



UniversitätsKlinikum Heidelberg

DIABETES & ADIPOSITAS ZENTRUM



UniversitätsKlinikum Heidelberg

Grenzüberschreitungen und Wendepunkte

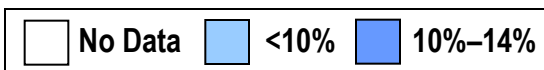
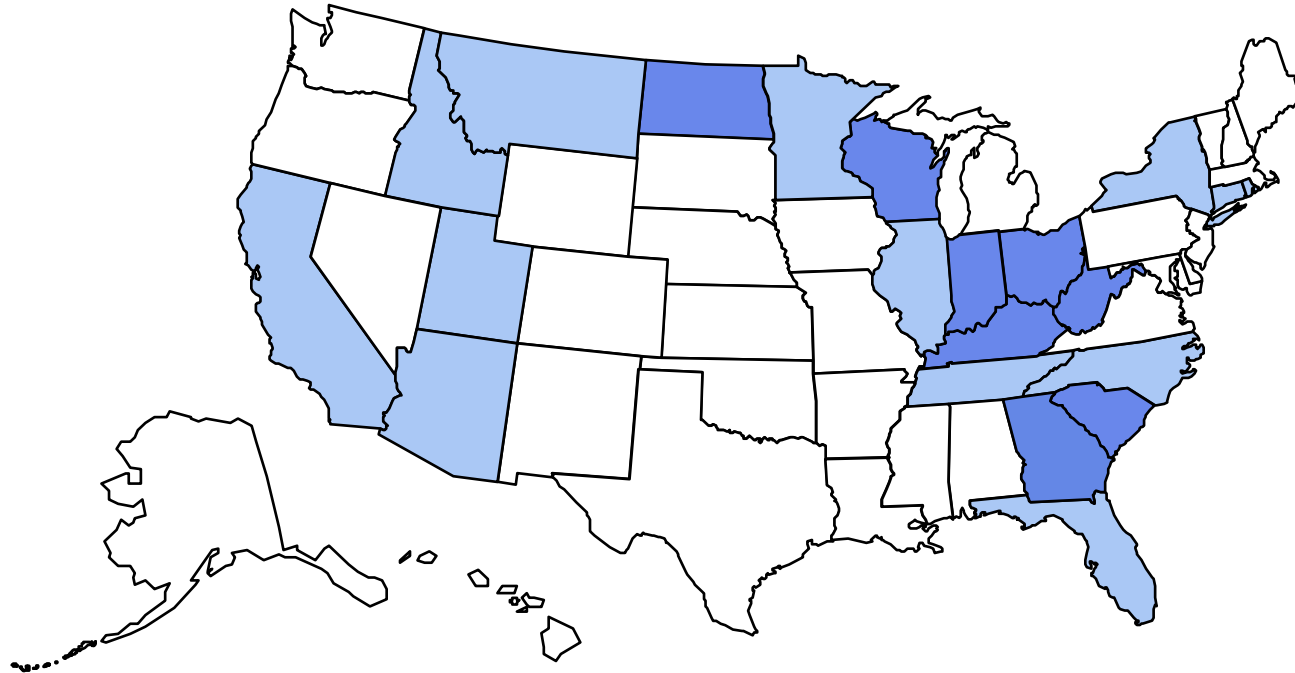
Die Chirurgie des Diabetes mellitus Typ 2

Beat Müller



Adipositas

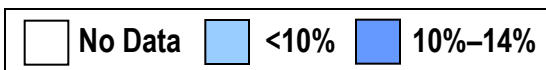
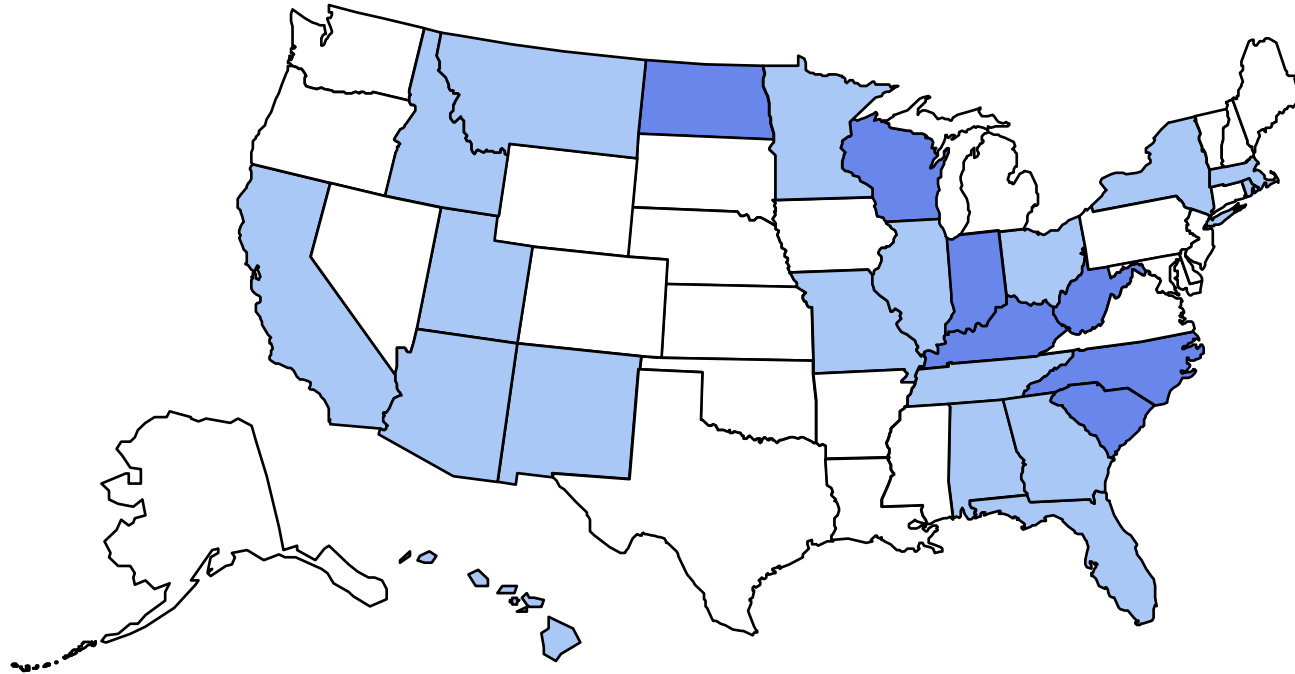
1985





Adipositas

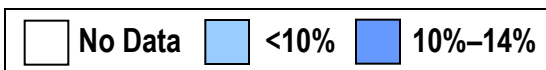
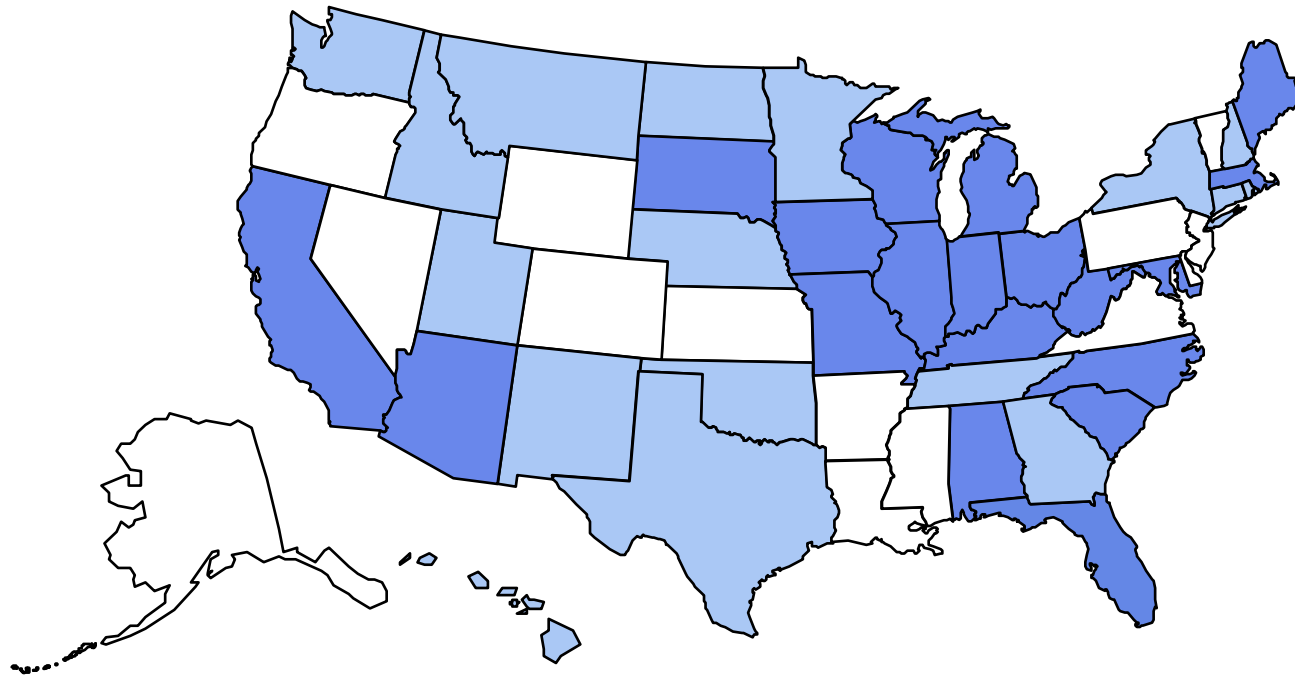
1986





Adipositas

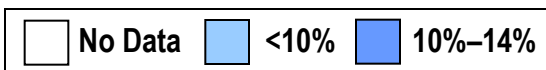
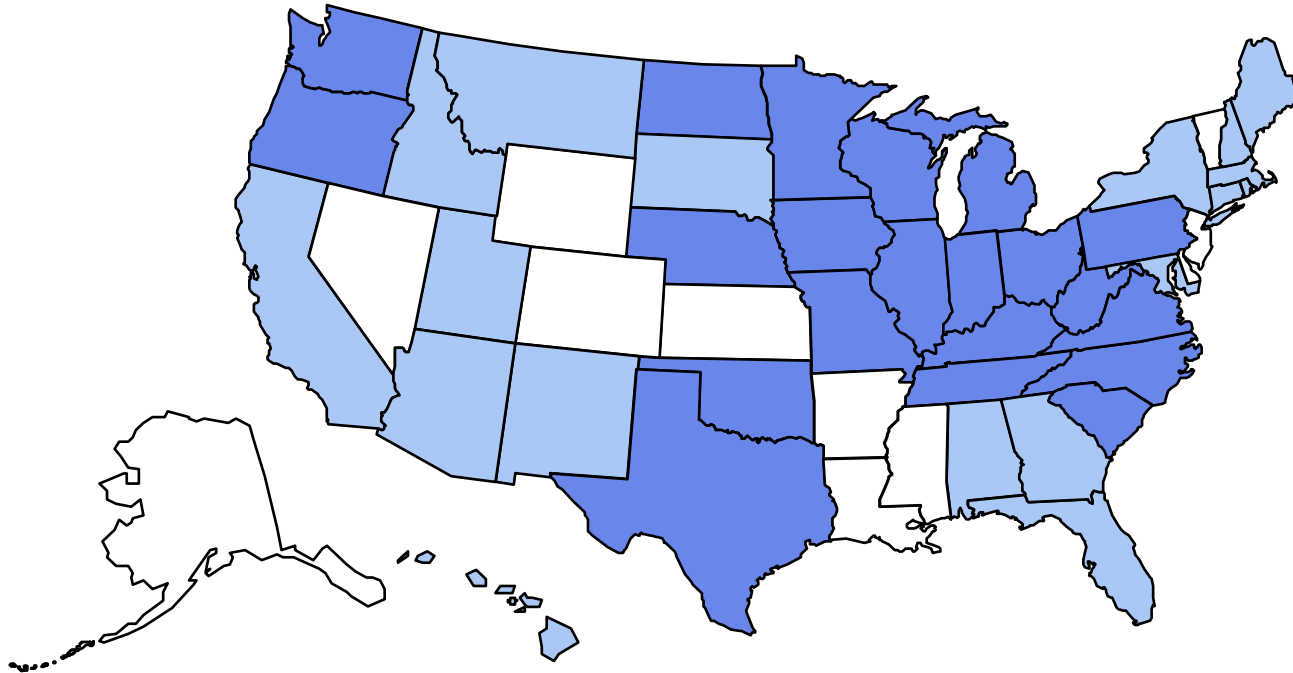
1988





Adipositas

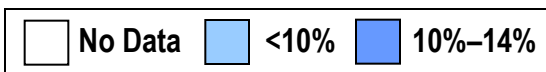
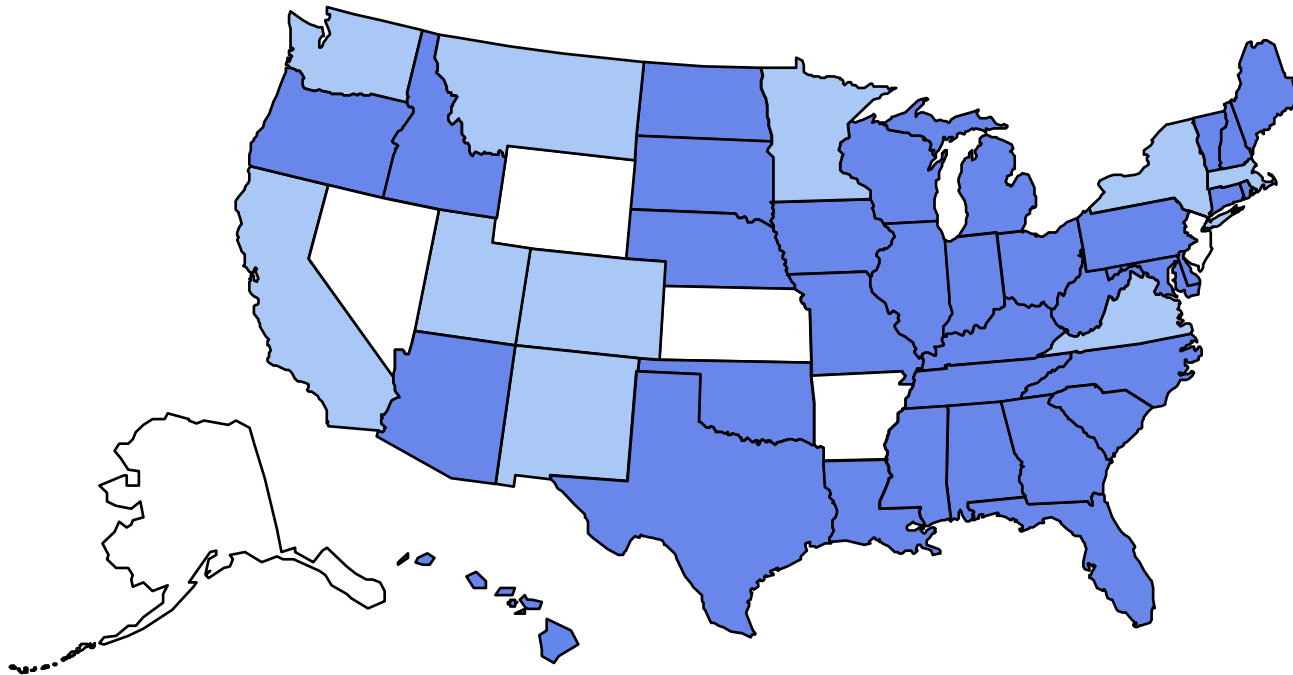
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Adipositas

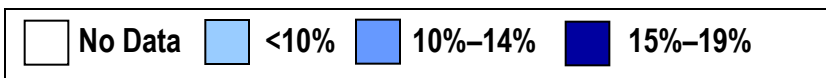
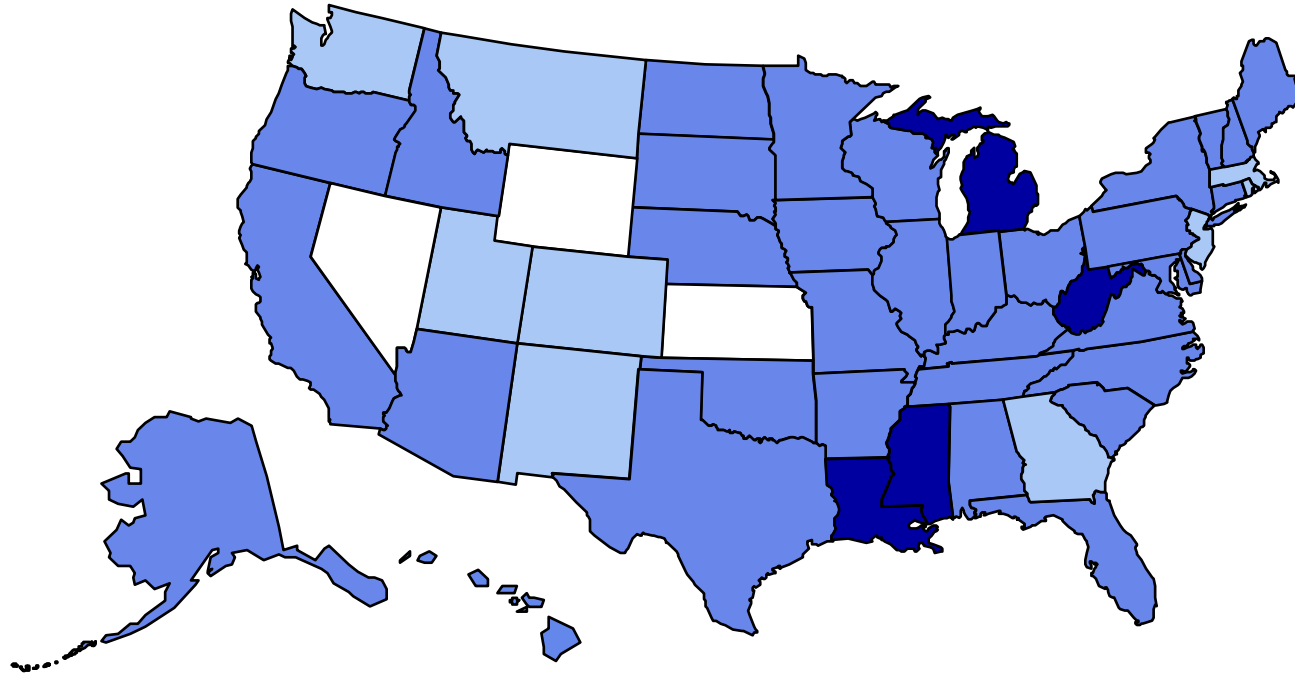
1990





Adipositas

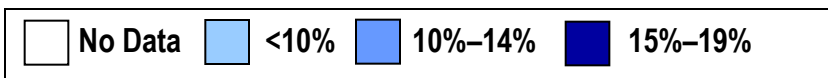
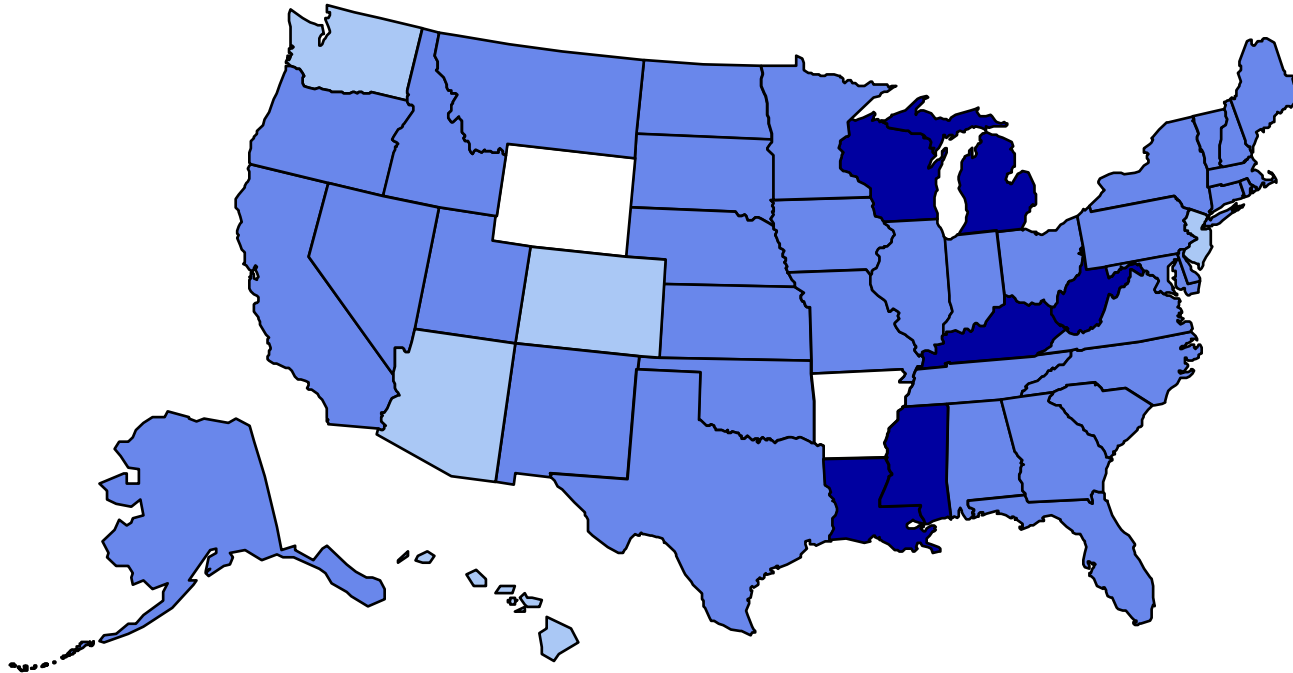
1991





Adipositas

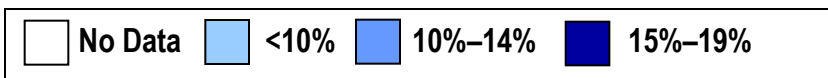
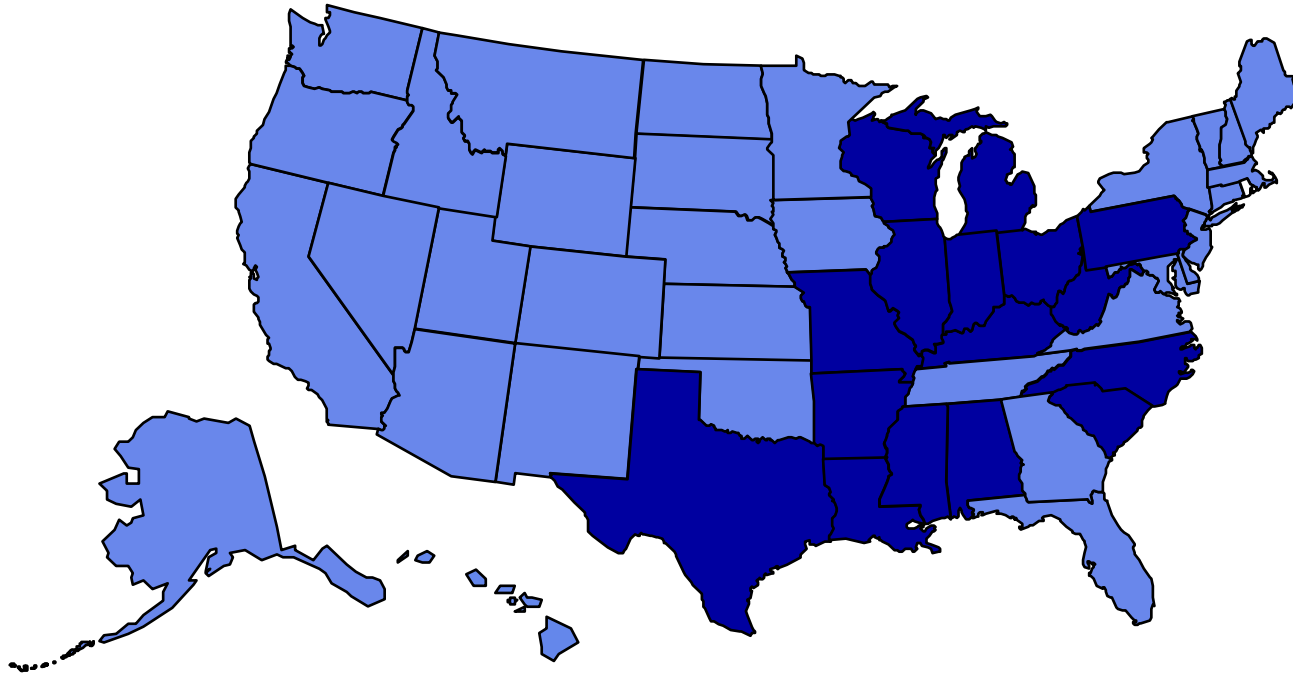
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Adipositas

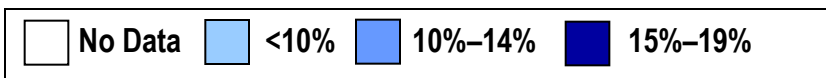
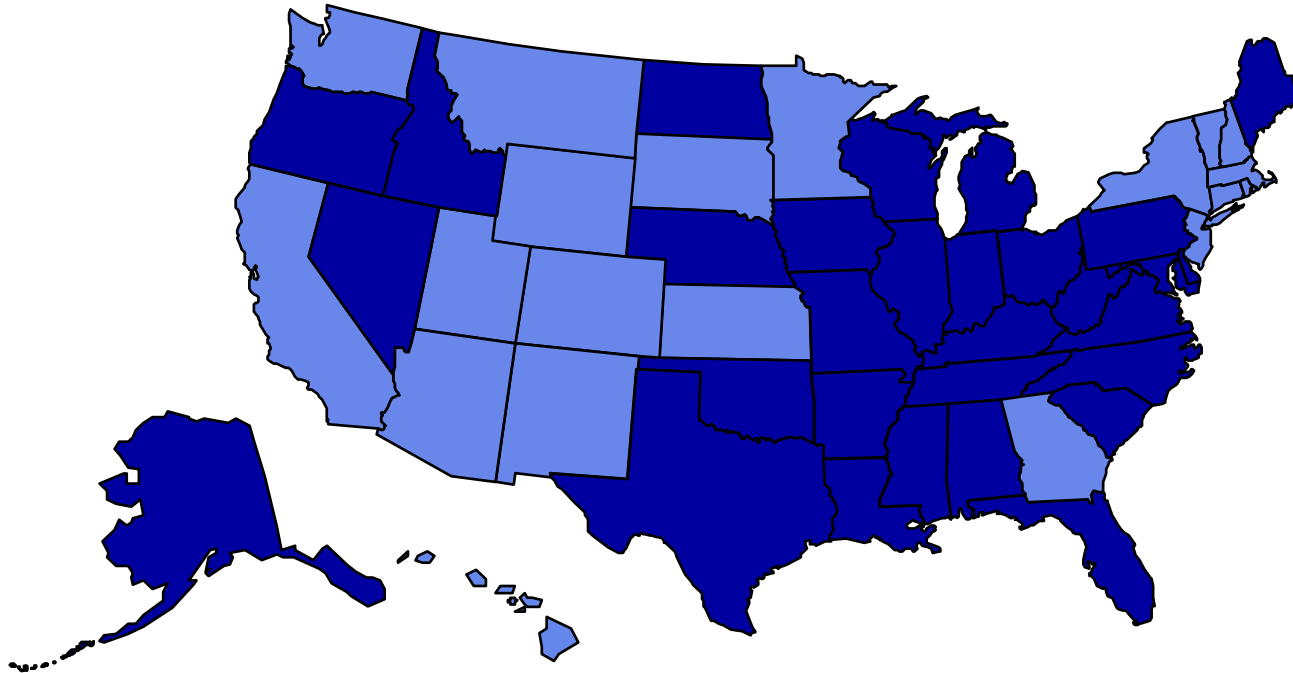
1994





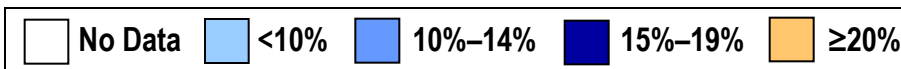
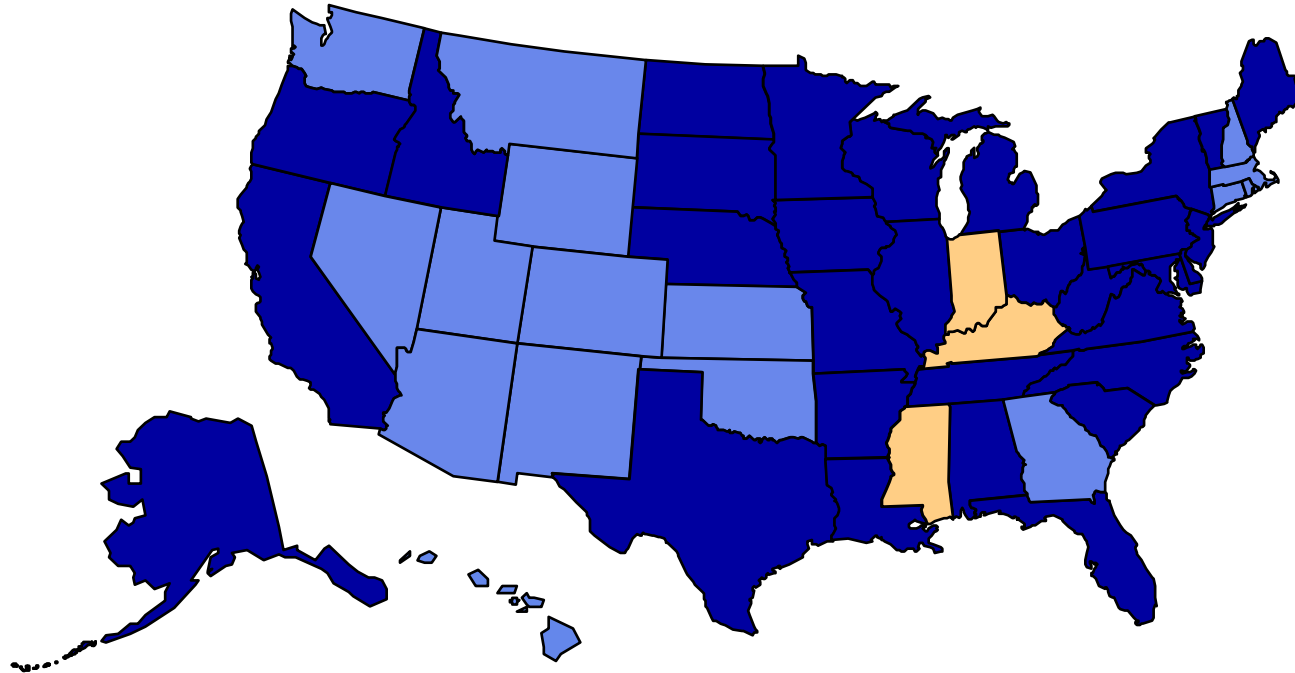
Adipositas

1996





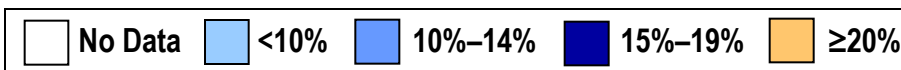
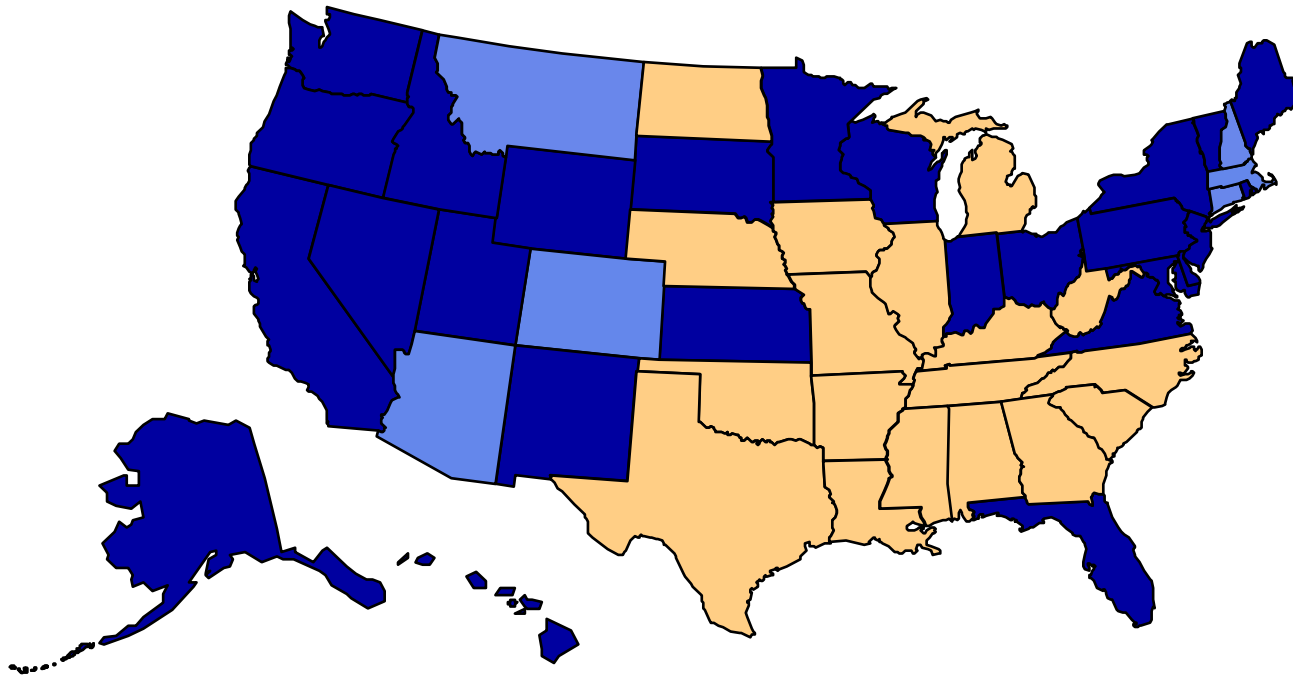
Adipositas 1997





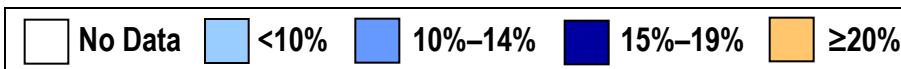
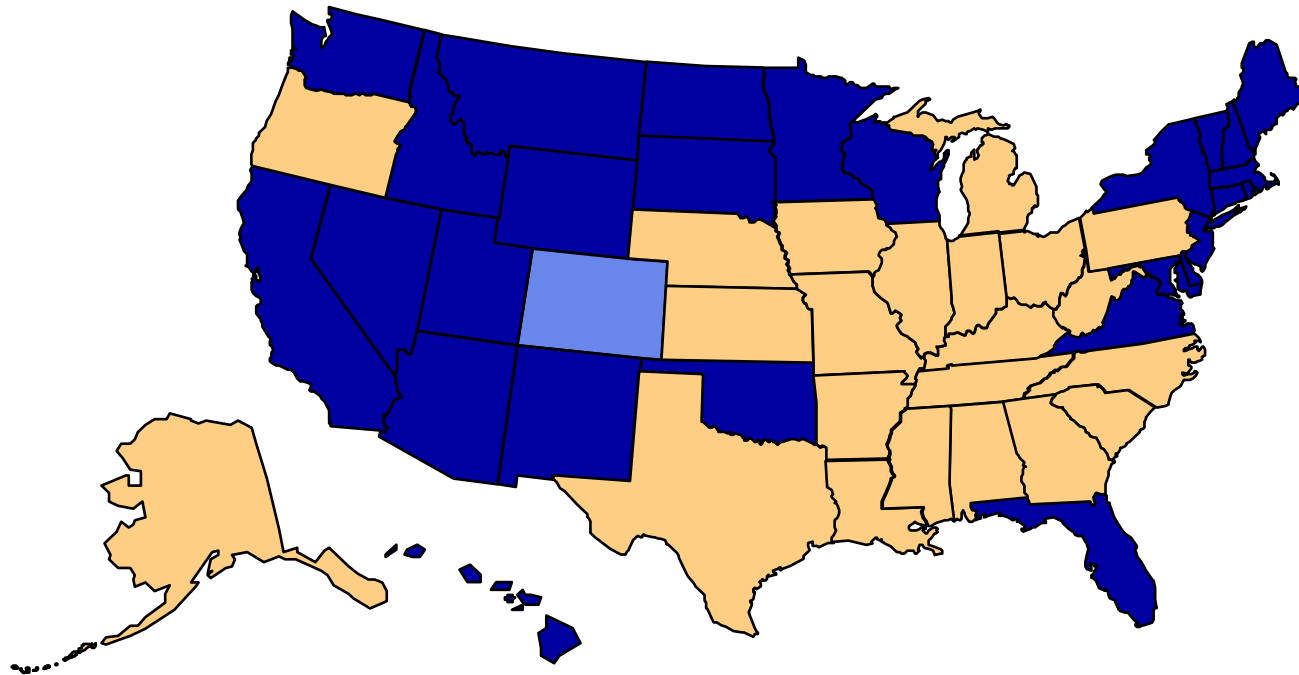
Adipositas

1999



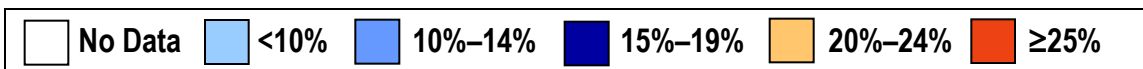
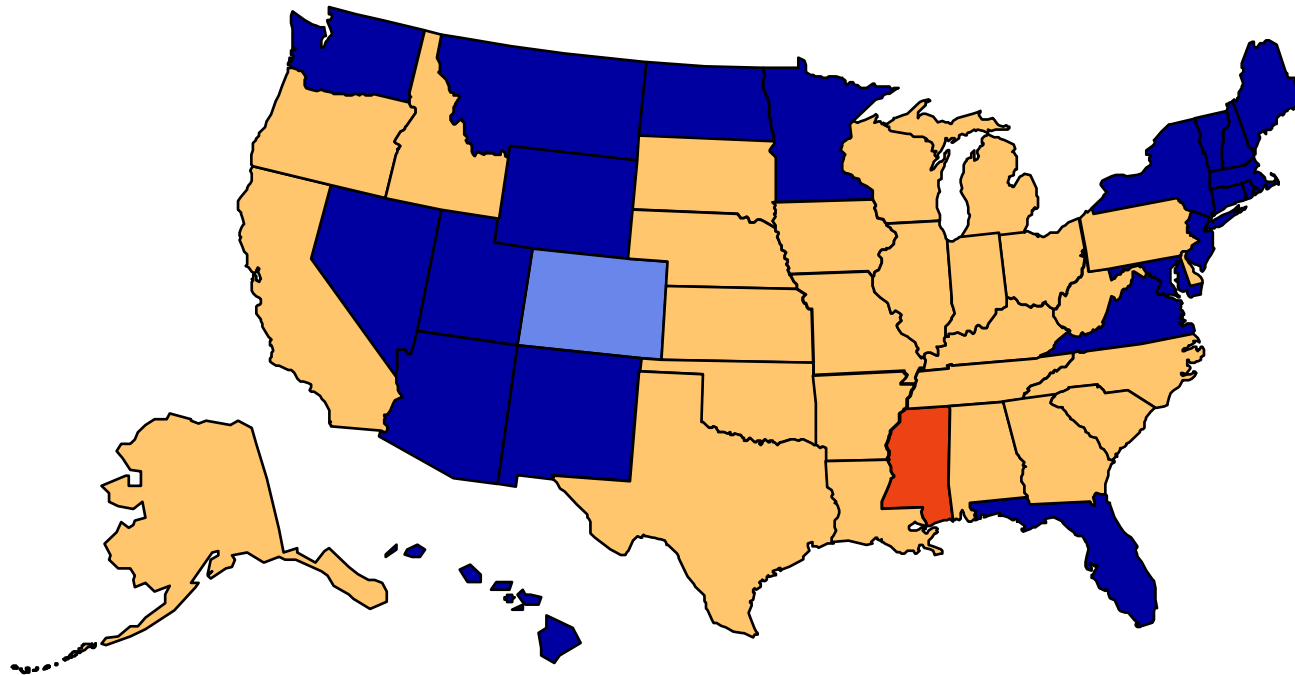


Adipositas 2000



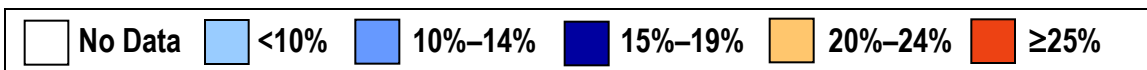
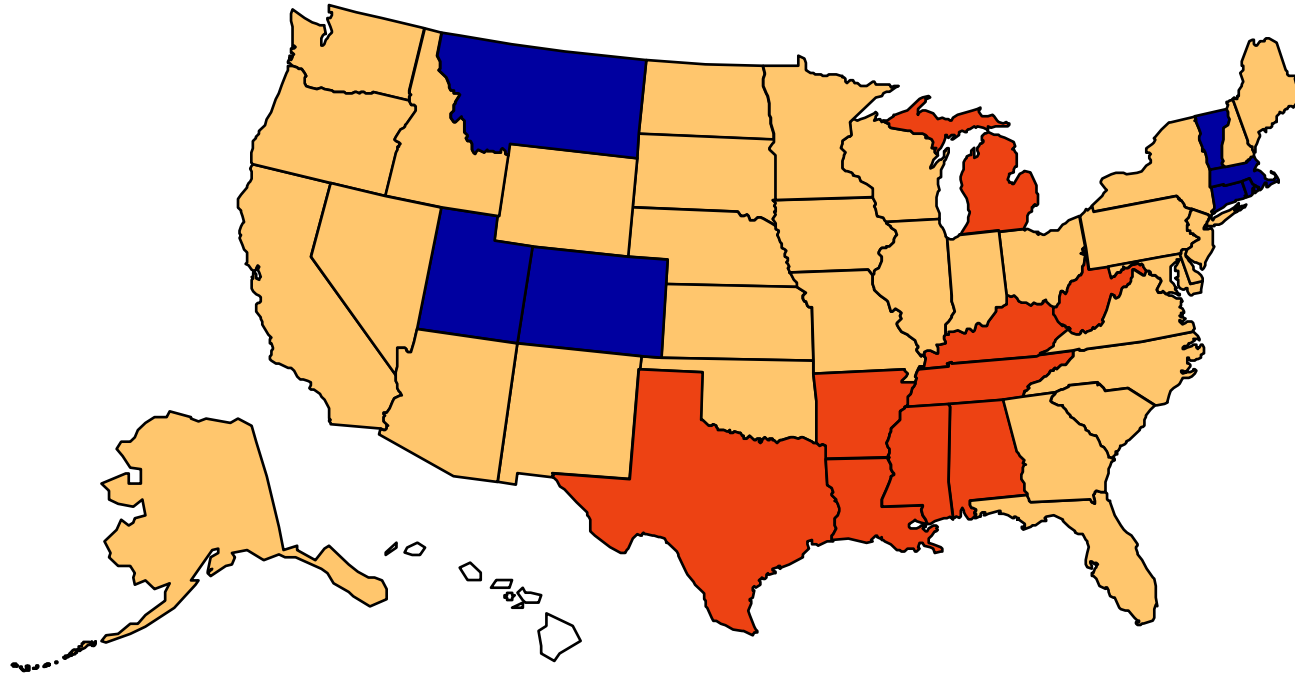


Adipositas 2001



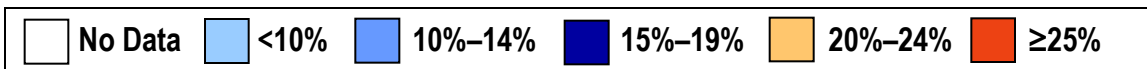
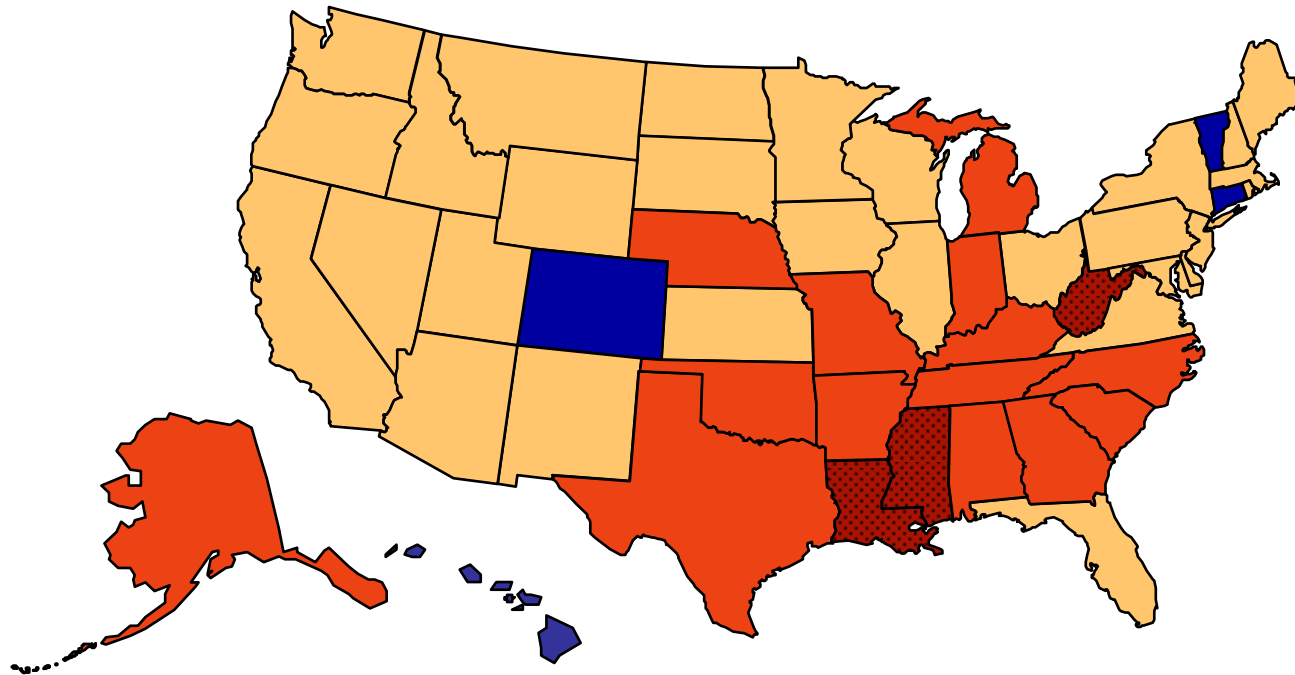


Adipositas 2004



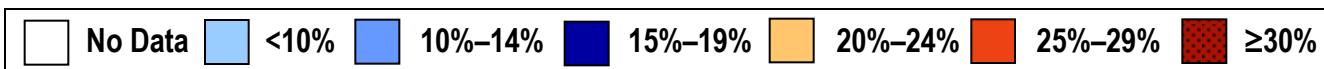
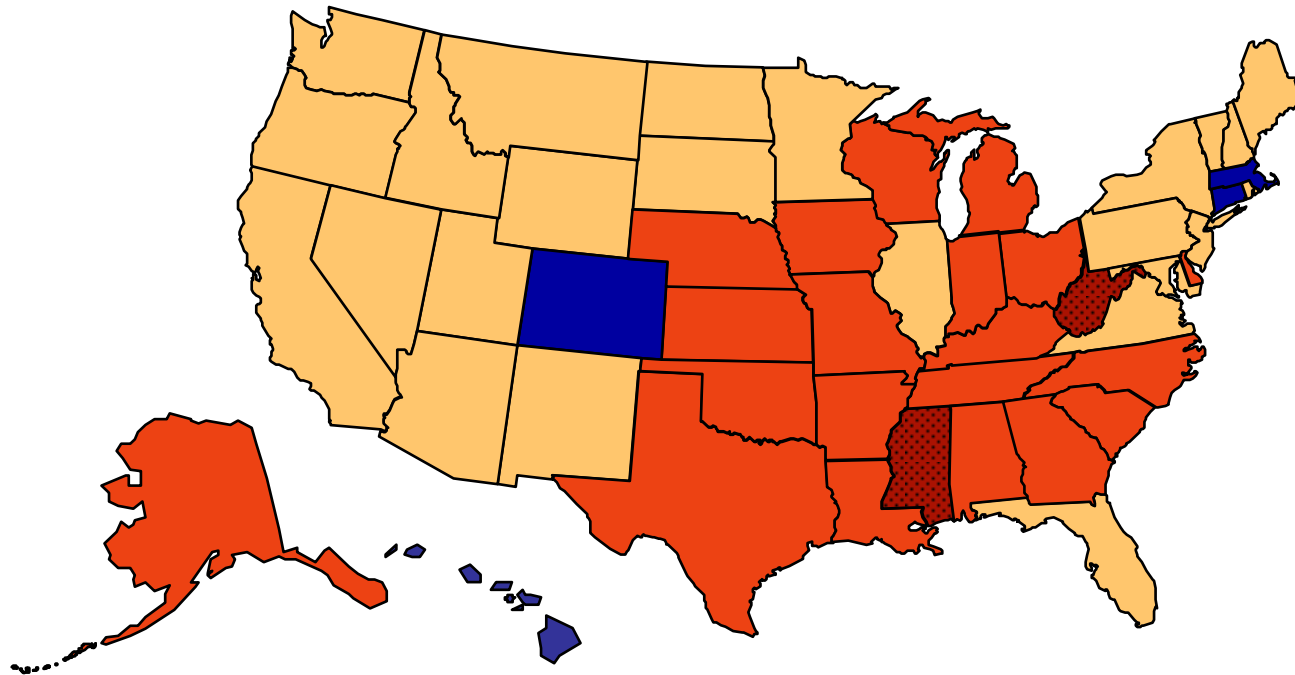


Adipositas 2005



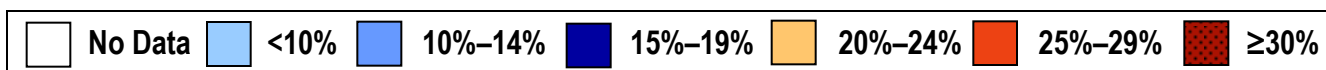
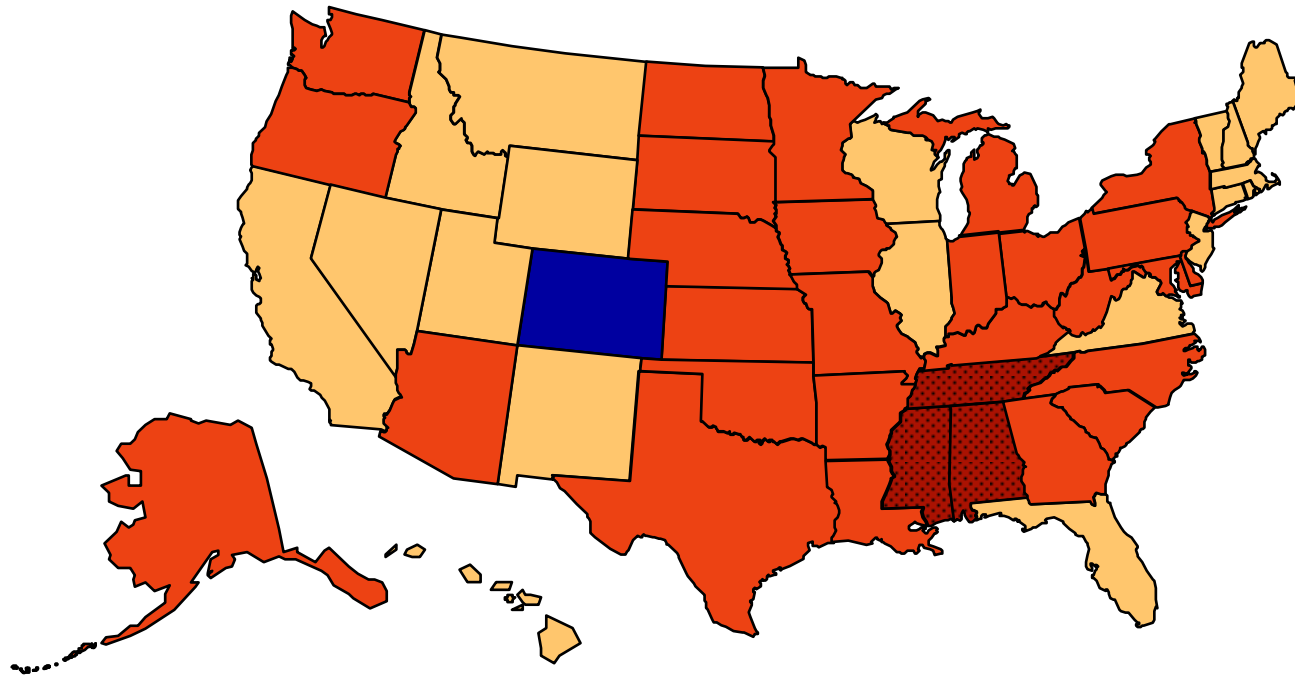


Adipositas 2006



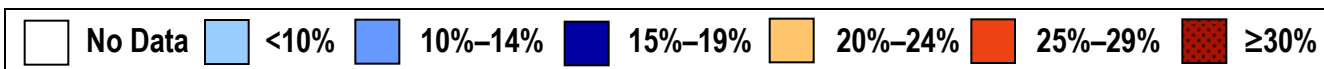
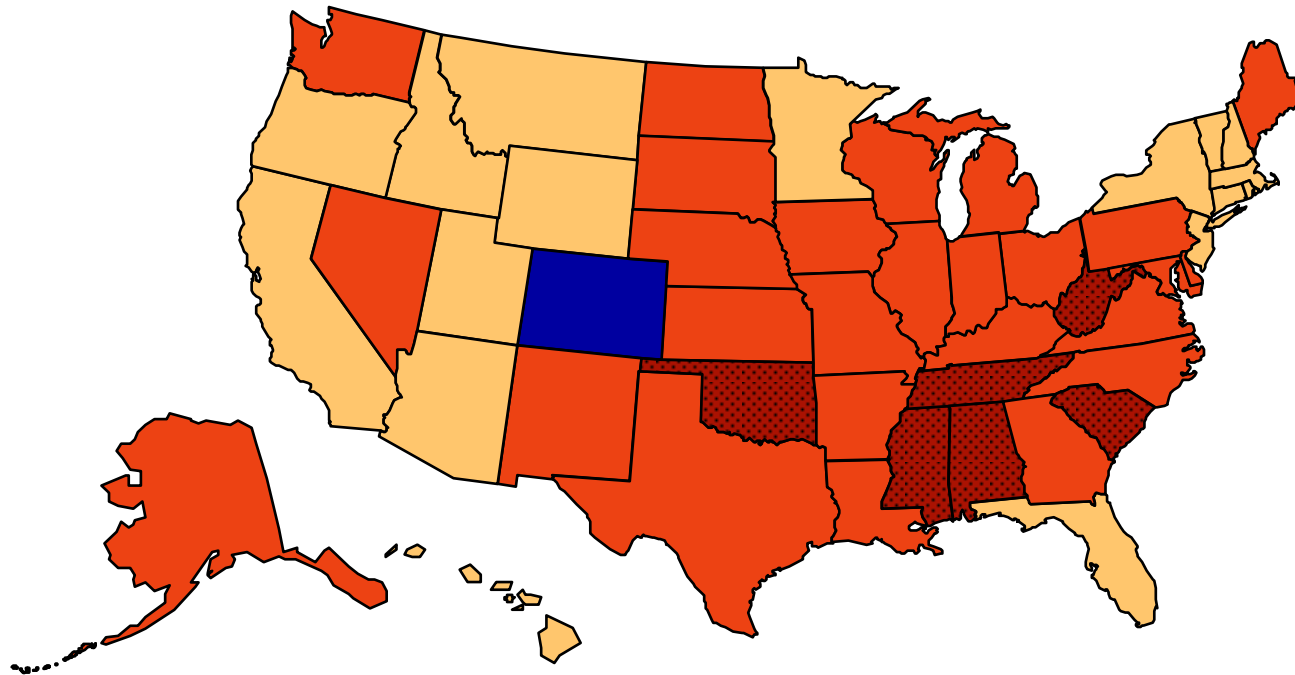


Adipositas 2007



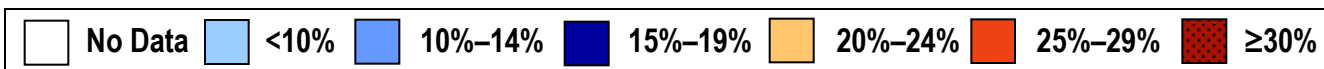
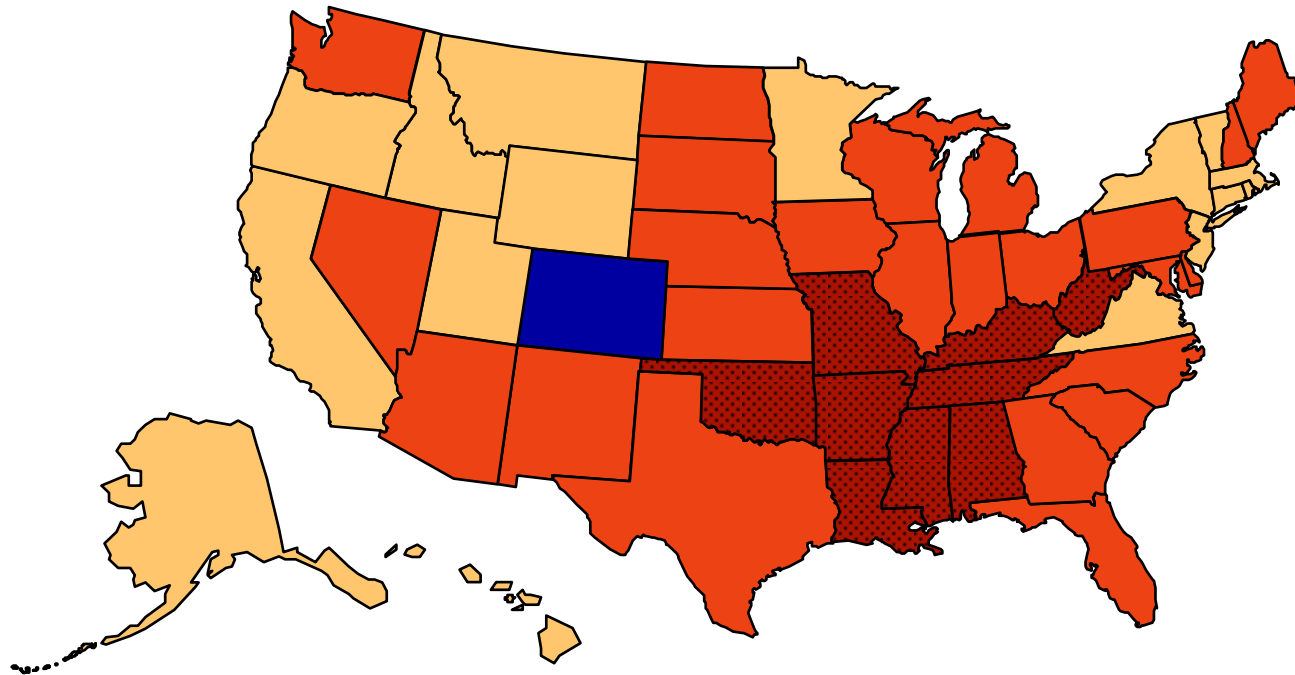


Adipositas 2008



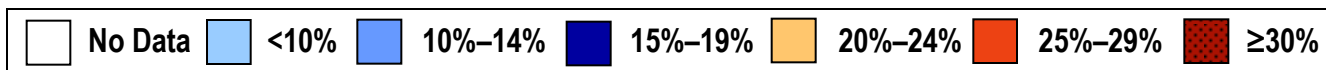
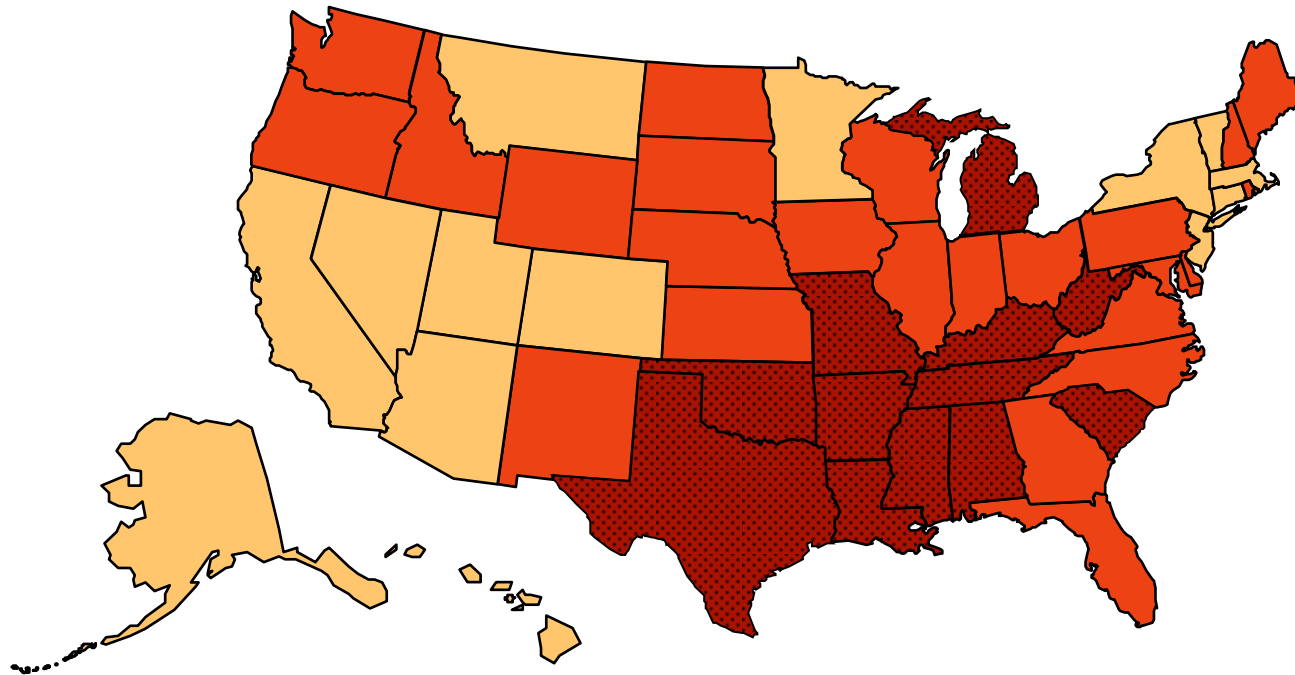


Adipositas 2009



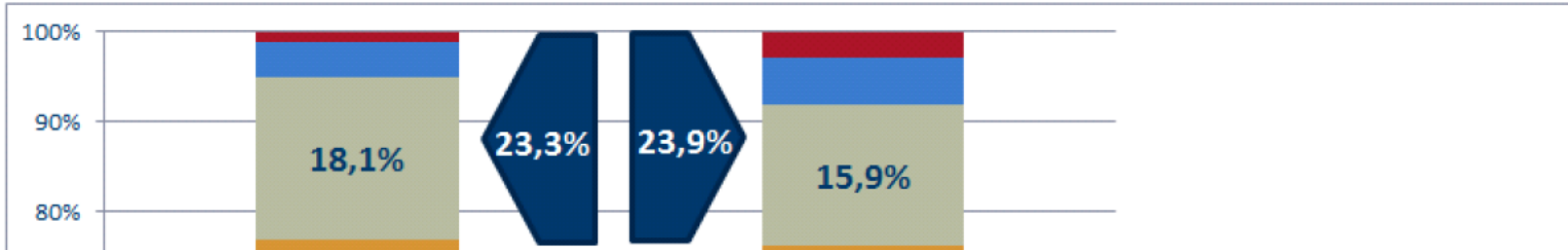


Adipositas 2010



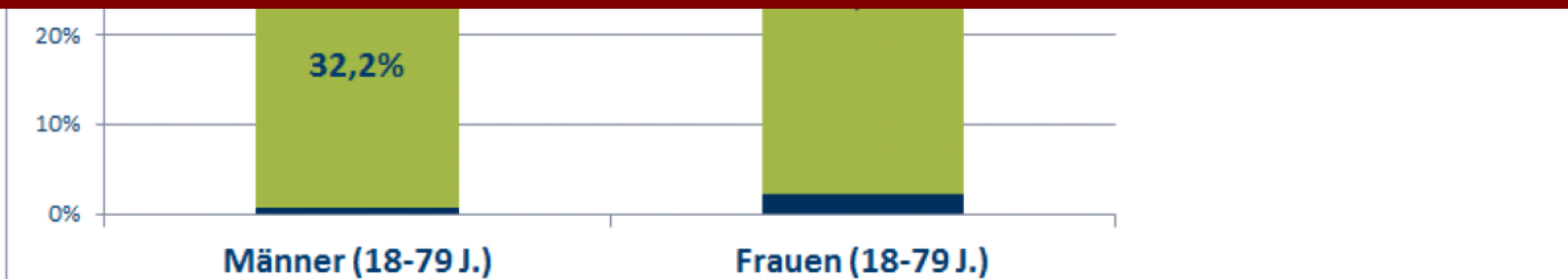


Adipositas Deutschland



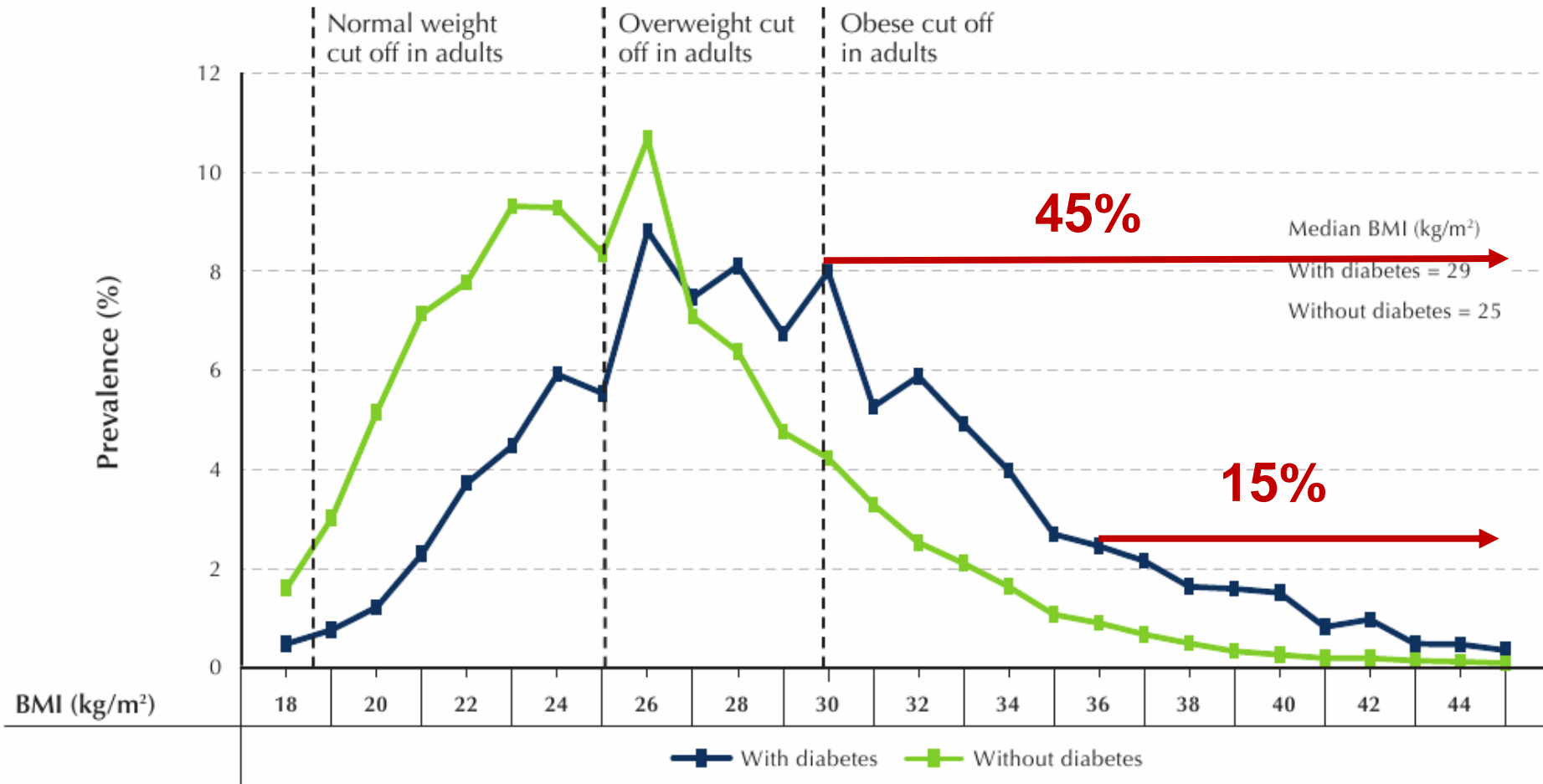
BMI > 40 kg/m²: 2 %

Also: 1,6 Millionen Deutsche!





Adipositas und Diabetes mellitus





Diabetes mellitus

The screenshot shows the website for World Diabetes Day. At the top center is a blue circular logo with the text "Weltdiabetestag" and "14. November" below it. Below the logo is a navigation bar with the following links: "Startseite", "Aktuelles", "Weltdiabetestag", "Thema", and "Veranstaltungen". The main content area features a heading "Weltdiabetestag - 14. November" followed by a paragraph of text.

Weltdiabetestag
14. November

Startseite Aktuelles Weltdiabetestag Thema Veranstaltungen

Weltdiabetestag - 14. November

Der Weltdiabetestag wird seit 1991 als ein Tag der Internationalen Diabetes-Föderation (International Diabetes Federation, IDF) und der Weltgesundheitsorganisation (World Health Organization, WHO) durchgeführt. Man hat den 14. November ausgewählt, da an diesem Tag Frederick G. Banting geboren wurde, der gemeinsam mit Charles Herbert Best 1921 das lebenswichtige Insulin entdeckte. Seit 2007 ist der Weltdiabetestag ein offizieller Tag der Vereinten Nationen (United Nations, UN). Er wurde im Dezember 2006 in der Resolution 61/225 verabschiedet. Damit ist er, neben dem Welt-AIDS-Tag, der im Jahre 1988 ausgerufen wurde, der zweite Tag, der einer Krankheit gewidmet ist.

Diabetes 2015



Über
400 Millionen
Erwachsene



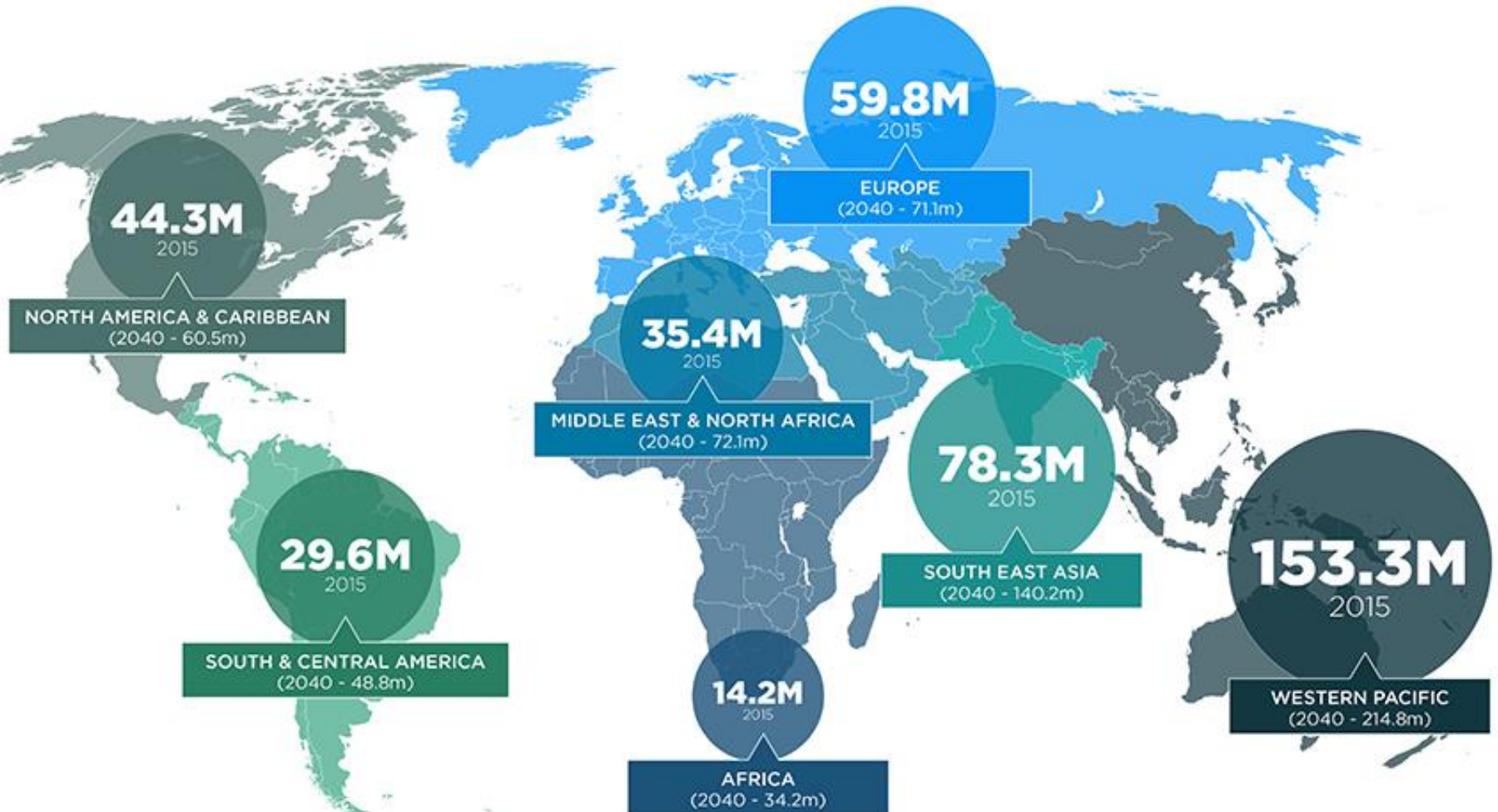
5 Millionen
Todesfälle jährlich



Über
670 Milliarden USD
Gesundheitsausgaben



Diabetes mellitus





14.11.2012 - 12:48 UHR | ABO | RSS | NEWSLETTER | VOLKS-SMARTPHONE | STROM-GAS-PREIS-VERGLEICH | KARRIERE-CHANCEN | „007“-HIGHTECH | VOLKS-VITAMIN | ISRAEL-REISE | TRAUMHAUS

Bild.de NEU REGISTRIEREN | LOGIN

THEMEN | BILD MOBIL | WETTER | GEWINN SPIELE | BILD-SHOP

HOME NEWS POLITIK GELD UNTERHALTUNG SPORT LIFESTYLE **RATGEBER** REISE AUTO DIGITAL SPIELE COMMUNITY REGIONAL **BILD.TV**

Home » Ratgeber » Gesundheit » Diabetes » Weltdiabetestag: Acht Millionen Deutsche haben Diabetes

ALLES ZUM
THEMA **Diabetes**



Gefällt mir 2

WELTDIABETESTAG: ACHT MILLIONEN DEUTSCHE HABEN
DIABETES

**Acht Millionen Deutsche
haben „Zucker“**

Kosten (CoDiM-Studie)

6.000 € pro Diabetiker pro Jahr

**>20.000 € bei Vorliegen spez.
Diabetes-bedingter
Komplikationen
(Dialyse, Amputation,
Insult, Gangrän)**



Diabetes-Komplikationen

Retinopathie
(Erkrankung der Netzhaut)

2,4

24,1

Diabetische Nervenkrankheit

4,3

23,0

Diabetische Nierenkrankheit

2,8

9,7

Diabetische Fußkrankheit

0,6

4,9

Schlaganfall

3,2

7,4

Herzinfarkt



5,4

11,1

**Arterielle Verschlusskrankheit
der Beinarterien**

3,1

12,1

-  Auftreten zu Beginn
(Angaben in Prozent)
-  Auftreten nach 11 und mehr Jahren
(Angaben in Prozent)

changing
diabetes®

Gesundheitsbericht Diabetes 2010
Changing Diabetes® ist eine eingetragene Marke
der Novo Nordisk A/S, Dänemark.





Therapie-Empfehlung der DDG

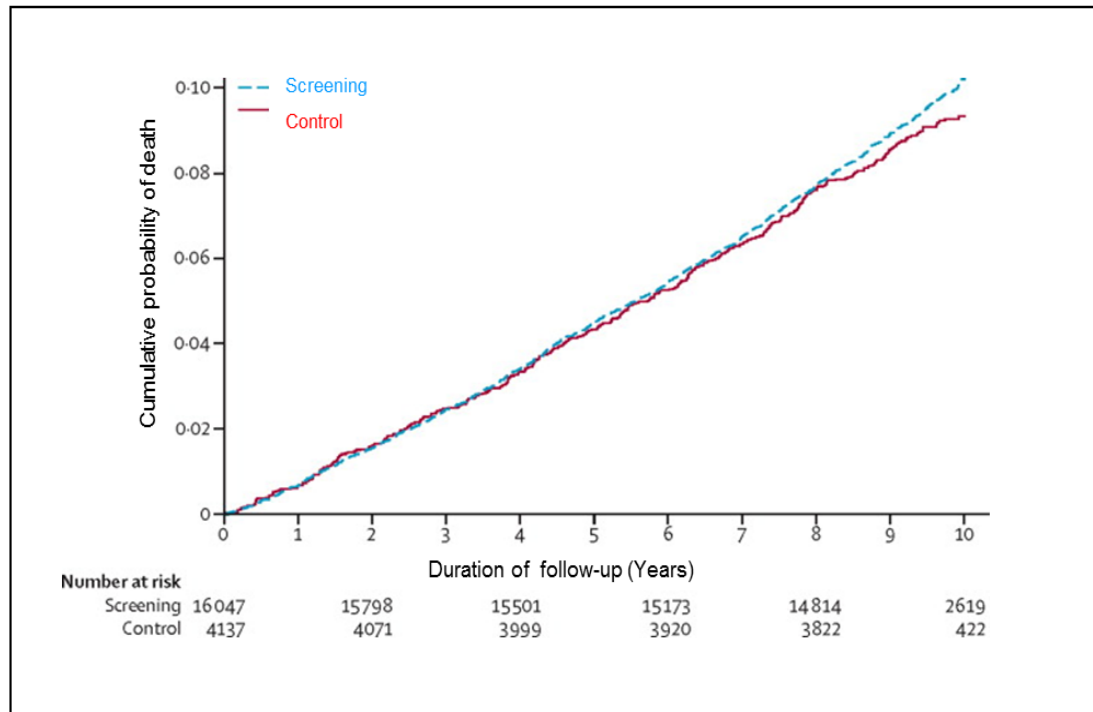
- Lifestyle-Intervention
 - Gewichtsabnahme, Sport, Ernährungsumstellung
- Medikamentöse Therapie
 - Tablette: Metformin (1. Wahl)
 - Zugabe von Basal-Insulin oder GLP-1 Agonist
 - Insulin-Therapie (intensiviert) +/- Tabletten





Wirksamkeit von Früherkennung

ADDITION-Cambridge trial

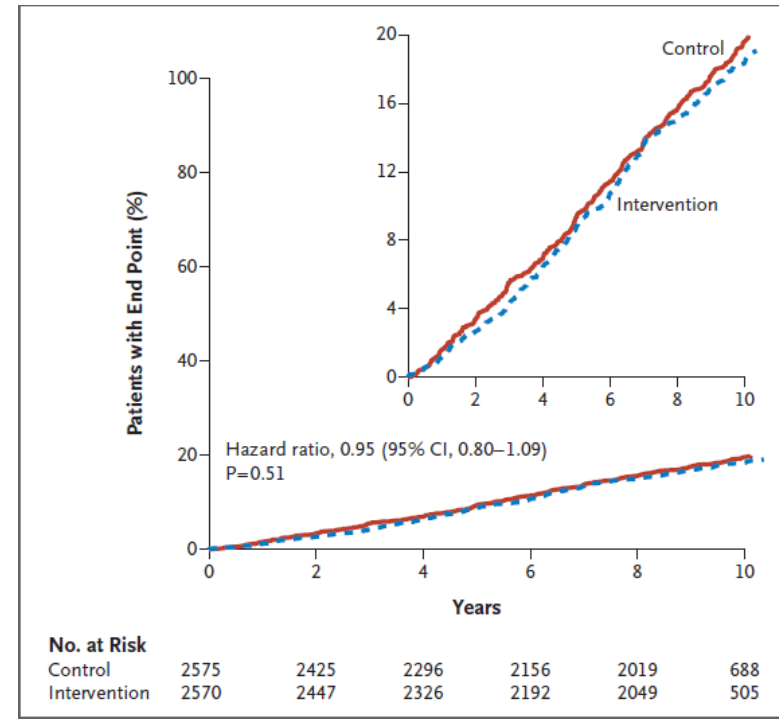
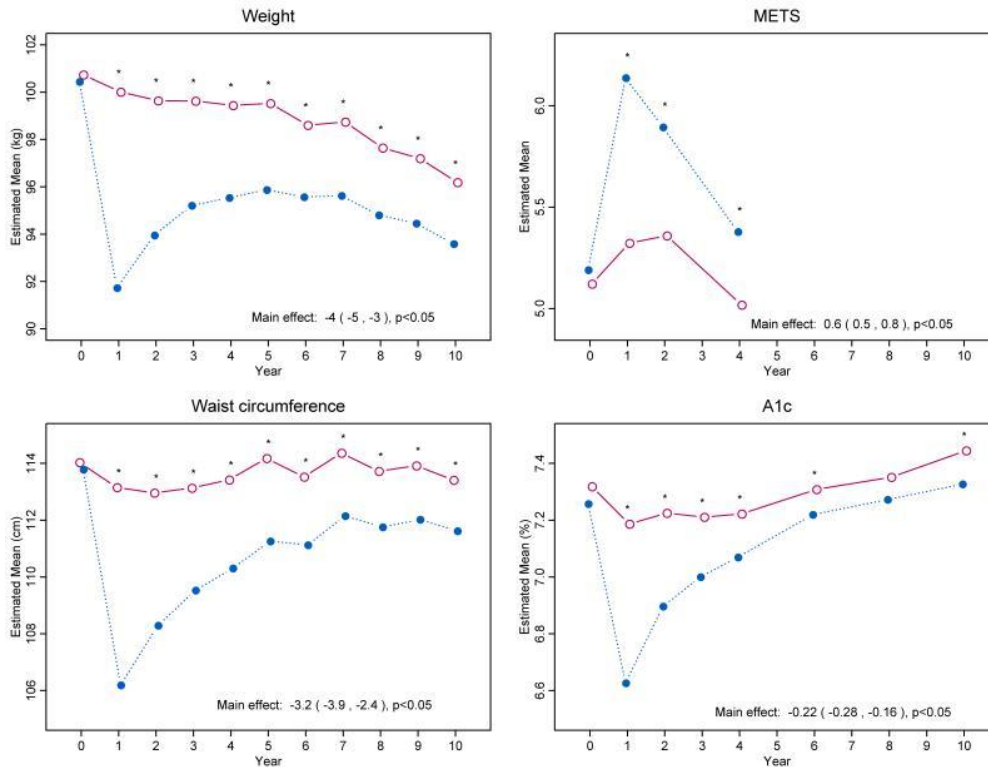


Cumulative incidence of death in the screening and no screening control groups in the ADDITION-Cambridge trial



Wirksamkeit konservativer Therapie

Look AHEAD study

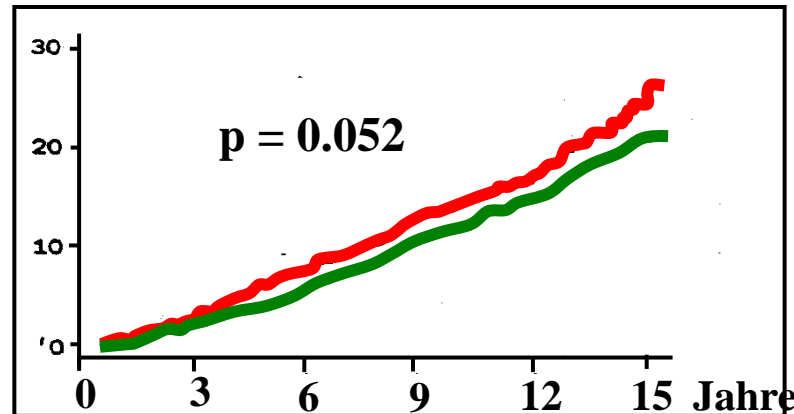




Wirksamkeit der Blutzuckereinstellung

Makrovaskulär

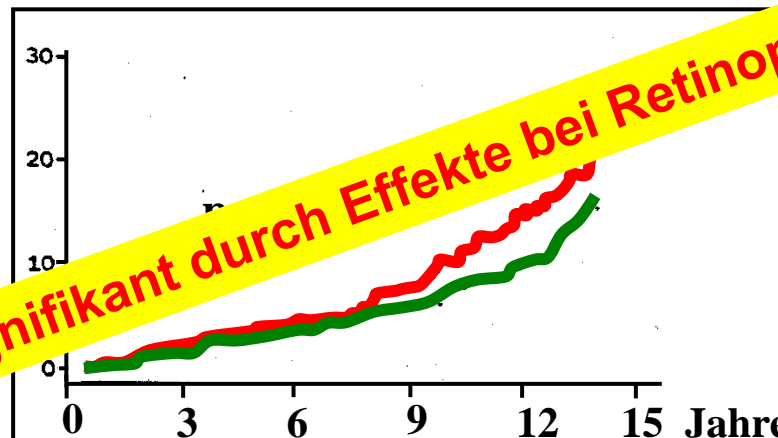
Myokardinfarkt,
plötzlicher Herztod



■ = HbA_{1c} 7.9
■ = HbA_{1c} 7.0

Mikrovaskulär

Nierenversagen,
Tod durch
Nierenvers. retinale
Laserkoagulation

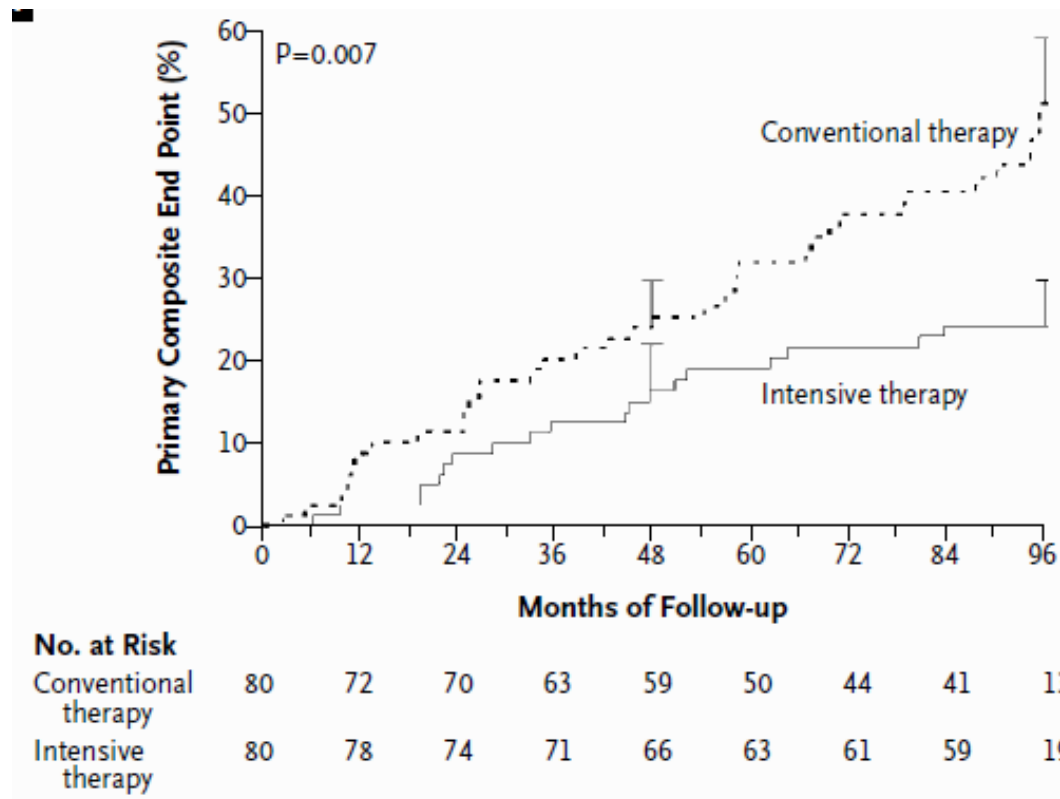


Nur signifikant durch Effekte bei Retinopathie



Wirksamkeit der Blutzuckereinstellung

Steno-2 study



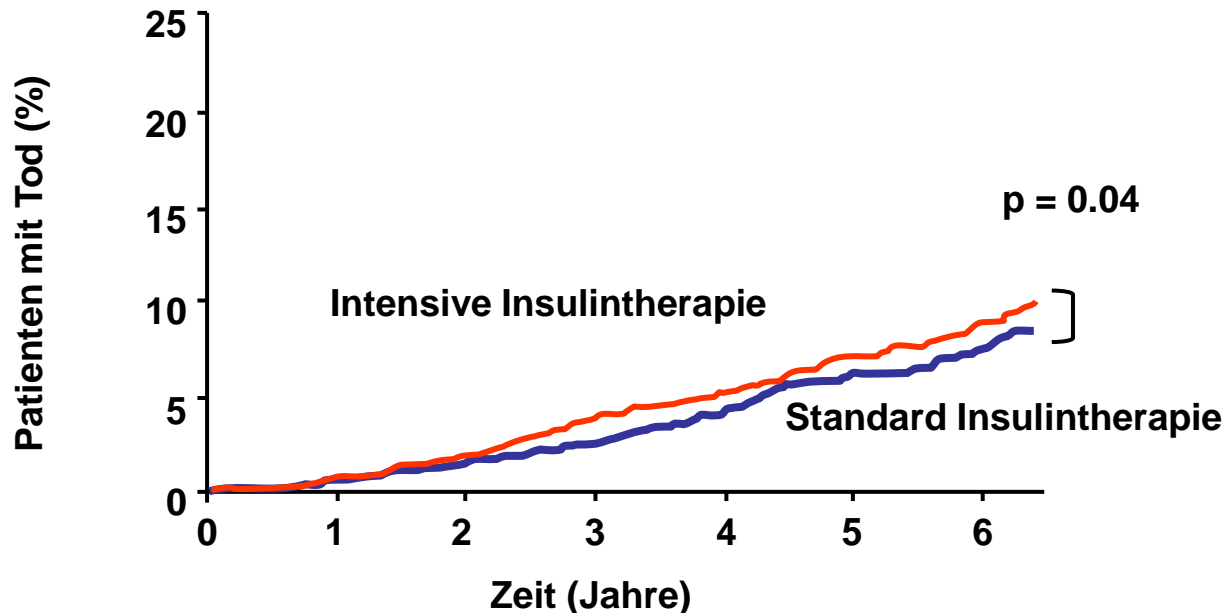
44%



24%



Problem der Blutzuckereinstellung **ACCORD study**

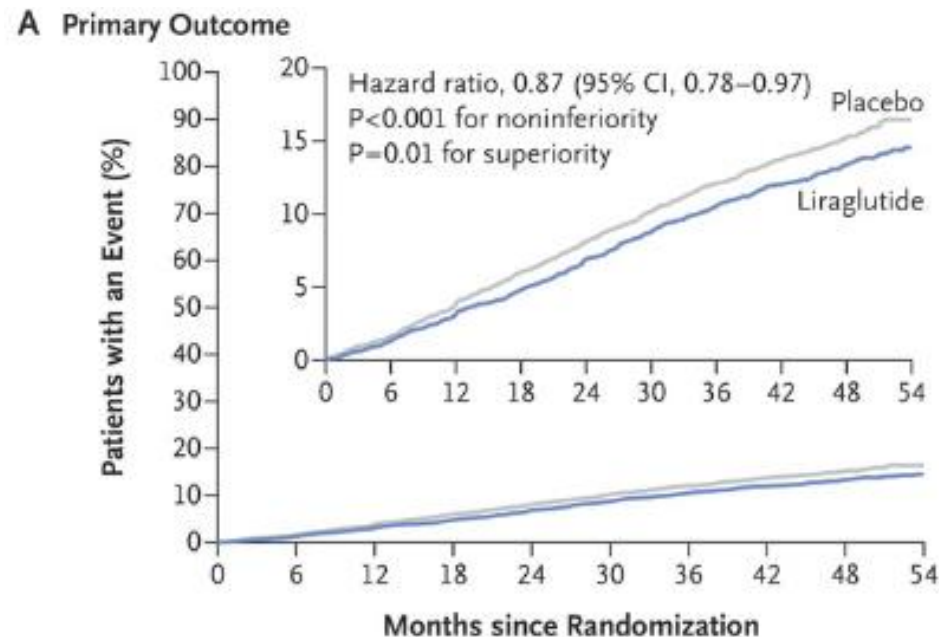


Tiefste Mortalität bei HbA1c um 7.5%



Neue Ansätze

Bsp.: GLP-1 Agonist



Teil des primären Endpunktes	ARR	NNT
Kardiovaskulärer Tod	0,98	102
Erster nichttödlicher Myokardinfarkt	0,62	162
Erster nichttödlicher Schlaganfall	0,23	430



Grenzüberschreitung und Wendepunkt ?



H.S. 17.12.1964 ♂



- 116 kg (BMI 34,3 kg/m²)
- Diabetes mellitus Typ 2, insulinpflichtig seit 1999
- Folgeerkrankungen:
 - Bluthochdruck
 - Polyneuropathie (Wadenkrämpfe, Potenzstörung)
- Medikamente:
 - Novorapid, Protaphane,
 - Lisinopril, Nifedipin
- Lebensqualität: schlecht (körperl. Aktivität, Partner)



H.S. 17.12.1964 ♂

Postoperativer Verlauf

**Magenbypass-OP
04/12**

**7.post-OP Tag:
Entlassung
Keine Wadenkrämpfe**

**1.post-OP Tag:
Blutzucker normwertig
Insulin abgesetzt**

**6 Monate post-OP:
Blutzucker normwertig
Kein Insulin
Keine Wadenkrämpfe
Normale Potenz
Medikamente: Nifedipin
Lebensqualität: stark verbessert
Gewicht: 88kg (BMI 26kg/m²)**



H.S. 17.12.1964 ♂

„5x ein neues Leben!“

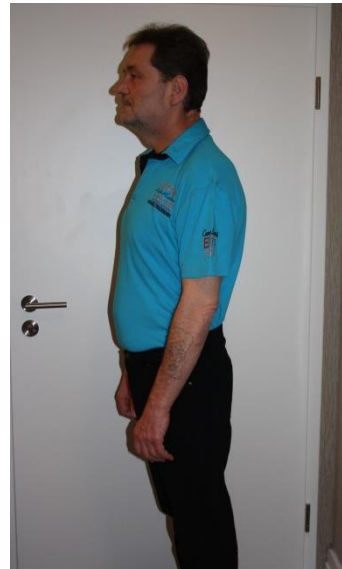
**Insulin
weg!**

Mehr Power!

Wadenkrämpfe weg!

**Bluthochdruck
weg!**

Potenz wieder da!





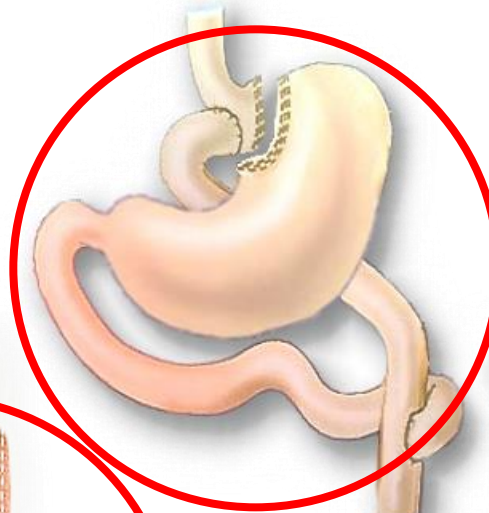
Adipositaschirurgie

Restriktiv

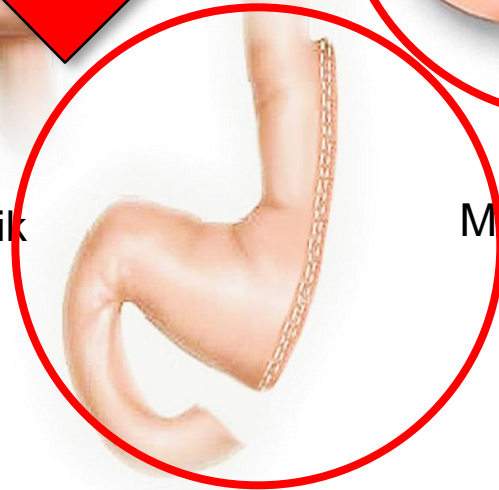
Malabsorptiv



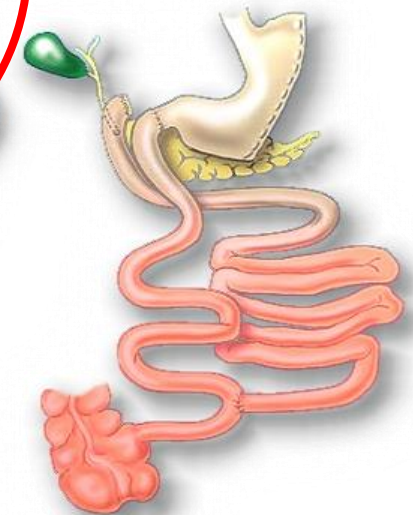
Magenplastik



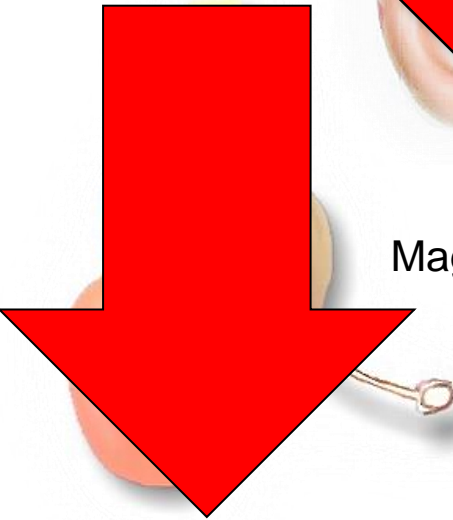
Magenbypass



Schlauchmagen



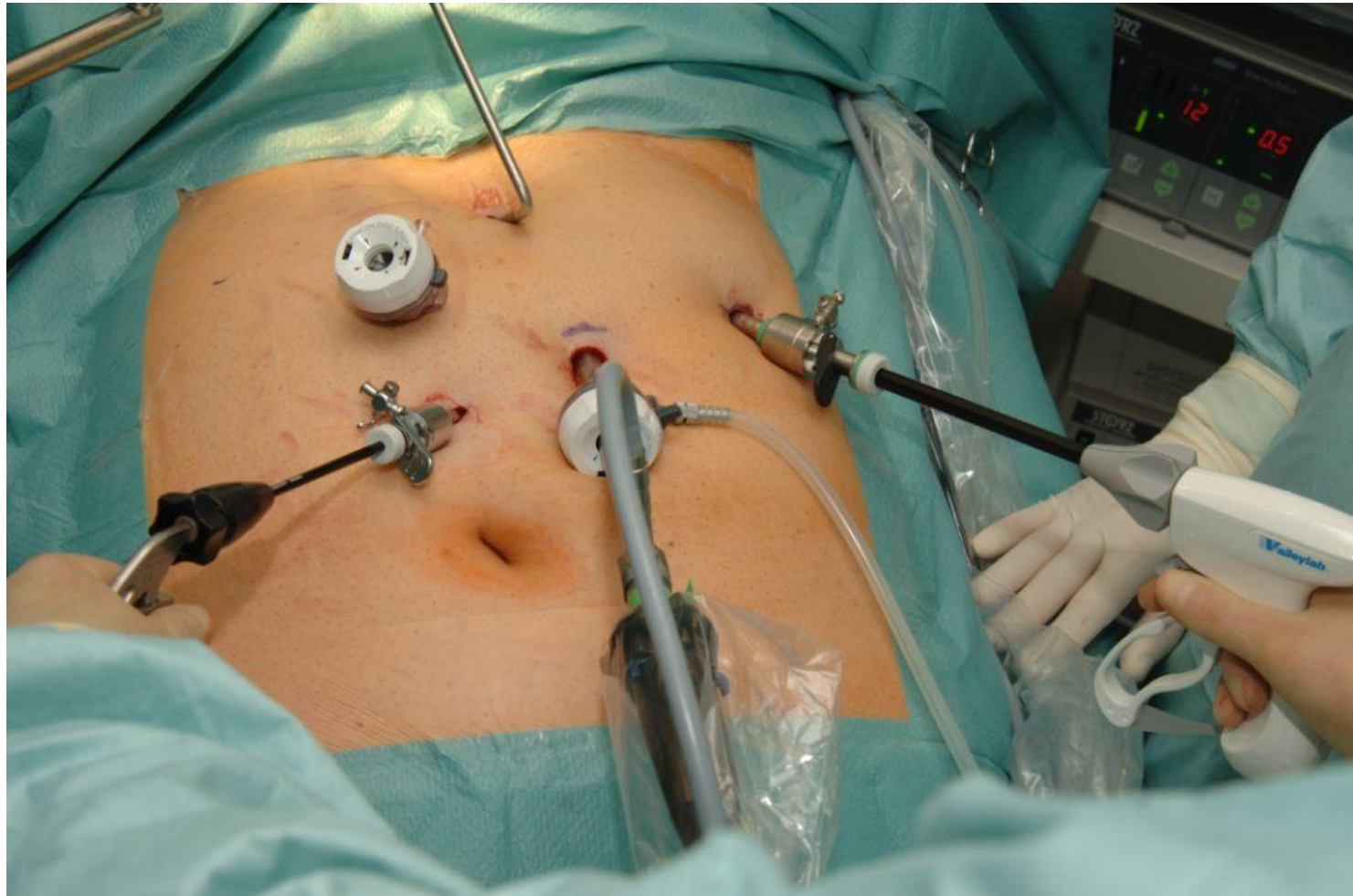
Duodenal Switch



Magenband

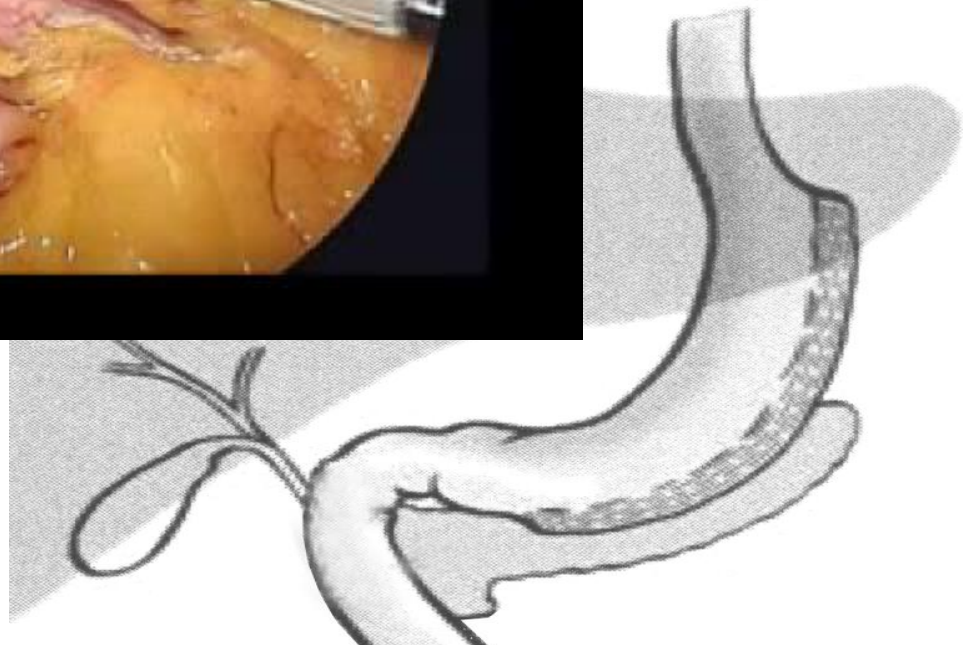
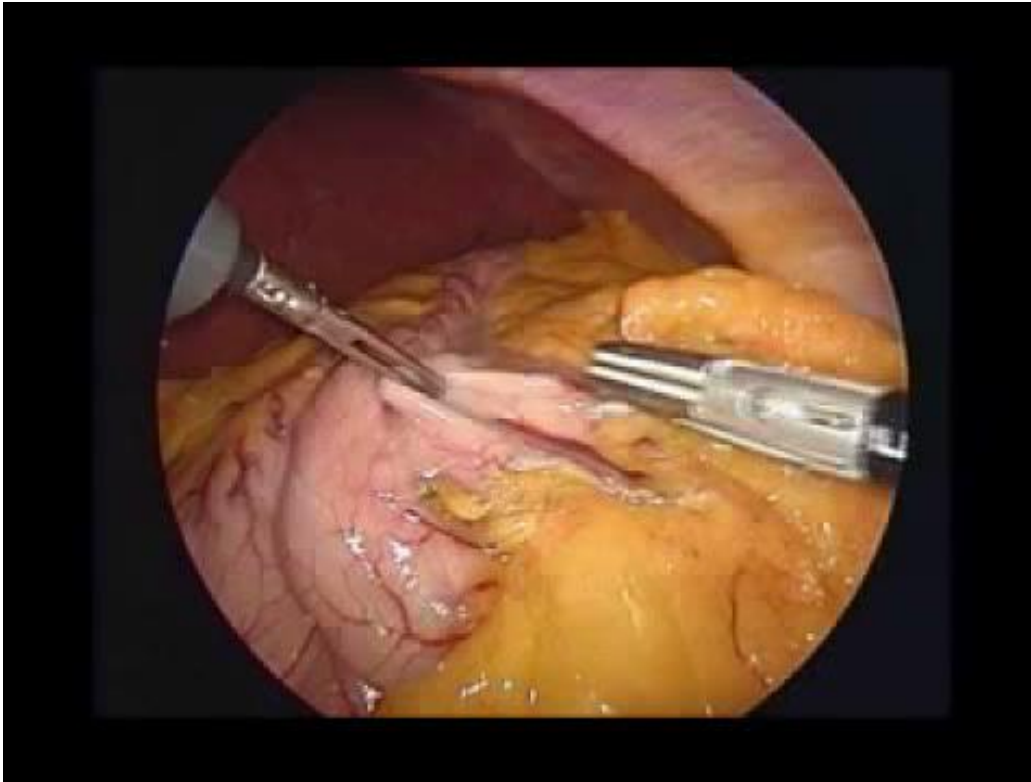


Adipositaschirurgie



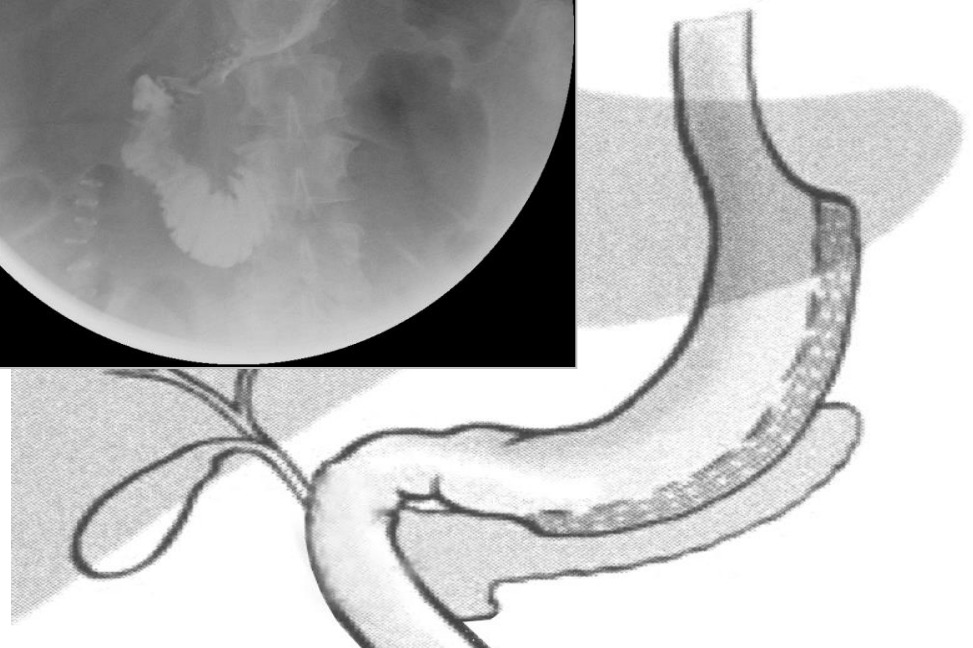


Schlauchmagen



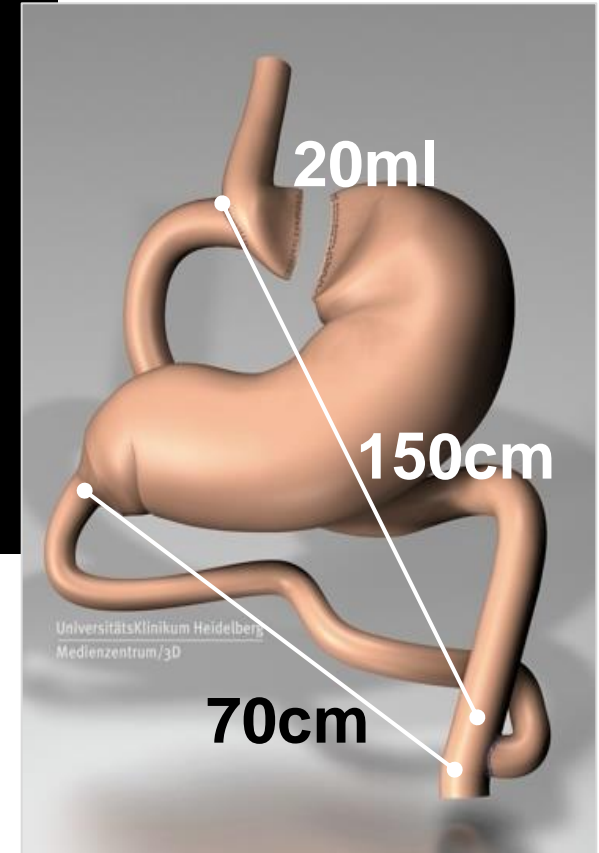
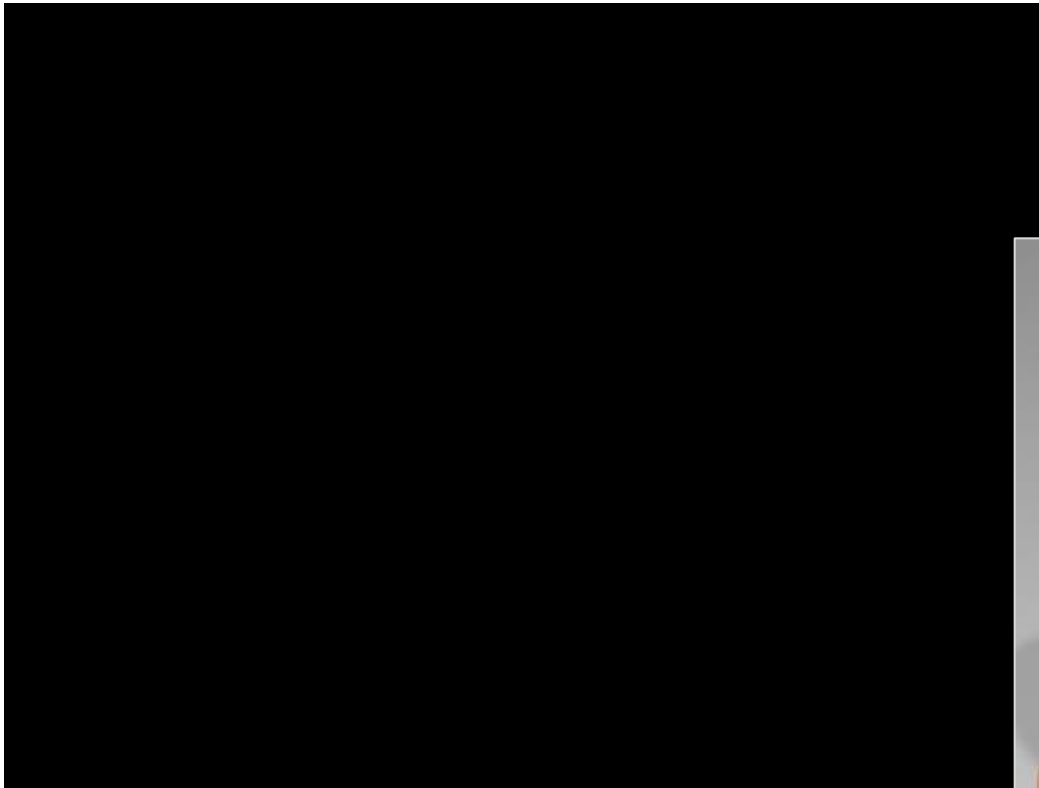


Schlauchmagen





Magenbypass





Adipositaschirurgie Risiko

Hospital Complication Rates With Bariatric Surgery in Michigan



Nancy J. O. Birkmeyer, Justin B. Dimick, David Share, Abdelkader Hawasli, Wayne J. English, Jeffrey Genaw, Jonathan F. Finks, Arthur M. Carlin, John D. Birkmeyer

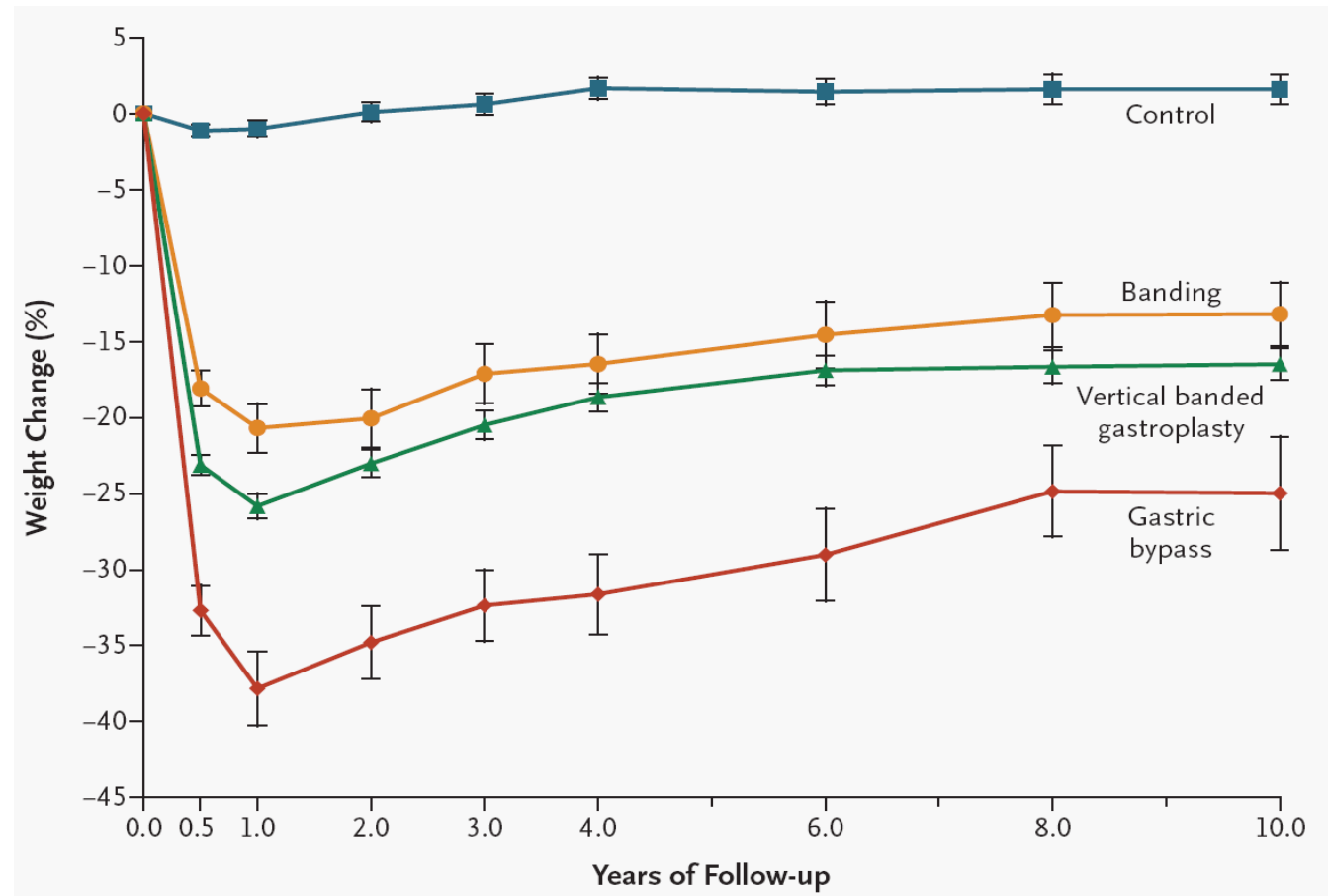
Table 3. Occurrence of Specific Perioperative Complications and Adverse Events by Procedure Type

Outcome	% (95% CI)				P Value ^a
	Overall (N=15 275)	Laparoscopic Adjustable Gastric Band (n=5380)	Sleeve Gastrectomy (n=854)	Gastric Bypass (n=9041)	
Any complication	7.3 (6.9-7.7)	2.3 (1.9-2.7)	5.9 (1.3-7.4)	10.3 (9.7-11.0)	<.001
Non-life-threatening	4.7 (4.4-5.1)	1.5 (1.2-1.8)	3.6 (2.5-5.1)	6.7 (6.2-7.3)	<.001
Potentially life-threatening	2.3 (2.0-2.5)	0.78 (0.56-1.1)	2.2 (1.3-3.5)	3.1 (2.8-3.5)	<.001
Permanently disabling	0.21 (0.14-0.30)	0.04 (0.01-0.13)	0	0.33 (0.22-0.47)	<.001
Fatal	0.10 (0.6-0.16)	0.04 (0.01-0.13)	0	0.14 (0.08-0.25)	.09
Combined serious complications ^b	2.6 (2.3-2.8)	0.86 (0.61-1.1)	2.2 (1.2-3.2)	3.6 (3.2-4.0)	<.001



Adipositaschirurgie ...und Gewichtsverlust

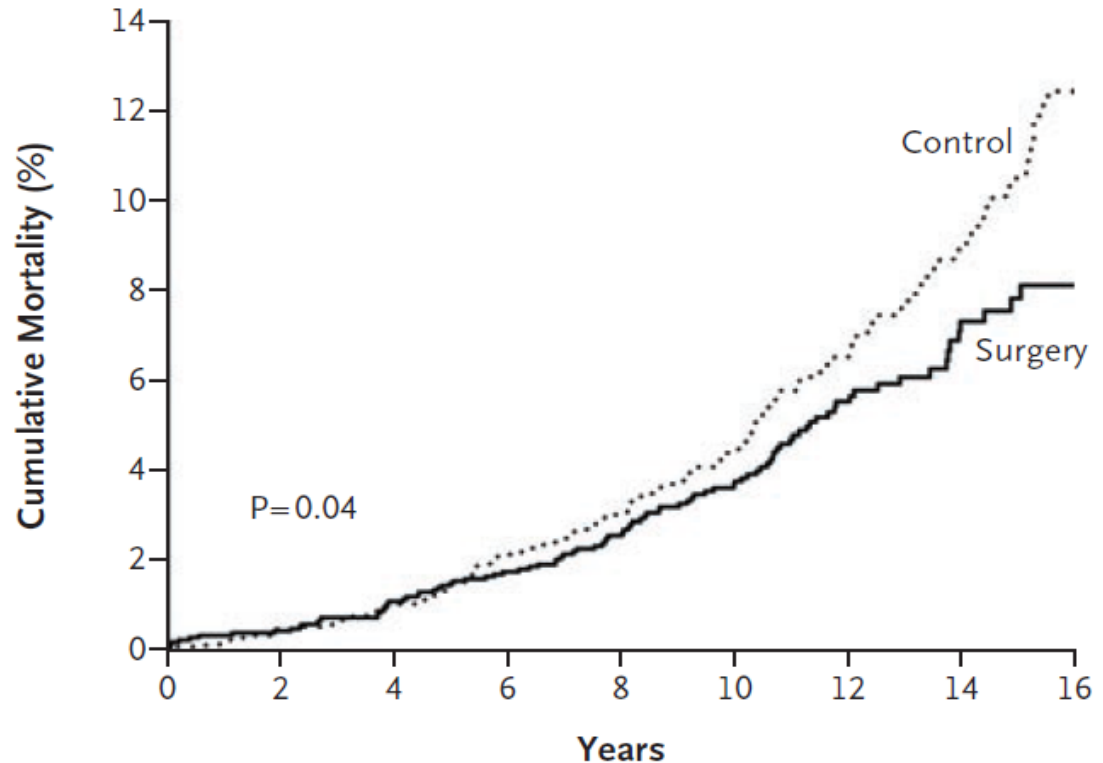
n = 4047
BMI ~ 40 kg/m²
FO = 10 Jahre





Adipositaschirurgie ...und Mortalität

n = 4047
BMI ~ 40 kg/m²
FO = 16 Jahre



No. at Risk

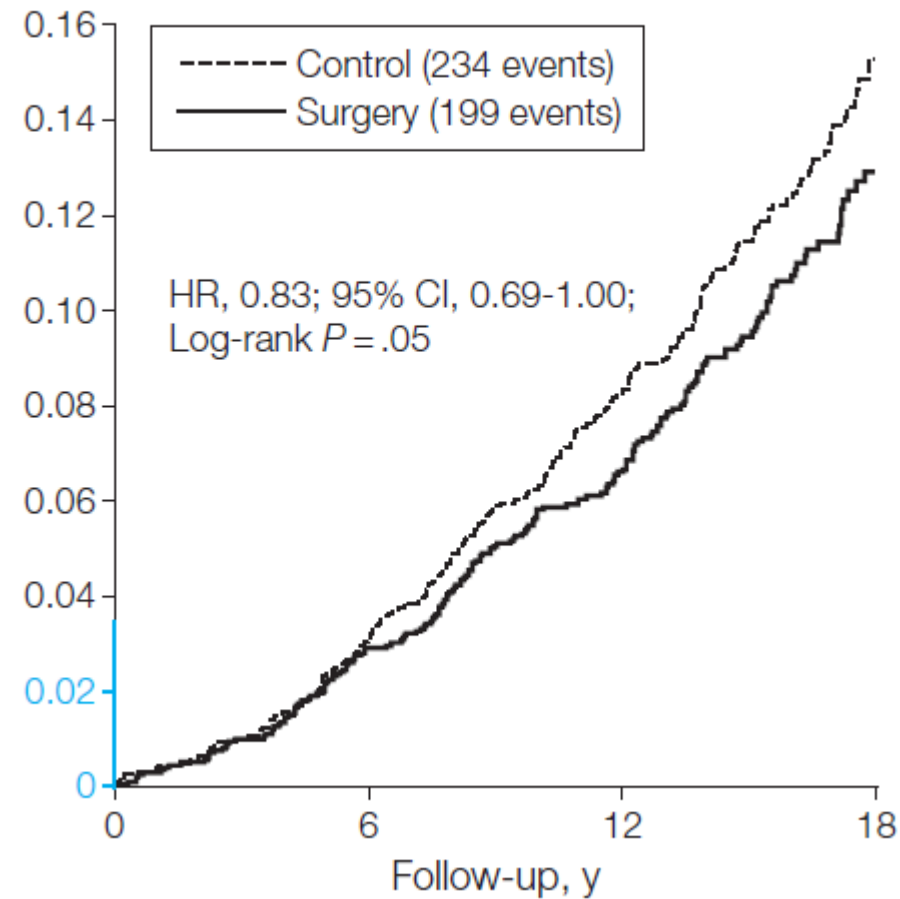
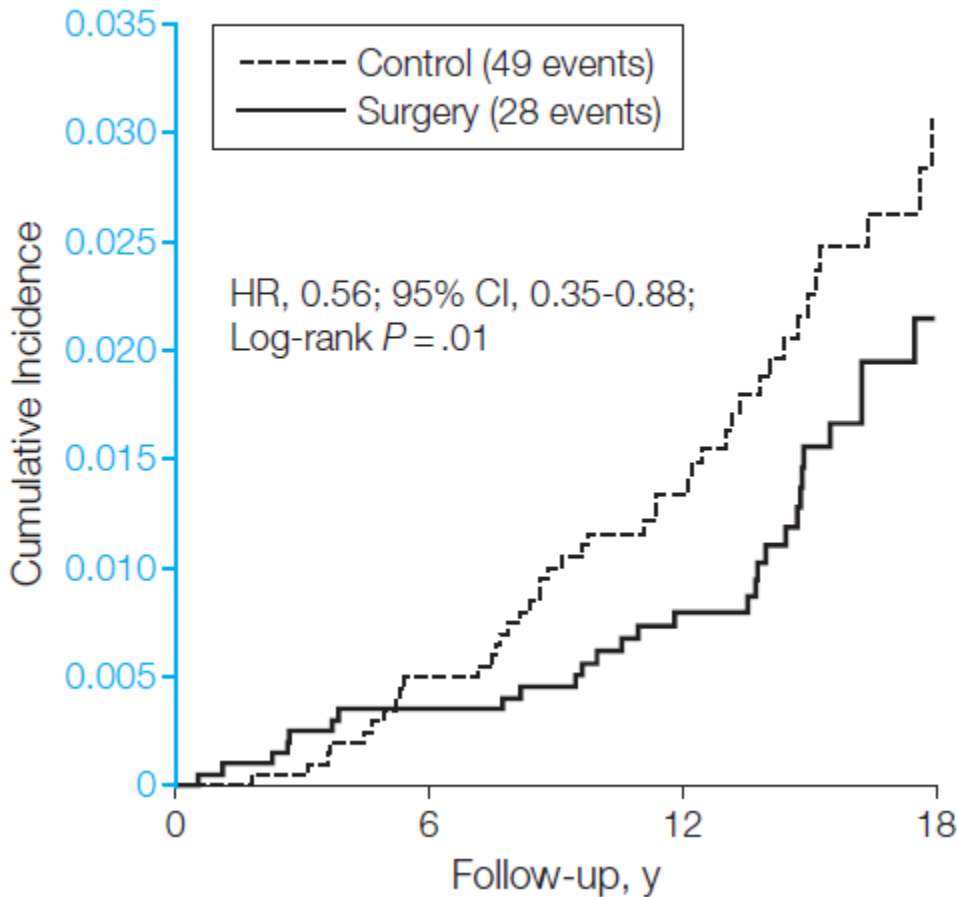
Surgery	2010	2001	1987	1821	1590	1260	760	422	169
Control	2037	2027	2016	1842	1455	1174	749	422	156



Adipositaschirurgie ...und Mortalität

Fatal cardiovascular events

Total cardiovascular events



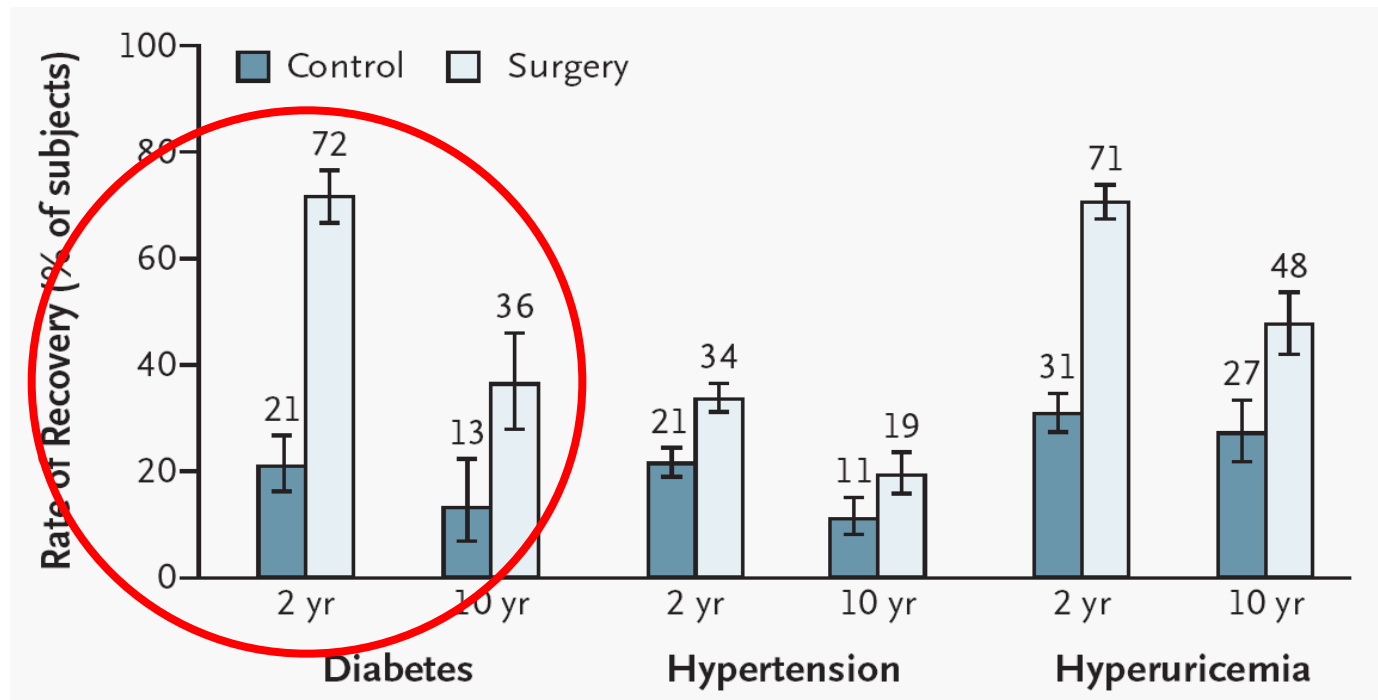
n = 4047, FO = 15 Jahre

Sjöström L et al. JAMA(2012)



Adipositaschirurgie ... und Diabetes mellitus (Evidenzlevel Iib)

Kohortenstudie
n = 4047
BMI ~ 40 kg/m²
FO = 10 Jahre





Adipositaschirurgie ... und Diabetes mellitus (Evidenzlevel IIa)

Meta-Analyse
n = 135,236

	Total	Gastric Banding	Gastroplasty	Gastric Bypass	BPD/DS
% EBWL	55.9	46.2	55.5	59.7	63.6
% Resolved overall	78.1	56.7	79.7	80.3	95.1
% Resolved <2 y	80.3	55.0	81.4	81.6	94.0
% Resolved \geq 2 y	74.6	58.3	77.5	70.9	95.9

%EBWL = percent excess body weight loss; BPD/DS = biliopancreatic diversion/duodenal switch.

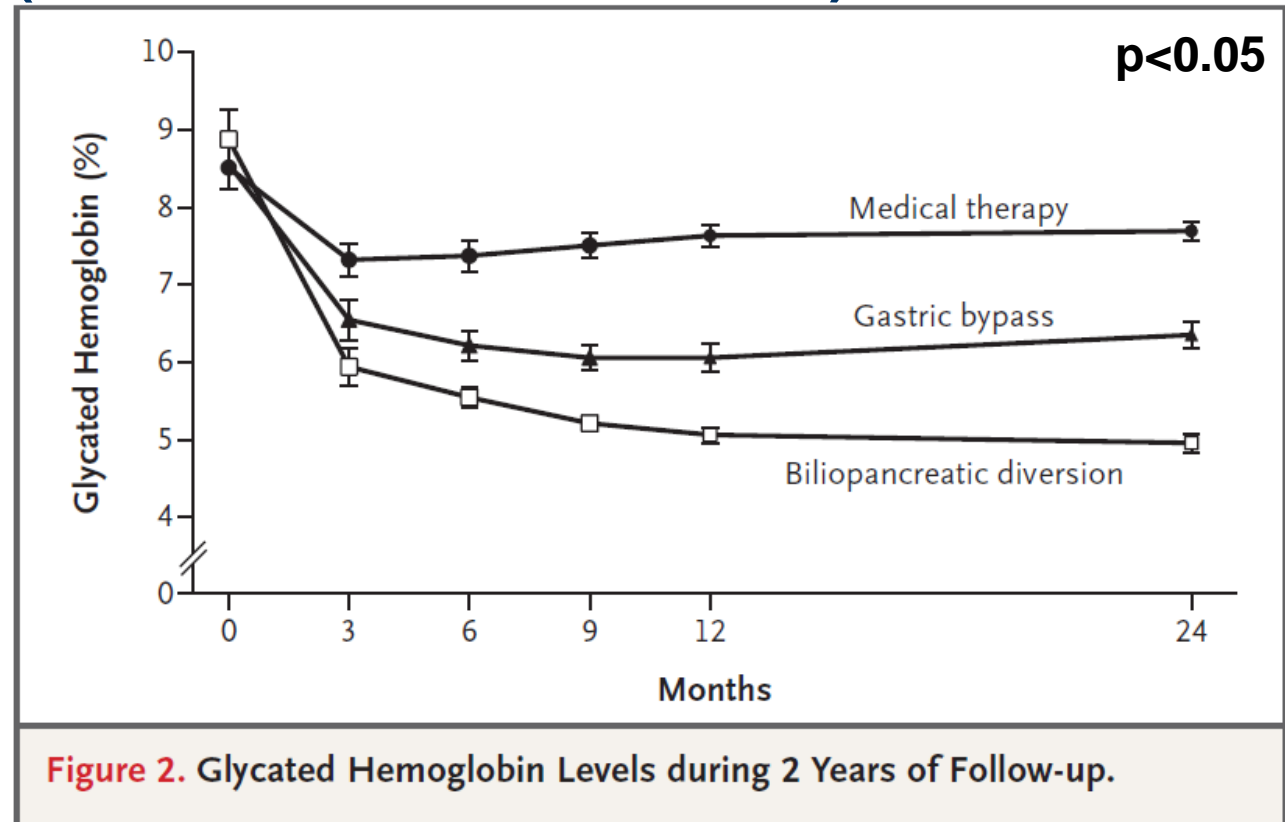


Adipositaschirurgie ... und Diabetes mellitus (Evidenzlevel Ib)

RCT
n = 60
BMI >35 kg/m²
FO = 2 Jahre

Remission
(Hb A1c < 6.5):

Insulin: 0%
LYGB: 75%
BPD: 95%





Diabeteschirurgie

=

unabhängig von BMI

(also auch BMI <35 kg/m²)



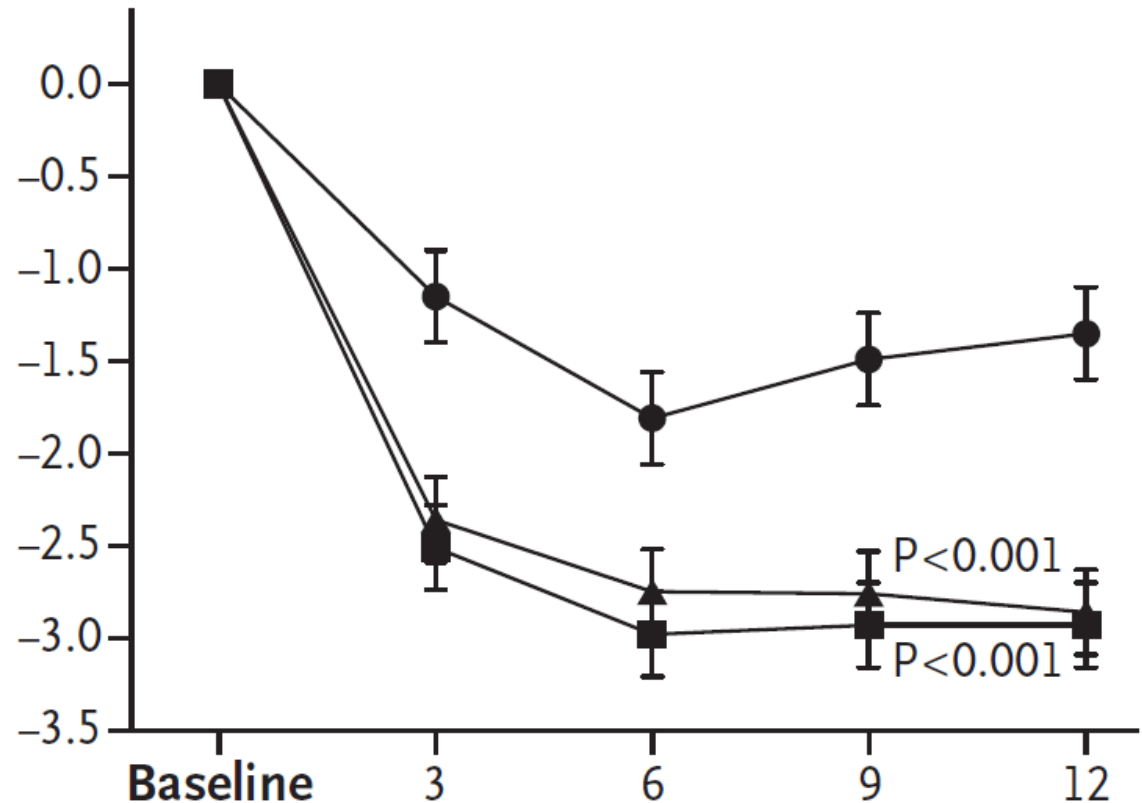
Diabeteschirurgie RCT (Evidenzlevel Ib)

n = 150
BMI 27-43 kg/m²
FO = 12 Mte.

Remission
(Hb A1c <6.0):

Insulin: 12%
LSG: 37%
LYGB: 42%

Change in Glycated Hemoglobin
(percentage points)



● Intensive medical therapy ■ Roux-en-Y gastric bypass ▲ Sleeve gastrectomy

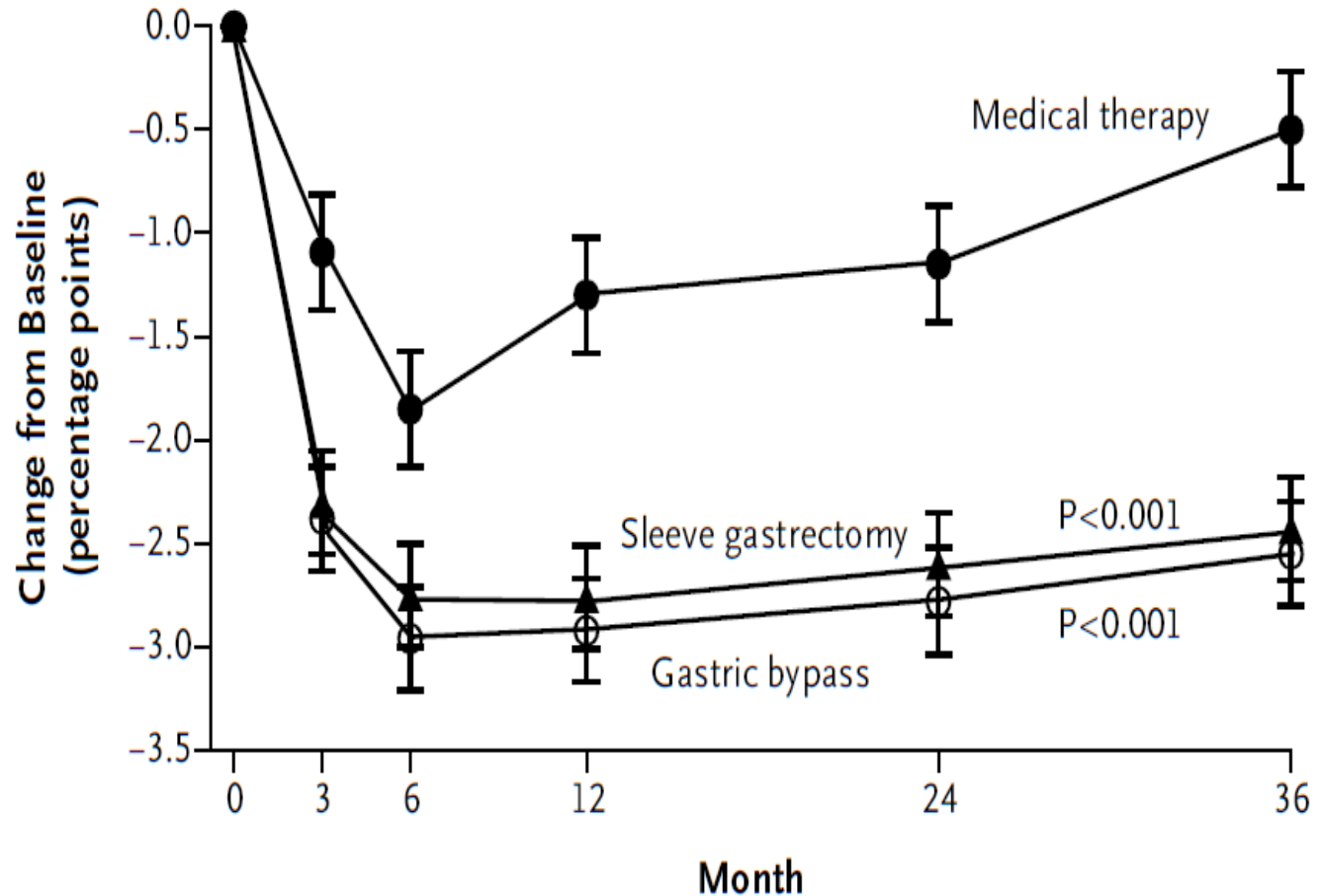


Diabeteschirurgie RCT (Evidenzlevel Ib)

n = 150
BMI 27-43 kg/m²
FO = 36 Mte.

Remission
(Hb A1c <6.0):

Insulin: 5%
LSG: 24%
LYGB: 38%





ANNALS OF SURGERY

META-ANALYSIS

Surgical Versus Medical Treatment of Type 2 Diabetes Mellitus in Nonseverely Obese Patients

A Systematic Review and Meta-Analysis

Beat P. Müller-Stich, MD, Jonas D. Senft, MD,* René Warschkow, MD,†¶ Hannes G. Kenngott, MD,*
Adrian T. Billeter, MD, PhD,* Gianmatteo Vit, MD,* Stefanie Helfert, MD,* Markus K. Diener, MD,*‡
Lars Fischer, MD,* Markus W. Büchler, MD,* and Peter P. Nawroth, MD§*



Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

- Chirurgische vs. medikamentöse Therapie
- Diabetes mellitus Typ 2
- BMI <35 kg/m²

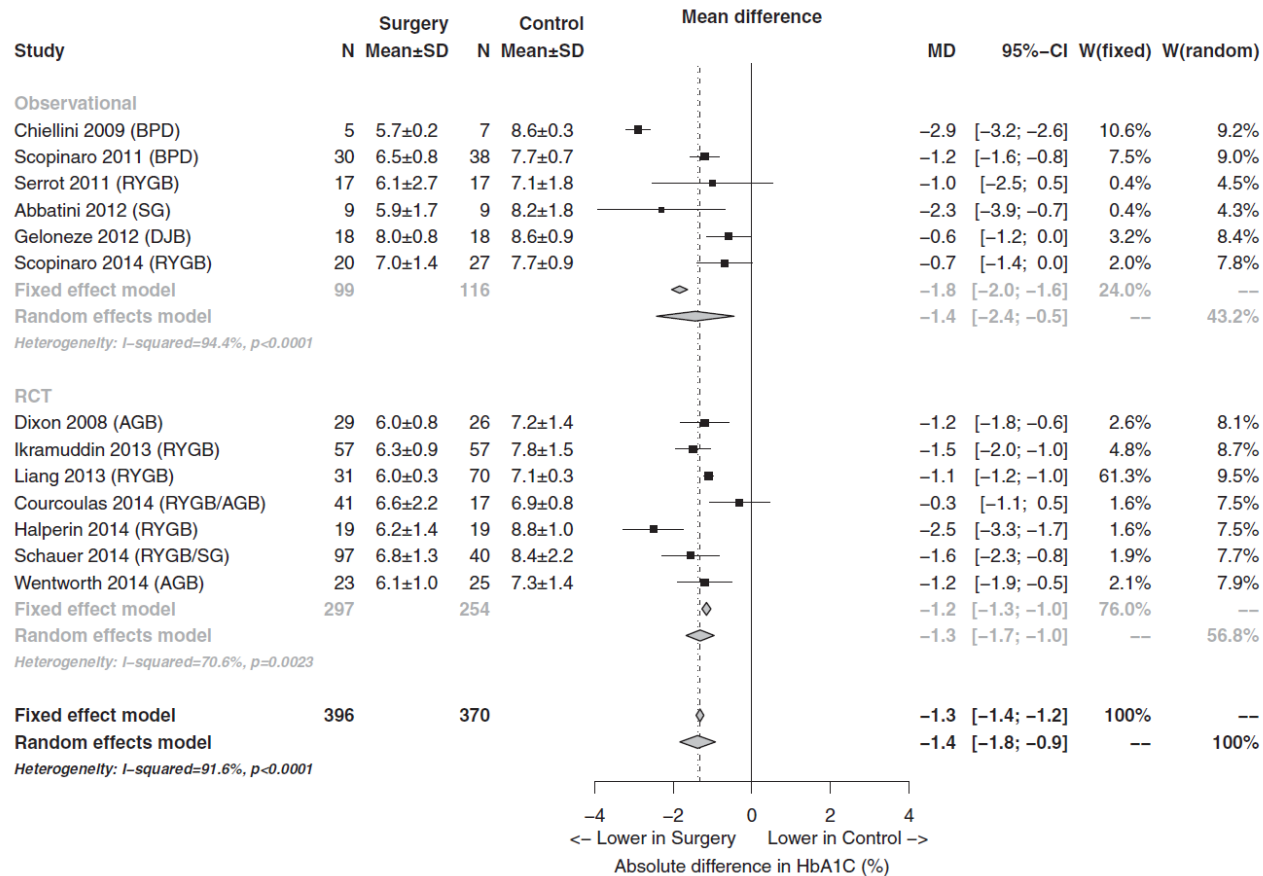
„Bariatric Surgery“[Title/Abstract] OR „Obesity Surgery“[Title/Abstract]
OR „Metabolic surgery“[Title/Abstract] OR „gastric bypass“[Title/Abstract] OR „gastric
banding“[Title/Abstract] OR „gastric band“[Title/Abstract] OR „gastric
sleeve“[Title/Abstract] OR „sleeve gastrectomy“[Title/Abstract] OR „duodenojejunal
bypass“[Title/Abstract] OR „ileal interposition“[Title/Abstract] OR „biliopancreatic
diversion“[Title/Abstract]
OR „bilio-pancreatic diversion“[Title/Abstract] AND „Diabetes“[Title/Abstract] NOT
(review OR comment OR letter) AND (randomized controlled trial OR controlled study
OR control group OR observational study OR matched study) NOT (animal
[Title/Abstract] OR rat [Title/Abstract] OR rats [Title/Abstract] OR mice [Title/Abstract])



Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

HbA1c

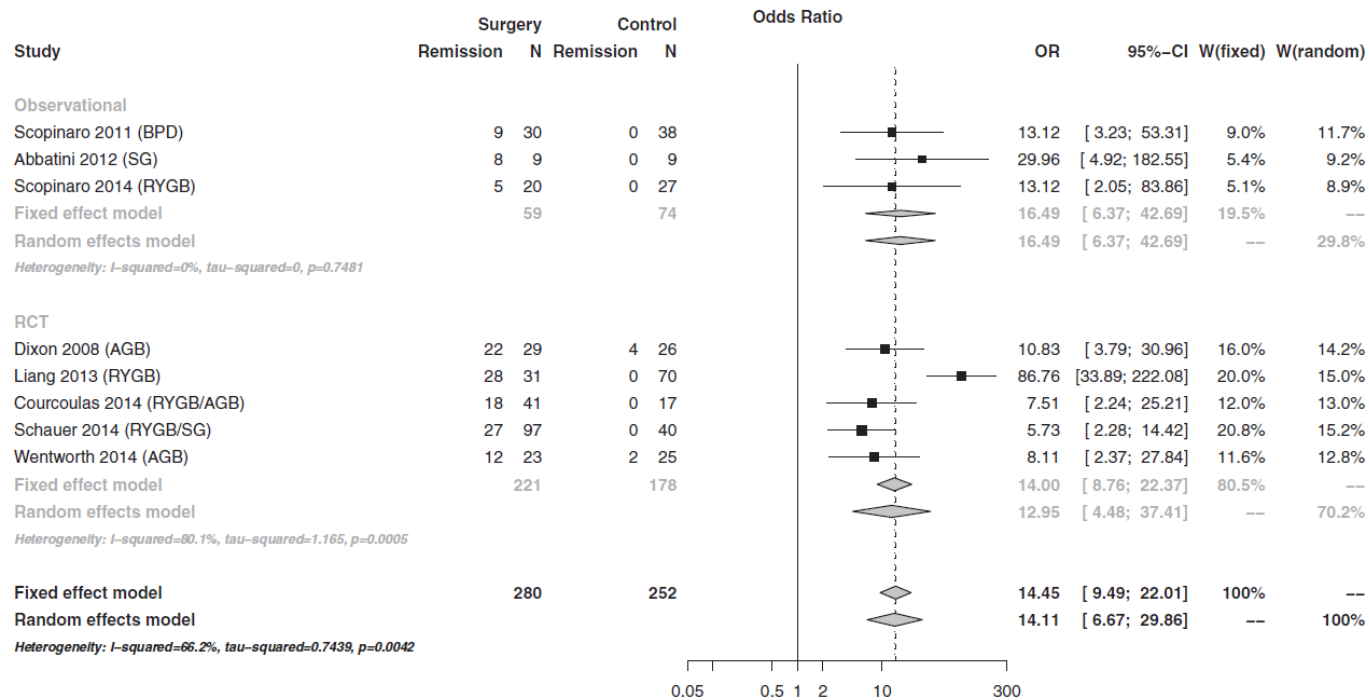




Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

Diabetes-Remission

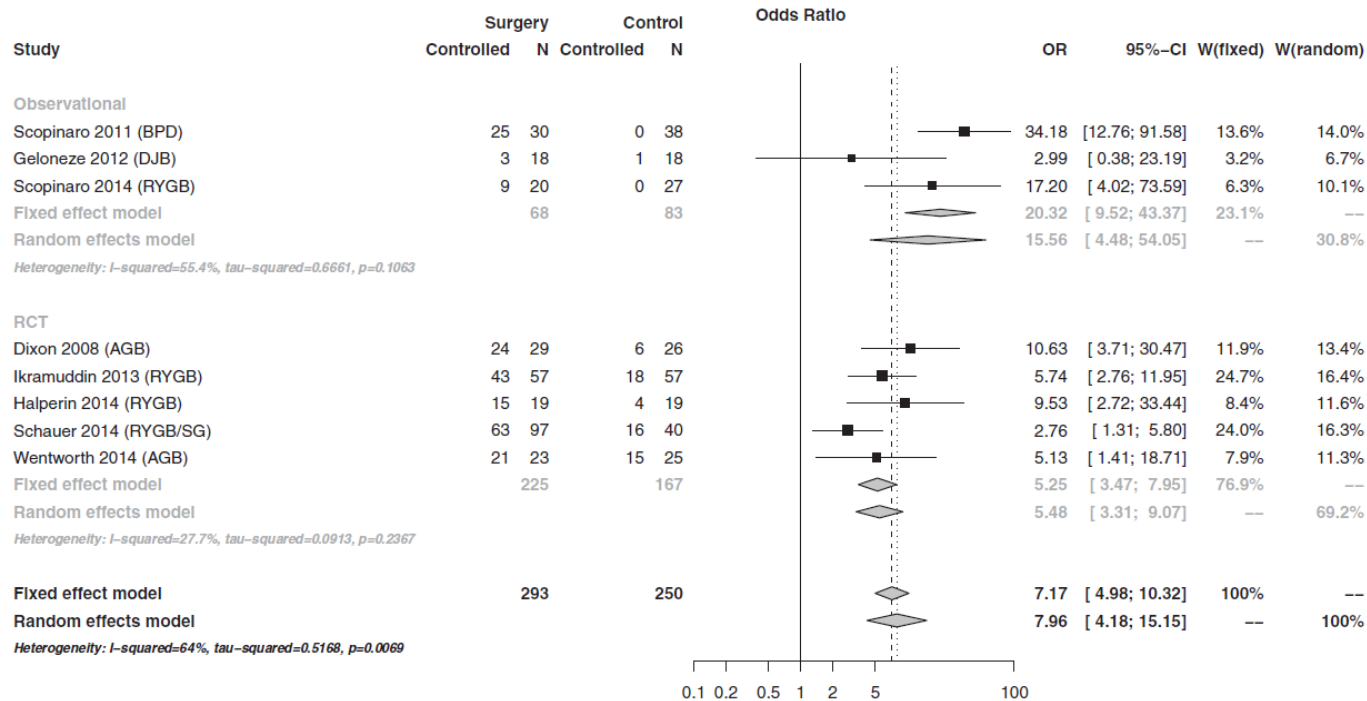




Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

Glykämische Kontrolle

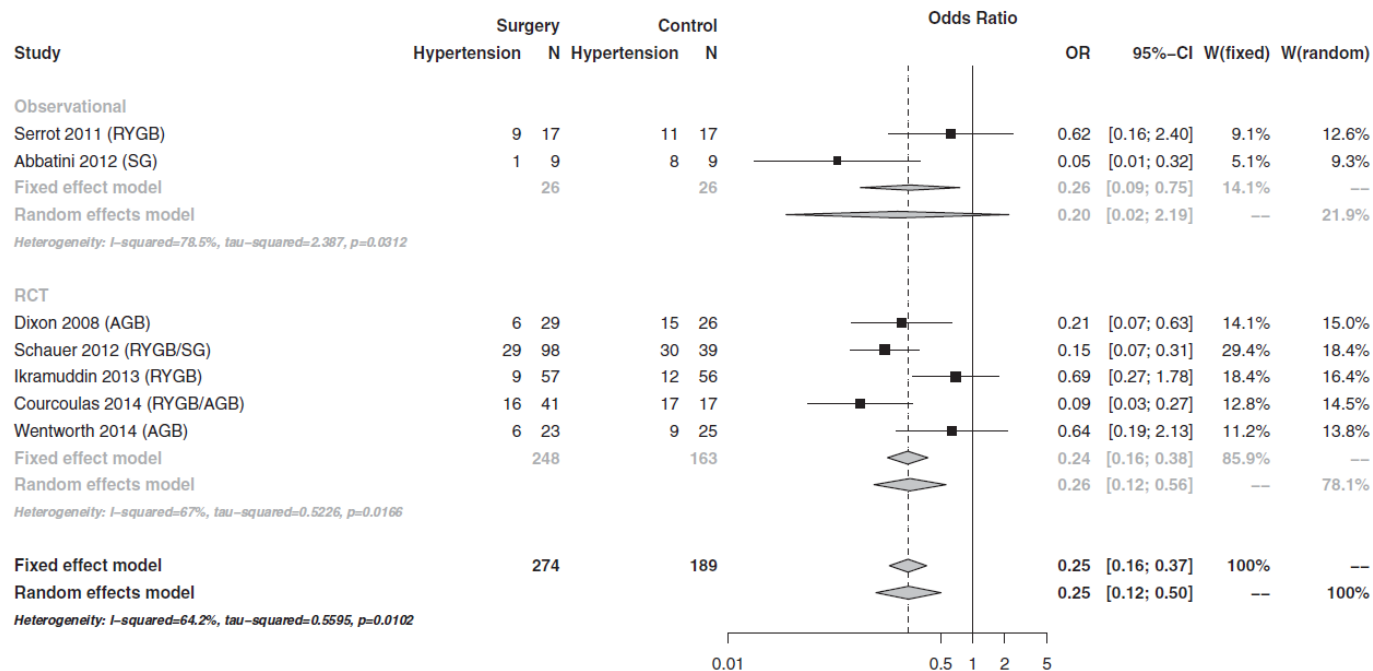




Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

Arterielle Hypertonie

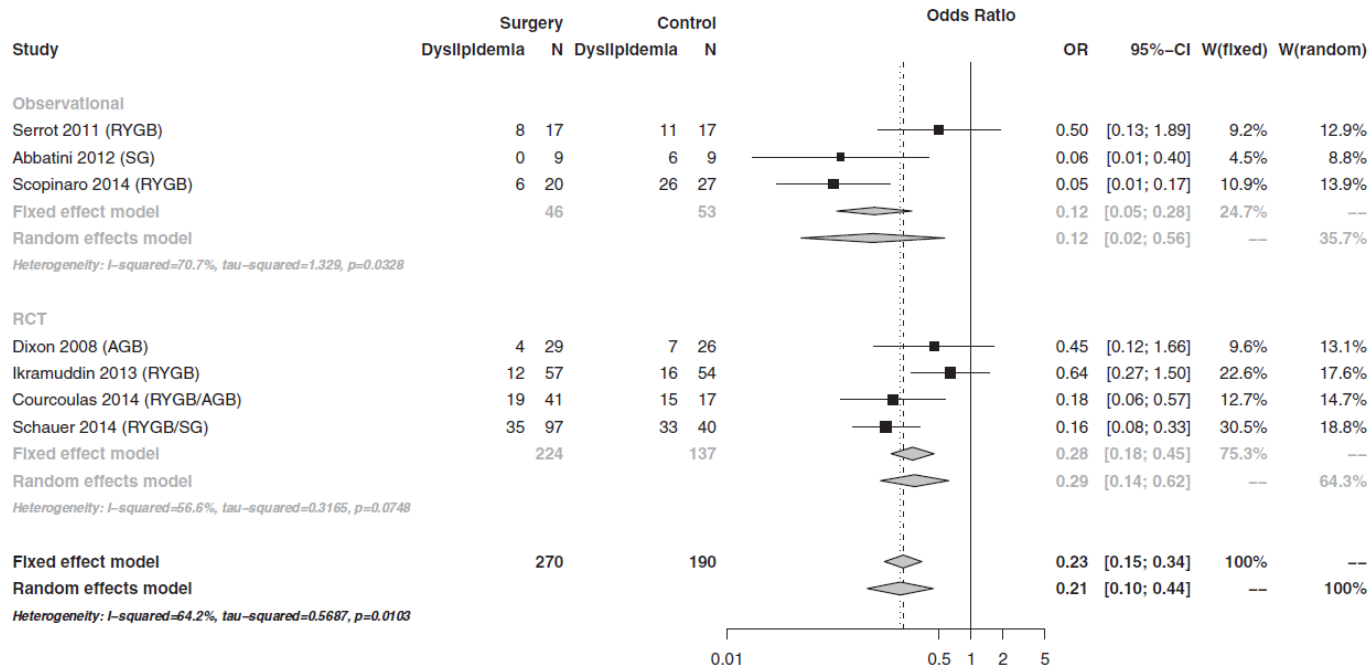




Diabeteschirurgie

Meta-Analyse (Evidenzlevel Ia)

Dyslipidämie





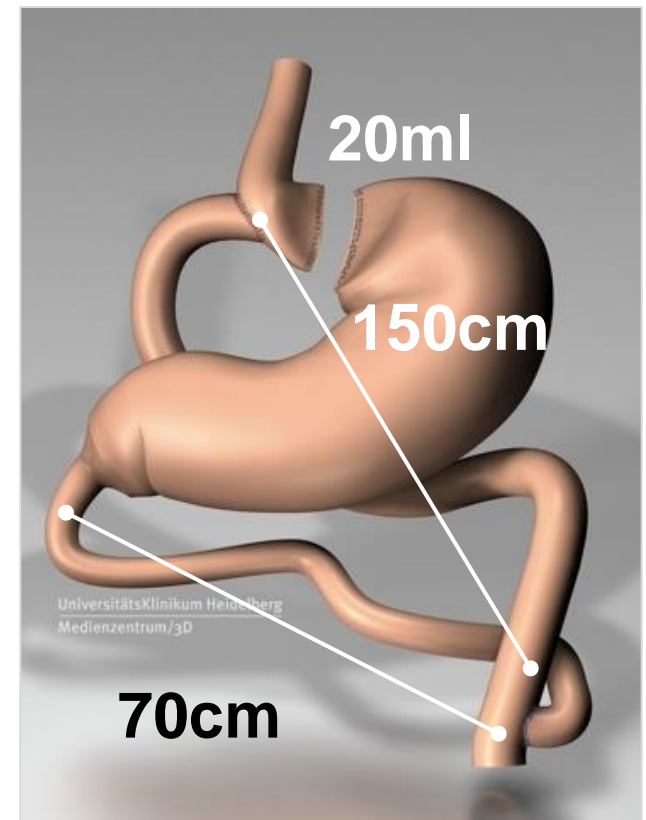
DiaSurg 1-Studie

(DRKS00004605)



DiaSurg 1-Studie Design

- Prospektive Kohortenstudie
- $n = 20$ (10 m, 10 f)
- Roux-en-Y Gastric Bypass





DiaSurg 1-Studie

Einschlusskriterien

- Diabetes mellitus Typ 2
- Body Mass Index 25 – 35 kg/m²
- Alter 18 – 70 Jahre
- Insulin > 3 Monate
- HbA1c > 7.0%
- Stimuliertes C-Peptid >1.5 ng/ml



DiaSurg 1-Studie

Ergebnisse

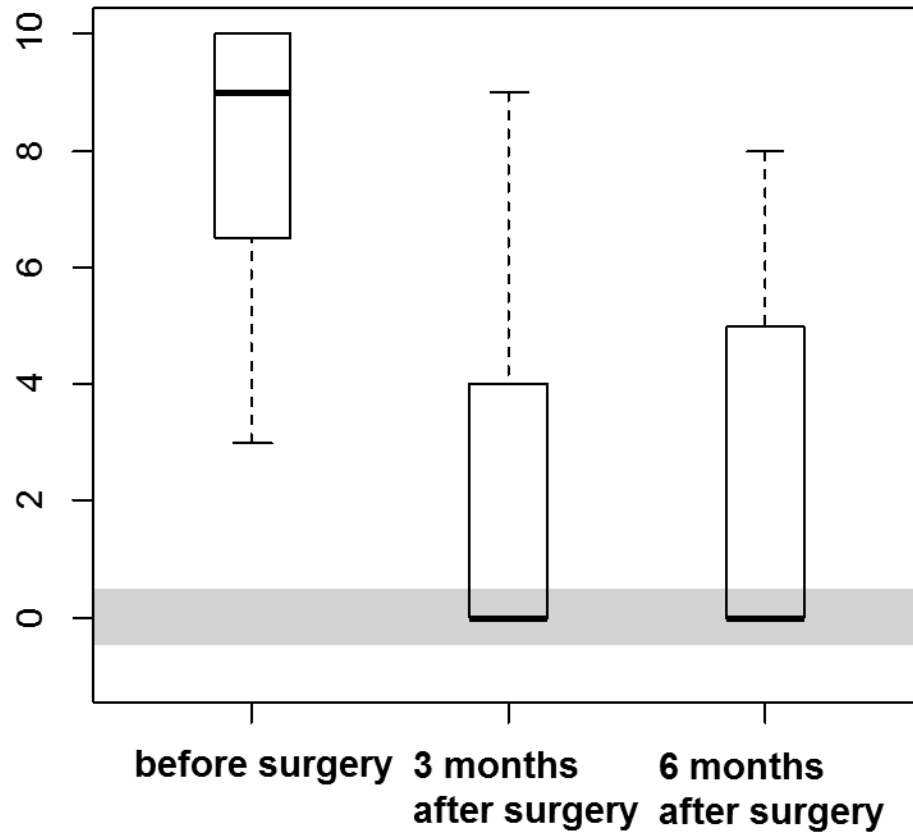
- Follow-up: 22,1 ± 5,0 (13-34) Monate
- BMI vor OP: 32,9 ± 2,36 (28,4-35,0) kg/m²
- BMI nach OP: 24,6 ± 5,84 (20-28,1) kg/m²
- EWL: 108 ± 35,8 (67,3-169,4) %
- HbA1c vor OP: 8,4 ± 1,2 (7-10,9) %
- HbA1c nach OP: 6,9 ± 1,9 (5,1-9,3) %
- Insulinfrei: 68% (13 von 19 Patienten)
- < 20% Insulin: 95% (18 von 19 Patienten)



Neuropathie

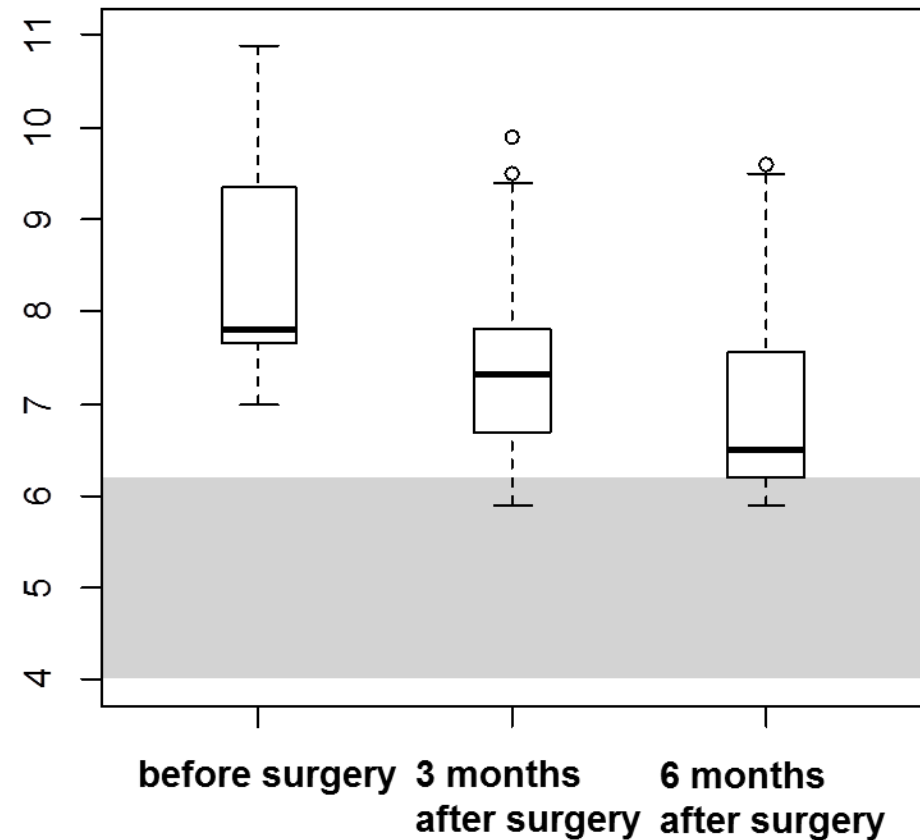
n = 12

NSS



HbA1c

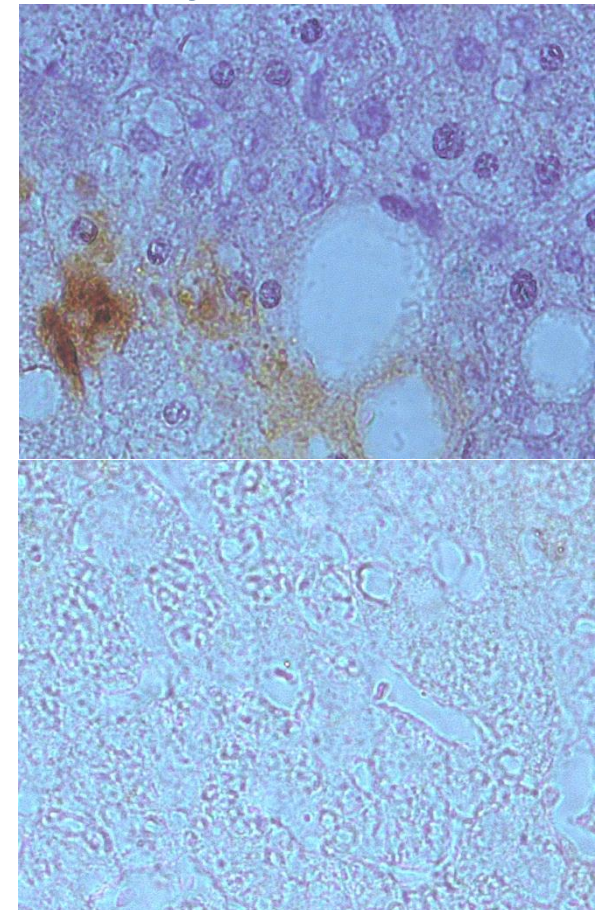
n = 20





Neuropathie und oxidativer Stress

Nitrotyrosin Leber

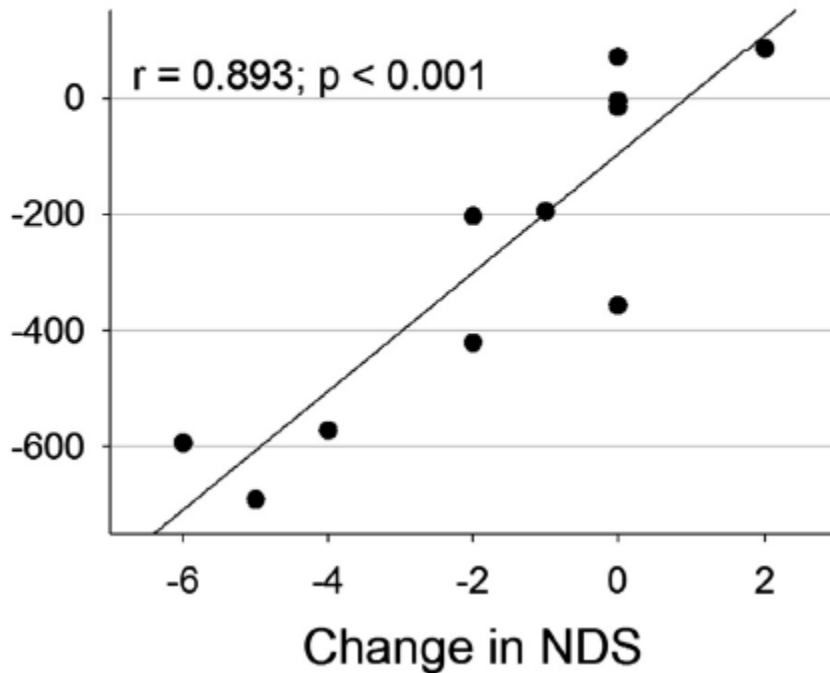


PräOP

PostOP

Müller-Stich et al., SOARD (2015)

A Change in Nitrotyrosine and Neuropathy
Deficit Score 6 Months after RYGB

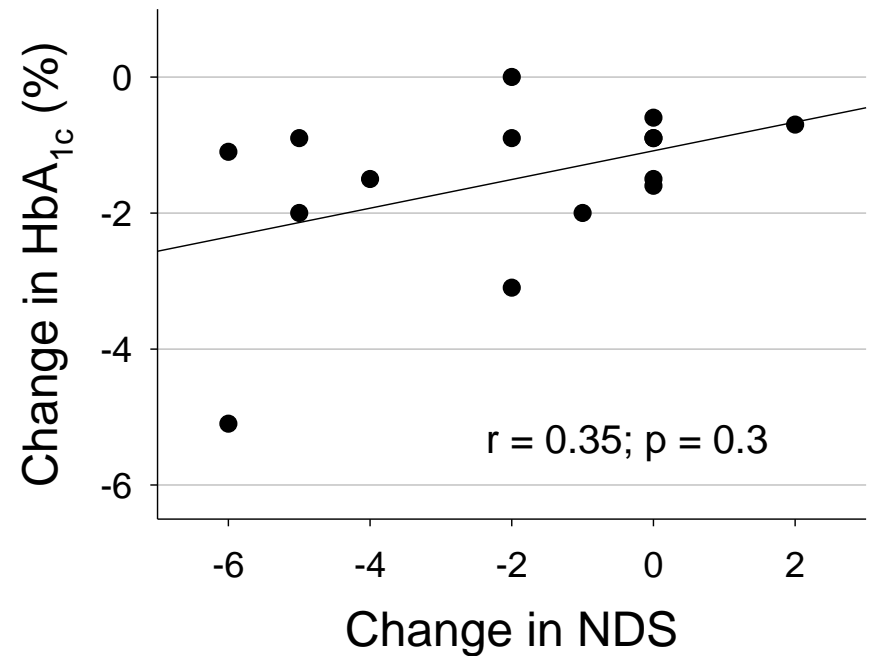
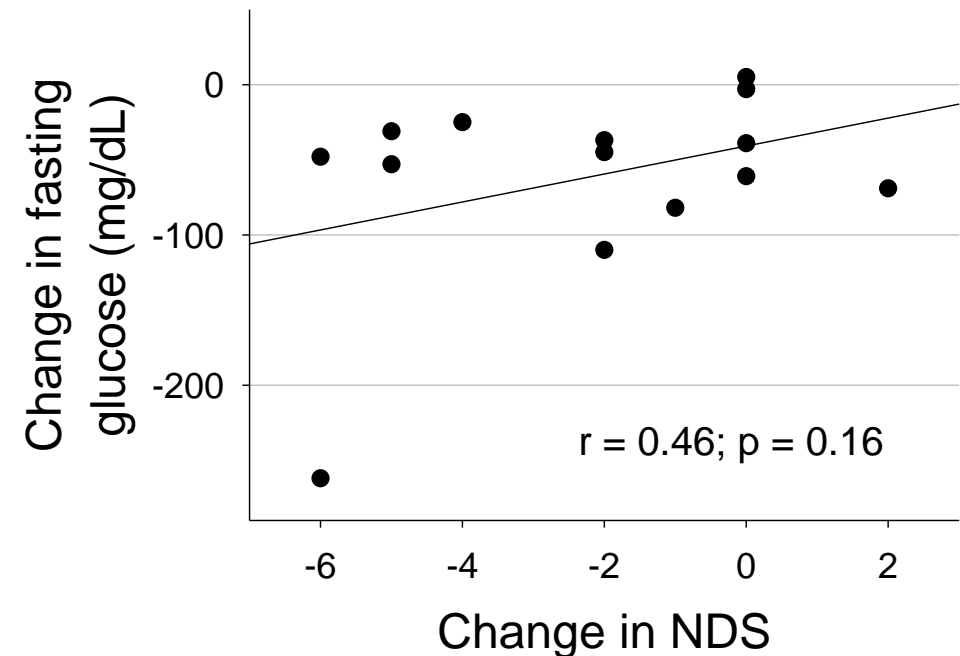




Neuropathie und glykämische Kontrolle

Fasting glucose 6 Months
after RYGB

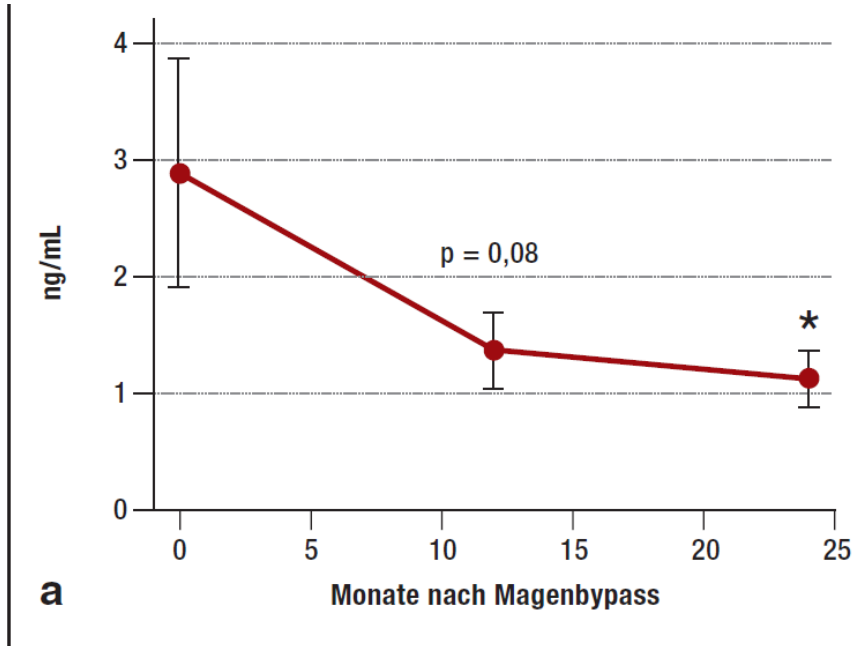
HbA_{1c} 6 Months after RYGB



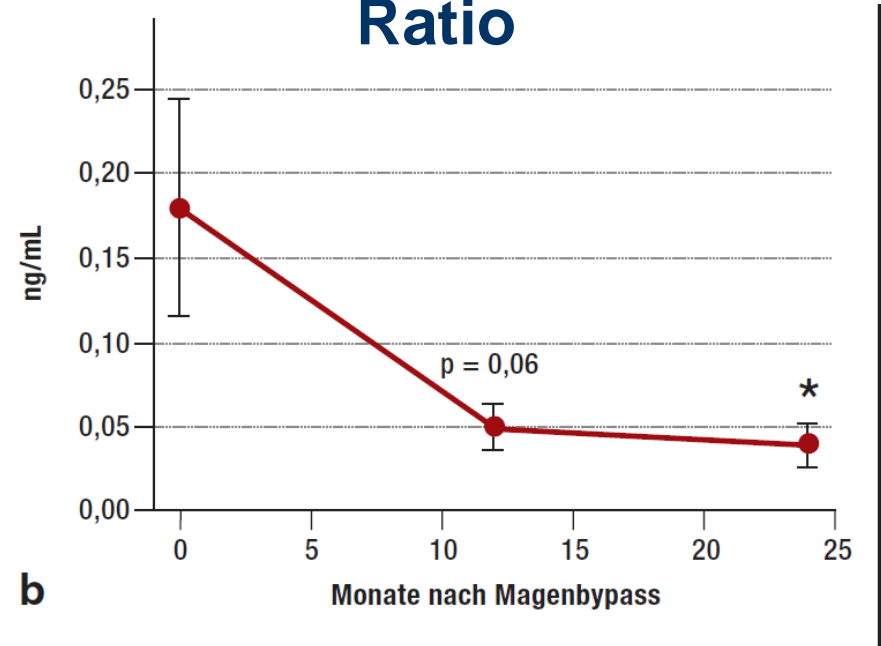


Nephropathie

Albumin/Kreatinin Ratio



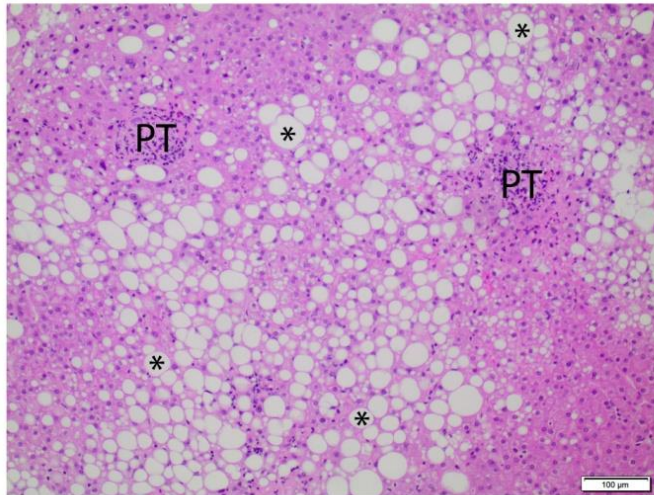
HMW-Adiponektin/Kreatinin Ratio



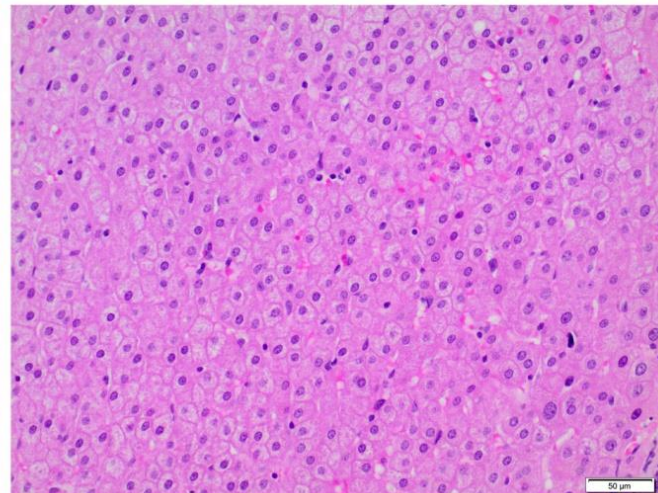
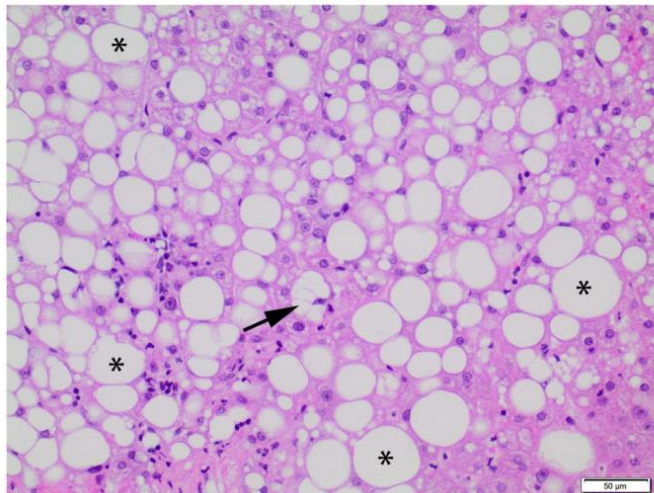
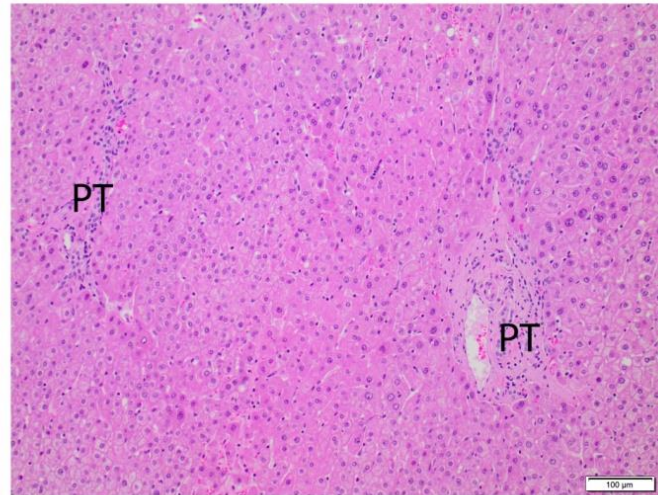


Hepatopathie

liver PreOP



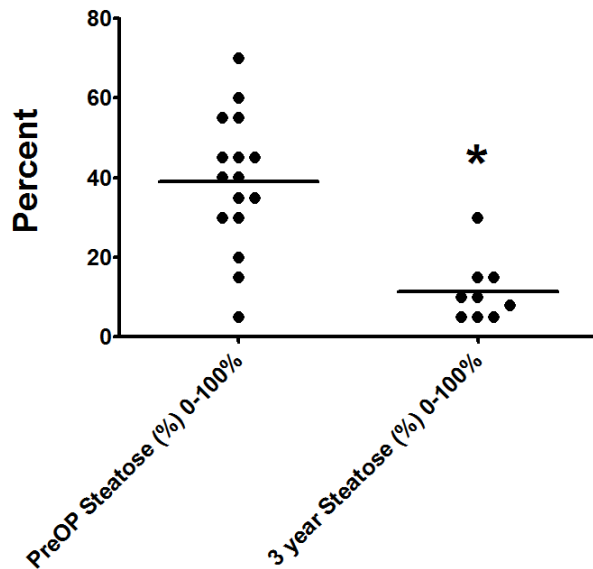
liver 36 months



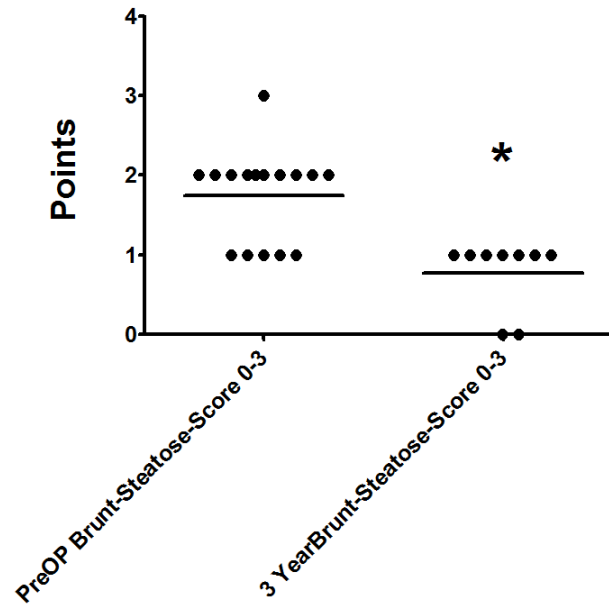


Hepatopathie Leberhistologie

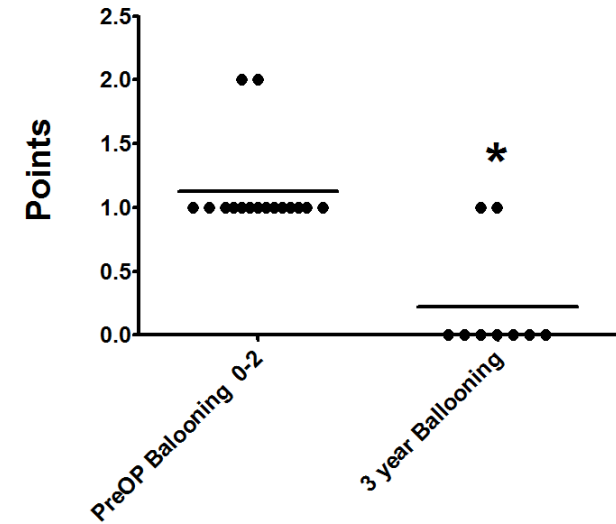
Steatosis



Brunt Steatosis Score



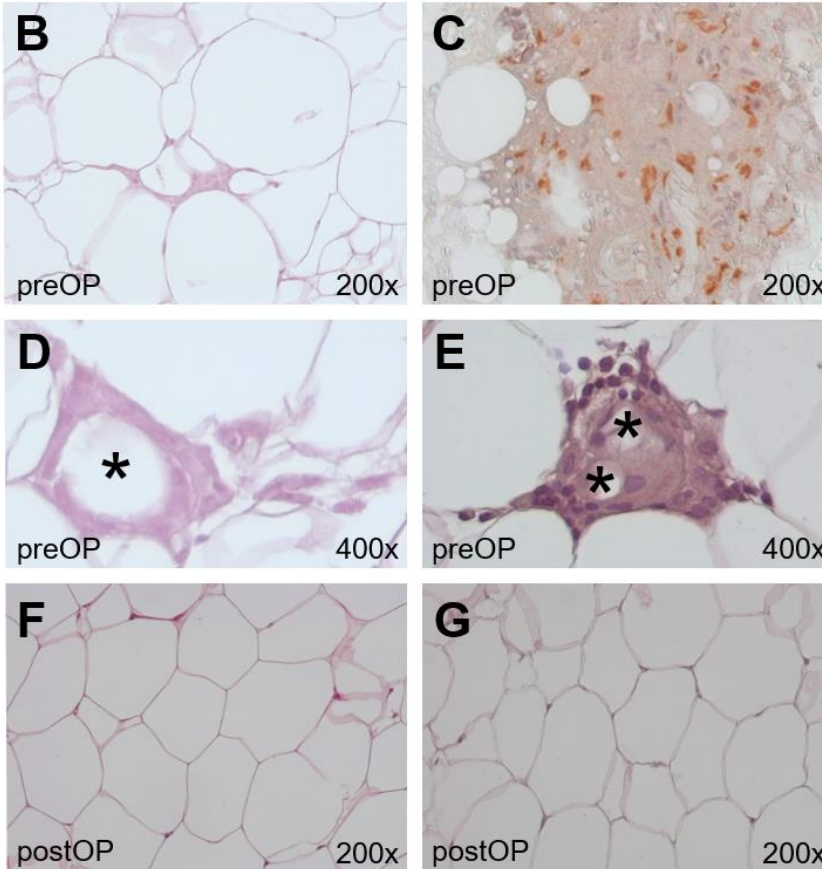
Ballooning of Hepatocytes





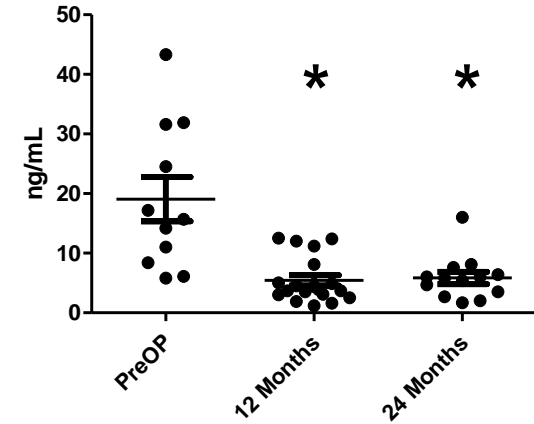
Fettgewebefunktion

Hematoxylin & Eosin Stain

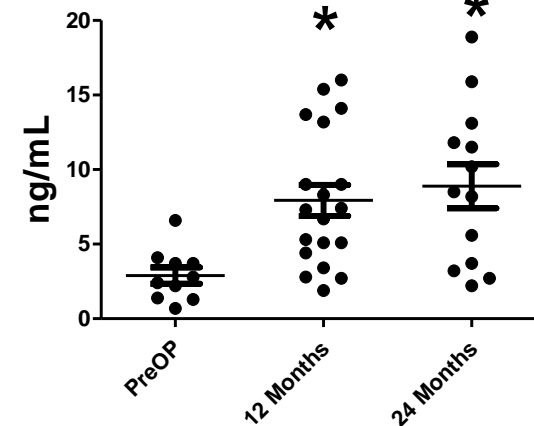


CD68 Immunostaining

Serum Leptin



Serum Adiponektin

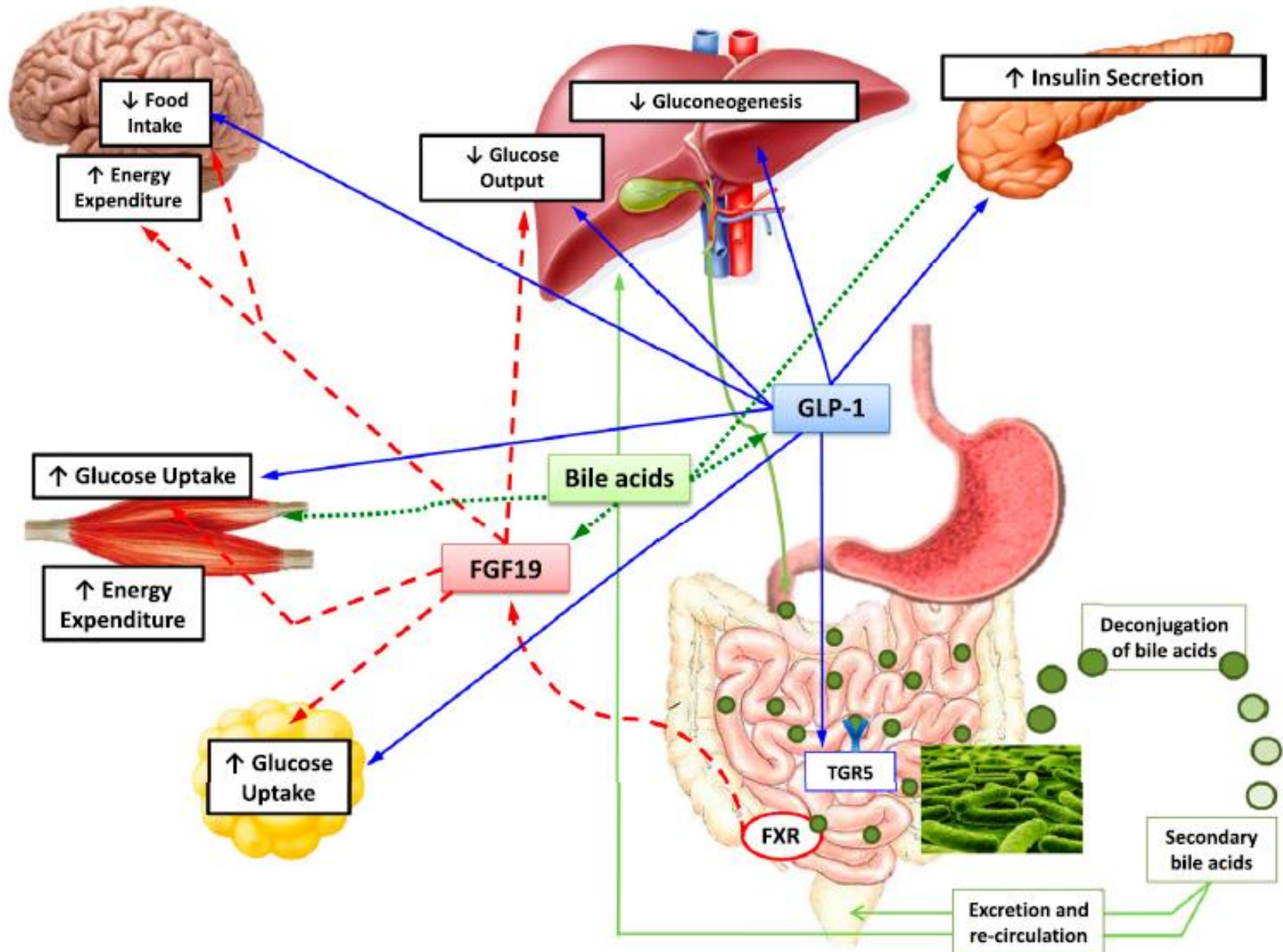




Was fehlt?

Mechanismen ?



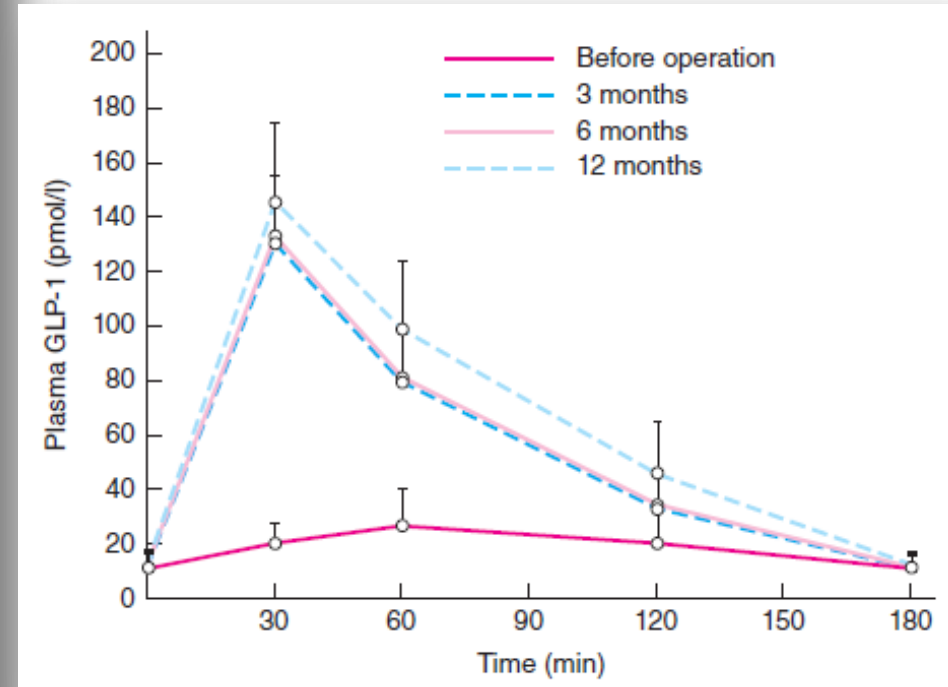
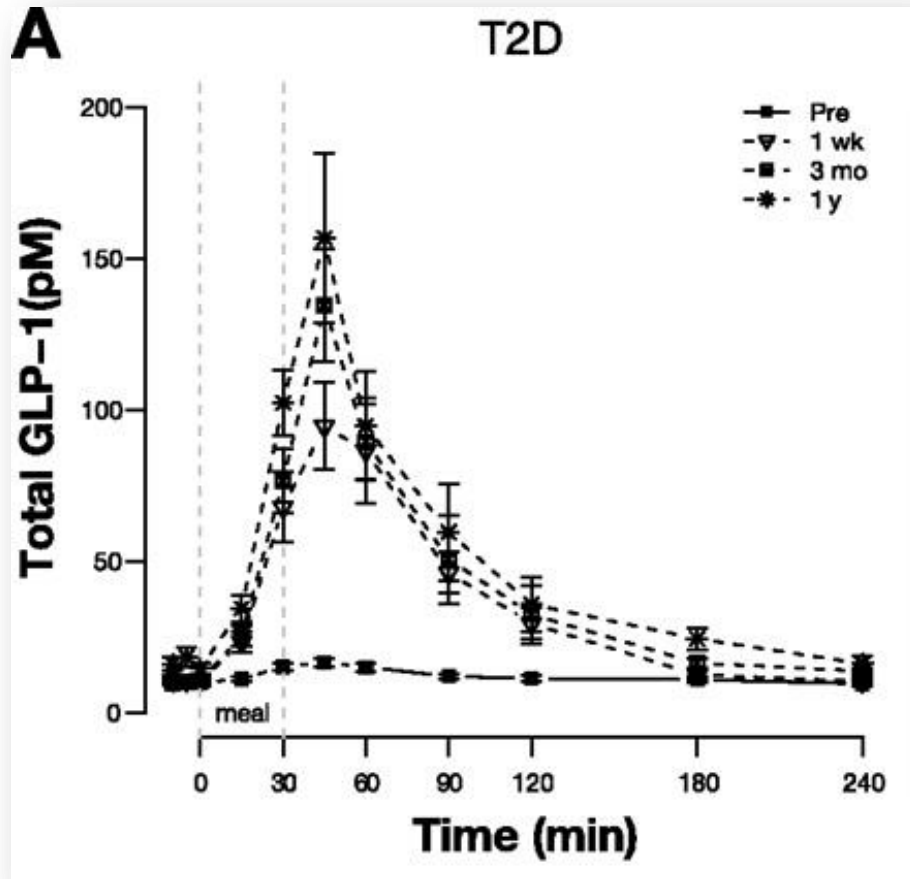




Erhöhte Inkretin-Antwort

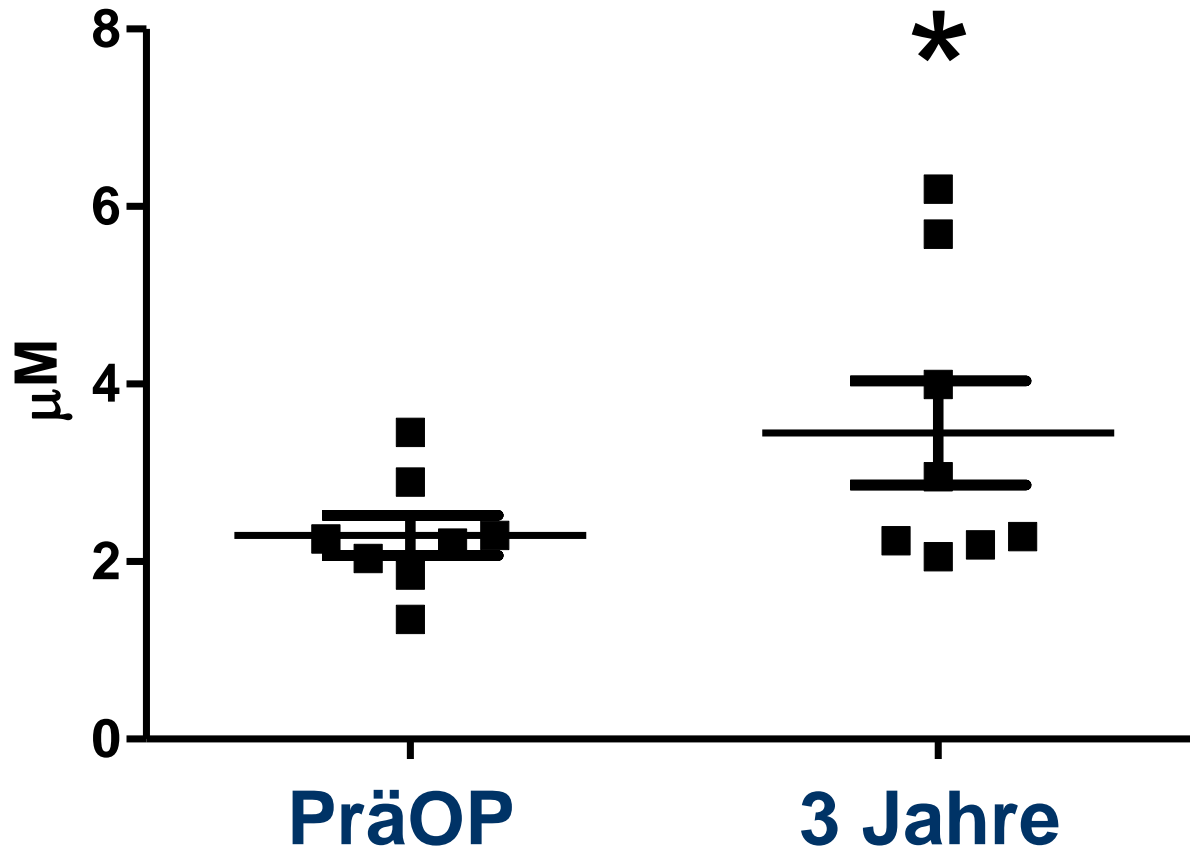
Roux-Y Gastric Bypass

Sleeve Gastrektomie





Erhöhte Gallensäuresekretion

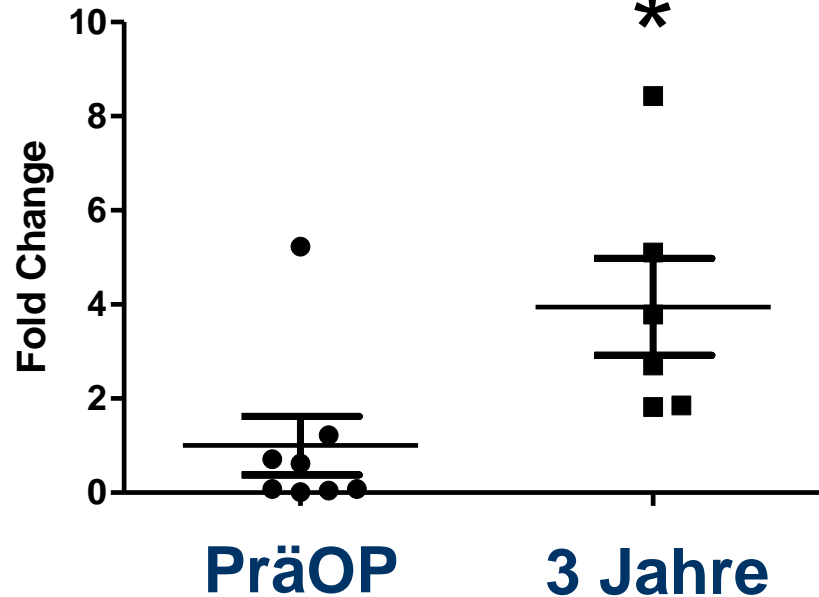


* Indicates $p < 0.05$

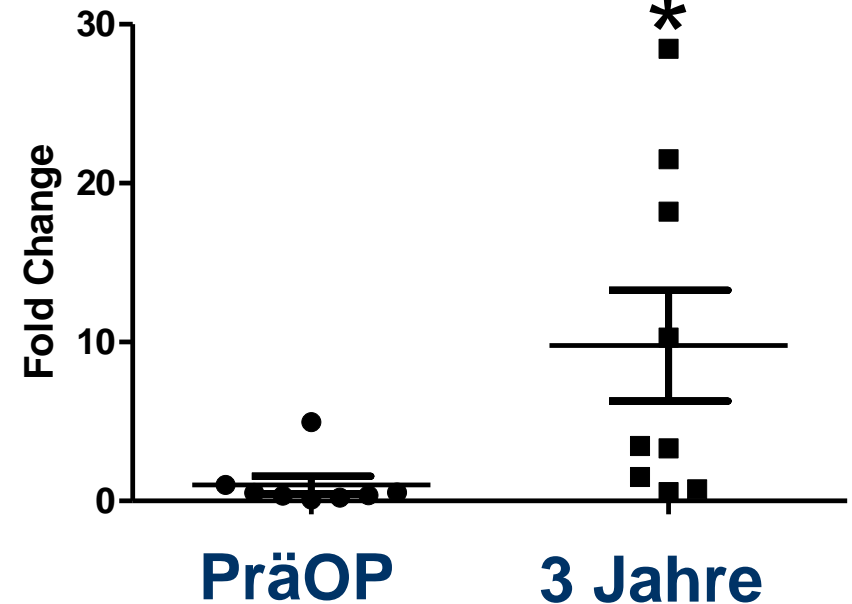


Erhöhte Gallensäuresekretion (zelluläre Ebene)

CYP7A1 mRNA



CYP8B1 mRNA



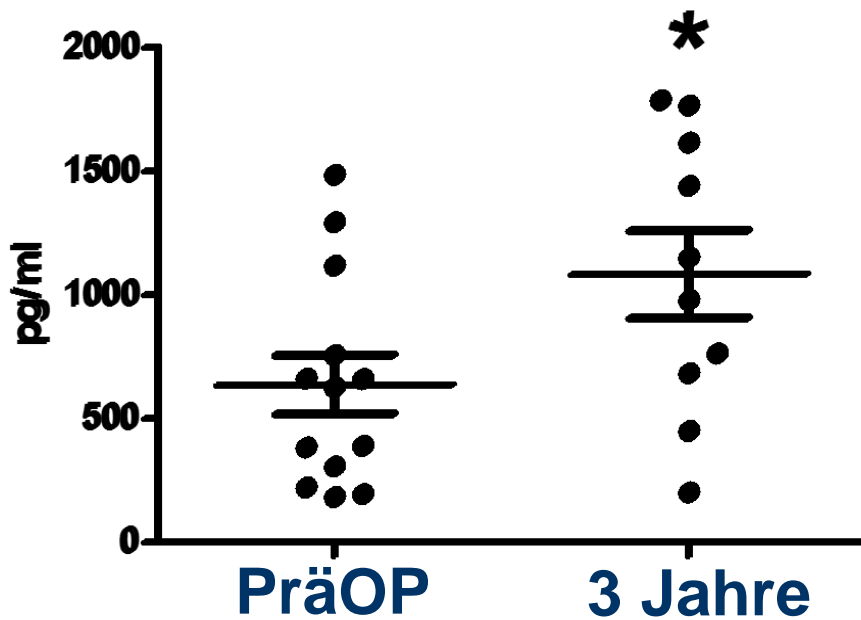
→ Erhöhte Gallensäureproduktion

* Indicates $p < 0.05$

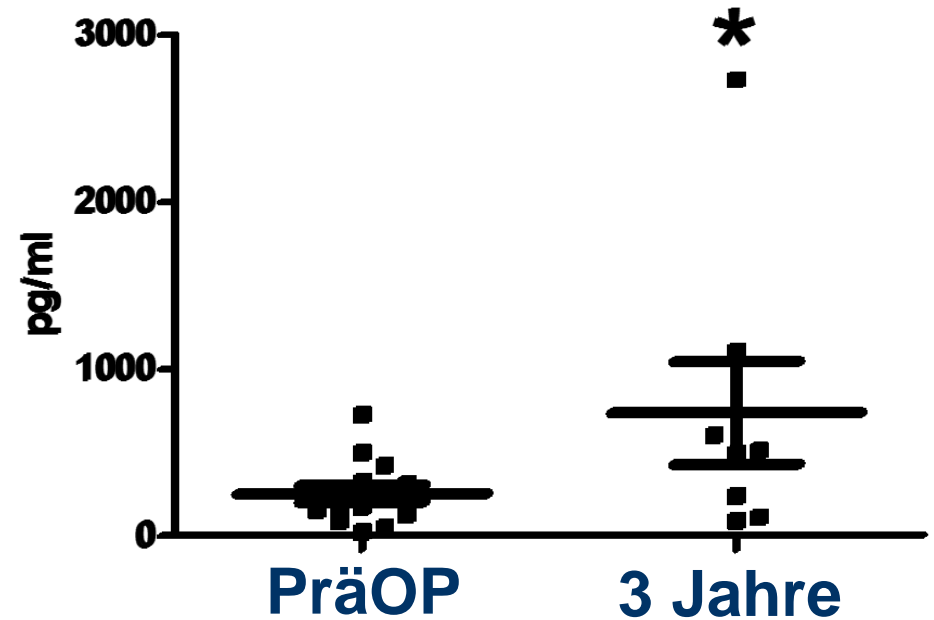


Erhöhte FGF-19 und FGF-21-Sekretion

FGF - 19



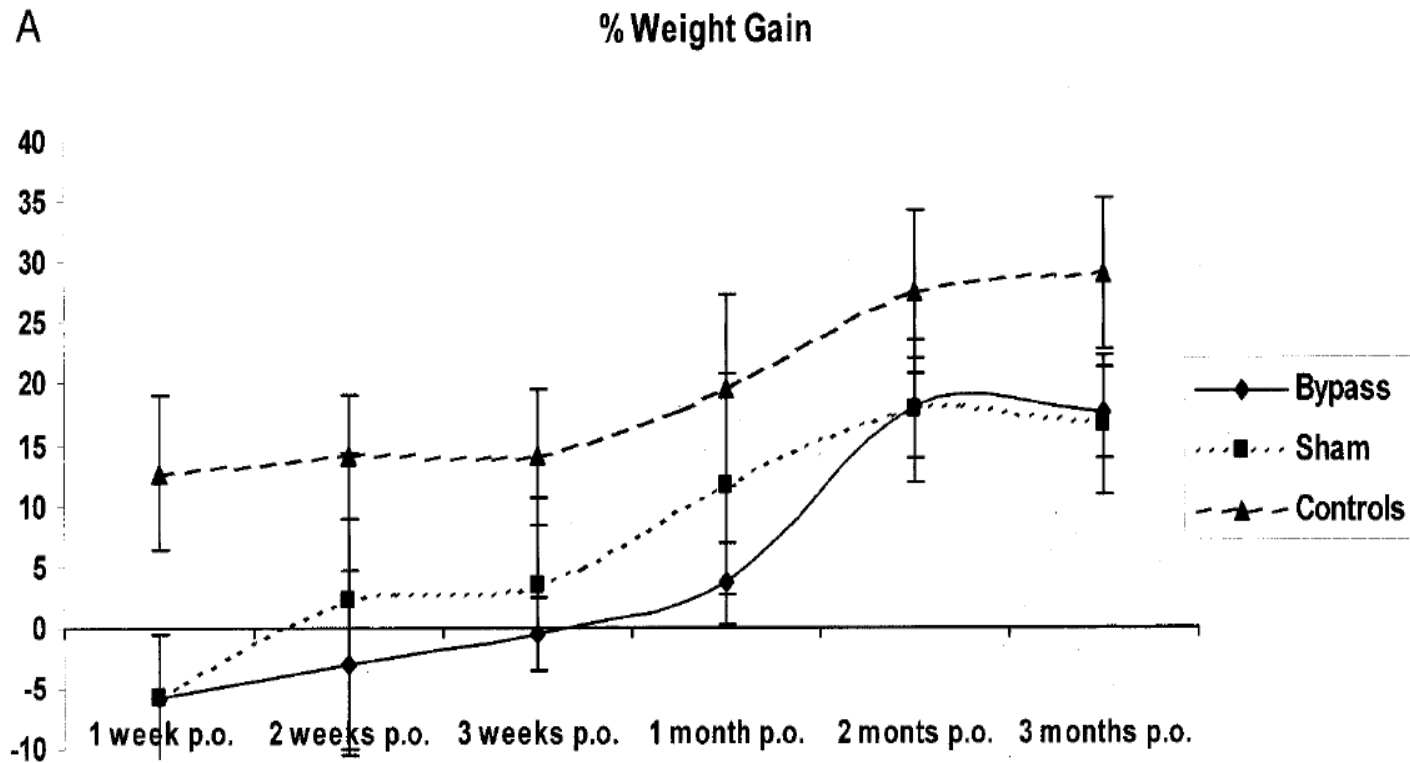
FGF - 21



* Indicates $p < 0.05$



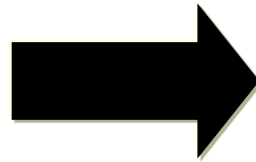
Einfluss auf Glukosetoleranz





Klinische Beobachtung

präoperativ



postoperativ



"I Don't Enjoy Burgers Anymore" Syndrome

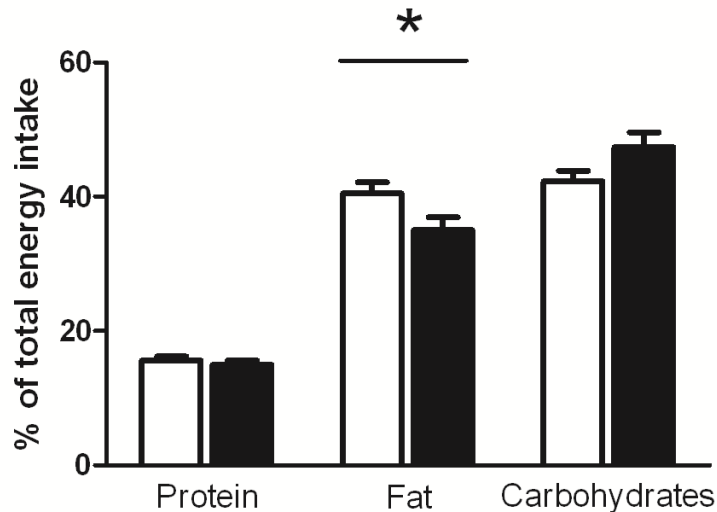
Paradox - Diäten erhöhen die Präferenz für fett-und zuckerreiche Speisen



Veränderung Nahrungspräferenz

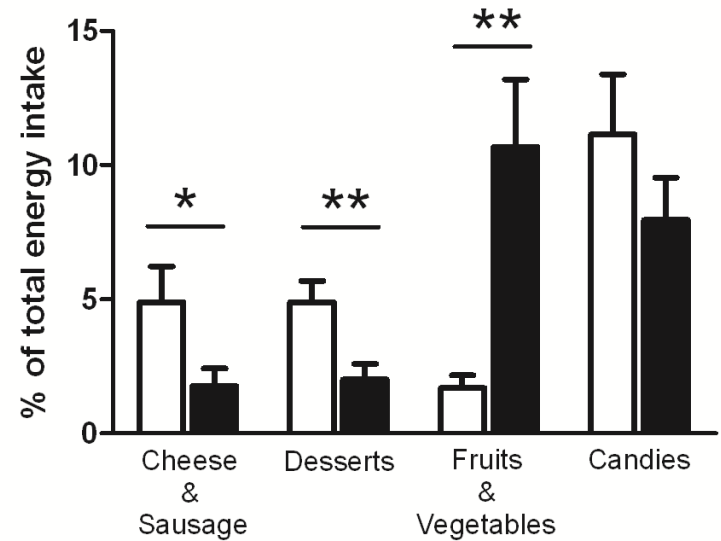
A

■ Gastric bypass (n=9)
□ Vertical-banded gastroplasty (n=7)



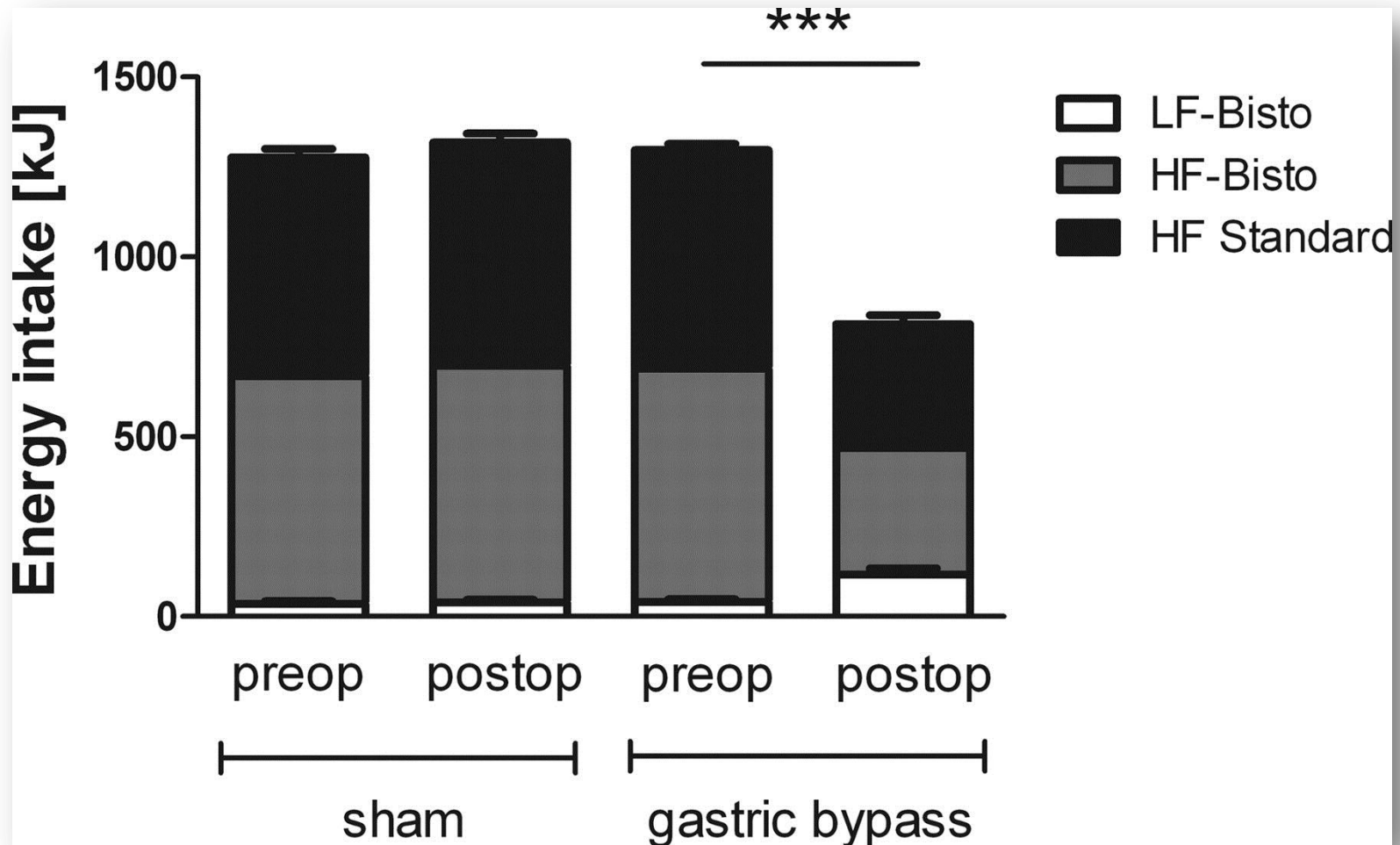
B

■ Gastric bypass (n=9)
□ Vertical-banded gastroplasty (n=7)





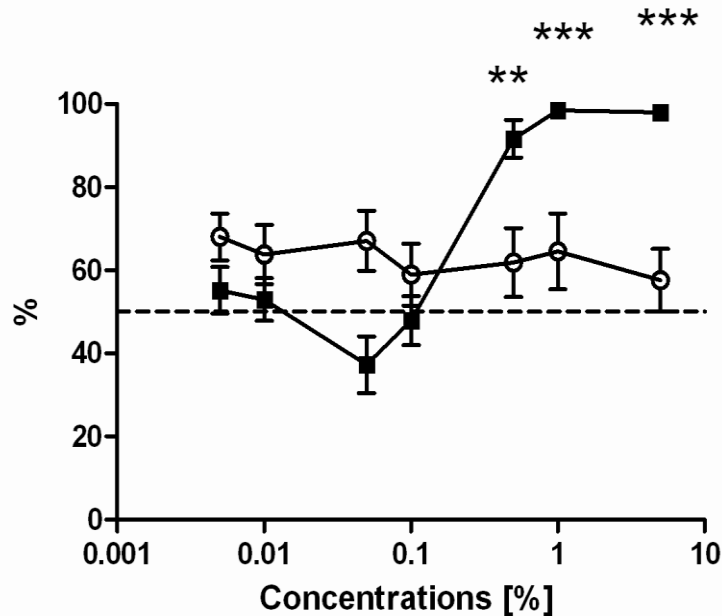
Reduzierte Fettaufnahme



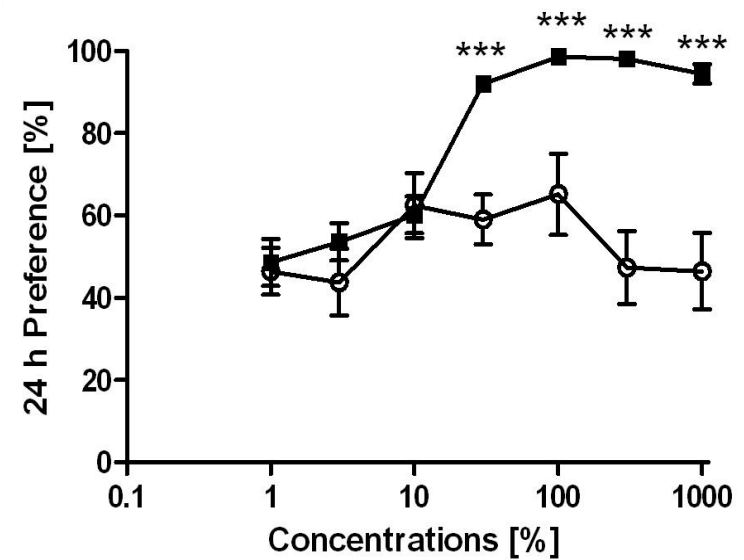


Veränderung Nahrungspräferenz

Intralipid© Präferenz



Sucrose Präferenz



Bueter M, Le Roux CW, Lutz TA et al, *Am J Physiology* 2011

Bueter M et al., *Physiology & Behavior* 2011



University of
Zurich ^{UZH}

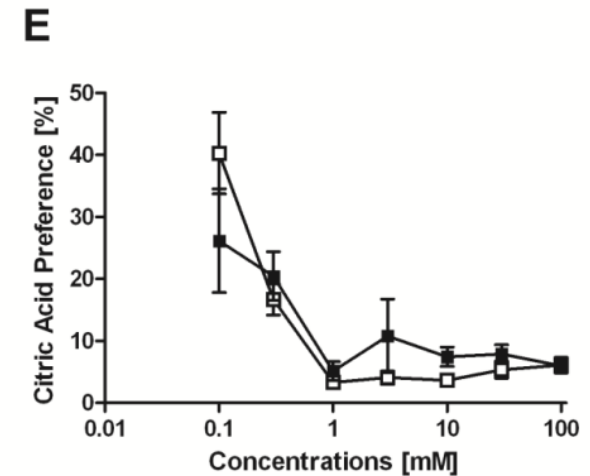
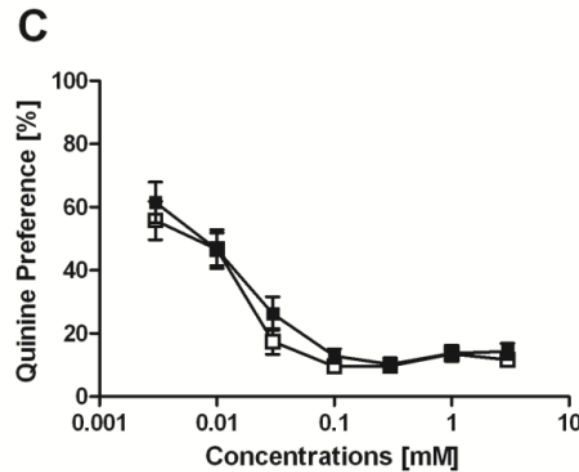
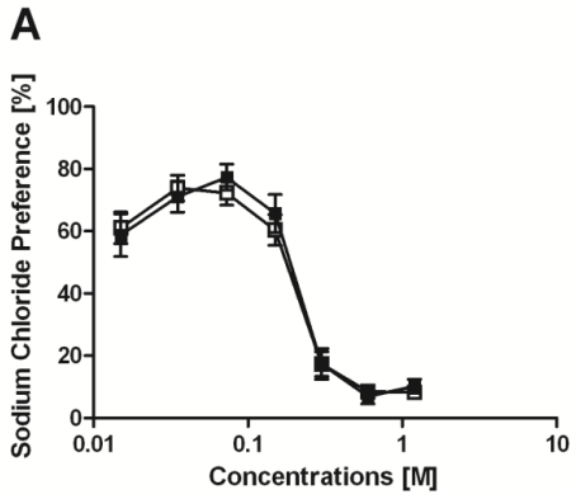


...aber nicht für alle Geschmacksqualitäten!

salzig

bitter

sauer



Bueter M et al., *Physiology & Behavior* 2011

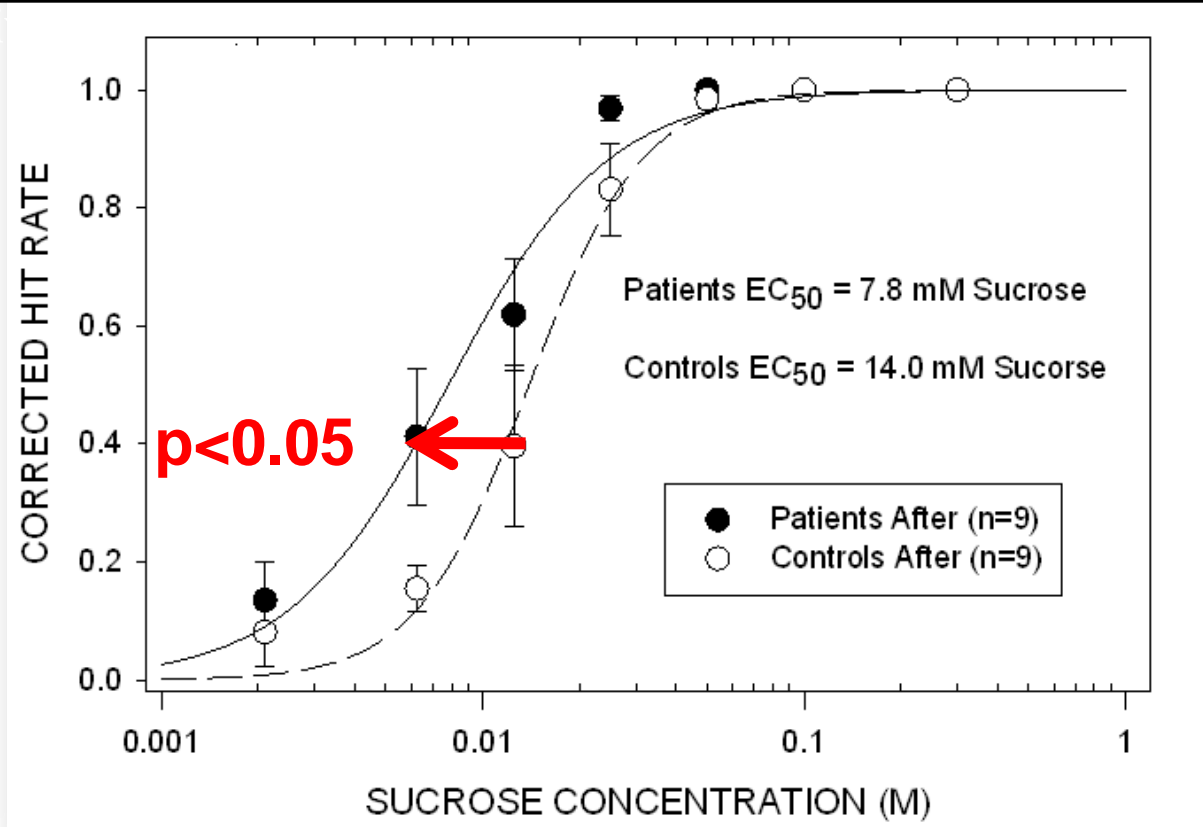


University of
Zurich^{UZH}

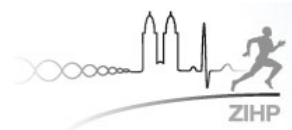


Geschmackssinn

RYGB Patienten schmecken niedrigere Zuckerkonzentrationen

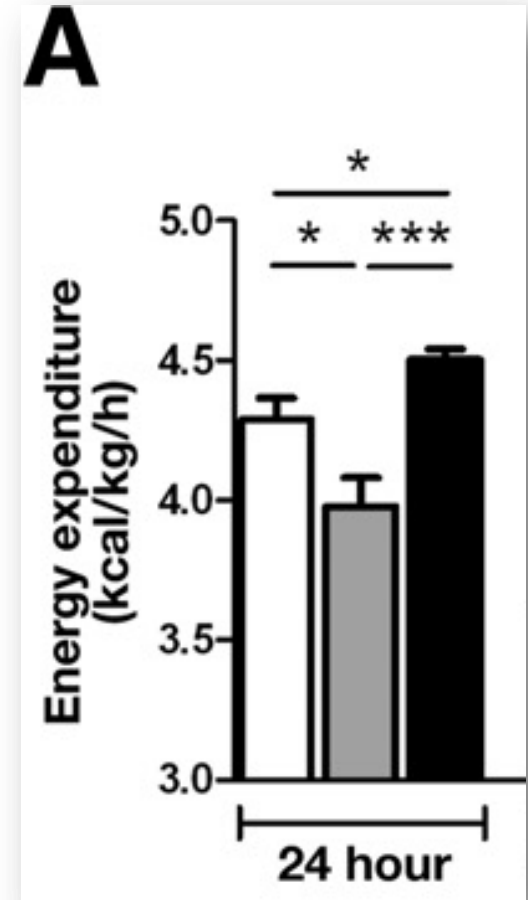
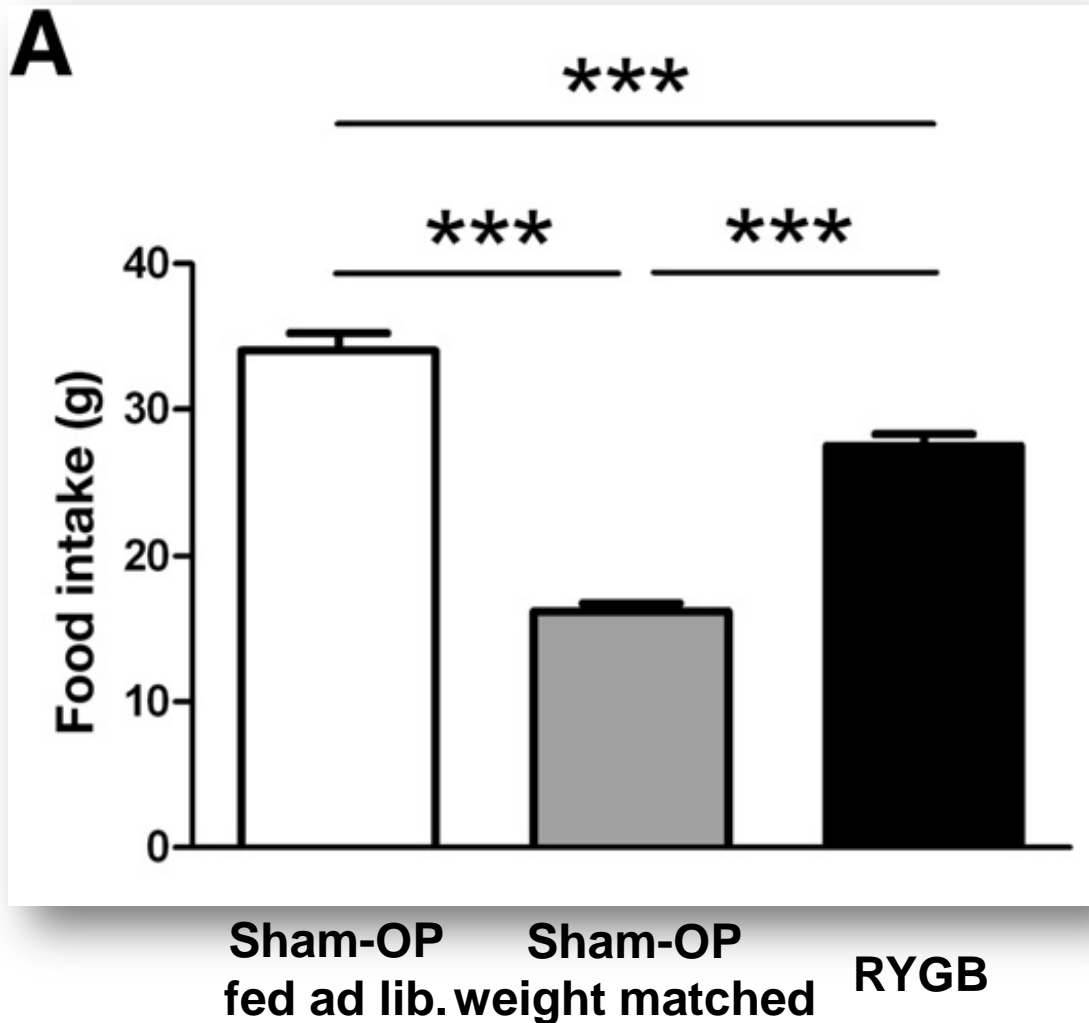


Bueter M et al. Physiology & Behavior (2011)



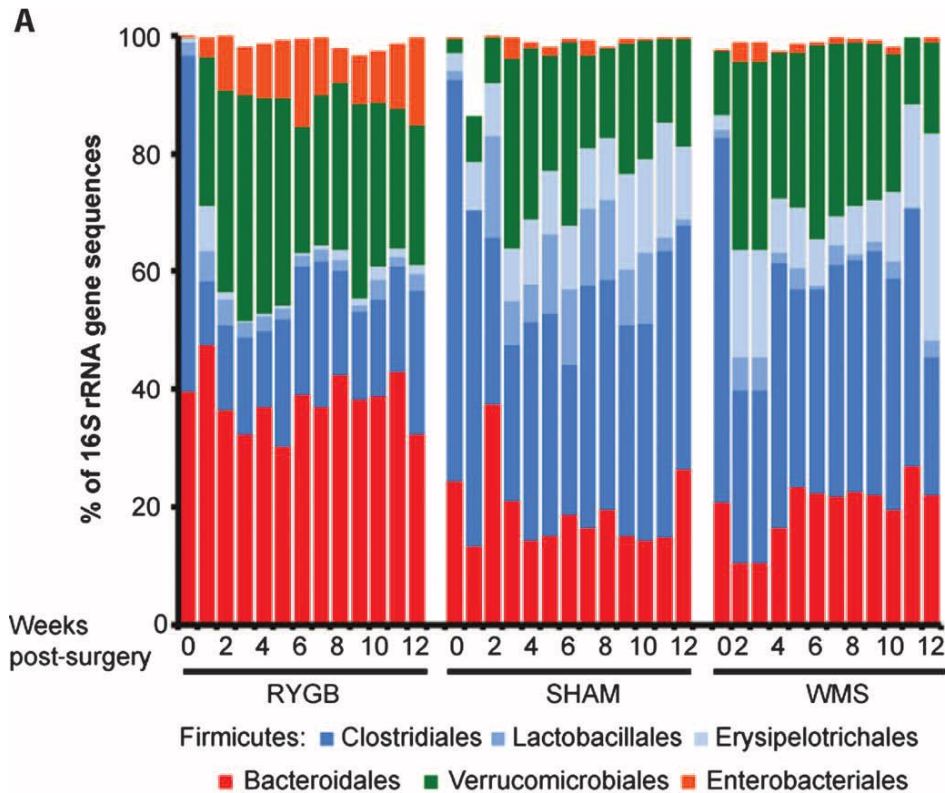


Erhöhter Energieumsatz

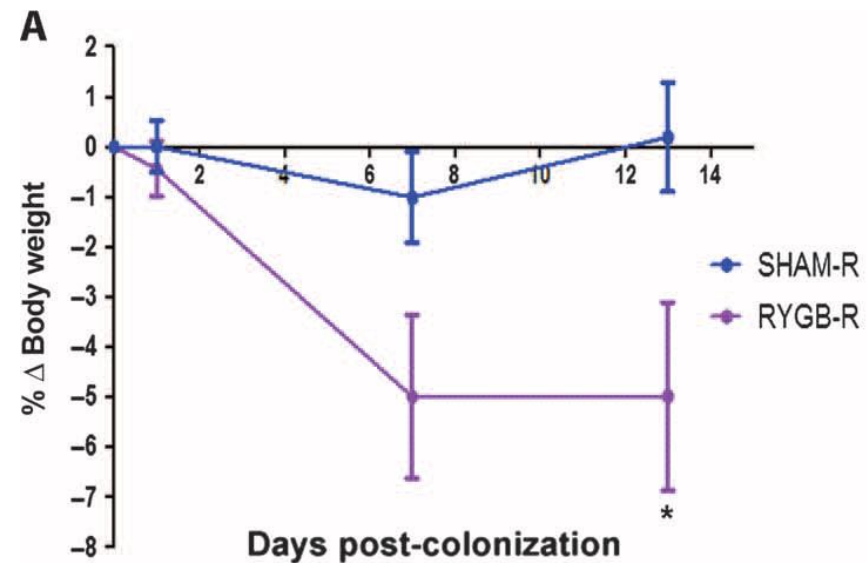




Mikrobiom



Stuhltransfer von RYGB-Mäusen Führt zu Gewichtsverlust





Was fehlt noch ?

Harte Endpunkte

+

Langzeit-Follow-up

+

Multizentrische Studien

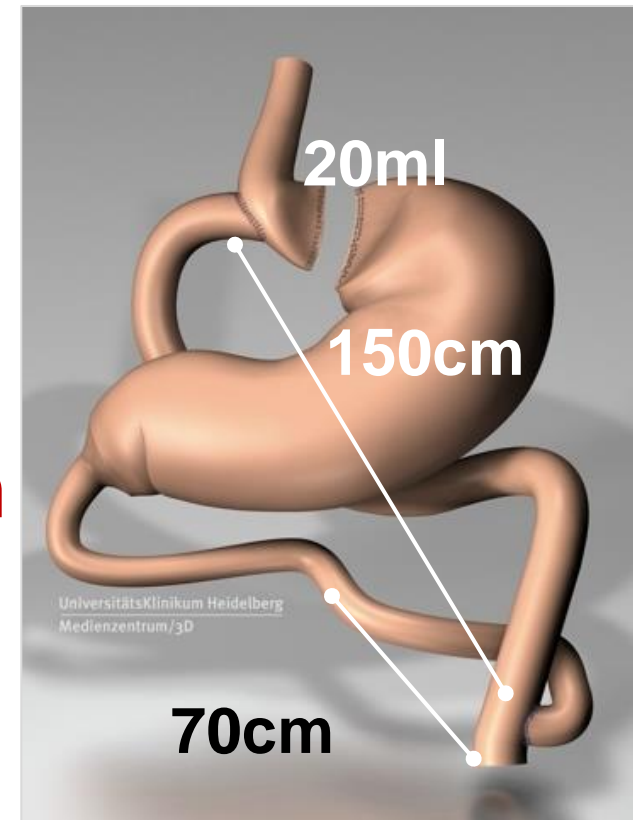




DiaSurg2-Studie **(DRKS00004550)**

Einschlusskriterien

- RCT
- Insulin vs. Magenbypass
- Type 2 Diabetes mellitus (Insulin >3 Mte.)
- **Mikrovaskuläre Komplikation**
- Pankreasrestfunktion
- Alter 30 – 65 Jahre
- BMI 26 – 35 kg/m²





Endpunkte

Primärer Endpunkt

- **Komposit-Endpunkt**

Sekundärer Endpunkt

- **Komplikationen und Mortalität**
- **Diabetes-assoziierte Erkrankungen**
- **Lebensqualität**
- **Kosten**



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 30, 2003

VOL. 348 NO. 5

Multifactorial Intervention and Cardiovascular Disease
in Patients with Type 2 Diabetes

Steno 2 Studie

Patientenselektion

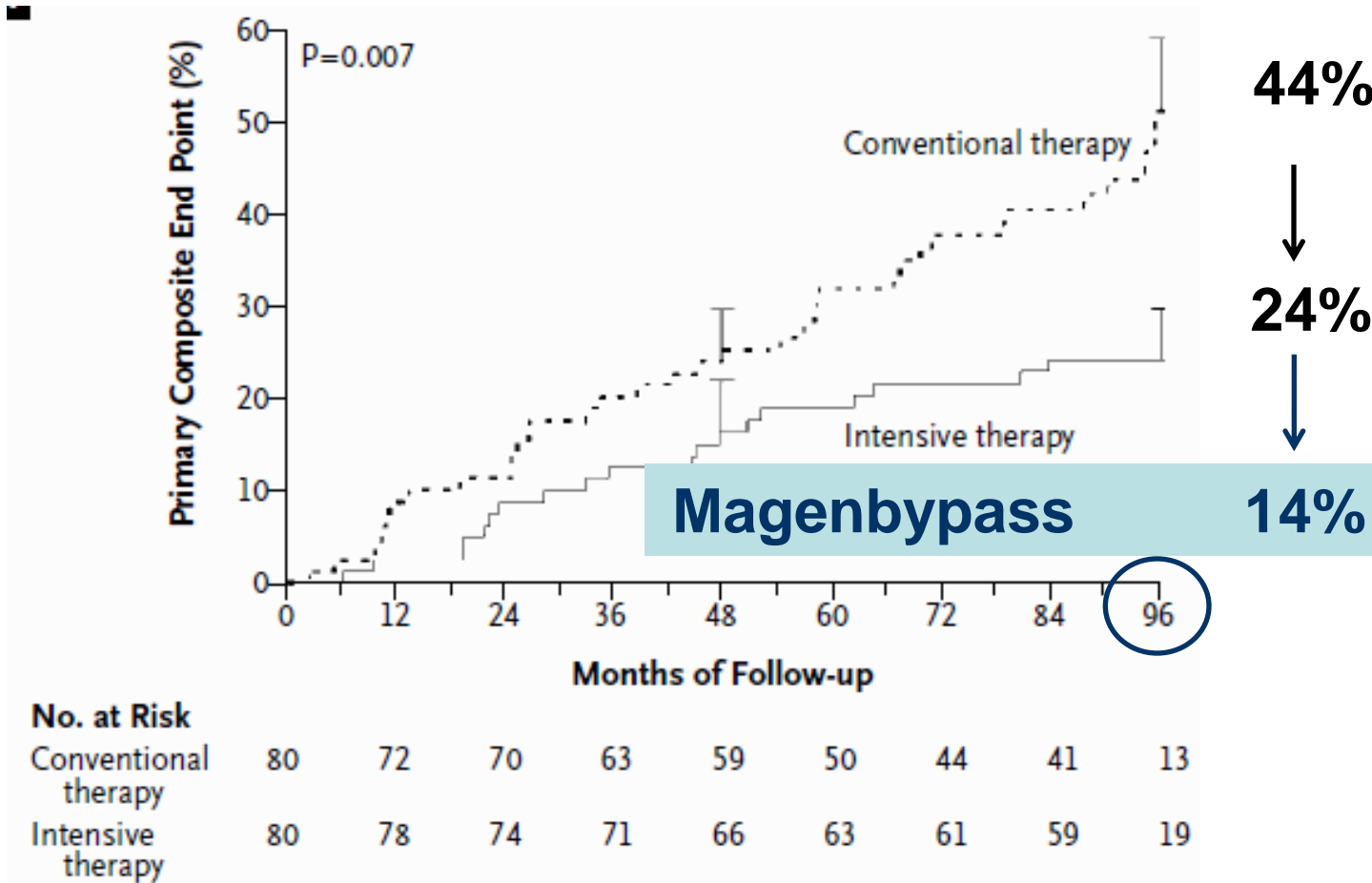
- Neuropathie
- Retinopathie
- Nephropathie

Komposit-Endpunkt

- Tod
- Myokardinfarkt
- Arterieneingriff
- Schlaganfall
- Amputation

Gaede P et al. New Engl J Med (2003)

Power-Analyse



N = 400 ($\alpha = 0.05$, $\beta = 0.8$, drop out = 0.2)



Zusammenfassung

- Chirurgie kann die effektivste Therapie des Diabetes mellitus Typ 2 werden !
- Der Wirkungsmechanismus scheint multifaktoriell zu sein – ein Vorteil gegenüber medikamentösen Therapien
- Vorteile hinsichtlich harter Endpunkte
Langzeitergebnisse fehlen (DiaSurg 2!)
- Weiter translationale und klinische Studien sind notwendig



Vielen Dank für Ihre Aufmerksamkeit

UniversitätsKlinikum Heidelberg
DIABETES & ADIPOSITAS ZENTRUM



Sekretariat: 06221 56 6883