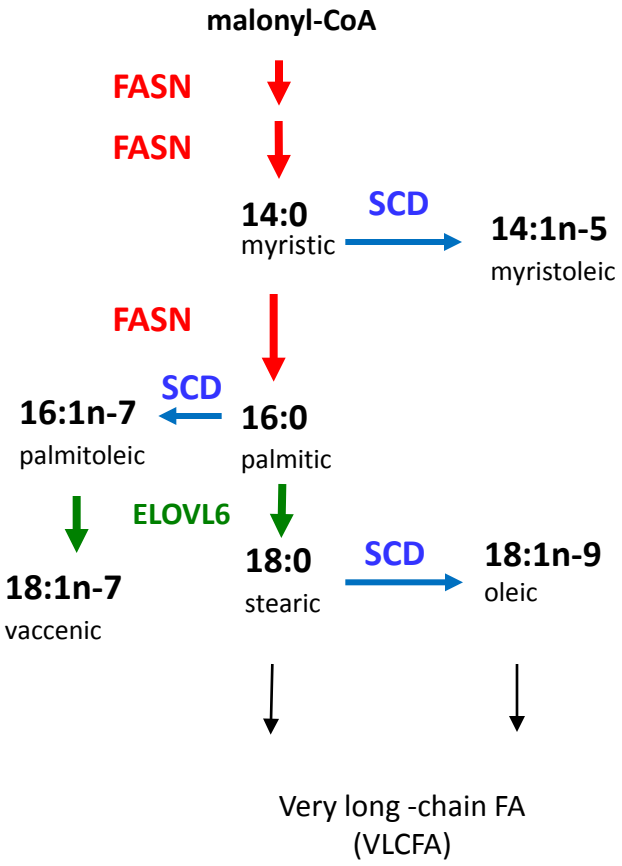
Regulation of Liver and Adipose Tissue Lipogenesis in Human Obesity

Ludger Scheja

NuGO Week 2011, Wageningen

Universitätsklinikum Hamburg-Eppendorf

De Novo Lipogenesis (DNL) Pathway



FASN: fatty acid synthase

SCD: stearoyl CoA desaturase

ELOVL6; fatty acid elongase-6

De Novo Lipogenesis (DNL) in Mice

- Mice efficiently convert dietary carbohydrates to fatty acids
- **Liver DNL** is up-regulated in obese mice; mechanisms:
  - Hyperinsulinemia (SREBP1c)
  - Increased glucose flux (ChREBP)

- DNL-linked fatty acid elongase ELOVL6 has adverse metabolic effects (Matsuzaka et al. 2007, Nat Med 13:1193)

- **Adipose Tissue** DNL is down-regulated in obesity
- DNL-derived palmitoleic acid (C16:1) counteracts insulin resistance (Cao et al. 2008, Cell 134:933)

De Novo Lipogenesis (DNL) in Humans

- Dietary carbohydrates is converted to fatty acids by fatty acid synthase (FASN)
- Obese subjects have a higher rate of hepatic DNL than lean subjects
- FASN mRNA is down-regulated in adipose tissue in obesity
- Common polymorphisms in FASN gene are associated with BMI

Aim of the Study

Characterize the regulation of DNL in human obesity

- Expression of biosynthetic enzymes
- DNL-derived fatty acids
- Link to metabolic disease parameters

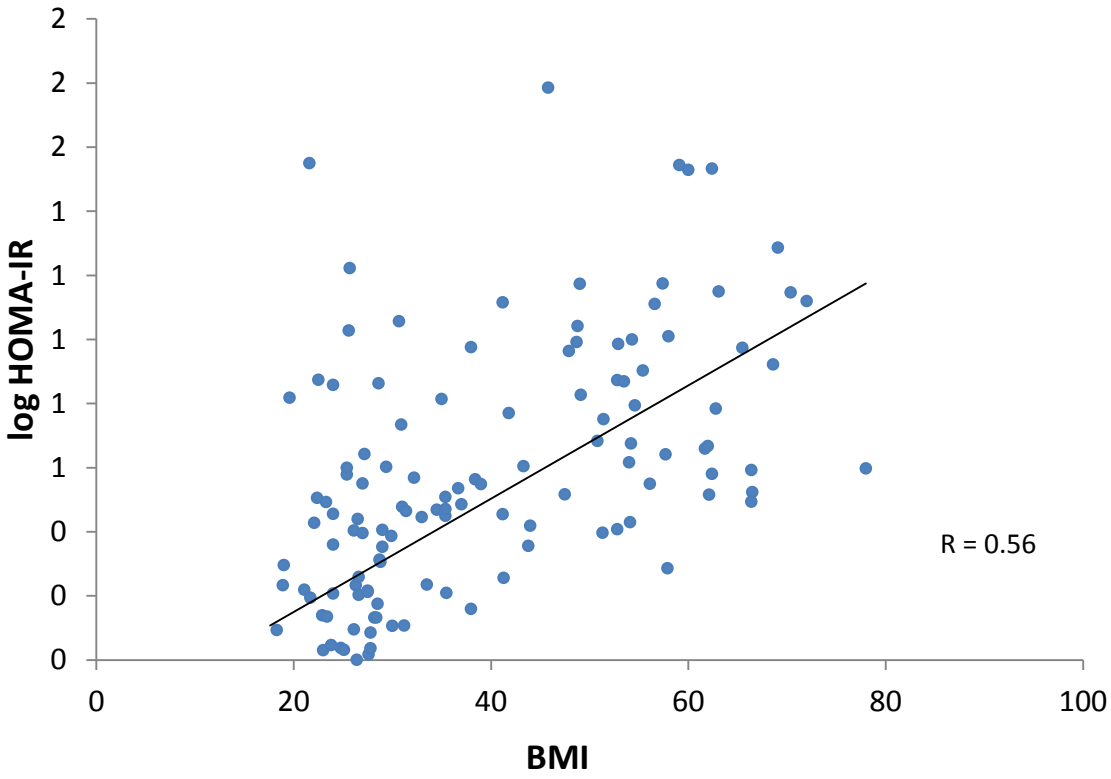
Study Cohort

- Tissue bank, Dept. of Surgery, University of Ulm
  (Anna Wolf, Uwe Knippschild)

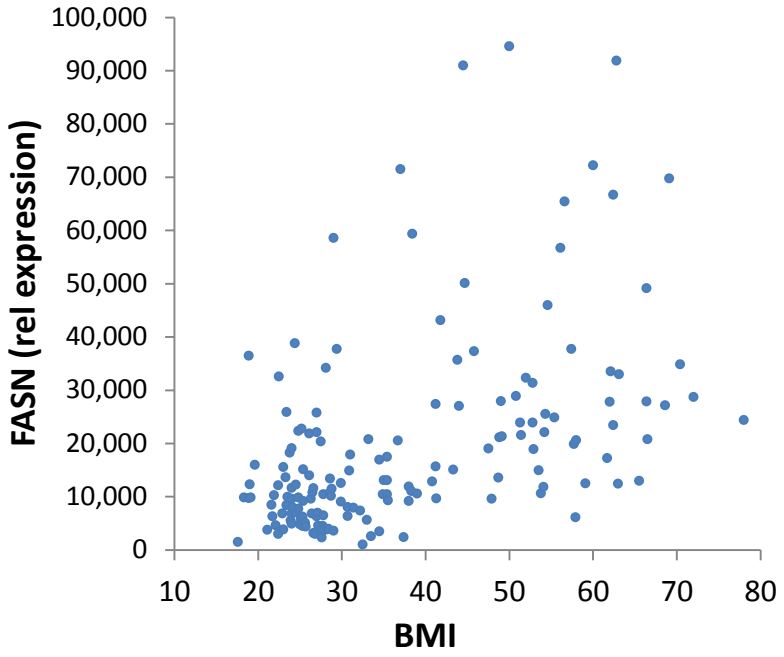
- Surgery patients: morbid obesity > non-metastatic cancer > other cases (no liver disease)

- Patients with liver and adipose tissue samples: n=165

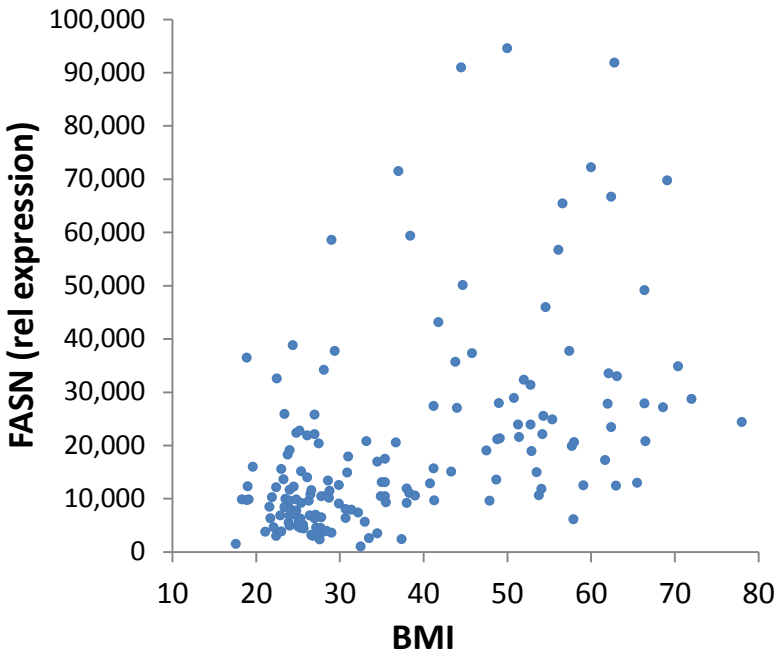
Study Cohort: HOMA-IR

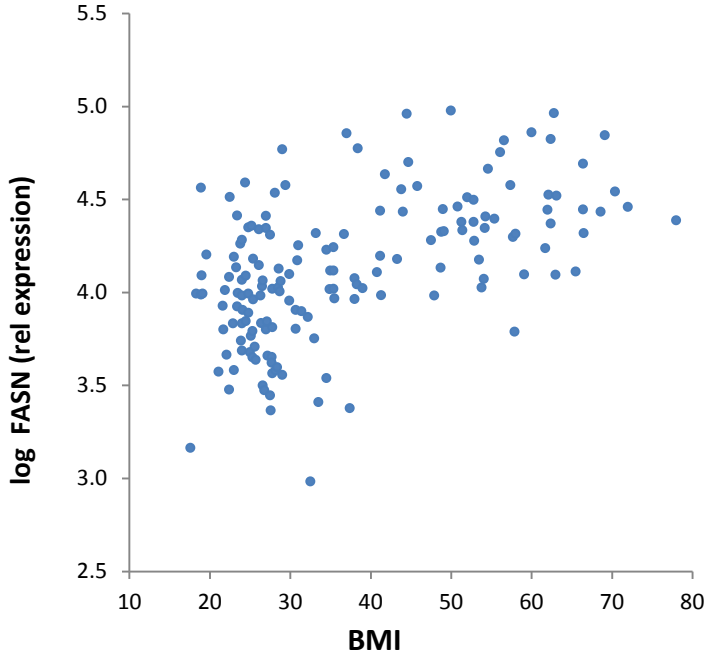


Liver FASN Expression versus BMI

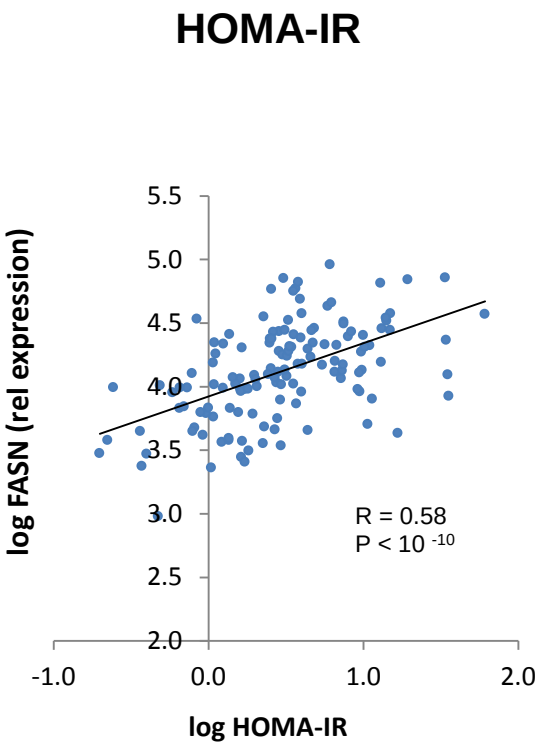


Liver FASN Expression versus BMI



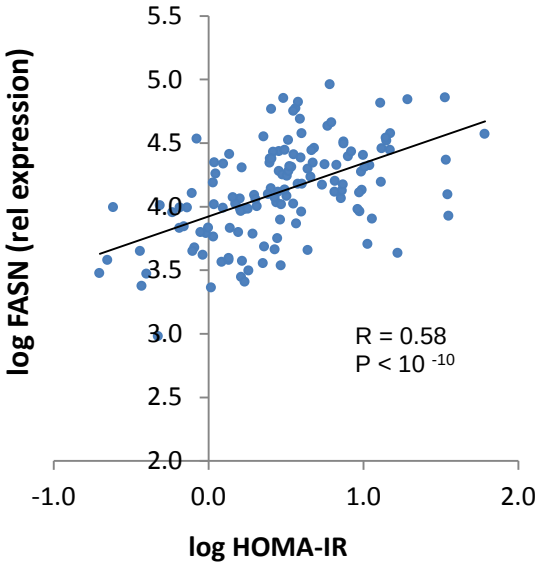


Liver FASN Expression versus HOMA-IR, Liver TG, CRP

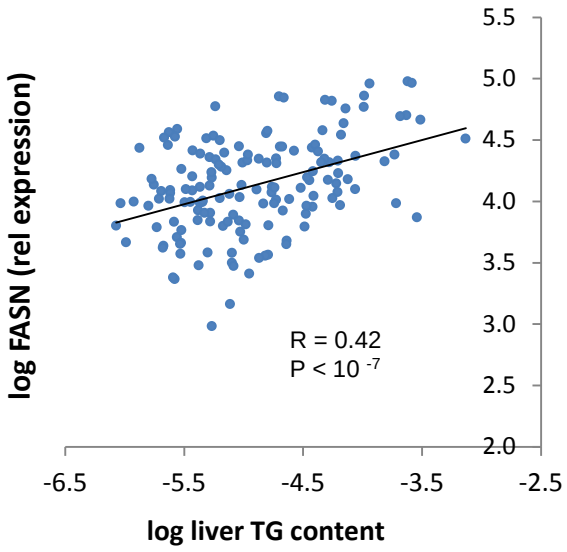


Liver FASN Expression versus HOMA-IR, Liver TG, CRP

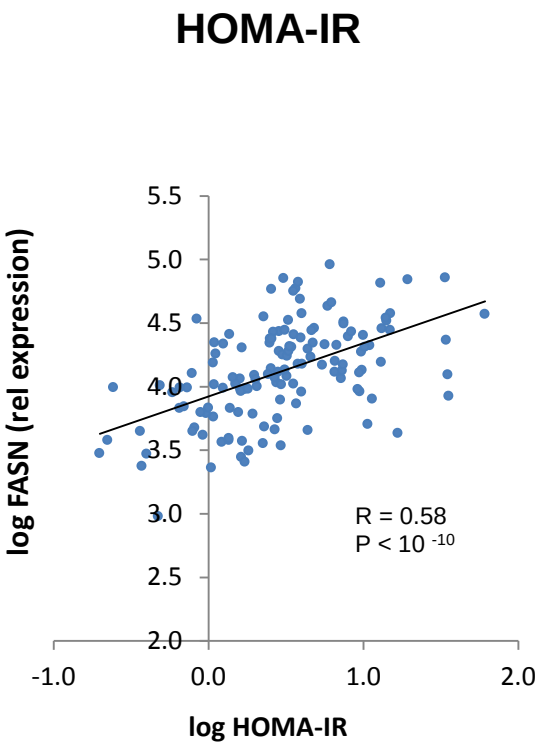
HOMA-IR

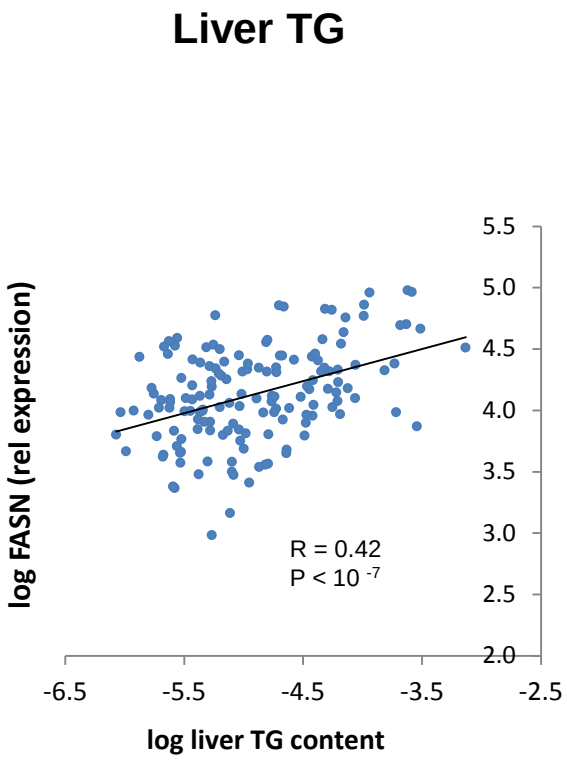


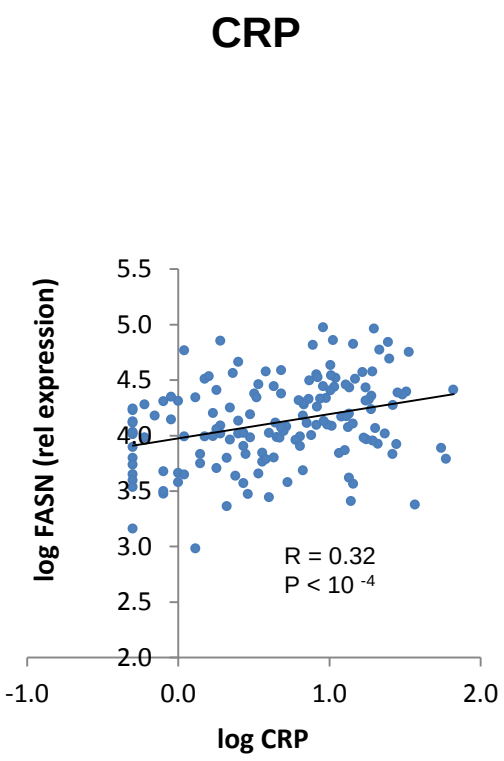
Liver TG



Liver FASN Expression versus HOMA-IR, Liver TG, CRP

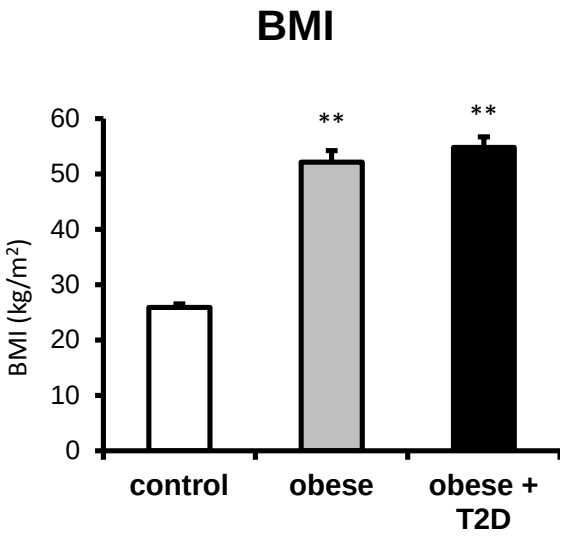






Experimental Subgroups

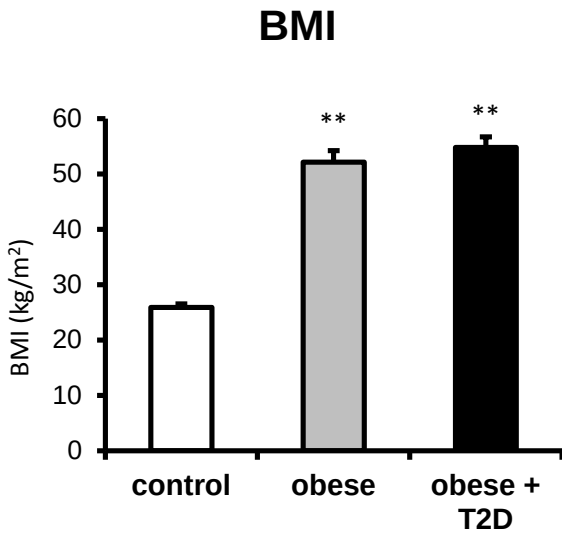
- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

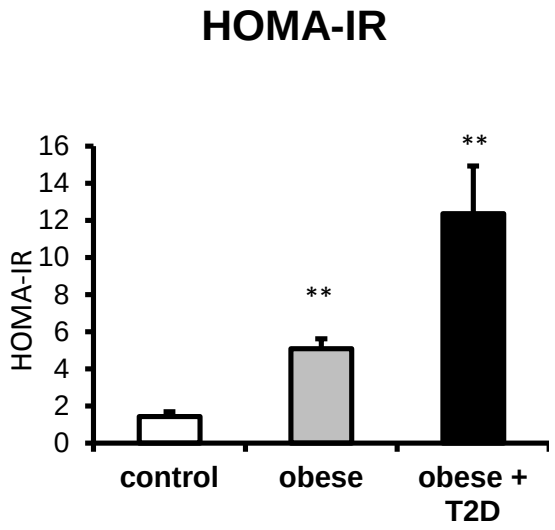


T-Test vs. controls, * p< 0.05, ** p< 0.001

Experimental Subgroups

- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

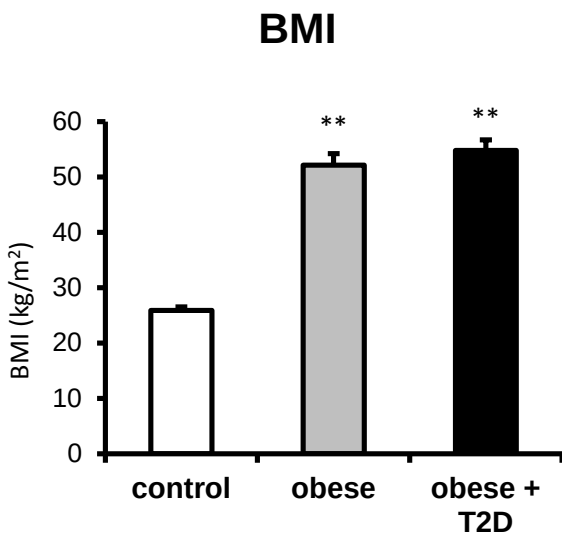


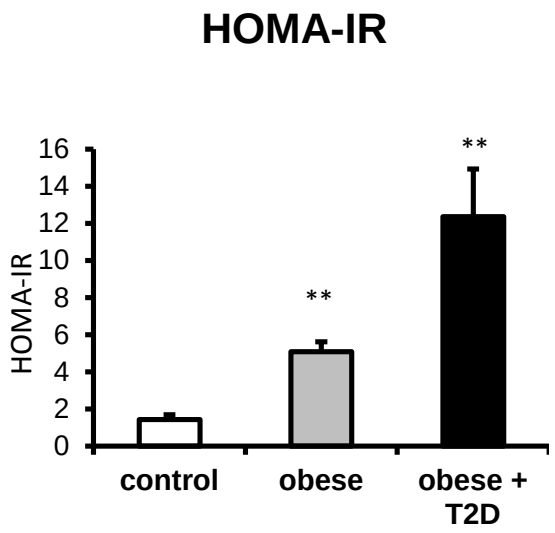


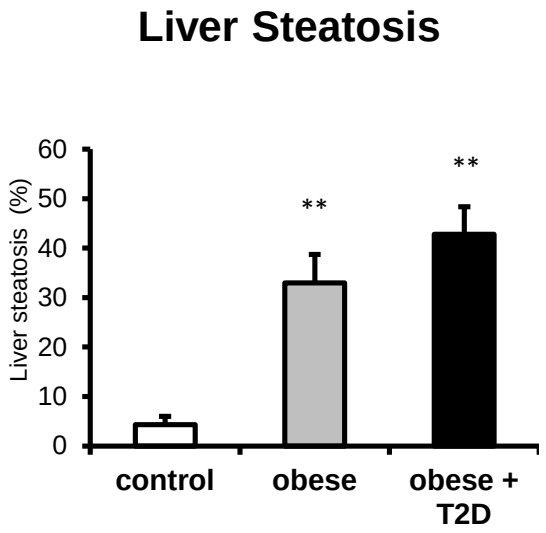
T-Test vs. controls, * p< 0.05, ** p< 0.001

Experimental Subgroups

- Gender-matched, (partially) age-matched, n=20, controls (lean and overweight), obese, obese+T2D (type 2 diabetes)

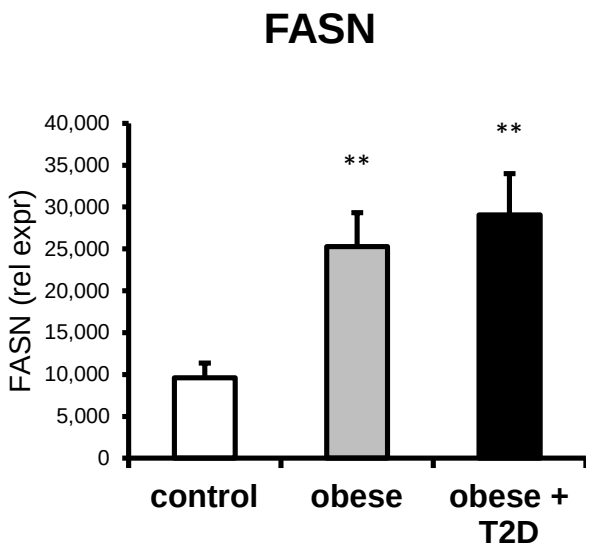






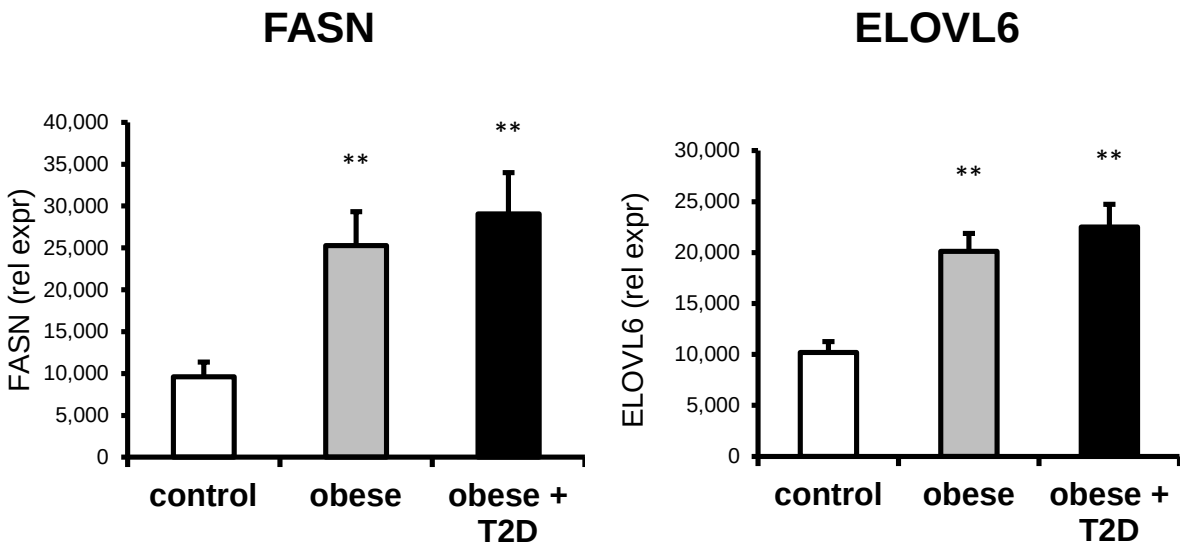
T-Test vs. controls, * p< 0.05, ** p< 0.001

Liver DNL Gene Expression



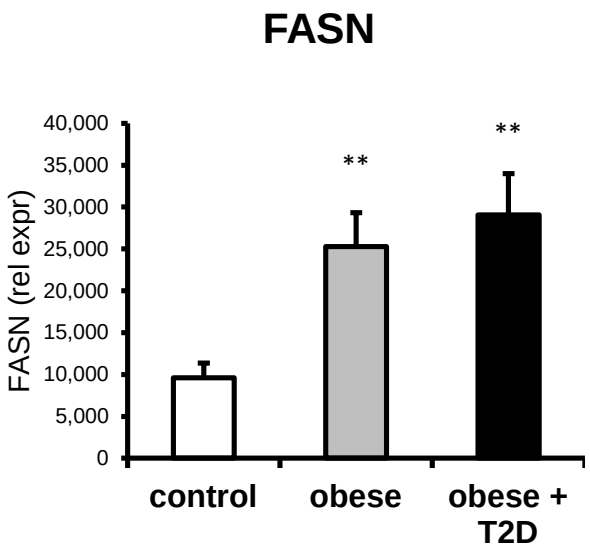
T-Test vs. controls, * p< 0.05, ** p< 0.001

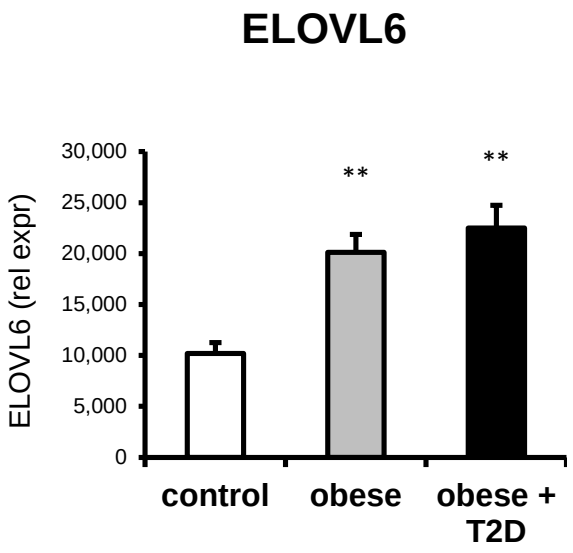
Liver DNL Gene Expression

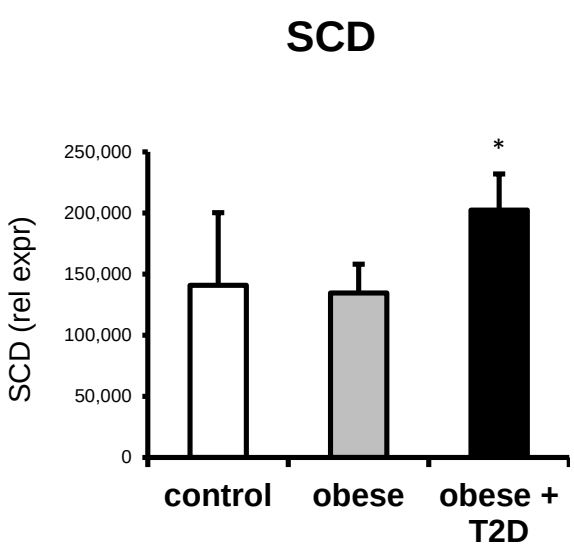


T-Test vs. controls, * p< 0.05, ** p< 0.001

Liver DNL Gene Expression

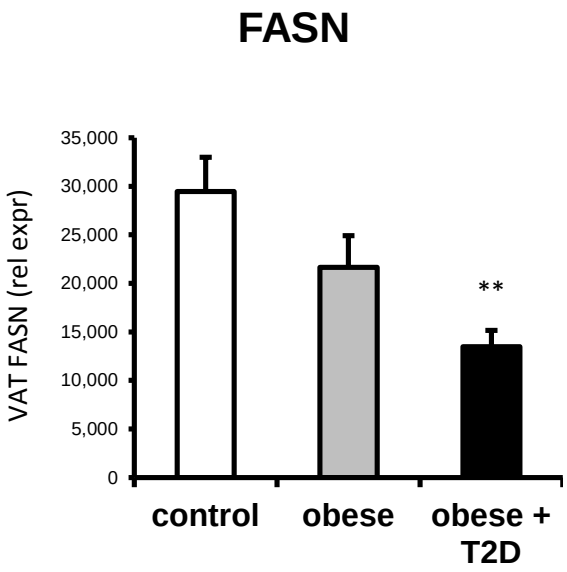






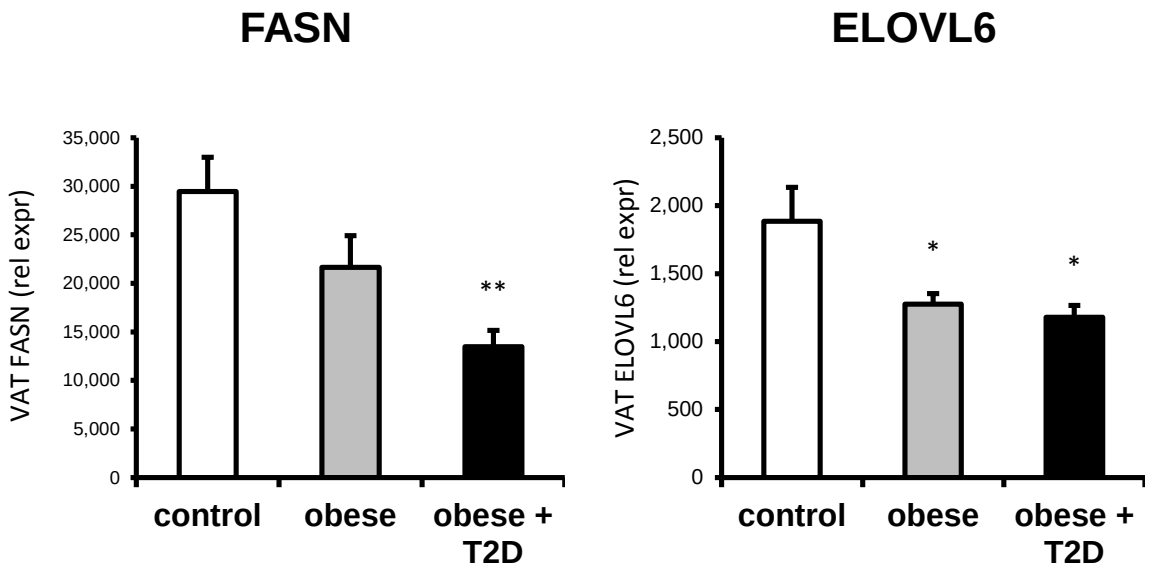
T-Test vs. controls, * p< 0.05, ** p< 0.001

Visceral Adipose Tissue (VAT) Lipogenic Gene Expression



T-Test vs. controls, * p< 0.05, ** p< 0.001

Visceral Adipose Tissue (VAT) Lipogenic Gene Expression



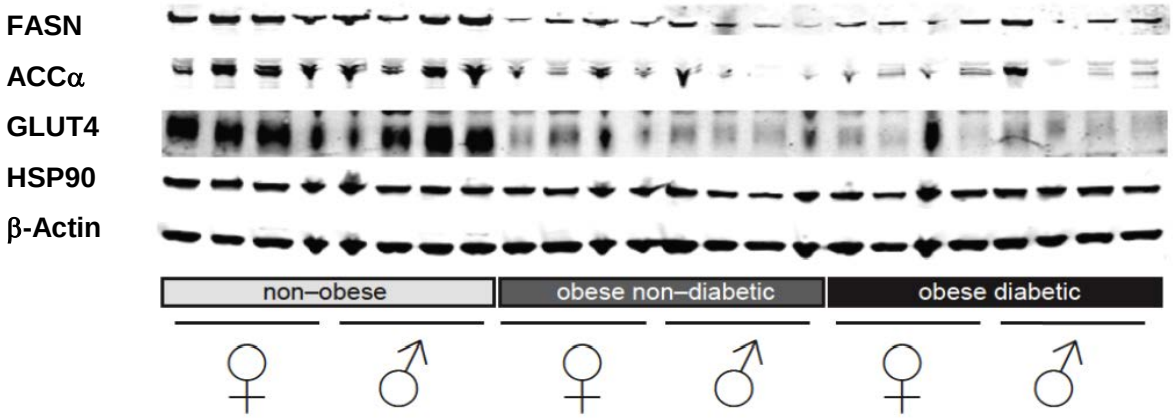
T-Test vs. controls, * p< 0.05, ** p< 0.001

Visceral Adipose Tissue (VAT) Lipogenic Gene Expression

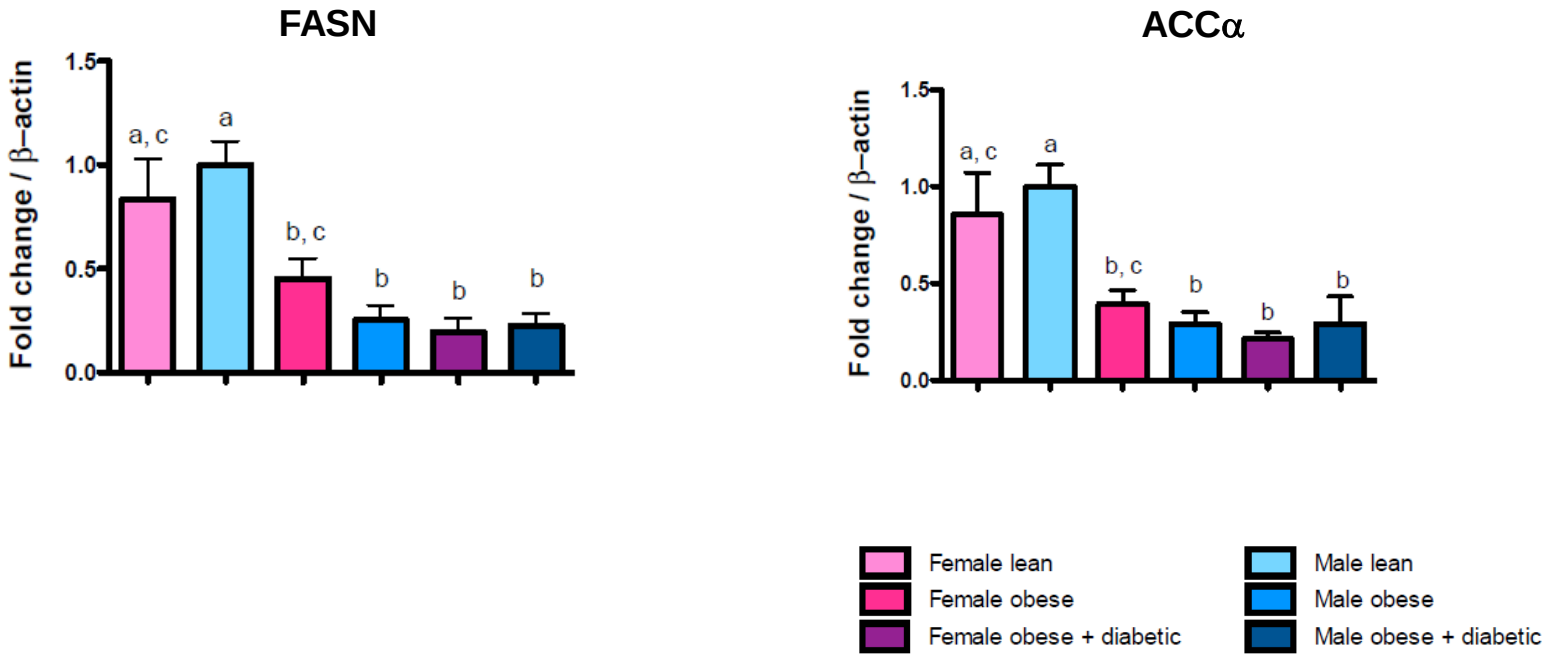
T-Test vs. controls, * p< 0.05, ** p< 0.001

VAT Westernblots

- FASN, upstream DNL proteins

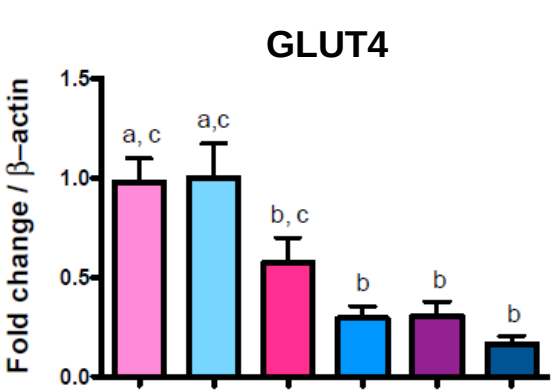


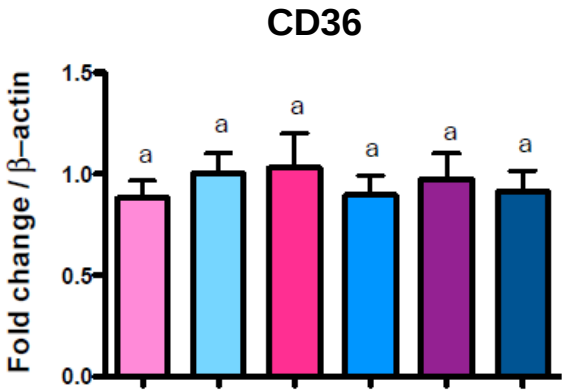
VAT Westernblots



1-way ANOVA: Repeated T-TEST
Tukey-Kramer test to correct for multiple comparison

VAT Westernblots





1-way ANOVA: Repeated T-TEST
Tukey-Kramer test to correct for multiple comparison

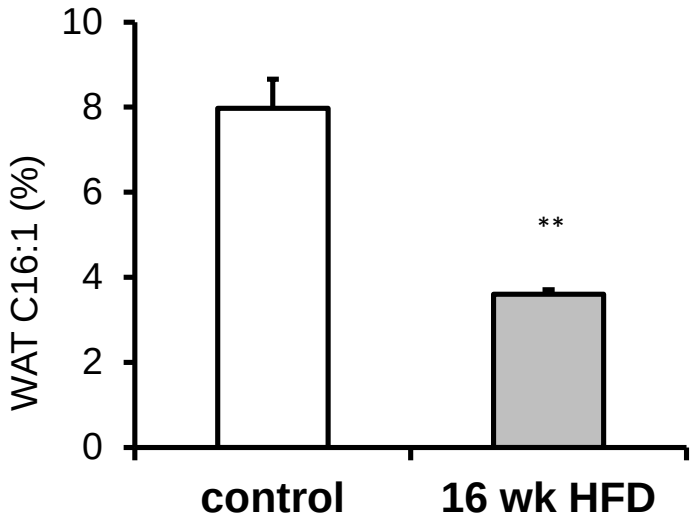
Palmitoleate (C16:1) in Mouse Adipose Tissue

- Biosynthetic capacity DNL severely impaired in obese adipose tissue => is this reflected in fatty acid patterns ?

T-Test vs. controls, * p< 0.05, ** p< 0.001

Palmitoleate (C16:1) in Mouse Adipose Tissue

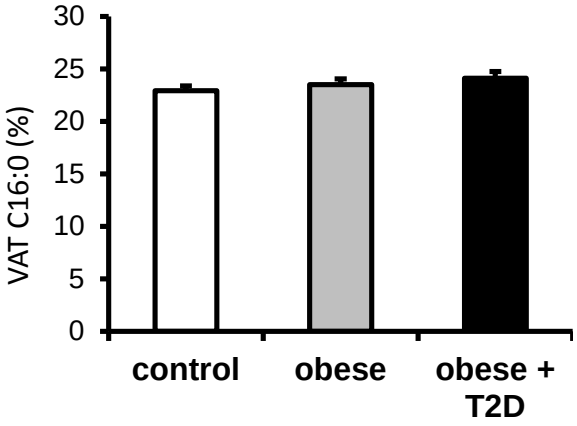
- Biosynthetic capacity DNL severely impaired in obese adipose tissue => is this reflected in fatty acid patterns ?



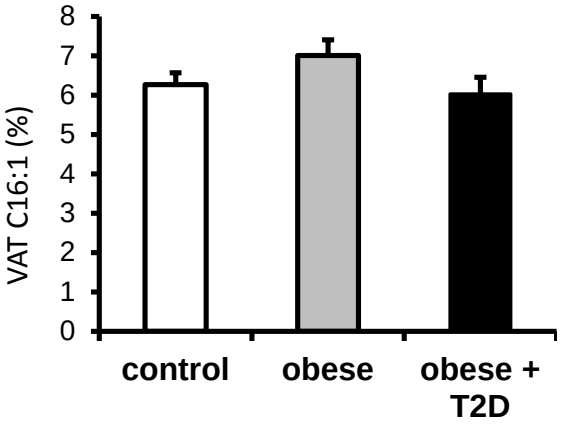
T-Test vs. controls, * p< 0.05, ** p< 0.001

DNL-Derived Fatty Acids in Human VAT

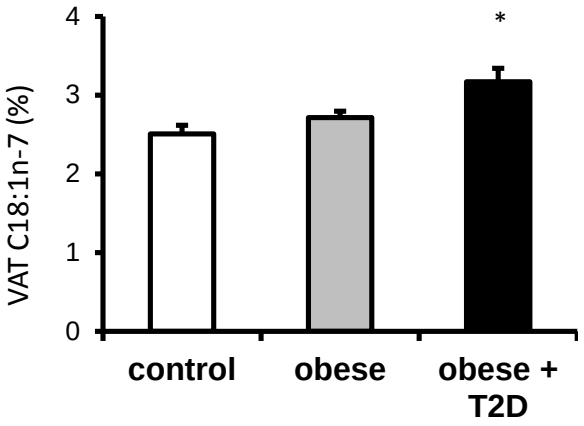
Palmitic Acid
C16:0



Palmitoleic Acid
C16:1n-7



Vaccenic Acid
C18:1n-7



T-Test vs. controls, * p< 0.05

Summary and Conclusions – Human Liver

- The DNL pathway is profoundly induced in liver of (morbidly) obese humans

Summary and Conclusions – Human Liver

- The DNL pathway is profoundly induced in livers of (morbidly) obese humans

- Liver FASN expression correlates strongly with HOMA-IR, indicating a link to liver insulin resistance/hyperinsulinemia

Summary and Conclusions – Human Liver

- The DNL pathway is profoundly induced in livers of (morbidly) obese humans

- Liver FASN expression correlates strongly with HOMA-IR, indicating a link to liver insulin resistance/hyperinsulinemia

- The induction of liver ELOVL6 may support insulin resistance by increasing synthesis of stearic acid (C18:0), as described in mice (Matsuzaka et al. 2007, Nat Med 13:1193)

Summary and Conclusions: Human VAT

- Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans

Summary and Conclusions: Human VAT

- Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans

- Down-regulation of GLUT4 protein in insulin resistant subjects is consistent with a crucial role of GLUT4 for whole body insulin sensitivity (Abel et al., 2001, Nature 409:729)

Summary and Conclusions: Human VAT

- Except for SCD, the DNL pathway is strongly suppressed in (diabetic) obese humans

- Down-regulation of GLUT4 protein in insulin resistant subjects is consistent with a crucial role of GLUT4 for whole body insulin sensitivity (Abel et al., 2001, Nature 409:729)

- Palmitoleate (C16:1) does not drop in obesity (compensation by liver)

Ongoing/Future Work

- Fatty acid profiling in liver and plasma
- Gene expression changes in adipose tissue after weight loss
- Study liver pathology
- Lipidomics (DNL biomarker)

Acknowledgements

Department of Surgery, Ulm
Uwe Knippschild
Anna Wolf

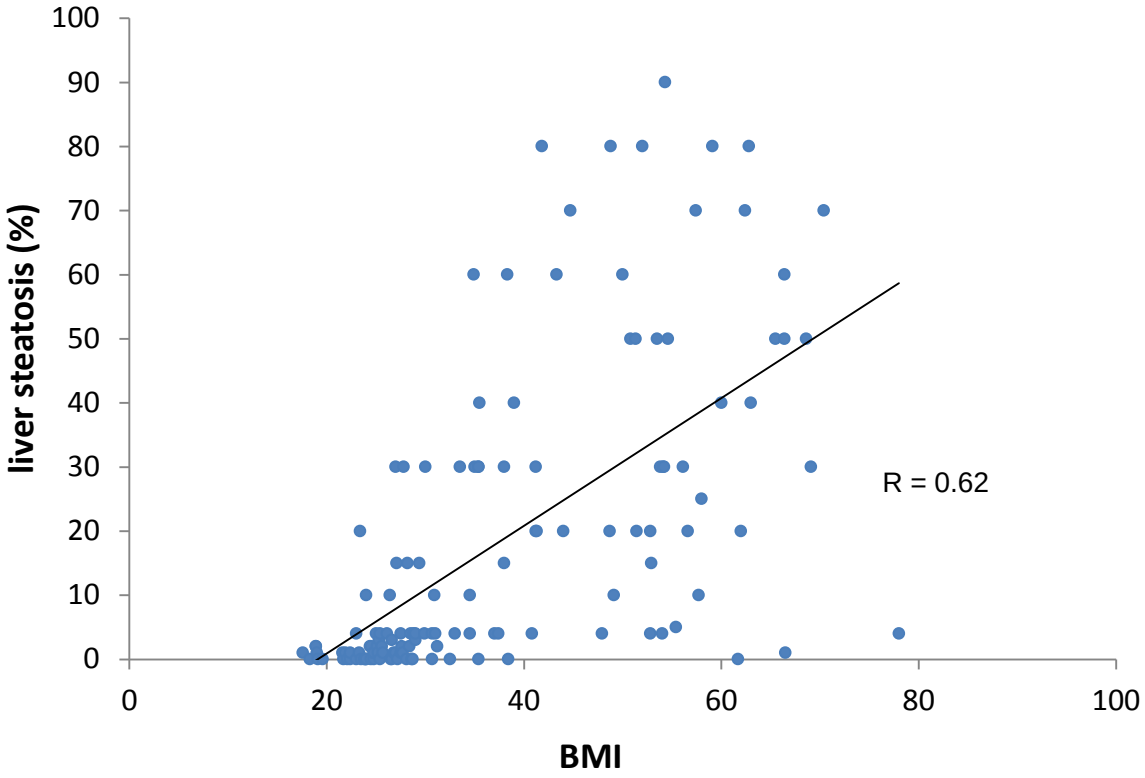
Mount Sinai School of Medicine, New York
Thomas Scherer
Christoph Büttner

Department of Surgery, Maastricht
Sander Rensen

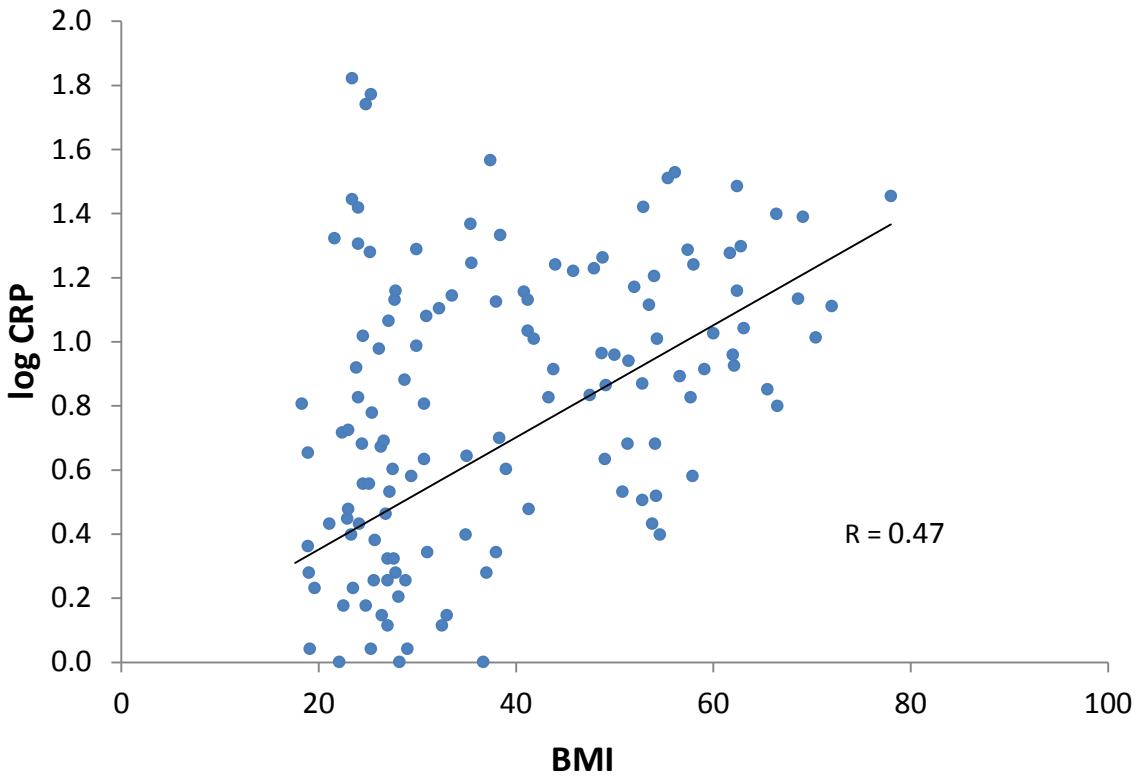
Dept. of Biochemistry, Hamburg
Leah Eissing
Klaus Tödter
Jörg Heeren

Appendix

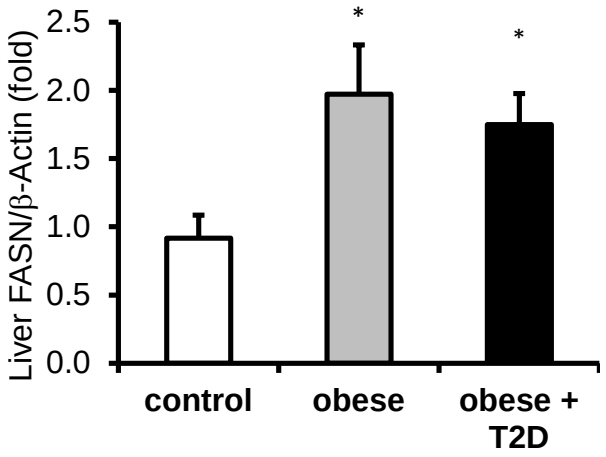
Study Cohort: Liver Steatosis



Study Cohort: CRP

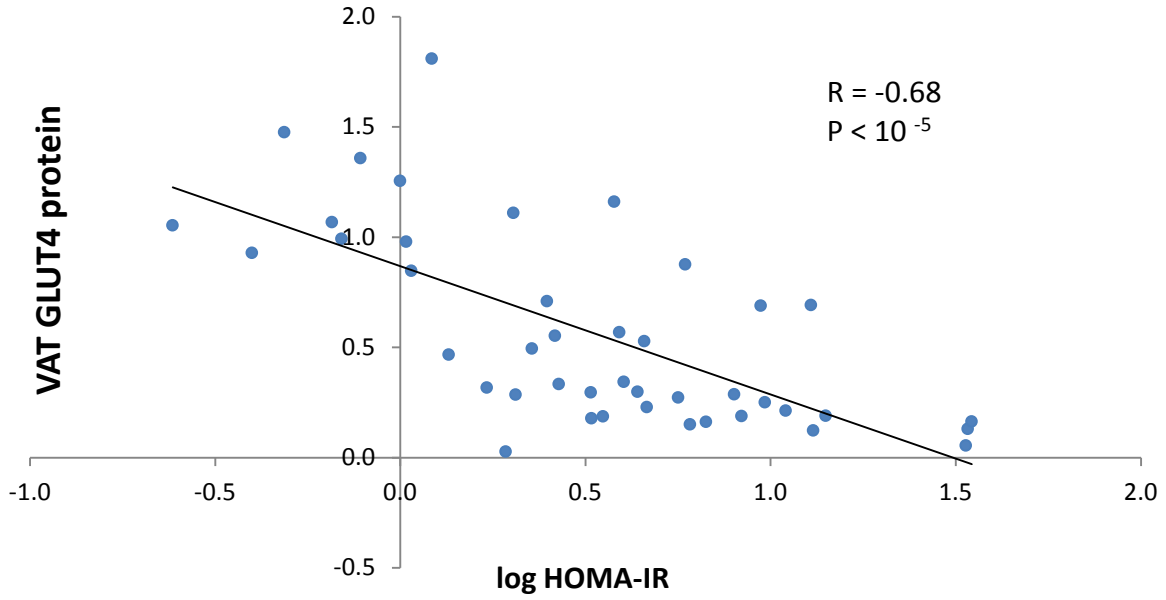


Liver FASN Westernblot



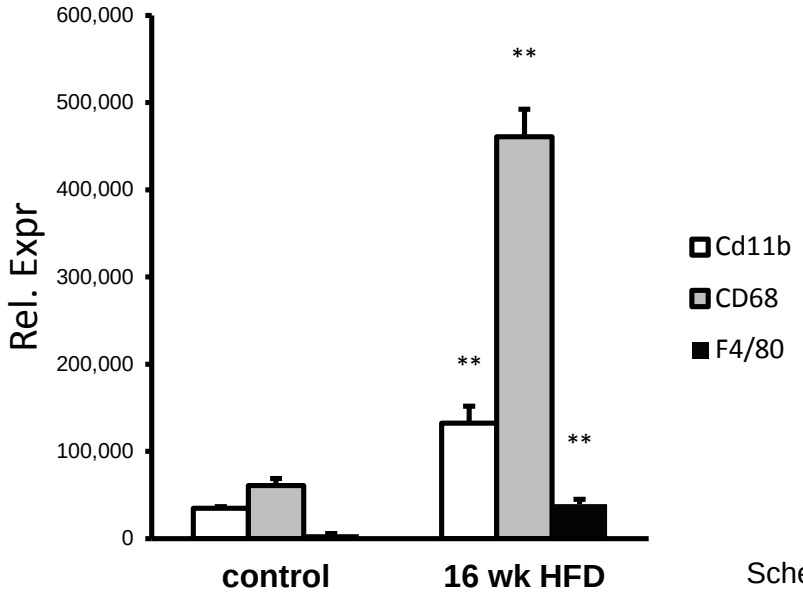
n > 8, T-Test vs. controls, * p< 0.05, ** p< 0.001

Correlation VAT GLUT4 - HOMA-IR



Mouse Adipose Tissue Macrophage Infiltration

- In mice, obesity is accompanied by massive macrophage infiltration in white adipose tissue

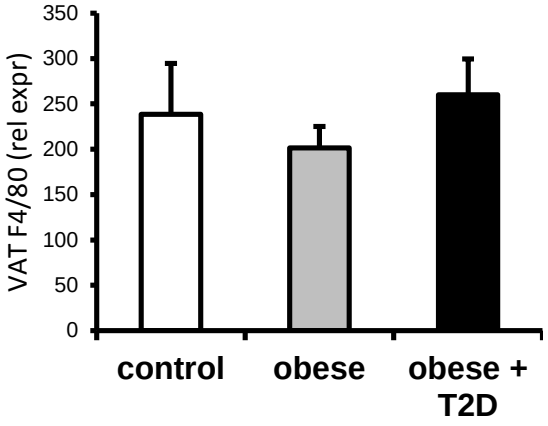


Scheja et al., 2011, BBRC 407:288

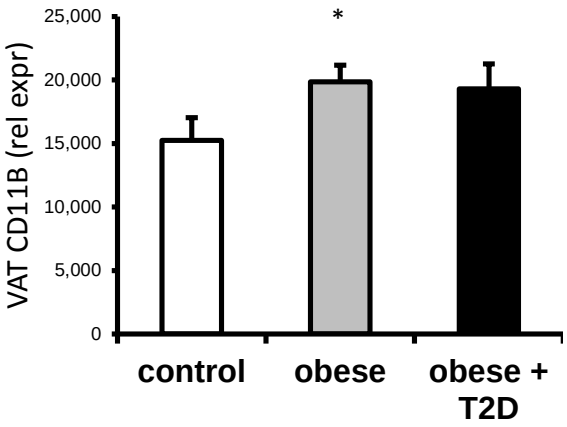
T-Test vs. controls, * p< 0.05, ** p< 0.001

Expression of Macrophage Markers in Human VAT

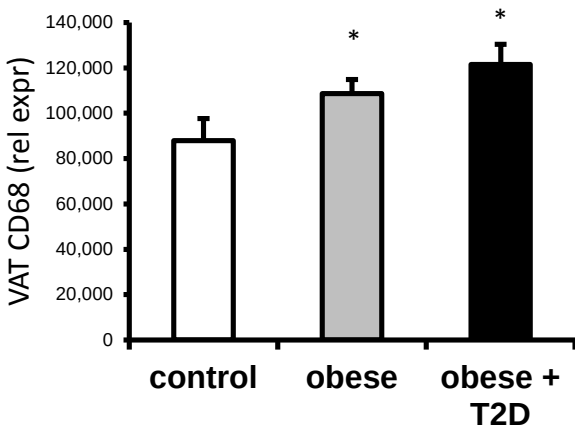
F4/80



CD11b

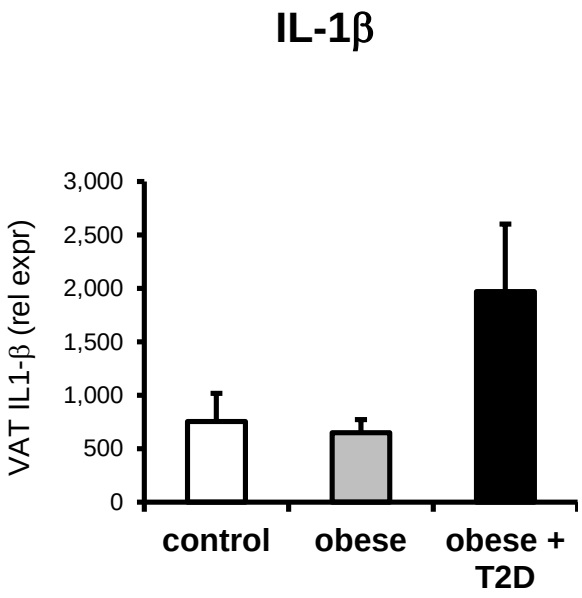


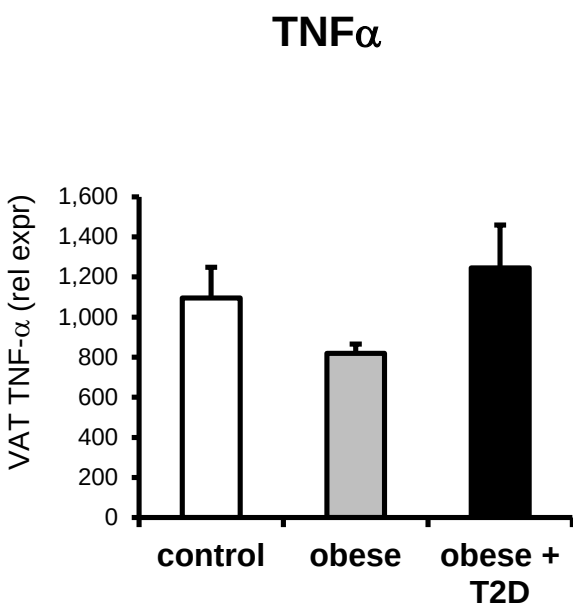
CD68

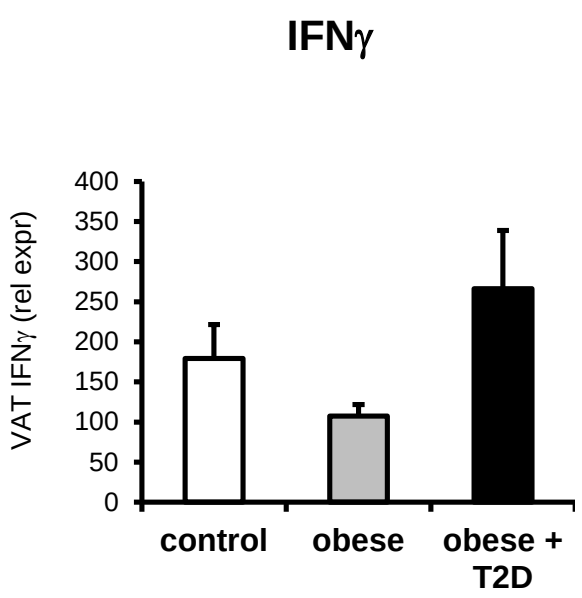


T-Test vs. controls, * p< 0.05, ** p< 0.001

Inflammatory Cytokine Expression in Human VAT



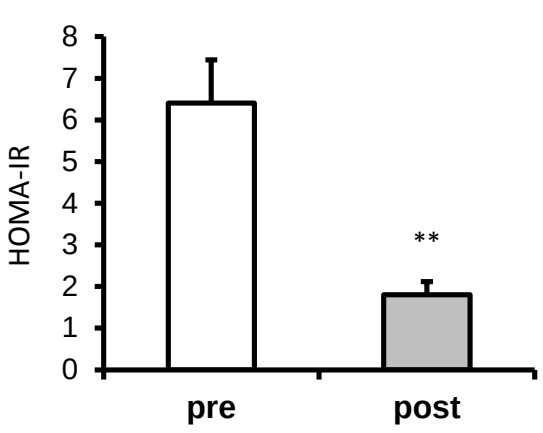


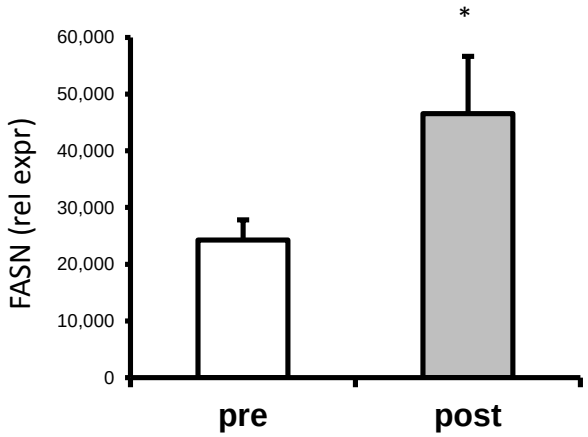


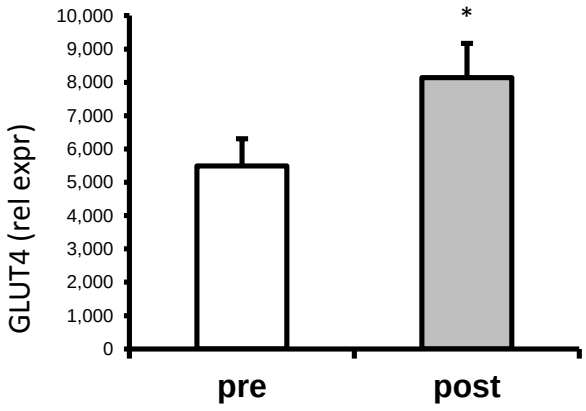
T-Test vs. controls, * p< 0.05, ** p< 0.001

Adipose Tissue Gene Expression After Weight Loss

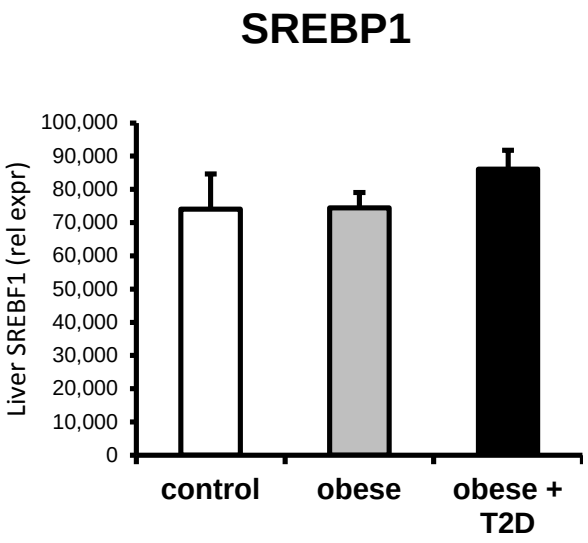
- Bariatric surgery, performed at Maastricht University Hospital
- Subcutaneous adipose tissue samples before and after intervention

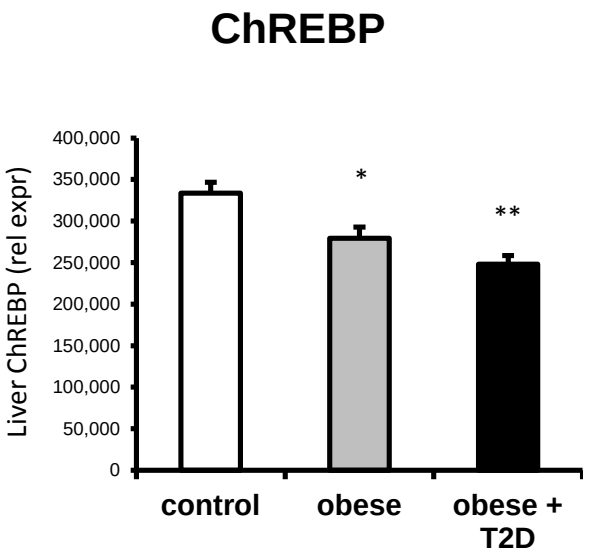


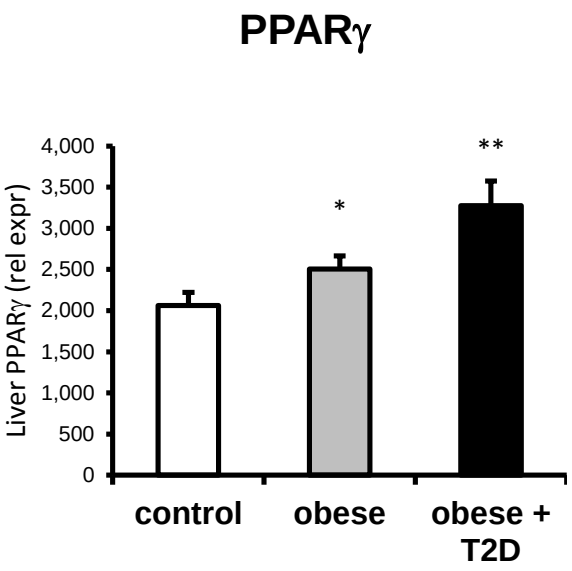




Liver Transcription Factor Expression





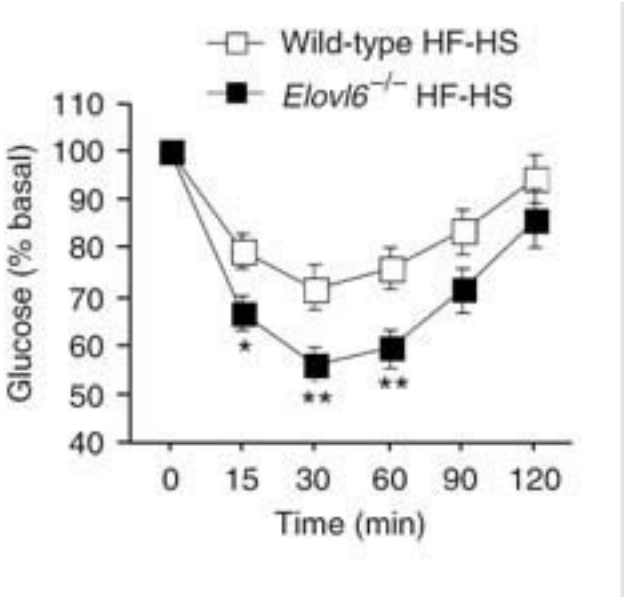


Title

Matsuzaka et al., Nature Medicine 13, (2007) **Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance**

Text

Elovl6 knockout



Elovl6 forced expression