Mit Fett gegen Fettleber

Nicolai Worm

www.nicolai-worm.de
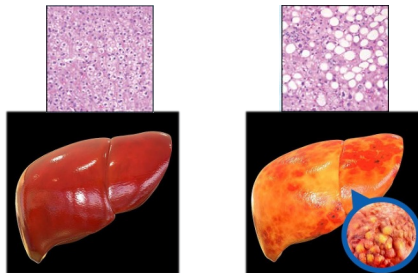
1

Definition

2

Definition: nicht-alkoholische Fettleber (NAFLD)
Häufigste chronische Lebererkrankung!

➢ wenn Fettgehalt der Leber > 5 %
➢ bei ≤ 20 g (Frauen) bzw. ≤ 30 g (Männer) Alkoholkonsum pro Tag
➢ und Ausschluss anderer Ursachen

normale Leber   Fettleber

3

Umbenennung der nichtalkoholischen Fettlebererkrankung (1)

Die Bezeichnung „nichtalkoholische Fettlebererkrankung" (NAFLD) ist out!

Von nun an sollen diese Bezeichnungen gelten:

Internationale Leberexperten haben sich geeinigt, jede Art der Steatose der Leber als steatotische Lebererkrankung (abgekürzt SLD vom Englischen Steatotic Liver Disease) zu bezeichnen.
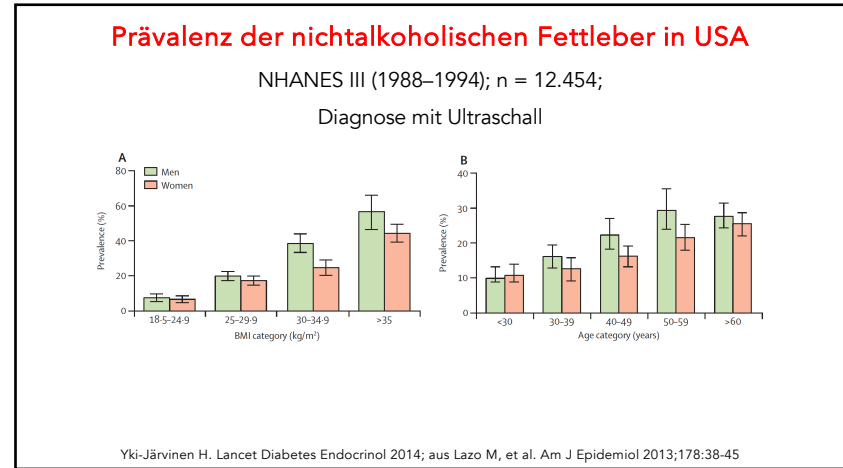
Bei Vorhandensein von einem oder mehreren kardiometabolischen Risiko-faktoren wird die Erkrankung jetzt als metabolische dysfunktionsassoziierte steatotische Lebererkrankung bezeichnet (abgekürzt: MASLD - vom Englischen Metabolic Dysfunction-Associated Steatotic Liver Disease).

Rinella ME, et al. J Hepatol. 2023:S0168-8278(23)00418-X.

4

Slide 5

Epidemiologie der NAFLD

5

Slide 6

Prävalenz der nichtalkoholischen Fettleber in USA

NHANES III (1988–1994); n = 12.454;

Diagnose mit Ultraschall

Yki-Järvinen H. Lancet Diabetes Endocrinol 2014; aus Lazo M, et al. Am J Epidemiol 2013;178:38-45

6

Slide 7

swiss HePa

Schweizer Leberpatienten Verein
Association Suisse des Patients Hépatologiques
Associazione Svizzera dei Pazienti Epatologici
Swiss Liver Patients Association

Zahlen ab 1994 erhoben und 92% mit Ultraschall!

Häufigkeit dieser Lebererkrankung

Die Fettlebererkrankung ist auf der ganzen Welt sehr weit verbreitet. Momentan ist rund ein Viertel der Schweizer Allgemeinbevölkerung von der Fettlebererkrankung betroffen. In Deutschland und weiteren europäischen Ländern sind diese Zahlen ähnlich. Beunruhigend ist dabei eine deutliche Zunahme der Erkrankung über die letzten Jahrzehnte.

Zugriff am 18.11.2023; https://www.swisshepa.org/lebererkrankungen/fettleber/

7

Slide 8

NAFLD Prävalenz in Deutschland

KORA Kohorte
(Kooperative Gesundheitsforschung in der Region Augsburg)

Repräsentative Zufallsstichprobe aller 25- bis 74jährigen im Raum Augsburg

n = 386 mit Ganzkörper-MRI

Prävalenz: 43%

KORA	
	Total (N=386)
Age (years)	56.2 (9.1)
Women	163 (42.2%)
BMI (kg/m^2)	28.1 (4.9)
Waist circumference (cm)	98.5 (14.3)
ALT (µkat/L)	0.5 (0.3, 0.6)
AST (µkat/L)	0.4 (0.3, 0.5)
GGT (µkat/L)	0.5 (0.3, 0.7)
Glucose tolerance status	
Normoglycaemic	239 (61.9%)
Pre-diabetes	95 (24.6%)
Diabetes	52 (13.5%)
PDFF (%)	4.62 (2.63, 11,89)
FLD	166 (43.0%)
Antihypertensive medication use	98 (25.4%)
Lipid-lowering medication use	41 (10.6%)
History of CVD	NA

Cai X, et al. BMJ Open Gastro 2021;8:e000709

8

Slide 9

Wie viele Menschen sind leiden an NAFLD?

Erwachsene	Übergewichtige	Typ-2-Diabetiker
30 – 50 %	70 %	70 – 90 %

9

Slide 10

Exploring the landscape of steatotic liver disease in the general US population

NHANES 2017–2020: n=3.173 repräsentativ, Diagonse mit Elastrografie;

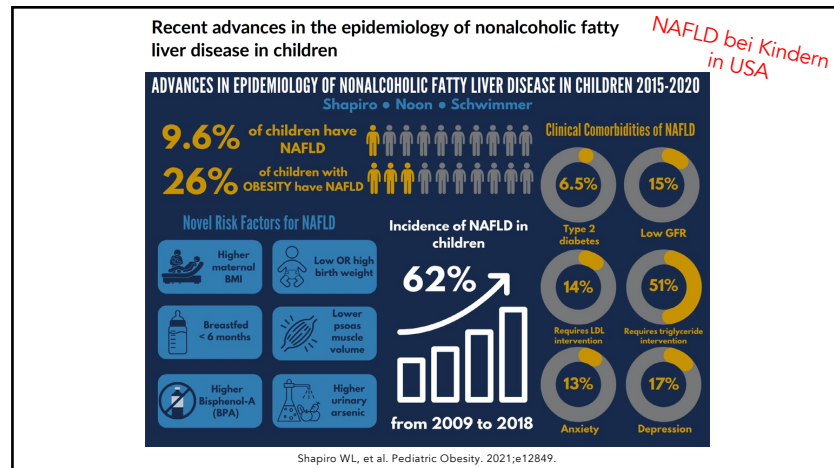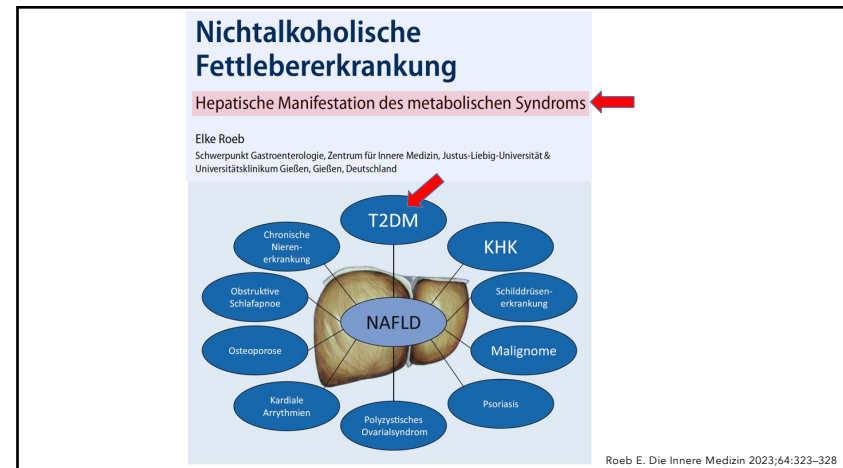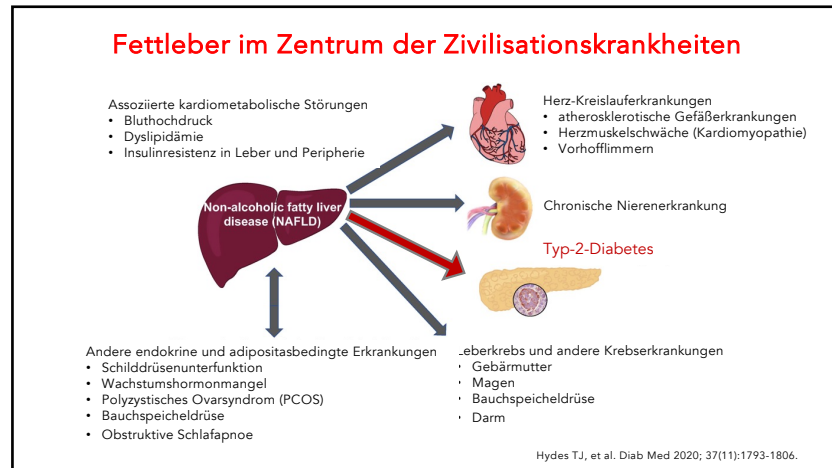Legend: MAFLD, MASLD, NAFLD

Prevalence (%) by group: Total, NHW, Hispanic, NHB, Other

Ciardullo S, et al. Liver International. 2023; online first Aug 17;

10

Slide 11

Recent advances in the epidemiology of nonalcoholic fatty liver disease in children

NAFLD bei Kindern in USA

ADVANCES IN EPIDEMIOLOGY OF NONALCOHOLIC FATTY LIVER DISEASE IN CHILDREN 2015-2020
Shapiro • Noon • Schwimmer

9.6% of children have NAFLD
26% of children with OBESITY have NAFLD

Clinical Comorbidities of NAFLD
6.5% Type 2 diabetes
15% Low GFR
14% Requires LDL intervention
51% Requires triglyceride intervention
13% Anxiety
17% Depression

Novel Risk Factors for NAFLD
Higher maternal BMI
Low OR high birth weight
Breastfed < 6 months
Lower psoas muscle volume
Higher Bisphenol-A (BPA)
Higher urinary arsenic

Incidence of NAFLD in children
62% from 2009 to 2018

Shapiro WL, et al. Pediatric Obesity. 2021;e12849.

11

Slide 12

Nichtalkoholische Fettlebererkrankung

Hepatische Manifestation des metabolischen Syndroms

Elke Roeb
Schwerpunkt Gastroenterologie, Zentrum für Innere Medizin, Justus-Liebig-Universität & Universitätsklinikum Gießen, Gießen, Deutschland

NAFLD: T2DM, KHK, Schilddrüsenerkrankung, Malignome, Psoriasis, Polyzystisches Ovarialsyndrom, Kardiale Arrythmien, Osteoporose, Obstruktive Schlafapnoe, Chronische Nierenerkrankung

Roeb E. Die Innere Medizin 2023;64:323–328

12

Slide 13

Fettleber im Zentrum der Zivilisationskrankheiten

Assoziierte kardiometabolische Störungen
- Bluthochdruck
- Dyslipidämie
- Insulinresistenz in Leber und Peripherie

Non-alcoholic fatty liver disease (NAFLD)

Herz-Kreislauferkrankungen
- atherosklerotische Gefäßerkrankungen
- Herzmuskelschwäche (Kardiomyopathie)
- Vorhofflimmern

Chronische Nierenerkrankung

Typ-2-Diabetes

Andere endokrine und adipositasbedingte Erkrankungen
- Schilddrüsenunterfunktion
- Wachstumshormonmangel
- Polyzystisches Ovarsyndrom (PCOS)
- Bauchspeicheldrüse
- Obstruktive Schlafapnoe

Leberkrebs und andere Krebserkrankungen
- Gebärmutter
- Magen
- Bauchspeicheldrüse
- Darm

Hydes TJ, et al. Diab Med 2020; 37(11):1793-1806.

13

Slide 14

Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals

Fettleber erhöht eine T2D-Wahrscheinlichkeit um das 2,2-fache – unabhängig vom Körpergewicht!

Results 33 studies with 501 022 individuals with NAFLD) and 27 953 cases of incident diabetes over a median of 5 years (IQR: 4.0–19 years) were included. Patients with NAFLD had a higher risk of incident diabetes than those without NAFLD (n=26 studies; random-effects HR 2.19, 95% CI 1.93 to 2.48; I^2=91.2%). Patients with more 'severe' NAFLD were also more likely to develop incident diabetes (n=9 studies; random-effects HR 2.69, 95% CI 2.08 to 3.49; I^2=69%). This risk markedly increased across the severity of liver fibrosis (n=5 studies; random-effects HR 3.42, 95% CI 2.29 to 5.11; I^2=44.6%). All risks were independent of age, sex, adiposity measures and other common metabolic risk factors. Sensitivity analyses did not alter these findings. Funnel plots did not reveal any significant publication bias.
Conclusion This updated meta-analysis shows that NAFLD is associated with a ~2.2-fold increased risk of incident diabetes. This risk parallels the underlying severity of NAFLD.
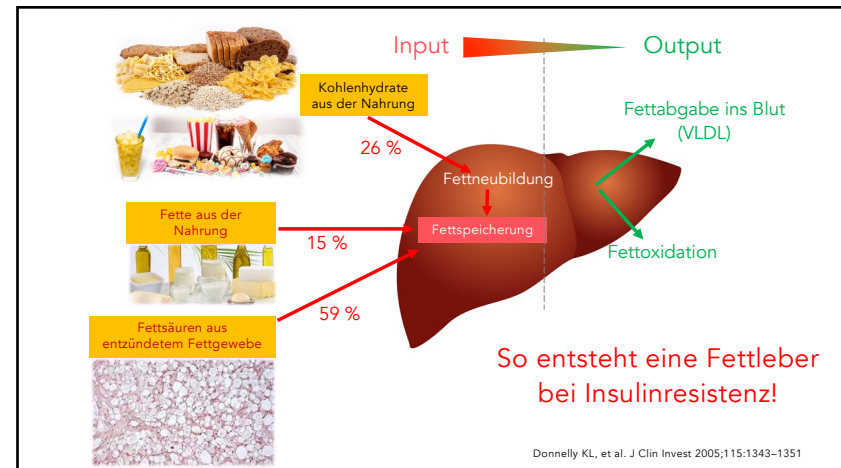
Prospective design	Random-effects HR 2.18 (95% CI 1.87 to 2.55) I^2=89.0% No of studies: 6 n=252 678
Retrospective design	Random-effects HR 2.22 (95% CI 1.86 to 2.66) I^2=91.1% No of studies: 20 n=165 886
Length of study follow-up	
Follow-up <5 years	Random-effects HR 1.96 (95% CI 1.67 to 2.29) I^2=90.1% No of studies: 11 n=198 455
Follow-up ≥5 years	Random-effects HR 2.37 (95% CI 2.01 to 2.80) I^2=86.2% No of studies: 15 n=220 109

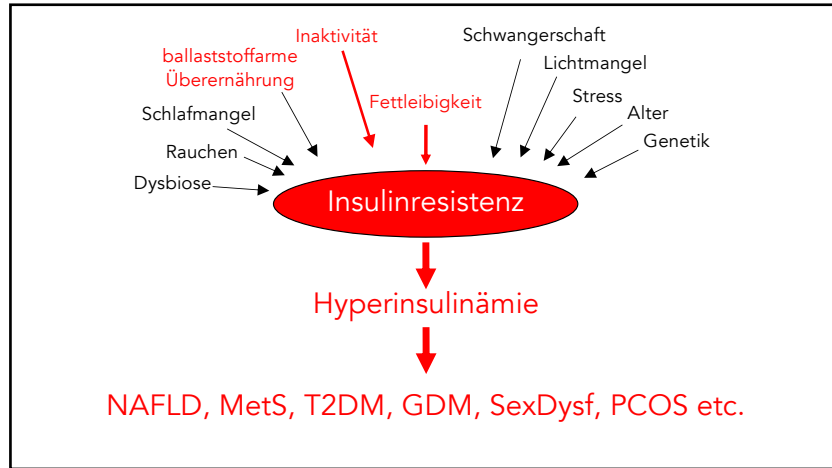Mantovani A, et al. Gut 2021;70(5):962-969.;

14

Slide 15

Pathophysiologie

15

Slide 16

Input — Output

Kohlenhydrate aus der Nahrung

26 %

Fette aus der Nahrung

15 %

Fettsäuren aus entzündetem Fettgewebe

59 %

Fettneubildung

Fettspeicherung

Fettabgabe ins Blut (VLDL)

Fettoxidation

So entsteht eine Fettleber bei Insulinresistenz!

Donnelly KL, et al. J Clin Invest 2005;115:1343–1351

16

Slide 17

Schlafmangel · Rauchen · Dysbiose
ballaststoffarme Überernährung · Inaktivität · Fettleibigkeit
Schwangerschaft · Lichtmangel · Stress · Alter · Genetik

Insulinresistenz

Hyperinsulinämie

NAFLD, MetS, T2DM, GDM, SexDysf, PCOS etc.

17

Slide 18

De-novo Lipogenese in Leber- und Fettzellen

Hohe Blutzucker- und Insulinspiegel aktivieren die Transkriptionsfaktoren ChREBP und SREBP-1

Fettzellen — Leberzellen

Ameer F, et al. Metabolism 2014;63:895-902.

18

Slide 19

Dysfunktionale Fettzellen und NAFLD

19

Slide 20

Metabolisch-vaskuläres Risiko durch ektopes Fett

Chartrand JD, et al. Curr Atheroscler Rep 2022;24(4):185-195;
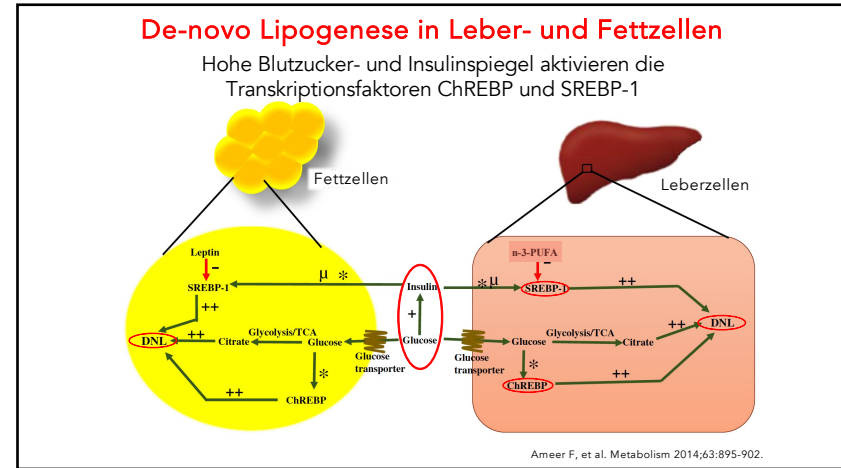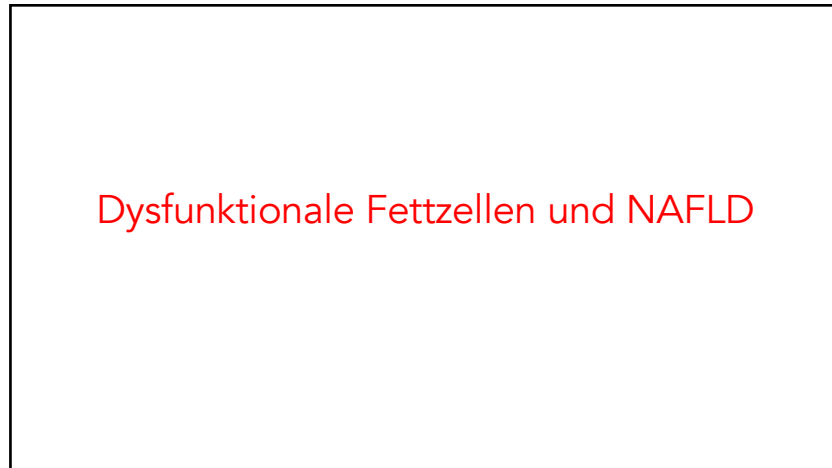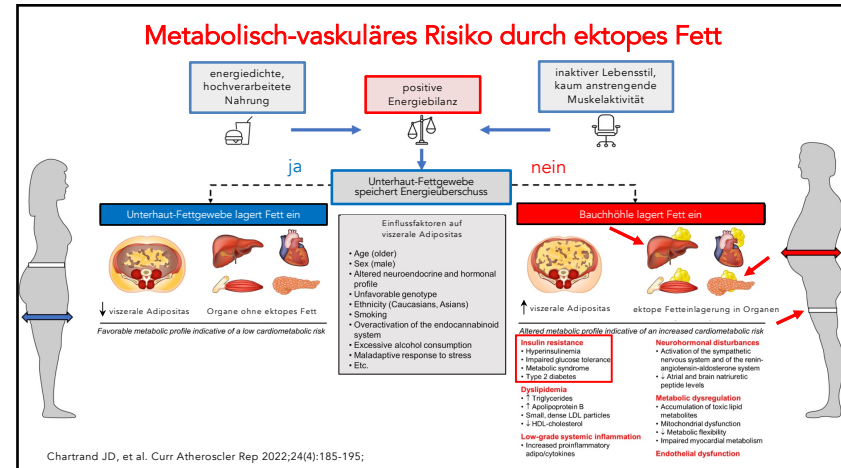
20

Slide 21

Kohlenhydrate bei Insulinresistenz als Risiko!

21

Slide 22

Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease

[1]Atkins Center of Excellence in Obesity Medicine, Center for Human Nutrition, John T. Milliken Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA. [2]Department of Nutritional Sciences and Toxicology, College of Natural Resources, University of California at Berkeley, Berkeley, California, USA. [3]Liver Imaging Group, University of California, San Diego, La Jolla, California, USA. [4]Merck & Co., San Francisco, California, USA.

|	Lean (n = 14)	Obese (n = 26)	Obese-NAFLD (n = 27)
BMI (kg/m²)	22.6 ± 0.4	37.0 ± 0.9[A]	38.9 ± 0.9[A]
Body fat (%)	29.4 ± 1.5	48.0 ± 1.2[A]	47.7 ± 1.1[A]
IHTG content (%)	1.8 ± 0.2	2.3 ± 0.2	18.0 ± 1.7[A,B]
IAAT volume (cm³)	400 ± 55	917 ± 71[A]	1864 ± 130[A,B]
ASAT volume (cm³)	937 ± 105	3716 ± 215[A]	3644 ± 240[A]
HbA1c (%)	5.0 ± 0.1	5.0 ± 0.1	5.7 ± 0.1[A,B]
TGs (mg/dL)	67 ± 8	67 ± 4	141 ± 13[A,B]
HDL cholesterol (mg/dL)	67 ± 4	55 ± 3[A]	43 ± 2[A,B]
LDL cholesterol (mg/dL)	99 ± 6	99 ± 5	118 ± 6
Fasting glucose (mg/dL)	85 ± 1	88 ± 1	101 ± 2[A,B]
Glucose: 2 hours OGTT (mg/dL)	96 ± 5	106 ± 3	170 ± 6[A,B]
Glucose: 24 hours AUC (mg/dL × 24 hours)	2260 ± 46	2302 ± 27	2732 ± 56[A,B]
Fasting insulin (μU/mL)	5.2 ± 0.5	11.8 ± 1.4	27.1 ± 3.4[A,B]
Insulin: 24 hours AUC (μU/mL × 24 hours)	564 ± 81	1059 ± 89	2168 ± 252[A,B]
HISI	10.8 ± 1.0	5.8 ± 0.4[A]	3.0 ± 0.2[A,B]
Glucose Rd during the HECP (μmol/kg FFM/min)	60.8 ± 3.5	48.3 ± 2.4[A]	27.6 ± 1.4[A,B]

3 Tage u. Nächte im Labor: kontrollierte Kost: 50 En% Kohlenhydrate, 35 En% Fett und 15 En% Protein;

Fettgehalt in Leber mit MRI;

Smith GI, et al. J Clin Invest. 2020;130(3):1453–1460.

22

Slide 23

Anteil der DNL an der Leberfettung in Abhängigkeit von Körperfett, Glukose- und Insulinspiegel
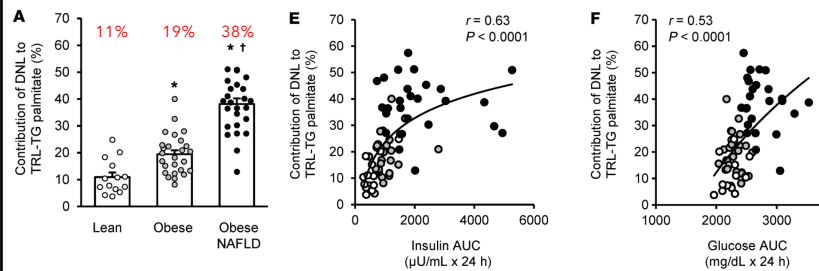
Bei NAFLD-Patienten stammt 38 % des Fettes in der Leber aus Kohlenhydraten!

Smith GI, et al. J Clin Invest. 2020;130(3):1453–1460.

23

Slide 24

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i8.1166

World J Gastroenterol 2013 February 28; 19(8): 1166-1172
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
© 2013 Baishideng. All rights reserved.
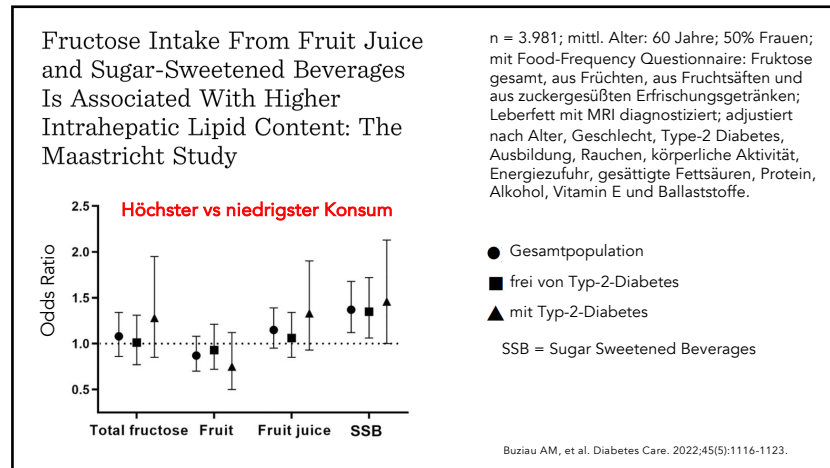
TOPIC HIGHLIGHT

Metin Basaranoglu, MD, PhD, Associate Professor, Series Editor

Fructose as a key player in the development of fatty liver disease

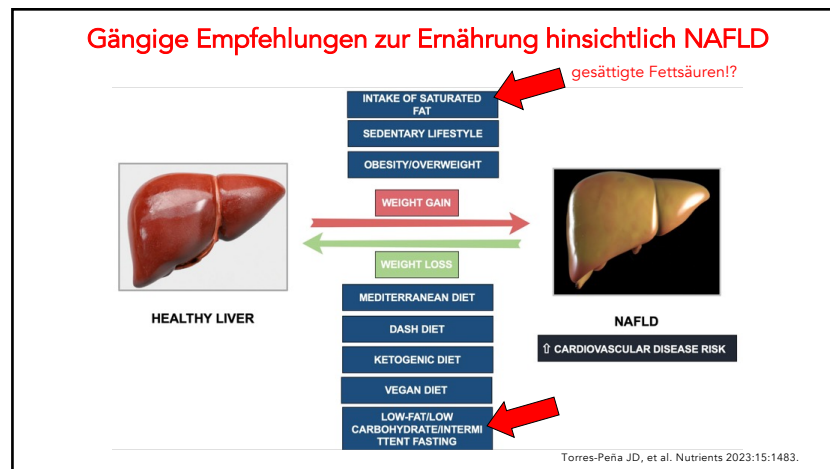Metin Basaranoglu, Gokcen Basaranoglu, Tevfik Sabuncu, Hakan Sentürk

24

Slide 25

Fructose Intake From Fruit Juice and Sugar-Sweetened Beverages Is Associated With Higher Intrahepatic Lipid Content: The Maastricht Study

Höchster vs niedrigster Konsum

n = 3.981; mittl. Alter: 60 Jahre; 50% Frauen; mit Food-Frequency Questionnaire: Fruktose gesamt, aus Früchten, aus Fruchtsäften und aus zuckergesüßten Erfrischungsgetränken; Leberfett mit MRI diagnostiziert; adjustiert nach Alter, Geschlecht, Type-2 Diabetes, Ausbildung, Rauchen, körperliche Aktivität, Energiezufuhr, gesättigte Fettsäuren, Protein, Alkohol, Vitamin E und Ballaststoffe.

● Gesamtpopulation
■ frei von Typ-2-Diabetes
▲ mit Typ-2-Diabetes

SSB = Sugar Sweetened Beverages

Buziau AM, et al. Diabetes Care. 2022;45(5):1116-1123.

25

Slide 26

Gesättigte Fettsäuren als Risiko?

Nahrungsmittel mit hohem Anteil gesättigter Fettsäuren ein NAFLD-Risiko?

26

Slide 27

Gängige Empfehlungen zur Ernährung hinsichtlich NAFLD

gesättigte Fettsäuren!?

INTAKE OF SATURATED FAT
SEDENTARY LIFESTYLE
OBESITY/OVERWEIGHT
WEIGHT GAIN
WEIGHT LOSS
HEALTHY LIVER
MEDITERRANEAN DIET
DASH DIET
KETOGENIC DIET
VEGAN DIET
LOW-FAT/LOW CARBOHYDRATE/INTERMITTENT FASTING
NAFLD
⇧ CARDIOVASCULAR DISEASE RISK

Torres-Peña JD, et al. Nutrients 2023;15:1483.

27

Slide 28

Sind Nahrungsmittel mit gesättigten Fettsäuren zu meiden/minimieren?

Milchfett ~ 60% gesättigte Fettsäuren

28

Milchfett: Fettsäuremuster in verschiedenen Milchsorten

Fettsäuren	konventionelle Milch	modifizierte Milch[1]	Alpenmilch
SFA	69,8	61,3	61,5
davon Palmitinsäure	33,0	22,8	21,2
MUFA	27,2	34,9	31,5
davon Ölsäure	19,7	25,0	26,0
PUFA	3,0	3,8	7,0
davon CLA	0,6	1,1	2,7
SFA/MUFA	2,6	1,7	2,0
n-6/n-3	3,2	2,1	1,5

[1]Verfütterung von Lein- und Rapssaatpresskuchen
SFA = gesättigte Fettsäuren, MUFA = einfach ungesättigte Fettsäuren, PUFA = mehrfach ungesättigte Fettsäuren,
CLA = konjugierte Linolsäure

Arnold C & Jahreis G. Ernährungs-Umschau 2011;4:177–181

29

Wir essen keine Nährstoffe, sondern Lebensmittel!

Entscheidend ist die Lebensmittelmatrix!

Die gesundheitlichen Auswirkungen eines Lebensmittels sind viel komplexer als die einzelner oder mehrerer einzelner Nährstoffe.

Die Struktur und Interaktion alle enthaltenen Nähr- und bioaktiven Wirkstoffe beeinflussen Absorption, Verdauung und Stoffwechsel und sind entscheidend.

30

Dairy Milk Protein–Derived Bioactive Peptides: Avengers Against Metabolic Syndrome

[1] Institute of Nutrition, Mahidol University, 999 Phutthamonthon 4 Road, Salaya, Nakhon Pathom 73170, Thailand
[2] Department of Nutrition and Dietetics, Central Campus of Technology, Tribhuvan University, Kirtipur, Nepal
[3] Department of Food Science, College of Food and Agriculture, United Arab Emirates University, Al Ain 15551, United Arab Emirates
[4] Department of Food Science and Nutrition, College of Agriculture and Food Sciences, King Faisal University, Al-Hofuf, P. O. Box 400, Al-Ahsa 31982, Saudi Arabia

MPDP = Milk Protein–Derived Peptides
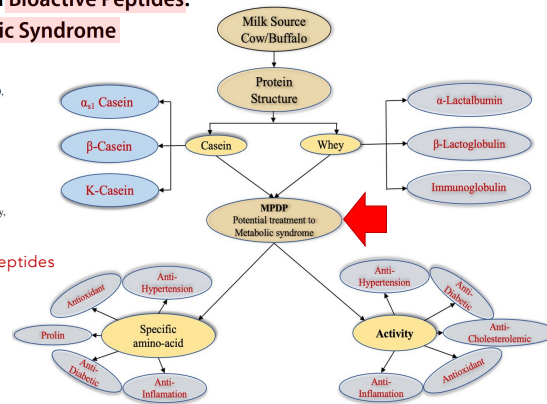
Koirala P, et al. Current Nutrition Reports 2023;12:299–317

31

Traditional plain yogurt: a therapeutic food for metabolic syndrome?
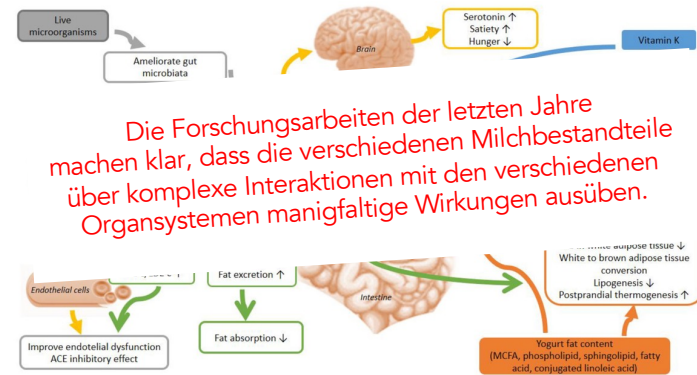
Die Forschungsarbeiten der letzten Jahre machen klar, dass die verschiedenen Milchbestandteile über komplexe Interaktionen mit den verschiedenen Organsystemen manigfaltige Wirkungen ausüben.

Baspinar B, et al. Crit Rev Food Sci Nutr. 2021;61(18):3129-3143.

32

Slide 33:

Milchprodukte und Risiko für NAFLD und assoziierte kardiometabolische Erkrankungen

33

Slide 34:

Dairy fat intake is associated with glucose tolerance, hepatic and systemic insulin sensitivity, and liver fat but not β-cell function in humans[1–3]

ABSTRACT

Background: Plasma phospholipid concentrations of *trans*-palmitoleic acid (*trans*-16:1n−7), a biomarker of dairy fat intake, are inversely associated with incident type 2 diabetes in 2 US cohorts.
Objective: The objective was to investigate whether the intake of *trans*-16:1n−7 in particular, or dairy fat in general, is associated with glucose tolerance and key factors determining glucose tolerance.
Design: A cross-sectional investigation was undertaken in 17 men and women with nonalcoholic fatty liver disease and 15 body mass index (BMI)- and age-matched controls. The concentrations of *trans*-16:1n−7 and 2 other biomarkers of dairy fat intake, 15:0 and 17:0, were measured in plasma phospholipids and free fatty acids (FFAs). Liver fat was estimated by computed tomography–derived liver-spleen ratio. Intravenous-glucose-tolerance tests and oral-glucose-tolerance test (OGTT) and hyperinsulinemic-euglycemic clamps were performed to assess β-cell function and hepatic and systemic insulin sensitivity.

Results: In multivariate analyses adjusted for age, sex, and BMI, phospholipid 17:0, phospholipid *trans*-16:1n−7, FFA 15:0, and FFA 17:0 were inversely associated with fasting plasma glucose, the area under the curve for glucose during an OGTT, and liver fat. Phospholipid *trans*-16:1n−7 was also positively associated with hepatic and systemic insulin sensitivity. None of the biomarkers were associated with β-cell function. The associations between dairy fat intake and glucose tolerance were attenuated by adjusting for insulin sensitivity or liver fat, but strengthened by adjusting for β-cell function.
Conclusion: Although we cannot rule out reverse causation, these data support the hypothesis that dairy fat improves glucose tolerance, possibly through a mechanism involving improved hepatic and systemic insulin sensitivity and reduced liver fat. This trial was registered at clinicaltrials.gov as NCT01289639.

Ergebnis: Milch/Milchprodukten mit verbesserter hepatischer Insulinsensitivität und reduziertem Leberfett-Gehalt assoziiert.

Kratz M, et al. Am J Clin Nutr. 2014;99:1385-96.

34

Slide 35:

Dairy product consumption and risk of non-alcoholic fatty liver disease: A systematic review and meta-analysis of observational studies

[a] Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada
[b] Department of Cell Biology, University of Alberta, Edmonton, Alberta, Canada
[c] Alberta Health Services, Edmonton, Alberta, Canada
[d] School of Public Health, University of Alberta, Edmonton, Alberta, Canada
[e] Department of Physiology, University of Alberta, Edmonton, Alberta, Canada

OR: NAFLD Risiko für Milch/Milchprodukte

Han (M) (2014)	1.72 (0.66, 4.34)
Han (F) (2014)	1.43 (0.54, 3.74)
Chan (B) (2015)	0.87 (0.52, 1.47)
Chiu (B) (2018)	1.02 (0.92, 1.14)
Mansour-Ghanaei (B) (2019)	0.70 (0.42, 1.19)
Kalafati (B) (2019)	1.19 (1.00, 1.42)
vanEekelen (M) (2019)	0.92 (0.86, 0.99)
vanEekelen (F) (2019)	0.97 (0.86, 1.06)
Watzinger (B) (2020)	0.31 (0.10, 0.98)
Hao (B) (2020)	0.65 (0.53, 0.80)
Zhang (B) (2020)	0.85 (0.75, 0.97)
Charatcharoenwitthaya (B) (2021)	0.42 (0.18, 0.99)
Lee (F>50y) (2021)	0.80 (0.71, 0.89)
Lee (F<50y) (2021)	0.99 (0.86, 1.12)
Lee (m) (2021)	0.88 (0.79, 0.97)
Overall, DL (I^2 = 67.8%, p = 0.000)	0.90 (0.83, 0.98)

Meta-Analyse von 11 Beobachtungsstudien zur Inzidenz von NAFLD, n=43.649, 11.020 Fälle;
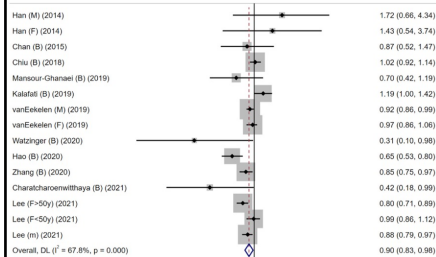
Milchprodukte:	OR=0,90; 95% KI: 0,83-0,98
Fettreiche Milchprod.:	OR=0,38; 95% KI: 0,19-0,75
Milch:	OR=0,86; 95% KI: 0,78-0,95
Joghurt:	OR=0,88; 95% KI: 0,82-0,96
Käse:	OR=1,01; 95% KI: 0,82-1,25

Yuzbashian E, et al. Nutr Metab Cardiovasc Dis. 2023;33:1461-1471.

35

Slide 36:

Yogurt improves insulin resistance and liver fat in obese women with nonalcoholic fatty liver disease and metabolic syndrome: a randomized controlled trial
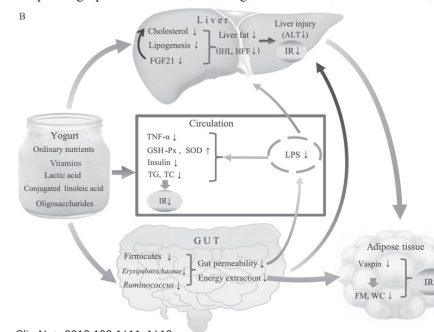
ABSTRACT
Background: Because consumption of conventional yogurt has beneficial effects in a healthy population, and insulin resistance (IR) is the mutual pathogenesis of nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS), we hypothesized that yogurt would ameliorate IR in patients with NAFLD and MetS.
Objectives: The aim of this study was to investigate the effects of yogurt on IR and secondary endpoints including liver fat, gut microbiota, and serum biomarkers of inflammation and oxidative stress in obese women with NAFLD and MetS.
Methods: One hundred obese women aged 36–66 y with both NAFLD and MetS were randomly assigned to consume 220 g/d of either conventional yogurt or milk for 24 wk. At baseline and week 24, we measured anthropometric indices, serum glucose, insulin, lipids, and cytokines in all participants, and liver fat and gut microbiota in 20 participants randomly selected from each group.
Results: Forty-eight participants from the yogurt group and 44 from the milk group completed the intervention. Compared with milk, yogurt significantly decreased the homeostasis model assessment of insulin resistance (−0.53; 95% CI: −1.03, −0.02), fasting insulin (−2.77 mU/L; 95% CI: −4.91, −0.63 mU/L), 2-h insulin (−25.5 mU/L; 95% CI: −33.0, −17.9 mU/L), 2-h area under the curve for insulin (−29.4 mU/L · h; 95% CI: −44.0, −14.8 mU/L · h), alanine aminotransferase (−4.65 U/L; 95% CI: −8.67, −0.64 U/L), intrahepatic lipid (−3.44%; 95% CI: −6.19%, −0.68%), and hepatic fat fraction (−3.48%; 95% CI: −6.34%, −0.63%). Yogurt also decreased serum LPS (−0.31 EU/mL; 95% CI: −0.48, −0.14 EU/mL), fibroblast growth factor 21 (−57.76 pg/mL; 95% CI: −86.32, −29.19 pg/mL), lipids, and biomarkers of inflammation and oxidative stress, and altered gut microbiota composition. Mediation analysis showed that yogurt may improve IR by reducing serum lipids, inflammation, oxidative stress, and LPS.

Conclusions: Yogurt was better than milk at ameliorating IR and liver fat in obese Chinese women with NAFLD and MetS, possibly by improving lipid metabolism, reducing inflammation, oxidative stress,

Chen Y, et al. Am Clin Nutr 2019;109:1611–1619.

36

Slide 37

Dairy Product Consumption in the Prevention of Metabolic Syndrome: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Meta-Analyse: 11 prospektiven Kohortenstudien Milch/Milchprodukte und Inzidenz des MetS
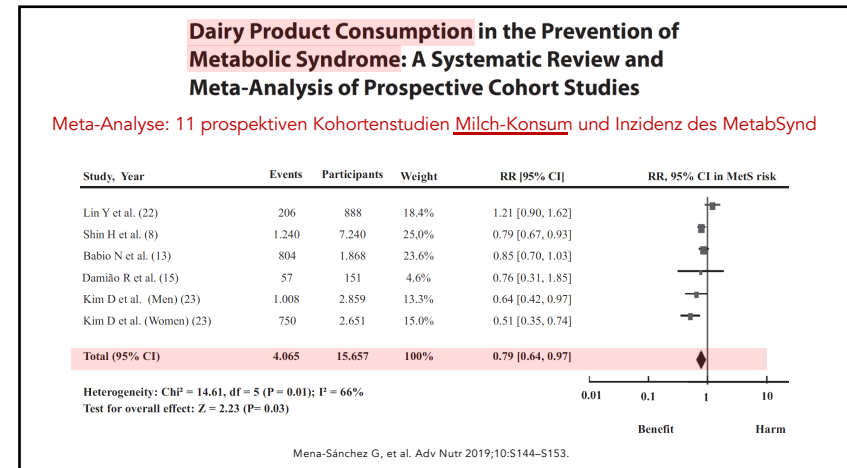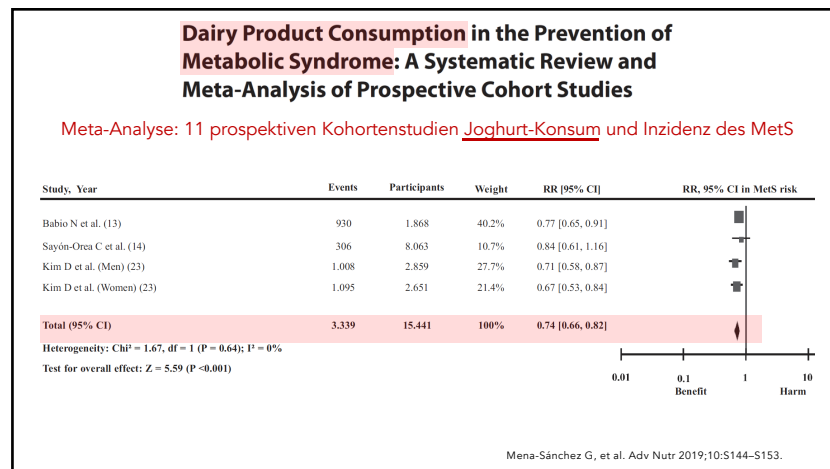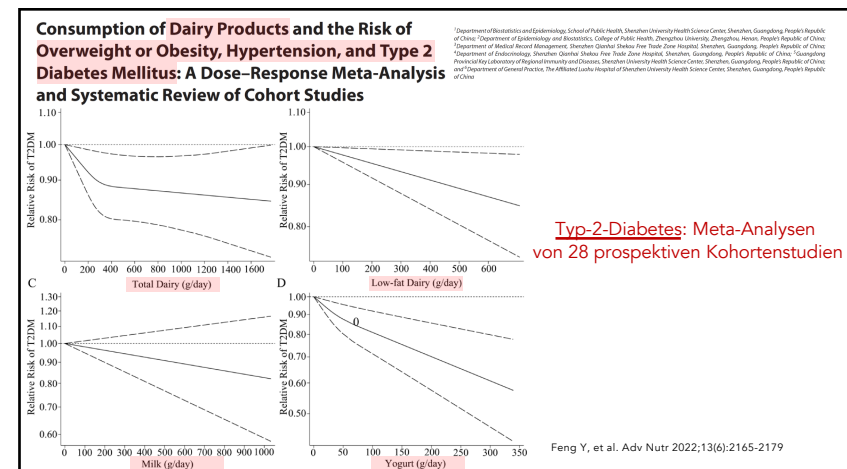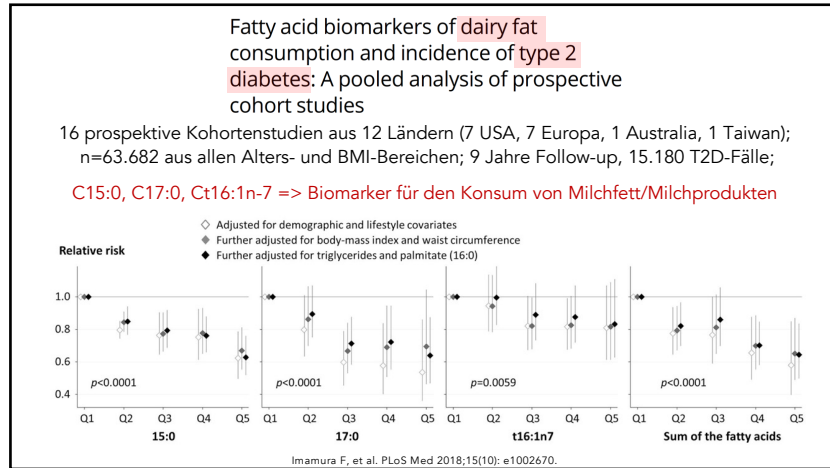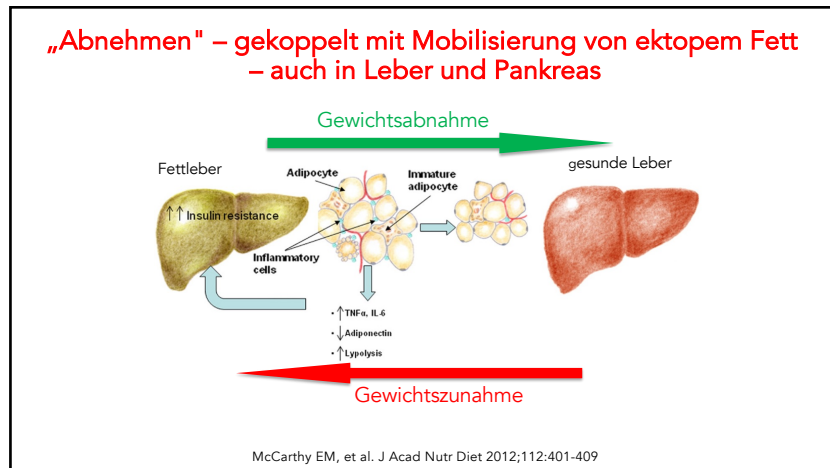
Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in MetS risk
Pereira MA et al. (20)	293	909	2.5%	0.38 [0.17, 0.84]	
Lutsey PM et al. (19)	3.782	9.514	18.5%	0.87 [0.77, 0.98]	
Snijder MB et al. (21)	215	885	5.3%	0.86 [0.52, 1.42]	
Louie JCY et al. (18)	155	1.824	1.8%	0.62 [0.24, 0.61]	
Baik I et al. (17)	1.325	5.251	15.2%	0.80 [0.66, 0.96]	
Shin H et al. (8)	1.240	7.240	16.6%	0.75 [0.64, 0.88]	
Babio N et al. (13)	930	1.868	15.1%	0.83 [0.69, 1.00]	
Kim D et al. (Men) (23)	1.008	2.859	12.2%	0.60 [0.47, 0.77]	
Kim D et al. (Women) (23)	1.095	2.650	12.7%	0.53 [0.42, 0.67]	
Total (95% CI)	**10.043**	**33.000**	**100,0%**	**0.73 [0.64, 0.83]**	

Heterogeneity: Tau² = 0.02; Chi² = 21.18, df = 8 (P = 0.007); I² = 62%
Test for overall effect: Z = 4.71 (P <0.001)

0.01 0.1 1 10
Benefit   Harm

Mena-Sánchez G, et al. Adv Nutr 2019;10:S144–S153.

37

Slide 38

Dairy Product Consumption in the Prevention of Metabolic Syndrome: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Meta-Analyse: 11 prospektiven Kohortenstudien Milch-Konsum und Inzidenz des MetabSynd

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in MetS risk
Lin Y et al. (22)	206	888	18.4%	1.21 [0.90, 1.62]	
Shin H et al. (8)	1.240	7.240	25,0%	0.79 [0.67, 0.93]	
Babio N et al. (13)	804	1.868	23.6%	0.85 [0.70, 1.03]	
Damião R et al. (15)	57	151	4.6%	0.76 [0.31, 1.85]	
Kim D et al. (Men) (23)	1.008	2.859	13.3%	0.64 [0.42, 0.97]	
Kim D et al. (Women) (23)	750	2.651	15.0%	0.51 [0.35, 0.74]	
Total (95% CI)	**4.065**	**15.657**	**100%**	**0.79 [0.64, 0.97]**	

Heterogeneity: Chi² = 14.61, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 2.23 (P= 0.03)

0.01 0.1 1 10
Benefit   Harm

Mena-Sánchez G, et al. Adv Nutr 2019;10:S144–S153.

38

Slide 39

Dairy Product Consumption in the Prevention of Metabolic Syndrome: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Meta-Analyse: 11 prospektiven Kohortenstudien Joghurt-Konsum und Inzidenz des MetS

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in MetS risk
Babio N et al. (13)	930	1.868	40.2%	0.77 [0.65, 0.91]	
Sayón-Orea C et al. (14)	306	8.063	10.7%	0.84 [0.61, 1.16]	
Kim D et al. (Men) (23)	1.008	2.859	27.7%	0.71 [0.58, 0.87]	
Kim D et al. (Women) (23)	1.095	2.651	21.4%	0.67 [0.53, 0.84]	
Total (95% CI)	**3.339**	**15.441**	**100%**	**0.74 [0.66, 0.82]**	

Heterogeneity: Chi² = 1.67, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 5.59 (P <0.001)

0.01 0.1 1 10
Benefit   Harm

Mena-Sánchez G, et al. Adv Nutr 2019;10:S144–S153.

39

Slide 40

Consumption of Dairy Products and the Risk of Overweight or Obesity, Hypertension, and Type 2 Diabetes Mellitus: A Dose–Response Meta-Analysis and Systematic Review of Cohort Studies

[1]Department of Biostatistics and Epidemiology, School of Public Health, Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China; [2]Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [3]Department of Medical Record Management, Shenzhen Qianhai Shekou Free Trade Zone Hospital, Shenzhen, Guangdong, People's Republic of China; [4]Department of Endocrinology, Shenzhen Qianhai Shekou Free Trade Zone Hospital, Shenzhen, Guangdong, People's Republic of China; [5]Guangdong Provincial Key Laboratory of Regional Immunity and Diseases, Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China; and [6]Department of General Practice, The Affiliated Luohu Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong, People's Republic of China

Typ-2-Diabetes: Meta-Analysen von 28 prospektiven Kohortenstudien

Feng Y, et al. Adv Nutr 2022;13(6):2165-2179

40

Slide 41

Fatty acid biomarkers of dairy fat consumption and incidence of type 2 diabetes: A pooled analysis of prospective cohort studies

16 prospektive Kohortenstudien aus 12 Ländern (7 USA, 7 Europa, 1 Australia, 1 Taiwan); n=63.682 aus allen Alters- und BMI-Bereichen; 9 Jahre Follow-up, 15.180 T2D-Fälle;

C15:0, C17:0, Ct16:1n-7 => Biomarker für den Konsum von Milchfett/Milchprodukten

◇ Adjusted for demographic and lifestyle covariates
◆ Further adjusted for body-mass index and waist circumference
◆ Further adjusted for triglycerides and palmitate (16:0)

Relative risk

p<0.0001   p<0.0001   p=0.0059   p<0.0001

Q1 Q2 Q3 Q4 Q5 | Q1 Q2 Q3 Q4 Q5 | Q1 Q2 Q3 Q4 Q5 | Q1 Q2 Q3 Q4 Q5
15:0   17:0   t16:1n7   Sum of the fatty acids

Imamura F, et al. PLoS Med 2018;15(10): e1002670.

41

Slide 42

Therapie:
Kontrollierte Diät-Interventionen

42

Slide 43

„Abnehmen" – gekoppelt mit Mobilisierung von ektopem Fett – auch in Leber und Pankreas

Gewichtsabnahme

Fettleber   gesunde Leber

↑↑ Insulin resistance
Adipocyte   Immature adipocyte
Inflammatory cells
• ↑TNFα, IL-6
• ↓Adiponectin
• ↑Lypolysis

Gewichtszunahme

McCarthy EM, et al. J Acad Nutr Diet 2012;112:401-409

43

Slide 44

Effekte bei Energie- bzw. Gewichtsreduktion

44

Slide 45

Effect of a ketogenic diet on hepatic steatosis and hepatic mitochondrial metabolism in nonalcoholic fatty liver disease

Panu K. Luukkonen[a,b,c], Sylvie Dufour[c,d], Kun Lyu[e], Xian-Man Zhang[e,d], Antti Hakkarainen[f,g], Tiina E. Lehtimäki[f], Gary W. Cline[a,d], Kitt Falk Petersen[a,d], Gerald I. Shulman[d,e,1,2], and Hannele Yki-Järvinen[b,c,1,2]

[a]Department of Internal Medicine, Yale School of Medicine, New Haven, CT 06520; [b]Minerva Foundation Institute for Medical Research, Helsinki 00290, Finland; [c]Department of Medicine, University of Helsinki and Helsinki University Hospital, Helsinki 00290, Finland; [d]Yale Diabetes Research Center, Yale School of Medicine, New Haven, CT 06520; [e]Department of Cellular & Molecular Physiology, Yale School of Medicine, New Haven, CT 06520; [f]Department of Radiology, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki 00290, Finland; and [g]Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, 00076 Espoo, Finland

n = 10; 6 Tage ad libitum ketogene Diät: Kohlenhydrate 183 g/d => 23 g/d
Energiezufuhr: 2.019 kcal/d => 1.444 kcal/d; Leberfett-Messung mit MRS;

Luukkonen PK, et al. Proc Nat Acad Sci 2020;201922344;

45

Slide 46

Effect of a ketogenic diet on hepatic steatosis and hepatic mitochondrial metabolism in nonalcoholic fatty liver disease

Leberfett: -31 %   GGT: -10 %   AP: -10 %

Luukkonen PK, et al. Proc Nat Acad Sci 2020;201922344;

46

Slide 47

Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction[1–3]

Jeffrey D Browning, Jonathan A Baker, Thomas Rogers, Jeannie Davis, Santhosh Satapati, and Shawn C Burgess

RCT: 2 Wochen kalorienreduzierte Diät vs Low-Carb-Diät

	Low-calorie diet ($n = 9$)	Low-carbohydrate diet ($n = 9$)	P value[2]
Energy intake (kcal/d)	1325 ± 180	1553 ± 517	0.229
Diet composition			
Protein (%)	16 ± 3	33 ± 4	<0.001
Fat (%)	34 ± 6	59 ± 7	<0.001
Carbohydrate (%)	50 ± 4	8 ± 5	<0.001
Protein (g/d)	53 ± 12	121 ± 34	<0.001
Fat (g/d)	49 ± 9	105 ± 44	0.002
Carbohydrate (g/d)	169 ± 33	26 ± 8	<0.001
Fat intake (%)			
Saturated	42 ± 8	37 ± 4	0.134
Monounsaturated	37 ± 2	38 ± 6	0.634
Polyunsaturated	18 ± 7	15 ± 4	0.221

Browning JD, et al. Am J Clin Nutr 2011;93:1048–52

47

Slide 48

Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction[1–3]

Jeffrey D Browning, Jonathan A Baker, Thomas Rogers, Jeannie Davis, Santhosh Satapati, and Shawn C Burgess

gleicher Gewichtsverlust von ca. 5 %

-28 %
-55 %

Low-Carb   Low-Fat

Browning JD, et al. Am J Clin Nutr 2011;93:1048–52

48

Slide 49:

Dietary carbohydrates and fats
in nonalcoholic fatty liver disease

Diät-Effekte bei Energiereduktion

- Low-fat–high carb
- High-fat–low carb

Yki-Järvinen H, et al. Nature Rev Gastroenterol Hepatol 2021;18:770–786

49

Slide 50:

Diät-Intervention bei Übergewichtigen mit Dyslipidämie

CENTRAL-Study (Israel)

18 Mon. kontrollierte Diät ad libitum:

mediterran Low-Carb: (< 70 g KH/Tag) + Walnüsse (28 g/Tag)

Low-Fat: ≤ 30 En% Fett, ≤10% SAFA, ≤ 300 mg Cholesterin/Tag

Gepner Y, et al. J Hepatol. 2019;71(2):379-388

50

Slide 51:

Nährstoff-Effekte ohne Kalorien-
und Gewichtsreduktion

51

Slide 52:

Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes

[1]German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; [2]German Center for Diabetes Research, Germany; [3]Department of Endocrinology, Diabetes and Nutrition, Campus Benjamin Franklin, Charité University Medicine,

- 6 Wo. eukalorische Ernährungsumstellung ohne Gewichtsreduktion
- identische Nährstoffrelation (30% Protein, 40% Kohlenh., 30% Fett)

n = 18 eukalorische Diät: tierisches Protein (Fleisch u. **Milchprodukte**)
n = 19 eukalorische Diät: pflanzliches Protein (v.a. Hüsenfrüchte)

Markova M, et al. Gastroenterology 2017;152:571–585e8

52

Slide 53

Proteinbetonte Diät und Leberfettgehalt

Tierisches vs pflanzliches Protein

Leberfett-Gehalt

tierisches Protein — pflanzliches Protein

- 48 %   - 36 %

Markova M, et al. Gastroenterology 2017;152:571–585e8

53

Slide 54
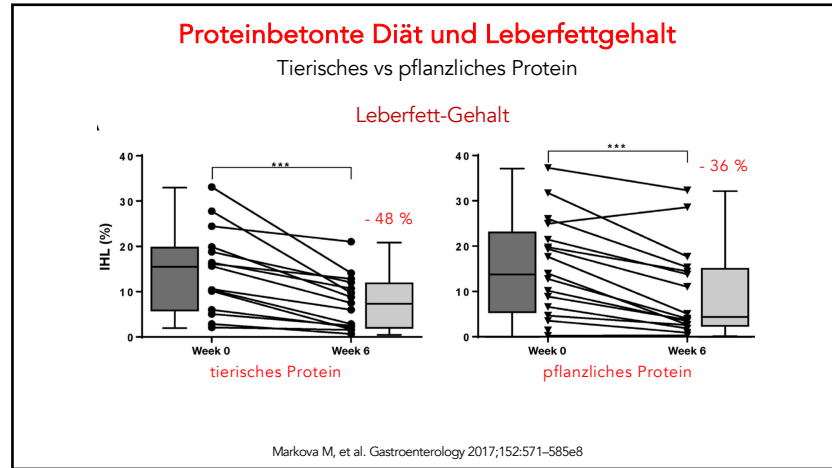
Molkenprotein und NAFLD

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

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

[a] Department of Physiology, University of Lausanne, 7, rue du Bugnon, 1005 Lausanne, Switzerland
[b] Department of Clinical Research/AMSM, University of Bern, Pavilion 52A, Inselspital, P.O. Box 35, 3010 Bern, Switzerland
[c] Service of Endocrinology, Diabetes and Metabolism, CHUV, 1011 Lausanne, Switzerland

- 11 übergewichtige Frauen mit 60 g Molkenprotein/Tag über 4 Wochen zusätzlich zur üblichen Kost

- nach 4 Wochen Molkenprotein-Supplement:

- Leberfettgehalt: - 21 %
- Serum Triglyceride: - 15 %
- Serum Cholesterin: - 7 %
- fettfr. Körpermasse: + 4 %

Bortolotti M, et al. Clinical Nutrition 2011;30:494-498

54

Slide 55

An Integrated Understanding of the Rapid Metabolic Benefits of a Carbohydrate-Restricted Diet on Hepatic Steatosis in Humans

Ketogene Diät bei NAFLD

- n = 10 (54 ± 4 Jahre; 2 Frauen, 8 Männer)
- NAFLD (> 5,5 % Leberfett mit MRS)
- BMI = 27– 40 kg/m^2
- 14 Tage Diät-Intervention
- isoenergetisch mit 3.115 kcal/Tag
- Kost: 40 En% KH, 43 En% F, 18 En% P;
- Diät: 4 En% KH, 72 En% F, 24 En% P;
- alle Gerichte durch Diätküche vorbereitet

Mardinoglu A, et al. Cell Metabolism 2018;27:1–13

55

Slide 56

Ketogene, iso- und eukalorische Diät bei NAFLD

Körpergewicht   Körperkompartimente   Leberfett

Mittel: -44 %

- n = 10
- 14 Tage Diät-Intervention
- isoenergetisch mit 3.115 kcal/Tag
- Diät: 4 En% KH, 72 En% F, 24 En% P;
- alle Gerichte durch Diätküche vorbereitet

Mardinoglu A, et al. Cell Metabolism 2018;27:1–

56

Slide 57

An Integrated Understanding of the Rapid Metabolic Benefits of a Carbohydrate-Restricted Diet on Hepatic Steatosis in Humans

Reduced Carbohydrate Consumption Has Rapid Effects on Liver Fat

(r = 0.91, p = 0.0015; Figure S2). We also analyzed the composition of VLDL-triglycerides and observed a decreased proportion of saturated fatty acids including myristic acid (14:0) and palmitic acid (16:0) and an increased proportion of unsaturated fatty acids such as oleic acid (18:1) (Table S1). These data are consistent with a significant increase in the number of double bonds per fatty acid chain observed by MRS of the liver over the study period (Table S1).

Reduzierter Kohlenhydratkonsum hat rasche Auswirkungen auf Leberfett

Wir analysierten auch die Zusammensetzung der VLDL-Triglyceride und beobachteten einen verringerten Anteil gesättigter Fettsäuren, einschließlich Myristinsäure (14:0) und Palmitinsäure (16:0) und einen erhöhten Anteil an ungesättigten Fettsäuren wie Ölsäure (18:1) (Tabelle S1).

Mardinoglu A, et al. Cell Metabolism 2018;27:1–13

57

Slide 58

Verschiedene nationale und internationale Leitlinien empfehlen neben einer Kalorienreduktion auch eine mediterrane Diät und raten, möglichst wenig gesättigte Fettsäuren zu konsumieren.

Omega-3-Fettsäuren erhalten meist keine Empfehlung.

58

Slide 59

Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss

Parker N. Hyde,[1] Teryn N. Sapper,[1] Christopher D. Crabtree,[1] Richard A. LaFountain,[1] Madison L. Bowling,[1] Alex Buga,[1] Brandon Fell,[1] Fionn T. McSwiney,[2] Ryan M. Dickerson,[1] Vincent J. Miller,[1] Debbie Scandling,[3] Orlando P. Simonetti,[3] Stephen D. Phinney,[4] William J. Kraemer,[1] Sarah A. King,[5] Ronald M. Krauss,[5] and Jeff S. Volek[1]

[1]Department of Human Sciences, The Ohio State University, Columbus, Ohio, USA. [2]Department of Sport and Exercise Science, Waterford Institute of Technology, Waterford, Ireland. [3]Davis Heart & Lung Research Institute, Department of Radiology; Department of Internal Medicine, Division of Cardiovascular Medicine; Wexner Medical Center, The Ohio State University, Columbus, Ohio, USA. [4]Virta Health, San Francisco, California, USA. [5]Department of Atherosclerosis Research, Children's Hospital Oakland Research Institute, Oakland, California, USA.

3 x 4 Wochen Cross-over mit isokalorischer, gewichtserhaltender, kontrollierter Nahrung: Low-Carb vs Medium-Carb vs High-Carb

Hyde PN, et al. JCI Insight. 2019;4(12):e128308

59

Slide 60

Low-Carb vs Medium-Carb vs High-Carb

3 x 4 Wochen Cross-over mit isokalorischer, gewichtserhaltender, kontrollierter Diät

Nutrient	High-Carb	Medium-Carb	Low-Carb
Energy (kcal)		2,950 (2035–3750)	
Protein (g)	144 (100–184)	146 (101–185)	150 (103–190)
Carbohydrate (g)	420 (290–534)	234 (161–297)	45 (31–58)
Fat (g)	77 (53–97)	159 (110–202)	242 (167–307)
Saturated fat (g)	40 (28–51)	70 (48–89)	100 (69–127)
Monounsaturated fat (g)	21 (15–27)	54 (37–69)	86 (59–110)
Polyunsaturated fat (g)	6 (5–8)	21 (14–26)	35 (24–45)
Cholesterol (mg)	334 (231–425)	503 (347–639)	1,015 (701–1291)
Cheese (g)	200 (138–255)	201 (139–256)	201 (139–256)
Calcium (mg)	2,151 (1484–2734)	2,229 (1537–2833)	2,177 (1502–2768)
Fiber (g)	25 (17–32)	20 (14–25)	14 (9–17)

Hyde PN, et al. JCI Insight. 2019;4(12):e128308

60

Slide 61

Gesättigte Fettsäuren und alternative Risikomarker

Plasma-Konzentration
von gesättigten Fettsäuren

Plasma-Palmitoleinsäure
(De novo Lipogenese)

Hyde PN, et al. JCI Insight 2019;4(12):e128308

61

Slide 62
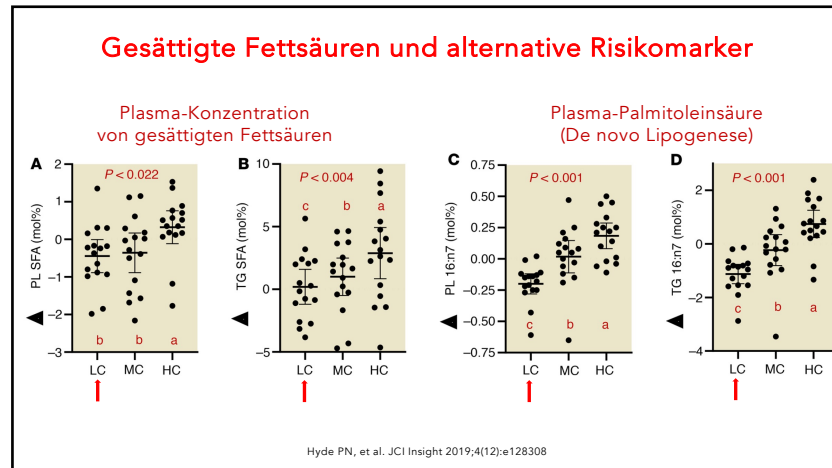
Nota bene:

Die Wirkung gesättigter Fettsäuren hängt maßgeblich vom Anteil gleichzeitig zugeführter Kohlenhydrate ab!

62

Slide 63

Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study[1–3]

Maria Maersk, Anita Belza, Hans Størdkilde-Jørgensen, Steffen Ringgaard, Elizaveta Chabanova, Henrik Thomsen, Steen B Pedersen, Arne Astrup, and Bjørn Richelsen

RCT bei 47 Übergewichtigen, 6 Monate täglich 1 Liter Test-Getränk;
Cola mit Saccharose (50% Fruktose/50% Glukose); Cola-Light; Milch mit 1,5% Fett;

	Sucrose-sweetened regular cola	Milk
Carbohydrate (g/100 mL)	10.6	4.7
Protein (g/100 mL)	0	3.4
Fat (g/100 mL)	0	1.5
Energy (kJ/d)	1800	1900
Volume (mL)	1000	1000
Energy density (kJ/g)	1.8	1.9

[1] The subjects drank 1 L of 1 of 4 test drinks daily for 6 mo.

Maersk M, et al. Am J Clin Nutr 2012;95:283–9.

63

Slide 64

Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study[1–3]

Maria Maersk, Anita Belza, Hans Størdkilde-Jørgensen, Steffen Ringgaard, Elizaveta Chabanova, Henrik Thomsen, Steen B Pedersen, Arne Astrup, and Bjørn Richelsen

bei ca. + 1,5 kg Gewicht

Muskelfett   Leberfett

Maersk M, et al. Am J Clin Nutr 2012;95:283–9.

64

Slide 65

Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study[1-3]

Maria Maersk, Anita Belza, Hans Stødkilde-Jørgensen, Steffen Ringgaard, Elizaveta Chabanova, Henrik Thomsen, Steen B Pedersen, Arne Astrup, and Bjørn Richelsen

Viszerales Fett

Bar chart: Relative change in VAT (%), y-axis from −200 to 30. Reg. cola ≈ 24; Milk ≈ −7 (*).

Maersk M, et al. Am J Clin Nutr 2012;95:283–9.

65

Slide 66

Effect of **Calorie-Unrestricted Low-Carbohydrate, High-Fat Diet** Versus High-Carbohydrate, Low-Fat Diet on Type 2 Diabetes and **Nonalcoholic Fatty Liver Disease**
A Randomized Controlled Trial

ad-libitum Diät-Intervention!

Characteristic	LCHF Diet (n = 110)	HCLF Diet (n = 55)
Mean age (SD), y	57 (9)	55 (12)
Female, n (%)	62 (56)	34 (62)
Country of origin, n (%)		
Denmark	108 (98)	54 (98)
Other	2 (2)	1 (2)
Metabolic syndrome†, n (%)	98 (89)	49 (89)
Arterial hypertension‡	92 (84)	40 (73)
Central obesity†	103 (94)	51 (93)
Low HDL cholesterol†	63 (57)	34 (62)
Elevated triglycerides†	46 (42)	25 (46)
Mean weight (SD), kg	97.8 (23)	99.9 (22)
Mean body mass index (SD), kg/m²§	33 (7)	35 (8)
Mean fat percentage (SD)‖	40.4 (8.1)	42.0 (8.5)

Hansen CD, et al. Ann Intern Med. 2023;176(1):10-21.

66

Slide 67

Ad-libitum Diät-Intervention: Low-Carb/High-Fat vs Low-Fat/High-Carb

Macronutrient Intake	LCHF Diet	HCLF Diet	Mean Difference Between Groups (95% CI)†	
Mean total energy intake per day (SD), kcal				
Before intervention	1813 (587)	1820 (362)	−7 (−246 to 232)	
During intervention	1715 (541)	1609 (461)	106 (14 to 198)	kcal: 1715 vs 1609
Mean protein (SD), % kcal				
Before intervention	18.7 (3.3)	17.2 (3)	1.5 (0.1 to 3.0)	
During intervention	22.8 (4.4)	20.6 (3.3)	2.1 (1.4 to 2.9)	
Mean fat (SD), % kcal				
Before intervention	36.2 (7.0)	34.9 (7.2)	1.3 (−1.9 to 4.4)	
During intervention	60.9 (6.4)	28.5 (5.4)	32.4 (31.3 to 33.5)	Fett: 61 En% vs 29 En%
Mean saturated fats (SD), % kcal‡				
Before intervention	12.7 (3.6)	12.0 (3.8)	0.8 (−0.9 to 2.4)	
During intervention	21.2 (5.2)	9.0 (2.5)	12.2 (11.4 to 13.0)	GFS: 21 En% vs 9 En%
Mean monounsaturated fats (SD), % kcal‡				
Before intervention	10.0 (6.1)	7.8 (2.8)	2.2 (−0.2 to 4.6)	
During intervention	18.7 (4.8)	8.2 (9.9)	10.6 (9.3 to 11.7)	
Mean polyunsaturated fats (SD), % kcal‡				
Before intervention	3.9 (1.6)	3.3 (1.0)	0.5 (−0.1 to 1.2)	
During intervention	9.1 (3.5)	3.7 (1.4)	5.3 (4.8 to 5.9)	
Mean carbohydrates (SD), % kcal				
Before intervention	41.2 (7.3)	44.1 (6.7)	−2.9 (−6.1 to 0.4)	
During intervention	13.1 (5.1)	46.2 (5.5)	−33.0 (−34.0 to −32.1)	KH: 13 En% vs 46 En%
Mean fiber (SD), % kcal				
Before intervention	2.5 (0.8)	2.6 (1.1)	−0.2 (−0.6 to 0.2)	
During intervention	2.0 (0.9)	3.4 (0.8)	−1.4 (−1.6 to −1.3)	
Mean sugars, % kcal				
Before intervention	12.5 (5.4)	12.4 (4.3)	0.0 (−2.3 to 2.3)	
During intervention	6.1 (2.8)	11.9 (3.8)	−5.8 (−6.4 to −5.3)	

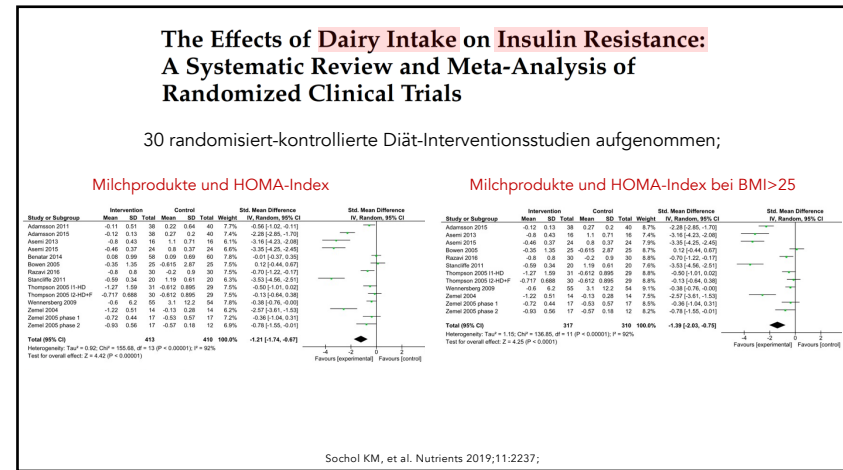Hansen CD, et al. Ann Intern Med. 2023;176(1):10-21.

67

Slide 68

Ad-libitum Diät-Intervention: Low-Carb/High-Fat vs Low-Fat/High-Carb

Primärer Endpunkt: Verbesserung des **NAFLD Activity Score (NAS)** => zur Quantifizierung der Aktivität der NAFLD (Ausprägung der Steatose, Entzündung und Ballonierung);

verbesserter NAS (n)

Bar chart: NAS ≥ 2 points, % — LCHF = 17; HCLF = 13.

	Estimated Mean Difference From Baseline (95% CI)			
Variable	LCHF Diet (n = 110)	HCLF Diet (n = 55)	Mean Difference in Change	P Value
Fat mass, %				
3 mo	–	–	–	
6 mo	−1.30 (−1.74 to −0.86)	−0.27 (−0.98 to 0.45)	−1.04 (−1.90 to −0.17)	0.020
9 mo†	–	–	–	
HOMA-IR				
3 mo	–	–	–	
6 mo	−2.38 (−3.39 to −1.38)	−0.25 (−1.53 to 1.02)	−2.13 (−3.84 to −0.42)	0.015
9 mo†	−0.81 (−1.74 to 0.13)	−0.30 (−1.51 to 0.92)	−0.51 (−2.03 to 1.02)	0.51

Hansen CD, et al. Ann Intern Med. 2023;176(1):10-21.

68

Slide 69

Ad-libitum Diät-Intervention: Low-Carb/High-Fat vs Low-Fat/High-Carb

Hansen CD, et al. Ann Intern Med. 2023;176(1):10-21.

69

Slide 70

The Effects of Dairy Intake on Insulin Resistance: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

30 randomisiert-kontrollierte Diät-Interventionsstudien aufgenommen;

Milchprodukte und HOMA-Index   Milchprodukte und HOMA-Index bei BMI>25

Sochol KM, et al. Nutrients 2019;11:2237;

70

Slide 71

Milk and Dairy Product Consumption and Inflammatory Biomarkers: An Updated Systematic Review of Randomized Clinical Trials

[1]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [2]Norwegian National Advisory Unit on Familial Hypercholesterolemia, Oslo University Hospital, Oslo, Norway; [3]Department of Biochemistry and Molecular Biology II, School of Pharmacy; and [4]Institute of Nutrition and Food Technology "José Mataix," Biomedical Research Center, University of Granada, Granada, Spain; [5]ibs.GRANADA, University Hospital Complex of Granada, Granada, Spain; and [6]CIBEROBN (CIBER Physiopathology of Obesity and Nutrition CB12/03/30028), Institute of Health Carlos III, Madrid, Spain

Systematische Übersicht von 16 Diät-Experimenten

The most common inflammatory markers analyzed were hs-CRP, IL-1β, IL-6, MCP-1, and TNF-α (23–29). Three reports included sICAM-1 and sVCAM-1 (23). Adiponectin (27), macrophage inflammatory protein-1α (MIP-1α) (25), and retinol-binding protein 4 (RBP-4) (29) were measured, however, with no significant changes or differences between the groups. Three studies, in addition to the study by Pei et al. (18), investigated the effect of the intervention on gene expression levels (24, 26, 27).

In conclusion, the consumption of milk or dairy products did not show a proinflammatory effect in healthy subjects or individuals who were overweight or obese or had other metabolic abnormalities. The evidence from long-term supplementation showed a weak anti-inflammatory effect in both healthy and metabolically abnormal adults. The evidence from acute and short-term interventions is scarce and thus inconclusive. Further studies need to be developed with enhanced designs and better reporting, and the characterization of the dairy products should be included.

Ergebnis: Keine oder leicht anti-entzündliche Effekte

Ulven SM, et al. Adv Nutr 2019;10:S239–S250.

71

Slide 72

Optimale Nahrungsfette zur Prävention und Therapie der NAFLD

Godos J, et al. Int J Food Sci Nutr. 2017 Feb;68(1):18-27.

72

Fettreiche Diät mit Olivenöl in der Therapie von NAFLD

n = 45; randomisiertes Cross-over à 8 Wochen <u>eukalorische Diät</u>,

52 %en KH ballaststoff-reich+30 %en Fett vs 40 %en KH + 42 %en Fett (28%en MUFA)

Bozzetto L, et al. Diabetes Care 2012;35:1429–1435

73

Fettbetone mediterrane Kost in der Therapie von NAFLD

n = 12; Cross-over 6 Wochen eukalorisch, ohne Gewichtsreduktion

Ryan MC, et al. J Hepatol 2013;59:138-43

74

Ein Polyphenol (sekundärer Pflanzenstoff) im Olivenöl schützt vor Fettleber und metabolischem Syndrom

Hydroxytyrosol

Hydroxytyrosol

Was ist Hydroxytyrosol?

In der Pflanzenwelt gibt es eine Art praktisch überall vorkommender natürlicher Verbindungen, die als "Phenole" bekannt sind. Diese gestatten es einer Pflanze oder Frucht unter anderem, sich vor dem Angriff von Pilzen, Bakterien und sonstigen Mikroorganismen zu schützen. **Hydroxytyrosol (HT)** gehört zu den bemerkenswertesten Phenolen der Olive.

Cao K, et al. Free Radical Biology and Medicine 2014;67:396–407

75

Omega-3-Fettsäuren in der Therapie der NALFD

Scorletti E, Byrne CD. Annu Rev Nutr 2013;33:231–48

76

Slide 77
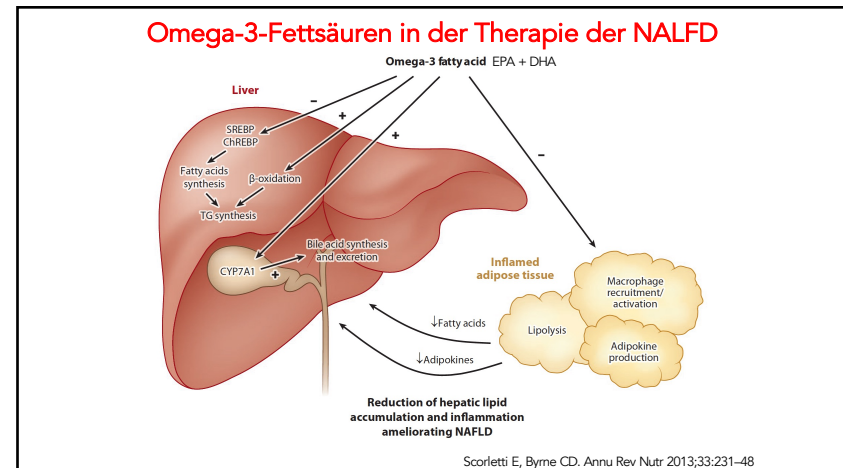
Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation on Non-Alcoholic Fatty Liver: A Systematic Review and Meta-Analysis

Abstract: (1) Aim: Non-alcoholic fatty liver disease (NAFLD) is a prevalent disease worldwide. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) bear anti-inflammatory action and can ameliorate hyperlipidemia. We wish to appraise the effects of n-3 PUFAs supplement on NAFLD. (2) Methods: We searched CENTRAL, Embase, and MEDLINE on 29 March 2020 for randomized control trials (RCTs) on the effects of n-3 PUFAs supplementation in treating NAFLD. The Cochrane Collaboration's tool was used to assess the risk of bias of included RCTs. (3) Results: We included 22 RCTs with 1366 participants. The risk of bias of included RCTs was generally low or unclear. n-3 PUFAs supplementation significantly reduced liver fat compared with placebo (pooled risk ratio 1.52; 95% confidence interval (CI) 1.09 to 2.13). n-3 PUFAs supplementation also significantly improved the levels of triglyceride, total cholesterol, high-density lipoprotein, and body-mass index, with pooled mean difference and 95% CI being −28.57 (−40.81 to −16.33), −7.82 (−14.86 to −0.79), 3.55 (1.38 to 5.73), and −0.46 (−0.84 to −0.08), respectively. (4) Conclusions: The current evidence supports the effects of n-3 PUFAs supplementation in improving fatty liver. n-3 PUFAs supplementation may also improve blood lipid levels and obesity.

Lee CH, et al. Nutrients 2020;12:2769;

77

Slide 78

Ernährungstherapeutische Ansätze bei Insulinresistenz, NAFLD und Typ-2-Diabetes

78

Slide 79

Diät-Konzepte bei NAFLD

Hypocaloric diet[1]
+ Conceptually simple
+ Calorie deficit is key („A calorie is a calorie")
− Dietary composition not considered

Low-carb diet
+ Improves insulin resistance[2]
+ Reduced glycemic load
? Adherence

Intermittent fasting
+ Conceptually simple
+ Different types of fasting
+ Stimulates ketogenesis[3]
? Circadian rhythm
? Sarcopenia/muscle loss
− Dietary composition not considered

Mediterranean diet
+ Plant-based diet
+ High adherence
+ High-quality nutrients (e.g., MUFA/PUFA)
+ Rich in „healthy" food groups (e.g., nuts/seeds)
+ Polyphenoles/antioxidants
+ Beneficial for cardiovascular health

Very-low carb diet (Ketogenic diet)
+ Stimulates ketogenesis[3]
− Low adherence
− Long-term effects unclear

General considerations
− Avoid sugar sweetened beverages
− Avoid added sugar, especially fructose
− Avoid highly processed food
+ Prefer white over red and processed meat
+ Nuts/seeds and coffee are recommended

NAFLD-specific diet:
Hypocaloric[1] Mediterranean diet low in carbohydrates (<40%) + intermittent fasting

Precision nutrition in NAFLD
? Environment
? Microbiome
? Genetics (e.g., PNPLA3)
? Circadian rhythm

[1] ~1500 kcal/day (♀) and 1800 kcal/day (♂)
[2] Pathophysiological hallmark of NAFLD
[3] Ketogenic insufficiency in NAFLD

Semmler G, et al. Clin Mol Hepatol. 2022 Dec 14; doi: 10.3350/cmh.2022.0364.

79

Slide 80

„Leberfasten" als integriertes Gesamtkonzept

80

Slide 81

„Leberfasten": Ernährungstherapeutischer Ansatz mit prinzipiellen und nährstoffspezifischen Effekte

1. Vier Grundprinzipien
- kalorienreduziert
- kohlenhydratreduziert
- proteinbetont (Molkenprotein)
- fettbetont

2. Nährstoffspezifische Effekte
- Omega-3-Fettsäuren
- Hydroxythyrosol (Olivenöl)
- β-Glukan
- Inulin
- Cholin
- Vitamin E
- Carnitin
- Taurin
- etc.

81

Slide 82

Leberfasten Intensiv-Seminar

Das Intensiv-Seminar 2024
Bodymed-Akademie

- Sa., 02. März 2024 | Salzburg
- Sa., 13. April 2024 | Fulda
- Sa., 15. Juni 2024 | Mannheim
- Sa., 28. September 2024 | Berlin
- Sa., 12. Oktober 2024 | Wien
- Sa., 23. November 2024 | Köln

82

Slide 83

„a modest amount of meat or whole grains can be part of a healthy diet."

New PURE Diet Score (6 healthy components)
FRUITS · VEGETABLES · NUTS · LEGUMES · FISH · DAIRY

LOWER RISK

CARDIOVASCULAR DISEASE (CVD) IN DIVERSE WORLD REGIONS

"PURE" DIET SCORE ASSOCIATIONS WITH CVD WERE SIMILAR TO A MEDITERRANEAN DIET SCORE, AND MUCH STRONGER THAN A "PLANETARY HEALTH" DIET SCORE

FINDING WERE FROM DIVERSE GLOBAL NATIONS INCLUDING LOW AND MIDDLE INCOME COUNTRIES

DAIRY WAS MOSTLY WHOLE FAT

AVOIDING RED MEAT DID NOT STRENGTHEN THE PURE DIET SCORE

Mozaffarian D. Eur Heart J. 2023;44(28):2580–2582

PURE-Studie: n = 245.000 aus 80 Ländern

DIE Flexi-CARB-PYRAMIDE für den Gewichtserhalt

83

Slide 84

Vielen Dank für Ihr Interesse und Ihre Aufmerksamkeit

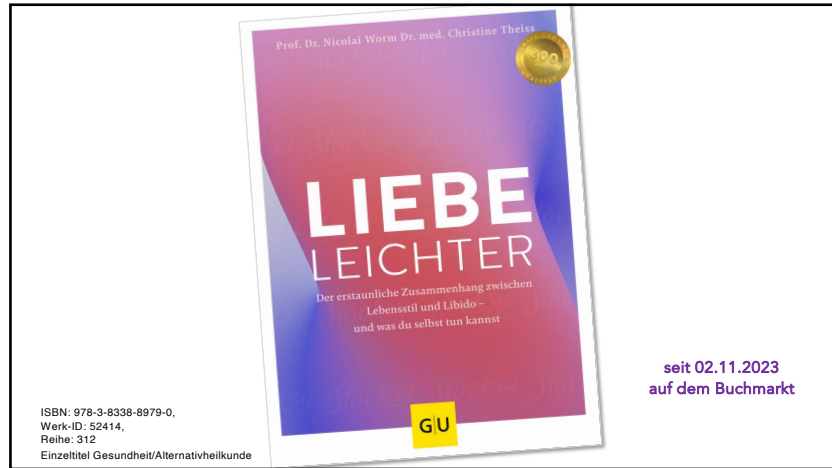www.nicolai-worm.de

84

85

www.nicolai-worm.de

86

Alle neuen
Erkenntnisse
laiengerecht präsentiert!

seit Dezember 2019
im Handel...

87

88

Prof. Dr. Nicolai Worm   Dr. med. Christine Theiss

LIEBE
LEICHTER

Der erstaunliche Zusammenhang zwischen
Lebensstil und Libido –
und was du selbst tun kannst

seit 02.11.2023
auf dem Buchmarkt

ISBN: 978-3-8338-8979-0,
Werk-ID: 52414,
Reihe: 312
Einzeltitel Gesundheit/Alternativheilkunde

GU

89

90