



# Metabolic syndrome

Clustering of risk factors or medical disorders that increases the risk of developing cardiovascular disease or type II diabetes

**Definition (IDF):**

- Central obesity  
(usually BMI > 30 kg/m<sup>2</sup>),  
plus 2 of the following:
- TGs > 150 mg/dL
  - HDL < 40-50 mg/dL
  - ↑ blood pressure
  - hyperglycemia

“ syndrome X...

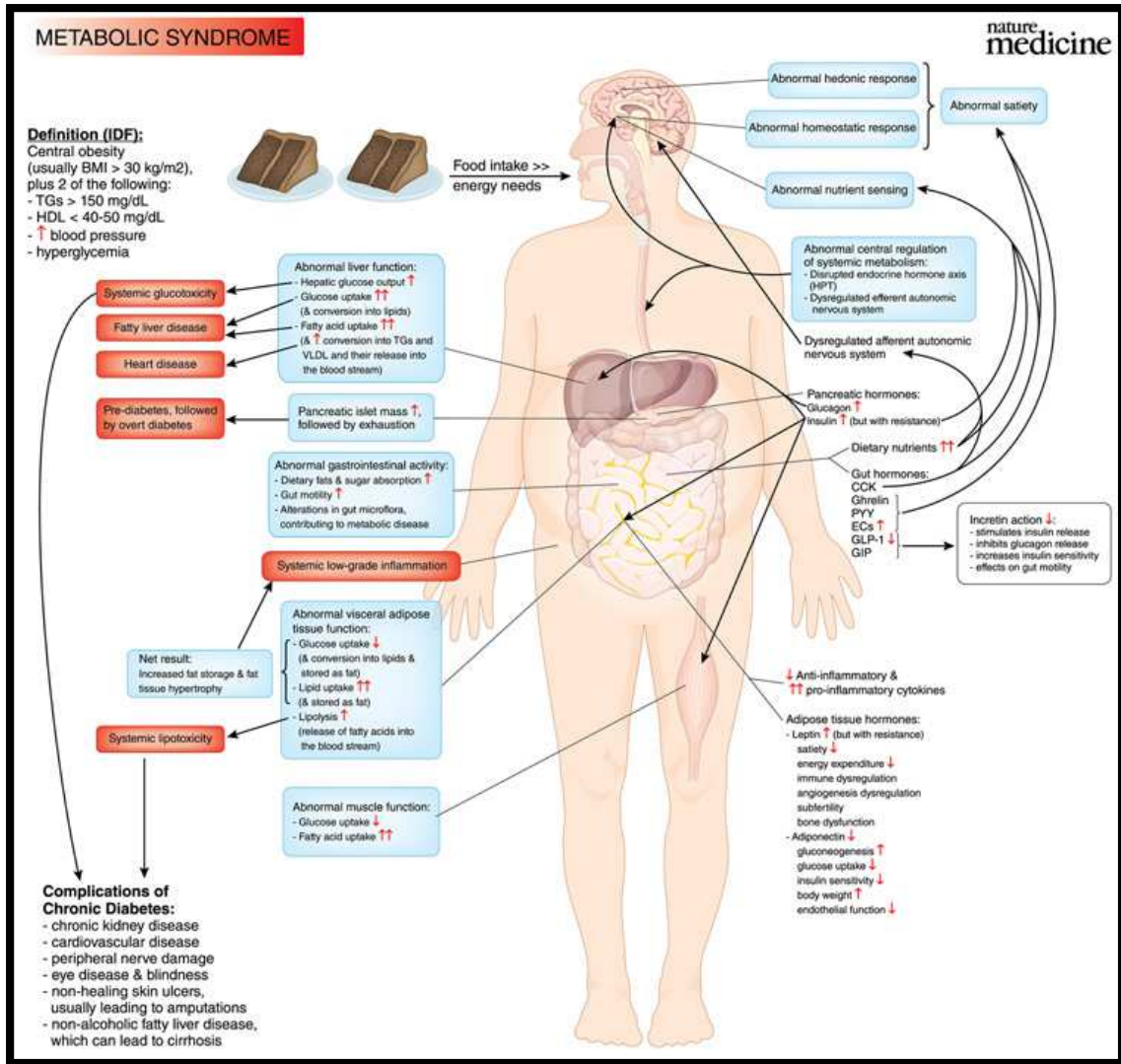
... cardiometabolic syndrome  
insulin resistance syndrome...  
... Reaven's syndrome “

... Reaven's syndrome “  
insulin resistance syndrome...  
... cardiometabolic syndrome

# Metabolic syndrome

Insulin resistance

Ectopic fat / lipotoxicity

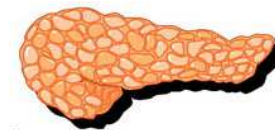
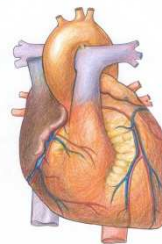
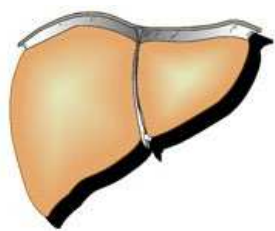


# Ectopic Fat / Lipotoxicity

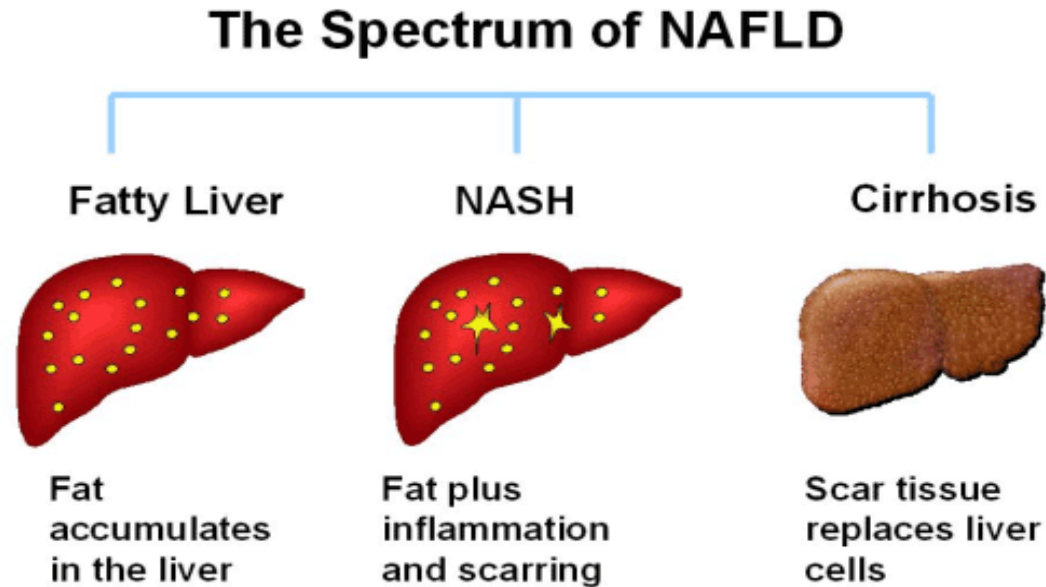
*'when tissues overeat'*

the deposition of triglycerides within cells of non-adipose tissue that normally contain only small amounts of fat

leading to cell dysfunction or cell death.



# Intra Hepatic lipids (IHL)



## ■ Consequences:

- *Hepatic insulin resistance*
- *Decreased insulin clearance*
- *Disturbed lipid metabolism*

## ■ High Prevalence

(e.g. 33.6% in the Dallas Heart study;  
*Szczepaniak, L.S. et al, 2005*)



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# DIETARY PROTEINS

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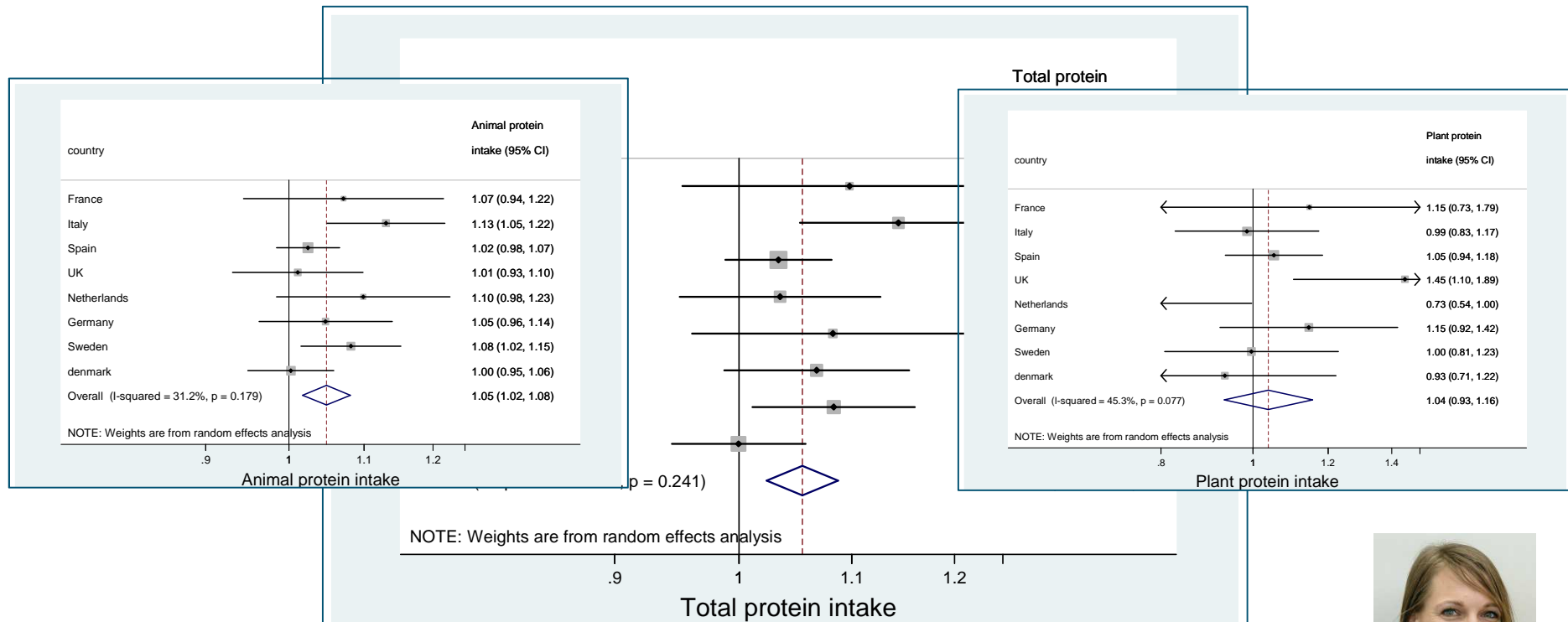
# Dietary Protein & Metabolic Syndrome

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- Epidemiological data
  - Increased risk type 2 diabetes mellitus



# Dietary protein intake and incidence of Type 2 Diabetes in Europe: The EPIC-InterAct Case-Cohort Study.





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# Dietary Protein & Metabolic Syndrome

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- Epidemiological data
  - Increased risk type 2 diabetes mellitus
- BCAA: biomarker associated with DM risk
  - Cross-sectional and prospective
- Infusion amino acids
  - Decrease insulin sensitivity

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# Dietary Protein & Metabolic Syndrome

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- Weight-loss, improved weight maintenance
  - Preservation lean mass
  - Increased satiety
  - Increased thermogenesis
  
- Metabolic improvements
  - Insulin secretion
  - Glucose homeostasis, insulin resistance
  
- Liver metabolism
  - Decrease IHL, lower circulating markers of liver dysfunction
  - reduced lipogenesis, increased gluconeogenesis and glycogen synthesis (*rodent data*)

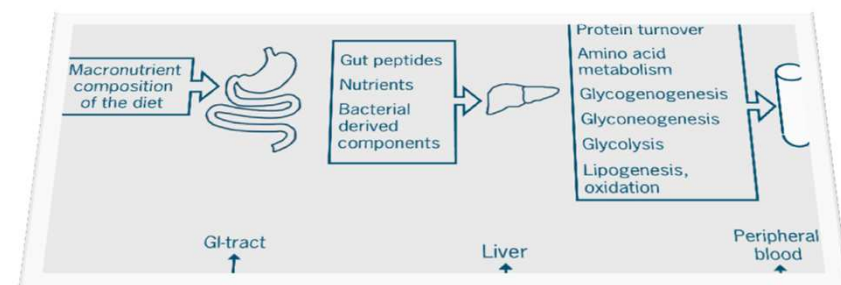


# Influence of dietary protein on metabolic phenotype and gene expression in the gut-liver axis



To understand the effects of **increasing protein intake at the expense of carbohydrates**, in a high-fat-hypercaloric-diet

- on **phenotype adaptation** of body composition, intra hepatic lipids and the gut.
- on *nutrients homeostasis*, risk of metabolic disorders and associated diseases.
- on *gene expression in liver, adipose tissue and intestine*



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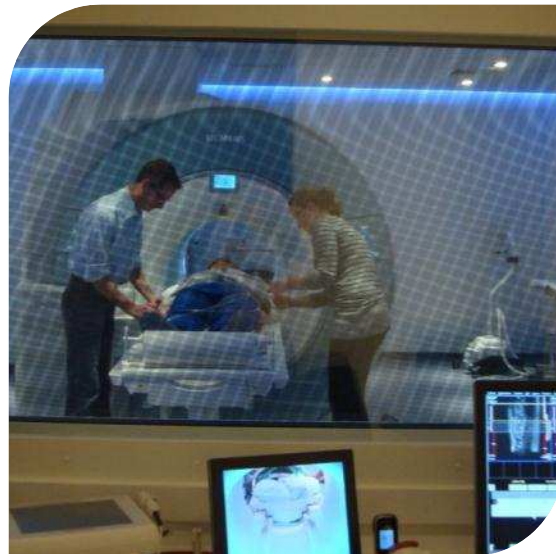
# Human Research Facilities

## *Division of Human Nutrition*

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Controlled intervention  
*Dietary Facilities*



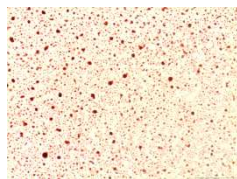
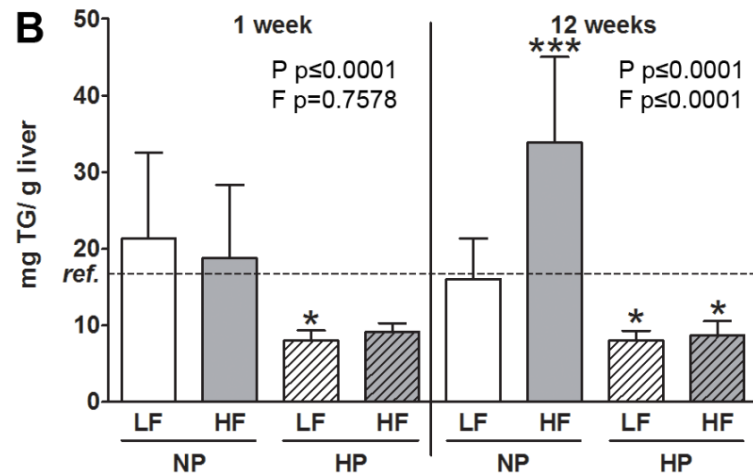
Hepatic steatosis  
*Nutritional Imaging*



Metabolism  
*Metabolic Ward*

# Protein manipulation modifying phenotype: *prevention of fat induced increase in liver fat*

## Mouse study:

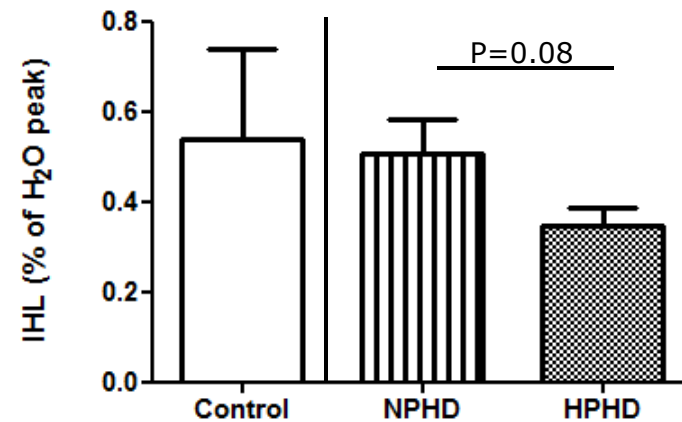


15 en% protein (NP)



50 en% protein HP

## Human study:



Rietman, A. unpublished data

Chaumontet, C. unpublished data

Schwarz, J. et al., PLoS ONE 2012.



# Dietary Protein and IHL

High protein intake reduces intrahepatocellular lipid deposition in humans<sup>1-3</sup>

*Murielle Bortolotti, Roland Kreis, Cyrille Debard, Bertrand Cariou, David Faeh, Maud Chetiveaux, Michael Ith, Peter Vermathen, Nathalie Stefanoni, Kim-Anne Lê, Philippe Schneiter, Michel Krempf, Hubert Vidal, Chris Boesch, and Luc Tappy*

HEPATOLOGY

## **Open-labeled pilot study of cysteine-rich whey protein isolate supplementation for nonalcoholic steatohepatitis patients**

Taned Chitapanarux,\* Prasong Tienboon,† Suwalee Pojchamarnwiputh‡ and Donrawee Leelarungrayub§

Effects of a whey protein supplementation on intrahepatocellular lipids in obese female patients

Murielle Bortolotti<sup>a,d</sup>, Elena Maiolo<sup>a,d</sup>, Mattia Corazza<sup>a,d</sup>, Eveline Van Dijke<sup>a,d</sup>, Philippe Schneiter<sup>a,e</sup>, Andreas Boss<sup>b,f</sup>, Guillaume Carrel<sup>a,e</sup>, Vittorio Giusti<sup>c,g</sup>, Kim-Anne Lê<sup>a,h</sup>, Daniel Guae Quo Chong<sup>b,f</sup>, Tania Buehler<sup>b,f</sup>, Roland Kreis<sup>b,f</sup>, Chris Boesch<sup>b,f</sup>, Luc Tappy<sup>a,c,\*</sup>

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<sup>c</sup>Service of Endocrinology, Diabetes and Metabolism, CHUV, 1011 Lausanne, Switzerland

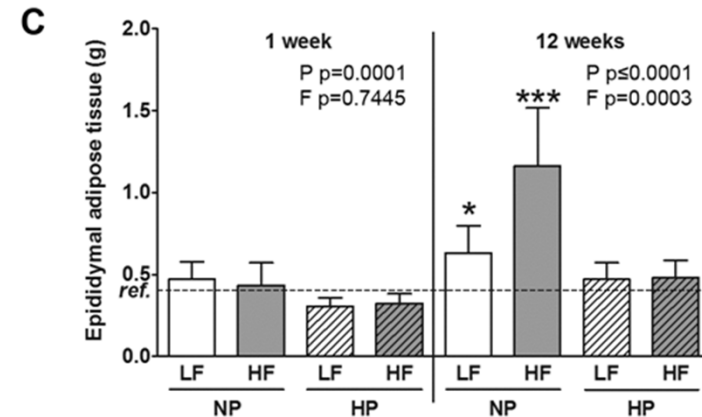
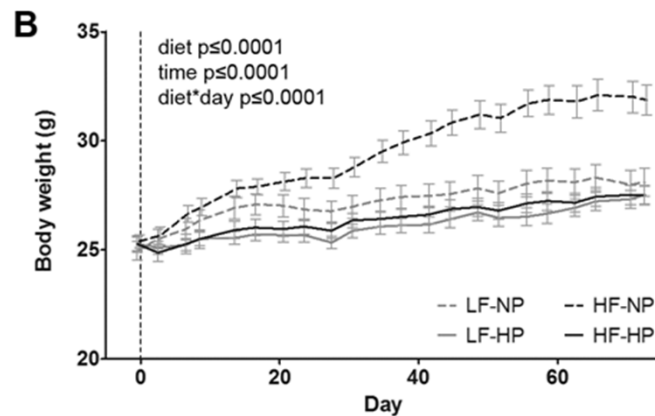


WAGENINGEN UNIVERSITY

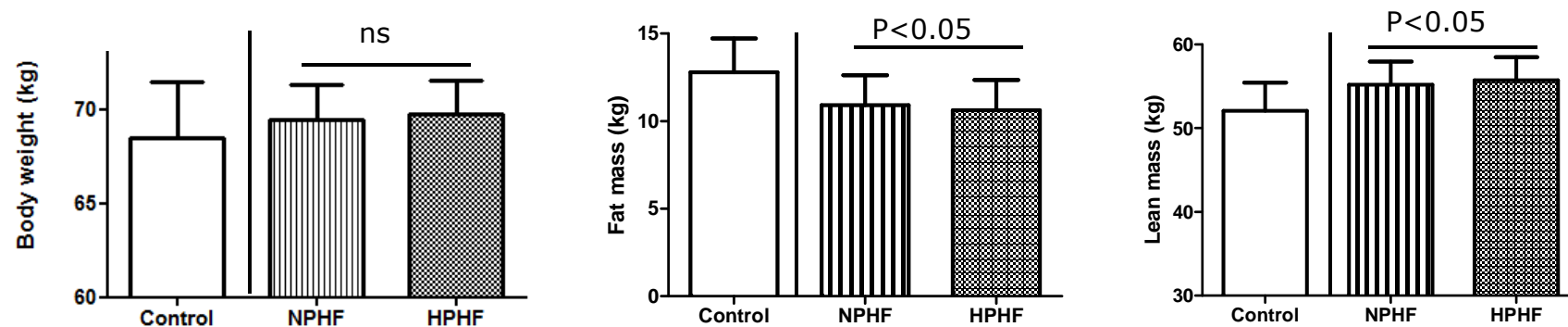
WAGENINGEN UR

# Protein manipulation modifying phenotype: *prevention of increase BW and adipose tissue*

## Mouse study:



## Human study:





# Protein manipulation modifying phenotype: *insulin resistance*

## Human study:

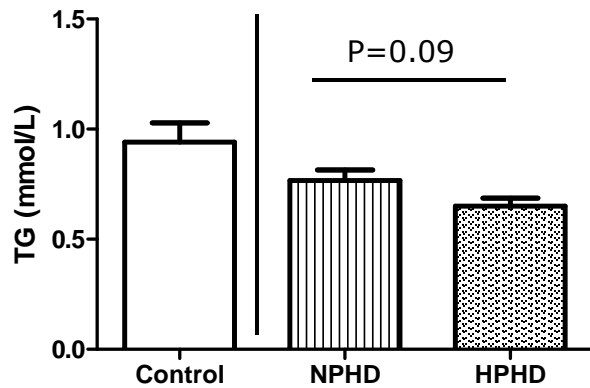
	control	HD	
	2 weeks	NPHF	HPHF
HOMA-IR <sup>2</sup> (mmol/L × μU/ml)	0.91 ± 0.14	0.95 ± 0.14	0.90 ± 0.15
Glucose (mmol/L)	5.07 ± 0.04	5.03 ± 0.08	5.05 ± 0.09
Insulin (μU/L)	4.01 ± 0.62	4.21 ± 0.62	3.95 ± 0.63

## Rat study:

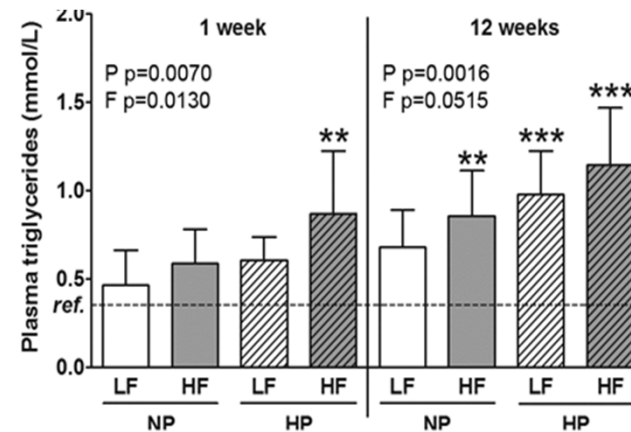
- No effect of increasing protein intake on several markers of insulin action and glycemic control

# Protein manipulation modifying phenotype: *blood lipids*

## Human study:



## Mouse study:



## Rat study:

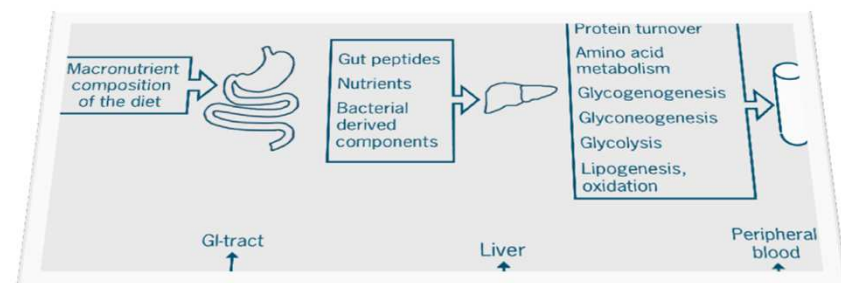
	NP			HP			
	C	HS	HS-HF	C	HS	HS-HF	
<b>Fasted</b>							
Triglyceride (mM/l)	0.9±0.9	1.0±0.4	1.1±0.3	0.6±0.1	0.6±0.1	0.6±0.1	P (<0.001)
Cholesterol (mM/l)	1.8±0.2	1.9±0.3	1.8±0.2	2.0±0.5	1.7±0.5	2.1±0.5	NS
HDL (mM/l)	1.2±0.1	1.2±0.2	1.2±0.1	1.4±0.3	1.2±0.3	1.4±0.3	P (<0.05)



# Conclusions

## Impact of high dietary protein on biomarkers of metabolic syndrome when fed a high-fat diet:

- Liver lipids (IHL): reduced
- *Central* adiposity: reduced
- Lipids
  - Triglycerides: decreased / increased
  - HDL-cholesterol: increased
- Insulin sensitivity:
  - no effect in a young, metabolic flexible population



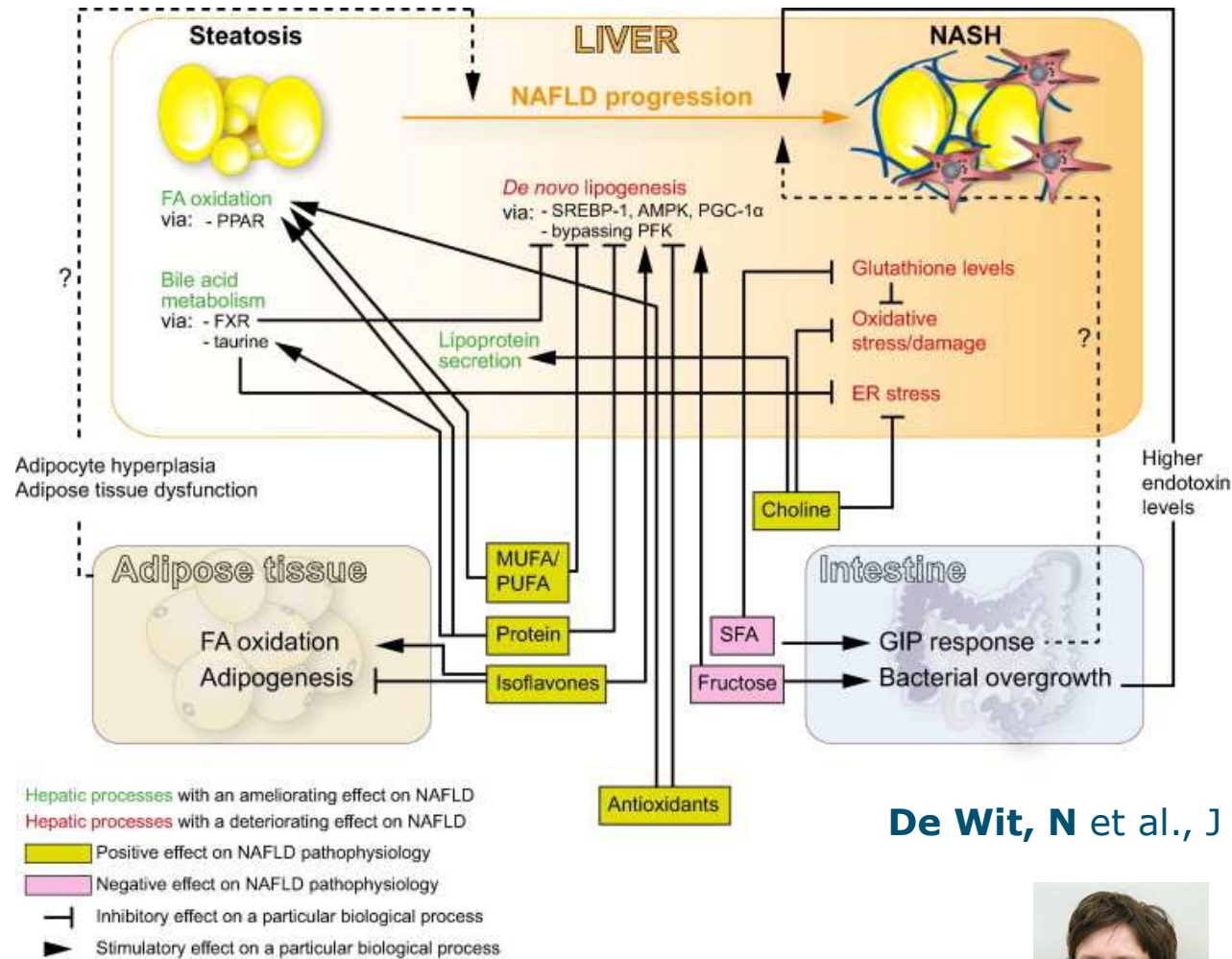
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# MARINE INGREDIENTS

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# 'Phenotyping the effect of diet on NAFLD'



De Wit, N et al., J Hepatol 2012.



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# Fish and NAFLD

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## ■ Fish oil

- consumption of n-3 fatty acids reduce inflammation, steatosis, and liver damage in NAFLD
  - *MUFA may be useful*
  - *Fish oil improves circulating lipids and lipoproteins*

## ■ Fish Protein

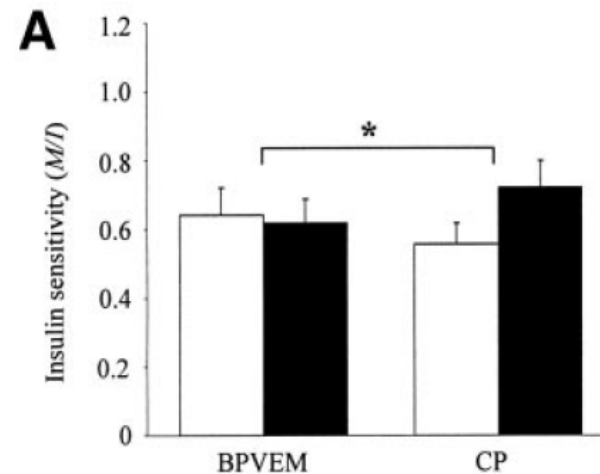
- Protein source important for steatosis (?)

## ■ Vitamin D

- Vitamin D concentrations have been shown to be associated with NAFLD

# Fish protein and glucose metabolism

- **Cod** versus BPVEM
- 4 weeks isocaloric diets
- 19 en% protein
- ~60% of protein cod
- Equivalent amounts SFA/MUFA/PUFA



(Ouellet et al, Diabetes Care 2007)

- Fish protein supplements improve glycemic control in overweight adults (Vikøren, British J Nutrition 2013)



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# Conclusion - *Opportunities*

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■ **High-protein diets** can be considered in people with the metabolic syndrome

- *supports weight loss and improves body composition*
  - *Improve insulin action/glucose homeostasis*
  - *Reduces intrahepatic lipids*
- *Need to know the consequences of (excess) protein*

■ **Fish protein** could be a good quality protein

- More well-controlled human intervention studies needed



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# Acknowledgements

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ALPRO FOUNDATION

