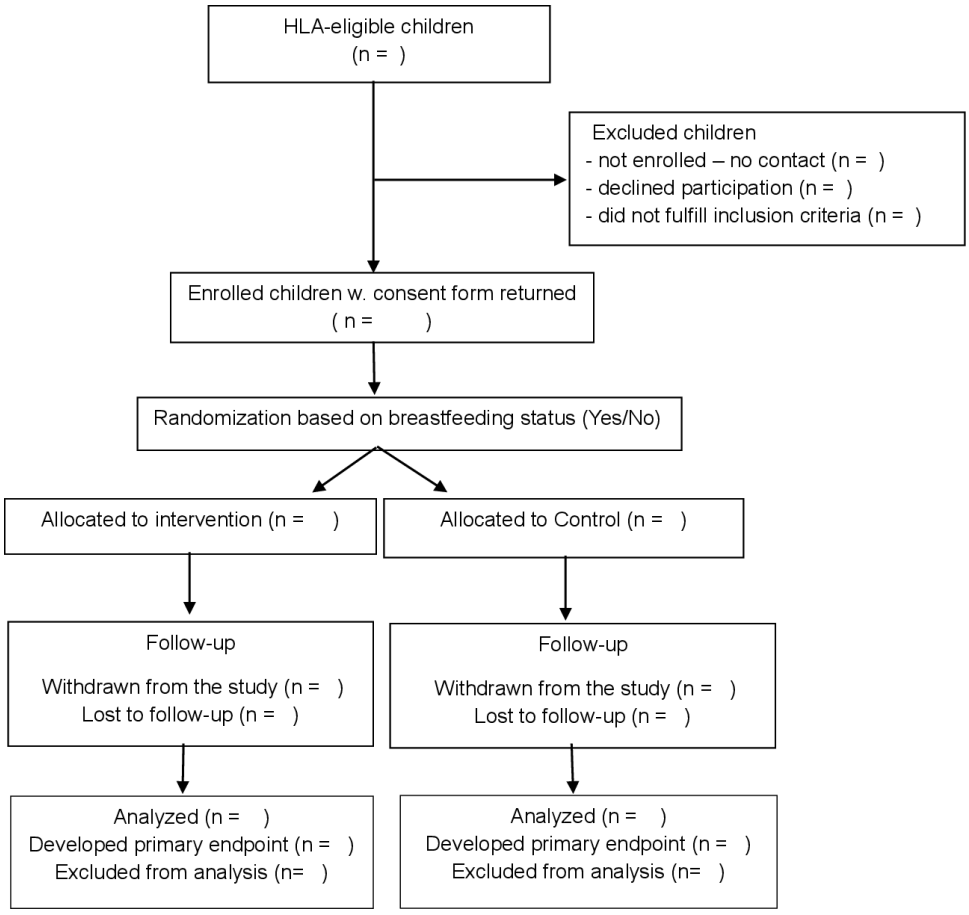

Figure 1 Flow chart illustrating enrolment and randomisation in the Intensive Dietary and Activity Counselling study. HLA, human leucocyte antigen.

proportion of foreign-born residents (24%) compared with the national average for Sweden. The number of births per year is around 14 000 and approximately 5000–6 000 000 infants are born per year with a written consent for genetic screening.

The IDAC study is currently conducted in Sweden, but the study protocol is planned to be implemented in GPPAD-centres in Germany and Belgium.

Participants and recruitment

Prior to enrolment to the IDAC study, the screening results of the GPPAD-02 study will be discussed with the custodial parents of these children. The information will be given in an on-site visit or remote (eg, by phone call or video conference), by an experienced study nurse.

The IDAC study will be introduced to the custodial parent(s) of potential participants. During this discussion, the inclusion and exclusion criteria will be reviewed, and the opportunity to participate in the study will be explained. Parents will be provided with written informed consent document and given the opportunity to ask questions regarding the consent process or study participation (online supplemental material). Families will have sufficient time to consider participation. If the family decides to enrol, the parents will be asked to sign and date the informed consent form prior to the baseline visit.

It is estimated that approximately 5% of the population screened for HLA genotypes associated with moderate increased (7%–10%) risk for type 1 diabetes are eligible for the study. Eligible children are born as of 1 January 2025. The planned recruitment period is 36 months, from March 2025 to March 2028. In parallel, children screened and found to have HLA genotypes associated with the highest risk (>10%) to develop type 1 diabetes related autoantibodies are recruited to other clinical trials within the GPPAD consortium. These children are not eligible for the IDAC study.

Eligibility criteria

Infants eligible for the study must meet all of the following criteria at randomisation:

- Have an increased genetic risk (7%–10%) to develop β-cell autoantibodies by the age of 6 years. The definition for increased genetic risk is for children without a first-degree family history of type 1 diabetes: having HLA DR3/DR4-DQ8, DR4-DQ8/DR4-DQ8 or DR4-DQ8/DR4-DQ7 rs6901541 C/T genotype and:
- for males having a genetic risk score greater than or equal to 18.2 but excluding those who are eligible for the current GPPAD clinical trial.

- for females having a genetic risk score greater than or equal to 14.5 but excluding those who are eligible for the current GPPAD clinical trial.
- For children with a first-degree family history of type 1 diabetes, all DR3/3, DR4-DQ8/DR4-DQ7 or DR4-DQ8/x where x is none of the following protective alleles: DRB1*1501, DQB1*0503, DRB1*1303 will be included regardless of genetic risk score.
- The age of the infant at time of enrolment should be 3.0 months (13 – 17 weeks).
- Written informed consent signed by the custodial parent(s).

Exclusion criteria

Infants who meet any of the following criteria will be excluded from participating in the study:

- Any medical condition, concomitant disease or treatment that may interfere with the assessments or may jeopardise the participant's safe participation in the study, as judged by the investigators.
- Preterm delivery <36 weeks of gestation.
- Any condition that could be associated with poor compliance.
- Diagnosis of diabetes prior to recruitment or randomisation.
- Current use of any investigational drug.

Intervention

Healthy dietary advice will be provided by a dietitian, via in-person meeting or online meetings with the primary caretakers, following current national infant nutrient recommendations.

The main messages cover:

- support continued breastfeeding (if the child is still being breastfed at time of randomisation) up until 12 months of age.
- if no breastfeeding is possible or terminated—review and advice on type of infant formulas used as an alternative to breastmilk.
- limit intake of milk and milk products during the first 2 years of life (max 150 mL/day, 5 g protein)
- review and advice on types of commercial gruels and/or porridges that contain less milk powder.
- support daily vitamin D supplementation up to the age of 2 years.

The amount of energy from dietary protein (E%) should not exceed 15% in the diet in children below 2 years.[24] This will be monitored via repeated 24 hours recalls and discussed with parents to the children randomised to the intervention arm. From the age of 12 months, these families will get access to a closed website with tailored advice and recipes. Other social media platforms will be used to improve adherence to the intervention protocol between clinic visits.

Outcomes

The primary outcome is β-cell health at the age of 36 months assessed by the fasting and stimulated proinsulin–to–C-peptide ratio (PI:C) during an oral glucose tolerance test (OGTT)[25] and the Disposition Index relative to insulin resistance (Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)).[26]

Secondary outcomes are accelerated growth during infancy, overweight at the age of 36 months and the elapsed time from randomisation to the development of persistent confirmed islet autoantibodies or type 1 diabetes diagnosis according to ADA criteria.[27]

Study duration and participant timeline

The study duration per participant will be a minimum from 4 months of age up to 3 years of age. The maximum duration per participant will be from 3 months of age up to 6 years of age. In addition to the baseline/randomisation visit, the intervention period includes 7 clinic visits 3 months apart, followed by a follow-up period that includes a maximum of four annual clinic visits (figure 2).

Sample size

The IDAC study aims to enrol 1244 children. We expect a withdrawal rate of 15% during the follow-up period of the study and similar to what we experienced in with previous dietary intervention studies. Approximately 1000 children will complete the study.

The sample size calculation is based on the numbers needed to test the hypothesis that IDAC will improve β-cell health in children with a moderate genetic risk to develop type 1 diabetes.

The trial numbers have been determined for 80% power to detect a 10% difference in PI:C ratio in the treated group who will receive intensive dietary and physical activity advice at a two-tailed significance of 0.05. The expected mean PI:C-peptide in children used to determine the trial numbers is 0.49 (SD 0.32).

Accounting for the assumed 15% loss to follow-up, a total of 1244 children would have to be included in the study. The sample size calculations were performed with: 'Georgiev G.Z.', 'Sample Size Calculator', (online) Available at

https://www.gigacalculator.com/calculators/power-sample-size-calculator.php URL (Accessed Date: 10 June 2024).

Randomisation

All children whose custodial parents give consent for participation and who fulfil the inclusion criteria will be randomised. The randomisation was stratified by the child's current breastfeeding status (currently breastfed vs not breastfed or breastfeeding stopped) due to different growth patterns during early infancy[28] and study site (three study sites) (figure 3). Within each site, approximately 60% of the participants are allocated to the breastfeeding group and 40% to the non-breastfeeding group, reflecting anticipated enrolment proportions. Within each breastfeeding stratum, participants are randomised 1:1 to either the intervention or control arm, ensuring balanced treatment allocation across groups. The

Visits	Baseline – Randomization (13 – 17 weeks)	Intervention Quarterly visits (6 – 24 m)	Follow-up Annual visits (36 – 72 m)
Procedure			
Informed consent	X		
Eligibility criteria	X		
Questionnaires			
- demographics	X		
- maternal pregnancy information	X		
- psychosocial status	X	X (12, 24 m)	
- infant feeding habits	X	X	
Anthropometrics	X	X	X
- weight, height	X	X	X
- skinfold measurements		X	X
Physical activity			
- questionnaire	X	X	
- accelerometer		X	
Dietary intake data			
- 24HR		X	
- Food Frequency Questionnaire		X (12, 24m)	X (36 m)
Blood samples	X	X	X
Stool samples		X (6, 12, 18 m)	
IDAC+			
- Dietary & Physical activity advice	X	X	

Figure 2 A summary of the schedule of procedures for the IDAC study. 24HR, 24 hours recalls; IDAC, Intensive Dietary and Activity Counselling.

randomisation master file remains with the study coordinator. The randomisation assignment is communicated to the parents by a study nurse using sealed envelopes that are opened together with the parents at the enrolment/baseline visit.

Data collection

Growth measures

At all clinic visits, height, weight and mid-upper arm circumference are measured on the participants (figure 2). Weight will be measured in grams (g). The infant will be weighed lying on his/her back without clothes and diaper. Children old enough to stand on a scale will be measured in light clothing on a scale. Length/height will be measured in centimetres (cm). Length will be measured on all children up to 2 years of age. It is measured with the child lying on his/her back from the bare heels to the top of the head avoiding toe pointing. From the age of 2 years, the standing height will be measured with the child standing barefoot. BMI-for-age Z-scores will be determined using WHO Child Growth Standards. Mid-upper arm circumference is measured (in millimetres) on the child's right arm, at the midpoint between his/her shoulder and elbow.

At the 6-month clinic visit and onwards, skinfold measures are conducted, with the aim to estimate the participants body fat. At least two measurements are taken at each location (triceps, biceps, suprailiac, and subscapular) using a Harpenden skinfold calliper. All measurements are taken on the right side of the body. The final value recorded is the average of the two most representative measurements.

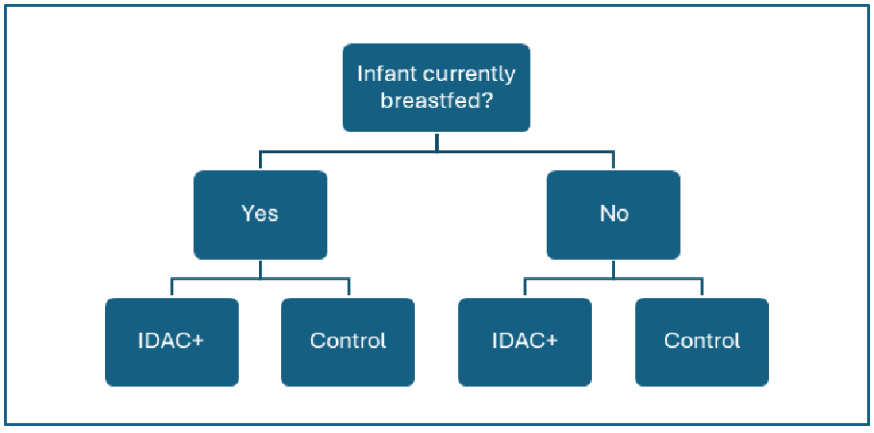

Figure 3 Randomisation scheme, stratified by the child's current breastfeeding status at time of enrolment visit. Definition of breastfeeding (BF) status at the baseline/enrolment visit (at 13–17 weeks of age): Yes (exclusively BF or predominantly BF), NO (never BF, BF stopped, predominately fed with infant formula). IDAC, Intensive Dietary and Activity Counselling.

In addition to the above-described measurements, information about the child's birth weight and weight/length measured at the 6-week child healthcare clinic visit are collected at the baseline visit and entered in the eCRF.

Serological markers

Whole blood (venous) is collected at all visits. The samples are analysed for several serological markers such as islet autoantibodies: IAA, GADA, islet antigen-2 (IA-2A) or zinc transporter 8 (ZnT8A), transglutaminase autoantibodies (tTGA) and thyroid autoantibodies (TPO-A) using automated multiplex Antibody Detection by Agglutination-PCR (ADAP) assays.[29] Positive samples will be confirmed using radioligand binding assay.[30] Aliquots will be stored in −80°C for future omics analysis.

Assessment of ß-cell dysfunction

The ratio of PI:C ratio has been proposed as a biomarker of ß-cell dysfunction and is associated with progression to type 1 diabetes.[31] Proinsulin is quantified using the U-PLEX Human Proinsulin assay from Meso Scale Diagnostics LLC (Rockville, USA) according to the manufacturer's instructions. The C-peptide quantification is done by Klinisk kemi, Labmedicin Malmö on the instrument Cobas Pro (Roche Diagnostics, Basel, Switzerland).[32] PI:C ratio is calculated at the 6, 9, 12, 18 and 24-month clinic visits. At the age of 36 months, an OGTT is performed, and fasting and stimulated proinsulin/C-peptide is measured.

Assessment of vitamin D levels

25(OH)D concentrations will be monitored at every visit for all participants. In the intervention group, daily vitamin D supplementation will be encouraged. If 25(OH)D concentrations fall below 75 nmol/L (30 ng/mL), the study centre will be notified and in turn inform the family and advise to introduce a daily vitamin D supplement or increase the dose or frequency of the supplement. In the control group, families will be informed about vitamin D insufficiency if the 25(OH)D concentrations fall below 50 nmol/L (20 ng/mL).

Stool samples

Studies have shown that an imbalance in gut microbiota may be closely related to the progression of overweight/obesity in children.[33 34] Factors such as mode of delivery, early infant diet and breastfeeding duration can cause changes in the gut microbiota, which in turn can increase the risk of paediatric overweight/obesity. An early difference in faecal microbiota in children may predict the occurrence of overweight. Stool samples will be collected at home and stored at −20°C in the freezer of the family. Samples are brought to the clinic in connection with the 6, 12 and 18-month clinic visits and stored in −80°C until analysis.

Dietary intake assessment methods

Information about early infant feeding is collected at all visits using questionnaires (breastfeeding duration, infant formula use, age at introduction of solid foods).

The primary aim of dietary assessment during the intervention phase is to investigate if the intervention group differs in nutritional intake compared with the controls. Primarily, a 24-hour dietary recall (24HR) is used. The 24HR is a structured interview intended to capture detailed information about all foods and beverages consumed by the participant in the past 24 hours. A trained dietitian conducts an interview with a parent (face-to-face or via online meeting). The interview consists of an uninterrupted recall of the food intake, followed by detailed questions such as asking about the exact quantities consumed and finally a review of all foods that were previously recalled. The dietitian asks guiding questions that are not directly related to the food intake, but are meant to refresh the parent's memory, such as the circumstances or location of consumption. This often helps to remember additional foods that could have otherwise been omitted. Portion size images and drawings will be used to allow the parent to determine the child's food intake as accurately as possible. The reported data are linked to a nutrient composition database. Nutrient intake from foods and beverages, as well as food group intake can be determined. The 24HR will be conducted on 6, 9, 12, 18 and 24-month clinic visits for all participants.

In addition, a Food Frequency Questionnaire consisting of 35 commonly consumed types of foods or food groups, grouped into five categories (meat and fish, dairy products, cereals, vegetables and legumes, miscellaneous foods) will be used to collect information about protein sources. The questionnaire will be distributed as a survey on the 12, 24 and 36-month clinic visit.

Follow-up of autoantibody positive participants

Participants with confirmed positive serological markers are followed within the study according to the study protocol. Participants with confirmed positive islet autoantibodies are followed according to protocol but with the addition of haemoglobin A1c (HbA1c) and random plasma glucose tests at the scheduled visits up to 2 years of age. After 2 years of age, when the visits in the IDAC study are reduced to once a year, additional visits with HbA1c and plasma glucose will be performed every third month. Participants with ≥2 confirmed positive islet autoantibodies will receive a blood glucometer to be used at home. Continuous glucose monitoring can be used if higher random glucose or HbA1c is measured, since OGTT is usually not performed in children below 3 years of age. All islet autoantibody positive participants will receive information about type 1 diabetes symptoms. After the IDAC study ends, children with positive confirmed islet autoantibodies will be offered continued follow-up until 15 years of age in our iT1D study (NCT06676566).

Participants with persistent positive confirmed tTGA will be referred to a paediatric gastroenterologist for management at the clinical discretion of their primary provider. Finally, participants with confirmed positive TPO-A will be sampled for Thyroid-stimulating hormone (TSH). If abnormal values, children will be referred to follow-up care at the paediatric clinic.

Parental and child questionnaires

Parental questionnaires are used at the baseline visit consisting of sociodemographic questions (country of birth, marital status, education, employment status, physical activity), maternal prepregnancy and pregnancy information (birth weight, gestational age, mode of delivery, maternal/paternal weight and height, gestational diabetes, infections during pregnancy, maternal smoking and alcohol consumption) and psychosocial status. A child questionnaire distributed at all visits contains information about infant feeding, special diets/food allergies, diseases and symptoms of disease since birth (or last visit).

Physical activity

A questionnaire will be used at the baseline visit, and 6 and 9 months to collect information about the child's activity level, for example tummy time, nap time and sleeping hours.

Habitual physical activity will be measured using accelerometers at the 12, 18 and 24-month visits. All participants will be asked to wear the Actigraph GT3x accelerometer for 7 consecutive days (including 2 weekend days) to measure valid data. Accelerometers are small lightweight devices that measure change in velocity over time (quantify the volume and intensity of movement in three axes). The accelerometer will be worn on the hip or lower-back, and sedentary and moderate to vigorous physical activity will be calculated.

From the parental questionnaires, information about parental leisure time physical activity will be collected at the baseline visit. For the mothers, habitual physical activity is reported before pregnancy starts.

Psychosocial impact of study participation

Infant genetic screening for type 1 diabetes raises parent anxiety when the child is at increased risk.[35] A set of validated questions will be used to measure parental distress (anxiety and depression) in response to the knowledge of their infant's at-risk status for type 1 diabetes and the impact of study participation. The questionnaire will be sent out as a survey for each of the custodial parents to complete separately, at baseline, 12-month and 24-month clinic visit.

Planned analyses and statistical methods

All analyses will be conducted using the intention-to-treat approach. Descriptive statistics will be presented as means (with SD) or medians (with IQR). All analyses will be stratified on breastfeeding strata and study site. Sensitivity analyses will be performed to compare drop-outs and completers to evaluate the potential impact of missing data on final study results. Regression models will be used to estimate the effects of the intervention on the primary outcomes; PI:C Ratio and Disposition Index adjusted for HOMA-IR to improve precision. Secondary outcomes (accelerated growth as defined by the weight-for-age z-score) will be analysed using linear regression model. For time to event analyses of the time to persistent islet autoimmunity, Cox proportional hazards models will be used (right censored). Interim analyses are not planned unless early efficacy/futility monitoring is specified. A statistical analytical plan will be developed before the final analysis begins.

Patient and public involvement

Patients and/or the public were not involved in the study design, conduct, or dissemination plans of this research. Participating families will be informed about the outcome of the study via letter, personal communication and via study website on the completion of the study.

ETHICS AND DISSEMINATION

Ethical approval

The research protocol was approved by the Swedish Ethical Review Authority (dnr 2024-05217-01, 2024-08622-02, 2025-01759-02). Study findings will be presented at national and international conferences, submitted for publication in peer-reviewed scientific journals, shared via press releases, on social media, popular science articles and through patient-education materials.

Data management

The study is conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The documentation of the clinical data will follow the CGP guidelines. The processing of the participants' personal data will be minimised by making use of a unique participant study number on all study documents and in any electronic database. No information about the participants' identity will be disclosed in the source documents (for example laboratory results). All information collected at the visit will be entered directly by the study nurse into a central electronic database using the web-based data collection and management application Research Electronic Data Capture (REDCAP).[36] All information and documents will be stored securely and only accessible by study staff and authorised personnel.

DISCUSSION

Innovation and significance

This study aims to contribute to filling the knowledge gaps in how to prevent islet autoimmunity and type 1 diabetes. We are aiming for primary prevention with lifestyle changes early in life, to evaluate if intense diet and activity advice can minimise β-cell stress and lower the risk of developing islet autoimmunity and in the long run type 1 diabetes in a cohort of children with elevated genetic

risk. We are by this randomised controlled trial with regular diet and activity counselling, testing the causality of the earlier reported findings. This study protocol outlines an approach to prevent development of islet autoantibodies that precedes the onset of type 1 diabetes. The triggers of this complex disease are largely unknown but avoiding rapid weight gain during infancy and early childhood may reduce later risks of development of islet autoimmunity. In addition, promoting and supporting breastfeeding and restricting high animal protein intakes in early childhood can contribute to a risk reduction.

If we succeed in finding a difference in β-cell health and development of early islet autoimmunity between the groups, our study on IDAC may have implication for the advice given by the well-baby clinics and in the long run decrease the incidence of type 1 diabetes in children.

Challenges

Dietary intervention trials in infants and young children are essential for understanding how early nutrition influences growth, development, and disease risk. However, several challenges must be addressed to ensure a successful trial. One of the major challenges is adherence and compliance, as the effectiveness of the intervention depends on parents' consistent implementation of the advice provided.

Ethical considerations may also arise, particularly regarding concerns about withholding potentially beneficial dietary changes. To address this, all enrolled families will receive current national infant feeding recommendations. In addition, results from serological tests and vitamin D levels will be reported back to parents throughout the study.

Generalisability represents another potential limitation. Families who agree to genetic screening and long-term participation may differ systematically from those who decline. To account for this, detailed sociodemographic information will be collected and incorporated into the analysis.

Finally, withdrawal rates must be considered, as early withdrawal can reduce statistical power and introduce bias. Contributing factors may include study length, protocol requirements (eg, regular venous blood draws), and intervention intensity. Family burden and life circumstances (such as changes in employment, family structure, or relocation) will also be monitored continuously.

Trial status

The protocol version number is version 1.3, dated 6 March 2025. Study recruitment began on 15 March 2025, and the approximate date when recruitment will be completed is 31 December 2028.

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Contributors HEL is the lead investigator and guarantor of the study. CAA, SH and HEL are responsible for study conception and design. HEL acquired funding for the trial. TG and EEH are responsible for recruitment of participants, collection of samples and record keeping. MM is responsible for the statistical analysis plan and randomisation plan. CAA wrote the first draft of the paper. All authors had an opportunity to revise the manuscript and all authors read and approved the final manuscript submitted for publication. The corresponding author attests that all listed authors meet authorship criteria.

Funding This study was supported by the Swedish Childhood Diabetes Foundation, LIONS Research Foundation Skåne, the Albert Påhlsson Foundation, The Gyllenstierna Krapperup's Foundation and a Type 1 Diabetes grant via Lund University Diabetes Centre.

Disclaimer The funders did not have any role in the design or conduct of the study, nor the analysis, or reporting of the study.

Competing interests HEL has given lectures with support from SANOFI aventis and Novo Nordisk. HEL held a research grant from SANOFI aventis for another study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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