University Hospital Galway
Ospidéal na h-Ollscoile, Gaillimh
GALWAY UNIVERSITY HOSPITALS

Bariatric Medicine

"Managing the Dysregulation of the Metabolic Milieu in Diabetes and Obesity"

Dr. Francis Finucane MD FRCPI

14th June 2016

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

SCOPE
SPECIALIST CERTIFICATION OF OBESITY PROFESSIONAL EDUCATION

Declaration of Interests:

- **Research Contracts:**
  - Novo Nordisk
- **Travel Grants/ Advisory Boards:**
  - Novo Nordisk
  - Astra Zeneca
  - Sanofi
  - Eli Lilly
- **Unrestricted Educational Grants:**
  - Bristol Myers Squibb
  - Sanofi
  - Eli Lilly
- **Other Grants**
  - HRB
  - IRC

Bariatric Medicine

Outline:

- Mechanisms underlying DM
- Epidemiology
- **Move away from “fatness” *per se***

Bariatric Medicine

Journal of the American College of Cardiology
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Vol. 39, No. 4, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(01)01802-2

Interventional Cardiology

The Impact of Obesity on the Short-Term and Long-Term Outcomes After Percutaneous Coronary Intervention: The Obesity Paradox?

Luis Gruberg, MD, Neil J. Weissman, MD, FACC, Ron Waksman, MD, FACC, Shmuel Fuchs, MD, Regina Deible, RN, Ellen E. Pinnow, MS, Lanja M. Ahmed, MD, Kenneth M. Kent, MD, PhD, FACC, Augusto D. Pichard, MD, FACC, William O. Suddath, MD, Lowell F. Satler, MD, FACC, Joseph Lindsay, Jr, MD, FACC

Washington, D.C.

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Table 3. In-Hospital Outcome

	Normal BMI (n = 1,923)	Overweight (n = 4,813)	Obese (n = 2,897)	p Value
Procedural success (%)	97.3	97.4	97.6	0.74
Clinical success (%)	93.8	94.2	95.0	0.09
Pulmonary edema (%)	4.0	2.8	2.6	0.002
Hypotension (%)	4.8	3.2	2.9	< 0.0001
Renal insufficiency (%)	6.6	4.8	5.2	0.005
Death (%)	1.3	1.0	0.7	0.06
Cardiac death (%)	1.0	0.7	0.4	0.001
Myocardial infarction (%)	14.8	14.7	13.7	0.41
Q-wave (%)	0.4	0.4	0.3	0.79
Non–Q-wave (%)	21.4	20.2	19.4	0.19
Emergency CABG (%)	1.6	1.6	1.7	0.99
Vascular complications (%)	5.9	3.6	3.9	< 0.0001
Major bleeding (%)	4.5	3.5	3.1	0.01

BMI = body mass index; CABG = coronary artery bypass grafting.

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Interventional Cardiology

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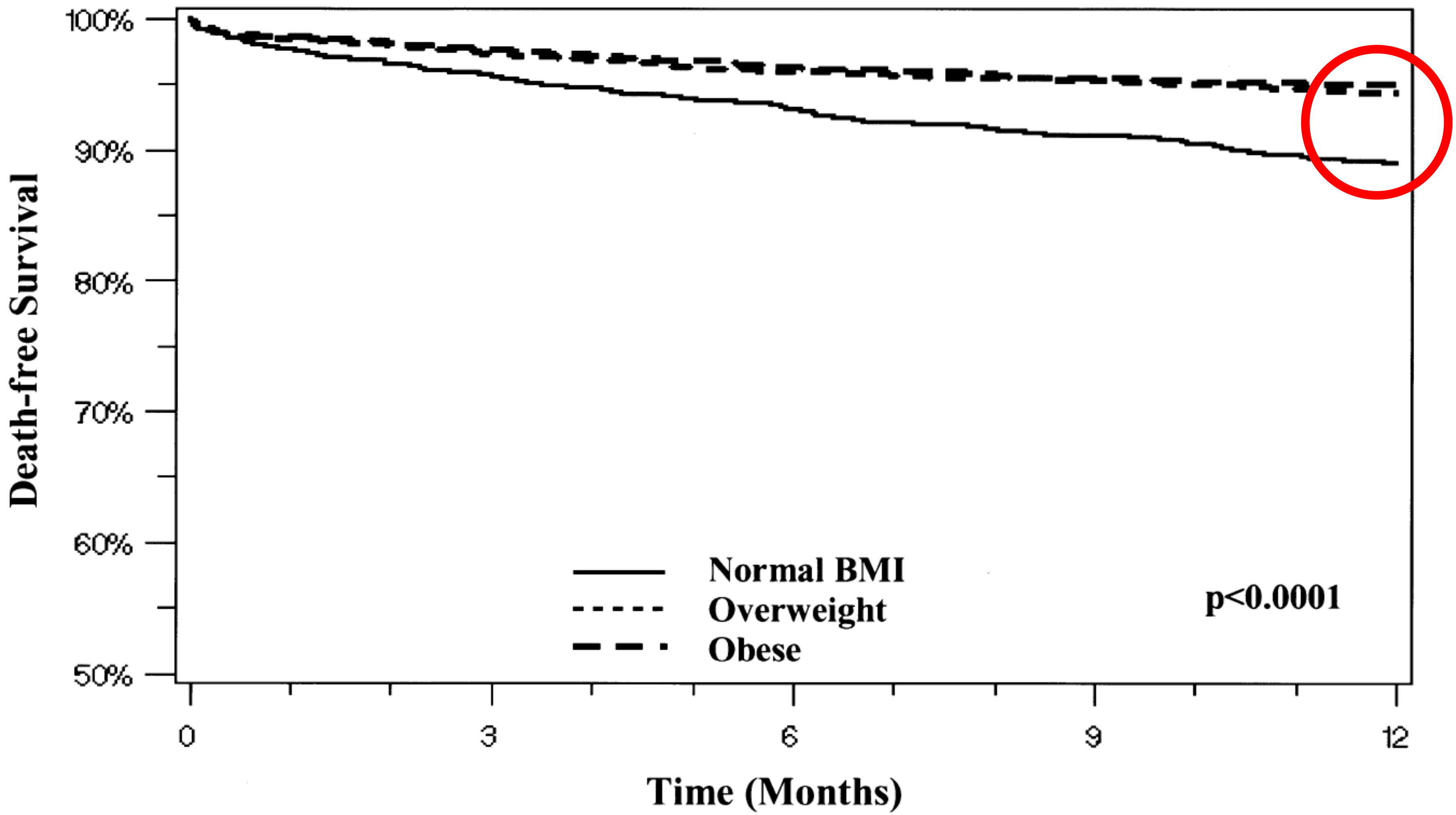
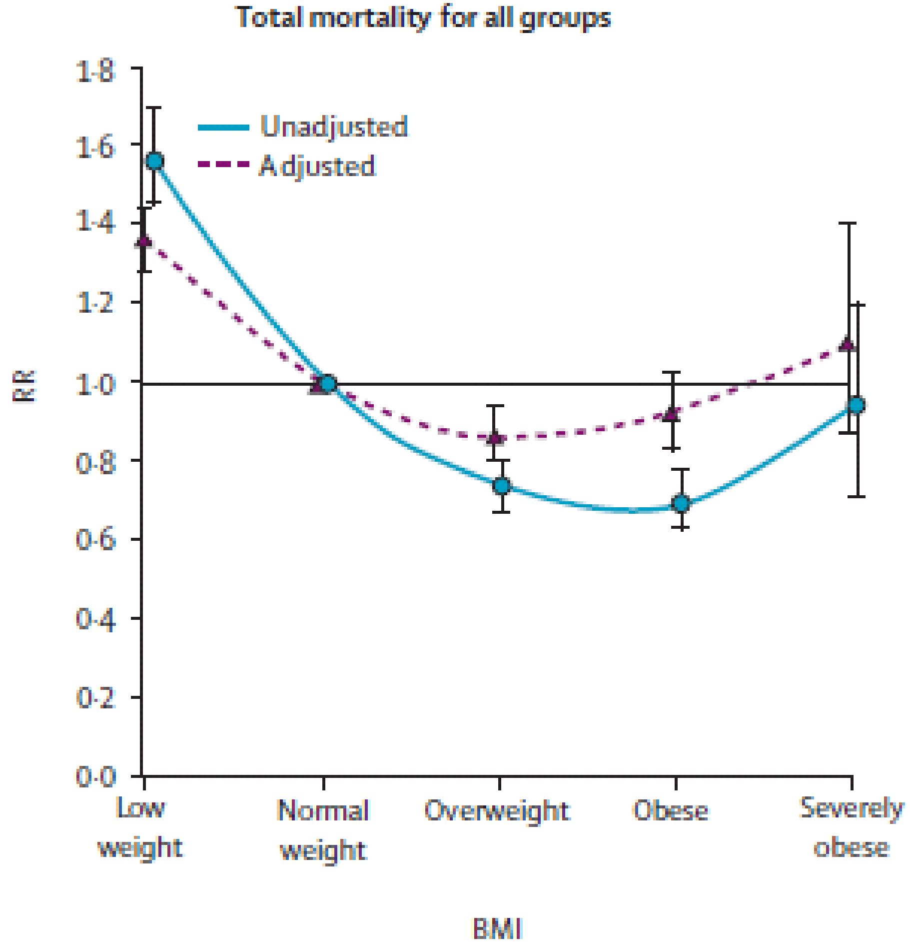


Figure 1. Kaplan-Meier curves illustrating death-free survival curves at 12 months follow-up. BMI = body mass index.

Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies

Lancet 2006; 368: 666–78

Abel Romero-Corral, Victor M Montori, Virend K Somers, Josef Korinek, Randal J Thomas, Thomas G Allison, Farouk Mookadam, Francisco Lopez-Jimenez



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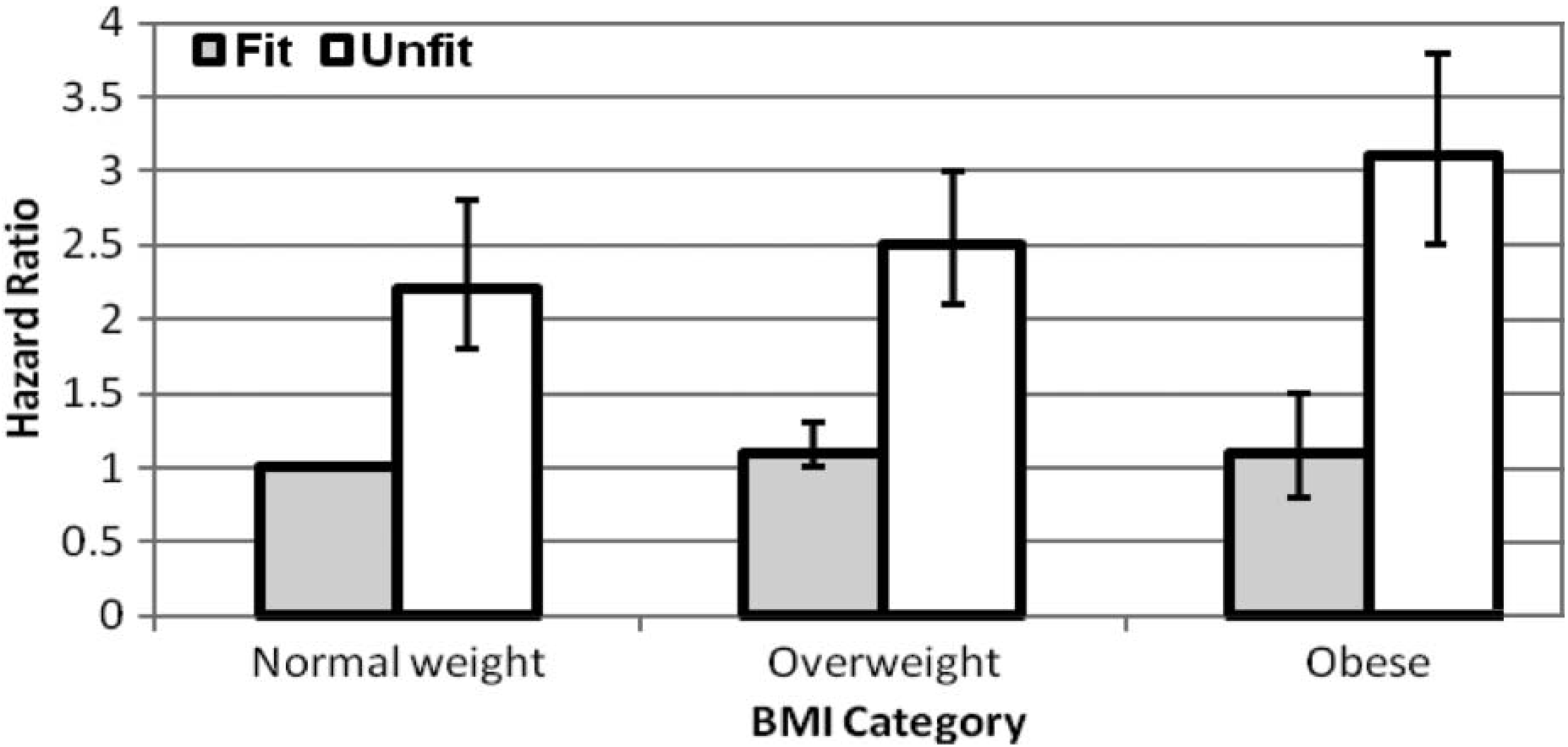
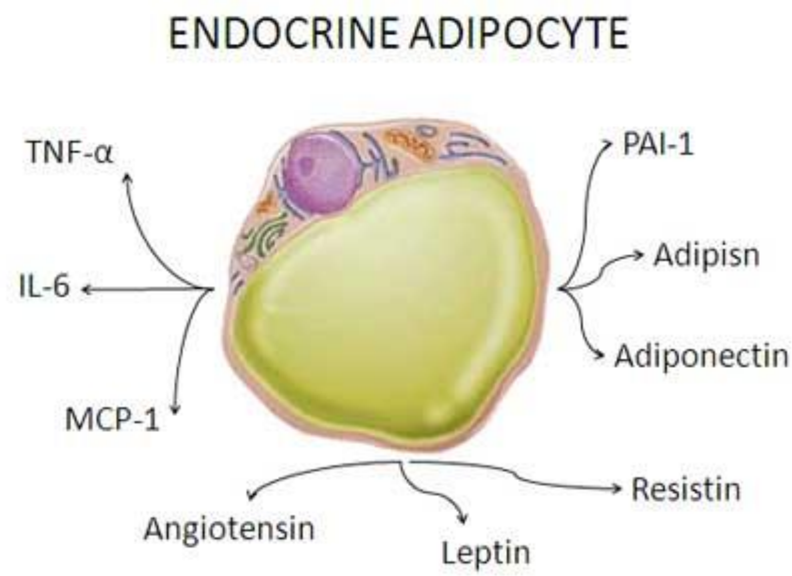


Figure 2. Multivariate hazard ratios for all-cause mortality by body mass index (BMI) and fitness level in 25,714 men from the Aerobics Center Longitudinal Study (ACLS) (adapted from Wei et al., 1999). Each bar represents the relative risk after adjustment

Obesity Paradoxes: Why?

- "BMI paradox"?
  - Body composition
  - Body fat distribution
  - Sarcopenia



- *Focus is now on* ***<u>adipocyte function</u>****:*

Diabetologia
DOI 10.1007/s00125-009-1508-3

SHORT COMMUNICATION

Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals

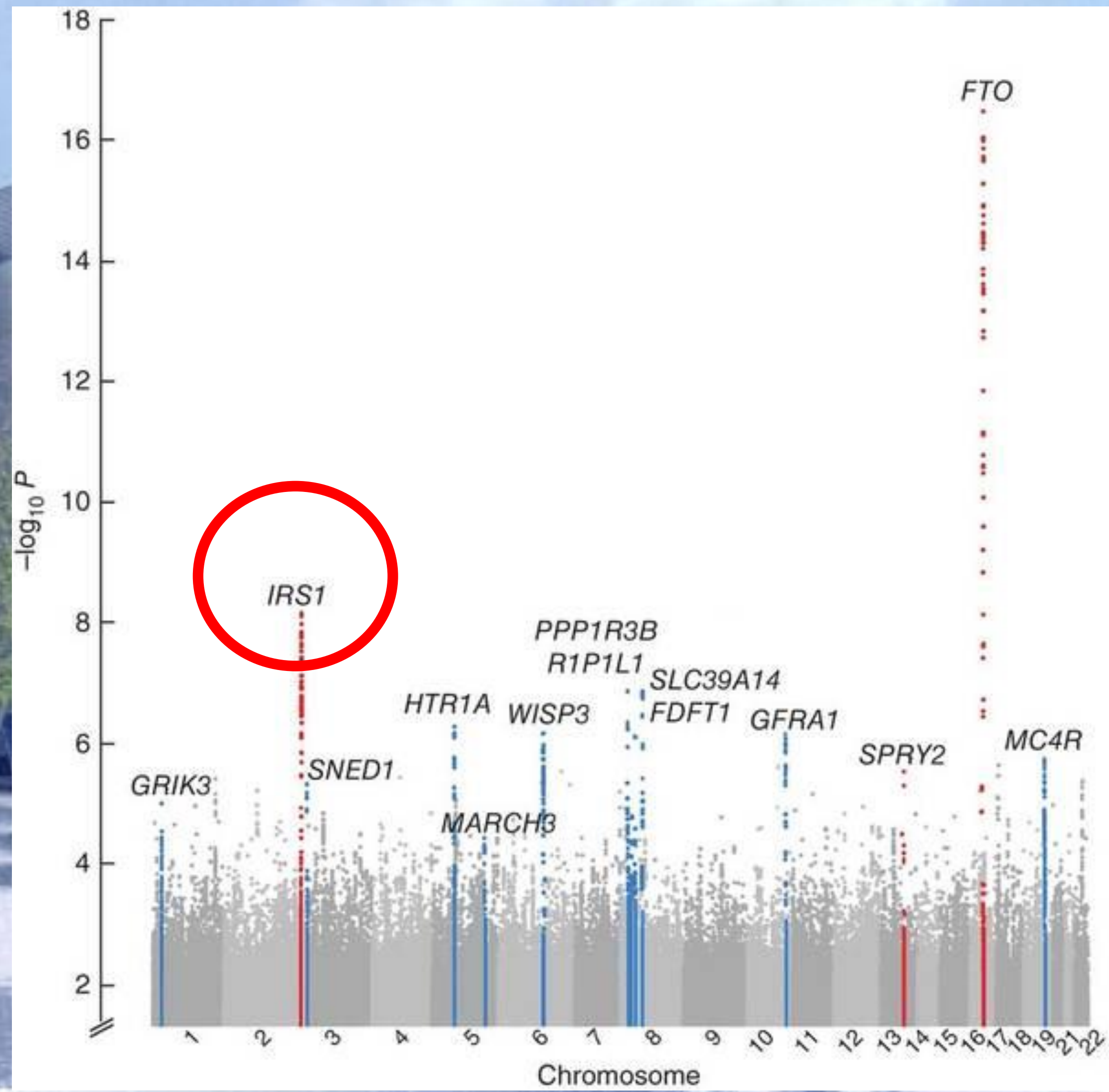
F. M. Finucane • J. Luan • N. J. Wareham • S. J. Sharp • S. O'Rahilly • B. Balkau • A. Flyvbjerg • M. Walker • K. Højlund • J. J. Nolan • (on behalf of the European Group for the Study of Insulin Resistance: Relationship between Insulin Sensitivity and Cardiovascular Disease Risk Study Group) • D. B. Savage

Which is the insulin resistant mouse?

Fat as they come. Researchers made a mouse that can accumulate huge amounts of fat, as the one on the left does by over-expressing adiponectin. The result: This mouse was insulin sensitive.

Bariatric Medicine

IMS Institute of Metabolic Science



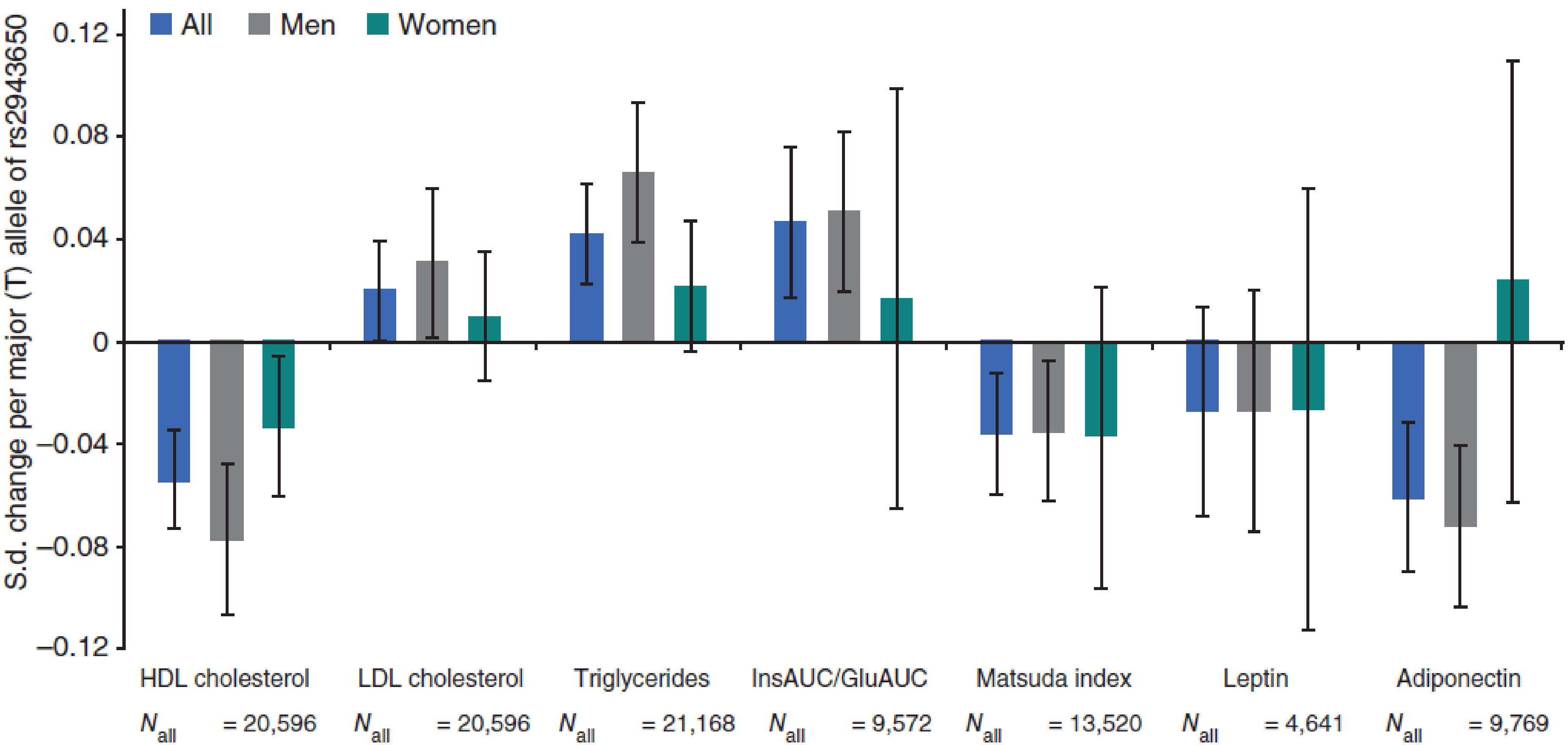
ARTICLES

nature genetics

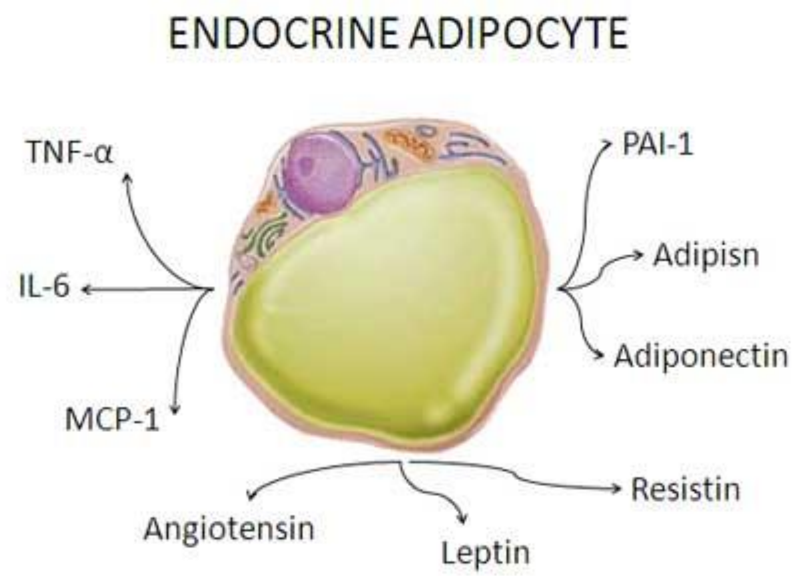
Genetic variation near *IRS1* associates with reduced adiposity and an impaired metabolic profile

Tuomas O Kilpeläinen[1*], M Carola Zillikens[2,3], Alena Stančáková[4], Francis M Finucane[1], Janina S Ried[5], Claudia Langenberg[1], Weihua Zhang[6], Jacques S Beckmann[7], Jian'an Luan[1], Liesbeth Vandenput[8], Unnur Styrkarsdottir[9], Yanhua Zhou[10], Albert Vernon Smith[11], Jing-Hua Zhao[1], Najaf Amin[12], Sailaja Vedantam[13,14], So-Youn Shin[15], Talin Haritunians[16], Mao Fu[17], Mary F Feitosa[18], Meena Kumari[19], Bjarni V Halldorsson[9,20], Emmi Tikkanen[21,22], Massimo Mangino[23], Caroline Hayward[24], Ci Song[25], Alice M Arnold[26], Yurii S Aulchenko[12], Ben A Oostra[12], Harry Campbell[27], L Adrienne Cupples[10,28], Kathryn E Davis[29], Angela Döring[5], Gudny Eiriksdottir[11], Karol Estrada[2,3,12], José Manuel Fernández-Real[30], Melissa Garcia[31], Christian Gieger[5], Nicole L Glazer[32,33], Candace Guiducci[13], Albert Hofman[3,12], Steve E Humphries[34], Bo Isomaa[35,36], Leonie C Jacobs[2], Antti Jula[37], David Karasik[38], Magnus K Karlsson[39,40], Kay-Tee Khaw[41], Lauren J Kim[31], Mika Kivimäki[42], Norman Klopp[5], Brigitte Kühnel[5], Johanna Kuusisto[4], Yongmei Liu[43], Östen Ljunggren[44], Mattias Lorentzon[8], Robert N Luben[41], Barbara McKnight[26,32], Dan Mellström[8], Braxton D Mitchell[17], Vincent Mooser[45], José Maria Moreno[30], Satu Männistö[46], Jeffery R O'Connell[17], Laura Pascoe[47], Leena Peltonen[15,21,22,75], Belén Peral[48], Markus Perola[21,22], Bruce M Psaty[32,49–52], Veikko Salomaa[46], David B Savage[53], Robert K Semple[53], Tatjana Skaric-Juric[54], Gunnar Sigurdsson[55,56], Kijoung S Song[45], Timothy D Spector[23], Ann-Christine Syvänen[57], Philippa J Talmud[34], Gudmar Thorleifsson[9], Unnur Thorsteinsdottir[9,56], André G Uitterlinden[2,3,12], Cornelia M van Duijn[3,12,58], Antonio Vidal-Puig[53], Sarah H Wild[27], Alan F Wright[24], Deborah J Clegg[29], Eric Schadt[59,60], James F Wilson[27], Igor Rudan[27,61,62], Samuli Ripatti[21,22], Ingrid B Borecki[18], Alan R Shuldiner[17,63], Erik Ingelsson[25,64], John-Olov Jansson[65], Robert C Kaplan[66], Vilmundur Gudnason[11,67], Tamara B Harris[31], Leif Groop[68], Douglas P Kiel[38], Fernando Rivadeneira[2,3,12], Mark Walker[47], Inês Barroso[15,53], Peter Vollenweider[69], Gérard Waeber[69], John C Chambers[6], Jaspal S Kooner[70], Nicole Soranzo[15], Joel N Hirschhorn[13,14,71], Kari Stefansson[9,56], H-Erich Wichmann[5,72], Claes Ohlsson[8], Stephen O'Rahilly[53], Nicholas J Wareham[1], Elizabeth K Speliotes[13,73], Caroline S Fox[74], Markku Laakso[4] & Ruth J F Loos[1]

Figure 3 Association of the body-fat-percentage–decreasing (T) allele of rs2943650 near *IRS1* with blood lipids, insulin sensitivity traits, leptin and adiponectin. The error bars indicate 95%



Better adipocytes – better metabolism?



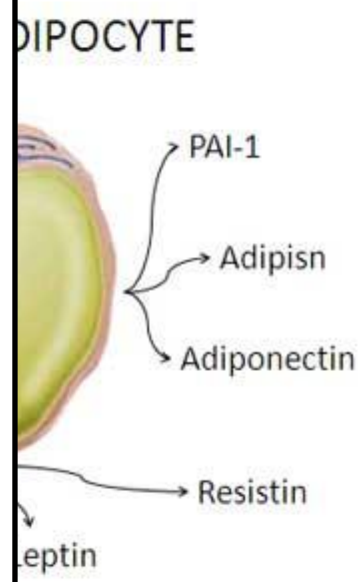
Better adipocytes – better metabolism?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 17, 2004 VOL. 350 NO. 25

Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease

Samuel Klein, M.D., Luigi Fontana, M.D., Ph.D., V. Leroy Young, M.D., Andrew R. Coggan, Ph.D., Charles Kilo, M.D., Bruce W. Patterson, Ph.D., and B. Selma Mohammed, M.D., Ph.D.



Bariatric Medicine

Better adipocytes – better metabolism?

The JOUR
ESTABLISHED IN 1

Absence of
and Ris

Samuel Klein, M.D., Luigi Fontan
Bruce W

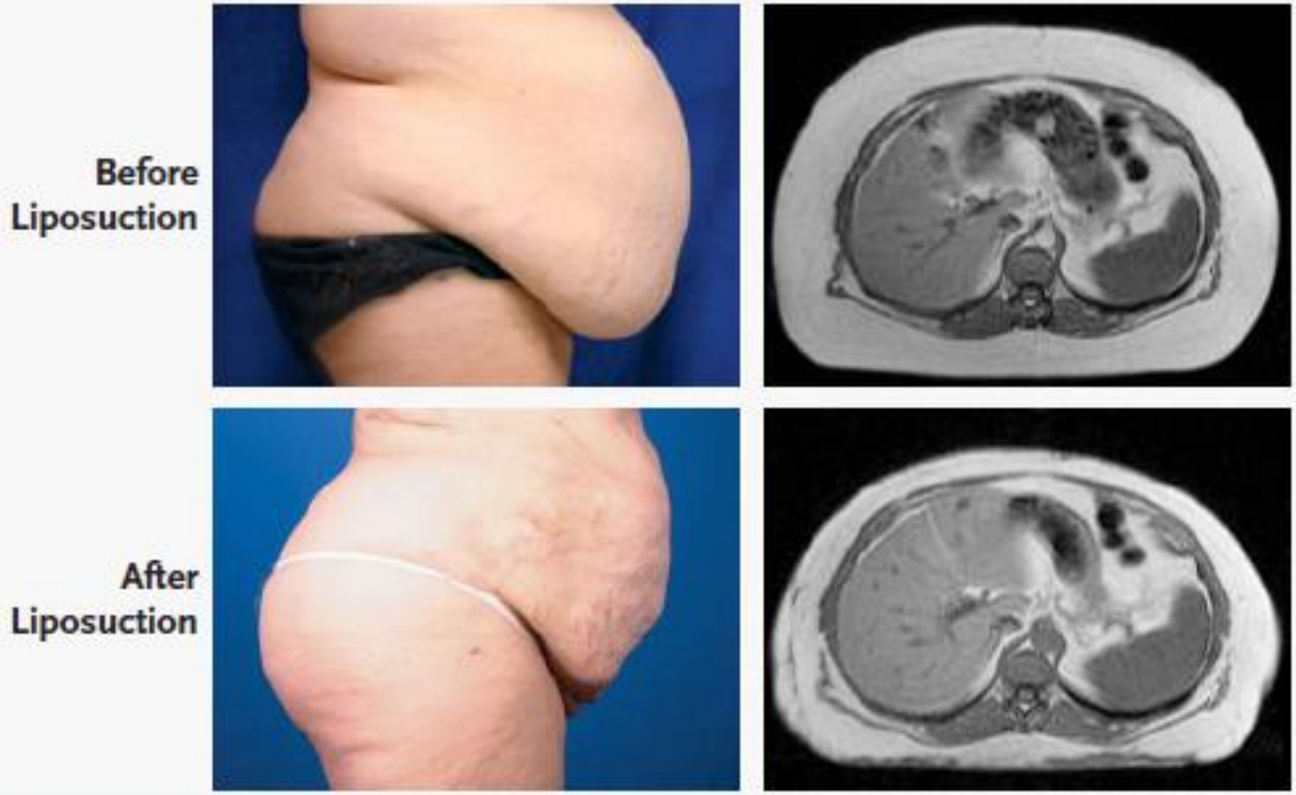


Figure 1. Photographs and Abdominal Magnetic Resonance Images Obtained before and after Liposuction.

The photographs of one study subject and images of another show the large amount of subcutaneous abdominal fat removed by liposuction.

Low Energy Liquid Diet

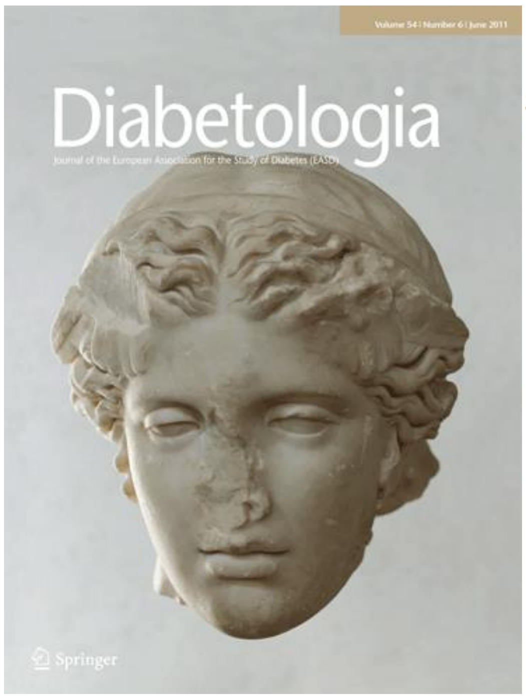
“SODA MILIS”

	Pre-Programme	After 24 weeks	P
BMI (Kg m^{-2})	48.8±8.1	41.3±8.3	<0.001
Excess body weight (%)	95.4±32.5	65±32.9	<0.001
HbA1c (mmol/mol)	65±22.2	49.1±13.4	0.046
Total Cholesterol (mmol/l)	4.3±1.1	3.7±1.1	0.002
LDL- Cholesterol (mmol/l)	2.2±1	1.9±0.9	0.007
HDL- Cholesterol (mmol/l)	1.1±0.4	1.1±0.5	0.31
Triglycerides (mmol/l)	2.1±1	1.6±0.8	0.02

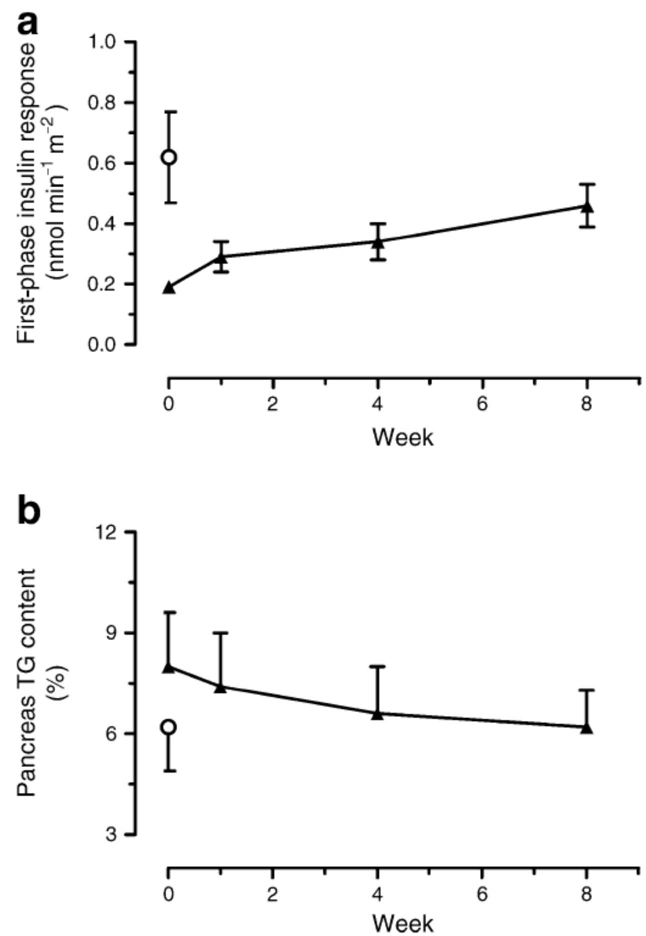
Bariatric Medicine

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

E. L. Lim • K. G. Hollingsworth • B. S. Aribisala •
M. J. Chen • J. C. Mathers • R. Taylor



5 May 2011



This study demonstrates that the twin defects of beta cell failure and insulin resistance that underlie type 2 diabetes can be reversed by acute negative energy balance alone. A

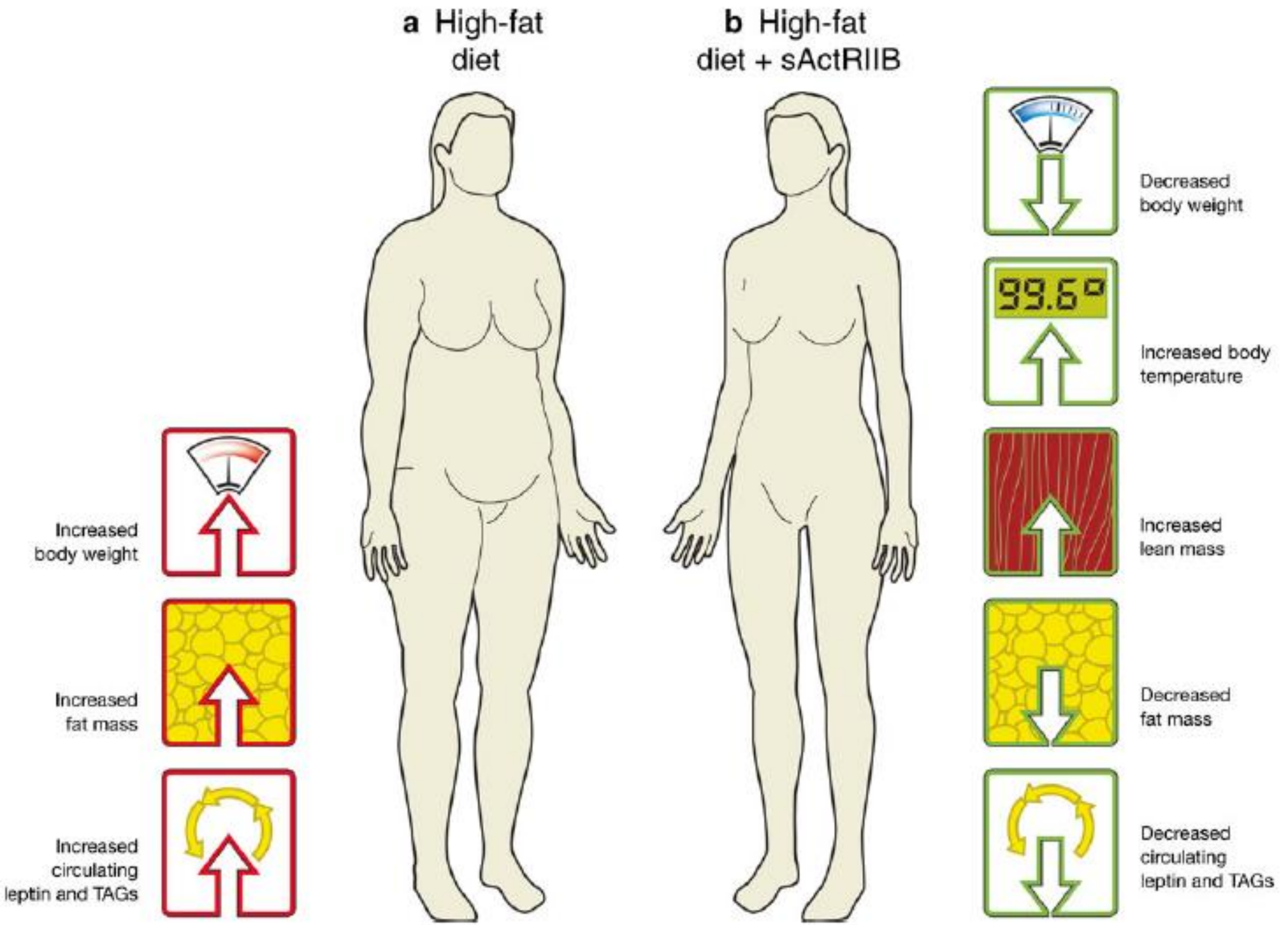
Bariatric Medicine

Diabetologia (2012) 55:13–17
DOI 10.1007/s00125-011-2361-8

Building muscle, browning fat and preventing obesity by inhibiting myostatin

N. K. LeBrasseur

Bariatric Medicine

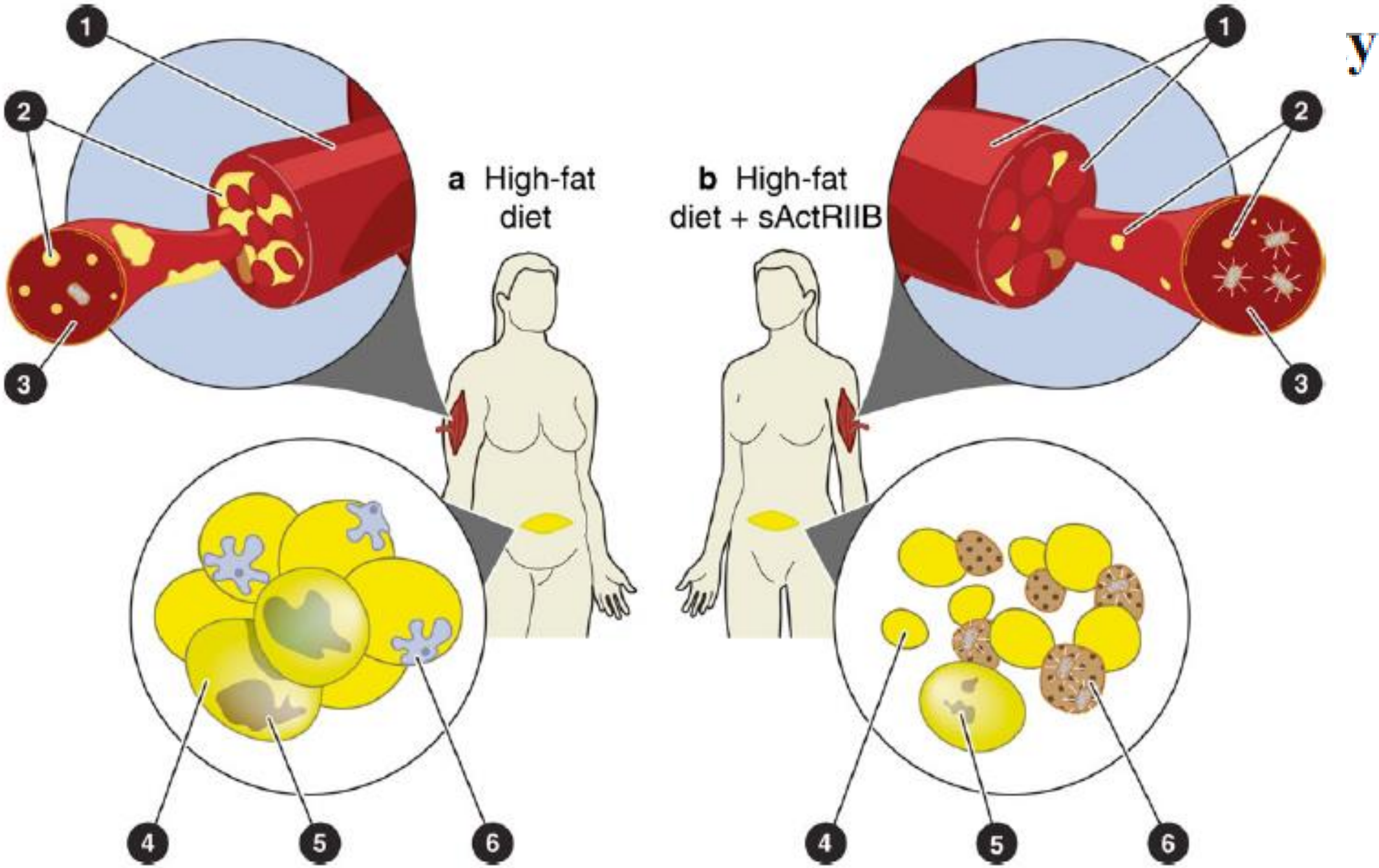

a High-fat diet
b High-fat diet + sActRIIB
Increased body weight
Increased fat mass
Increased circulating leptin and TAGs
Decreased body weight
99.6°
Increased body temperature
Increased lean mass
Decreased fat mass
Decreased circulating leptin and TAGs

Diabetologia (2012) 55:13–17
DOI 10.1007/s00125-011-2361-8

B

b

y



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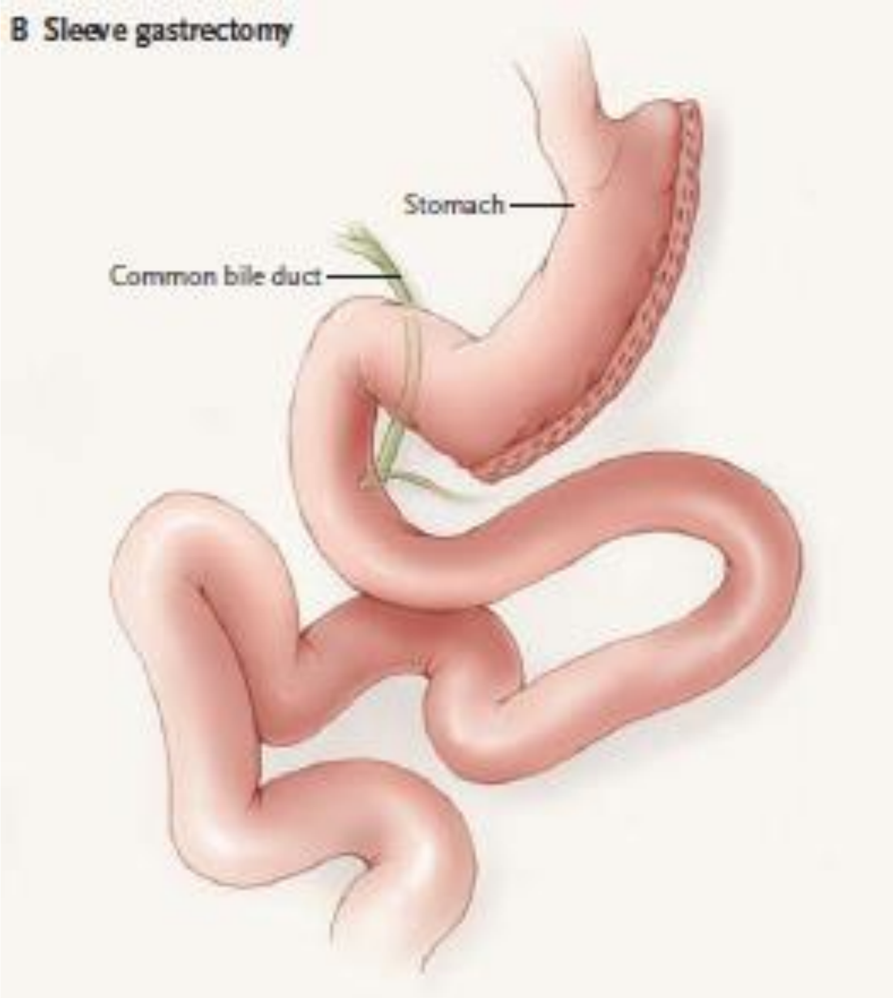
Bariatric Surgery: Sleeve Gastrectomy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D., Caterina Guidone, M.D., Amerigo Iaconelli, M.D., Laura Leccesi, M.D., Giuseppe Nanni, M.D., Alfons Pomp, M.D., Marco Castagneto, M.D., Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.

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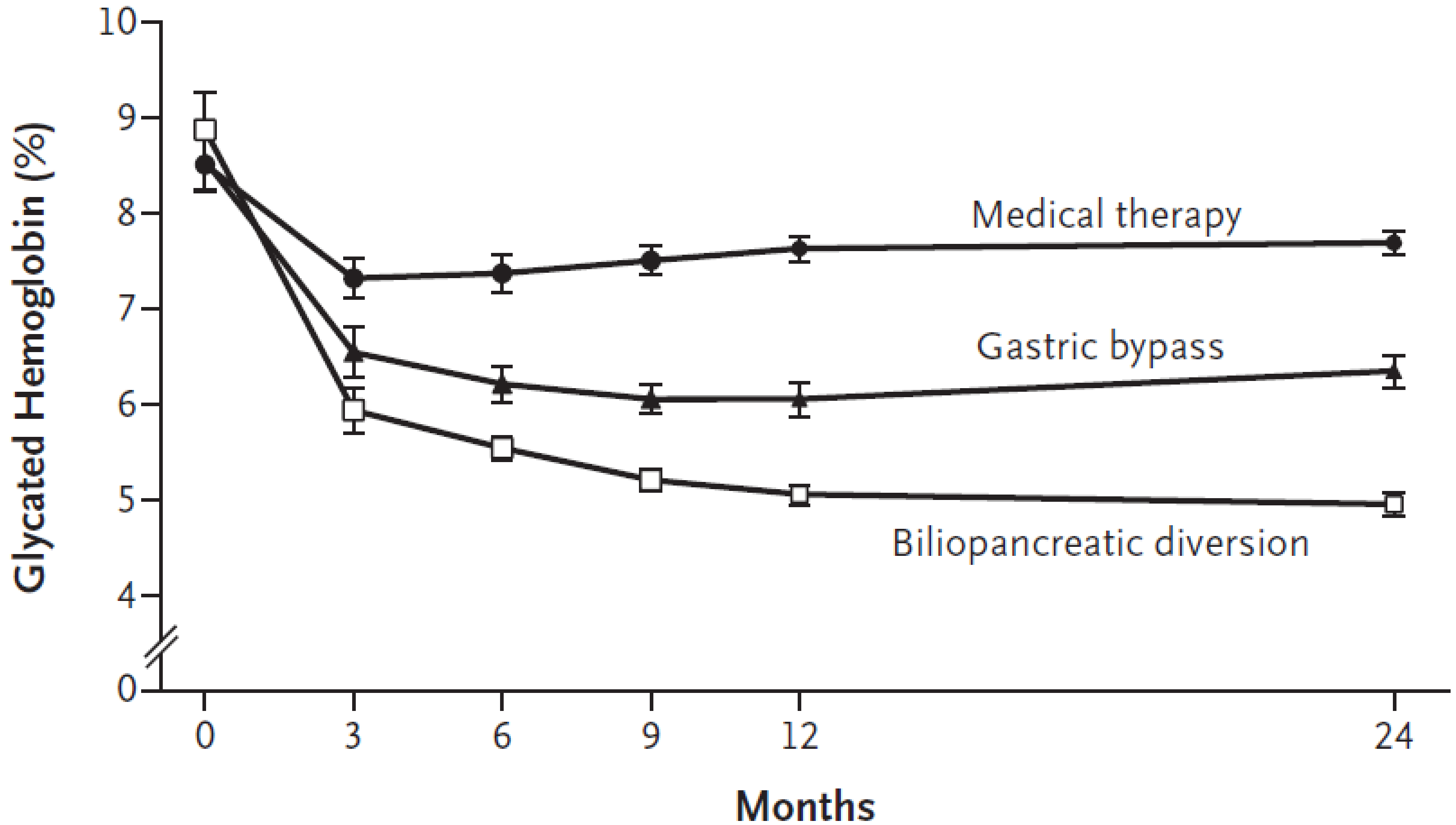

Figure 2. Glycated Hemoglobin Levels during 2 Years of Follow-up.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Ali Aminian, M.D., Claire E. Pothier, M.P.H., Esther S.H. Kim, M.D., M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*

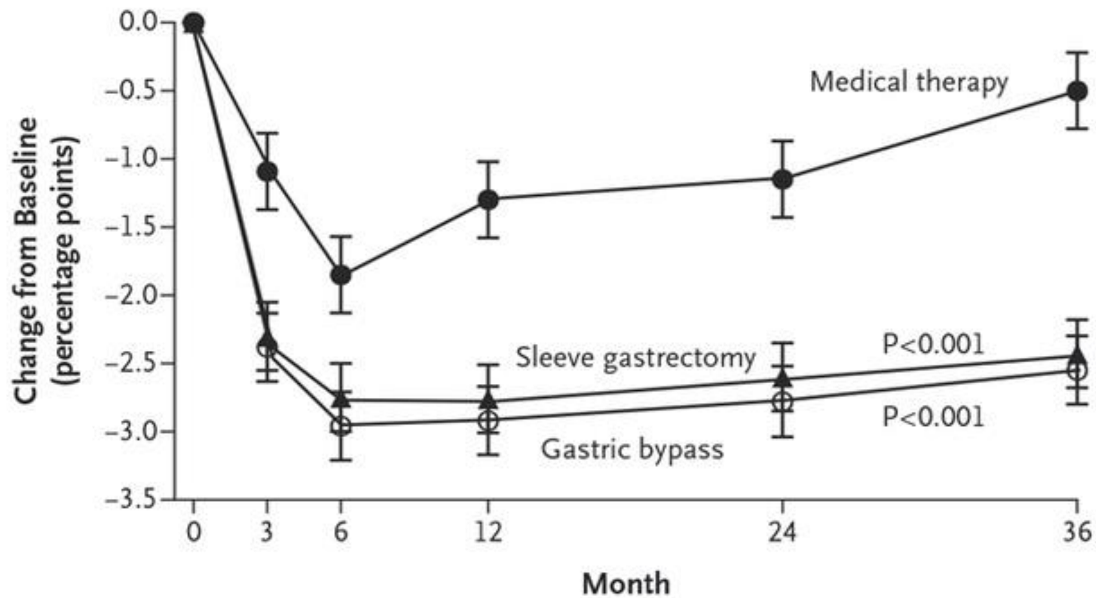
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

Kat ... H.,

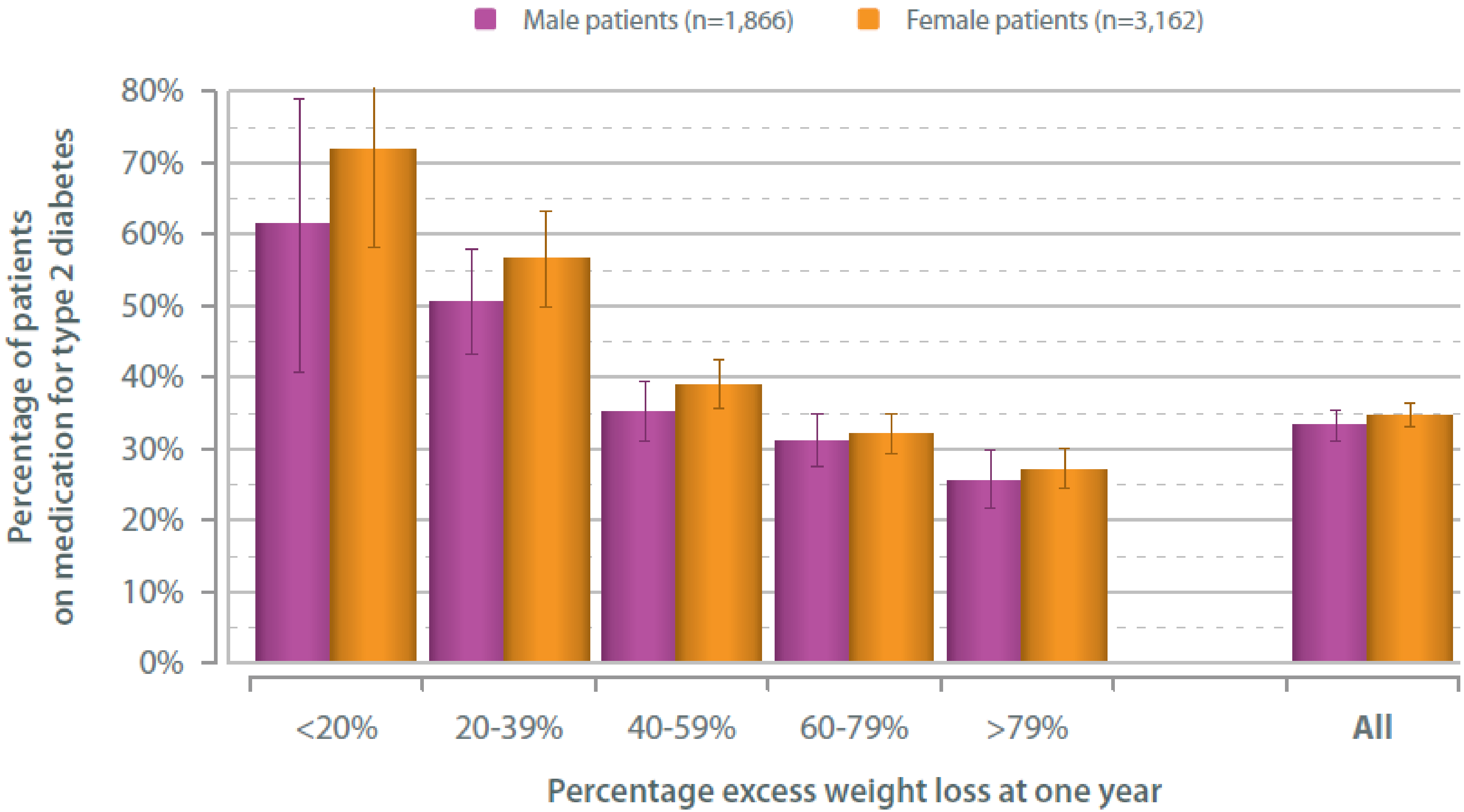
A Glycated Hemoglobin



Value at Visit

Medical therapy	9.0 (8.5)	7.1 (6.8)	7.5 (6.9)	7.7 (7.3)	8.4 (7.6)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.6 (6.4)	6.8 (6.8)	7.0 (6.6)
Gastric bypass	9.3 (9.2)	6.3 (6.2)	6.3 (6.1)	6.5 (6.4)	6.7 (6.6)

Primary surgery for patients on medication for type 2 diabetes: % on medication 12 months after surgery adjusted for %EWL and gender; 2009-2013



Surgical Management of Obesity and the Relationship to Cardiovascular Disease

Amanda R. Vest, MBBS; Helen M. Heneghan, MD, PhD; Philip R. Schauer, MD;
James B. Young, MD

Table 2. Rates of Comorbidity Reduction After Bariatric Surgery

Disease or Symptom	Percent Improvement or Remission at ≤2 y if S	Percent Improvement or Remission at 10 y
Diabetes mellitus	72% (Sjöström et al[23])	36% (Sjöström et al[23])
Hypertension	24% (Sjöström et al[23])	41% (Sjöström et al[23])
Hypertriglyceridemia	62% (Sjöström et al 2004[23])	46% (Sjöström et al[23])
Hypercholesterolemia	22% (Sjöström et al[23])	21% (Sjöström et al[23])

40% CVD risk reduction

Circulation
Journal of the American Heart Association

Bariatric Surgery in the United Kingdom: A Cohort Study of Weight Loss and Clinical Outcomes in Routine Clinical Care

Ian J. Douglas[1]*, Krishnan Bhaskaran[1], Rachel L. Batterham[2,3,4], Liam Smeeth[1]

PLOS | MEDICINE

N=3800, 4 years

T2DM	↓32%
BP	↓65%
Angina	↓41%
MI	↓72%
OSAS	↓45%

Bariatric Medicine

Diabetes Care Volume 39, June 2016

Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery

Rachel L. Batterham[1,2,3]
David E. Cummings[4]

Diabetes Care 2016;39:893–901 | DOI: 10.2337/dc16-0145

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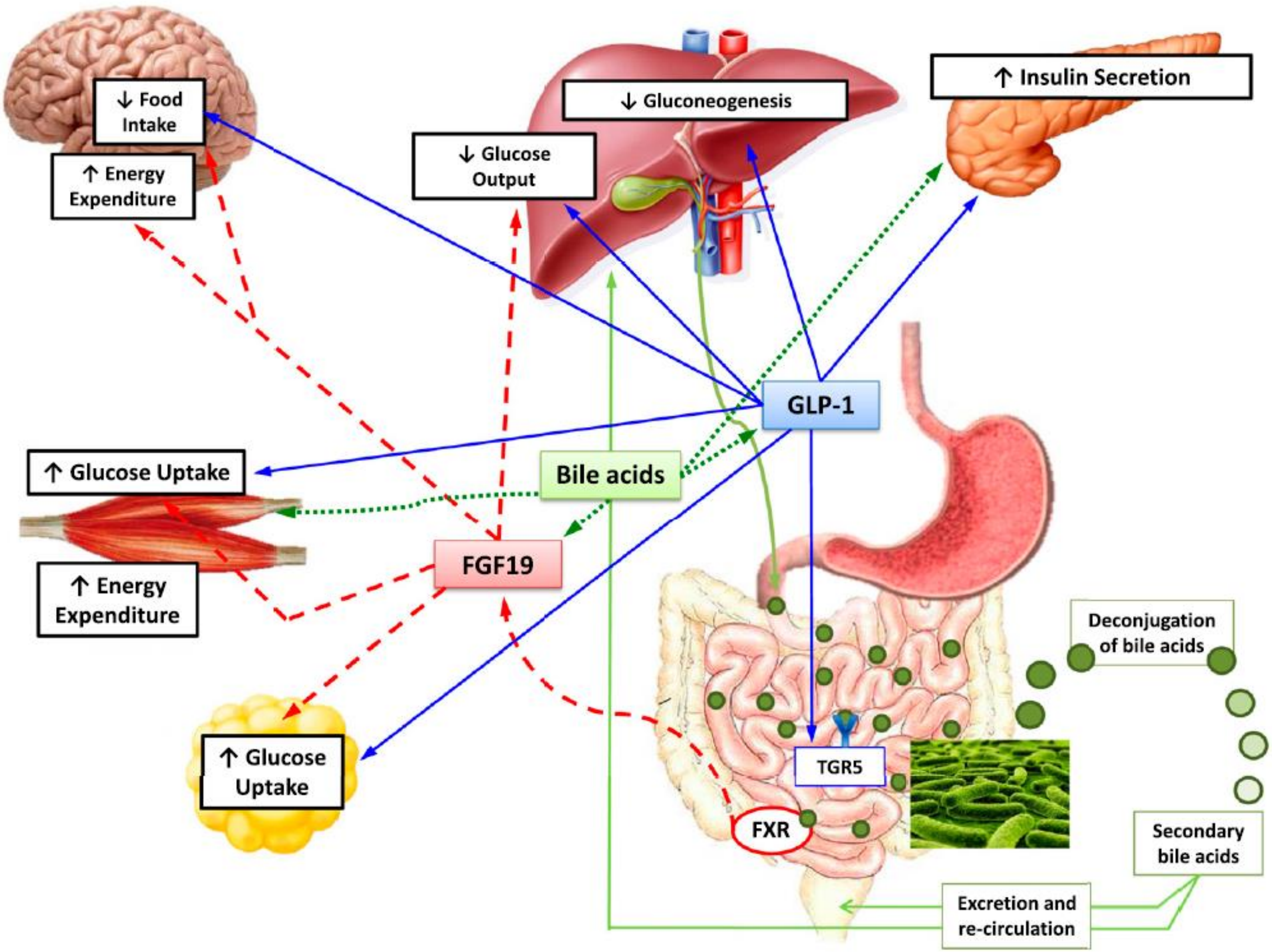
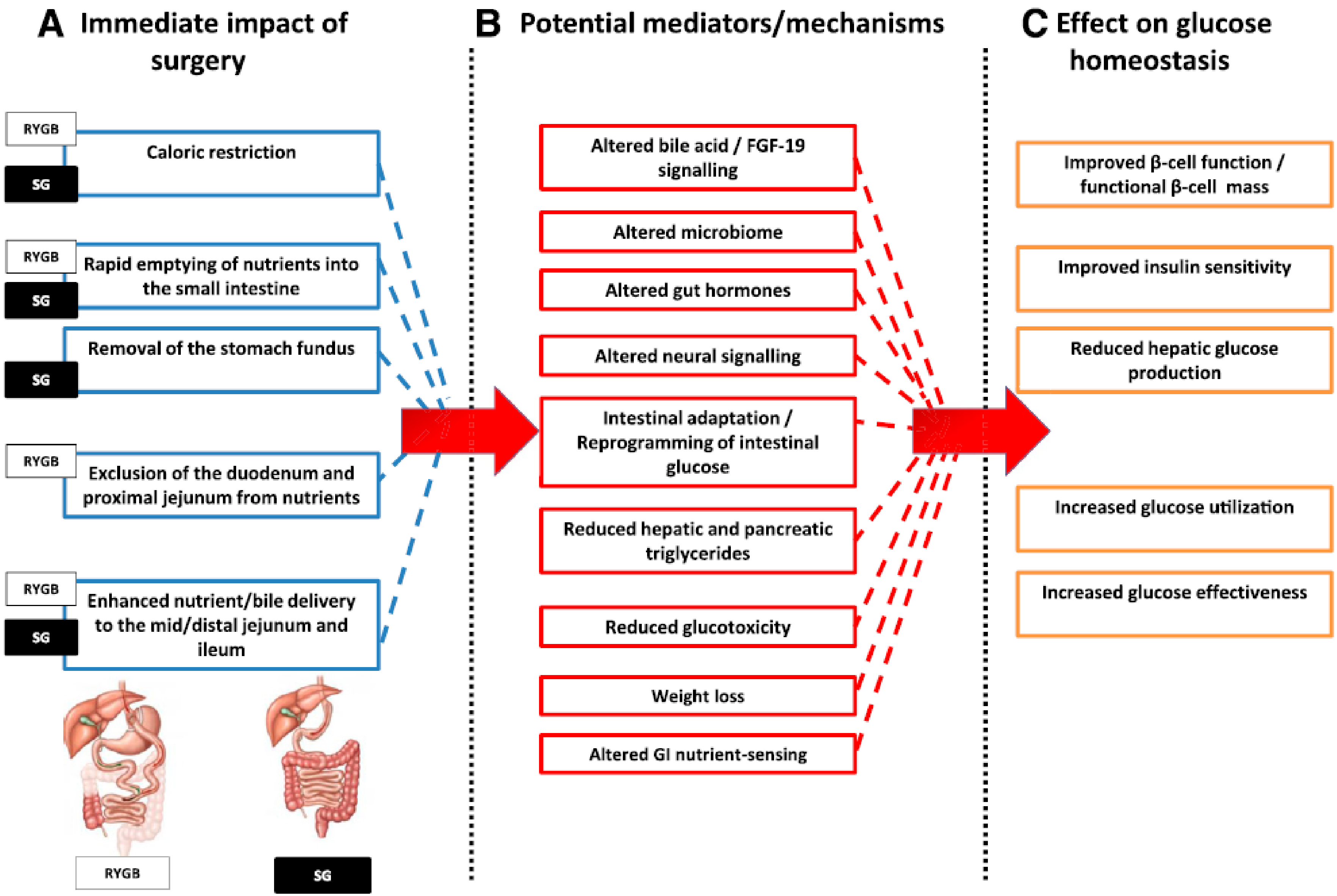


m[1,2,3]
s[4]

Figure 2—Diagram of some of the metabolic effects and cross talk among BAs, GLP-1, and FGF-19.


A Immediate impact of surgery
B Potential mediators/mechanisms
C Effect on glucose homeostasis
RYGB
SG
Caloric restriction
RYGB
SG
Rapid emptying of nutrients into the small intestine
SG
Removal of the stomach fundus
RYGB
Exclusion of the duodenum and proximal jejunum from nutrients
RYGB
SG
Enhanced nutrient/bile delivery to the mid/distal jejunum and ileum
RYGB
SG
Altered bile acid / FGF-19 signalling
Altered microbiome
Altered gut hormones
Altered neural signalling
Intestinal adaptation / Reprogramming of intestinal glucose
Reduced hepatic and pancreatic triglycerides
Reduced glucotoxicity
Weight loss
Altered GI nutrient-sensing
Improved β-cell function / functional β-cell mass
Improved insulin sensitivity
Reduced hepatic glucose production
Increased glucose utilization
Increased glucose effectiveness

Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations

Diabetes Care 2016;39:861–877 | DOI: 10.2337/dc16-0236

Francesco Rubino,[1] David M. Nathan,[2] Robert H. Eckel,[3] Philip R. Schauer,[4] K. George M.M. Alberti,[5] Paul Z. Zimmet,[6] Stefano Del Prato,[7] Linong Ji,[8] Shaukat M. Sadikot,[9] William H. Herman,[10] Stephanie A. Amiel,[1] Lee M. Kaplan,[2] Gaspar Taroncher-Oldenburg,[11] and David E. Cummings,[12] on behalf of the Delegates of the 2nd Diabetes Surgery Summit*

Bariatric Medicine

Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by

Francesco Rubino,[1] David M. Nathan,[2] Robert H. Eckel,[3] Philip R. Schauer,[4] K. George M.M. Alberti,[5] Paul Z. Zimmet,[6] Stefano Del Prato,[7] Linong Ji,[8] Shaukat M. Sadikot,[9] William H. Herman,[10]

RESULTS

Given its role in metabolic regulation, the gastrointestinal tract constitutes a meaningful target to manage T2D. Numerous randomized clinical trials, albeit mostly short/midterm, demonstrate that metabolic surgery achieves excellent glycemic control and reduces cardiovascular risk factors. On the basis of such evidence, metabolic surgery should be *recommended* to treat T2D in patients with class III obesity (BMI ≥40 kg/m^2) and in those with class II obesity (BMI 35.0–39.9 kg/m^2) when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy. Surgery should also be *considered* for patients with T2D and BMI 30.0–34.9 kg/m^2 if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications. These BMI thresholds should be reduced by 2.5 kg/m^2 for Asian patients.

Bariatric Medicine

Summary:

- Fat tissue mass less NB than function
- Mechanistic basis for metabolic improvements multifactorial
- Better knowledge finally translating into better bariatric patient care

Bariatric Medicine

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Jenni Jones
Neil Johnson
Katie Cunningham
Claire Kerins

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Maura Shiels
Michelle Queally
Cate Crowe
Rosemary Geoghegan
Claudia Cortez
Siobhan Moran
John O'Farrell
Conor Murphy

NUIG/ Saolta:
Katriona Kilkelly
Mary Hynes
Brian McGuire
Tim O'Brien
Oliver McAnena
Chris Collins
Helena Griffin
Marie Gately
Paula O'Shea

Others:
Nick Wareham
Simon Griffin
John Nolan
Donal O'Shea
Carel Le Roux