

Uppsala Longitudinal Study of Childhood Obesity: Protocol Description



WHAT'S KNOWN ON THIS SUBJECT: Childhood obesity poses a serious threat to human health. Obesity is caused by genetic and environmental factors and linked to type 2 diabetes and cardiovascular disease. Pediatric obesity cohorts aim at understanding early events in the pathophysiology of obesity-related complications.



WHAT THIS STUDY ADDS: Cohort subjects are examined at consecutive visits, including measurements of glucose tolerance and hormones regulating nutrient handling (enhanced glucose tolerance tests) and body composition (MRI and bioimpedance). Mechanisms causing obese children to progress to type 2 diabetes are delineated.

abstract

BACKGROUND AND OBJECTIVE: The prevalence of childhood obesity has risen considerably on a global scale during the past decades, and the condition is associated with increased risk of morbidity. The objective is to describe the Uppsala Longitudinal Study of Childhood Obesity (ULSCO) cohort, including some baseline data, and outline addressed research areas that aim at identifying factors implicated in and contributing to development of obesity and obesity-related diseases, including type 2 diabetes.

METHODS: Severely obese and lean control subjects are examined at enrollment and at subsequent annual visits by using detailed questionnaires, anthropometric measurements, indirect calorimetry, and functional tests such as oral glucose tolerance tests. Some subjects undergo additional characterization with MRI, subcutaneous fat biopsies, frequent blood sampling, and hyperglycemic clamps. Biological samples are obtained and stored in a biobank.

RESULTS: Active recruitment started in 2010, and standard operating procedures have been established. A high participation rate and annual follow-ups have resulted in a cohort exceeding 200 subjects, including 45 lean controls (as of October 2013). Initial research focus has been on traits of the metabolic syndrome, hyperinsulinemia and identifying risk factors for type 2 diabetes.

CONCLUSIONS: The ULSCO cohort serves as an important resource in defining and understanding factors contributing to childhood obesity and development of obesity-related diseases. Given the comprehensive characterization of the cohort, factors contributing to disease development and progression can be identified. Such factors are further evaluated for their mechanistic role and significance, and noncommunicable metabolic diseases are especially addressed and considered. *Pediatrics* 2014;133:e386–e393

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KEY WORDS

childhood obesity, cohort, MRI, pediatric, type 2 diabetes mellitus, ULSCO

ABBREVIATIONS

OGTT—oral glucose tolerance test

MRI—magnetic resonance imaging

T2DM—type 2 diabetes mellitus

ULSCO—Uppsala Longitudinal Study of Childhood Obesity

WHO—World Health Organization

Dr Forslund is employed as the senior pediatrician at the obesity clinic and has been involved in the planning and formation of the Uppsala Longitudinal Study of Childhood Obesity (ULSCO); he regularly conducts assessments of clinical and research subjects and coauthored, revised, and critically reviewed the final manuscript as submitted; Dr Staaf holds a medical degree and is a PhD student, working with the ULSCO cohort; he was involved in the planning and formation of ULSCO, has contributed to ethics applications, and is involved in examination of subjects and various analysis; he coauthored, revised, and critically reviewed the final manuscript as submitted; Dr Kullberg works as a researcher, focusing on MRI, and has been involved in writing aspects of the ethics application and planning and execution of the MRI section of ULSCO; he revised and critically reviewed the final manuscript as submitted; Dr Ciba works as a pediatrician at Uppsala University Children's hospital and has been involved in the ULSCO research, assessing and examining subjects as well as working on the questionnaires; she revised and critically reviewed the final manuscript as submitted; Ms Dahlbom works as a research nurse with the ULSCO cohort and is conducting a majority of the examinations; she has been involved in the planning and execution of ULSCO, written standard operating procedures, and recruited many of the lean control subjects; she revised and critically reviewed the final manuscript as submitted; Dr Bergsten is a professor at the department of Medical Cell Biology and has been involved in the planning and formation of ULSCO; he has worked with all aspects of ULSCO and coauthored, revised, and critically reviewed the final manuscript as submitted; and all authors approved the final manuscript as submitted.

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The worldwide prevalence of obesity was estimated at approximately half a billion afflicted individuals in 2008 and is expected to exceed 1 billion individuals in 2030.^{1,2} The cause of obesity is multifactorial, for which genetics, environment, socioeconomic status, culture, and ethnicity are some primary factors.^{3,4} Thus, the pathophysiology of obesity is a result of a complex interaction between environmental and genetic factors^{5,6} that still are not fully delineated and understood. Obesity is defined as a body mass index (BMI) ≥ 30 and overweight as a BMI ≥ 25 in adults.² In children, BMI is adjusted for age and gender.^{7,8} Obesity is related to increased risk of morbidity and mortality. In a recent report by the World Health Organization (WHO), obesity and overweight were estimated to account for 44% of health problems related to type 2 diabetes mellitus (T2DM), 23% of health problems related to ischemic heart disease, and 7% to 41% of health problems related to certain forms of cancer.²

Particularly concerning is that the number of children suffering from obesity has increased worldwide,⁹ with extensive consequences for national and international health and related health care budgets.¹⁰ Childhood obesity is the focus of the WHO Childhood Obesity Surveillance Initiative, which recently reported a prevalence between 6% and 12% in the European region.¹¹ In the same report, the prevalence of overweight children was between 19% and 28%. The Centers for Disease Control and Prevention have published numbers for obesity rates in the United States. For children and adolescents aged 2 to 19 years, the prevalence of obesity was as high as 17%.¹² Whereas the percentages in the WHO study were obtained by using the standard WHO criteria for overweight and obesity,⁸ the Centers for Disease Control and Prevention's 2000 growth

charts were used in the latter study.¹³ In Sweden, the percentages for obese and overweight children in the WHO report were 6% and 23%, respectively.¹¹ The latter percentages reflect a substantial increase in the number of Swedish children suffering from obesity or overweight during recent decades. Indeed, the tendency in Sweden, especially among young girls, is that the average age-adjusted BMI of children tends to increase over time.¹⁴

In response to the increasing prevalence of childhood obesity, the pediatric obesity clinic at the Uppsala University Children's Hospital was established in 2008. The clinic functions as a regional referral center for children with severe obesity. Its main objective is to help patients with severe obesity and, in close collaboration with the patients' families, find ways to improve their health, where weight reduction is a cornerstone. In this task, which is carried out by a multidisciplinary team, gathering information about the patients, including both medical history and results from various examinations is fundamental. At the clinic, not only routine clinical work is being carried out but also extensive research on childhood obesity. Children and their legal guardians are asked if they wish to take part in the current research study, aiming to create a better understanding of underlying causes and mechanisms in development of childhood obesity and related diseases, in particular T2DM. Those who wish to take part are recruited into the Uppsala Longitudinal Study of Childhood Obesity (ULSCO) cohort, which was initiated in 2010.

The aim of this article is to present the protocol description used in ULSCO characterization, provide some baseline data, and indicate research topics that are addressed by the cohort. The main research areas of the childhood obesity cohort include:

- dynamic changes in levels of hormones regulating nutrient homeostasis;
- levels and function of different lipid classes;
- white and brown adipose tissue and organ fat content;
- new candidate genes of obesity and T2DM; and
- biomarkers of obesity and risk factors for development of obesity-related T2DM.

METHODS

Subject Enrollment

Children ≤ 18 years old with severe obesity (age-adjusted BMI ≥ 35) in Uppsala and surrounding regions who have been referred to the pediatric obesity clinic at Uppsala University Children's Hospital are eligible for enrollment into ULSCO. Lean (age-adjusted BMI < 25) healthy age- and gender-matched control children are enrolled through collaboration between Uppsala University and local schools in the Uppsala area as well as through advertisement. Parents and siblings of subjects are also asked to be included for genetic analysis. At enrollment, the project is described to the subject and legal guardians and informed consent is obtained. Inclusion criteria are primarily based on age-adjusted BMI. Exclusion criteria include serious psychiatric disorders, and severe diseases, such as malignancies.

Protocols

The procedures, including clinical assessments, examinations, and questionnaires (Table 1), are conducted at enrollment and at annual follow-up visits (Fig 1). These procedures are also conducted in lean subjects. Special attention is given to examinations addressing body composition, metabolism, and hormones regulating nutrient handling during an oral glucose tolerance test (OGTT) or

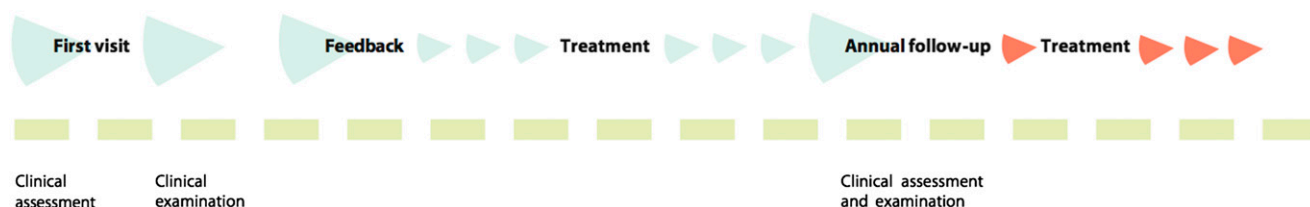


FIGURE 1

Time chart of visits by subjects at the pediatric obesity clinic and specified times when assessments and examinations are conducted within the ULSCO cohort. Red arrowheads indicate a potential new treatment strategy and/or research focus.

prolonged glucose challenge with intravenous hyperglycemic clamp.

Blood Sampling

All examination procedures, including sample collection and storage, are conducted according to established

standard operating procedures. A nurse conducts the blood sampling from a peripheral vein. Local anesthesia with Eutectic Mixture of Local Anesthetics (EMLA) (AstraZeneca AB, Södertälje, Sweden) is offered to subjects before venipuncture. Blood

volumes drawn are calculated on the basis of the subject's age and weight. Research samples are collected by using both EDTA and P800 (BD AB, Stockholm, Sweden) tubes. Samples are immediately placed on ice and centrifuged at $2500 \times g$ for 10

TABLE 1 Procedures Performed in ULSCO Subjects of Different Ages

	Subject Age			
	0–6 Years	6–10 Years	10–12 Years	12–18 Years
Clinical assessments	Patient medical history Physical examination Blood pressure Information about ULSCO	Patient medical history Physical examination Blood pressure Information about ULSCO	Patient medical history Physical examination Blood pressure Information about ULSCO	Patient medical history Physical examination Blood pressure Information about ULSCO
Clinical examinations	Weight Height Waist/hip circumference Skinfold thickness (caliper) Bioimpedance Indirect calorimetry Accelerometer	Weight Height Waist/hip circumference Skinfold thickness (caliper) Bioimpedance Indirect calorimetry Accelerometer Bodpod 6-minute-walk test	Weight Height Waist/hip circumference Skinfold thickness (caliper) Bioimpedance Indirect calorimetry Accelerometer Bodpod 6-minute-walk test	Weight Height Waist/hip circumference Skinfold thickness (caliper) Bioimpedance Indirect calorimetry Accelerometer Bodpod 6-minute-walk-test
Questionnaires	Goals Nutrition Sleep Well-being/welfare Stress Physical activity Relationships/network	Goals Nutrition Sleep Well-being/welfare Stress Physical activity Relationships/network	Goals Nutrition Sleep Well-being/welfare Stress Physical activity Relationships/network	Goals Nutrition Sleep Well-being/welfare Stress Physical activity Relationships/network
Fasting blood samples	2–3 EDTA/P800 tubes, ^a plasma and whole blood	3–4 EDTA/P800 tubes, plasma and whole blood	4–5 EDTA/P800 tubes, plasma and whole blood	4–5 EDTA/P800 tubes, plasma and whole blood
Oral glucose tolerance test	Samples obtained at 5, 10, 15, 30, 60, 90, and 120 min using EDTA tubes	Samples obtained at 5, 10, 15, 30, 60, 90, and 120 min using EDTA/P800 tubes	Samples obtained at 5, 10, 15, 30, 60, 90, and 120 min using EDTA/P800 tubes	Samples obtained at 5, 10, 15, 30, 60, 90, and 120 min using EDTA/P800 tubes
Frequent blood sampling ^b	—	Sampling every 1–2 min using EDTA tubes	Sampling every 1–2 min using EDTA tubes	Sampling every 1–2 min using EDTA tubes
MRI ^b	—	—	DSAT/SSAT and VAT, BAT, liver fat, pancreatic fat	DSAT/SSAT and VAT, BAT, liver fat, pancreatic fat
Clamps ^b	—	—	—	Using hyperinsulinemic and hyperglycemic clamp techniques
Tissue biopsies ^b	—	—	—	SSAT

BAT, brown adipose tissue; DSAT, deep subcutaneous adipose tissue; SSAT, superficial subcutaneous adipose tissue; VAT, visceral adipose tissue. —, examination not conducted.

^a P800 tubes are used to prevent degradation of glucagon-like peptide 1, glucagon, gastric inhibitory peptide, and ghrelin.

^b Performed on a subset of individuals within the ULSCO cohort.

minutes in a +4°C centrifuge. Plasma is then separated into aliquots and stored in a local -70°C freezer within 1 hour of sampling. In addition, selected samples are immediately taken to the laboratory for analyses, and some samples are stored as whole blood for DNA analyses (Table 2).

OGTT

OGTT is performed in subjects after an overnight fasting period of at least 10 hours. Instructions are given to avoid major changes in dietary habits and physical exercise levels during at least 3 days before the examination. After obtaining fasting blood samples, the subject is instructed to drink a glucose solution of 1.75 g glucose/kg bodyweight (maximum 75 g) mixed carefully in ~300 mL of water. Additional blood samples are obtained by using EDTA and P800 tubes at specified intervals of time. For routine OGTT the time points are 5, 10, 15, 30, 60, 90, and 120 minutes (Table 1). In some subjects, an extended OGTT is performed, with sampling at 180 minutes. Frequent blood sampling is performed in

selected subjects to investigate the dynamics of insulin secretion. Small amounts of blood are sampled with 1- to 2-minute intervals in fasting state. In subjects ≥ 10 years old, hyperglycemic and hyperinsulinemic clamps are performed in a subgroup of subjects.

Body Composition

Waist circumference is measured with a flexible tape midway between the superior border of the iliac crest and the lowest rib on a standing subject, and hip circumference at the greatest circumference of the hip (Table 1).¹⁵ Skinfold thickness is measured by using a Harpenden skinfold caliper (Baty International, Burgess Hill, West Sussex, UK) on the following sites (duplicate measurements at each site): triceps, biceps, subscapularis, and suprailiac. Body composition is calculated by bioimpedance using an InBody S20 bioimpedance device (Biospace, Seoul, Korea) on a fasting subject who is instructed to empty the bladder before the examination. Additional estimation of body composition is acquired by air

displacement plethysmography, using a Bodpod 1-800-4 (LMI-Life Measurement, Inc, Concord, CA). Magnetic resonance imaging (MRI), using a 1.5-T clinical scanner (Achieva; Philips Healthcare, Best, The Netherlands), is conducted in subjects ≥ 10 years of age (Table 1). The examination targets white adipose tissue in the deep and superficial subcutaneous adipose tissue and visceral depots, brown adipose tissue, as well as pancreatic and liver fat. The subcutaneous fat biopsies are obtained by a physician from the lateral region of the abdomen with local anesthesia, with minimal risk to the subject.

Metabolism, Physical Activity, and Fitness

For indirect calorimetry, a V_{\max} Encore 29 device (SensorMedics, CareFusion Corp, San Diego, CA) is used. Physical activity is assessed by registration with the accelerometer Actical (Respironics, Inc, Murrysville, PA) on the subject's wrist and ankle during several consecutive days and nights. Physical fitness is evaluated by a 6-minute walk test (Table 1).¹⁶

TABLE 2 Blood Parameters Currently Analyzed in the ULSCO Cohort

	Pancreatic Hormones and Metabolism	Lipid Profile	Incretins and Adipokines	Hematology and Inflammation	Growth and Sex Hormones	Liver and Kidney Status	Genetics
Fasting	Insulin	Cholesterol	GLP-1	Hemoglobin	GH	AST	Target genes
	Proinsulin	Triglycerides	GIP	Leukocytes	IGF-1	ALT	Epigenetics
	C-peptide	HDL	Ghrelin	Thrombocytes	FSH	ALP	
	Glucagon	LDL	Adiponectin	C-reactive protein	LH	γ -GT	
	Glucose	Apolipoproteins	Leptin	IgA, IgG, IgM	SHBG	Bilirubin	
	HbA1c	NEFAs	Visfatin	TNF- α	Testosterone	Albumin	
	TSH	Sphingolipids	Resistin	Interleukin-1 β	Estrogen	Creatinine	
	Triiodothyronine		PAI-1	Interleukin-6		Cystatine-C	
Thyroxine					Uric acid		
OGTT	Insulin	NEFAs	GLP-1	—	—	—	—
	Proinsulin						
	C-peptide						
	Glucose						
	Glucagon						
Frequent blood sampling	Insulin	—	—	—	—	—	—
	C-peptide						
Clamps	Insulin	—	—	—	—	—	—
	Glucose						

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; FSH, follicle-stimulating hormone; γ -GT, γ -glutamyl transpeptidase; GH, growth hormone; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; Ig, immunoglobulin; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; LH, luteinizing hormone; NEFA, nonesterified fatty acid; PAI-1, plasminogen activator inhibitor 1; SHBG, sex hormone binding globulin; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone. —, parameters not measured.

Questionnaires

All subjects and legal guardians answer questionnaires, which include questions about medical history, nutrition, physical activity, well-being, stress, relationships/networks, and goals (Fig 2). The questionnaires also include screening questions for sleeping habits as well as attention-deficit/hyperactivity disorder.

Biobank

Blood samples in the fasting state as well as during a glucose challenge are obtained from both severely obese and lean subjects (Table 1). All collected biological samples, which are not analyzed immediately, are stored in a centralized biobank (Uppsala Biobank registration number 822). Storage of samples is carefully monitored with information about freeze-thaw cycles, hemolysis, and aliquot volumes. The biobank is located at Uppsala University and contains -70°C freezers with a centralized alarm and access to backup freezers.

Ethical Considerations

Conducting clinical research on children raises several ethical questions,¹⁷ which include considerations regarding safety, discomfort during examinations, benefit-risk assessment, etc. The protocols and examinations performed within the ULSCO cohort have been approved by the Uppsala Regional Ethics Committee (registration numbers 2010/036 and 2012/318). Before enrollment, informed and written consent is obtained from legal guardians. For subjects ≥ 12 years of age, written consent is also obtained from the subjects themselves. Participation in the cohort is voluntary, and consent can be withdrawn at any time by subjects and legal guardians without having to state a reason.

Calculations of Glucose Tolerance and Metabolic Syndrome

The WHO criteria for diabetes, impaired glucose tolerance, impaired fasting glucose, and normoglycemia were used

for individuals who underwent a 2-hour OGTT.¹⁸ The metabolic syndrome was evaluated on the basis of the International Diabetes Federation's criteria for pediatric populations.¹⁹

Statistical Analyses

Power calculations are performed to determine the required sample size before each study, using material from the cohort. Comparisons between groups are performed by using ANOVA and Student's *t* tests or non-parametric tests. Linear regression models are used to assess correlations between various parameters. Statistical analyses are currently conducted by using GraphPad Prism 6.0c (GraphPad Software, Inc, La Jolla, CA). *P* values $< .05$ are considered statistically significant.

RESULTS

The ULSCO pediatric cohort was established in 2010 and serves as a large longitudinal study, continuously recruiting children with severe obesity as well as lean age- and gender-matched control subjects. Currently (as of October 2013), the cohort contains data and biological samples from 208 subjects (97 girls and 111 boys). One hundred sixty-three subjects are severely obese, and 45 subjects serve as lean controls. Subjects with severe obesity

are enrolled during visits to the pediatric obesity clinic. At the visits, lifestyle-related issues are addressed (Fig 2), examinations conducted (Table 1), and parameters determined (Table 2) by a multidisciplinary team consisting of pediatricians, nurses, psychologists, dieticians, epidemiologists, radiologists, and basic scientists. Whereas the age at enrollment of severely obese subjects varies between 3 to 18 years, the ages of the lean subjects are currently between 6 and 17 years (Fig 3). Annual follow-up visits of the severely obese and lean subjects are a crucial part of ULSCO (Fig 1). Currently, >100 annual follow-up examinations have been conducted, most of them during the 2012 and 2013 (Fig 4). For some subjects, 3-year time-series data sets have been obtained and are currently being analyzed.

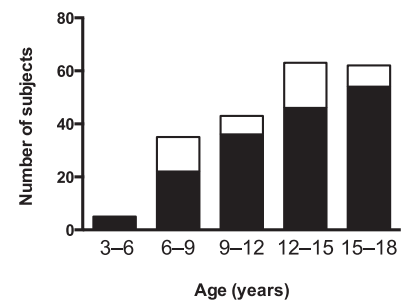


FIGURE 3 Age at enrollment of severely obese (black bars) and lean (white bars) subjects into the ULSCO cohort.

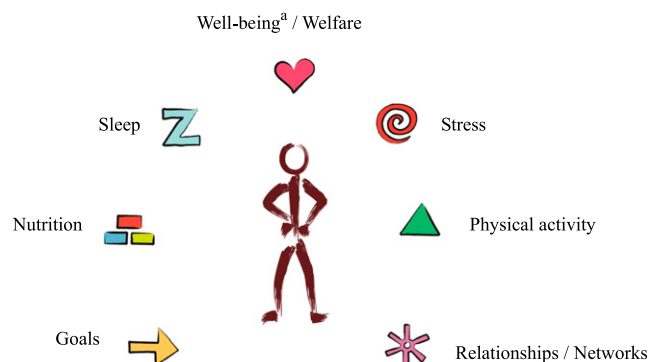


FIGURE 2 Areas covered by the ULSCO cohort questionnaires that address factors contributing to development of obesity. ^aIncludes determining the psychological and psychiatric status of the subject.

Initially, the subjects of the ULSCO cohort were characterized with regard to glucose tolerance and manifestations of the metabolic syndrome. In the current cohort, ~54% of the severely obese subjects are normoglycemic, approximately 4% suffer from T2DM, whereas the remaining subjects are in a glycemic state of prediabetes with impaired glucose tolerance or impaired fasting glucose. Among lean subjects, 1 subject has impaired glucose tolerance, whereas all others are characterized as normoglycemic. The metabolic syndrome, as defined by the International Diabetes Federation, is present in 34% of the subjects >10 years of age with severe obesity. None of the lean subjects suffers from the metabolic syndrome. Furthermore, severely obese children display fasting hyperinsulinemia amounting to an

~3.5-fold increase compared to lean subjects. Preliminary results from MRI data indicate large differences in subcutaneous adipose tissue, visceral adipose tissue, and liver fat measurements between severely obese and lean subjects, as well as within the group of severely obese subjects (Fig 5).

DISCUSSION

The ULSCO cohort was initiated to increase the knowledge and understanding of early causes of childhood obesity and obesity-related diseases. Within the study, clinical information is gathered and systematized and biological samples are collected and stored in a biobank. The ULSCO cohort therefore constitutes a significant resource when addressing questions related to childhood obesity and diseases associated with obesity, including the areas of metabolism, cardiovascular disease, endocrinology, and neuropsychiatry.

In the cohort, approximately every third severely obese subject >10 years of age suffers from the metabolic syndrome, which is comparable to numbers obtained in other countries.³ In addition, many subjects have impaired glucose tolerance and some have already developed overt T2DM in their adolescent years. T2DM was previously a disease of the elderly, but due to the current increase in childhood obesity,

guidelines and recommendations for treatment of T2DM in adolescents have been established²⁰ and are currently implemented around the world. Children with obesity are at increased risk of adult obesity,²¹ stressing the importance of increased knowledge and effective measures of early interventions. ULSCO subjects are enrolled at an early age. This approach allows us to study initial metabolic events that trigger metabolic disorder and disease development, when compensatory biological mechanisms are less significant. In addition, most of the subjects are drug-naive, which makes it easier to evaluate underlying pathophysiologic mechanisms. These conditions render the cohort value in identifying factors implicated in obesity and related disease processes.

The design of ULSCO, especially the aspect of storing biological samples from carefully phenotyped subjects in a biobank, opens possibilities for multiple future studies. Indeed, ULSCO is already contributing to a larger translational research initiative, where results from the cohort are further evaluated mechanistically in national and international collaborative efforts. An important aspect of ULSCO is that it enrolls healthy lean subjects. The scarcity of reference data in the pediatric population makes the characterization of normal-weight children

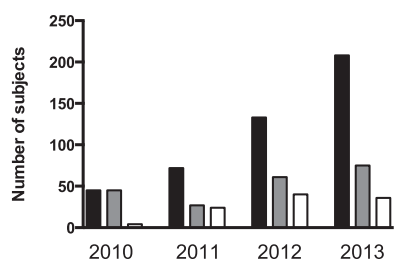


FIGURE 4

Total number of subjects (black bars), number of newly enrolled subjects (gray bars), and number of subjects attending annual follow-ups (white bars) in the ULSCO cohort during the period 2010–2013.

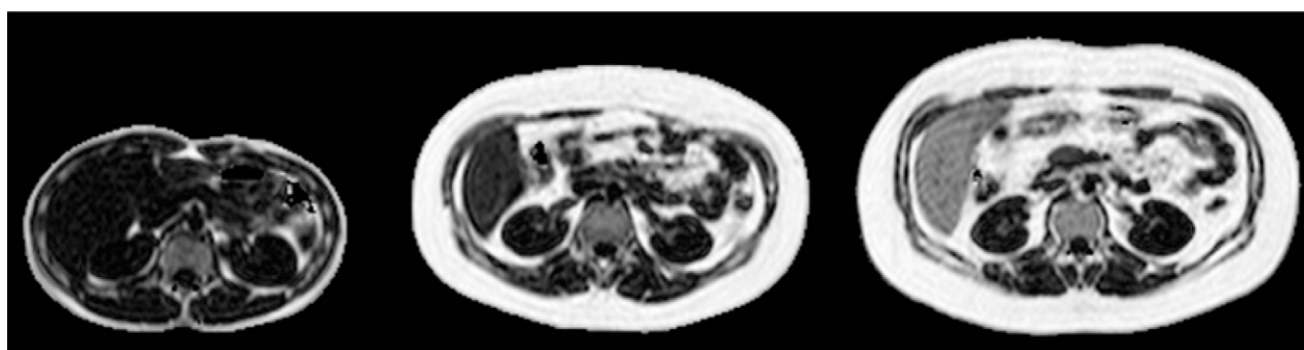


FIGURE 5

Example of MRI data from the abdominal adipose tissue volumetric scan from three 13-year-old boys. One lean (left) and 2 severely obese (middle and right) subjects. The imaging protocol maps absolute fat content from 0% (black) to 100% (white). These examples show large differences in subcutaneous and intraabdominal (visceral) adipose tissue volumes as well as liver fat infiltration.

important, not only to understand and discriminate metabolic abnormalities and pathologies in children with obesity but also to serve as reference values, obtained for different age and gender groups, for future pediatric disease cohorts. Currently, the cohort contains >200 subjects, with a biobank harboring thousands of biological samples in aliquots. Approximately 100 new subjects are expected to be enrolled in 2014. Access to data and samples is controlled by the ULSCO board, which receives applications for research initiatives involving the cohort.

Childhood obesity has become a serious health threat, with patients at increased risk of future morbidity and mortality.²² Therefore, childhood obesity is addressed in several cohorts such as the Danish National Birth Registry,²³ the Avon Longitudinal Study of Parents and Children,²⁴ the Leipzig Research Centre for Civilization Diseases (LIFE) Child Study,²⁵ and the Millennium Study Cohort.²⁶ These initiatives have different emphases with regard to geographic and ethnic variations, which have been documented as important determinants in obesity

development.²⁷ In this respect to ethnic and geographic considerations, the ULSCO cohort represents an important contribution. Furthermore, the ULSCO cohort has adopted strict procedures for enrollment, characterization, sampling and examination. Therefore, results from ULSCO can be merged in larger study initiatives and collaborations with similar standard operating procedures. Such mergers of results allow complex issues to be investigated, where meta-analysis of large numbers of children often is required. Indeed, with large cohorts in different regions of the world, issues such as genetics and environmental factors in development of obesity and subsequent disease progression can better be addressed.²⁸ In addition and importantly, the ULSCO cohort has focused on extensive and careful characterization and phenotyping of the subjects at enrollment and annual follow-up visits. Highly specialized assessments and examinations, including MRI, frequent blood sampling and subcutaneous adipose biopsies, are important parts of the characterization.

CONCLUSIONS

The ULSCO pediatric cohort enrolls both severely obese and lean children. Subjects of the cohort are examined and characterized at multiple, consecutive visits, when biological samples are obtained and stored. Through the ULSCO initiative detailed high-resolved time-series data and samples are available, which generate opportunities to study disease progression. Indeed, one objective of the ULSCO cohort is to identify risk factors of future disease in children with severe obesity. Identification of such risk factors is expected to contribute to defining and understanding mechanisms involved in development of both childhood obesity and related diseases. The knowledge generated is expected to allow us to define novel genetic, environmental and metabolic mechanisms associated with childhood obesity.

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