

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

SFEFS Projekt 353

INW, D-AGRL, ETHZ

Prof Dr Nori Geary

Prof Dr vet med Wolfgang Langhans

Dr Lori Asarian

Ostschweizer Kinderspital, St. Gallen

PD Dr med Dagmar l'Allemande

Dr med Iso Hutter

ILW, D-AGRL, ETHZ

PD Dr med Michael Zimmerman

Presented 19.10.2009

ETH Zürich

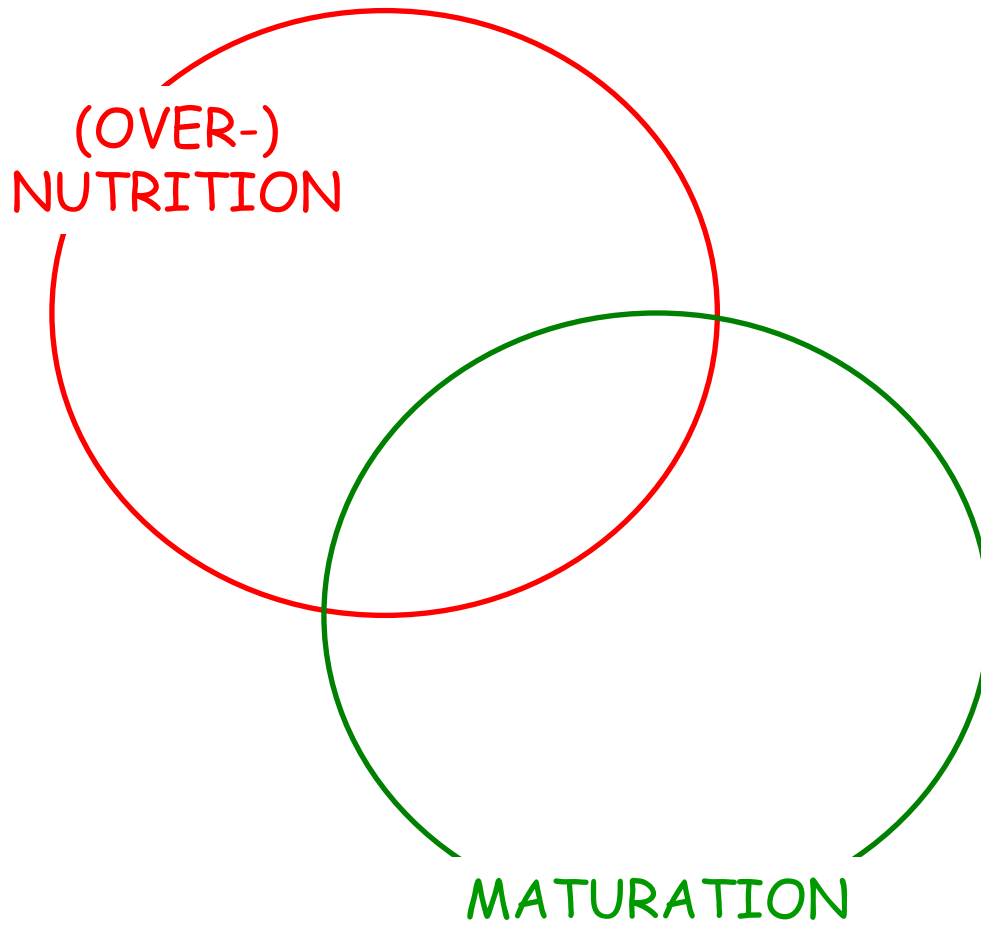
SFEFS Jubiläum

Changes in plasma levels of inflammatory molecules during puberty in **overweight and obese** children and their association with co-morbidities

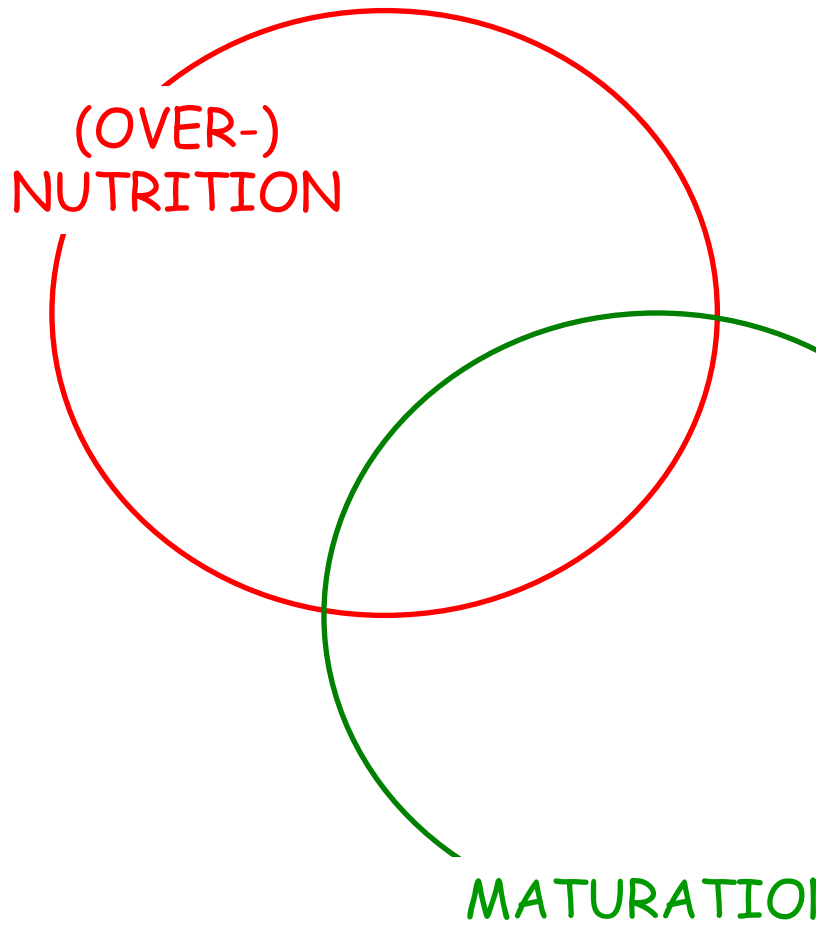


(OVER-)
NUTRITION

Changes in plasma levels of inflammatory molecules
during puberty in **overweight and obese** children and
their association with co-morbidities

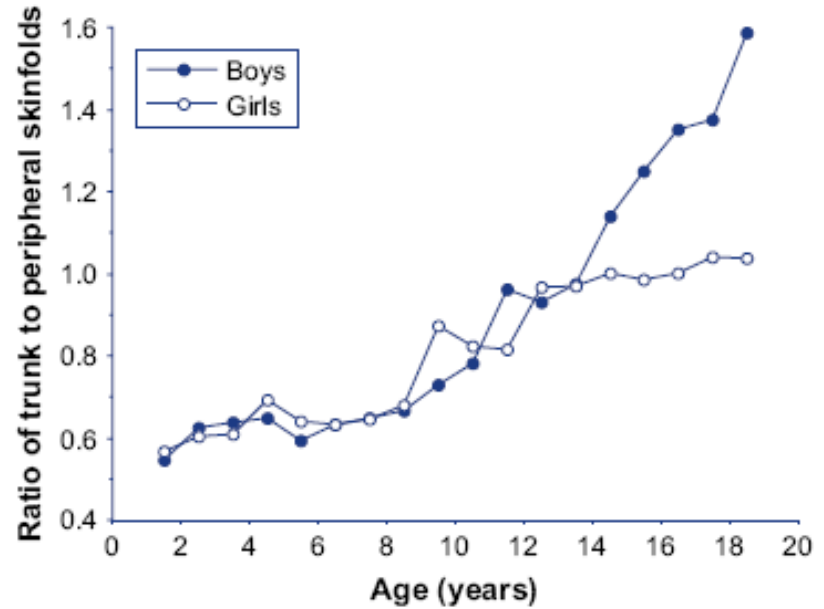
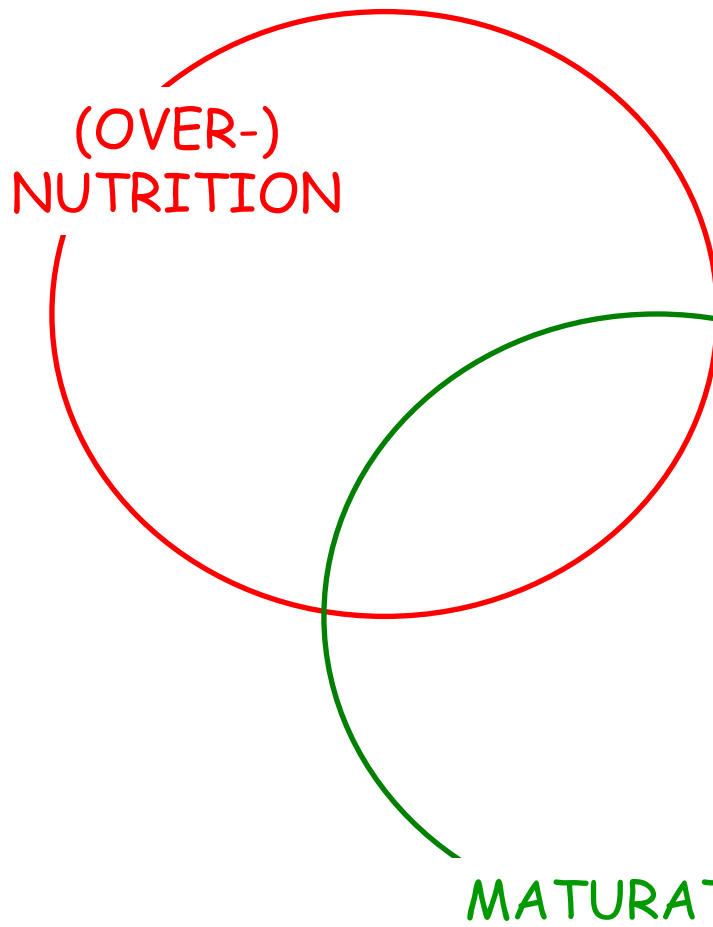


Changes in plasma levels of inflammatory molecules during puberty in **overweight and obese** children and their association with co-morbidities



Distribution and Physiology of adipose tissue differs in men and women, ...

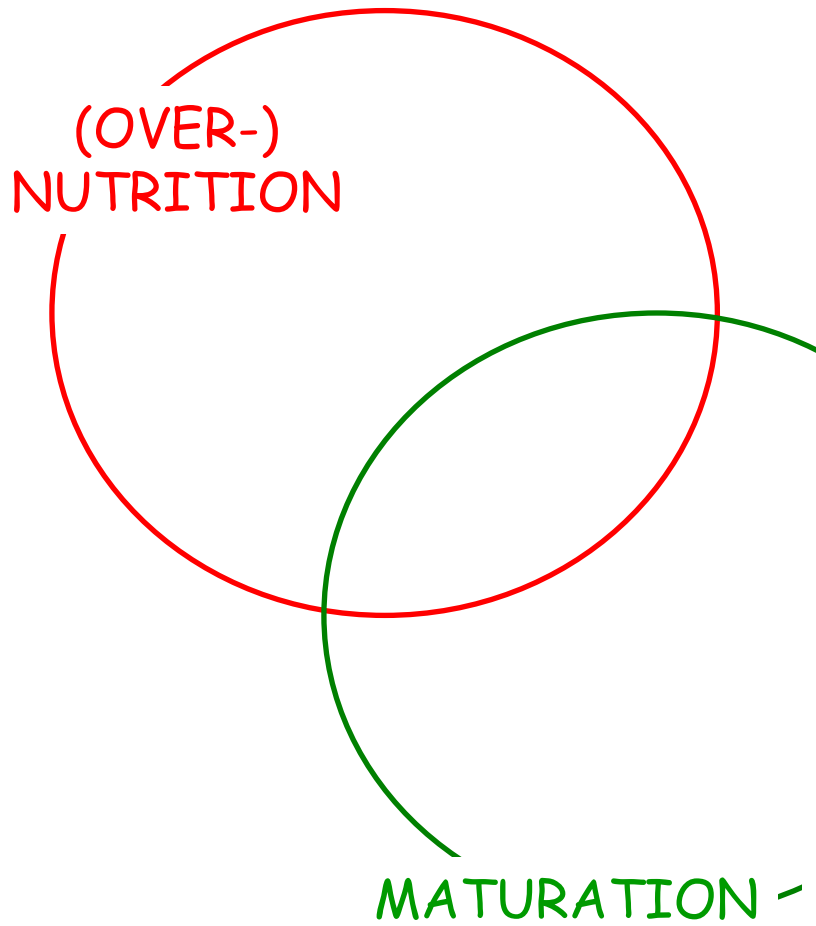
Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities



Rolland-Cachera et al., 1990

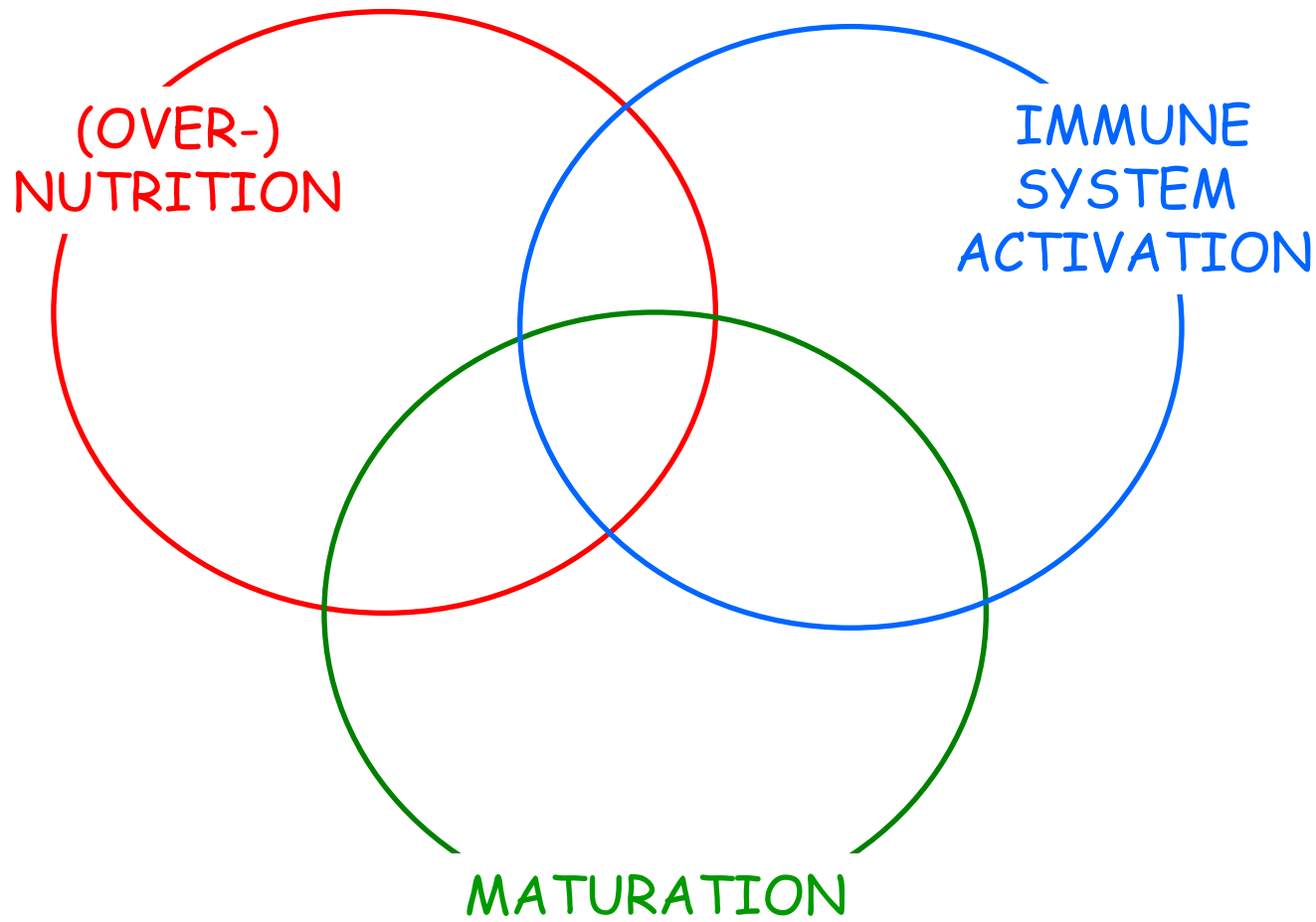
Distribution and Physiology of adipose tissue differs in men and women, but not in young boys and girls

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities



Distribution and Physiology of adipose tissue differs in men and women, but not in young boys and girls... and fat in different parts of the body has different health risks

Changes in plasma levels of **inflammatory molecules** during **puberty** in **overweight and obese** children and their association with co-morbidities



Changes in plasma levels of **inflammatory molecules** during **puberty** in **overweight and obese** children and their association with co-morbidities

IMMUNE SYSTEM ACTIVATION

Immune System

Adaptive Immune System

Formation of antibodies to recognize and neutralize pathogens - recognizes any non-self molecule

Innate Immune System

Built-in receptors to several common pathogens.

Phagocytosis and elimination

Inflammatory response

Rubor (increases blood flow, redness)

Rigor (swelling, stiffness)

Dolor (pain)

Caldor (heat)

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

IMMUNE SYSTEM ACTIVATION

Innate Immune System

Several cell types

Macrophages, neutrophils, ...

Phagocytosis and elimination

Several signalling molecules (pro- / anti-inflammatory)

Tumor necrosis factor- α

Interleukins

and many more ...

Local inflammation spills over to systemic response

Signalling molecules in plasma

Other organs involved

With too much activation, defense

turns into deterioration ... septic shock

Changes in plasma levels of **inflammatory molecules** during **puberty** in **overweight and obese** children and their association with **co-morbidities**

IMMUNE SYSTEM ACTIVATION

Innate Immune System

With too much activation,
defense turns into deterioration

Some major pathophysiological consequences of obesity are now thought to be caused by chronic stimulation of the innate immune system

Atherosclerosis
Type 2 diabetes mellitus (T2DM)
Fatty-liver disease (NASH)

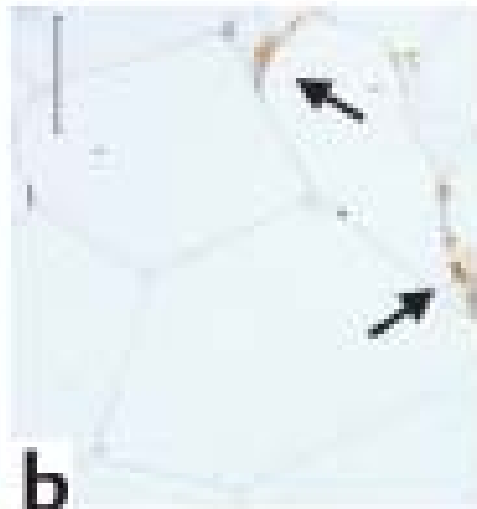
Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

OBESITY IS NOW RECOGNIZED AS AN INFLAMMATION-LIKE STATE



Slightly overweight

Small-medium size
Fat cells

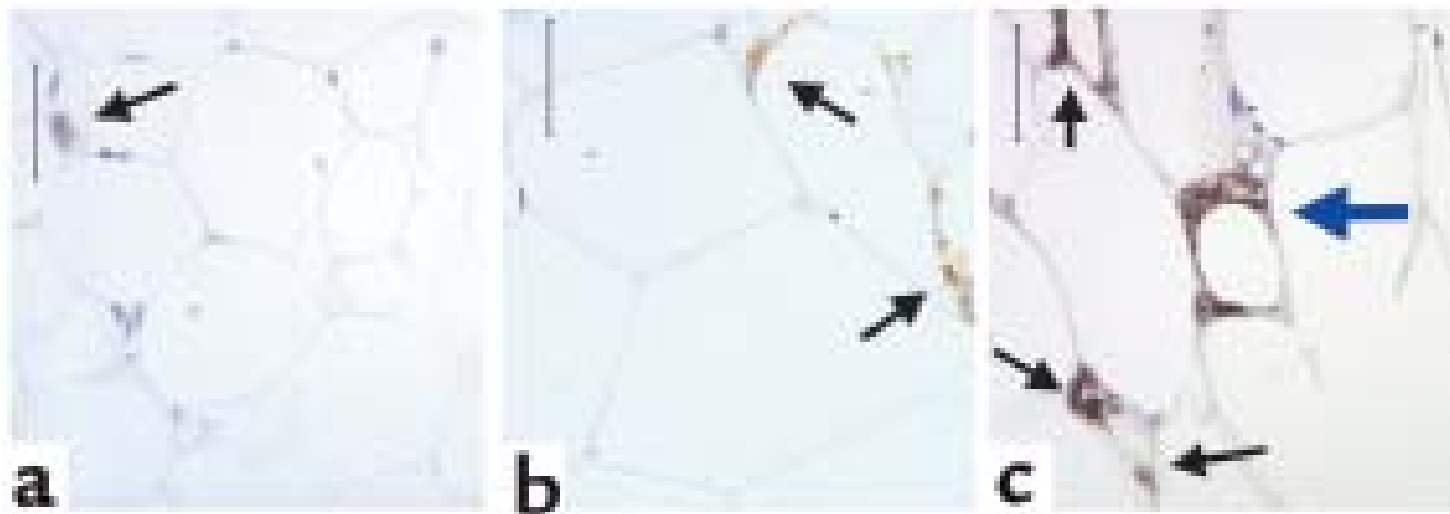


Obese

Very Large
Fat cells

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

OBESITY IS NOW RECOGNIZED AS AN INFLAMMATION-LIKE STATE



Slightly overweight

Obese

Obese

Small-medium size
Fat cells

Very Large
Fat cells...

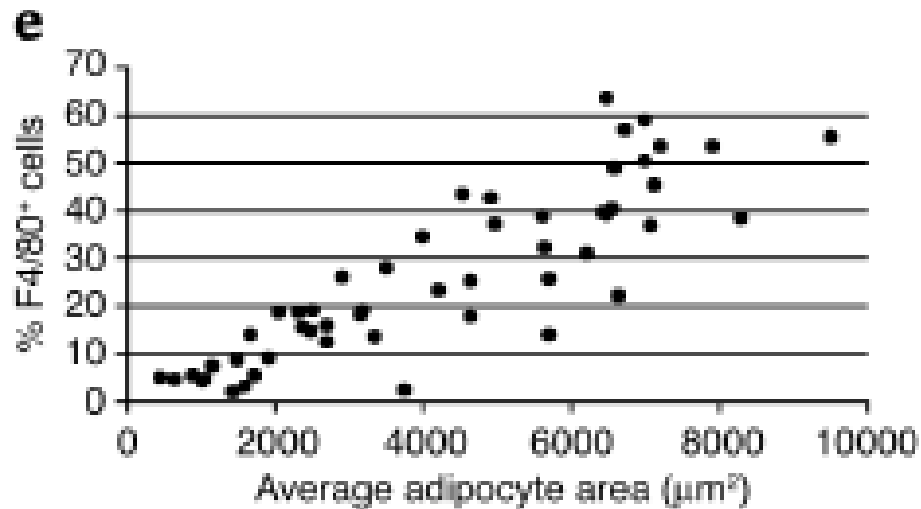
And
Macrophages !

Weisberg et al., 2003

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

OBESITY IS NOW RECOGNIZED AS AN INFLAMMATION-LIKE STATE

Macrophages



Obese

Obese

Very Large
Fat cells

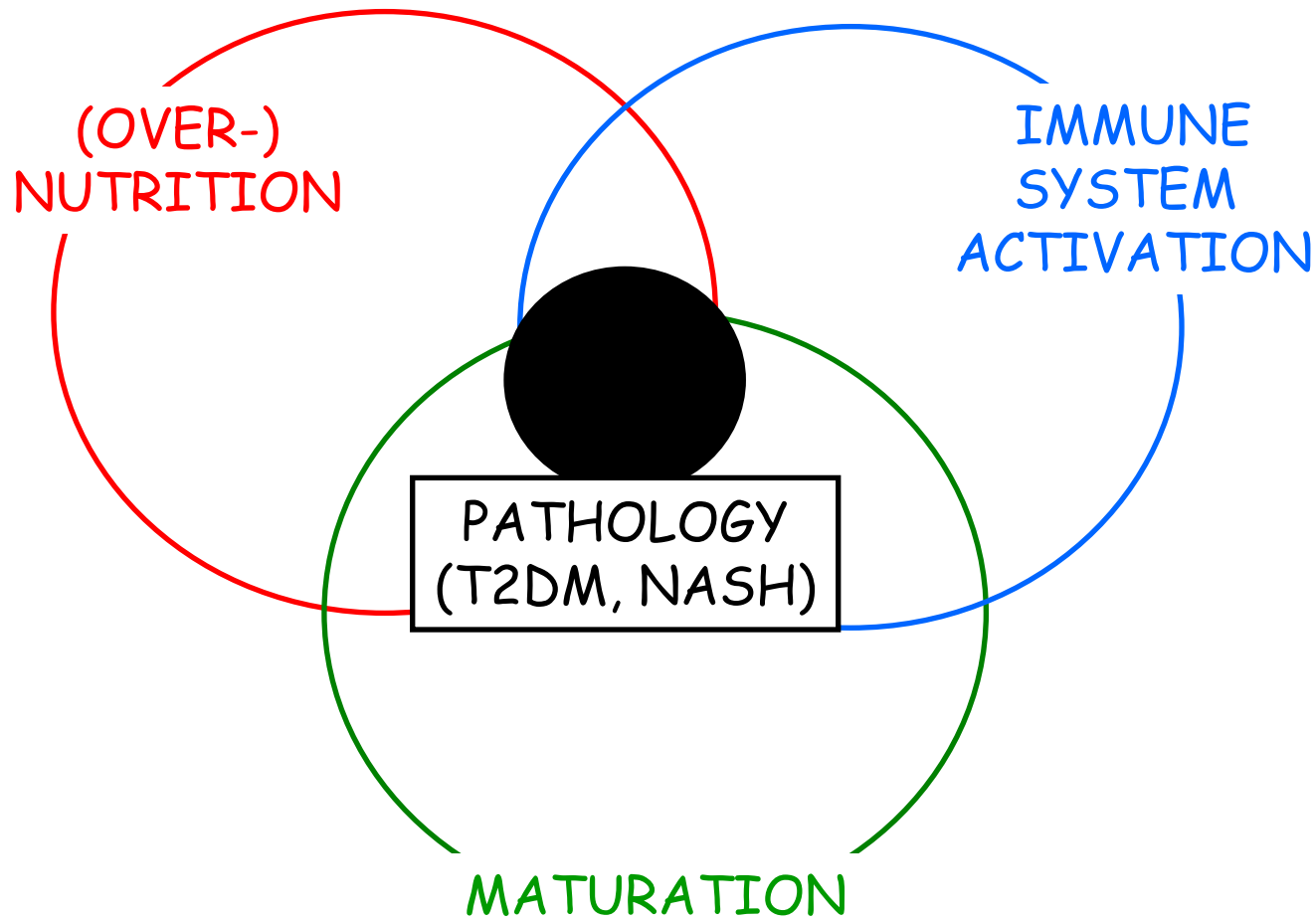
And
Macrophages !

Weisberg et al., 2003

Immune Signaling Molecules Elevated in Obese Adults

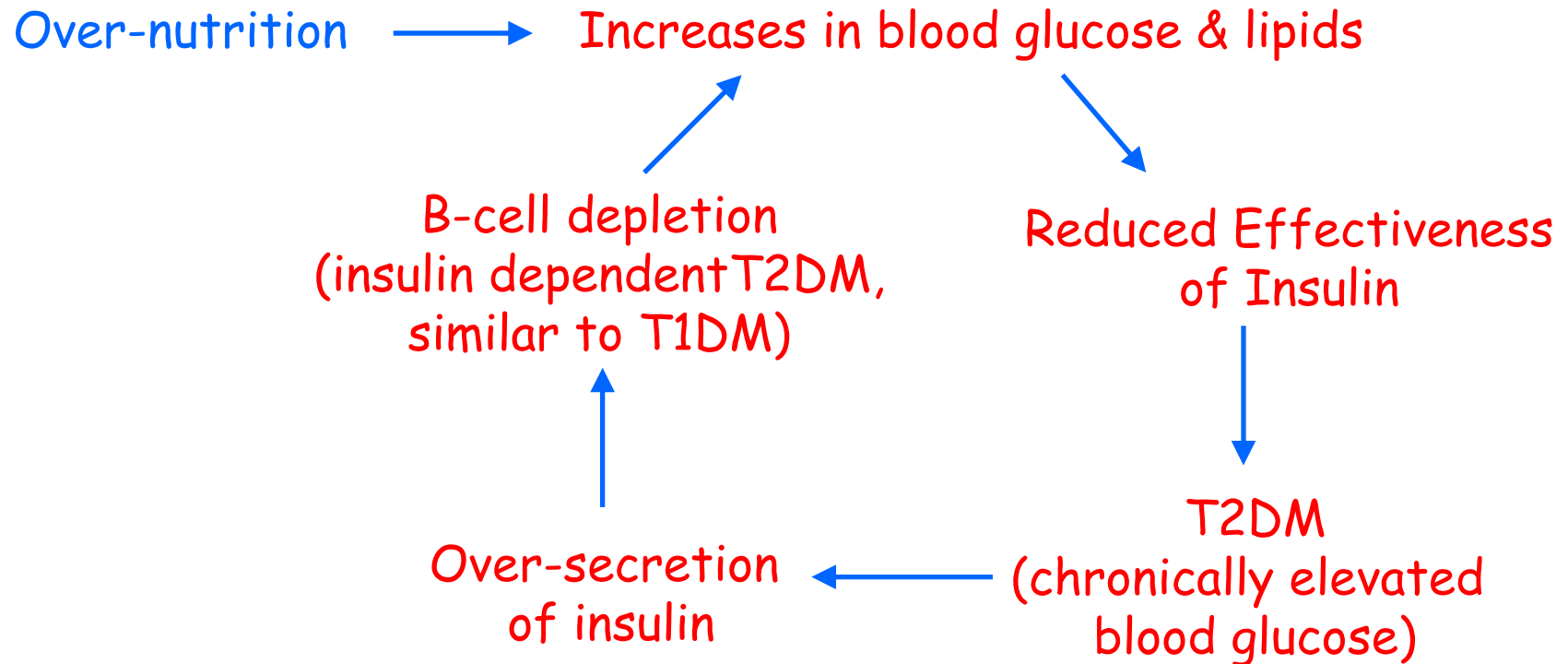
Molecule (Abbreviation)	Function
Tumor necrosis factor-alpha (TNF- α)	Proinflammatory Cytokine
soluble TNF-a receptor (s TNF- α R)	Proinflammatory Cytokine
Interleukin 1-alpha (IL-1 α)	Proinflammatory Cytokine
Interleukin 1-beta (IL-1 β)	Proinflammatory Cytokine
Interleukin 6 (IL-6)	Proinflammatory Cytokine
Interleukin 8 (IL-8)	Proinflammatory Cytokine
Interleukin 10 (IL-10)	Anti-inflammatory Cytokine
Interferon gamma (INF- γ)	Proinflammatory Cytokine
Interleukin-1 receptor antagonist (IL-1ra)	Anti-inflammatory Cytokine
Soluble CD 14 (sCD 14)	Endotoxin receptor
C-polysaccharide reactive protein (CRP)	Bacterial recognition factor
Sialic acid	Complement protection
Monocyte chemoattractant protein-1 (MCP-1)	Chemokine attractant
Macrophage migration inhibitory factor (MIF)	Chemokine attractant
Adipsin	Adipocyte hormone
Adiponectin	Adipocyte hormone, complement
Leptin	Adipocyte hormone
Resistin	Adipocyte hormone
Plasminogen activator inhibitor-1 (PAI-1)	Antifibrinolytic
Retinal binding protein (RBP)	Vitamin A transporter & pro-inflammatory

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities



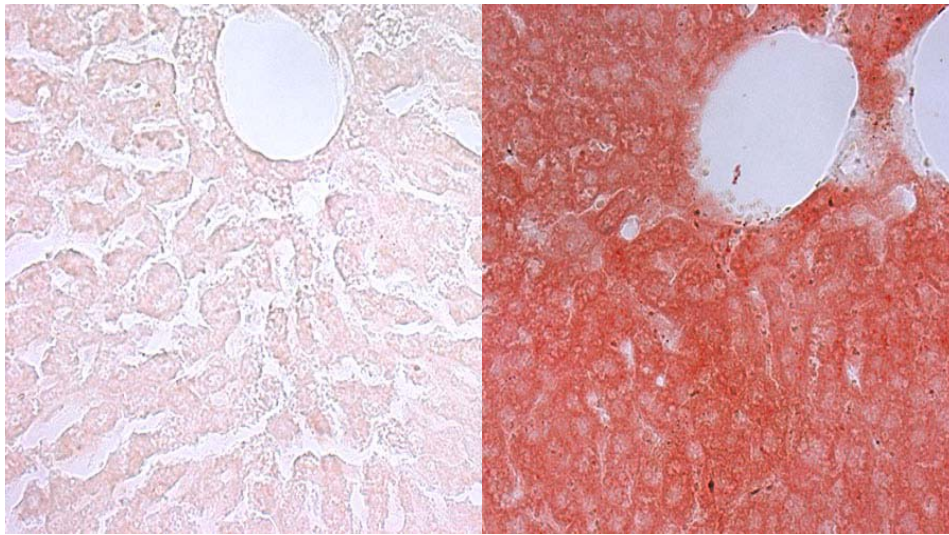
Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

T2DM = Type 2 Diabetes Mellitus



Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

NASH = Non-Alcoholic Fatty Liver Disease



Liver fat stained red in normal weight (left) and obese (right) subject

Fat livers do not function well, eventually cirrhose (deteriorate); no cure

Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with **co-morbidities**

DESIGN

DESIGN

Cross-sectional design comparing plasma samples from 46 boys and 27 girls, aged 6-18 y, visiting Pediatric Endocrinology Unit, KISPI St Gallen

Groups

- A:** healthy children with normal or moderate overweight;
- B:** overweight or obese children who had no co-morbidities
- C:** B plus metabolic co-morbidities (e.g., elevated blood glucose)
- D:** C plus risk of NASH

Adiposity

Height (m) and weight (kg) were used to compute body mass index (BMI; m/kg^2); obesity rated with standard pediatric methods.

(Maturation

Pubertal status according to Tanner staging) (not shown)

NASH risk

Diagnosed with sonography or >1.2 fold elevation of \geq one liver enzyme (ALAT / ASAT / gGT).

Plasma levels of immune signalling molecules were assayed with ELISA:

Immune Signaling Molecules Elevated in Obese Adults

Molecule (Abbreviation)	Function
Tumor necrosis factor-alpha (TNF- α)	Proinflammatory Cytokine
soluble TNF-a receptor (s TNF- α R)	Proinflammatory Cytokine
Interleukin 1-alpha (IL-1 α)	Proinflammatory Cytokine
Interleukin 1-beta (IL-1 β)	Proinflammatory Cytokine
Interleukin 6 (IL-6)	Proinflammatory Cytokine
Interleukin 8 (IL-8)	Proinflammatory Cytokine
Interleukin 10 (IL-10)	Anti-inflammatory Cytokine
Interferon gamma (INF- γ)	Proinflammatory Cytokine
Interleukin-1 receptor antagonist (IL-1ra)	Anti-inflammatory Cytokine
Soluble CD 14 (sCD 14)	Endotoxin receptor
C-polysaccharide reactive protein (CRP)	Bacterial recognition factor
Sialic acid	Complement protection
Monocyte chemoattractant protein-1 (MCP-1)	Chemokine attractant
Macrophage migration inhibitory factor (MIF)	Chemokine attractant
Adipsin	Adipocyte hormone
Adiponectin	Adipocyte hormone, complement
Leptin	Adipocyte hormone
Resistin	Adipocyte hormone
Plasminogen activator inhibitor-1 (PAI-1)	Antifibrinolytic
Retinal binding protein (RBP)	Vitamin A transporter & pro-inflammatory

RESULTS (1)

No significant changes detected in:

Interleukin (IL)-1

IL-6

IL-8

Tumor-necrosis factor- α (TNF- α)

TNF- α receptors I and II.

RESULTS (2)

BOYS					
Group	n	BMI	Leptin	RBP	IL-1Ra
A	9	24.8	22.3	48.2	476
B	11	28.4	39.5*	39.4	672
C	13	29.7	33.8*	55.2	998*
D	13	32.2	46.5*	61.1*+	1026*+
GIRLS					
Group	n	BMI	Leptin	RBP	IL-1Ra
A	2	22.5	32.1	44.1	544
B	10	27.9	38.1	44.6	776
C	4	28.3	33.4	37.9	832
D	11	31.5	44.3*	45.2	1145*+

* P < 0.05 vs. Group A; + P < 0.05 vs. Group B

DISCUSSION

We discovered surprisingly few increases in systemic levels of immune signalling molecules that are thought to cause or exacerbate the pathophysiology of obesity-related diseases.

The subjects included many very obese children, and they displayed signs of metabolic disease and even incipient fatty liver disease. Similarly morbid adults typically have elevations in most or all of the immune signalling molecules that we measured.

This suggests that children may be relatively protected from obesity-related innate immune activation.

DISCUSSION

This suggests that children may be relatively protected from obesity-related innate immune activation.

Why might this be the case?

Larger absolute amounts of adipose tissue may be required to produce systemic changes in immune signalling molecules.

Puberty may bring changes that are necessary for the full activation of the innate immune system (increased testosterone, progesterone, or estradiol).

Immune cells in the adipose tissue may be less sensitive in children because of the presumably relatively low lifetime immune activation in pediatric patients ("allostatic load").

DISCUSSION

These data have not yet been fully analyzed.

In progress:

- *Inclusion of effects of pubertal development stage
- *Multivariate regression to investigate relative influences of different independent variables on cytokine levels

ACKNOWLEDGEMENTS

Thanks to the SFEFS and ETH Zürich for financial support
for this project.

Thank you for your attention!

Danke für Ihre Aufmerksamkeit!