COMPLICATIONS OF CHILDHOOD OBESITY

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AUTHORS

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Five book chapter, twenty-five original papers and number of abstracts, which can be cited, have been published (impact factor: 50.198 /without abstracts/, citations: 388). She is a member in several national and international societies, she takes part in the work of European Childhood Obesity Group (ECOG) since 1993. She was the Vice-President of ECOG between 2010-2013, then the Scientific Advisor 2014-2017, now she is also a Board Member. She was the President of Endocrine Working Group of Hungarian Paediatric Society between 2012-2014, now she is still a Board Member there, and she is the Secretary of the Childhood Diabetes Section of Hungarian Diabetes Association.

Margherita Caroli (MD, PhD) is a paediatrician and a nutritionist with a PhD in Paediatric nutrition. She has been the head of the Nutrition Unit of the Prevention Dept of the Azienda Locale Brindisi for 20 years. Founder member and President of ECOG for the term 2007-2010 and member of the Italian Society of Obesity and the Italian Society of Preventive and Social Paediatrics. She has been the scientific coordinator of several national and European projects and author or co-author of more than 400 items including published papers and lectures. She has had a role as expert for several European DGs (DG SANCO, RESEARCH, AGRI, and DGJRC) and she is often temporary advisor for WHO.

Anders Forslund (MD, PhD) is an Associate Professor at the Department of Women´s and children´s health, Uppsala University, Sweden.
He defended his thesis 1998 with the title *”The Effect of Protein Intake and Physical Excercise on Energy Turnover and Substrate Utilisation at Energy Balance in Man”.*
He has published > 40 articles around nutrition, energy turnover, body composition, substrate utilization, metabolic disorders and childhood obesity.
He has been working as a Paediatrician since 2007, and working clinically with childhood obesity > 10 years. He is the head of the Childhood Obesity Unit at Uppsala University Hospitals since 2007.
He is a member of the Swedish childhood obesity society, and a Board Member in the European Childhood Obesity Group (ECOG).

Dénes Molnár (MD, PhD, DSc) is professor in pediatrics, nutrition and metabolism, at Dept. Paediatr. Univ. Pécs. He was the chairman of the Dept. Pediatr. Univ. Pécs from 2007 until 2015. Served as the president and for two terms the scientific advisor of the European Childhood Obesity Group (ECOG), and the vice-president of the Hungarian Association for the Study of Obesity. He was the president of the Hungarian Paediatric Association in the period of 2012-2015. He is the member of the editorial board of *Obesity Facts and Nutrition*, *Metabolism and Cardiovascular Diseases*, *Journal of Pediatric Biochemistry* and *The Scientific World Journal*; besides that of more national journals. He participated in 9 international research programs, and won 11 national research grants. He is PhD program leader in the topic of *Nutritional research in children and infants*. Special interest: metabolic disorders, eating disorders, prevention of adult diseases in childhood. He has published 396 original articles in peer-reviewed journals and 18 book chapters (cumulative IF: 950,47; number of citations ~ 7700, Hirsch index: 45

OBJECTIVES OF THIS MODULE

At the end of this module you should

- Be sure about the fact that childhood obesity can cause a number of problems from difficulties in daily activity to serious health conditions.
- Know how to define hypertension in children and which guideline is the best for it.
- Know the key sign of insulin resistance, risk factors for Type 2 diabetes mellitus (T2DM) and the possibilities to evaluate the disorders of glucose metabolism.
- Be aware of the questions about the definitions of metabolic syndrome and know the screening possibilities for non-alcoholic fatty liver disease as the most frequent asymptomatic complications of children with obesity.
- Know some real and quasi endocrine conditions which are the consequences of childhood obesity.
- Know the most frequent pulmonary complications in children with obesity
- Recognize some orthopedic conditions which are commonly present in children with obesity and differentiate among them

ALGORYTHM FOR THE EXAMINATION OF AN OBESE CHILD

Family and personal history, diet, psychomotor development

Early beginning (< 6 years of age) Delayed psychomotor development	Early beginning (< 6 years of age) Normal psychomotor development	**No age specific** **Decreased linear growth** **Delayed bone age**	**No age specific** **normal or increased linear growth** **normal psychomotor development**
Suspect genetic syndrome e.g. Prader Willi Bardet Biedl Fragile X....	Suspect gene mutation of the appetite regulation pathway e.g. leptin, leptin receptor, MC4R,	**Suspect endocrine disease** **Negative investigation**	**Primary obesity**

79 genetic syndromes including obesity are described nowadays and only partly elucidated.
Primary obesity may be of polygenic or epigenetic origin.

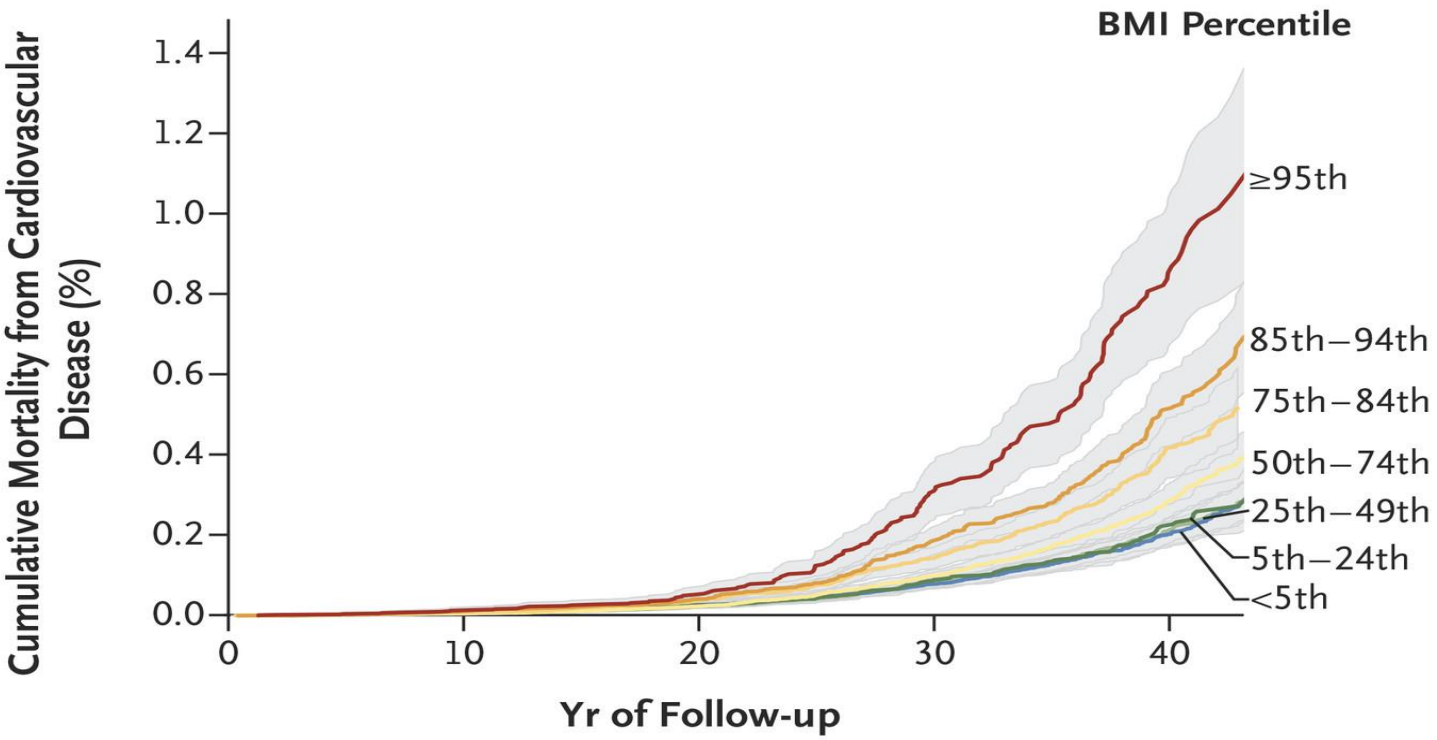
Ref 14

COMPLICATIONS OF PRIMARY OBESITY

- Children with primary obesity are at high risk for multiple complications which may affect almost any organ in the body.
- 26 % of 1-2- years-old and 83 % of 10-14 - years-old children with obesity will become obese adults.
- The severity of complications increases with the degree and duration of obesity.
- Early onset obesity increases mortality rate in adulthood
- The purpose of the evaluation of children with obesity is to assess obesity-related comorbidities resulting from excess fat mass and body weight overload.

Ref 2, 3, 9, 13

BODY MASS INDEX (BMI) DURING ADOLESCENCE AND SUBSEQUENT CARDIOVASCULAR MORTALITY



No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardio-vascular deaths	185	609	1,577	2,676

2,298,130 participants

Ref 10

Complications of obesity in children and adolescents

Metabolic & cardiovascular

Chronic inflammation
Insulin resistance
Dyslipidaemia
Atherosclerosis
Hypertension
Stroke
Cardiac remodelling & dysfunction
Hyperuricemia

Respiratory

Asthma
Hypoventilation
Obstructive sleep apnoea (OSA)
Exercise intolerance

Liver and digestive tract

Non alcoholic fatty liver disease (NAFLD/NASH)
Gallstone

Renal

Glomerulosclerosis

Neurological

Idiopathic intracranial hypertension (pesudotumor cerebri)

Adverse effect on cognitive function

Endocrine

Type 2 diabetes
Early onset/delayed puberty
Menstrual irregularities
Accelerated linear growth
Polycystic ovary syndrome
Hypogonadism/Gynecomastia
Pseudogynecomastia

Musculoskeletal

Pain & impaired mobility
Slipped femoral epiphysis
Tibia vara
Blount's disease
Ankle sprains
Genu valgum & Flat foot

Psychosocial

Social stigmatization
Low health-related quality of life
Poor self-esteem
Anxiety
Depression
ADHD/ADD
Eating disorders

Dermatological

Hyperandrogenism (acne, hirsutism)
Acanthosis nigricans
Hidradenitis suppurativa
Intertrigo

CARDIOVASCULAR AND METABOLIC COMPLICATIONS

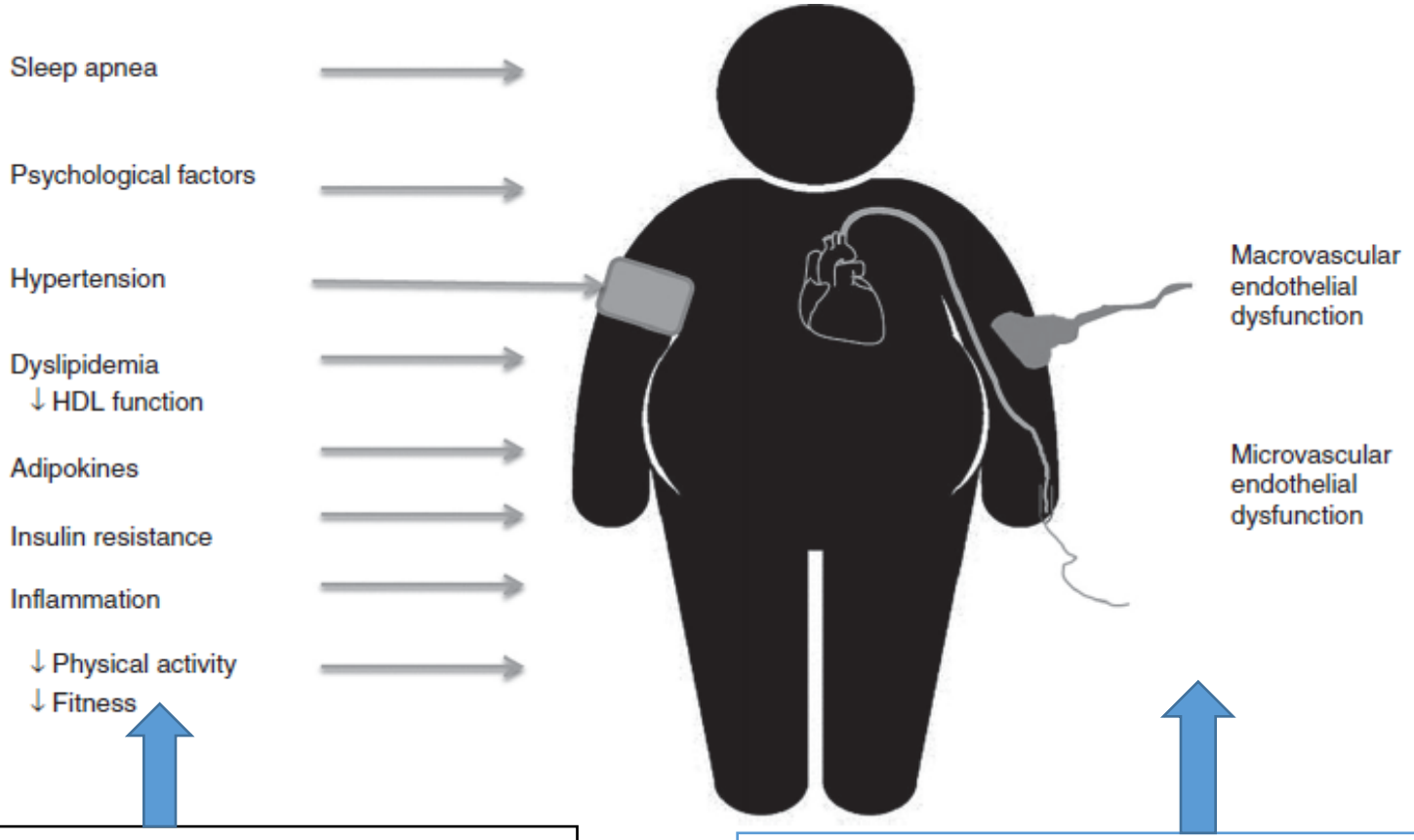
- vast majority of short and long term complications of childhood obesity
- common background including micro vascular alterations ,
- mild chronic inflammation
- Include
  - Hypertension
  - Insulin resistance and type 2 diabetes
  - Dyslipidaemia
  - Non alcoholic fatty liver disease

And their combinations into the *"metabolic syndrome"*

are partly reversible with weight loss

DETERMINANTS OF OBESITY RELATED ENDOTHELIAL DYSFUNCTION *in children*

Dysfunction of small resistance vessels is the primum movens in the pathogenesis of atherosclerosis



Cardiovascular risk factors influencing endothelial dysfunction

Non invasive techniques of investigation of micro- and macrovascular dysfunction

Ref 15

HYPERTENSION

- The risk of hypertension is 2.5 – 3.7 times higher in children with obesity compared to children with normal weight.
- Prevalence of hypertension is ~ 25 % or higher among overweight and obese children.
- New definition and reference of blood pressure (BP) at rest according to sex, age and height percentile in children and adolescents were published in 2017. (ref 5.)
- **Early cardiac remodeling and dysfunction**
  - Increased thickness of intraventricular septum
  - Left ventricular hypertrophy
  - Increased left ventricular and left atrial diameter
  - Systolic and diastolic dysfunction

Ref 5, 7, 12 , 19

DEFINITION OF HYPERTENSION

Age range	0-13 years	> 13 years
Normal	< 90th percentile	<120/<80 mmHg
Elevated blood pressure (BP)	≥ 90th percentile to < 95th percentile or 120/80 mmHg to < 95th percentile	120/<80 to 120/<89 mmHg
Stage 1. hypertension	≥ 95th percentile to < 95th percentile+ 12 mmHg or 130/80 to 139/89 mmHg	130/80 to 139/89 mmHg
Stage 2. hypertension	≥ 95 th percentile + 12 mmHg or ≥ 140/90 mmHg	≥ 140/90 mmHg

Note: adapted BP cuffs size is of critical importance in children in order to avoid under or overestimation of BP

Ref 5

RECOMMENDED SIZE OF BP CUFF

Ages	Width (cm)	length (cm)	Circumference of arm (maximum -cm)
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Adolescent	10	24	26
Adult	13	30	34

The cuff bladder length should encircle 80% to 100% of the arm circumference;

A cuff bladder with a width-to-arm circumference ratio 0.45 to 0.55 is recommended.

For children with severe obesity in whom the appropriate cuff size is difficult to determine, the midarm circumference should measured as the midpoint between the acromion of the scapula and olecranon of the elbow, with the shoulder in a neutral position and the elbow flexed to 90°).

Ref 5, 12

HYPERTENSION
Ambulatory blood pressure monitoring (ABPM)

ABPM should be performed

1. **for confirmation of HTN** in children and adolescents
   - with office BP measurements in the elevated BP category for 1 year or more
   - or with stage 1 HTN over 3 clinic visits.

2. **by using a standardized approach**
   - with monitors that have been validated in a pediatric population
   - results should be interpreted by using pediatric normative data

Ref 5

DISTURBANCES OF GLUCOSE METABOLISM IN OBESE CHILDREN AND ADOLESCENTS

Insulin resistance

- one of the commonest metabolic disturbances of obesity
- key element of the metabolic syndrome
- may evolve toward type 2 diabetes
- increases cardiovascular risk

Additional risk factors

- family history of diabetes in first or second degree of relatives
- ethnicity
- SGA
- Smoking during gestation

Clinical features linked to insulin resistance

- Acanthosis nigricans
- PCOS
- NAFLD
- Hypertriglyceridemia

Ref 1, 2, 3, 5,6

SCREENING FOR DISTURBANCES OF GLUCOSE METABOLISM

- **ISPAD criteria for overweight children**
  - 2 or more risk factors
  - at the beginning of puberty or at the age of 10 years.
- **ECOG position : *idem* but no age threshold should be applied**
- **Screening tests**
  - fasting plasma glucose (no caloric intake for at least 12 hours),
  - hemoglobin A1C (HbA1C),
  - 2-hours oral glucose tolerance test.
- **Derived indexes of insulin resistance**
  - useful in paediatric settings but widely accepted international standards are needed.

***HOMA – IR** : homeostasis model assessment for insulin resistance*

Fasting insulin (µU/ml)xfasting glucose (mmol/l)/22.5

***QUICKI** : quantitative insulin-sensitivity check index*

1/(log fasting insulin [µU/ml] + log glucose [mg/dl])

Ref 1, 2, 5

ACANTHOSIS NIGRICANS
a key sign of insulin resistance
Aspects according to skin phototype

White skin | Light brown skin | Dark skin

Ref 6

CARDIOMETABOLIC COMPLICATION
Dyslipidaemia

- **Definition of dyslipidaemia**
  - elevated total cholesterol, LDL-cholesterol, triglyceride (TG),
  - decreased HDL-cholesterol
- **Prevalence**
  - the most common consequence of childhood obesity
  - Reaches up to 40 % of adolescents with obesity

- Before lab tests 12 hours of fasting needed to get reliable results. If the first result is positive then repeated measurement is needed.

Ref 2, 3, 6

Non Alcoholic Fatty Liver Disease

Overweight/Obesity

Insulin Resistance

Metabolic Syndrome

Hypercaloric Diet

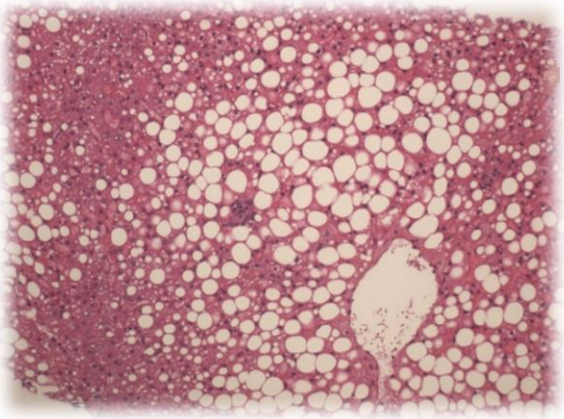
FFA

Oxidative Stress

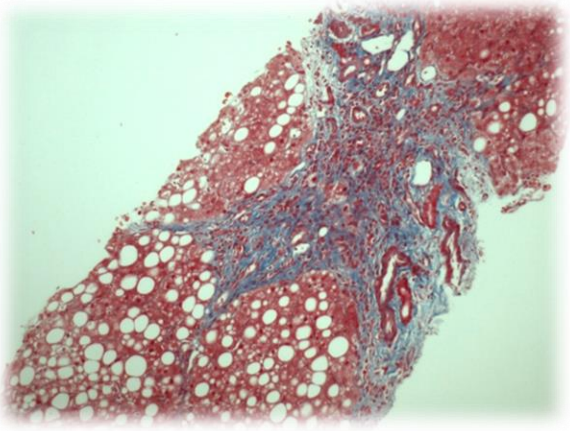
Mitochondrial dysfunction

Pro-inflammatory cytokines

Gut dysbiosis & endotoxin



NAFLD



NASH

V Nobili, Ref 6

HEPATIC COMPLICATIONS

- The spectrum of nonalcoholic fatty liver disease (NAFLD) ranges from simple steatosis, to nonalcoholic steatohepatitis, cirrhosis and to end-stage liver disease.
- Prevalence of NAFLD varies by the sensiblity and specificity of the method of detection such as screening by alanine aminotransferase (ALT) or imaging for steatosis or confirmation by liver biopsy.
- Depending on the type of diagnostic tool the prevalence of NAFLD is estimated to be between 3–12%.
- For the diagnosis of NAFLD, the measurement of ALT is recommended. If the ALT level in obese children exceeds the sex-specific upper normal level 2 times or more, the diagnosis of NAFLD is very likely. In the case that ALT is less than 2 times higher than the upper normal value, but elevated then diagnoses can be confirmed by an additional raised GGT.
- NAFLD in obese children is of concern because of:

  high risk of the progression to nonalcoholic steatohepatatis (NASH) and cirrhosis (the latter has been reported as early as 8 years of age).

Always evaluate NAFLD in patients with Metabolic syndrome (MS)
Always evaluate MS in patients with NAFLD

Ref 2, 3, 6

METABOLIC SYNDROME (MS)

- Already detectable in children with obesity
- Prevalence increases with age and/or duration of obesity.
- No general consensus on definition in children.
- The most widely accepted definition for MS given by the *International Diabetes Federation* (IDF) in 2007

  - BUT several questions are still raised :

  - **age threshold**: does it exist before the age of 10 yrs ?
  - **age, gender and population specific standards for lipids and blood pressure are not taken into account.**
  - **no international waist circumference standards exist for children .**

Ref 2, 3, 6, 11

DEFINITIONS OF PEDIATRIC METABOLIC SYNDROME

Definition	Excess adiposity	Blood pressure	Blood lipids	Blood glucose/ insulin
IDF*	WC $\geq$ 90th percentile	SBP $\geq$ 130 mmHg or DBP $\geq$ 85 mmHg	Triacylglycerols $\geq$ 150 mg/dl or HDL cholesterol $<$ 40 mg/dl	Impaired fasting glucose $\geq$ 110 mg/dl
IDEFICS-monitoring level**	WC $\geq$ 90th percentile	SBP $\geq$ 90th percentile **or** DBP $\geq$ 90th percentile	Triacylglycerols $\geq$ 90th percentile **or** HDL cholesterol $\leq$ 10th percentile	HOMA-insulin resistance $\geq$ 90th percentile **or** Fasting glucose $\geq$ 90th percentile
IDEFICS-action level	WC $\geq$ 95th percentile	SBP $\geq$ 95th percentile **or** DBP $\geq$ 95th percentile	Triacylglycerols $\geq$ 95th percentile **or** HDL cholesterol $\leq$ 5th percentile	HOMA-insulin resistance $\geq$ 95th percentile **or** Fasting glucose $\geq$ 95th percentile

***IDF=International Diabetes Federation**

**** IDEFICS= Identification and prevention of Diatery and lifestyle-induced health EFfects in Children and infantS**

Altogether 18 169 aged 2-9 years children from 8 European countries participated in IDEFICS study. European standards for components of the MS have been developed.

Ref 8, 11

ENDOCRINE COMPLICATIONS

impact on puberty and linear growth

- Increased adiposity (particularly central) mediates alterations in leptin and insulin secretion/sensitivity thus interfering with the process of pubertal development at different levels.
- Obesity is associated with accelerated linear growth and bone age in both sexes, but final height is not affected.

Girls
Early onset of puberty
Hyperandrogenism
Polycystic ovary syndrome

Boys
Delayed onset of puberty
Gynecomastia alone/pseudogynecomastia
Hidden penis

Ref 2, 6

ENDOCRINE COMPLICATIONS
Thyroid

- An estimated 7 to 23 % of obese children are reported to have moderately elevated TSH levels together with normal FT4 or slightly elevated FT4 and/or FT3.
- These changes do not reflect abnormal thyroid function and do not require further investigation nor treatment.

In which children or adolescents with obesity should endocrine investigations be performed?

According to the newest recommendation there is no need for routine laboratory evaluations for endocrine etiologies of pediatric obesity unless the patient's stature and/or height velocity are attenuated.

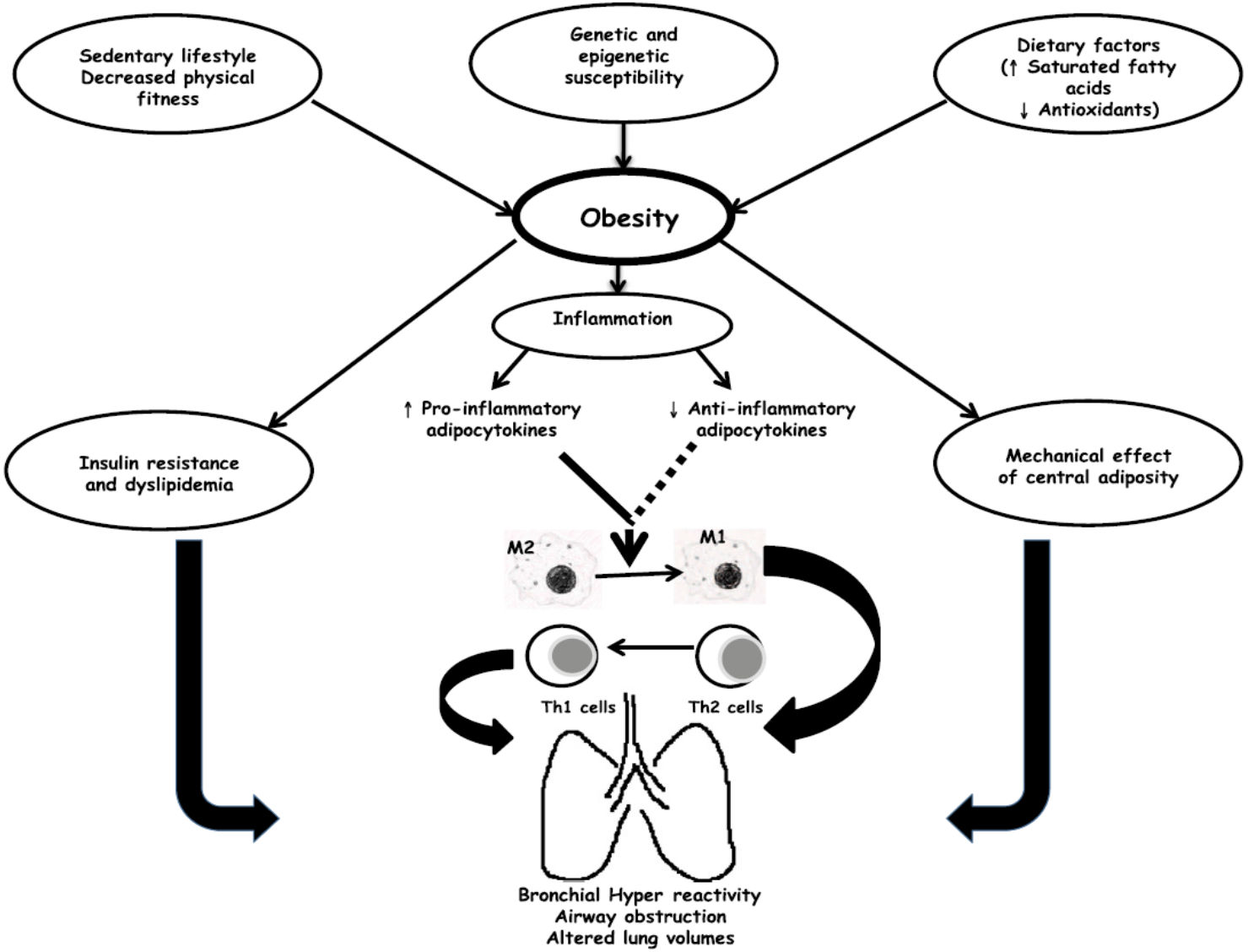
Ref 4, 6

RESPIRATORY DISEASE AND PAEDIATRIC OBESITY

- **Impact of obesity on the cardiorespiratory system on**
  - respiratory mechanics
  - respiratory muscle strength and endurance
  - airway resistance
  - lung volume and function
  - gas exchange
  - control of breathing
- **Role of metabolic dysregulation on paediatric obesity related asthma through**
  - Non atopic systemic mild inflammation
  - lower airways obstruction
  - Exercise induced bronchoconstriction
  - Lower responsivness to steroid treatment
- **ROHHAD**
  - Rapid onset Obesity with Hypothalamic Dysfunction, hypoventilation and autonomic dysfunction
  - rare paediatric syndrome
- **Obstructive sleep apnoea**

Ref 16, 17, 18

PAEDIATRIC OBESITY RELATED ASTHMA



Obesity is an independent risk factor for asthma.

Increased prevalence of asthma in childhood obesity results from the combination of adiposity mediated inflammation and mechanic constraints .

Ref 17

RESPIRATORY COMPLICATIONS AND SLEEP DISORDERS

- Pulmonary and sleeping problems are associated with obesity.

- Children with obesity have higher risk to develop asthma which is connected with inflammatory markers.

- The severity of obstructive sleep apnoea (OSA) increases with the degree of obesity.

- Epidemiological studies show that obesity, defined by the body mass index (BMI) higher than 28 kg/m2, increases the risk for OSA by 4-5 times in a group of children aged 2-18 years.

- The risk developing OSA is much greater if there is a family history of it.

- Children with severe obesity may have alveolar hypoventilation which can cause severe oxygen desaturation.

Ref 2, 3, 6, 18

OBSTRUCTIVE SLEEP APNOEA (OSA)

- OSA is documented 1-5 % in children.
- If the children have got a positive history for OSA, refer to pulmonology for nocturnal polysomnography or if it's not available-overnight oximetry.
- Unrecognized and untreated OSA may affect nearly every major system, causing daytime fatigue, growth delay, cardiovascular dysfunction, hypertension, behavior disorders, cognitive impairment.

Ref 18

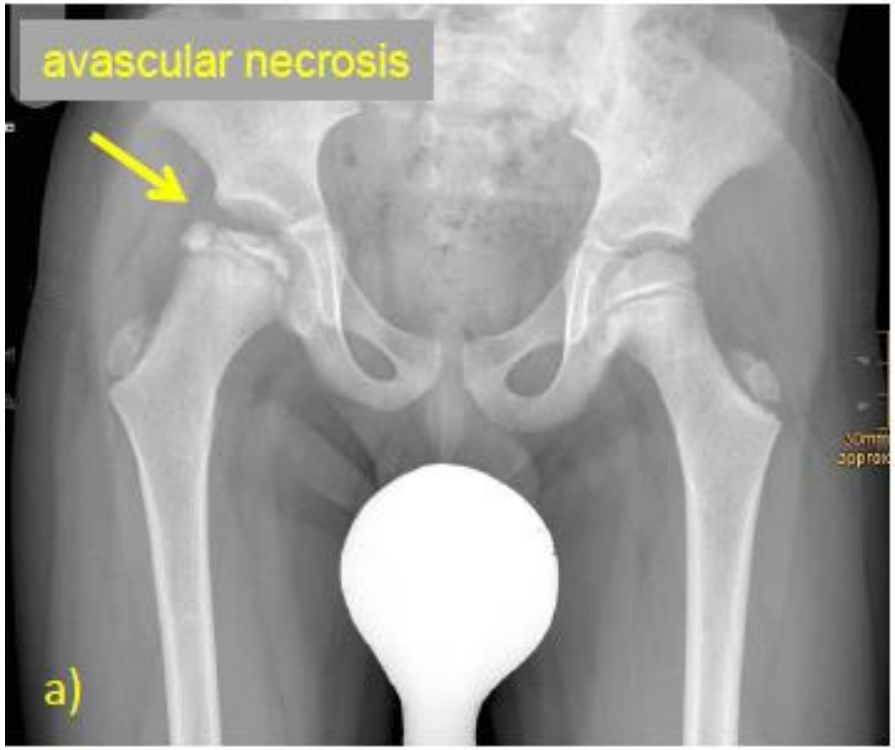
ORTHOPAEDIC COMPLICATIONS

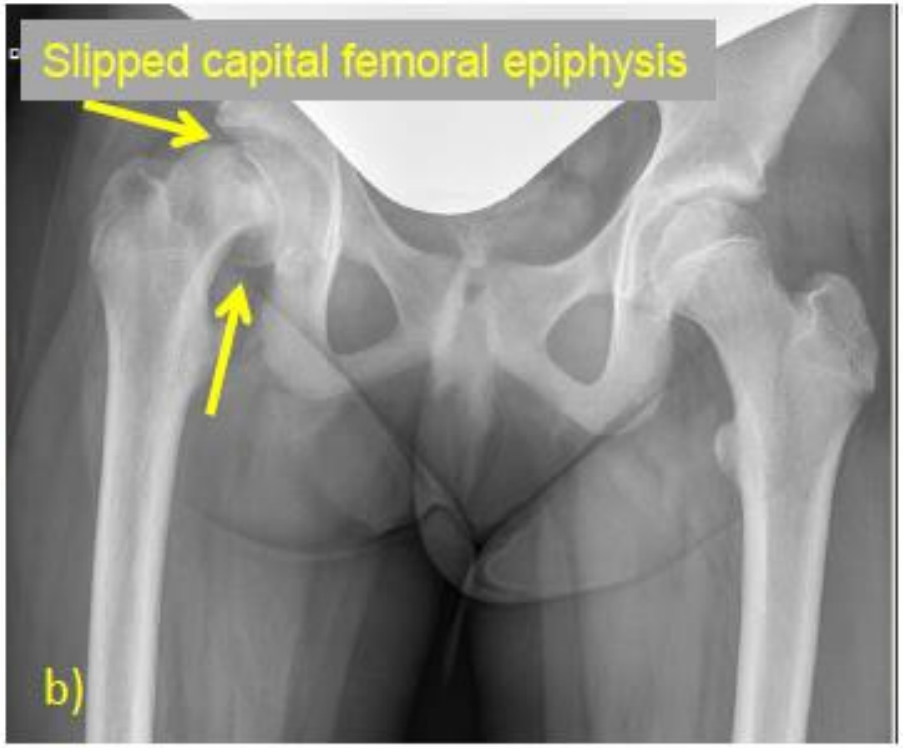
The orthopaedic conditions that tend to present more commonly in children with obesity include:

- Perthes' disease (avascular necrosis)
- Slipped capital femoral epiphysis
- Blount's disease
- Misalignment of the legs axis
- Flat foot

Ref 2, 6

ORTHOPEDIC COMPLICATIONS



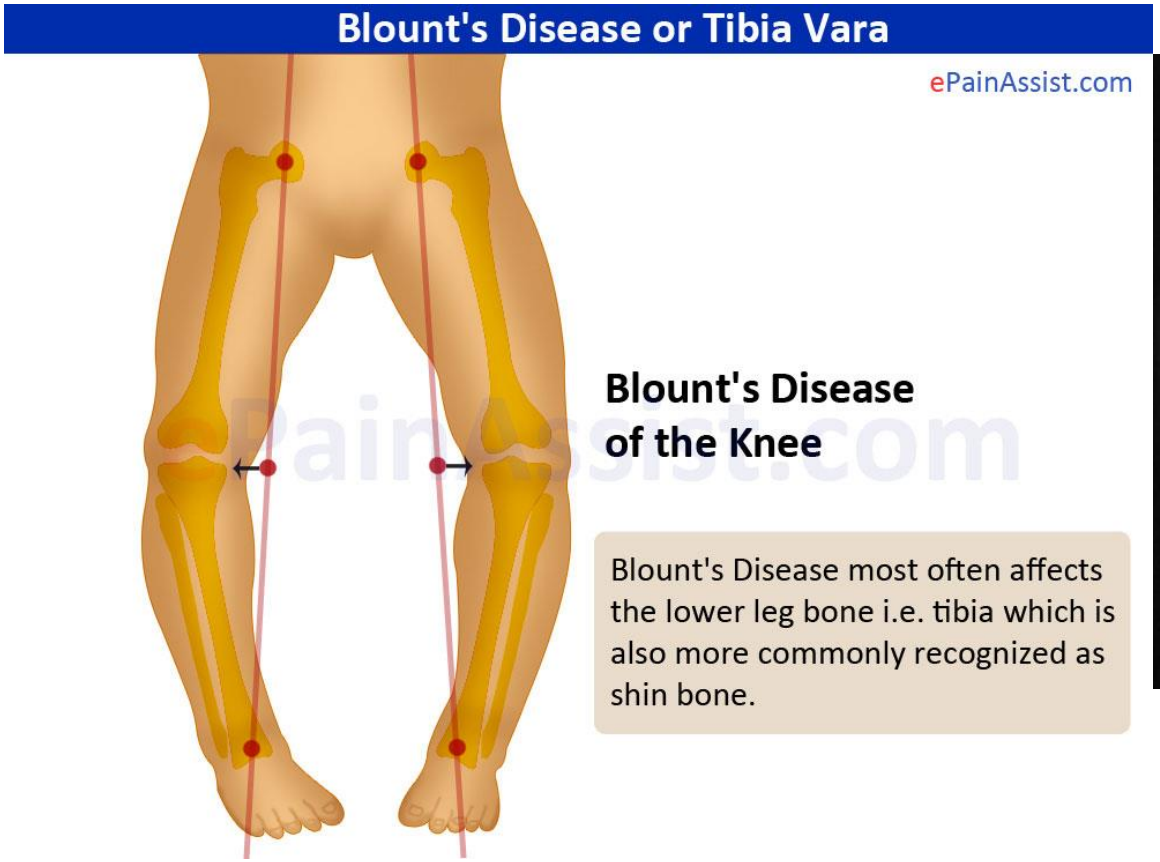


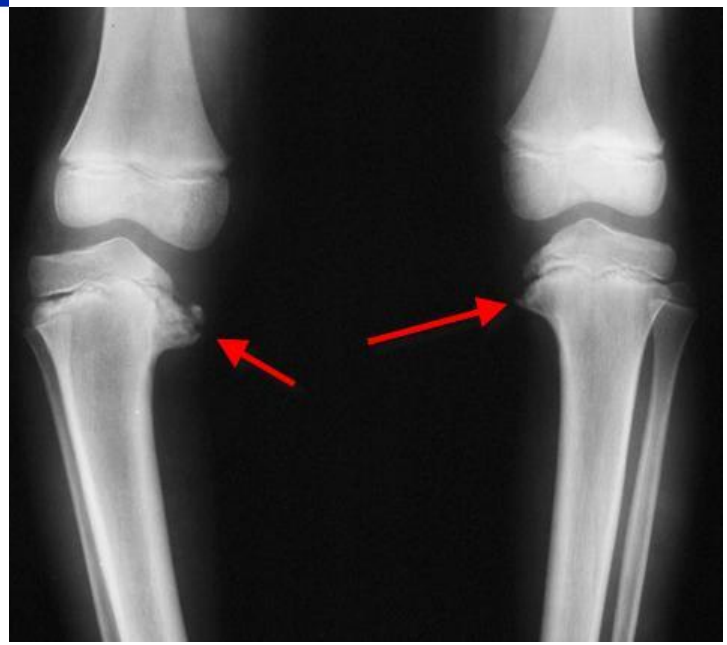
- More frequent in male at the age of 5-7 years
- Clinical signs: hip pain - worsens with movement, and limitation of mobility.
- In the initial phase the X-ray may not show any signs of skeletal alteration, therefore Magnetic Resonance is recommended.

It develops slowly or precipitated by a trauma
Clinical signs: uncertain pain and persistent limping in a child with obesity.
Diagnoses: comparison image of the hips in anterior and frog-leg lateral views.

Ref 6

BLOUNT’S DISEASE





MISALIGNMENT OF THE LEGS AXIS

- The anatomical shape of the leg axis needs to be distinguished between
  - **an abduction adjustment** (with normal anatomical axis of the leg but with pathological positioning) and
  - **genu valgum** as pathology of the anatomic leg axis in its osseous form.

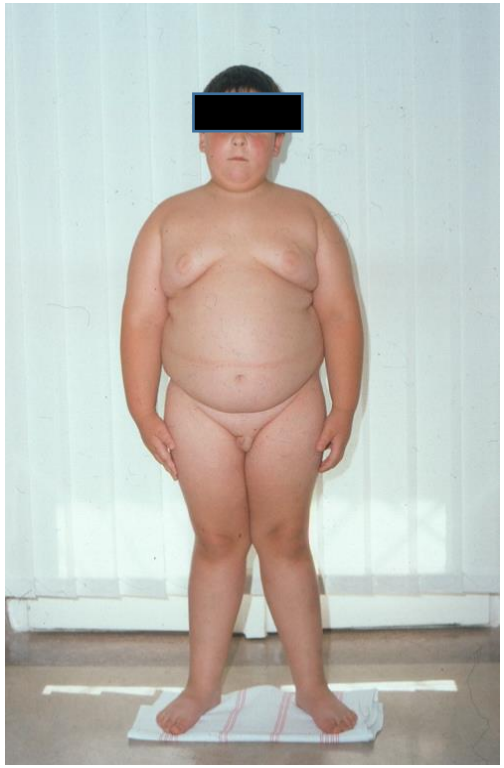
- Genuine genu valgum has a static consequence, but also dynamic implications, so it requires a guided correction of angular deformity of the knee to avoid osteotomy or osteoarthritis later in life.

- Orthopaedic examination is a mandatory part of the clinical examination of any child or adolescents with obesity.

Ref 6

PRIMARY OBESITY WITH GENU VALGUM

<u>False genu valgum</u> by abduction adjustment due to the fat mass of the tights
(*from Lechevallier, 2013*)



Severe form of genu valgum

FLAT FOOT

- The most common clinically diagnosed deformity in children with obesity
- Develops when the greater mid-foot contact surface is no longer sufficient to compensate for the patient's overweight.
- Physiotherapy and insertion of a temporary orthotic may be useful to optimize the position of the foot during gait.

Flat foot is a common early feature of child and adolescent obesity
Hollow feet in obesity should draw the attention toward an underlying neurological disease .

Reference 6

PSYCHOLOGICAL COMPLICATIONS

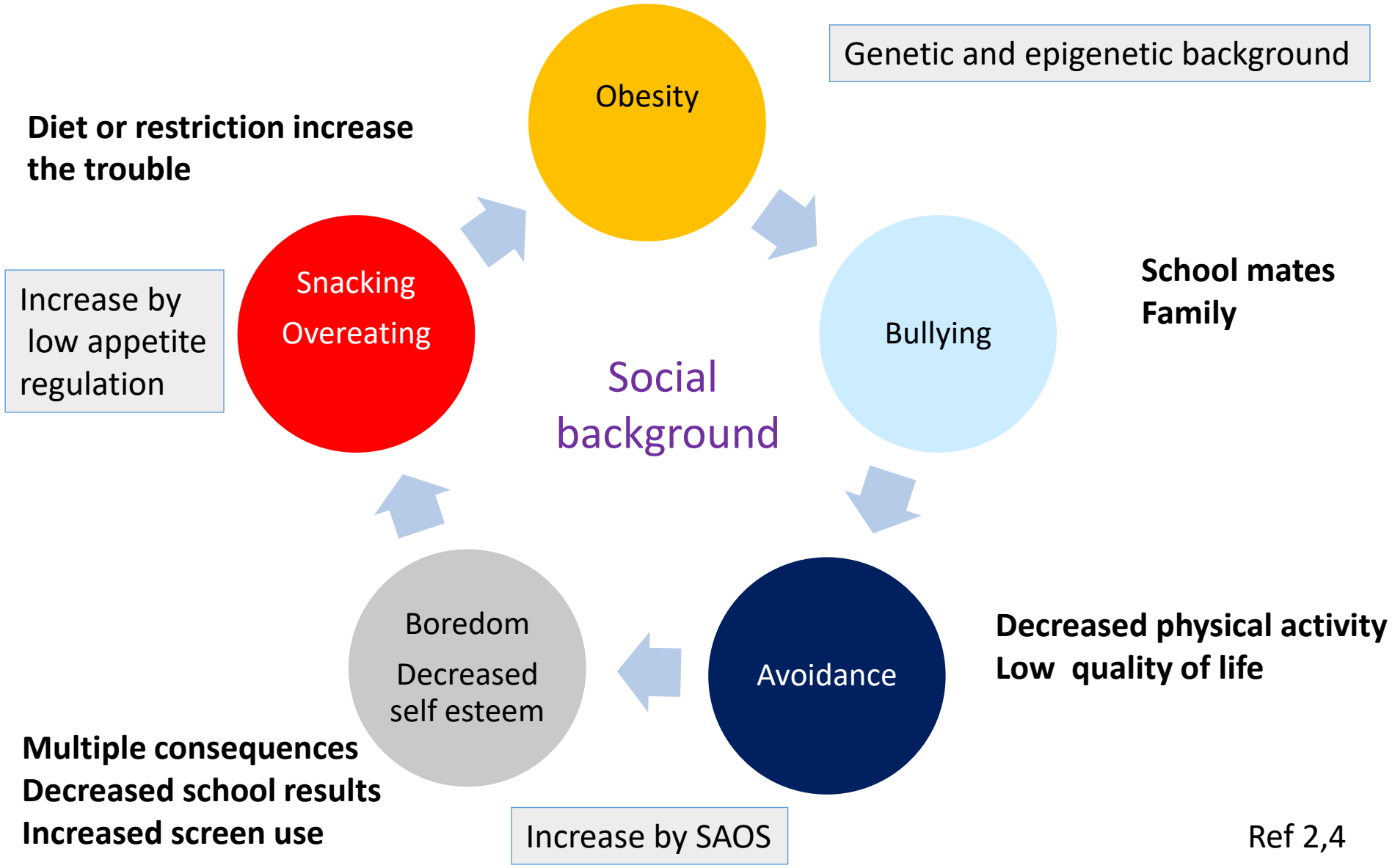
Child and adolescent obesity may either be the cause or the consequence of psychological disturbances or both

- Psychological consequences are early and sometimes severe .
- Psychological complications require a precise evaluation and follow up.
- Decreased quality of life is a key common complication.
- A vicious circle is generated in most cases (cf next slide)
- The role of the clinician is to try to disentangle causes and consequences prior to settle therapeutic goals.
- Physical complications such as SAOS which have psychological consequences should be identified .
- If children with obesity have a positive history of psychosocial complications refer them to mental health specialist.

For more information, please refer to emodule on Psychological assesment

Ref 2,4

PSYCHOLOGICAL COMPLICATIONS
The vicious circle of childhood obesity



Ref 2,4

QUESTIONS

- Can the severity and duration of obesity influence the severity of complications in children ? – **yes**
- What parameters are important in the assessment of hypertension according to the newest guideline ?- **sex, age, height percentile**
- What type of screening tests can be used for evaluating the disturbance of glucose metabolism in children ? – **fasting plasma glucose, HbA1c, 2-hours oral glucose tolerance**
- What's the prevalence of dislipidaemia in adolescents with obesity ? – **up to 40 %**
- When would you evaluate the risk of NAFLD in a child with obesity ? – **in patients with metabolic syndrome**
- Is it necessary to examine children with obesity for endocrine etiology ?- **no, just in case if the patient's stature and/or height velocity are attenuated.**
- Do children with obesity have higher risk to develop asthma ? - **yes**
- What is the difference in the clinical signs of Perthes' disease and slipped capital femoral epiphysis? - **pain**

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