REGION SJÆLLAND
HOLBÆK SYGEHUS
– vi er til for dig

KØBENHAVNS UNIVERSITET
DET SUNDHEDSVIDENSKABELIGE FAKULTET

EN GENNEMGANG AF RESULTATER FRA THE HOLBÆK STUDY

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INDHOLD

- Baggrund
  - The HOLBÆK Study
  - Kohorterne
  - Undersøgelser og prøveindsamling
- Resultater
  - Komplikationer til overvægt
  - Behandlingseffekt
  - Referenceværdier – biomarkører
  - Genetik
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TAKE HOME MESSAGE

Behandling af overvægt/svær overvægt:

Holbæk-modellen

- Effektiv i mange aspekter af barnets/den unges liv og helbred
- Vedvarende og med stabile resultater i forskellige sektorer

Forskning:

The HOLBÆK Study

- Store, veldefinerede kohorter
- Dybdegående fænotype- og genotypebestemmelse

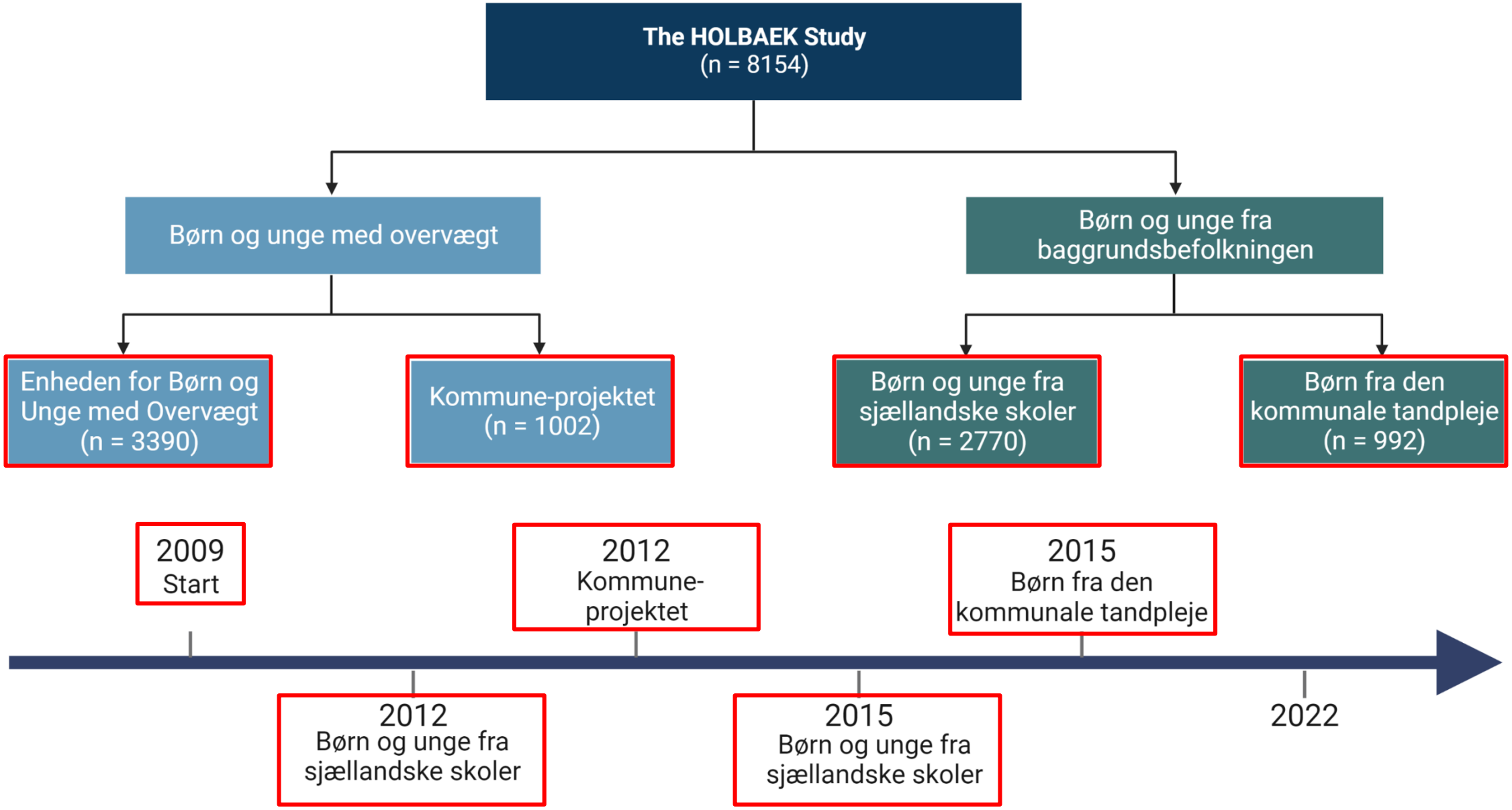
THE HOLBAEK STUDY

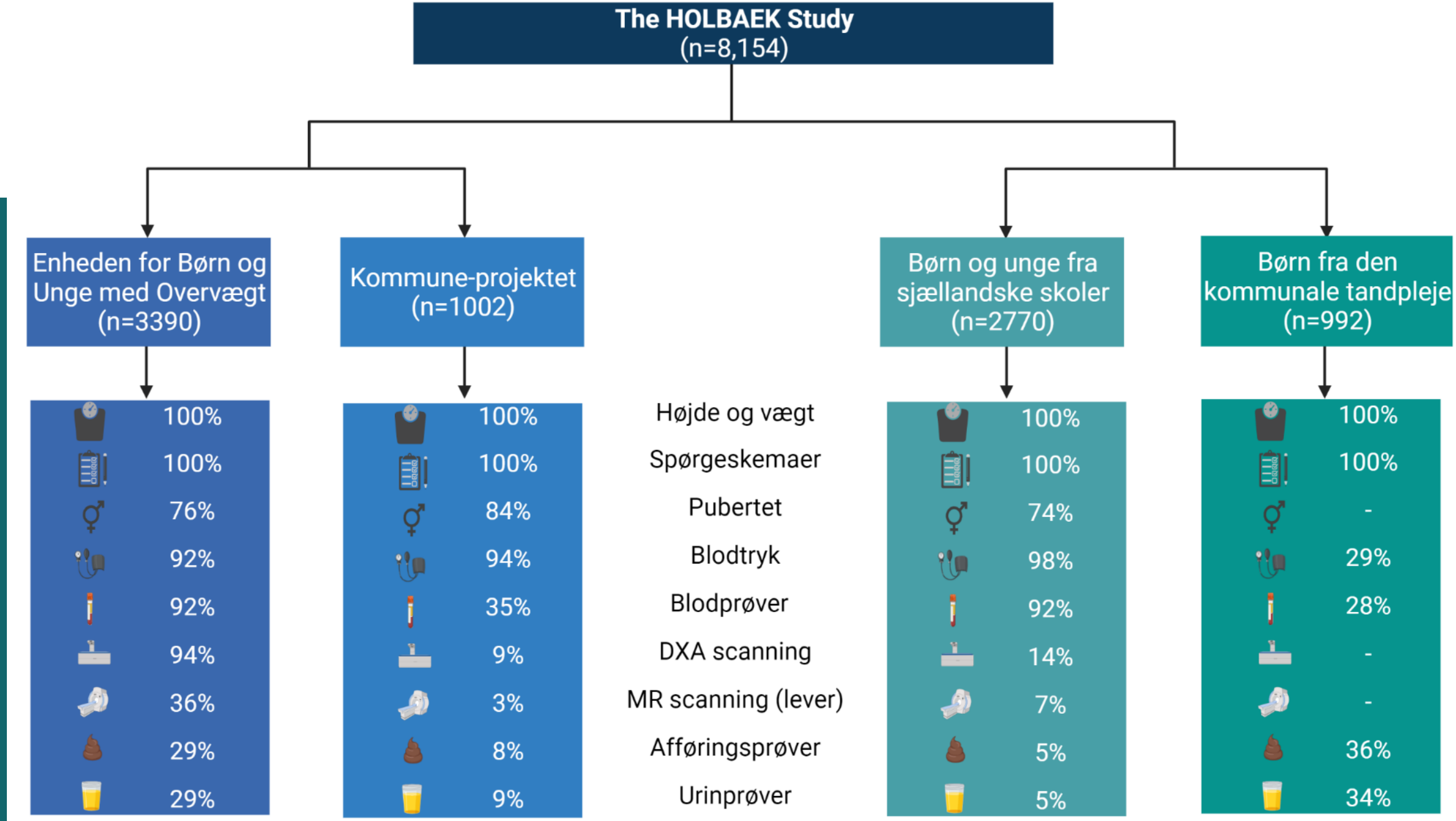
2007: **Holbæk-modellen**

- Udviklet af klinisk lektor og forskningsleder Jens-Christian Holm, Holbæk, Danmark
  - Holistisk, personcentreret, familiebaseret model til behandling af overvægt
  - Effektiv både på hospitaler og i kommuner
  - 5 timers sundhedsprofessionel tid per patient per år
  - Høj grad af patient-uddannelse

2009: **The HOLBÆK Study**

- (tidligere kendt som Den Danske Data- og Biobank for Børn og Unge med Overvægt)
  - Klinisk lektor og forskningsleder Jens-Christian Holm (Enheden for Børn og Unge med Overvægt, Holbæk Sygehus)
  - Professor Torben Hansen (Novo Nordisk Foundation Center for Basic Metabolic Research, Københavns Universitet, DK)
  - Professor Michael Christiansen (Statens Serum Institut, DK)


The HOLBAEK Study
(n = 8154)
Børn og unge med overvægt
Børn og unge fra baggrundsbefolkningen
Enheden for Børn og Unge med Overvægt (n = 3390)
Kommune-projektet (n = 1002)
Børn og unge fra sjællandske skoler (n = 2770)
Børn fra den kommunale tandpleje (n = 992)
2009
Start
2012
Kommune-projektet
2015
Børn fra den kommunale tandpleje
2012
Børn og unge fra sjællandske skoler
2015
Børn og unge fra sjællandske skoler
2022


The HOLBAEK Study
(n=8,154)
Enheden for Børn og Unge med Overvægt (n=3390)
Kommune-projektet (n=1002)
Børn og unge fra sjællandske skoler (n=2770)
Børn fra den kommunale tandpleje (n=992)
Højde og vægt
Spørgeskemaer
Pubertet
Blodtryk
Blodprøver
DXA scanning
MR scanning (lever)
Afføringsprøver
Urinprøver
100%
100%
76%
92%
92%
94%
36%
29%
29%
100%
100%
84%
94%
35%
9%
3%
8%
9%
100%
100%
74%
98%
92%
14%
7%
5%
5%
100%
100%
-
29%
28%
-
-
36%
34%

KOMPLIKATIONER TIL OVERVÆGT

- 75% med lavt selvværd, selvtillid eller livskvalitet
- 82% med forstyrret spisning
- 50% med hypertension eller præ-hypertension
- 28% med dyslipidæmi
- 60% med vitamin-D insufficiens
- 14% med prædiabetes
- 45% med søvnapnø
- 31% med hepatisk steatose

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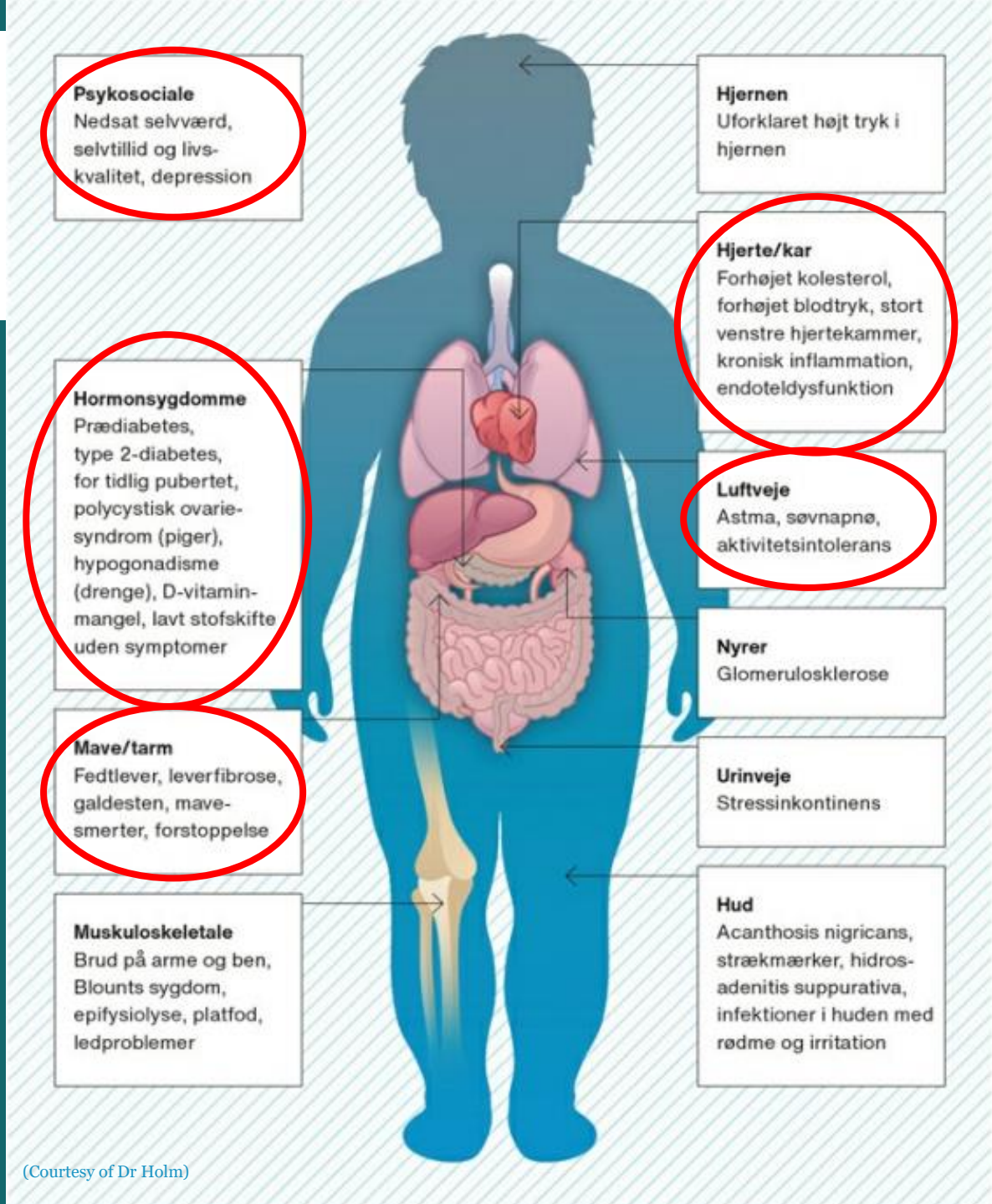

(Courtesy of Dr Holm)

KOMPLIKATIONER TIL OVERVÆGT

- En prediktiv model som med brug af undersøgelsesresultater der allerede forefindes, giver mulighed for at identificere personer med risiko for at udvikle fedtlever.

- Forhøjet glucagon er associeret til øget kardiometabolisk risiko, hos børn og unge med overvægt.

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Clinical Research Article

Hyperglucagonemia in Pediatric Adiposity Associates With Cardiometabolic Risk Factors but Not Hyperglycemia

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Abstract

Context: In adults, hyperglucagonemia is associated with type 2 diabetes, impaired glucose t
pediatric overweight/obesity remains unclear.

Objective: We examined whether fasting concentrations of glucagon are elevated in youth wit
ates with cardiometabolic risk profiles.

Methods: Analyses were based on the cross-sectional HOLBAEK study, including children an
weight/obesity from an obesity clinic group (n = 2154) and with normal weight from a population-
of plasma glucagon and cardiometabolic risk outcomes were assessed, and multiple linear and l

Results: The obesity clinic group had higher glucagon concentrations than the population-base
ciated with body mass index (BMI) standard deviation score (SDS), waist, body fat %, liver fat
C-reactive protein, homeostasis model assessment of insulin resistance, insulin, C-peptide, LD
blood pressure, and was inversely associated with fasting glucose. The inverse relationship bet
individuals with high BMI SDS and high fasting insulin. Glucagon was associated with a higher
dyslipidemia, and hypertension, but not with hyperglycemia. Glucagon was positively associated

Conclusion: Compared with normal weight peers, children and adolescents with overweight/ob
cagon, which corresponded to worsened cardiometabolic risk outcomes, except for hyperglycer
may precede impairments in glucose regulation.

Key Words: adolescent, cardiometabolic risk, child, glucagon, hyperglycemia, obesity

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; GLP-1, glucag
HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistan
interquartile range; LDL-C, low-density lipoprotein-cholesterol; LLOQ, lower limit of quantitation; OR, odds r

Glucagon opposes the glucose-lowering actions of insulin and stimulates hepatic glucose production (1). Glucagon also mediates several nonglucose-related metabolic effects, including regulation of amino acid metabolism (ureagenesis) (2); stimulation of insulin secretion (3); break down of fatty acids and lipogenesis inhibition in the liver (4); potential reduction of food intake (5); increased energy expenditure (6); and possibly regulation of heart rate and contractility (7), although the latter effects may not be physiological. The regulation of glucagon secretion paracrine, endocrin Inhibitors of glucag beta cell–derived fa delta cell–derived s feedback; gastrointe tide-1 (GLP-1); and and glucose. Conve include amino acids

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ORIGINAL RESEARCH

Pediatric OBESITY WILEY

Possible prediction of obesity-related liver disease in children and adolescents using indices of body composition

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Summary

Background: Diagnosis of nonalcoholic fatty liver disease in children and adolescents currently requires advanced or invasive technologies.

Objectives: We aimed to develop a method to improve diagnosis, using body composition indices and liver biochemical markers.

Methods: To diagnose non-alcoholic fatty liver disease, 767 Danish children and adolescents underwent clinical examination, blood sampling, whole-body dual-energy X-ray absorptiometry scanning and proton magnetic resonance spectroscopy for liver fat quantification. Fourteen variables were selected as a starting point to construct models, narrowed by stepwise selection. Individuals were split into a training set for model construction and a validation test set. The final models were applied to 2120 Danish children and adolescents to estimate the prevalence.

Results: The final models included five variables in different combinations: body mass index–standard deviation score, android-to-gynoid-fat ratio, android-regional fat percent, trunk-regional fat percent and alanine transaminase. When validated, the sensitivity and specificity ranged from 38.6% to 51.7% and 87.6% to 91.9%, respectively. The estimated prevalence was 24.2%–35.3%. Models including alanine transaminase alongside body composition measurements displayed higher sensitivity.

Conclusions: Body composition indices and alanine transaminase can be used to estimate non-alcoholic fatty liver disease, with 38.6%–51.7% sensitivity and 87.6%–91.9%, specificity, in children and adolescents with overweight (including obesity). These estimated a 24.2%–35.3% prevalence in 2120 patients.

KEYWORDS
adolescents, body composition, children, DXA-scan, MAFLD, NAFLD

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; AIC, Akaike information criterion; ALT, alanine transaminase; AUC, area under the curve; BMI SDS, body mass index–standard deviation score; DXA, whole-body dual-energy X-ray absorptiometry; MAFLD, metabolic dysfunction–associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; VAT, visceral adipose tissue.

Holbæk-modellen

4-5 timer sundhedsprofessionel tid pr. patient pr. år

Reducerer graden af overvægt hos 74-76% (op til 90%) af børn og unge med overvægt

Fogh, M., J Paediatr Child Health 2020; Mollerup, P., PLoS One 2017; Most, SW., BMC Pediatr. 2015; Nielsen TRH., PLoS One 2018;

Reducerer graden af dyslipidæmi Nielsen, TRH., Child Obes. 2012	Reducerer graden af hypertension Hvidt, KN., J Hypertens. 2014	Reducerer graden af fedtlever Fonvig, CE., BMC Pediatr. 2015	Reducerer graden af overvægt hos forældrene Trier, C., PLoS One. 2016	Reducerer appetit og mobning Fonvig, CE., Qual Life Res. 2017
Implementeret i primær og sekundær sektor Holm, J-C., Int J Pediatr Obes. 2011; Mollerup, P., PLoS One 2017	Livskvalitet og selvværd øges Mollerup, P., Qual Life Res. 2017	Uafhængigt af genetisk risikoscore (15 gener) Hollensted, M., Obes. 2018	eHealth løsning (vægtreduktion hos 72-85% voksne) Langkjær, IOJ., Mhealth. 2022	Vægtreduktion hos 80-85% voksne i Norge Unpublished
Uafhængigt af SØS og graden af overvægt ved start J-C., Int J Pediatr Obes. 2011	Uafhængigt af familiær disponering til overvægt Nielsen, LA.. PLoS ONE 2015	Uafhængigt af sukkerindtag Trier, C., Pediatri Obes. 2016	Uafhængigt af insulinresistens Kloppenborg, JT., Pediatr Diabetes 2018	Uafhængigt af forstyret spisning Fogh, M., J Paediatr Child Health 2020

REFERENCE VÆRDIER - BIOMARKØRER

- Adipokiner: Resistin, Leptin og Adiponectin
- Plasmalipider (Total kolesterol, LDL, HDL og triglycerider)
- Lever biomarkører (ALT, AST, LDH, GGT og ALP)
- Sukkerstofskiftet (glukose, HbA1c, insulin, C-peptide og HOMA-IR)
- Energistofskiftet (TSH, T3 og T4)
- Vitamin D, kalcium, fosfat og PTH
- Immunoglobuliner (ikke publiseret)
- Jern (ikke publiseret)

GENETIK

Genetik

- 6 nye gener associeret med overvægt (konsortier-studier)
- MC4R-recepter-mutationer i ~3%
  (Trier et al., Int J Obs. 2021)

Disponering

- Familiær disponering til type 2 diabetes er associeret med en større grad af overvægt hos børn og unge.
  (Nielsen et al., Obes Facts. 2015)

FREMTID

- Randomiset, kontrolleret forsøg: HOT versus COT
  - Holbæk-modellen (HOT) versus konventionel behandling af overvægt (COT)
- Longitudinelle studier
  - Langsigtet behandlingseffekt hos børn og unge med overvægt
  - Langsigtet opfølgning på gruppen af børn og unge i befolkningsgruppen
- The HOLBÆK Study
  - Forbinder dybdegående fænotype- og genotypebestemmelse

TAKE HOME MESSAGE

Behandling af overvægt/svær overvægt:

Holbæk-modellen

- Effektiv i mange aspekter af barnets/den unges liv og helbred
- Vedvarende og med stabile resultater i forskellige sektorer

Forskning:

The HOLBÆK Study

- Store, veldefinerede kohorter
- Dybdegående fænotype- og genotypebestemmelse

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Participants in The HOLBAEK Study

Doctors
Nurses
Dieticians
Research year students
Secretaries

Consortia:
EGG
TARGET
BIOCHILD
MicrobLiver

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SPØRGSMÅL?