Gut peptides and appetite in upper gastrointestinal surgery

BAPEN Annual Conference 2016

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HRB
Wellcome Trust - HRB Clinical Research Facility at St. James's Hospital

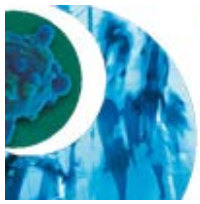
Original article

Malnutrition after oesophageal cancer surgery in Sweden — BJS

Cancer

Health-related Quality of Life Among Patients Cured by Surgery for Esophageal Cancer

Quality of life and persisting symptoms after oesophageal cancer surgery



EJC
EUROPEAN JOURNAL OF CANCER

Remapping the Body: Learning to Eat Again After Surgery for Esophageal Cancer

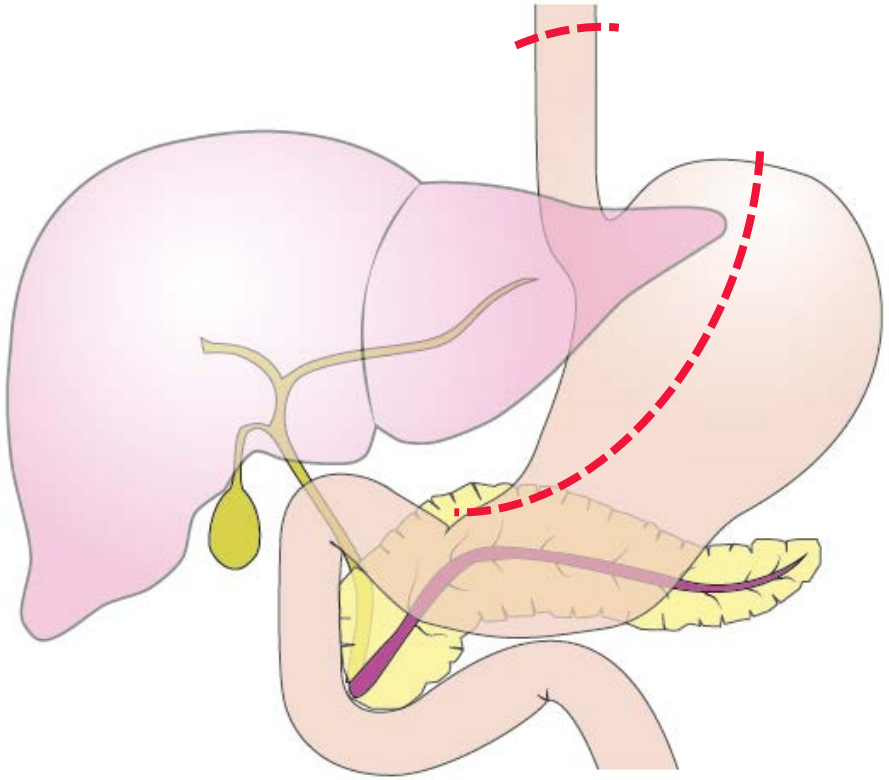
World Journal of Surgery

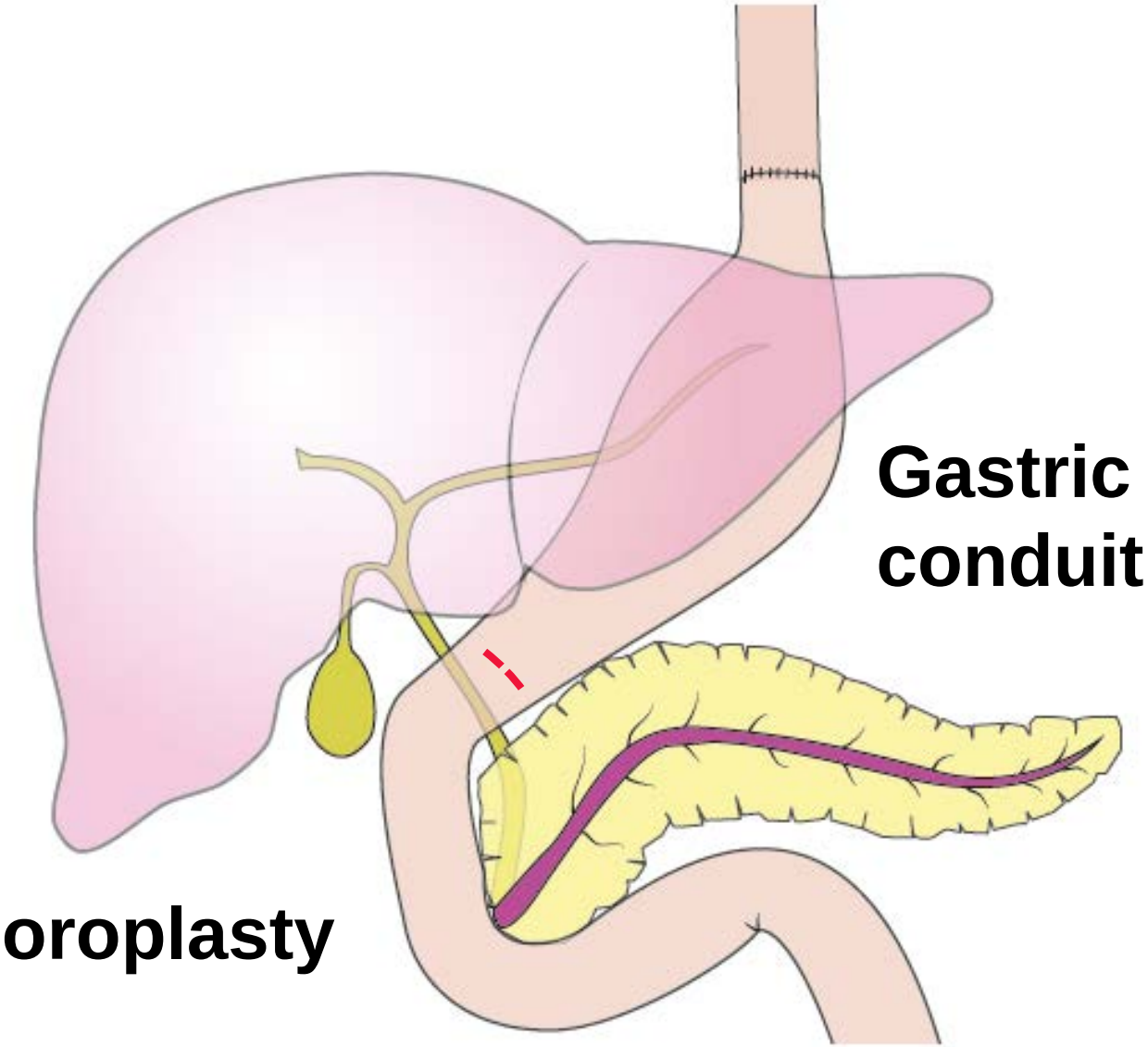
Presence and Persistence of Nutrition-Related Symptoms During the First Year Following Esophagectomy with Gastric Tube Reconstruction in Clinically Disease-Free Patients

Overview

- Surgical anatomy
- Nutrition in survivorship
  - LBM, weight, bone, biochemical, oncologic?
  - Mechanisms
- Gut hormones
- Postoperative changes in enteroendocrine physiology
  - Oesophagectomy, Whipple’s, total gastrectomy
- Therapeutic strategies
  - Dietary, octreotide, BAS, nutraceuticals?

Postoperative anatomy
Oesophagectomy



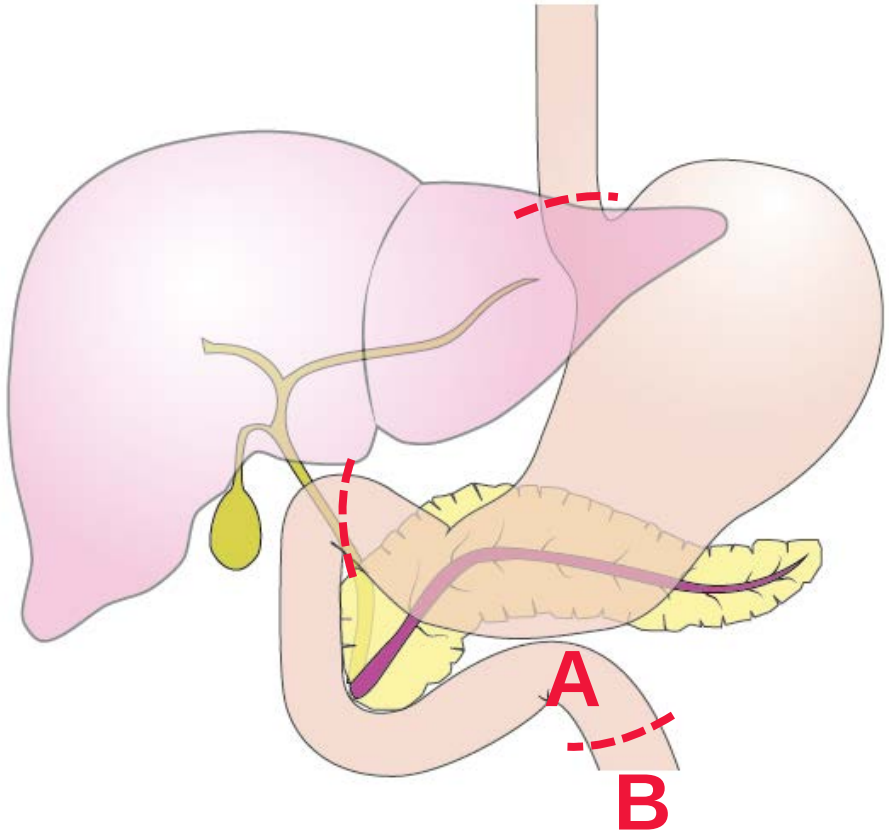


Gastric conduit

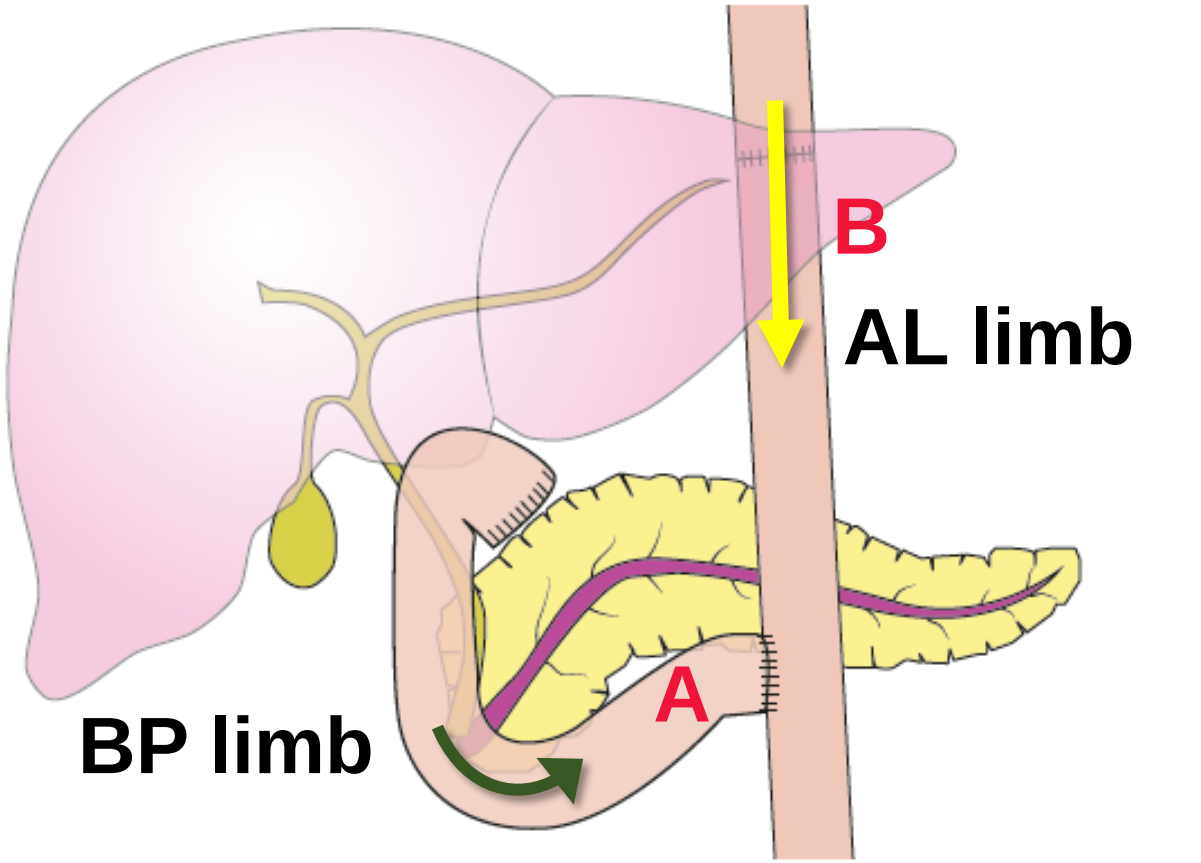
Pyloroplasty

Postoperative anatomy

Total gastrectomy



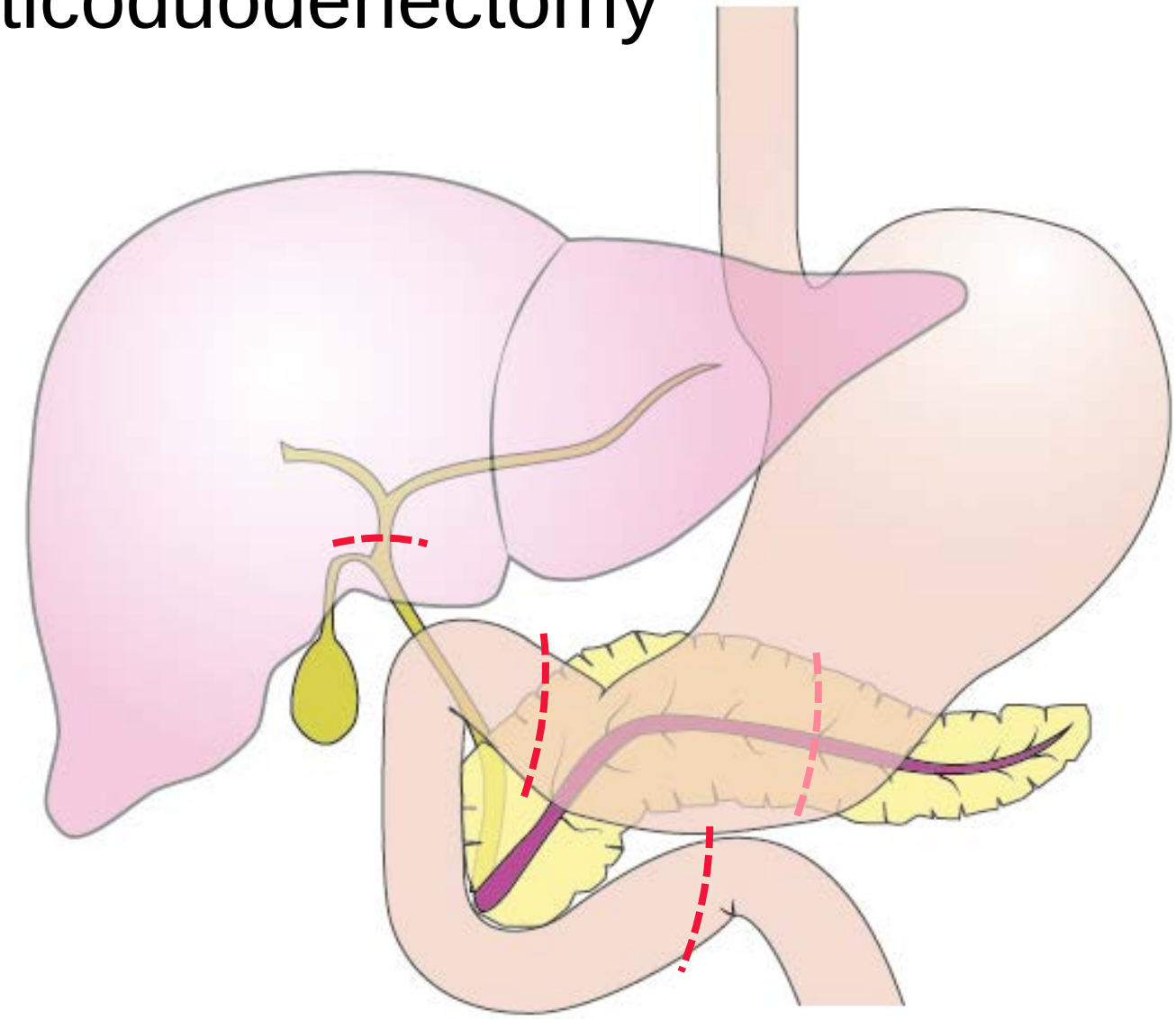
Oesophagojejunal anastomosis



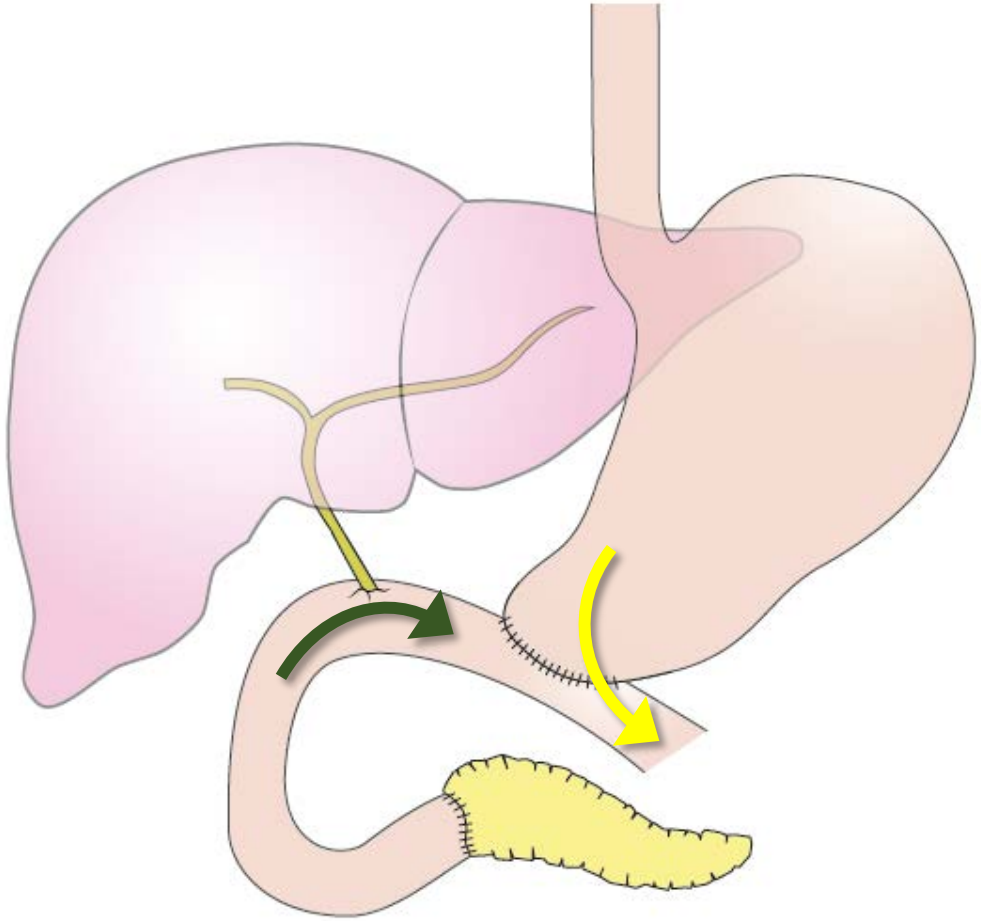
Jejunojejunal anastomosis

Common Channel

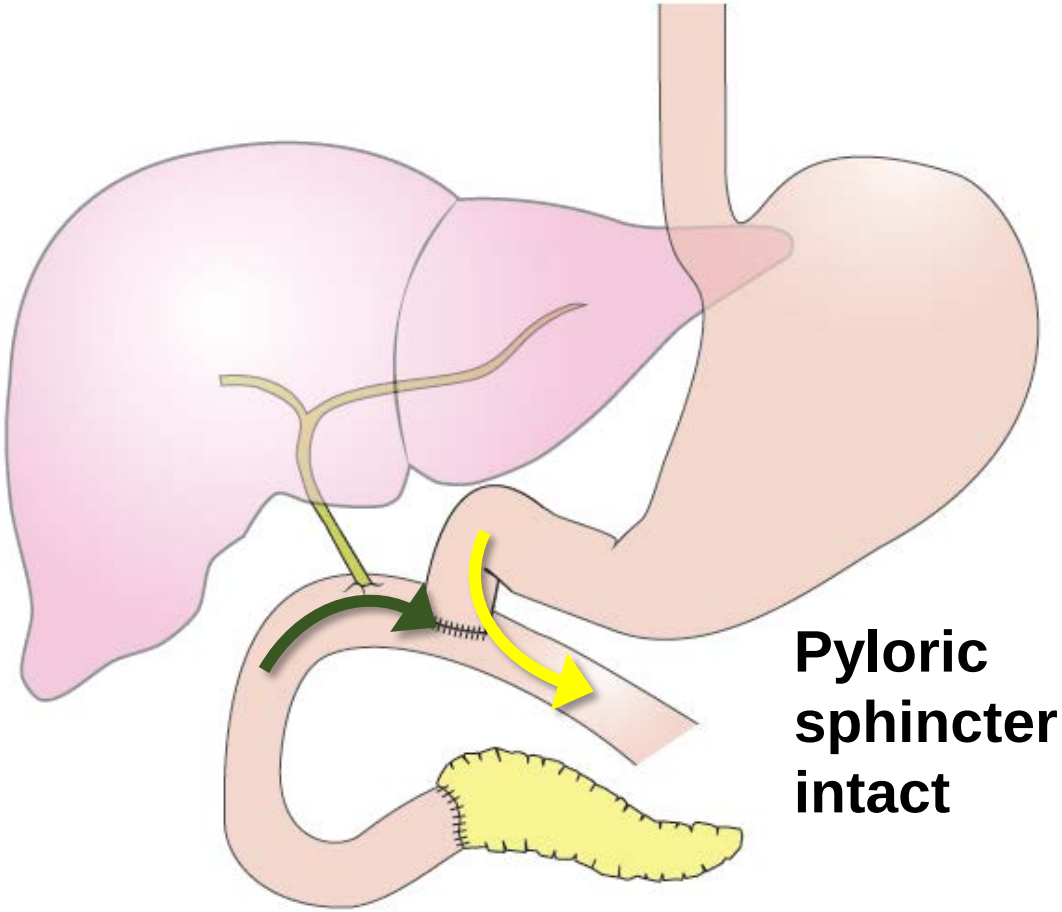
Postoperative anatomy
Pancreaticoduodenectomy



Postoperative anatomy
Pancreaticoduodenectomy



Standard Whipple's



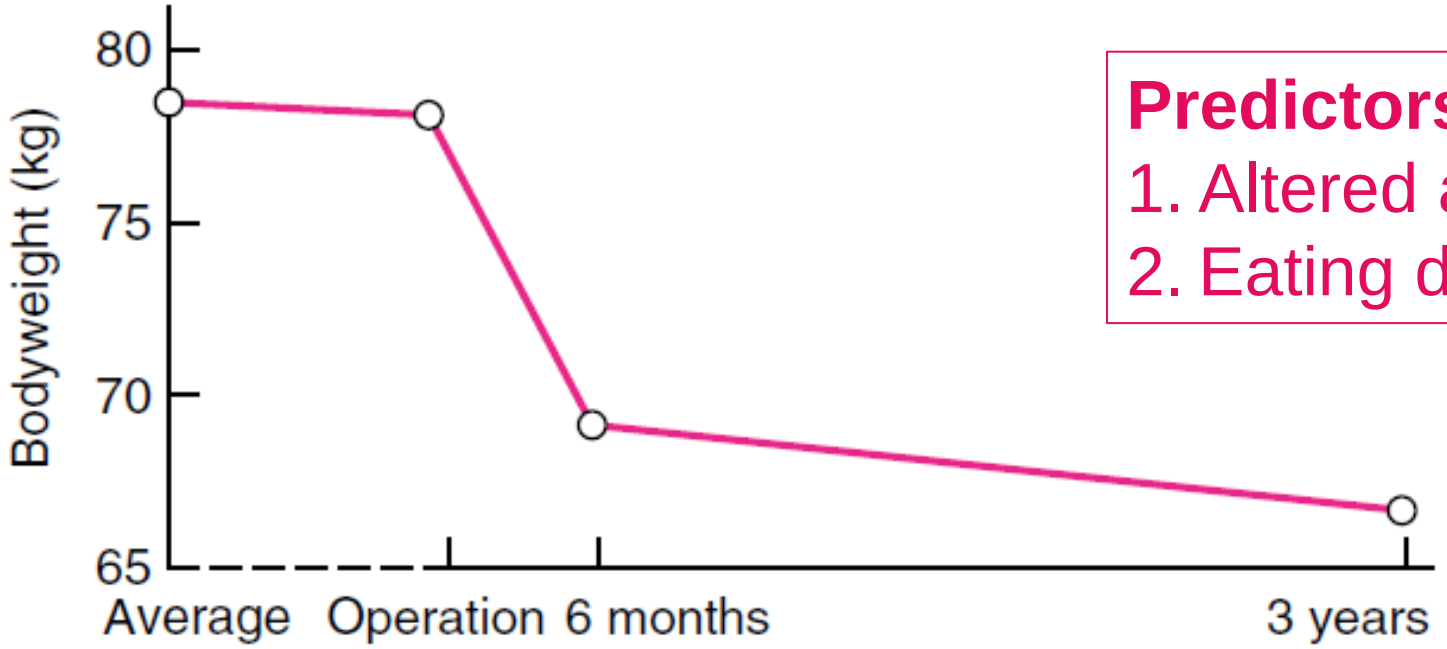
Pylorus-preserving pancreaticoduodenectomy

Original article

BJS

Malnutrition after oesophageal cancer surgery in Sweden

L. Martin, J. Lagergren, M. Lindblad, I. Rouvelas and P. Lagergren



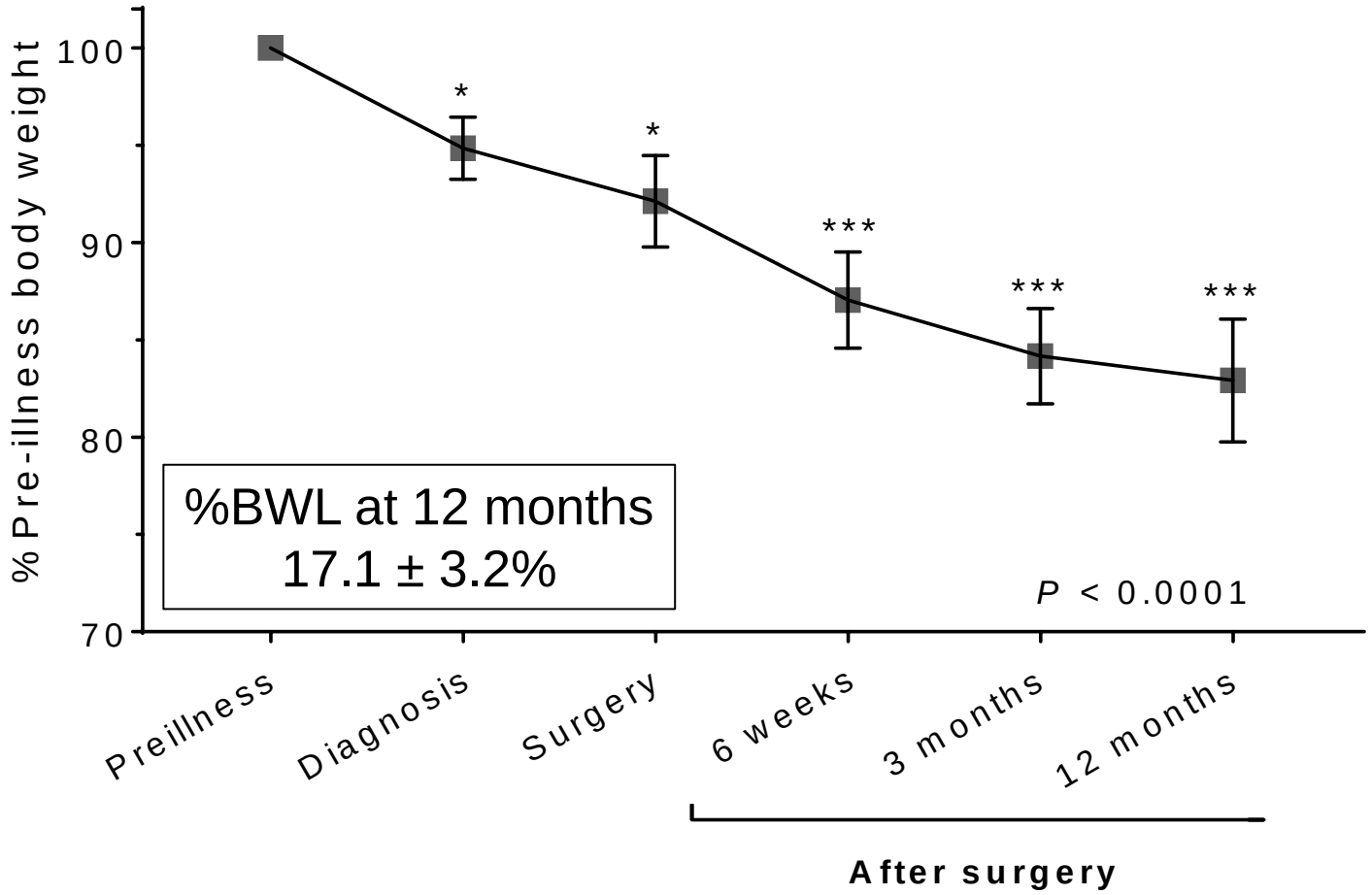
Predictors of weight loss:
1. Altered appetite
2. Eating difficulties

64% had >10% weight loss at 6 months

20% had >20% weight loss at 6 months

Martin *et al.* BJS. 2007, 2009

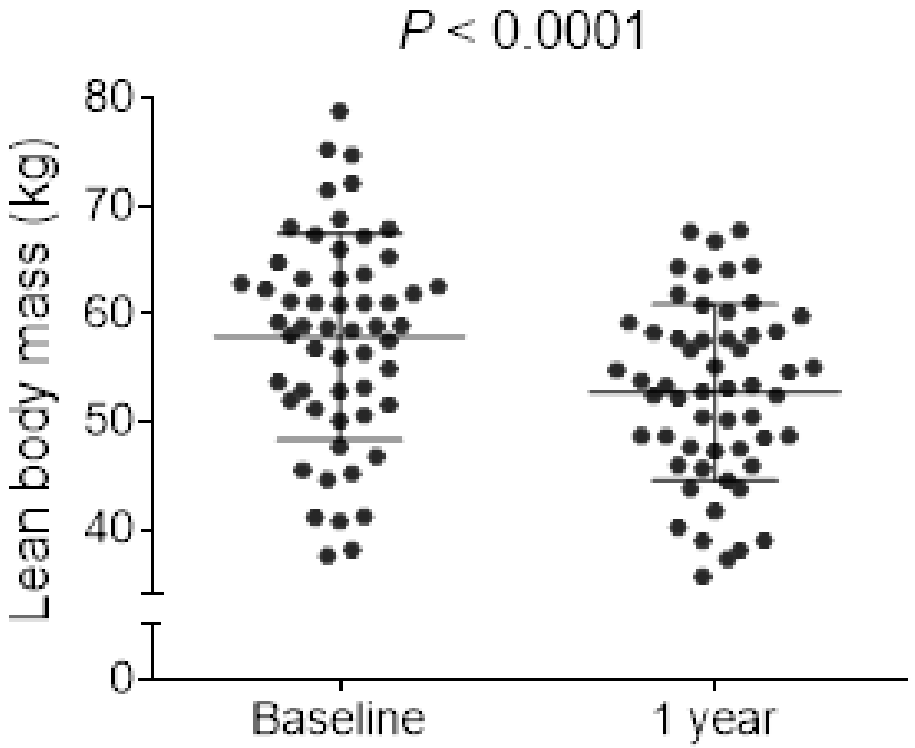
Significant body weight loss after oesophagectomy

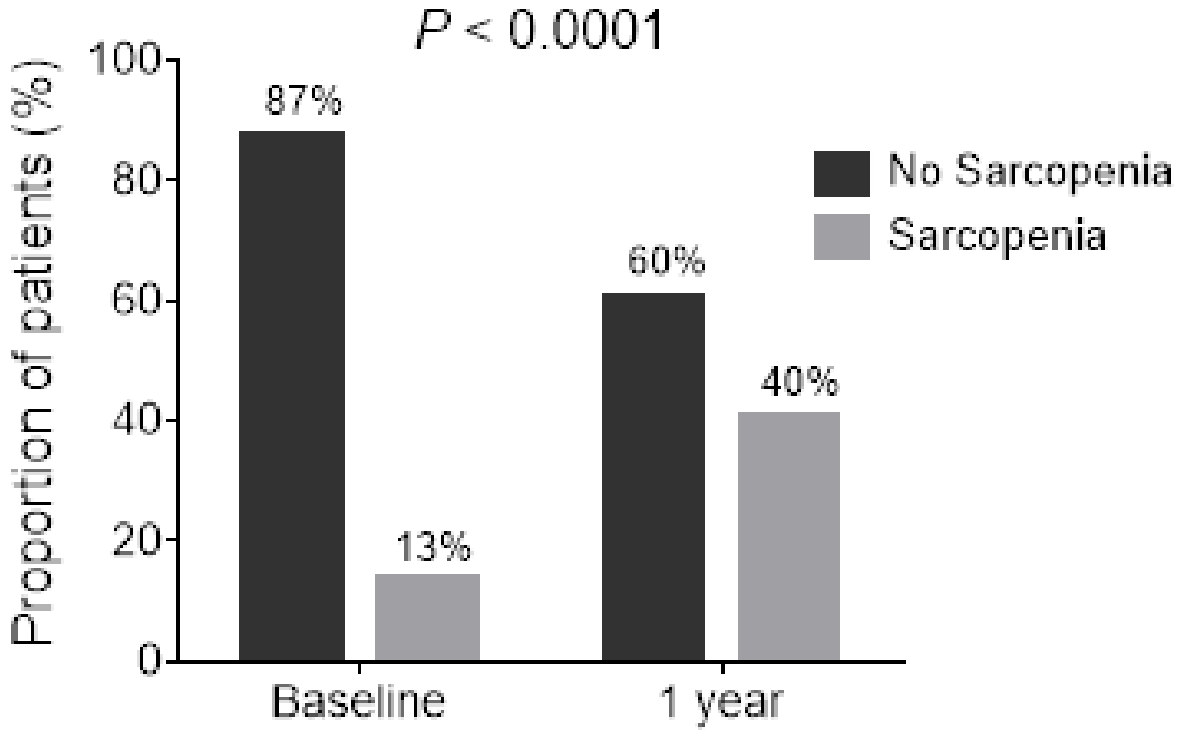


83% had >10% weight loss at 12 months

42% had >20% weight loss at 12 months

What is the impact of weight loss and nutritional impairment in survivorship?



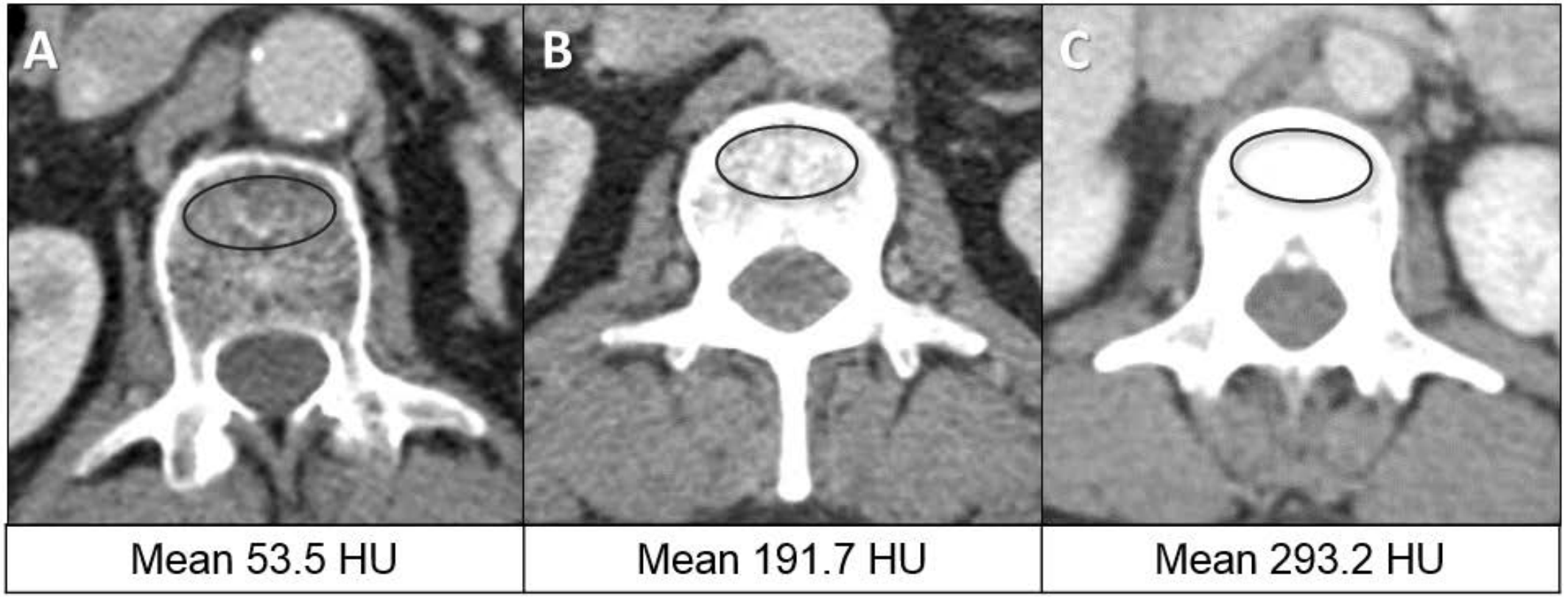


Patients achieving long-term disease-free survival -

Significant loss of LBM and 40% prevalence of sarcopenia

Elliott JA *et al*. 2016 (in press)

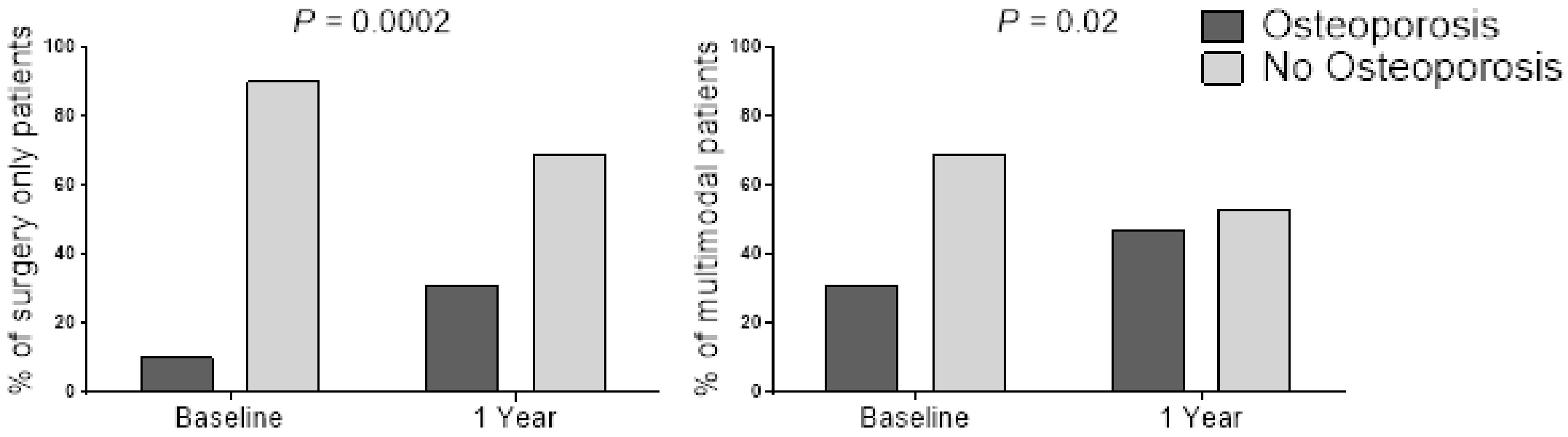
What is the impact of weight loss and nutritional impairment in survivorship?



Osteoporosis **Normal bone mineral density**

Elliott JA *et al*. 2016 (in press)

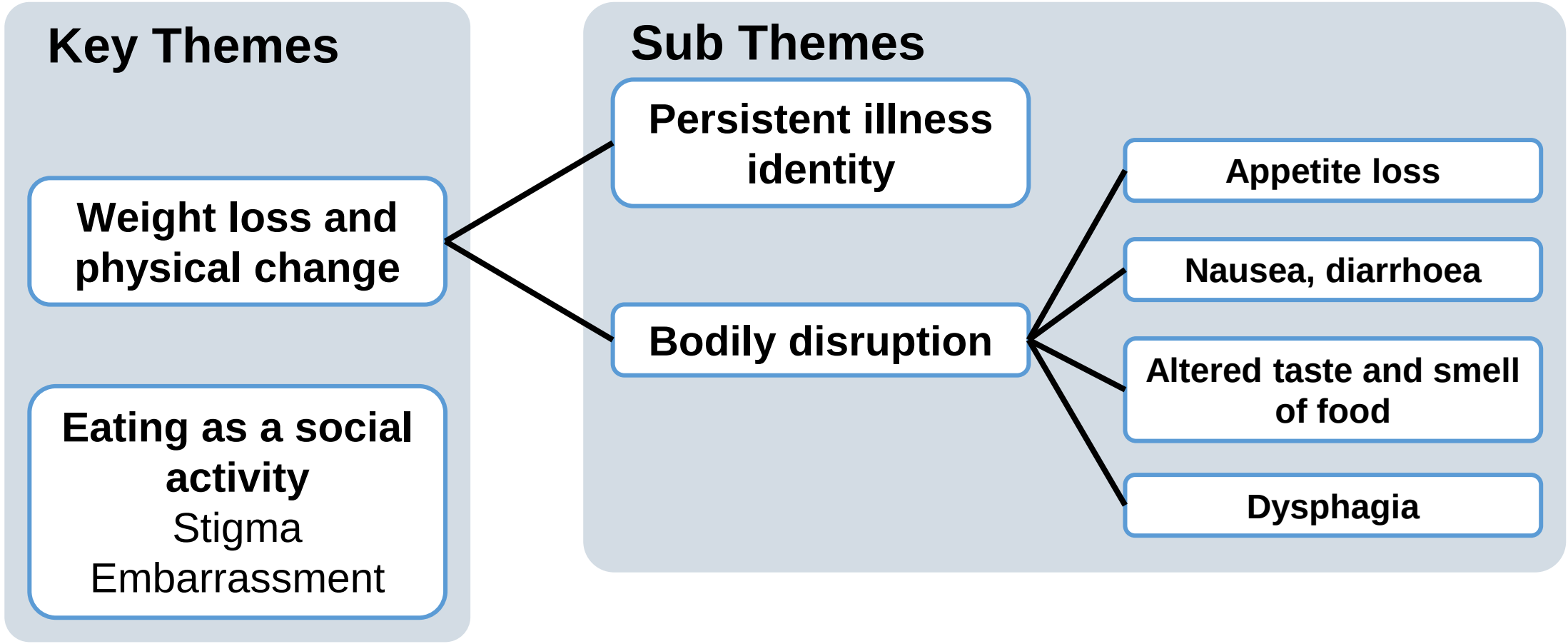
What is the impact of weight loss and nutritional impairment in survivorship?



Overall prevalence of osteoporosis increased from 25% to 38% in the first postoperative year (*P* = 0.049)

Elliott JA *et al*. 2016 (in press)

What is the impact of weight loss and nutritional impairment in survivorship?



Adapted from Wainwright, Blazeby *et al*.
Qualitative Health Research, 2007

What is the impact of weight loss and nutritional impairment in survivorship?

> I think if I could get back to 11st which would be about like a stone on since when I came out of hospital, if I can get a stone on me I would feel I was getting somewhere . . . also it is a big worry especially at the moment . . . I have got to watch out for weight loss in case the cancer has come back again. So I would say that plays on my mind as well.

The meaning of weight loss

> *Respondent:* I don't look particularly skeletal you know it is just the fact of compared to how I was I look a lot thinner and now and again you get a little thing that sort of upsets you. Some friends of ours, their daughter lives round the corner, and I was on one of my little daily walks and that is the first time I seen her since the operation and she walked straight past me you know, couldn't believe it, she didn't recognize me at all and things like that sort of upset you a bit, you know. It doesn't matter . . .
> *Wife:* I think it is, what you said, it is how people perceive you and as *[informant]* has said, if he had lost all his hair as well and the weight, people look at you and think "Oh."

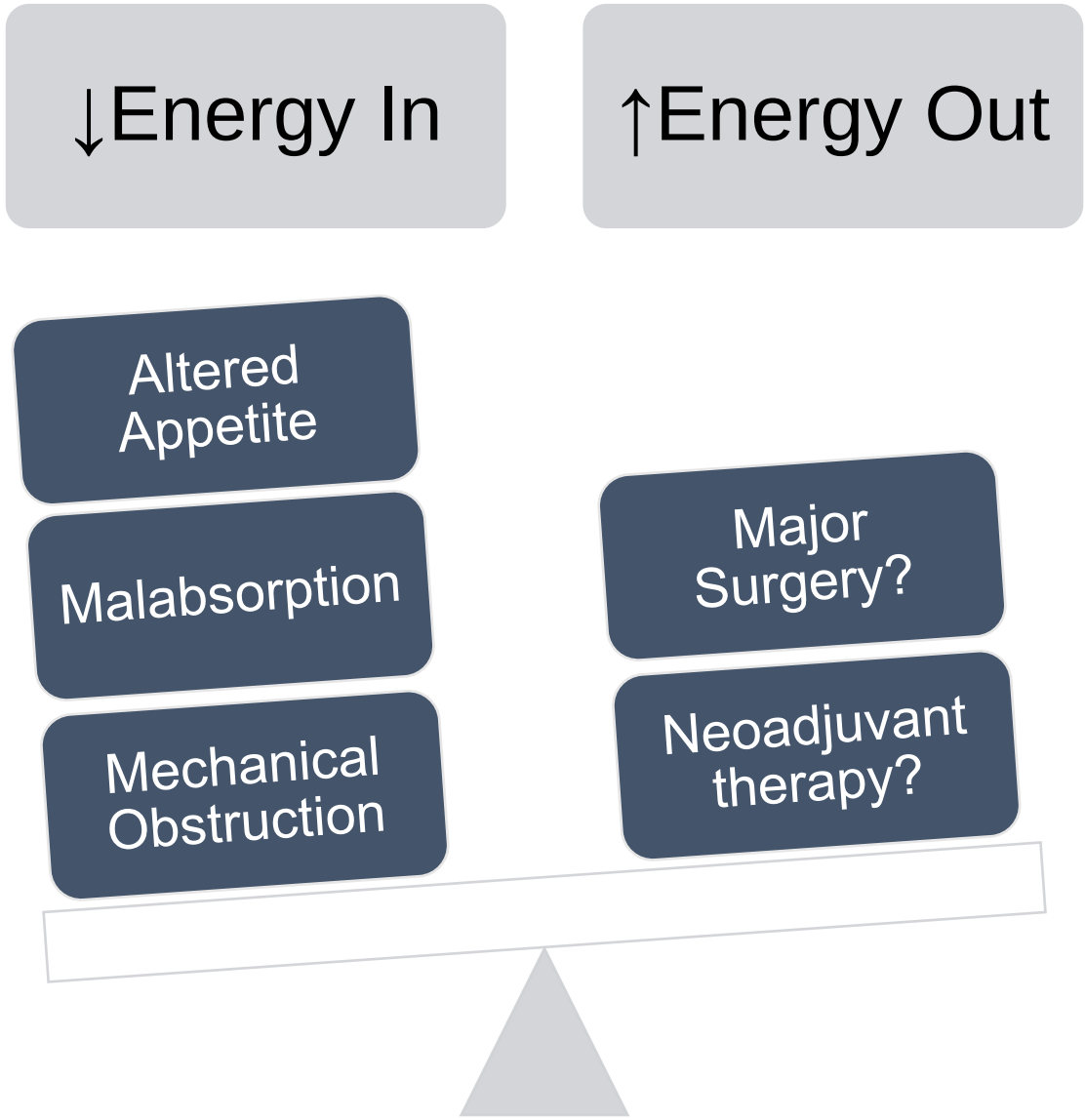
Persistent illness identity

> We went to Sainsbury's shopping and went into the café beforehand and I was actually sick in there and you know that really is a total turn off isn't it? It frightens the life out of me; so I am almost getting reclusive you know. I mean the family came at the weekend and [wife] fed all them and I had my tea separately. I was just absolutely terrified that I was going to be ill in front of them you know. . . . so we don't actually go out for meals at the moment. I am looking forward to the day when we can you know and I didn't realize what an important thing it was. It isn't so much the food it is sort of more of a social thing isn't it?

Eating as a social activity

Wainwright, Blazeby *et al*. Qual Health Res, 2007

Why do patients lose weight?



Why do patients lose weight?

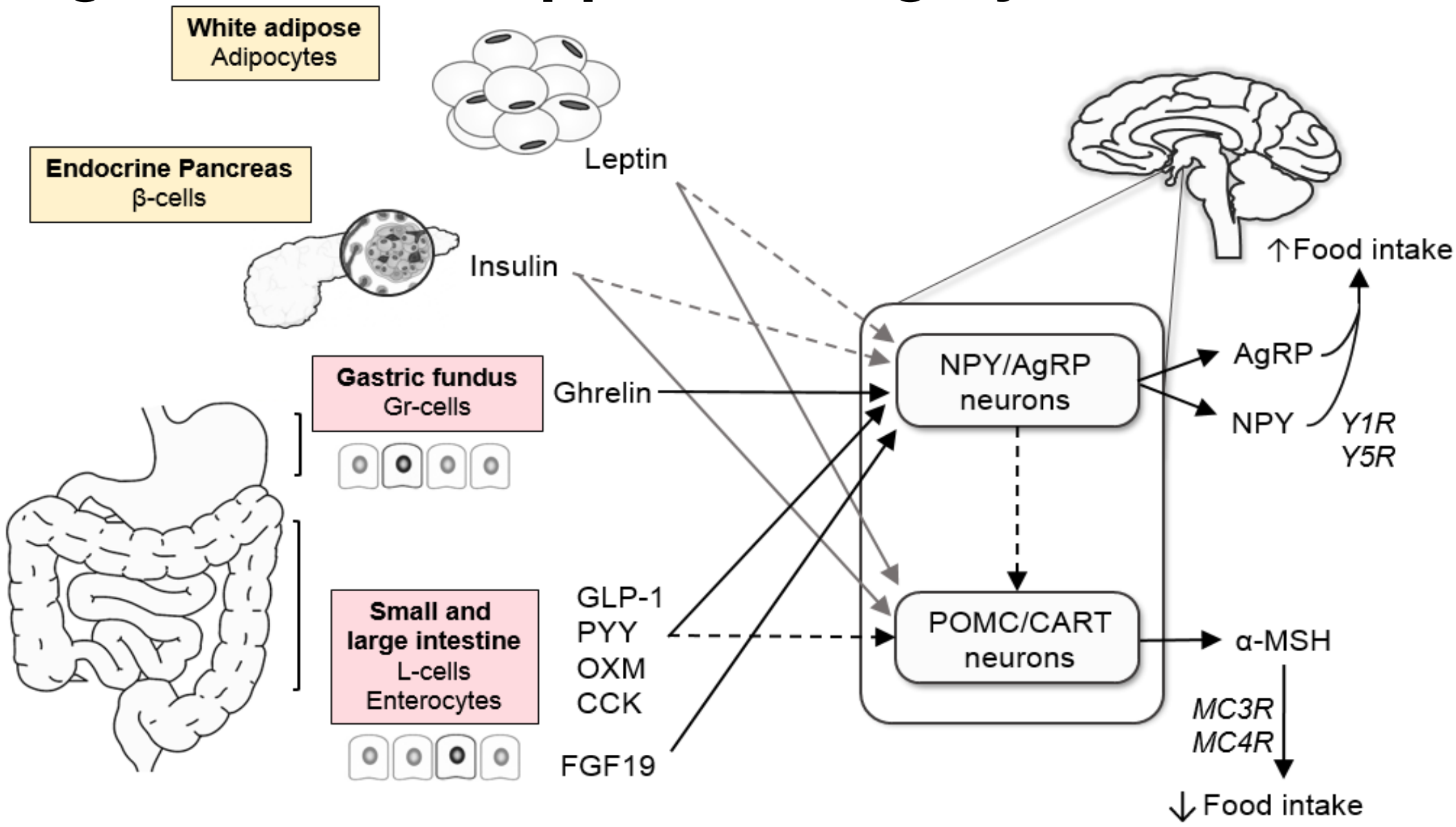
	%Δ Lean body mass	*P*-value
Baseline weight		0.096
Baseline BMI		0.28
Baseline LBM		0.001
Baseline FM		0.13
Dysphagia score		
0	-9.8 ± 8.8	
1	-10.4 ± 5.3	0.32
2	-6.6 ± 9.3	
3 – 4	-5.1 ± 4.1	
Clinical T stage		
1	-9.6 ± 6.8	
2	-3.6 ± 7.7	0.19
3 – 4	-8.9 ± 8.3	
Clinical N stage		
0	-8.8 ± 6.9	0.61
≥1	-7.7 ± 9.2	

	%Δ Lean body mass	*P*-value
Pathologic T stage		
0	-4.6 ± 7.2	
1	-8.2 ± 5.0	0.30 ǂ
2	-9.5 ± 7.2	
3	-10.0 ± 10.0	
Pathologic N stage		
pN-	-7.9 ± 6.9	0.40
pN+	-10.2 ± 12.2	
Neoadjuvant therapy		
Yes	-8.3 ± 8.4	0.98
No	-8.3 ± 7.4	
Operation type		
Transhiatal	-12.9 ± 11.6	
2-stage	-7.7 ± 6.2	0.049
3-stage	-5.2 ± 6.1	
HDU/ICU days		0.77

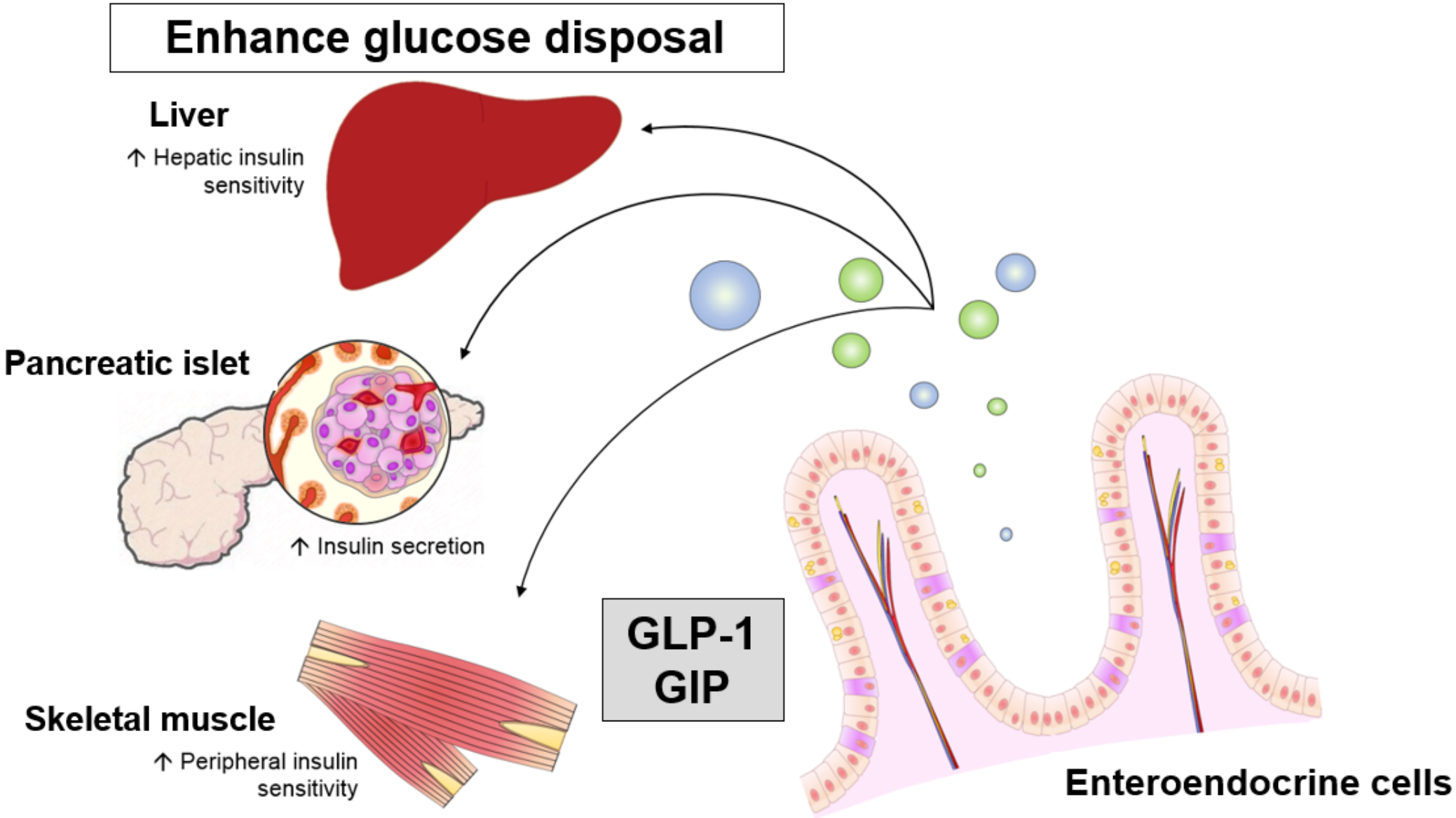
Postoperative LBM loss is not a result of neoadjuvant treatment or surgical complications

Elliott JA *et al*. 2016 (in press)

Candidate mediators of altered appetite and weight loss after upper GI surgery



Satiety and incretin gut hormones



Hypothesis

Gut hormones are **pathophysiologic mediators** of altered appetite and weight loss after upper GI surgery

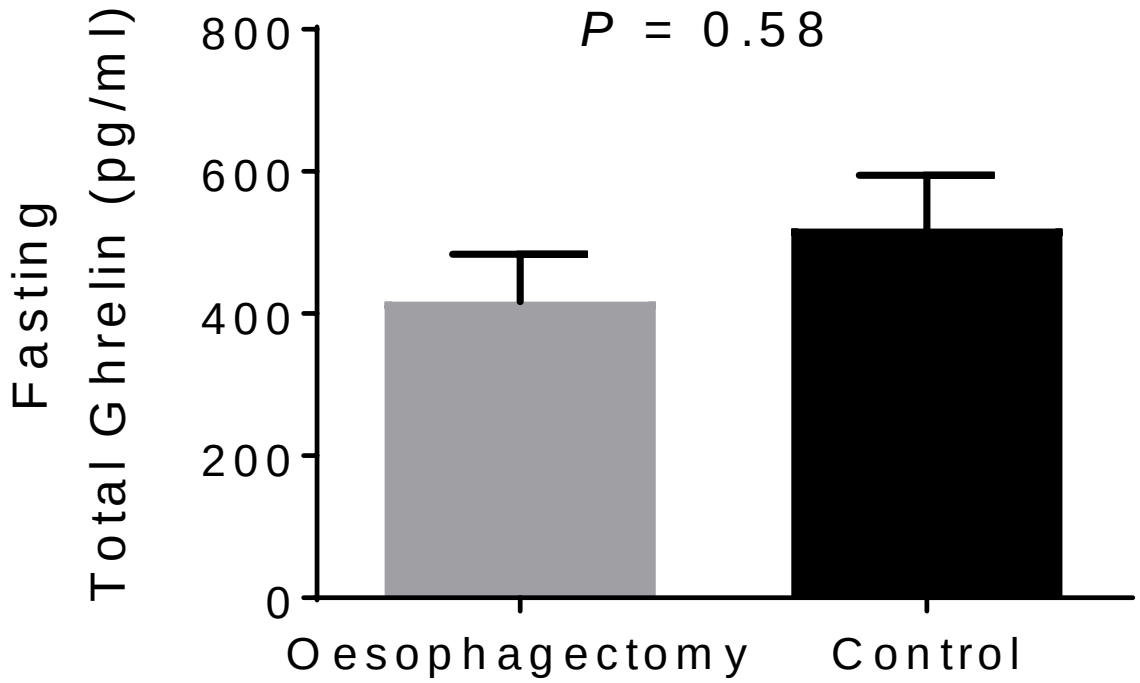
Questions

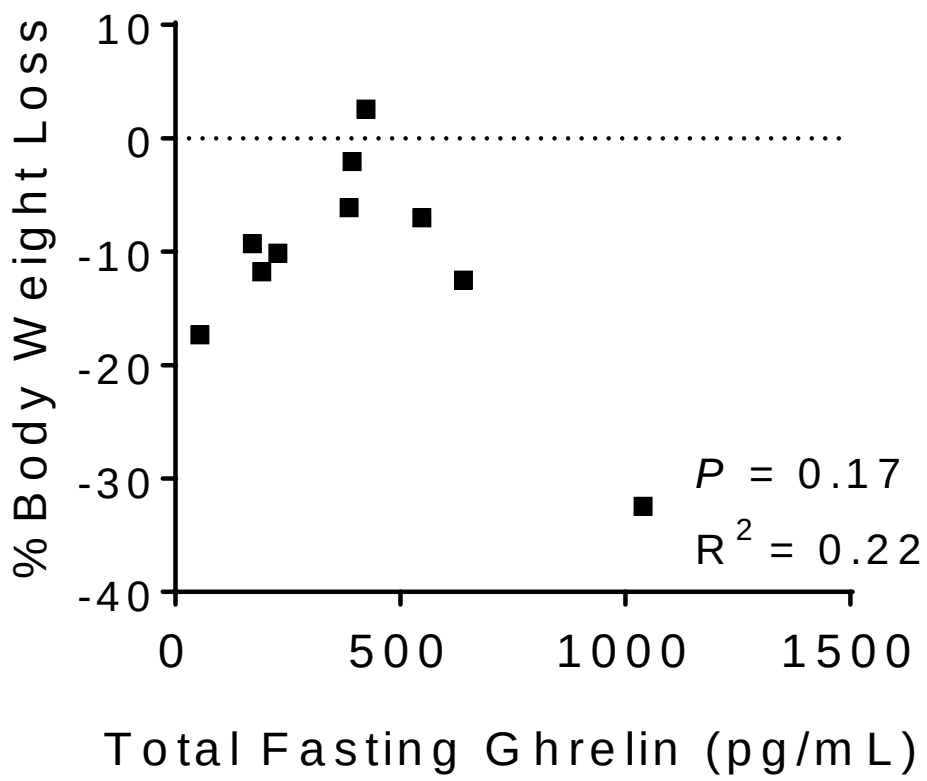
1. What happens to the gut hormone profile after upper gastrointestinal surgery?

2. Are gut hormones pathophysiologically linked to reduced appetite in this cohort?

3. If so, what can we do about it?

Question 1: What happens to gut hormones after upper gastrointestinal surgery?

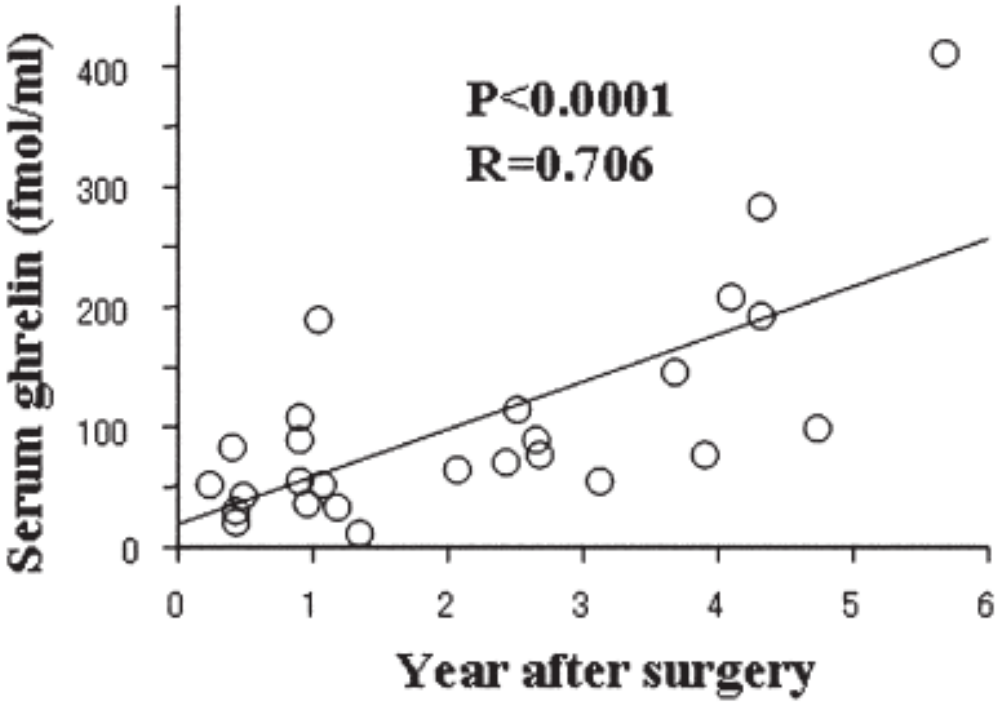




Fasting ghrelin does not correlate with %BWL in long-term disease-free patients

Elliott JA *et al*. Ann Surg (2015)

Question 1: What happens to gut hormones after upper gastrointestinal surgery?

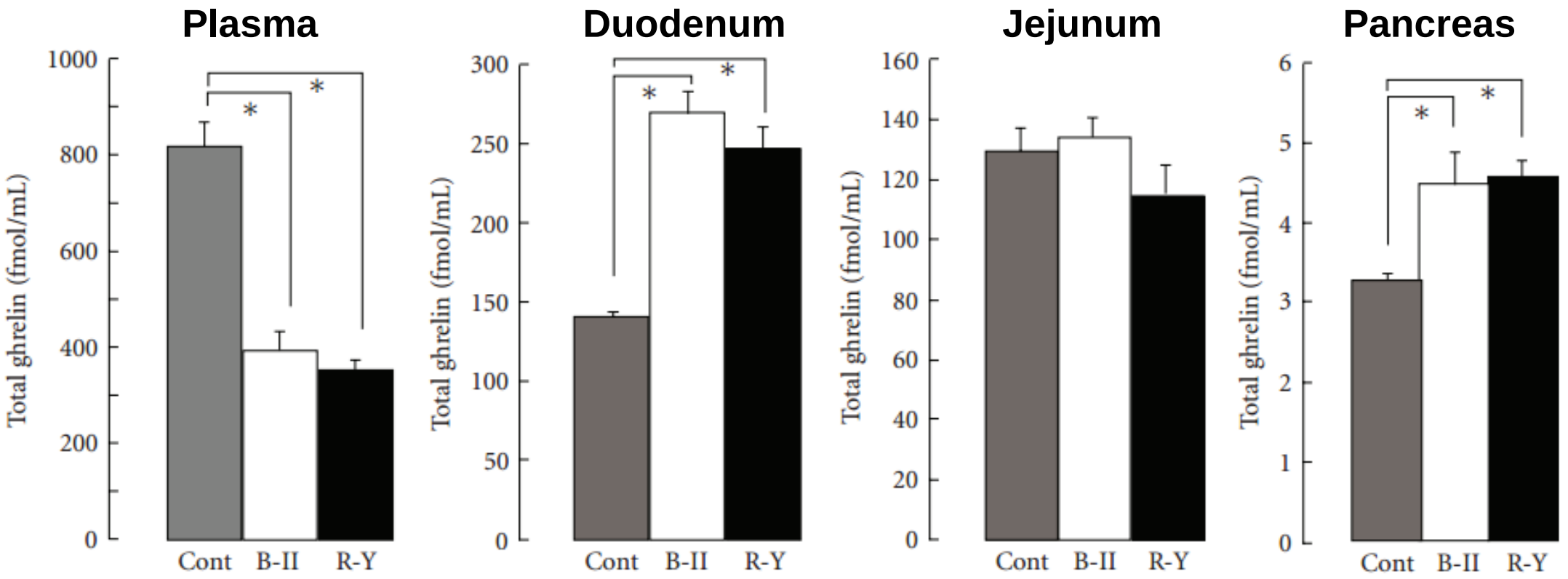


Authors	Year	N	Time-point	%control
Doki *et al.*	2006	26	25 (3-67) months	107.4%
Koizumi *et al.*	2011	22	6 months 12 months	99.7% 125.0%
Miyazaki *et al.*	2012	25	22 (6-24) months 53 (39-80) months	56.0% 111.6%

Ghrelin levels fall initially, but recover to baseline within 6 – 24 months

Appropriate upregulation?

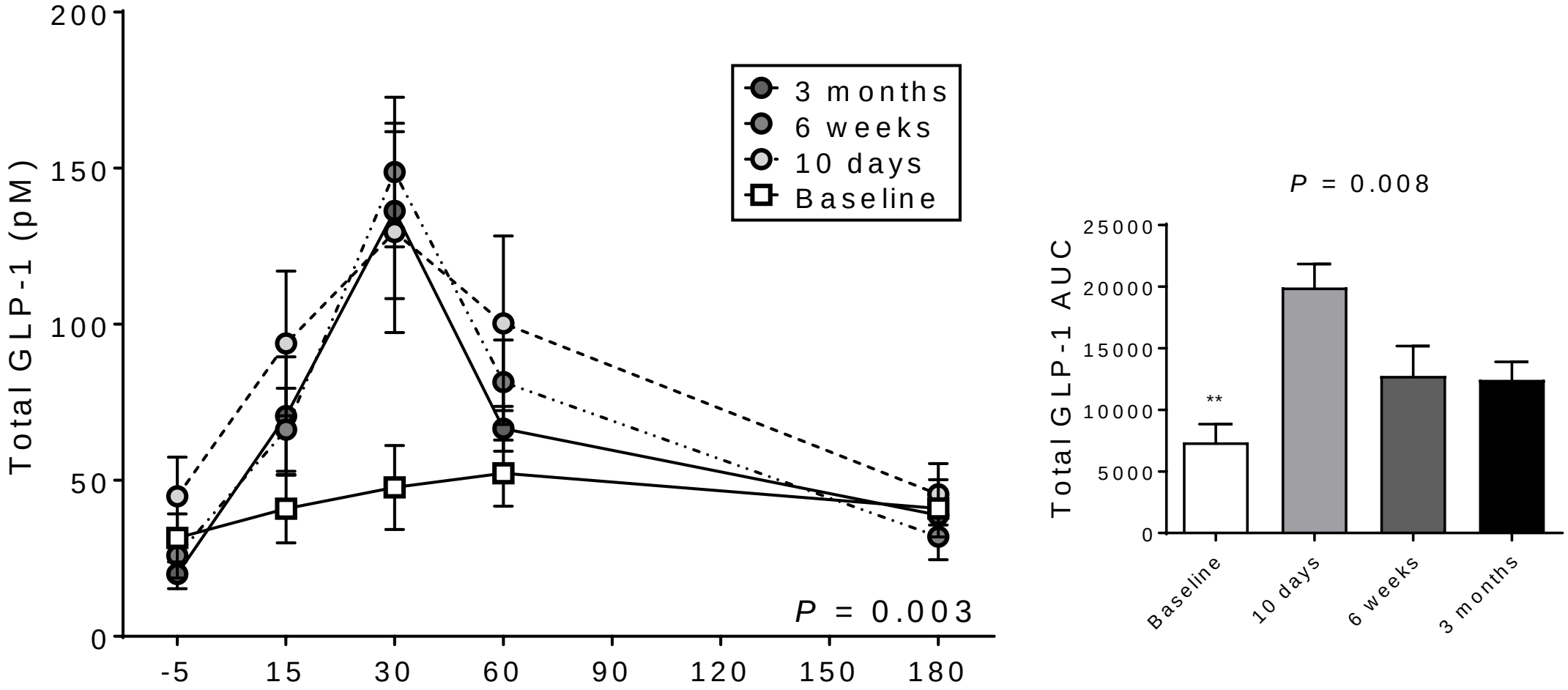
Question 1: What happens to gut hormones after upper gastrointestinal surgery?



Partial recovery of ghrelin production after total gastrectomy may be explained by increased expression at *extra-gastric* sites

Koizumi *et al*. Int J Pept (2009)

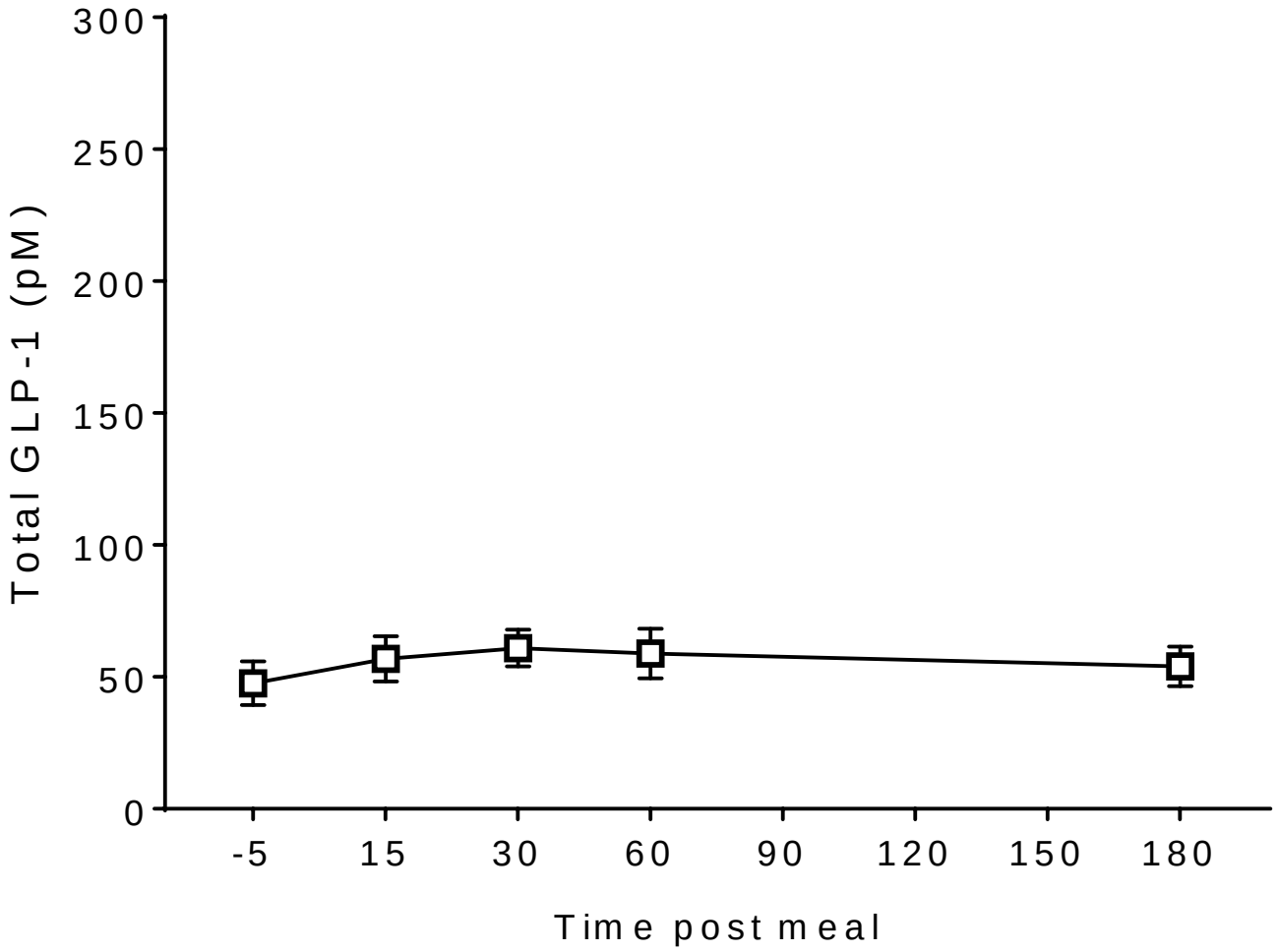
Question 1: What happens to gut hormones after total gastrectomy with Roux-en-Y?

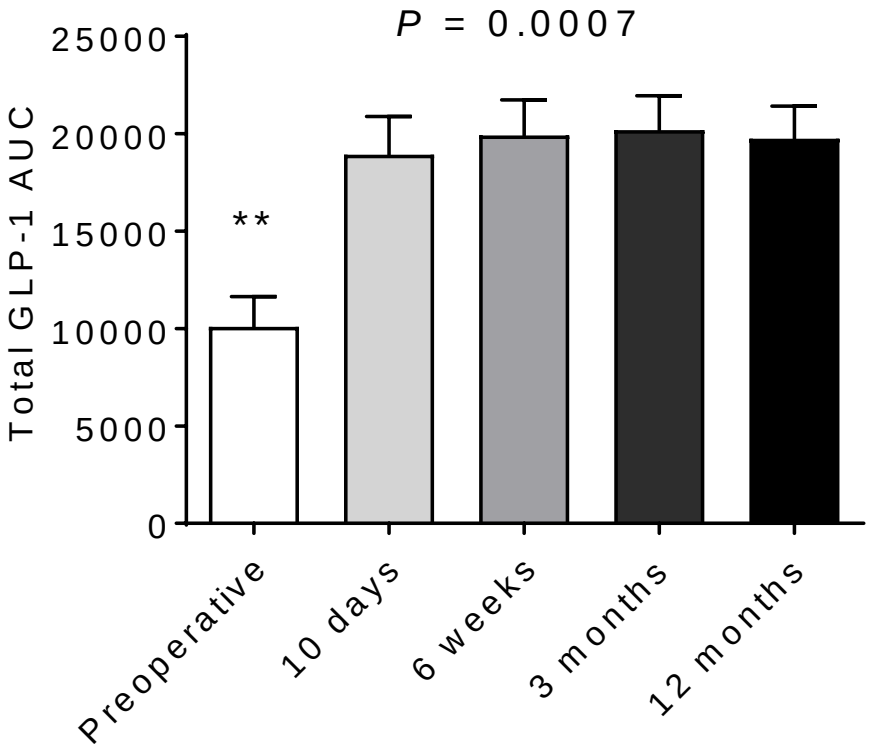


The satiety gut hormone response is exaggerated after gastrectomy R-Y

Unpublished data

Question 1: What happens to gut hormones after oesophagectomy?





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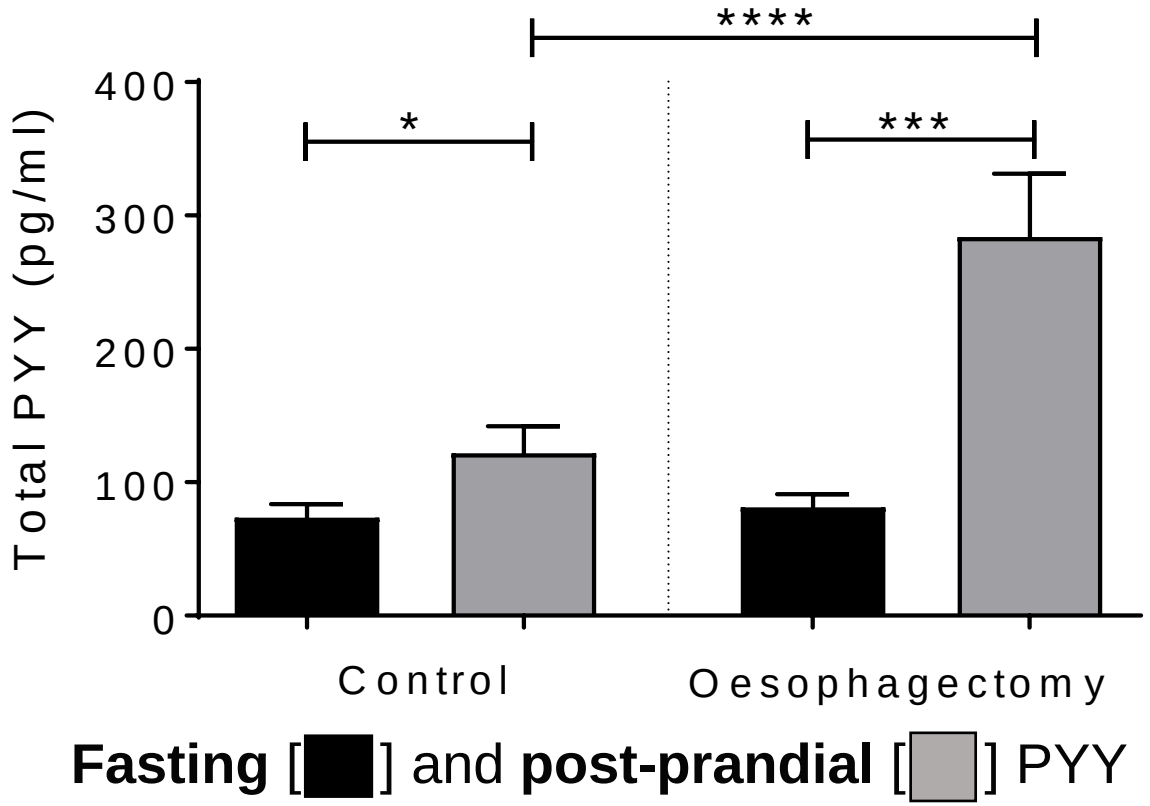
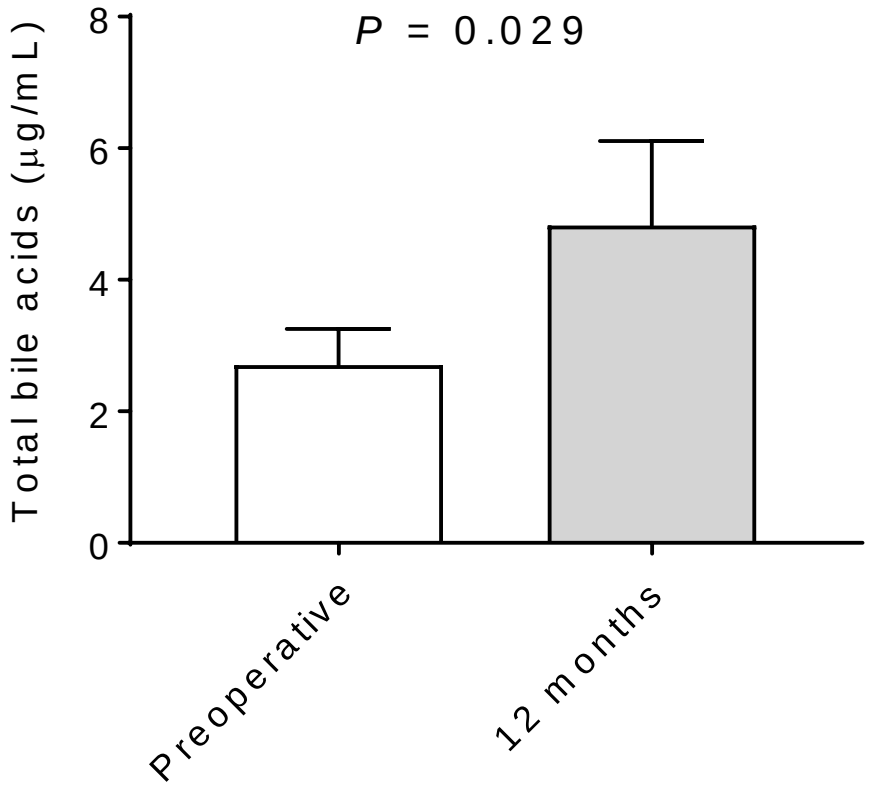
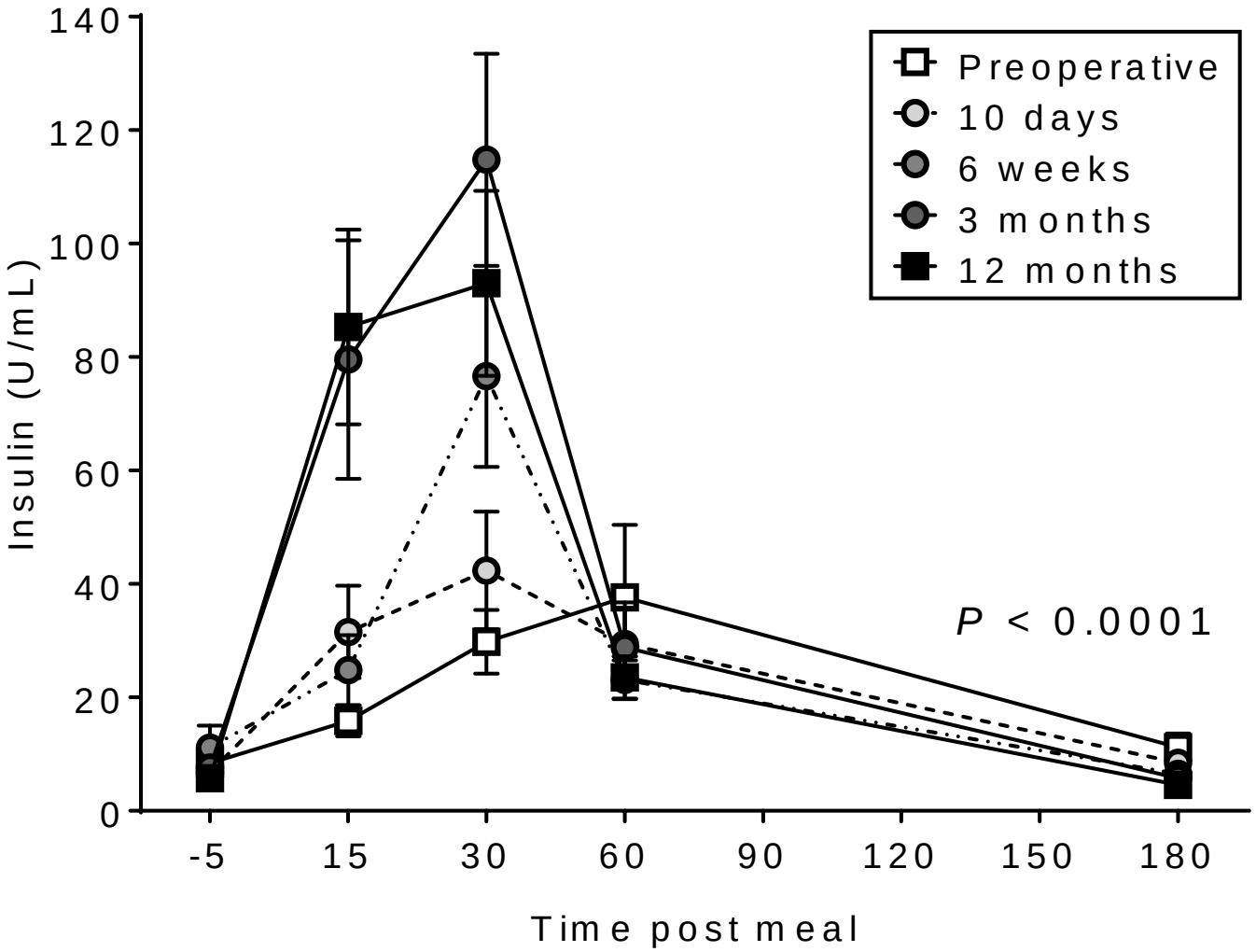


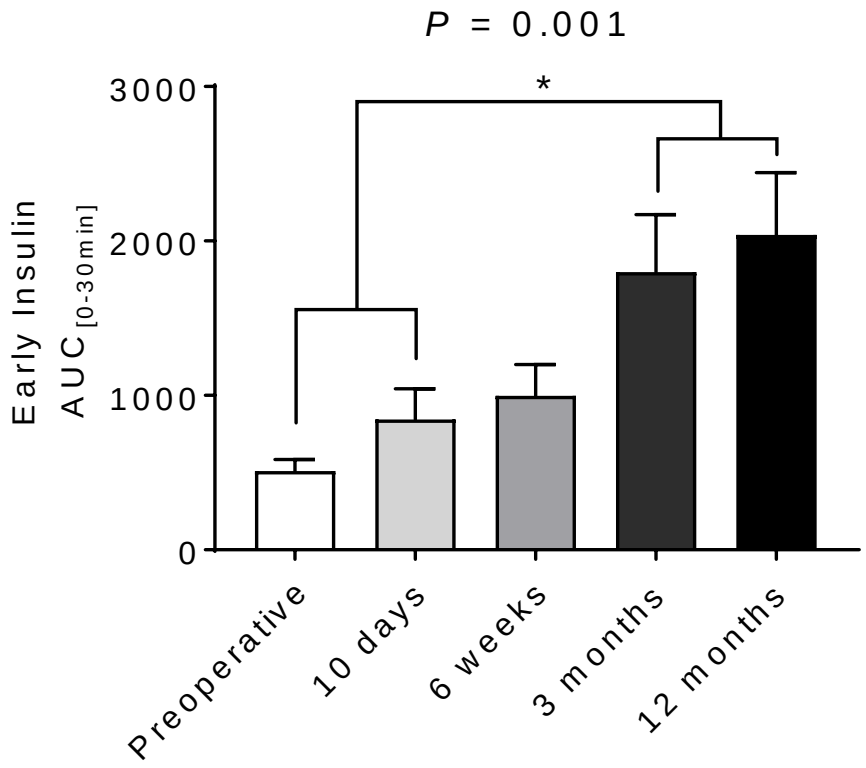


PYY and total bile acids are increased after oesophagectomy

Elliott JA *et al*. Ann Surg (2015) and unpublished data

Question 1: What happens to gut hormones after oesophagectomy?

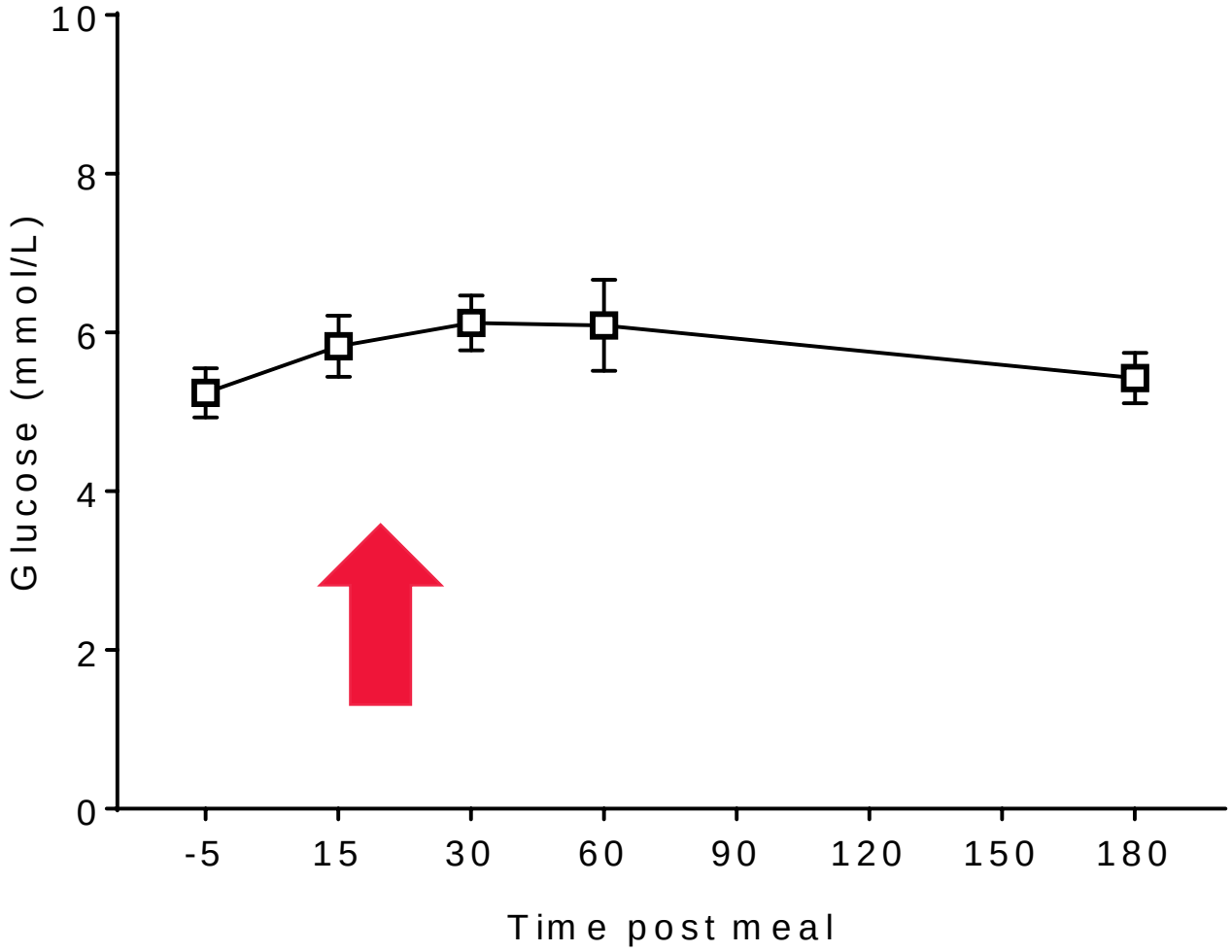


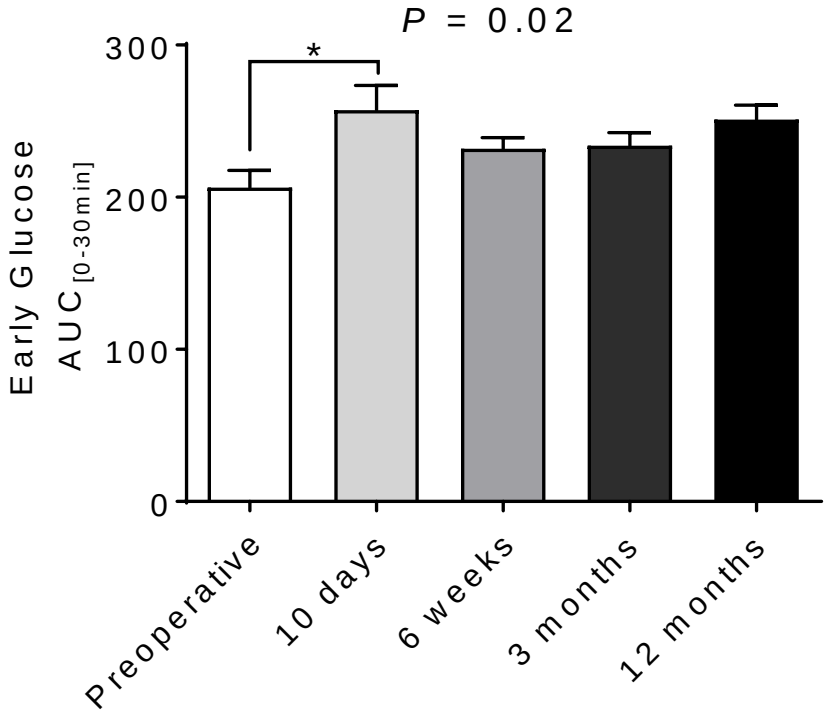


The insulin response increases progressively

Unpublished data

Question 1: What happens to gut hormones after oesophagectomy?



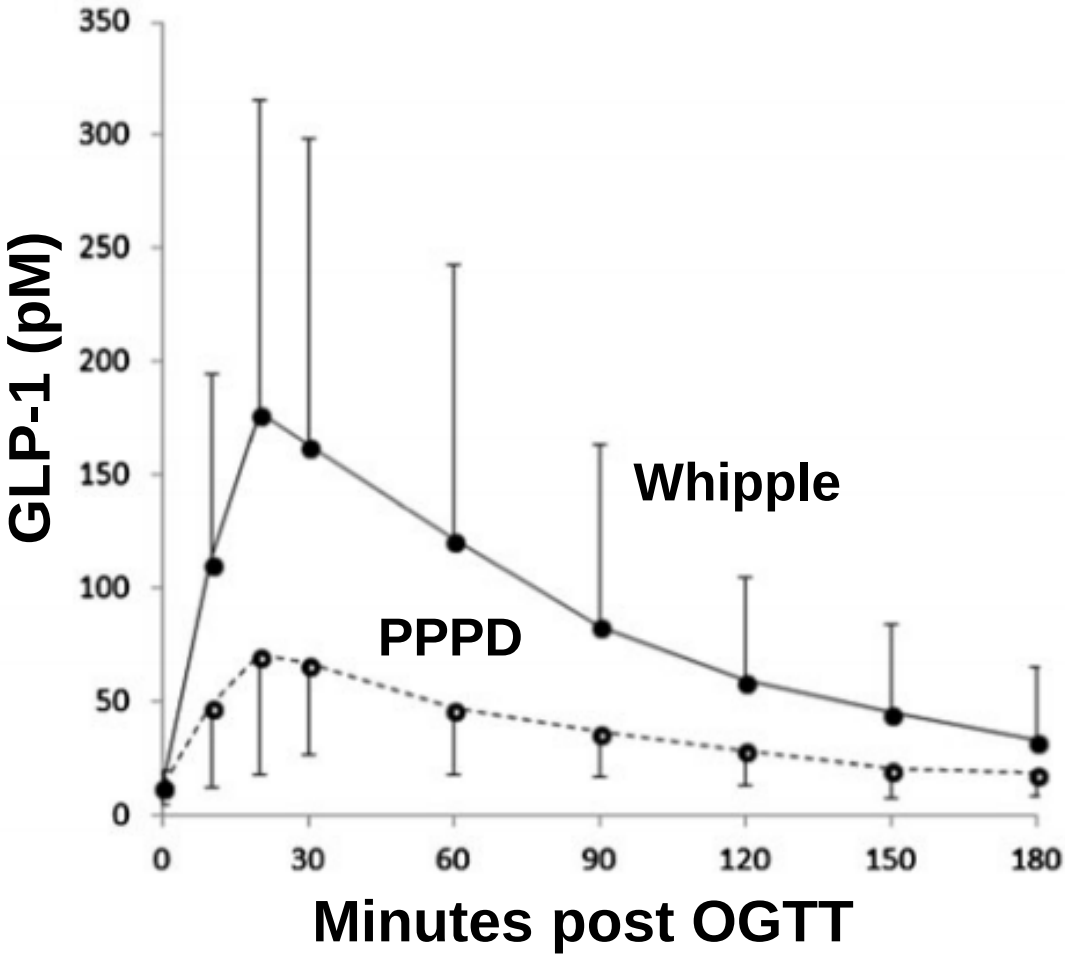


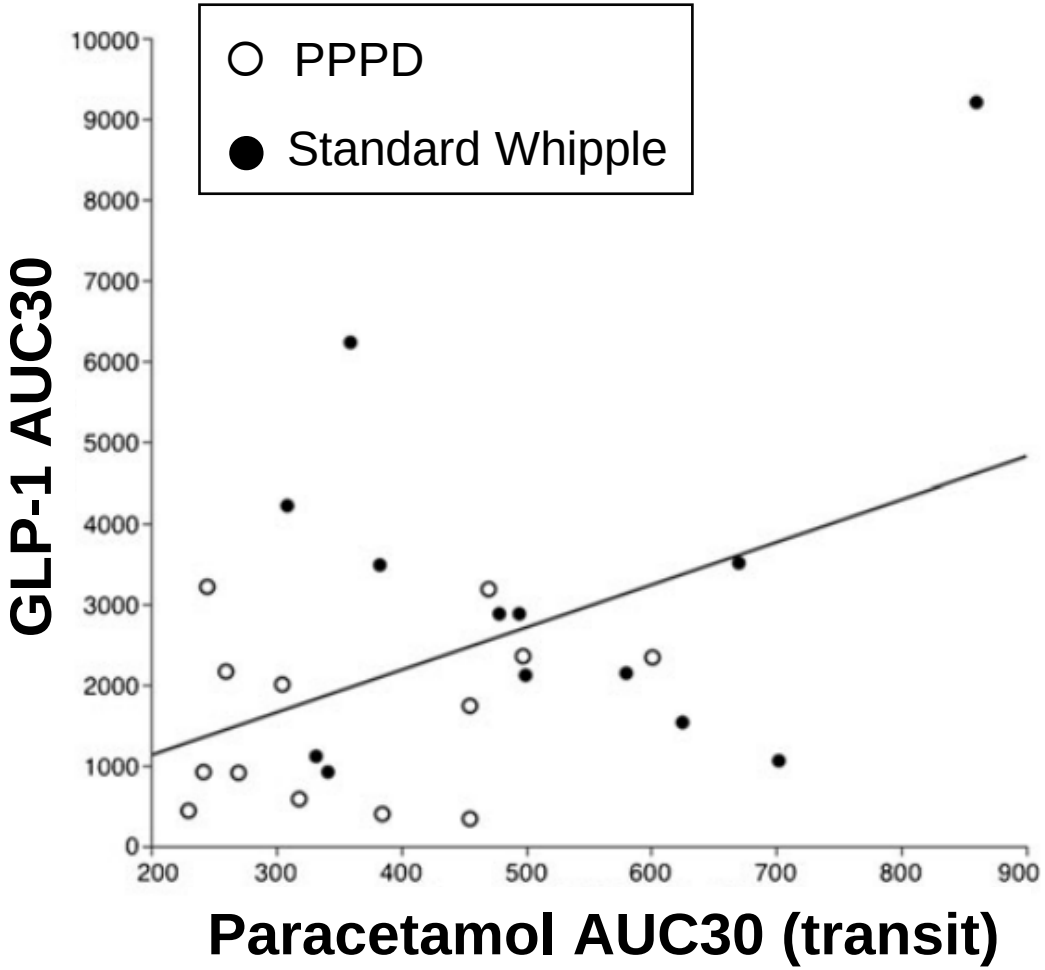
The rapid and transient spike in post-prandial glucose suggests rapid nutrient transit

17% of patients experienced late post-prandial hypoglycaemia with a mixed meal at one year post-operatively

Unpublished data

Question 1: What happens to gut hormones after pancreaticoduodenectomy?





Pyloric sphincter preservation attenuates the GLP-1 response

S Harmuth *et al*. J Gastrointest Surg, 2013

Questions

Question 1: What happens to the gut hormone profile after upper gastrointestinal surgery?

- **Increase in post-prandial satiety gut hormones**
- **Progressive increase in insulin response**
- **Long-term development of post-prandial hypoglycaemia**
- **Intact pyloric sphincter function may attenuate these effects**

Question 2*: Are gut hormones pathophysiologically linked to reduced appetite in this cohort?*

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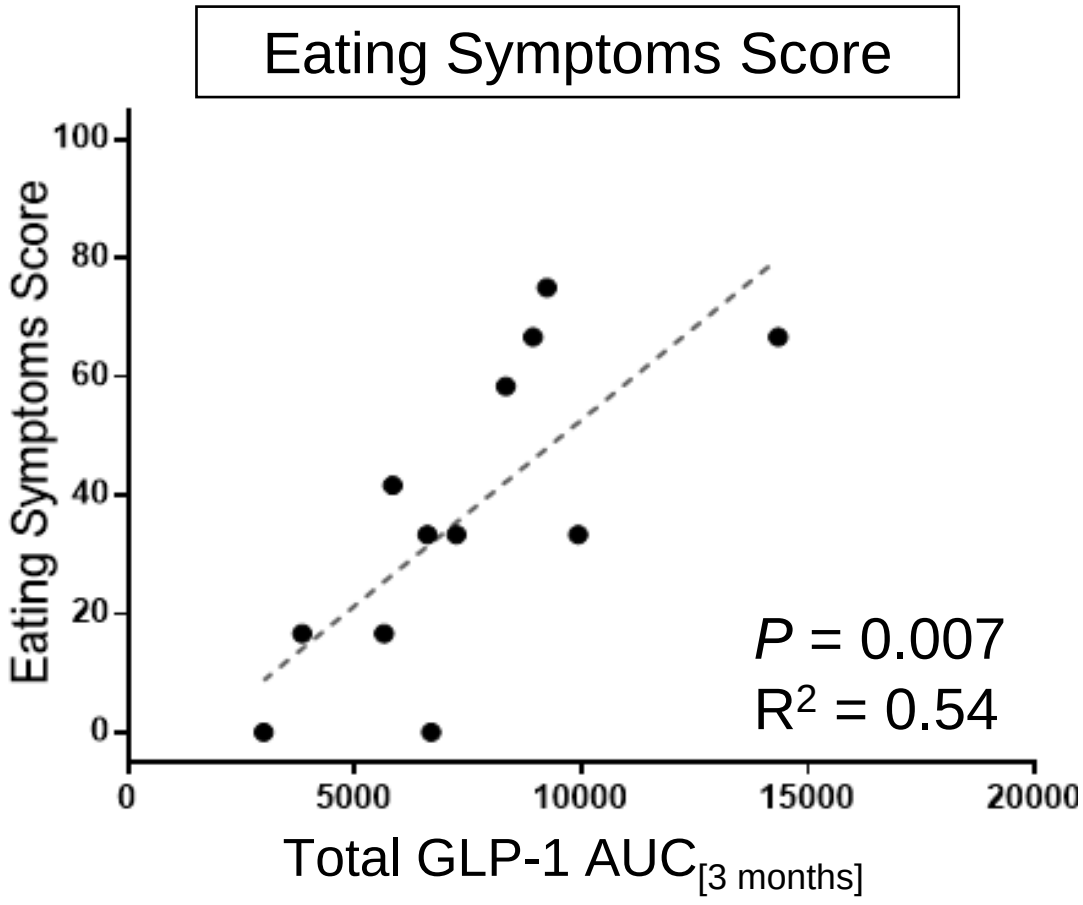
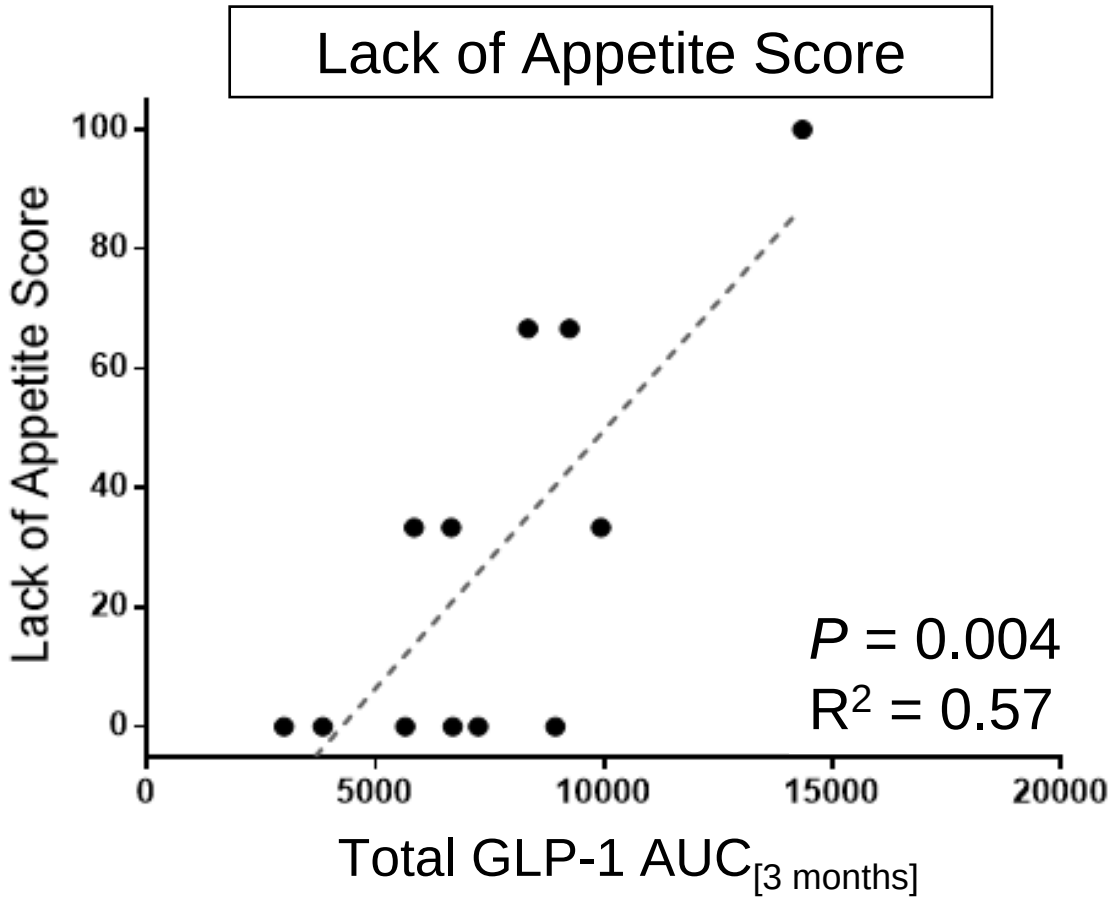
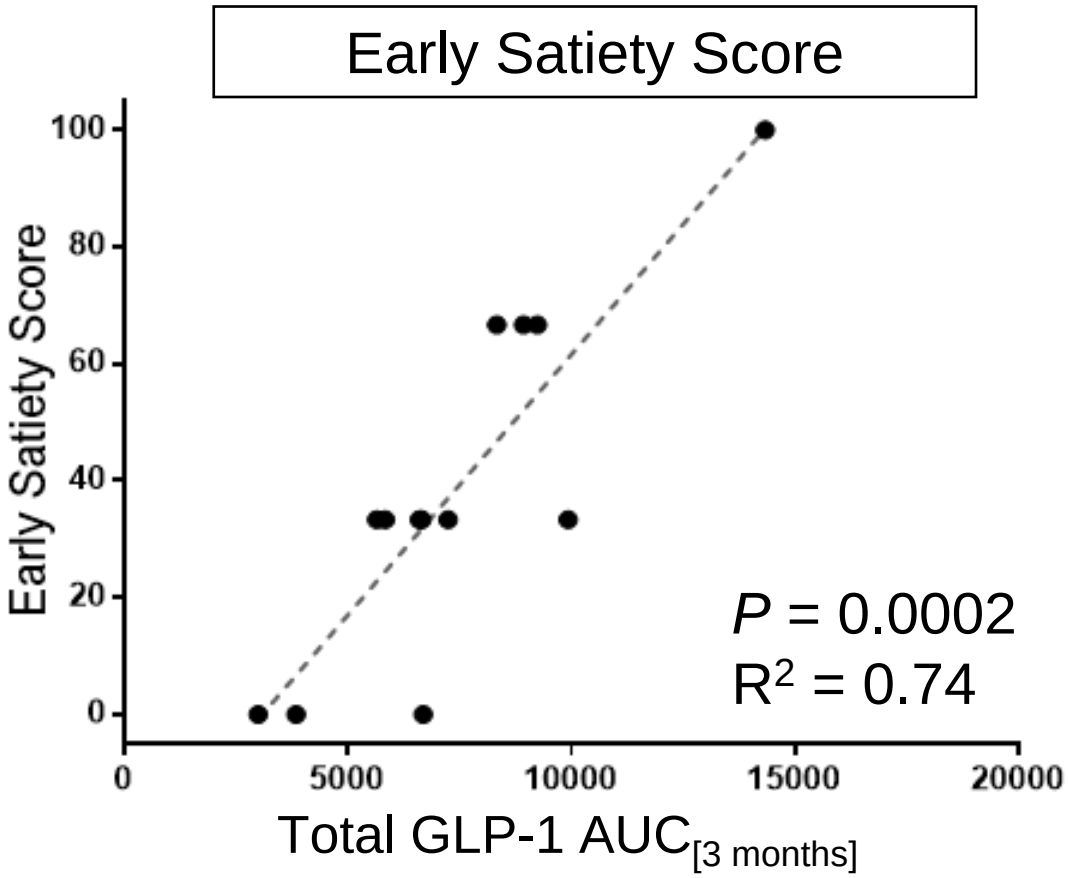
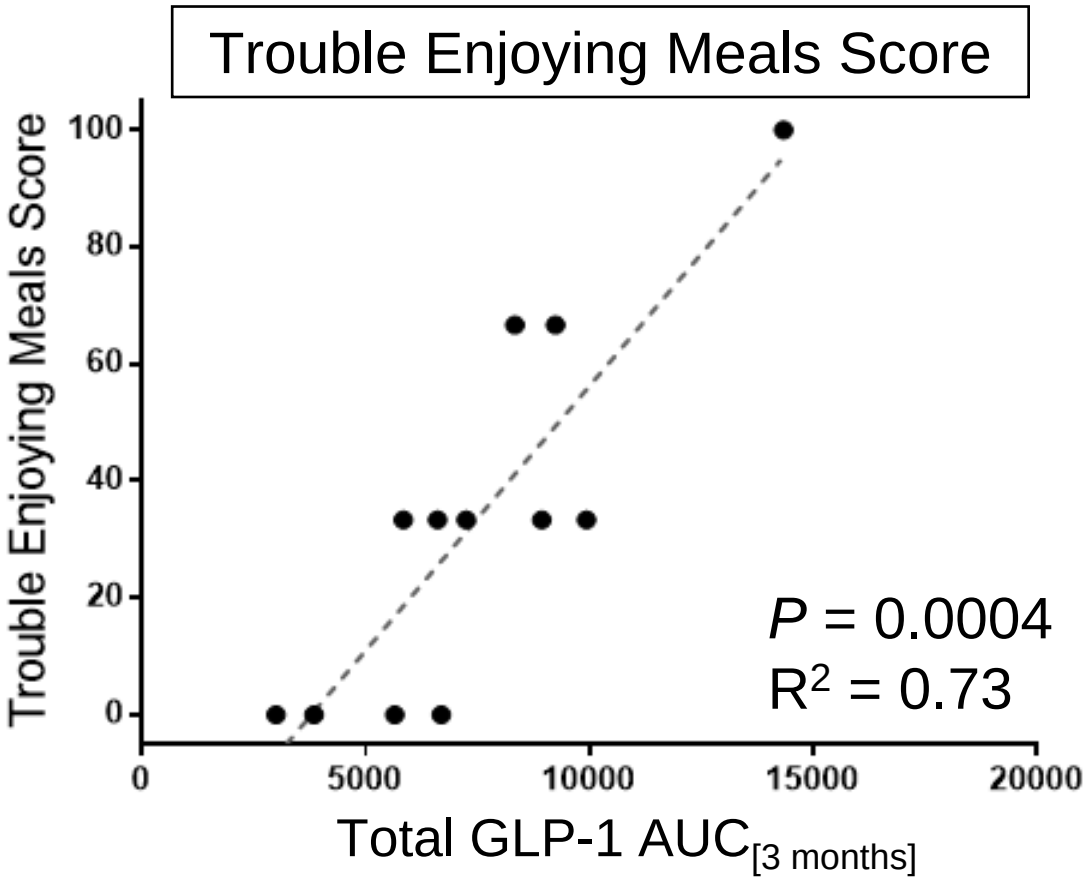




Elliott JA *et al*. Ann Surg (2016)

Question 2: Are gut hormones pathophysiologically linked to reduced appetite in this cohort?





Elliott JA *et al*. Ann Surg (2016)

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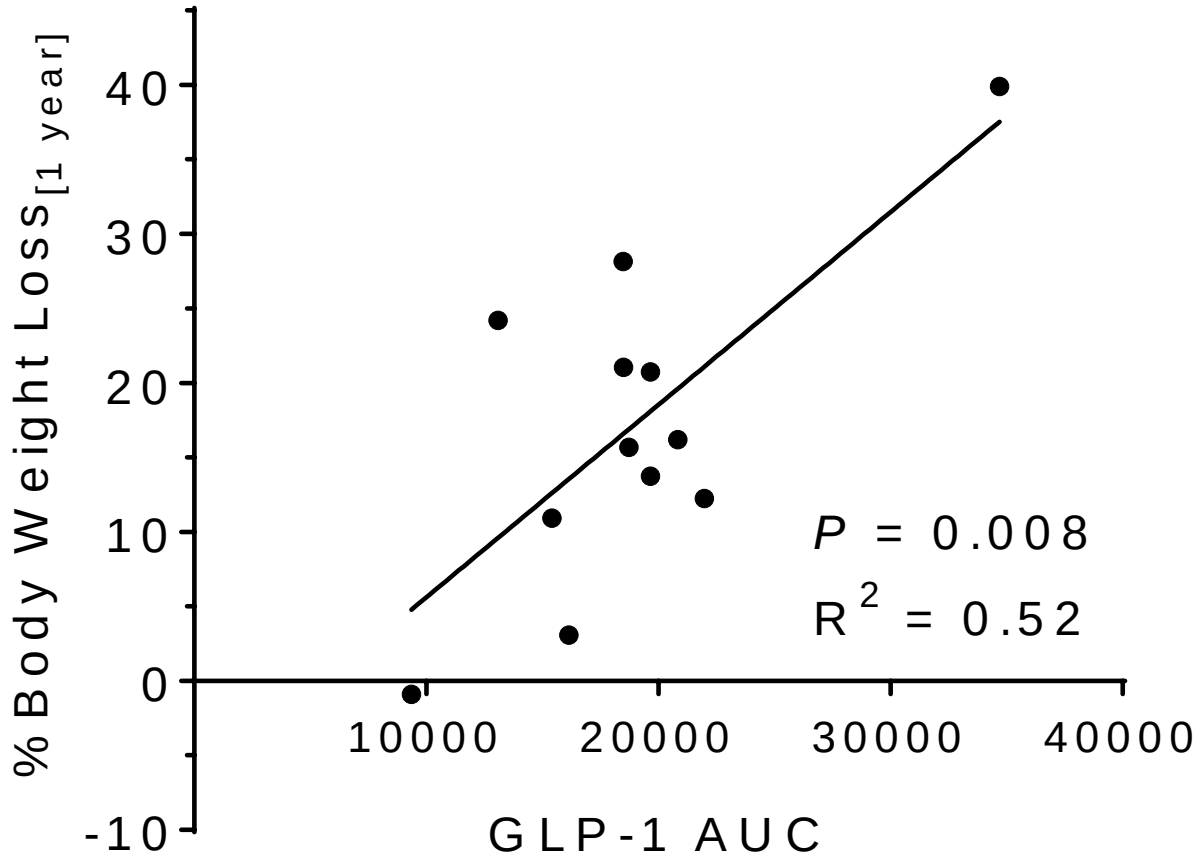
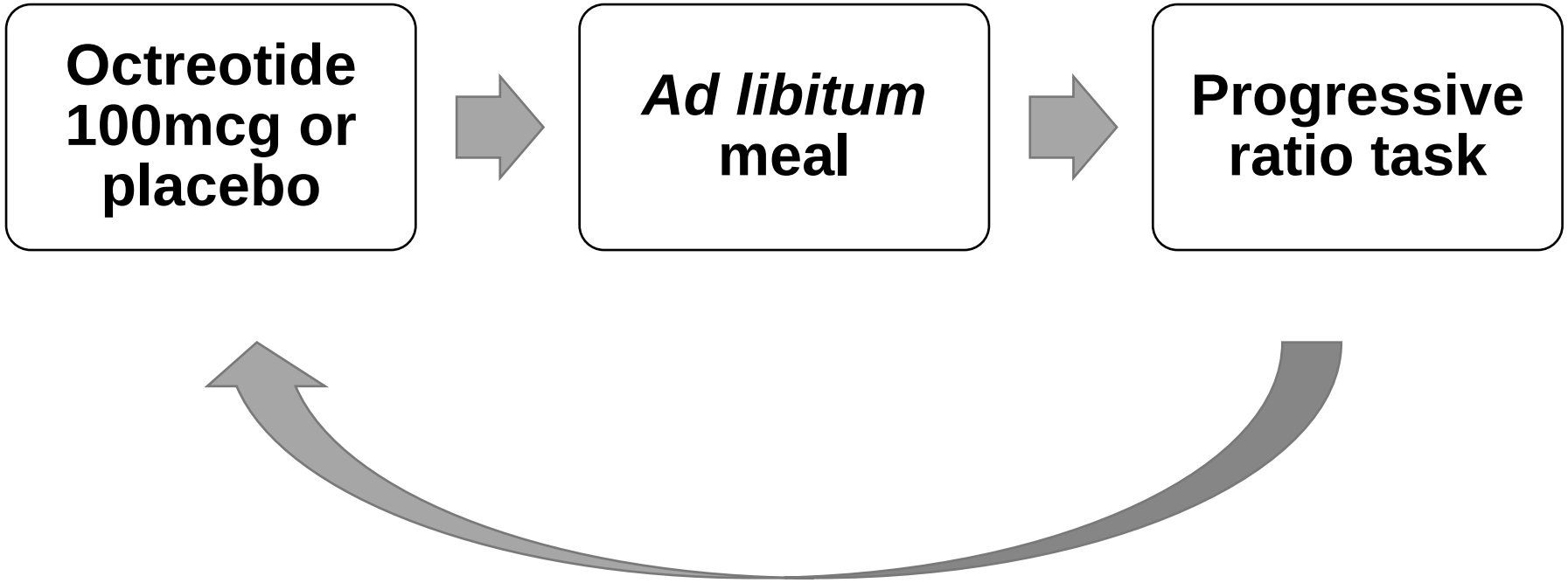


On multivariate analysis, the GLP-1 AUC was the sole independent predictor of %BWL at one year

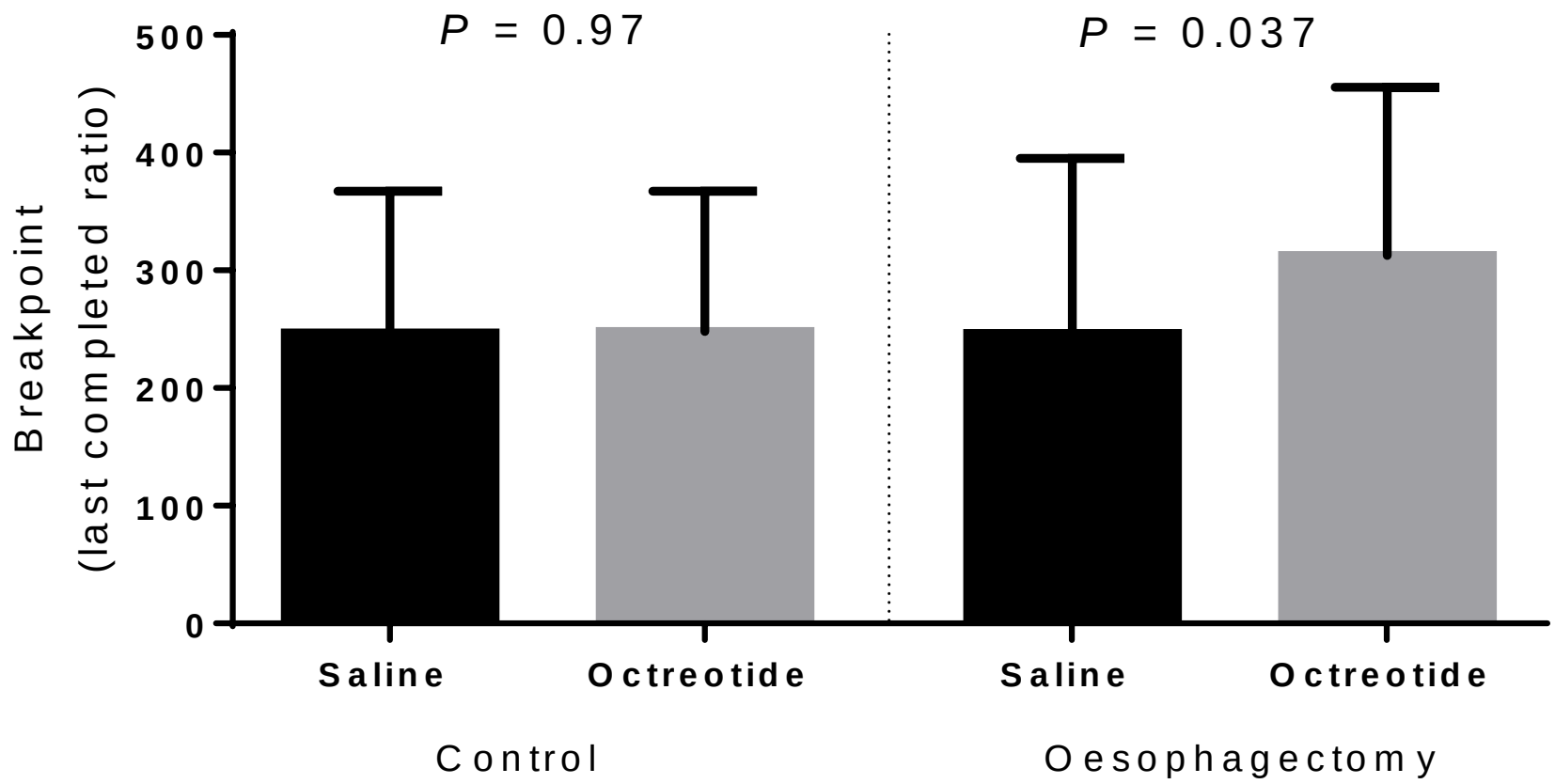
Unpublished data

Question 2: Are gut hormones pathophysiologically linked to reduced appetite in this cohort?



YouTube video (lab)

Question 2: Are gut hormones pathophysiologically linked to reduced appetite in this cohort?



Breakpoint ≈ Reward value of stimulus

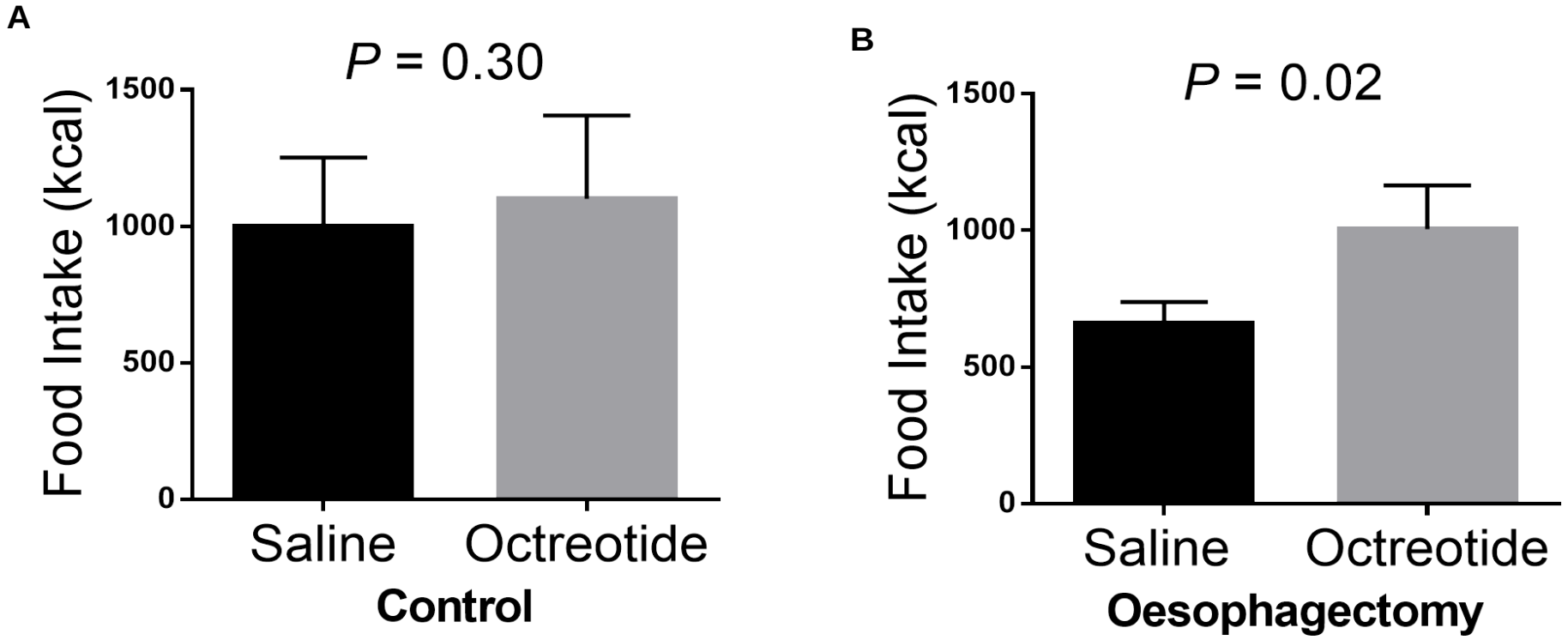
Unpublished data

ANNALS OF SURGERY

PAPER OF THE 22ND ANNUAL ESA MEETING

Gut Hormone Suppression Increases Food Intake After Esophagectomy With Gastric Conduit Reconstruction

Jessie A. Elliott, MB, BCh,† Sabrina Jackson, BSc,* Sinead King, BSc,† Ruth McHugh, MSc (Pharm),‡ Neil G. Docherty, PhD,* John V. Reynolds, MD, FRCS,† and Carel W. le Roux, FRCP, FRCPath, PhD*§*



Elliott *et al.* Ann Surg, Nov 2015

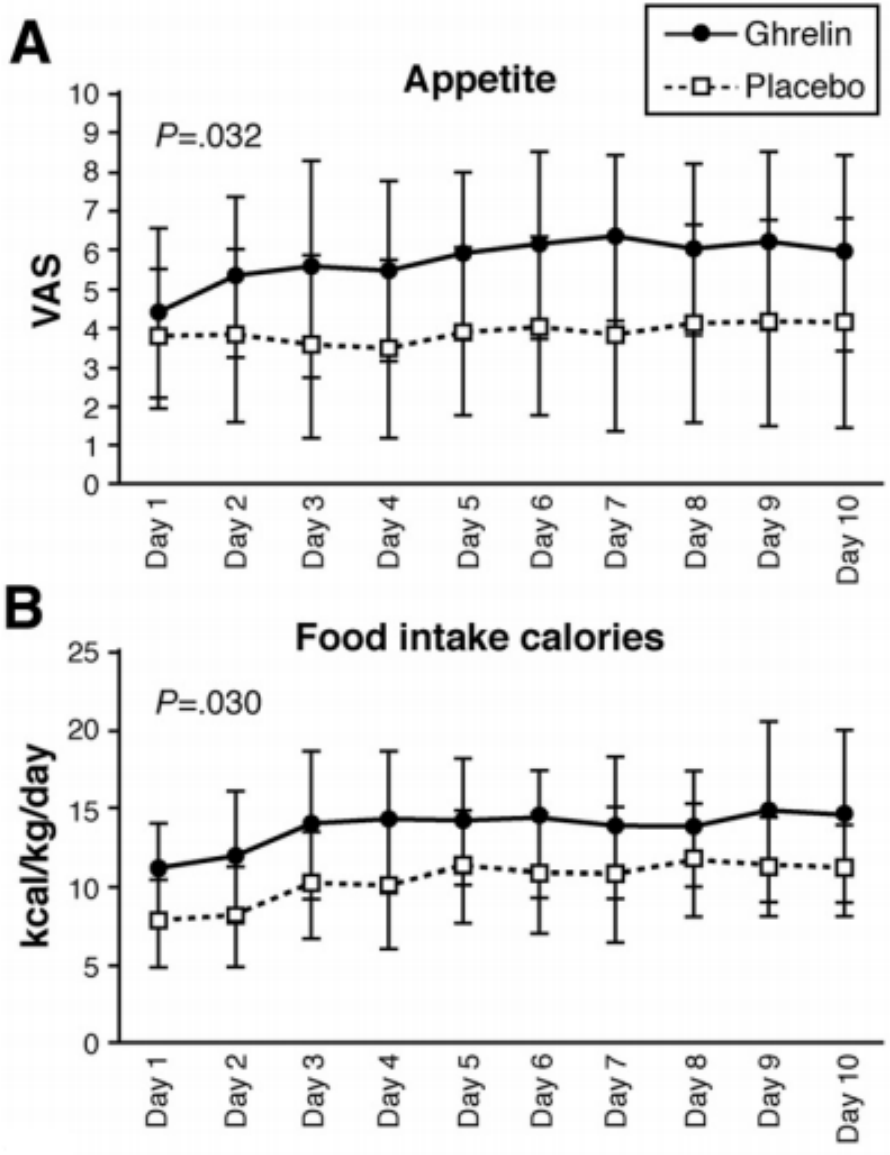
Questions

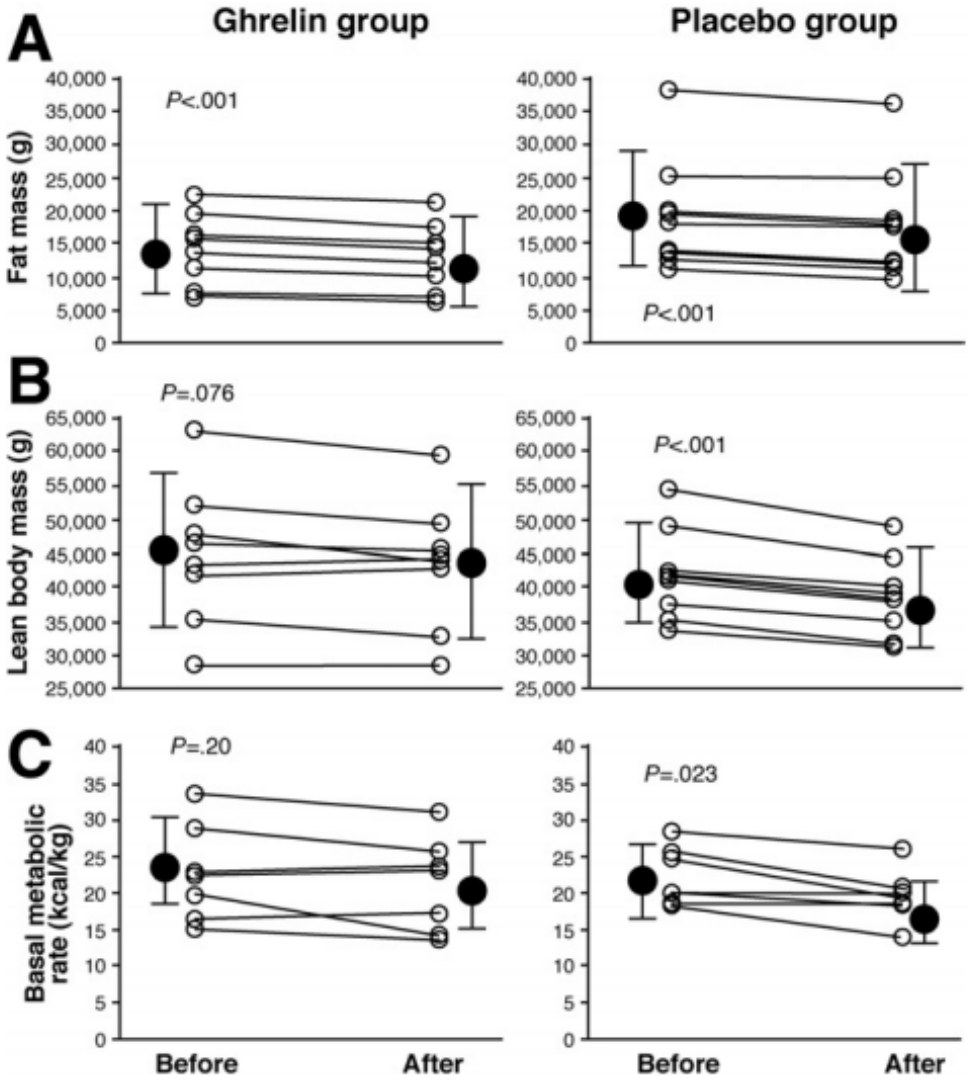
Question 2: Are gut hormones pathophysiologically linked to reduced appetite in this cohort?

- **The magnitude of the gut hormone response is associated with altered appetite, early satiety and weight loss**
- **Blockade of gut hormones increases appetitive behaviour and food intake**

Question 3*: If so, what can we do about it?*

Question 3: If so, what can we do about it?
Exogenous ghrelin – limited data





Adachi *et al.* Gastroenterology (2010)

What can we do about it?
Anamorelin – a novel, orally bioavailable, ghrelin receptor agonist

- **Is this a Gr or a GH effect?**
- **Will this work in patients where intake is limited by post-prandial symptoms and early satiety?**
- **Functional outcomes?**
- **Is there any effect on oncologic outcome?**
  - Gatrointestinal malignancies*

*See Tian *et al*, Mol Cell Biochem (2013)
Ghrelin induces gastric cancer cell proliferation, migration, and invasion through GHS-R/NF-κB signaling pathway

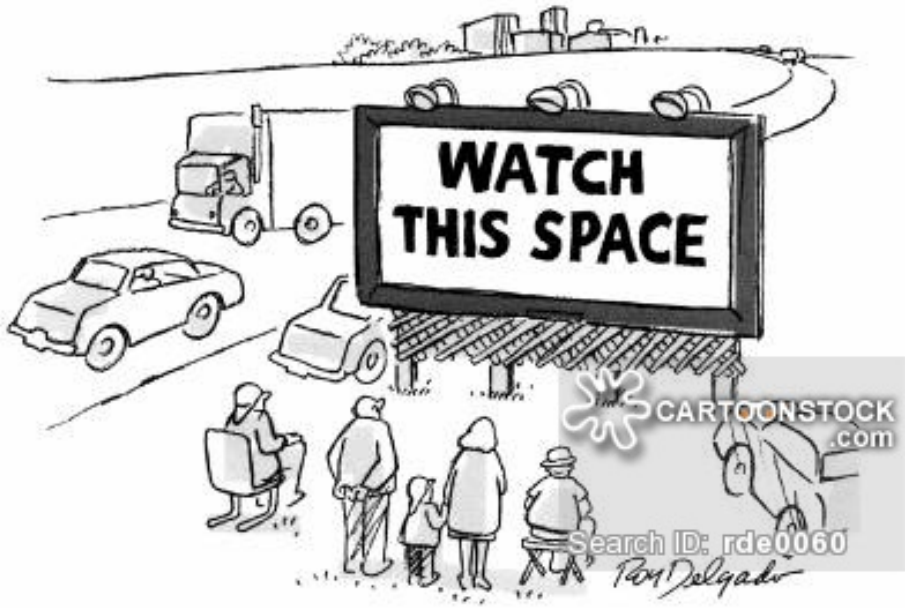
Question 3: If so, what can we do about it?
Pre-meal octreotide

Efficacy of depot long-acting release octreotide therapy in severe dumping syndrome

C. PENNING*, J. VECHT† & A. A. M. MASCLEE*
*Department of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden; †Department of Gastroenterology, Isala Clinics, Zwolle, The Netherlands

Accepted for publication 7 September 2005

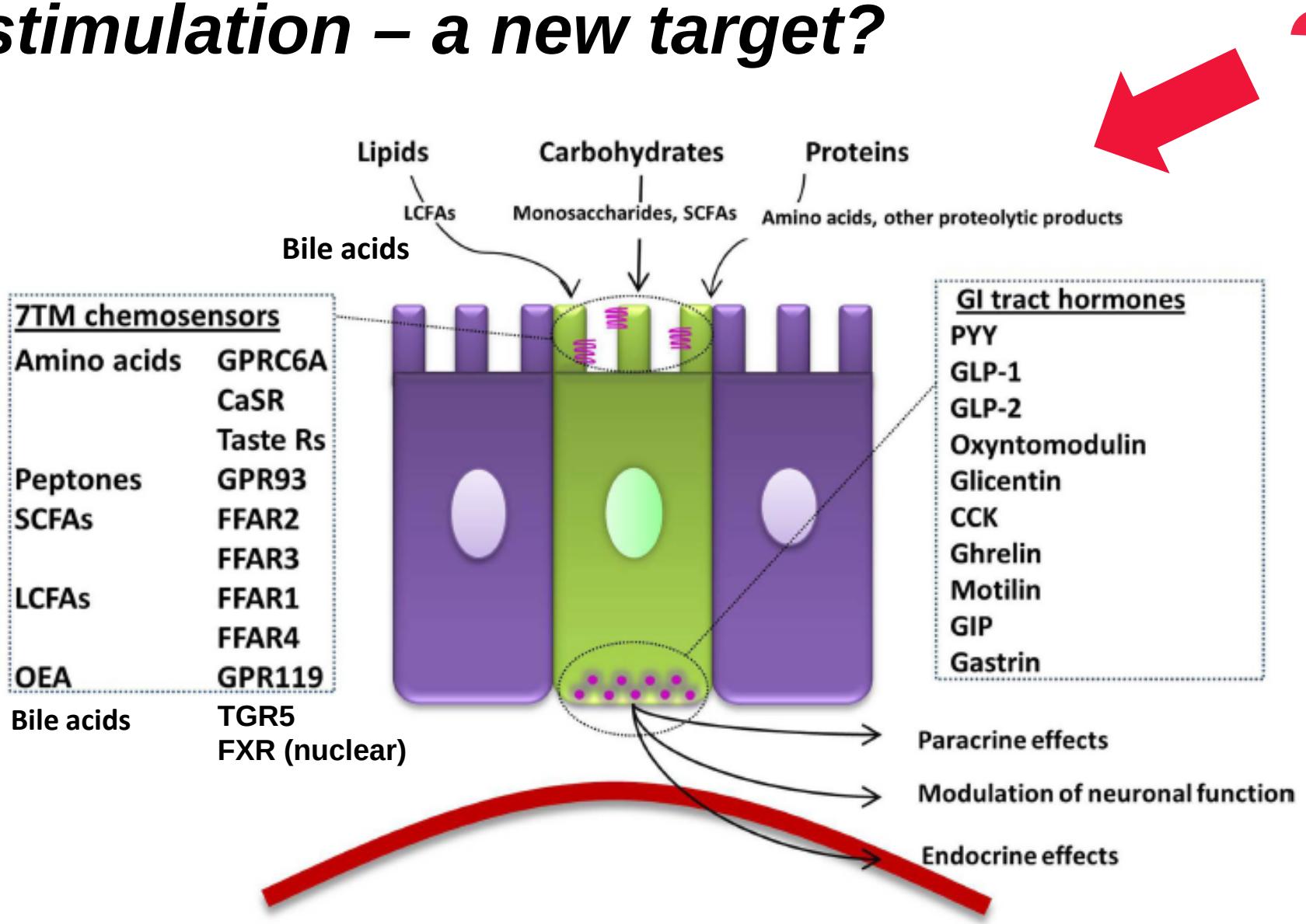
During Sandostatin-LAR treatment, body weight increased (66 ± 4 to 70 ± 3 kg; *P* = 0.19)



Efficacy of Octreotide Acetate in Treatment of Severe Postgastrectomy Dumping Syndrome

…and an average weight gain of 11% during a 12 month period

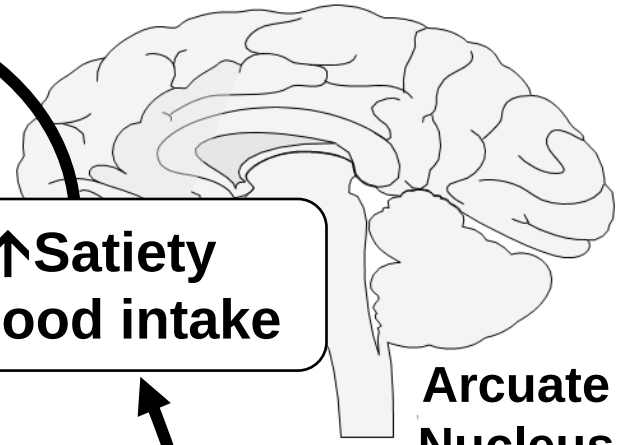
Question 3: If so, what can we do about it?
L-cell stimulation – a new target?



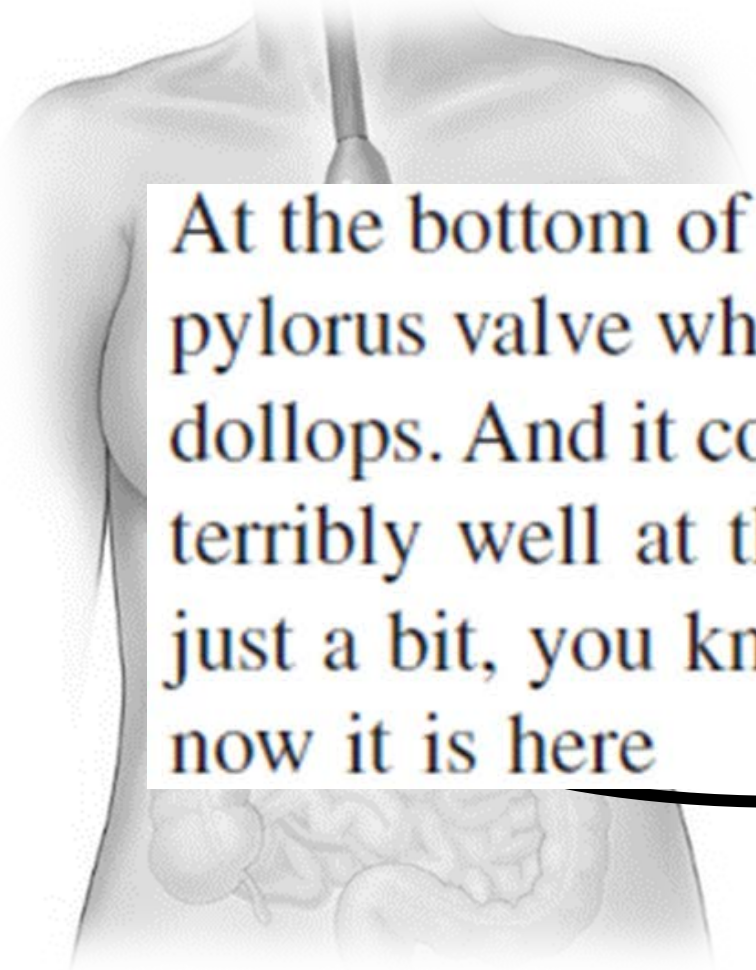
Conclusion

↓ Body weight
↓ QoL

↑Satiety
↓Food intake

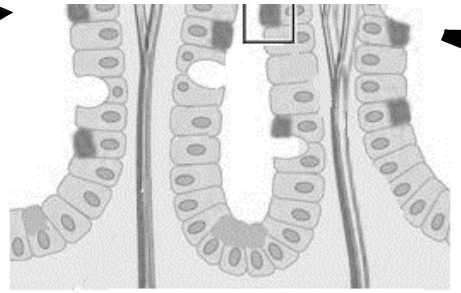


Arcuate Nucleus

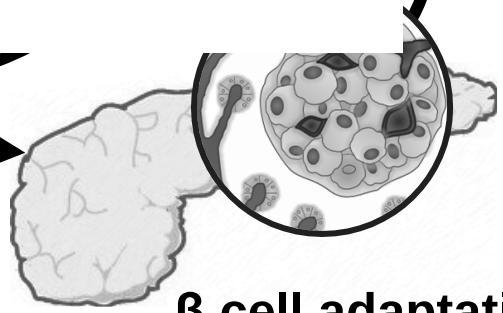


At the bottom of the stomach there's a thing called a pylorus valve which allows the food to go through in dollops. And it could well be that is not synchronized terribly well at the moment, and the whole body is just a bit, you know, something used to be here and now it is here

Rapid nutrient transit
↑early glucose



Enteroendocrine L-cell



β cell adaptation
(data not shown)

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Sinead King

Jenny Moore

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Gut peptides and appetite in upper gastrointestinal surgery

BAPEN Annual Conference 2016

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HRB Surgical Research Fellow

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ST. JAMES'S HOSPITAL
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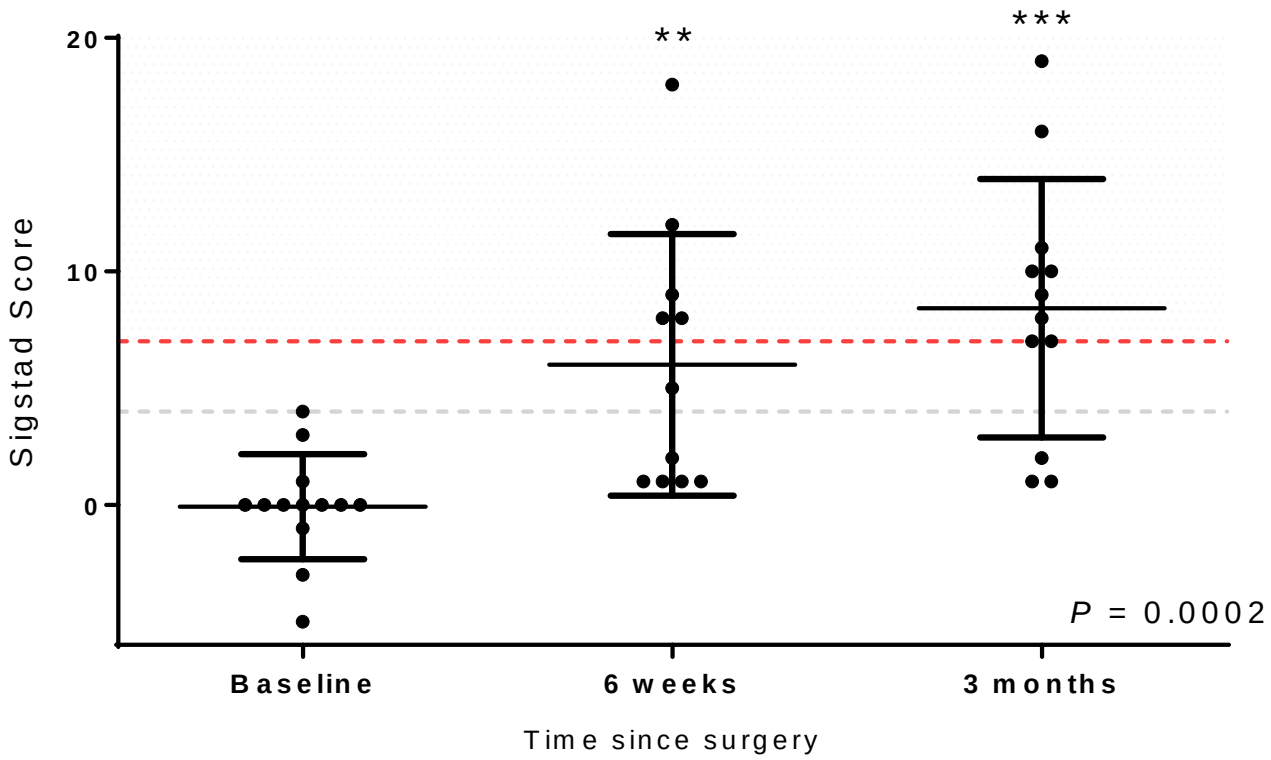
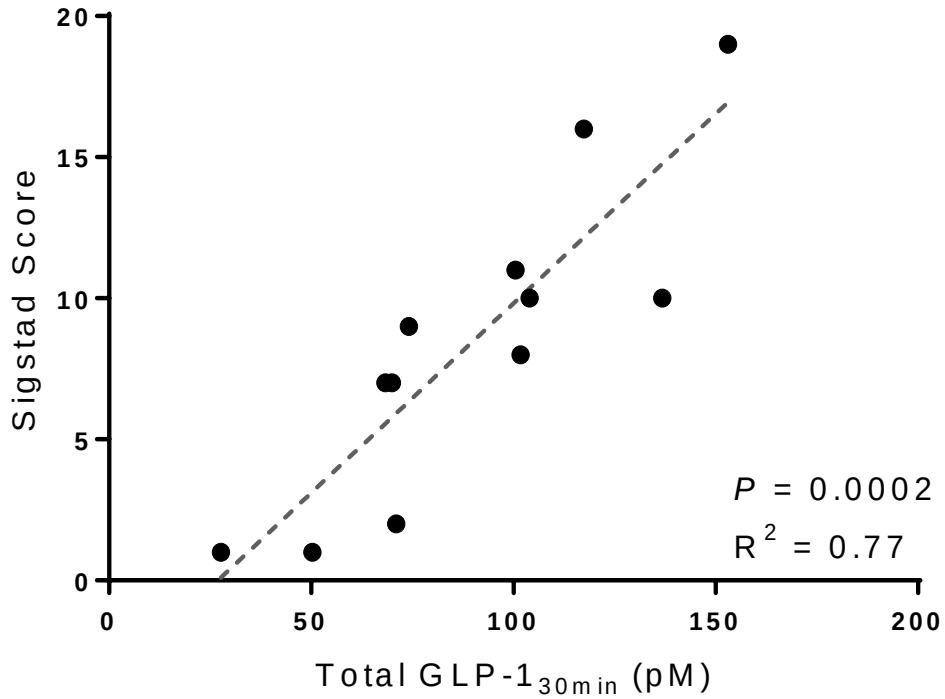
Results

Post-ingestive symptoms and GLP-1 peak





Mechanisms of increased gut nutrient sensing post-bariatric surgery – parallels after esophagectomy?

OPEN ACCESS Freely available online

PLOS | ONE

Hypertrophy Dependent Doubling of L-Cells in Roux-en-Y Gastric Bypass Operated Rats

Carl Frederik Hansen[1,2], Marco Bueter[3,4], Nadine Theis[5], Thomas Lutz[4,5], Sarah Paulsen[1], Louise S. Dalbøge[1], Niels Vrang[1], Jacob Jelsing[1]*

ANNALS OF SURGERY

Gut Hypertrophy After Gastric Bypass Is Associated With Increased Glucagon-Like Peptide 2 and Intestinal Crypt Cell Proliferation

Carel W. le Roux, MRCP, PhD, Cynthia Borg, FRCS,† Katharina Wallis, MRCP,* Royce P. Vincent, MBChB,* Marco Bueter, MD,* Robert Goodlad, PhD,‡ Mohammed A. Ghatei, PhD,* Ameet Patel, FRCS,† Stephen R. Bloom, FRCP, DSc,* and Simon J. B. Aylwin, FRCP, PhD§*

Gut hormones

You only got a little space so you can only eat a certain amount . . . so you got to sort of get adjusted to that . . . but I am now, I know roughly how much I can eat.

From another informant:

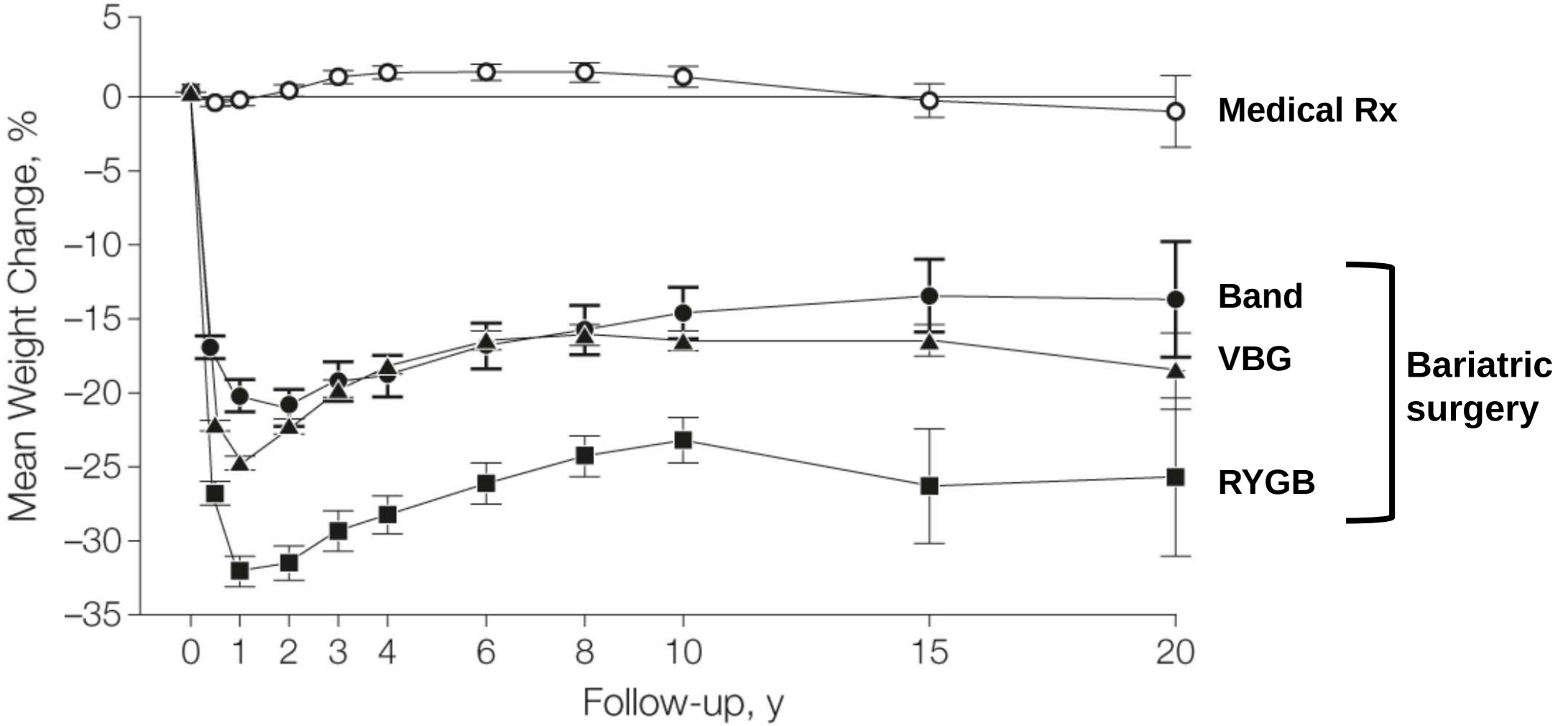
I tried to cook the things for a meal that I would normally eat before I went into hospital. And I found that before I got through a quarter of it I started feeling sick, getting the stomachache and diarrhea.

I think I could drink a big tumbler of orange squash now and nothing would happen, but if I drank a cup of milk I could be almost guaranteed to either get the stomach-ache or feel sick after.

At the bottom of the stomach there's a thing called a pylorus valve which allows the food to go through in dollops. And it could well be that is not synchronized terribly well at the moment, and the whole body is just a bit, you know, something used to be here and now it is here and it just takes a little bit of time to get back, it is like this rib that is missing you know and it is gone but my mind thinks it is still there.

Long-term body weight reduction after bariatric surgery vs standard medical therapy

Swedish Obese Subjects “SOS” study (n = 4047)

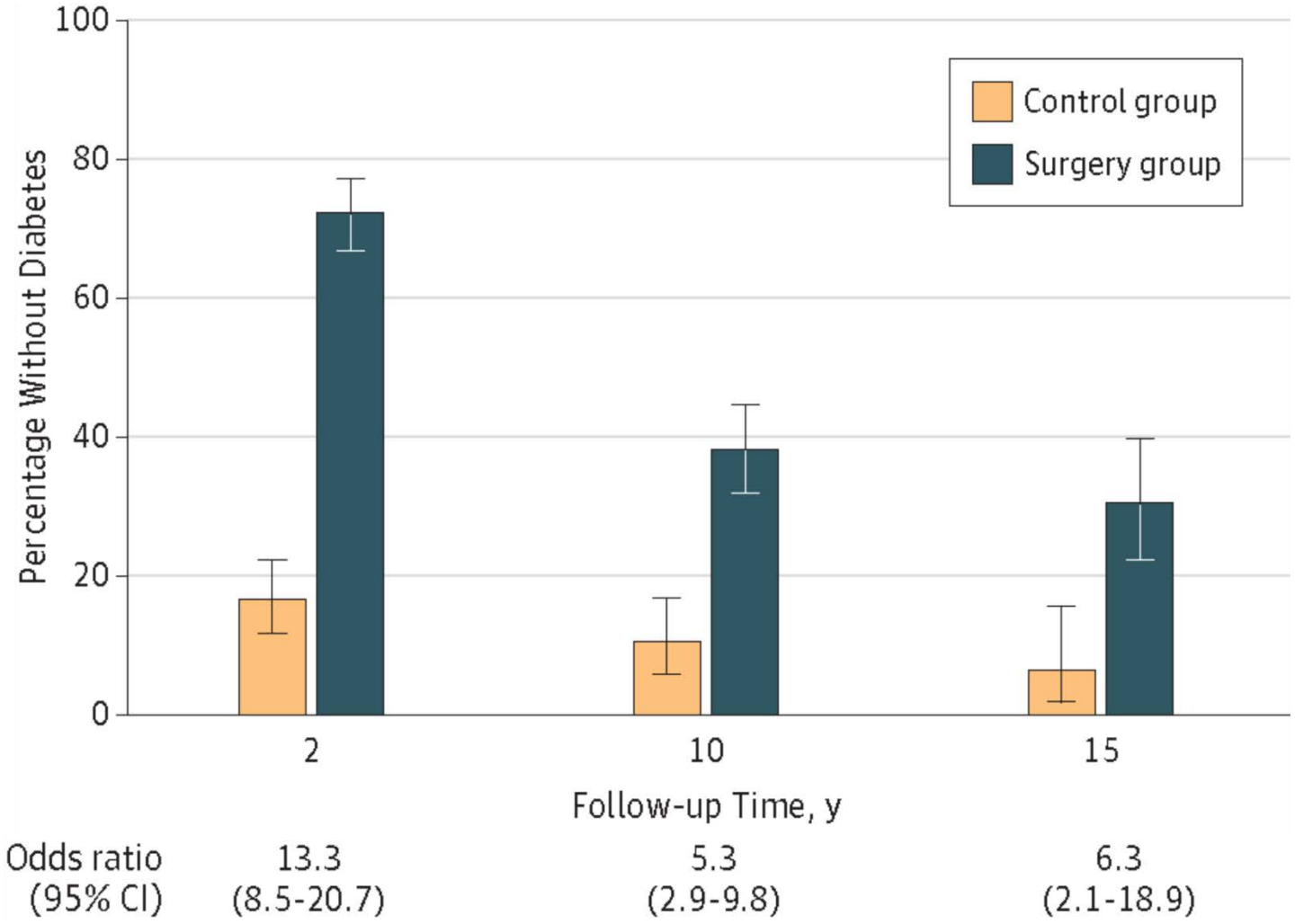


The JAMA Network

Sjöström *et al*., JAMA, 2007

Reduced prevalence of diabetes after bariatric surgery vs standard medical therapy

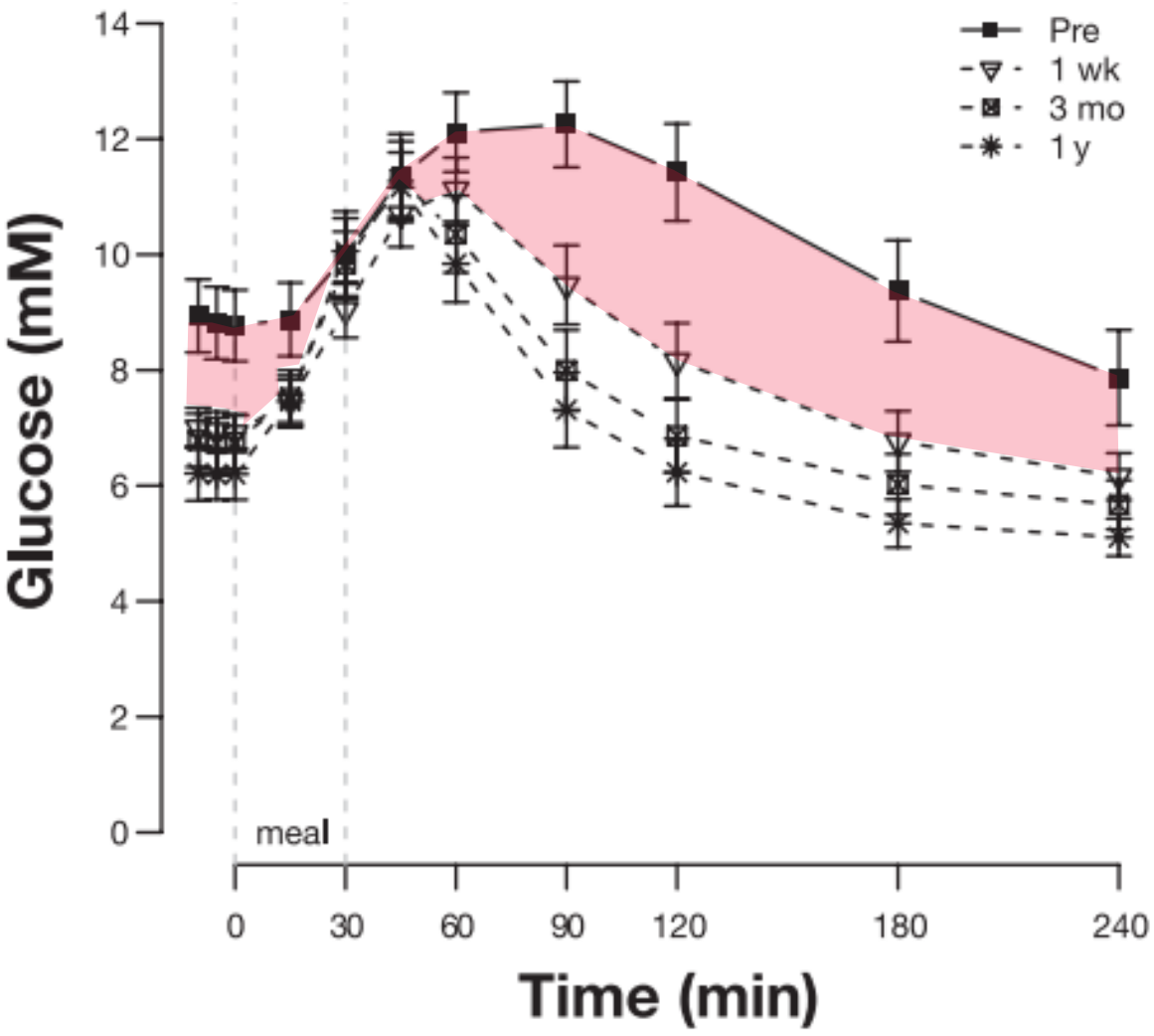
Swedish Obese Subjects (SOS) study



The JAMA Network

Sjöström *et al*., JAMA, 2014

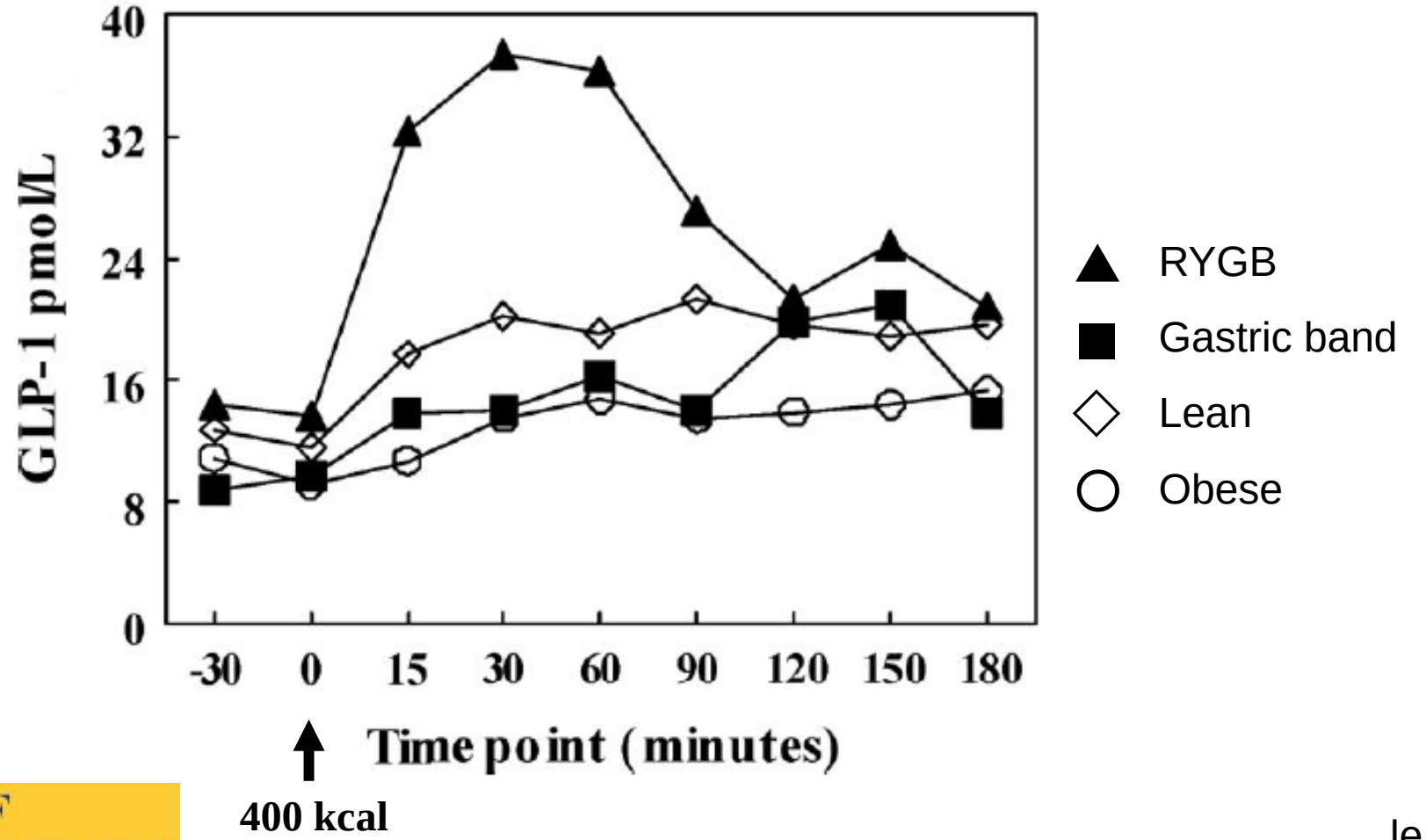
Early weight loss independent effects of RYGB and VSG on glucose metabolism at 1 week post-operatively



	Preop	1 wk	3 mo	1 yr
Days	-2.7 ± 2.8	5.4 ± 1.1	98 ± 13	384 ± 25
Weight	129 ± 14	127 ± 13	112 ± 15	101 ± 20
%BWL	0%	2 ± 2%	13 ± 4%	22 ± 9%

NB Jørgensen, JJ Holst *et al*.
Am J Physiol Endocrinol Metab, 2012

Gut Hormone Profiles Following Bariatric Surgery Favor an Anorectic State, Facilitate Weight Loss, and Improve Metabolic Parameters



ANNALS OF SURGERY

le Roux *et al.*
Annals of Surgery, 2006

Glucagon-like peptide-1: a potent regulator of food intake in humans

J-P Gutzwiller, B Göke, J Drewe, P Hildebrand, S Ketterer, D Handschin, R Winterhalder, D Conen, C Beglinger

Table 1 Effect of graded doses (pmol/kg/min) of human glucagon-like peptide-1 (GLP-1) or 5% glucose on eating behaviour in 16 healthy male subjects

		GLP-1		
Treatment	*Control*	*0.375*	*0.75*	*1.5*
Food quantity (g)	587 (36)	531 (35)*	516 (40)*	384 (34)***
Calorie intake (kcal)	1627 (97)	1520 (95)	1451 (101)*	1107 (84)***
Meal duration (min)	38 (3)	35 (3)	34 (3)*	30 (3)*
Fluid intake (ml)	708 (57)	748 (52)	689 (48)*	584 (45)**

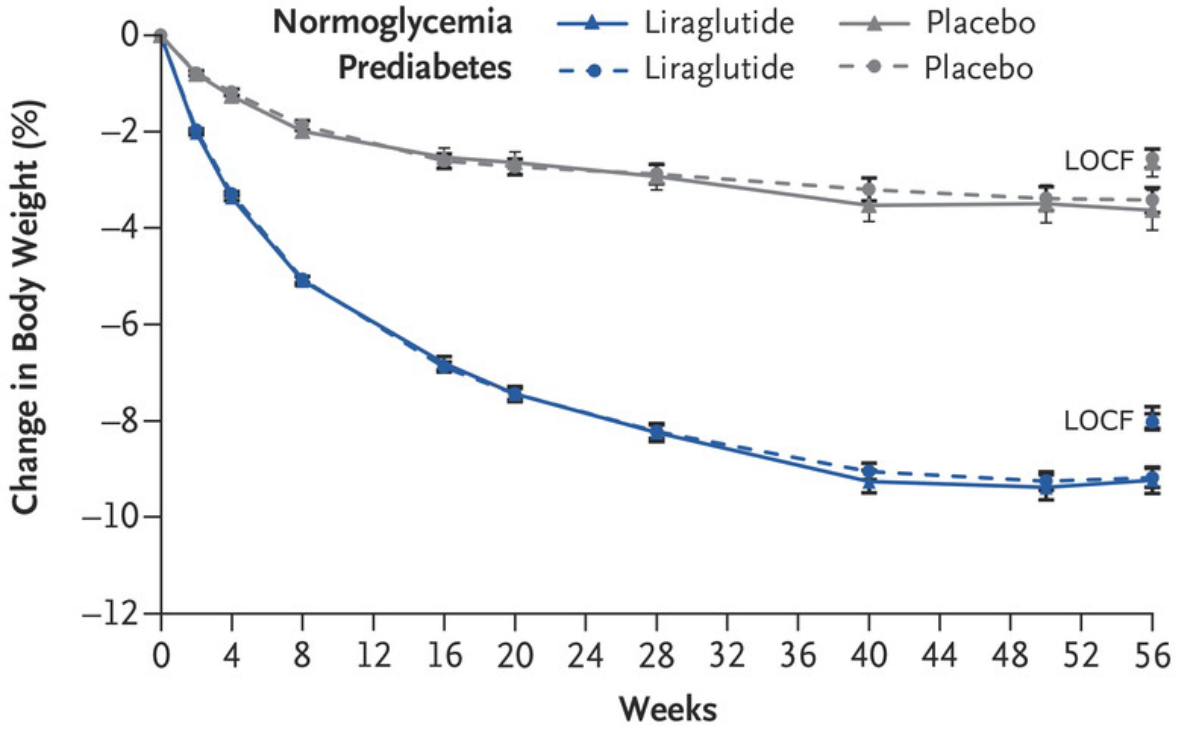
Values are expressed as mean (SEM).
*p<0.05, **p<0.01, ***p<0.001 *v* control.

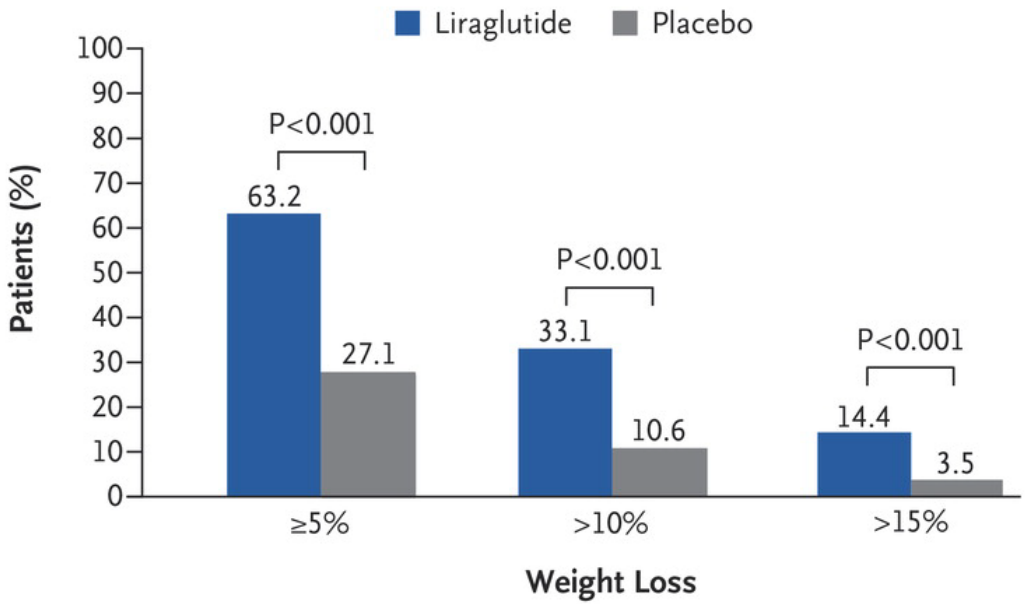
32% reduction in *ad libitum* calorie intake

Gutzwiller *et al.*
Gut, 1999

The NEW ENGLAND JOURNAL of MEDICINE

SCALE™ Satiety and Clinical Adiposity – Liraglutide Evidence in Nondiabetic and Diabetic Subjects



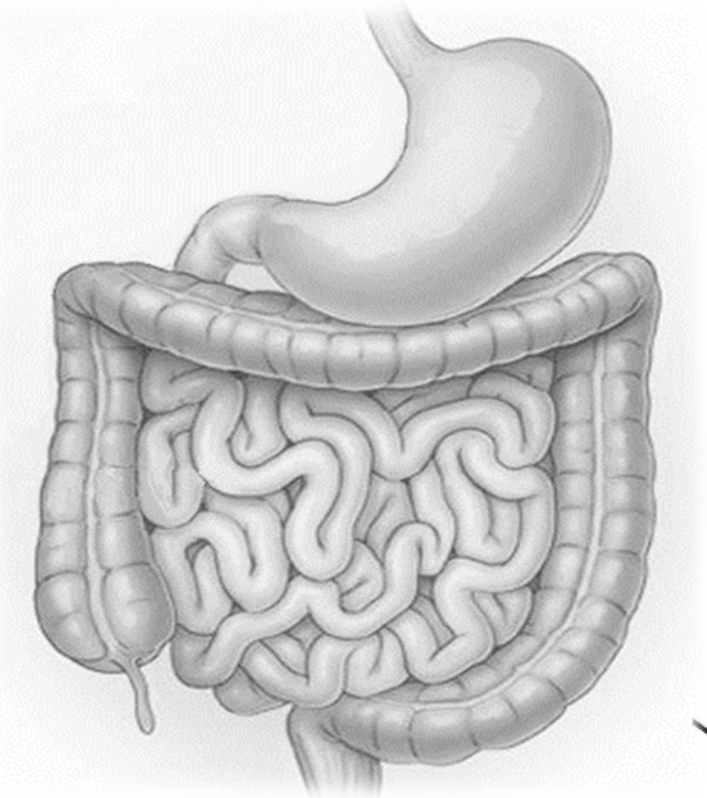


The "SCALE" RCT

- 3.0 mg Liraglutide (GLP-1 analogue) versus Placebo
- 3731 patients, 2:1 allocation ratio, 56-week treatment period
- Obese/overweight, non-diabetic
- Placebo-adjusted BWL = 5.6%

Pi-Sunyer *et al*. NEJM, 2015
NCT01272219

Enteroendocrine regulation of nutrient intake



Gastric fundus
Gr cells

Ghrelin

Proximal small intestine
L-cell subtypes

CCK
GLP-1

Distal small intestine and colon
L-cell subtypes

GLP-1
OXM
PYY
PP

Stomach, small and large intestine, pancreas
D-cells

Somatostatin

Hypothalamic Arcuate Nucleus

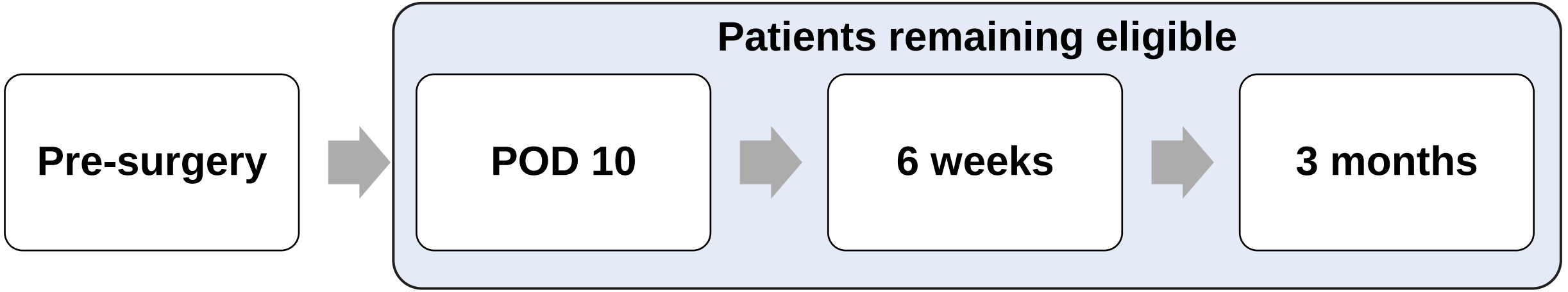
NPY/AgRP neurons

Increase food intake

POMC neurons

Reduce food intake

Methods: Aim 1
Prospective Study



Inclusion criteria

1. Planned for oesophagectomy with curative intent
   - Gastric conduit reconstruction
   - Pyloroplasty

Exclusion criteria

1. Unable to eat
2. Previous GI surgery
3. Medications affecting gut hormones
4. Poorly controlled T2DM

ClinicalTrials.gov NCT02381249

Methods: Aim 1
Prospective Study

Time (mins)	-5	0	15	30	60	90	120	150	180
Plasma sample	●		●	●	●	●	●	●	●
400 kcal meal stimulation		●							
Visual analogue scale	●		●	●	●	●	●	●	●
Sigstad score (dumping syndrome)	●								
Quality of life (QLQ C30, OES18, OG25)	●								
Body weight, anthropometry	●								

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ClinicalTrials.gov NCT02381249

Symptoms I have when I eat...

Please tick any of the below that have affected you in the last week			
Statement	**Yes**	**No**	Score *Team to complete*
I have had been told I had low blood pressure after eating.			
I have fainted or collapsed after a meal.			
After a meal, I often need to sit or lie down.			
Sometimes I feel out of breath or "caught" for breath after eating.			
After a meal, I feel weak or tired.			
I often "nod off" or feel very sleepy after eating.			
When I have had a meal, I sometimes feel my heart beating fast in my chest.			
I feel restless after a meal. I become anxious or can't sit still.			
Eating can sometimes make me feel dizzy.			
I commonly get headaches after eating.			
Sometimes when I eat a feeling of warmth comes over me, I feel clammy or sweaty.			
I frequently feel nauseated after eating.			
I feel full after eating a small amount of food.			
My tummy gets "bloated" after eating.			
You can often hear my tummy making noises after I eat.			
I belch/burp quite a lot after eating.			
Sometimes I get sick (vomit) after eating.			

If you have any questions, please ask the team.
Thank you for your time.

Team to complete
Total score: _____

A total score >7 is suggestive of dumping syndrome, whereas a score <4 suggests other diagnoses

- Shock +5
- Fainting, syncope, unconsciousness +4
- Desire to lie or sit down +4
- Breathlessness, dyspnea +3
- Weakness, exhaustion +3
- Sleepiness, drowsiness, apathy, falling asleep +3
- Palpitation +3
- Restlessness +2
- Dizziness +2
- Headaches +1
- Feeling of warmth, sweating, pallor, clammy skin +1
- Nausea +1
- Abdominal fullness, meteorism +1
- Borborygmus +1
- Eructation –1
- Vomiting –4

Sigstad H.
Acta Med Scand. 1970

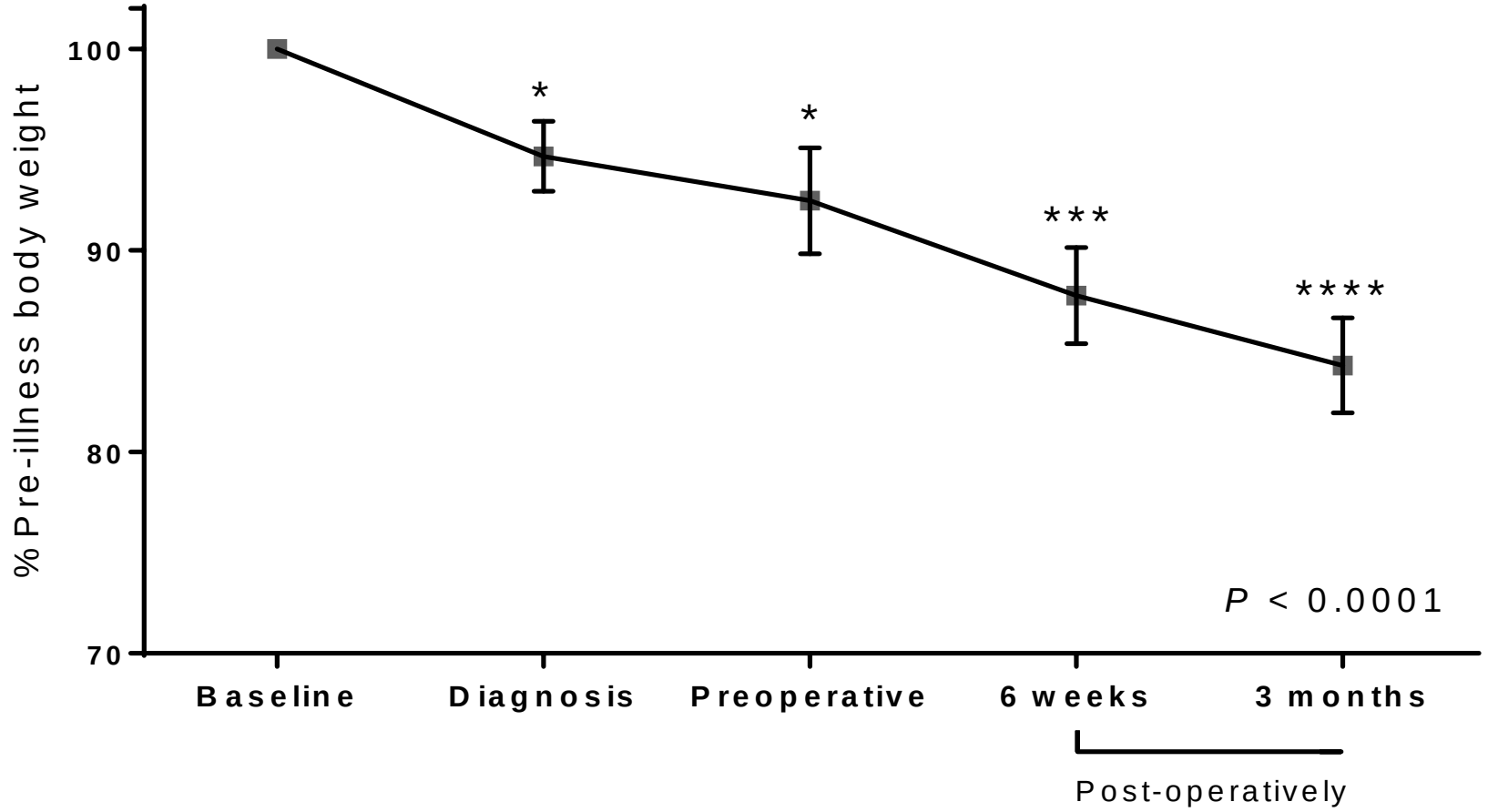
Results: Aim 1

Patient characteristics (n = 13)

Sex	
N (%female)	4 (31%)
Pre-illness weight (kg)	
Median (range)	88 (63 – 124)
Histologic type	
Adenocarcinoma	8 (62%)
Squamous cell carcinoma	5 (38%)
Type of operation	
2 Stage	9 (69.2%)
3 Stage	3 (23.1%)
Transhiatal	1 (7.7%)
Age (years)	
Median (range)	63 (46 – 79)
Pre-illness BMI (kg/m^2)	
Median (range)	30.3 (23.5 – 46.1)
Neoadjuvant therapy	10 (77%)
Pathologic Stage	
T1	5 (38.5%)
T2	1 (7.7%)
T3	7 (53.8%)
N0	6 (46.2%)
N1	4 (30.8%)
N2	3 (23.1%)

Results: Aim 1

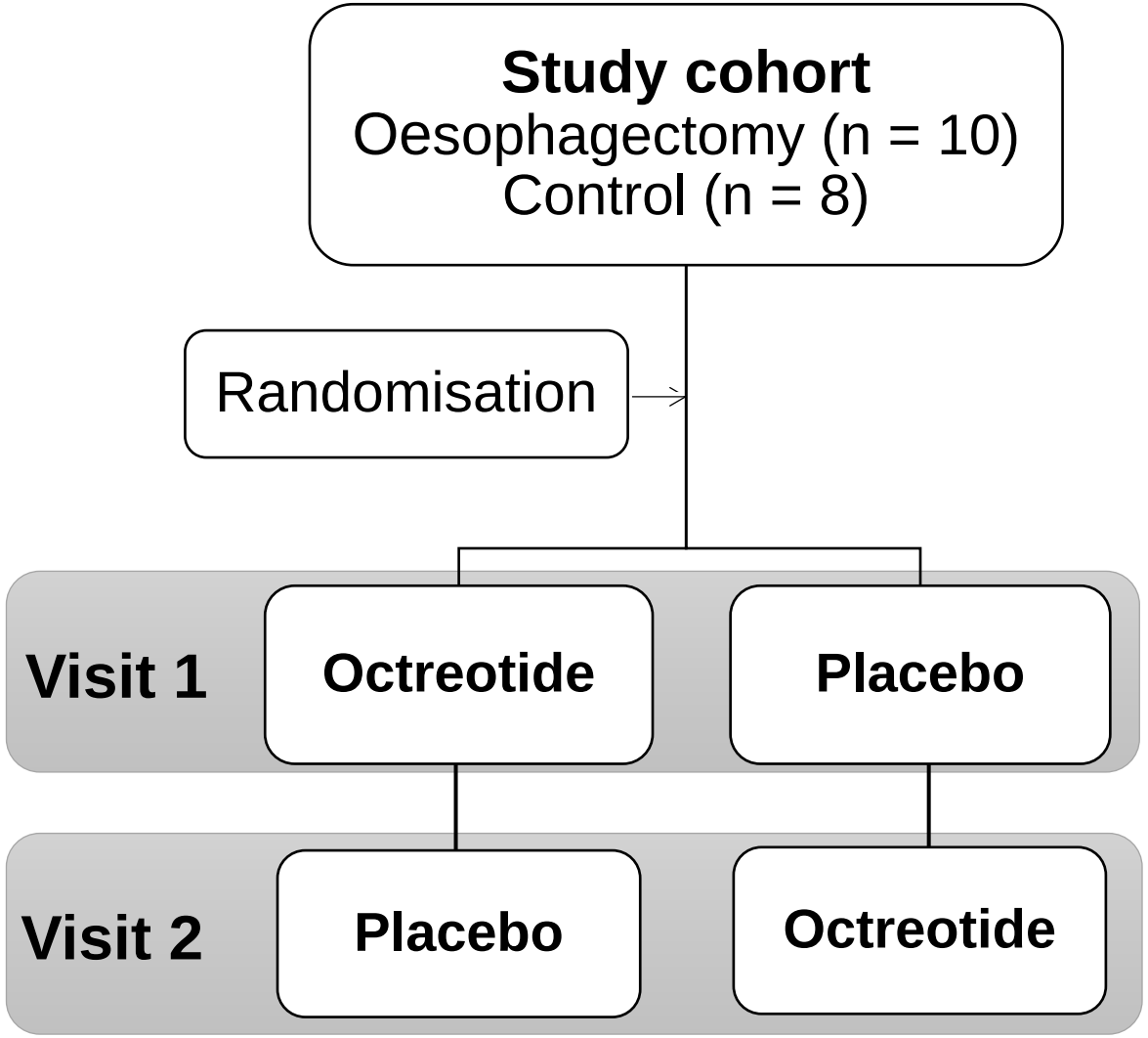
Significant body weight loss after oesophagectomy



Weight, kg *Median (range)*	**88 (63–124)**	**79 (63-102)**	**81 (65-96)**	**76 (60-91)**	**72 (60-92)**

3 month %BWL = 14.3% (3.8 – 30.7%)

Methods: Aim 2
Crossover study



Oesophagectomy

1. Oesophagectomy
   - 5cm gastric conduit
   - Pyloroplasty
2. Disease-free ≥1 year post-op
3. No clinically significant dysphagia
4. No previous GI surgery

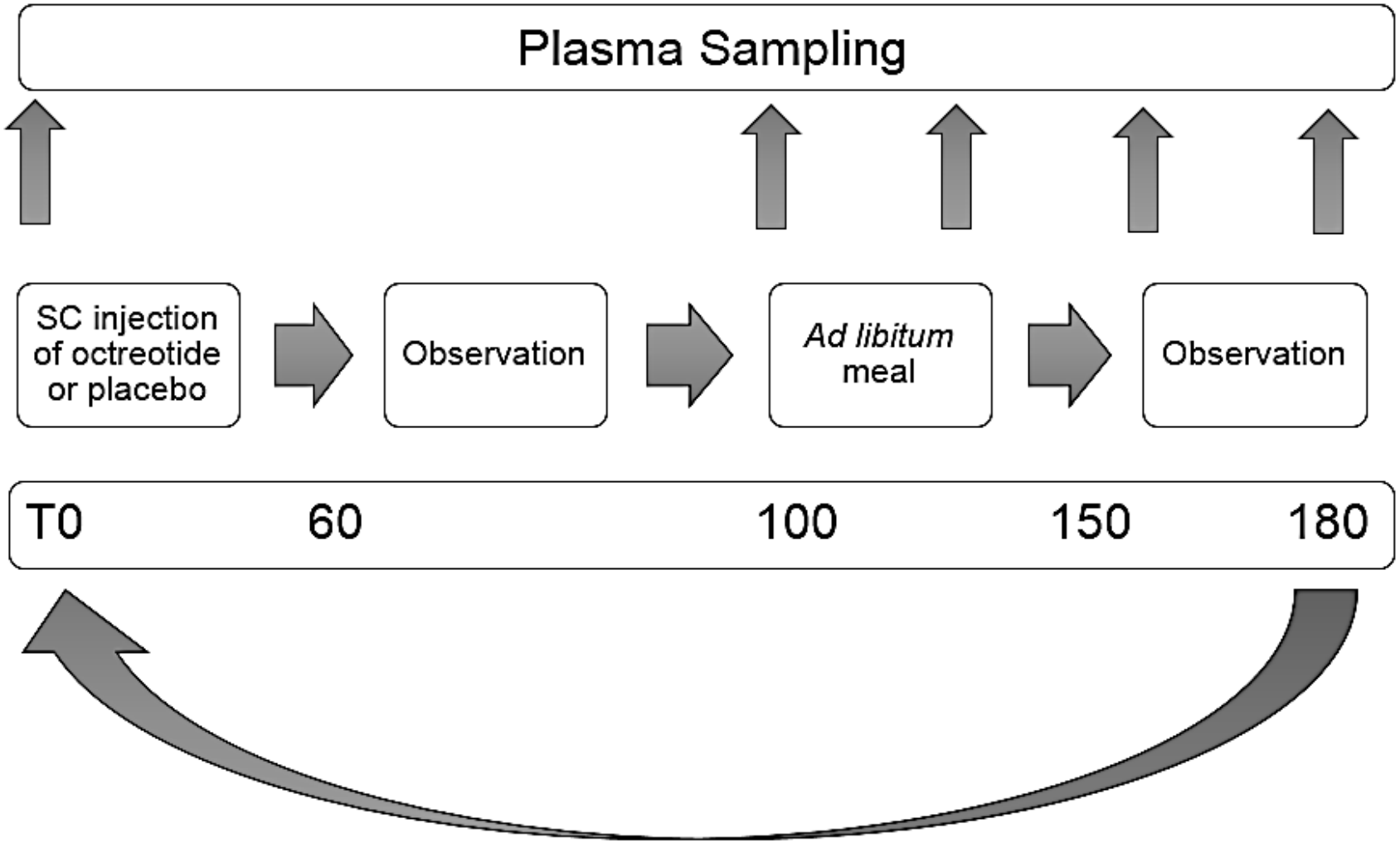
Control

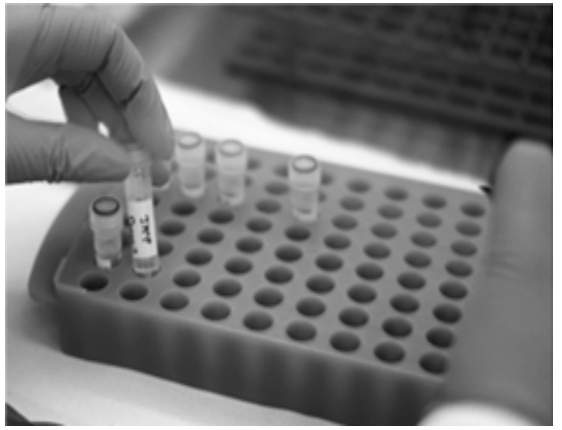
1. Barrett's oesophagus
2. No previous GI surgery
3. Age, weight and gender matched to esophagectomy group

ClinicalTrials.gov NCT02385617

Methods: Aim 2

Crossover study





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Results: Aim 2

Baseline characteristics of study population

	Control (n = 8)	Oesophagectomy (n = 10)	*P*-value
Gender (%female)	3/10 (30%)	2/8 (25%)	0.61
Age	58.5 ± 4.7	62.5 ± 2.8	0.47
Body mass index	28.9 ± 0.9	Post-op: 25.5 ± 0.9 Pre-op: 28.8 ± 1.5	0.044 0.96

Mean ± standard error

Results: Aim 2

Clinicopathologic characteristics of oesophagectomy group

Years since surgery, median (range)	2.17 (1.53 – 3.65)

Histologic type	
Adenocarcinoma	10 (100%)

Pathologic Stage			
T0	2 (20%)	N0	9 (90%)
T1	6 (60%)	N1	1 (10%)
T2	0 (0%)		
T3	2 (20%)		

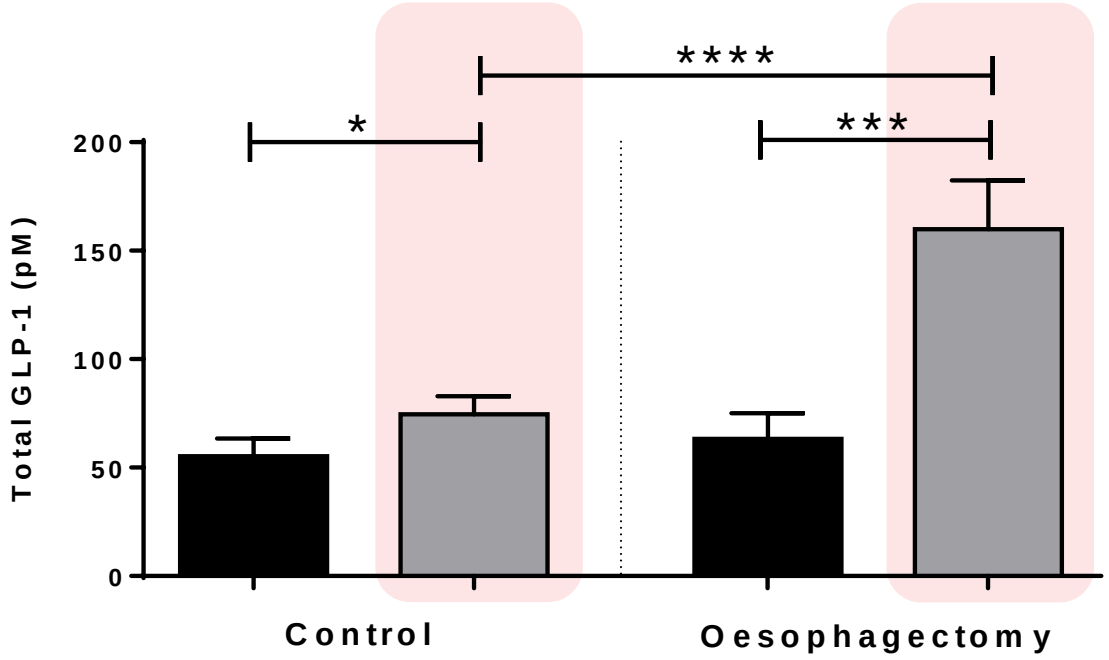
Neoadjuvant CRT	4 (40%)

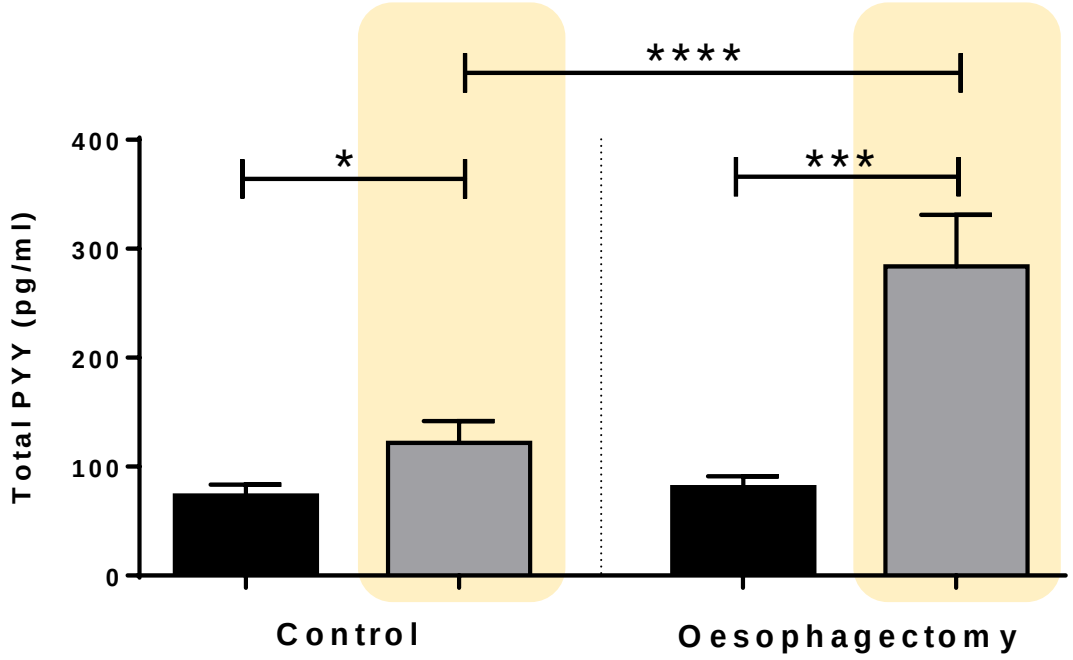
Type of operation	
Ivor-Lewis	6 (60%)
Transhiatal	4 (40%)

1 year %BWL (mean±SE)	10.3 ± 4.0%

Aim 2: Results

Oesophagectomy is associated with an exaggerated post-prandial satiety gut hormone response

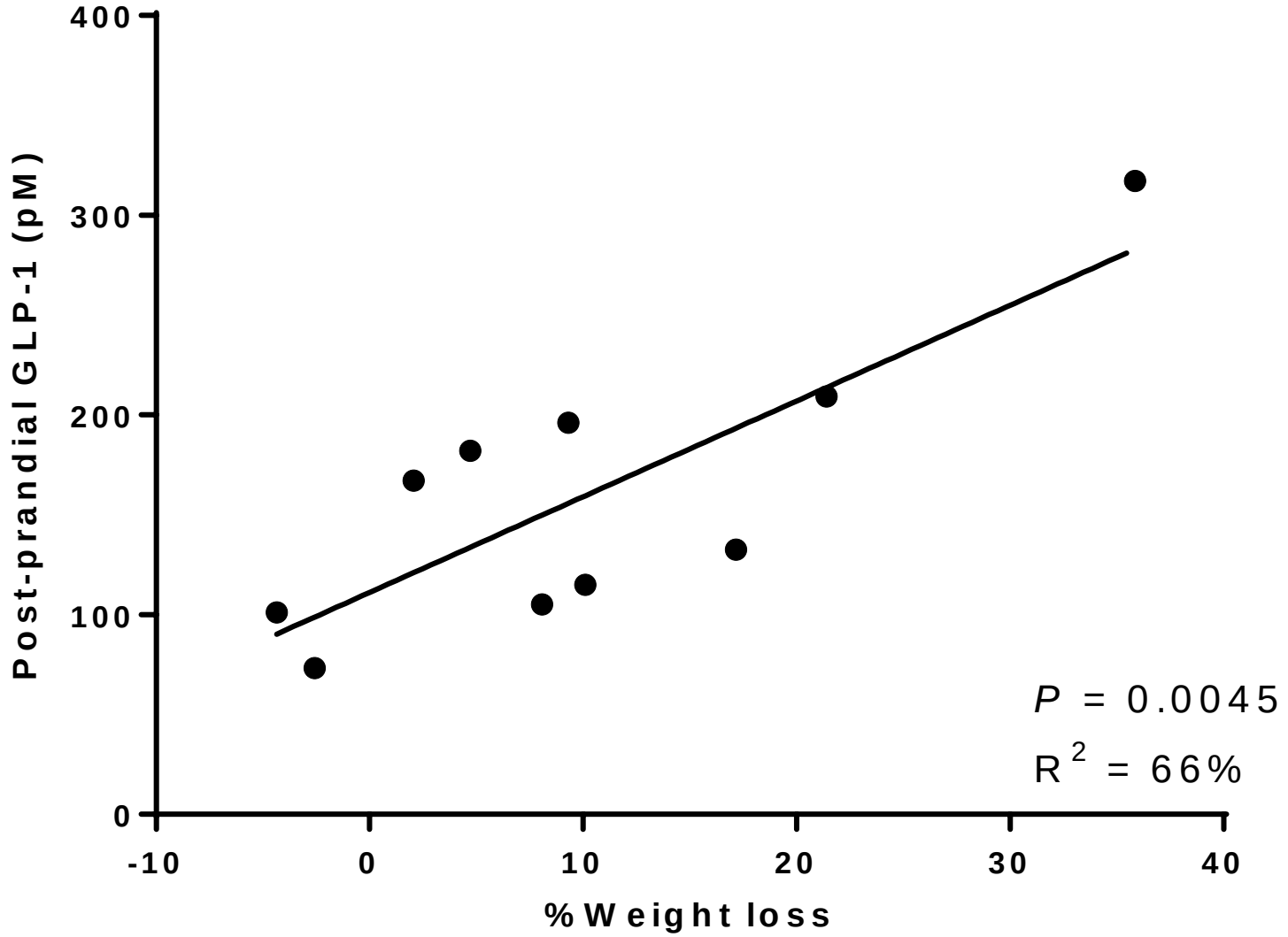




Saline day fasting [■] and post-prandial [▒] plasma GLP-1 and PYY concentrations

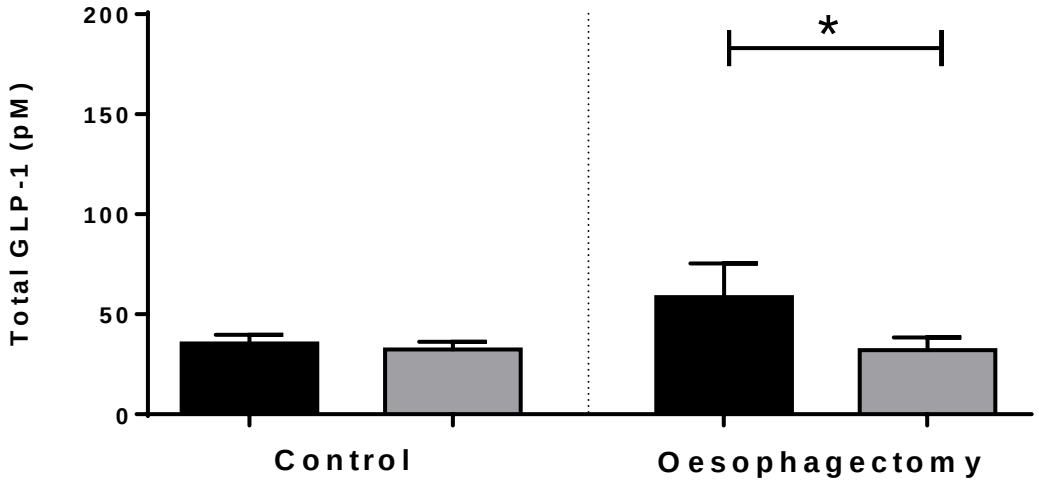
Aim 2: Results

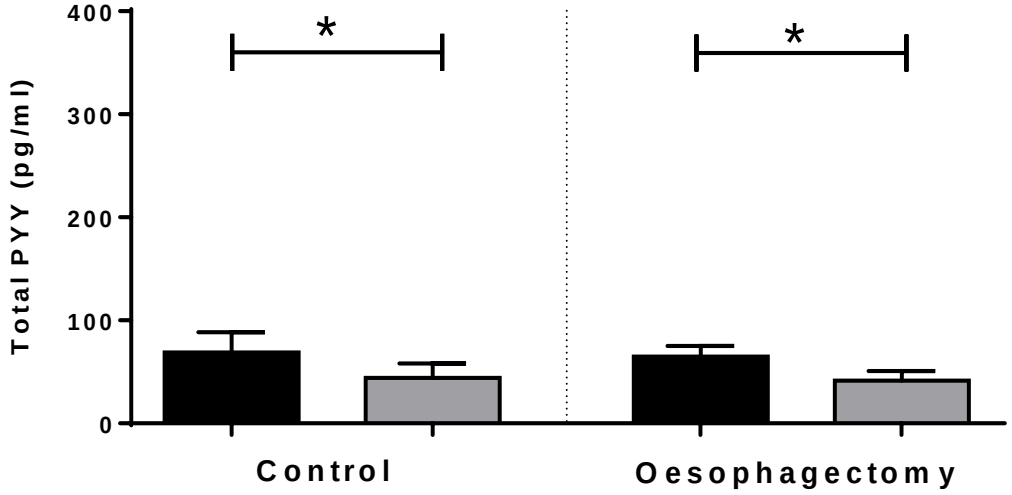
Post-prandial GLP-1 levels significantly correlated with %weight loss post-oesophagectomy



Aim 2: Results

Octreotide attenuates the post-prandial satiety gut hormone (GLP-1 and PYY) response





Octreotide day fasting [■] and post-prandial [□] plasma GLP-1 and PYY concentrations

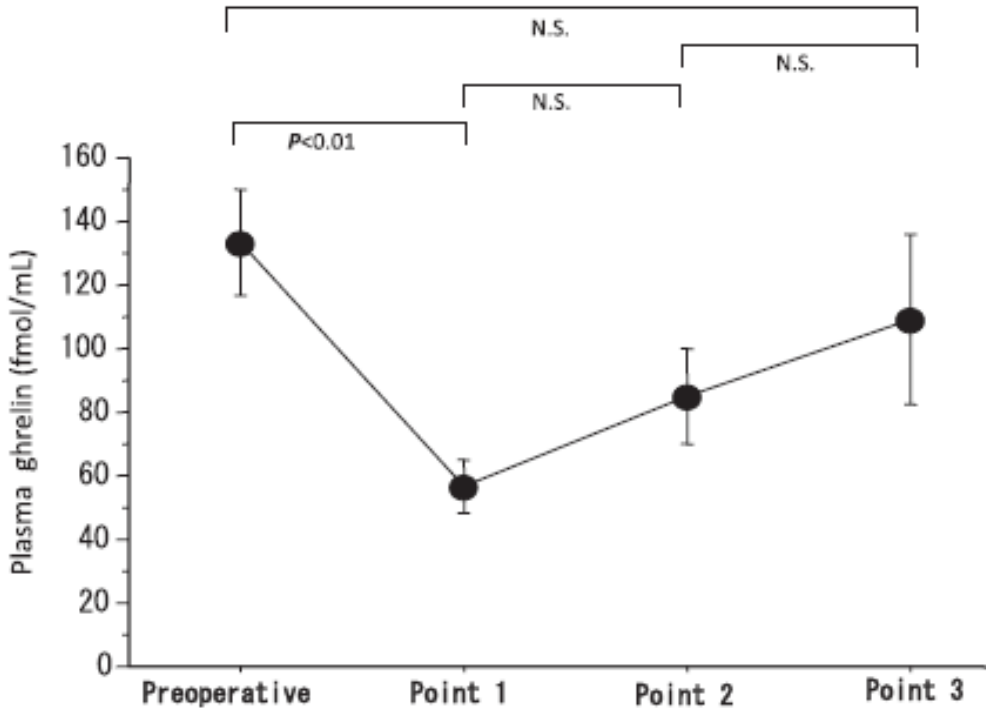
Ghrelin and body weight loss after oesophagectomy

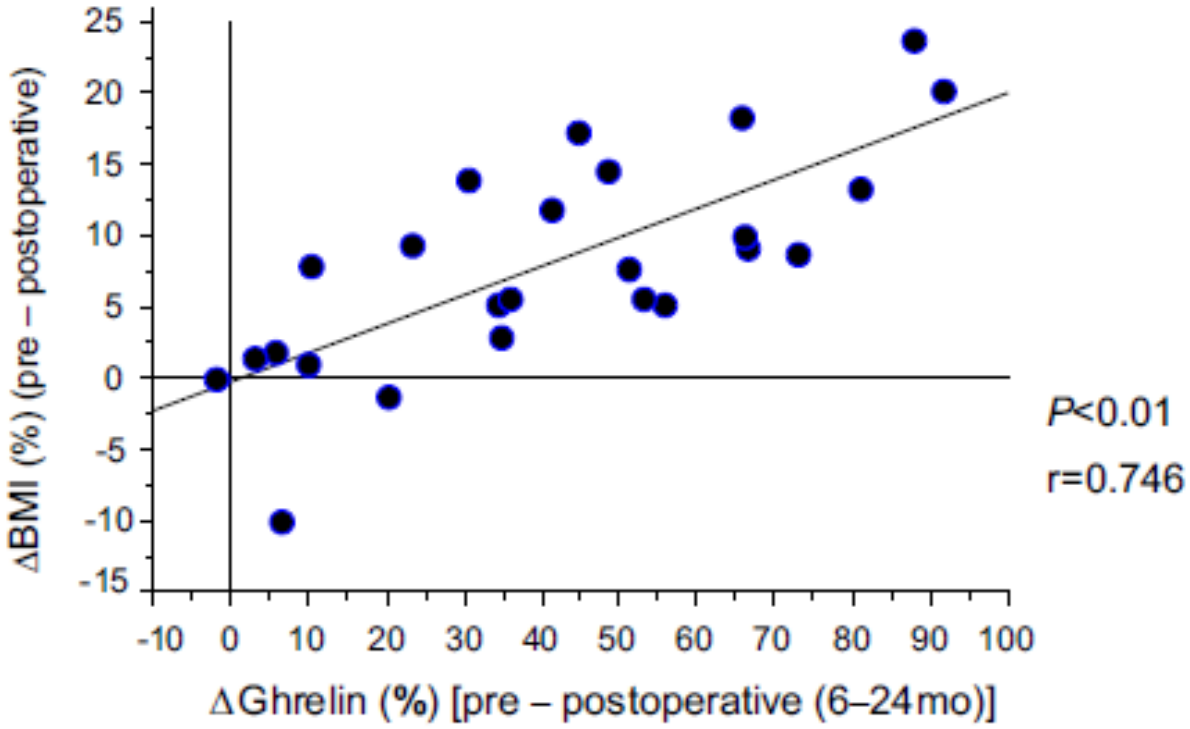
Author	Year	N	Surgery	DF	Time-points	Outcome
Doki	2006	9, 26	• 2SE • WS (28), GCC (7) • Digital pyloric bougie	Yes	• 3 and 7 days (n=9) • 25 (3-67) months (n=26)	• 51.4% and 49.8% of baseline at days 3 and 7 • 107.4% of baseline at 25 (5-67) months • Ghrelin levels negatively correlated with ΔBMI at <36 months • Ghrelin levels positively correlated with time since surgery • No difference between WS or GCC reconstruction
Koizumi	2011	22	• 2SE/3SE • GCC • Digital pyloric bougie	No	• Pre-operative • 1, 3, 6, 12 months post	• Ghrelin reduction at 1 month (63.9%) recovered to 75.8%, 99.7% at 3, 6 months post • Appropriate rebound at 12 months (125.0%) but continued BWL • Appetite score increases over time from surgery • Correlation between appetite score and ghrelin
Miyazaki	2012	25	• 2SE/3SE • GCC	No	• Pre-operative • 7 days • 6-24 months • >36 months	• 38.7% of baseline at day 7 ($P < 0.01$) • 56.0% of baseline at 22.1 (6-24) months ($P < 0.05$) • 111.6% of baseline at 53.4 (39–80) months • %ΔGhrelin correlated with %BWL at 6-24 months, but not at >36 months
Yamamoto	2013	20	• 3SE • GCC	Yes	• Pre-operative • Day 0, 1, 3, 10	• 33% (15-90%) baseline at day 1 • 50% baseline at day 3-10

DF, disease-free; 2SE, 2-stage oesophagectomy; 3SE, 3-stage oesophagectomy; WS, whole stomach; GCC, greater curvature conduit; BMI, body mass index; BWL, body weight loss

Miyazaki *et al.* 2012

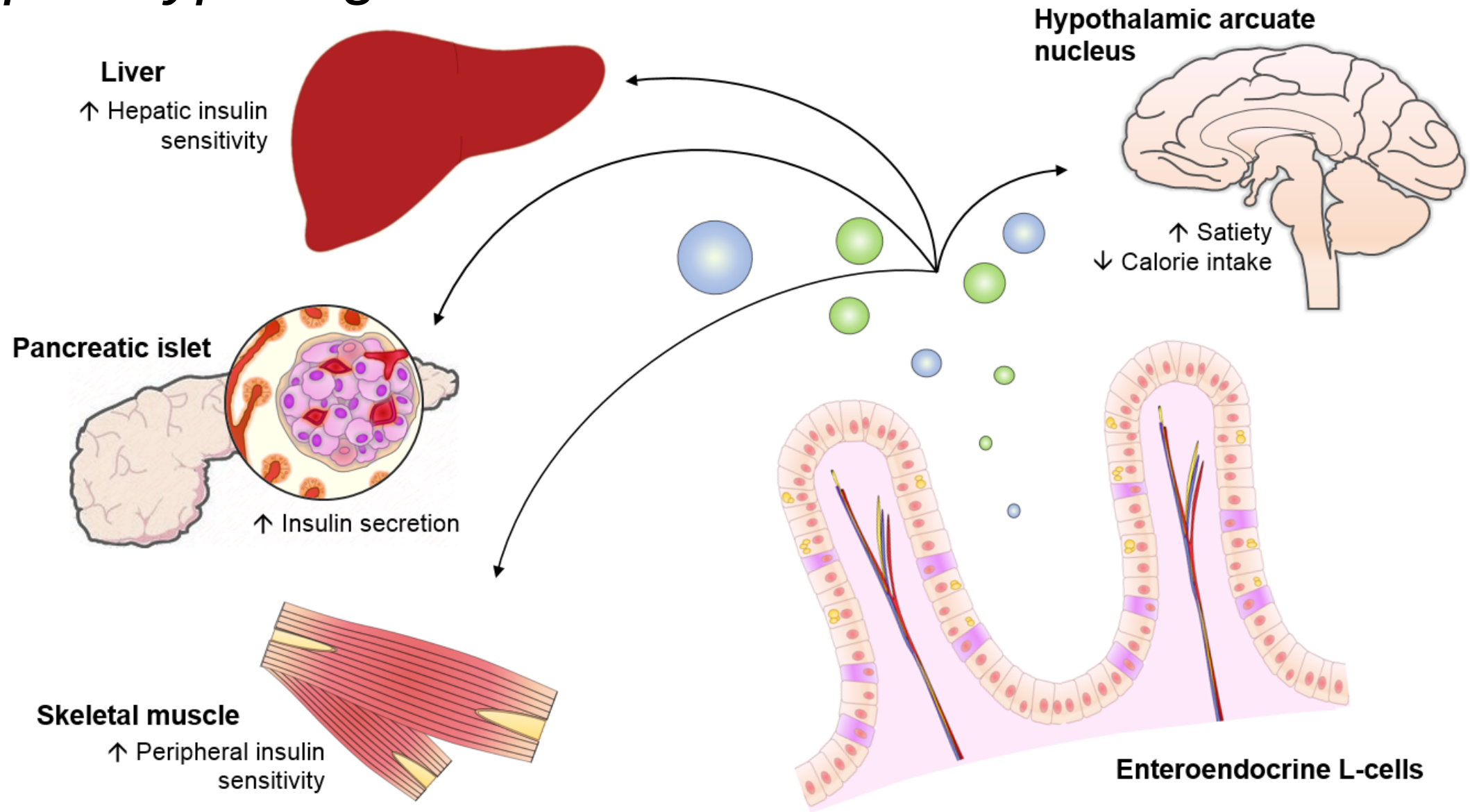
Weight loss at 6-24 months post-oesophagectomy correlates with %Δghrelin





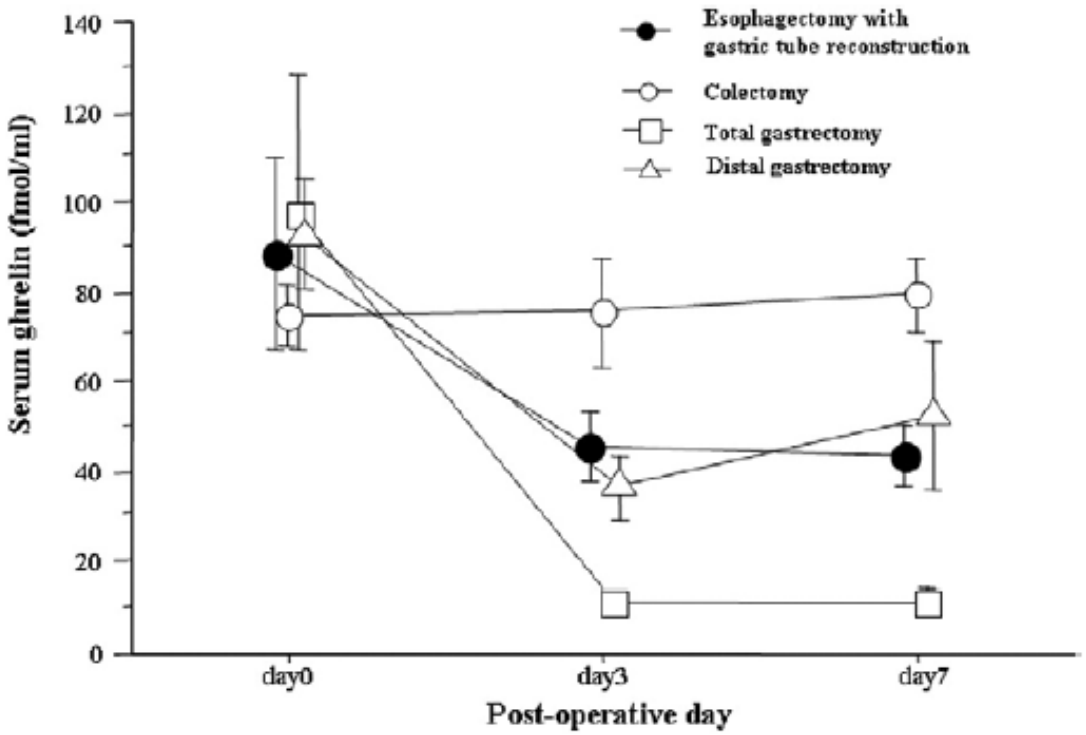
But weight loss continues despite recovery of ghrelin levels to baseline by approximately 36 months post-operatively

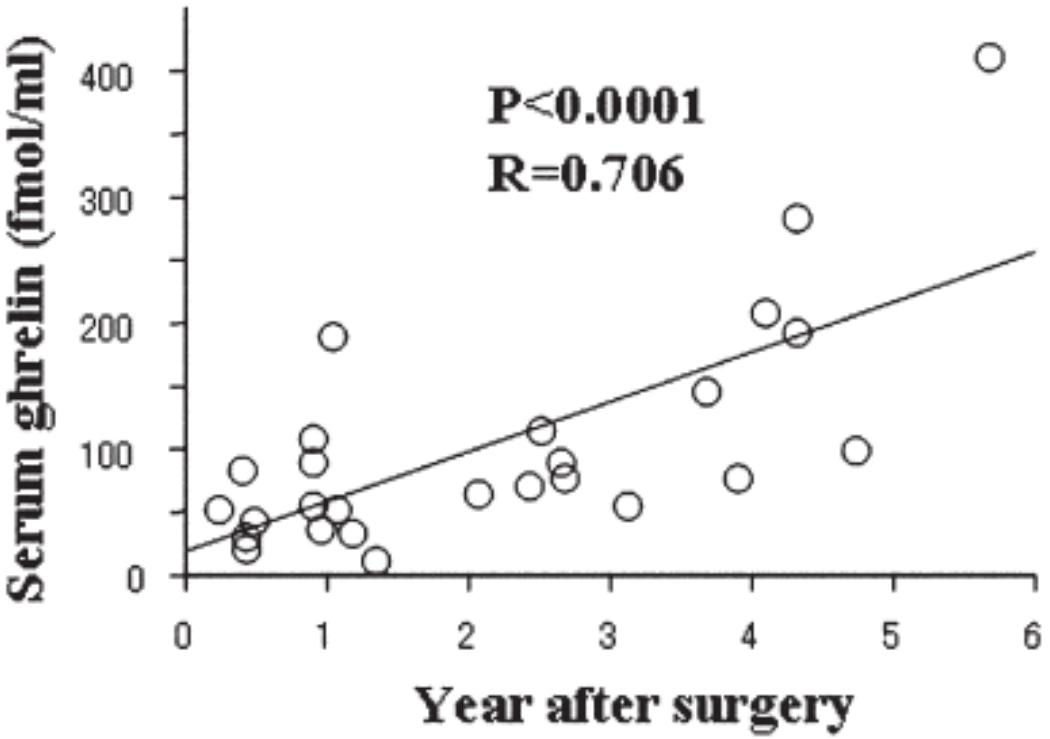
GLP-1
A prototypical gut hormone



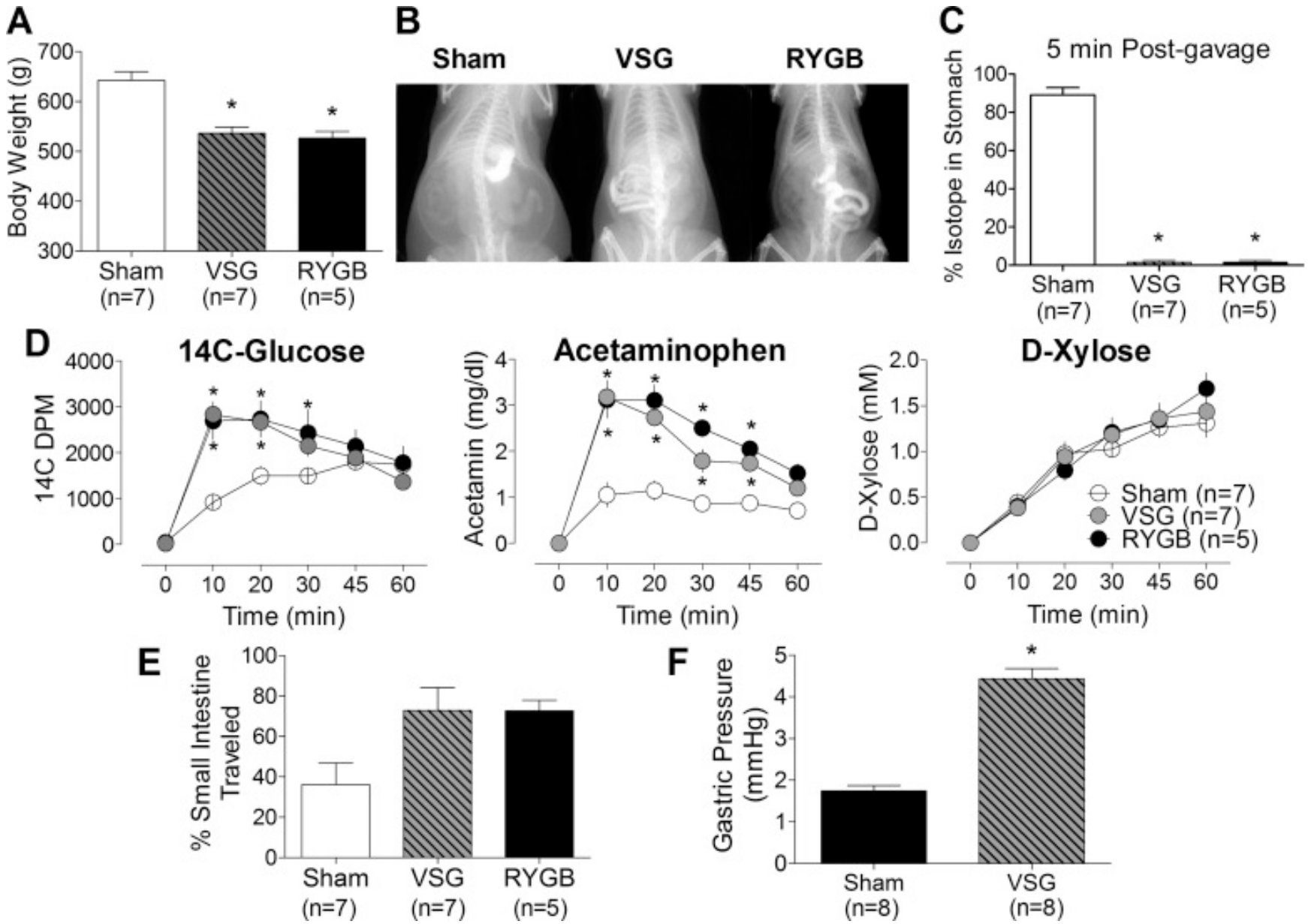
Doki *et al.* 2006

Temporal recovery of early reduced ghrelin production post-esophagectomy with either whole stomach or gastric conduit reconstruction

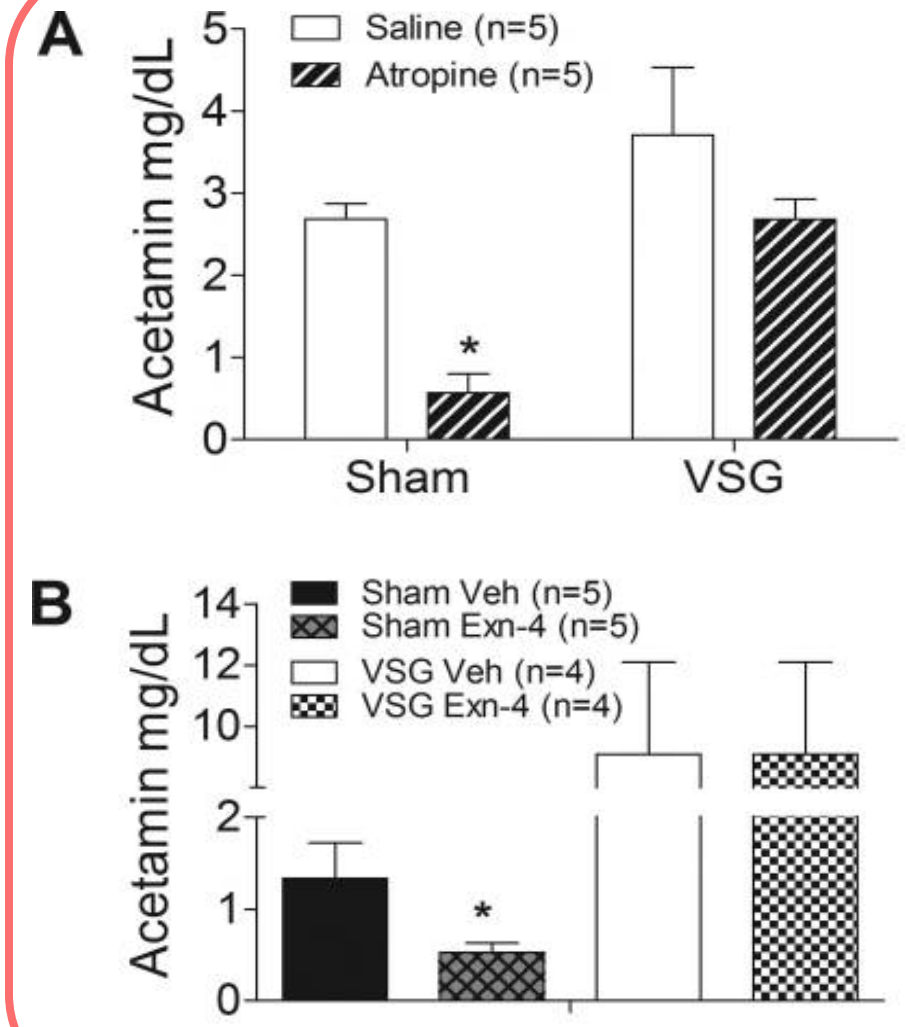




Rapid nutrient transit after VSG



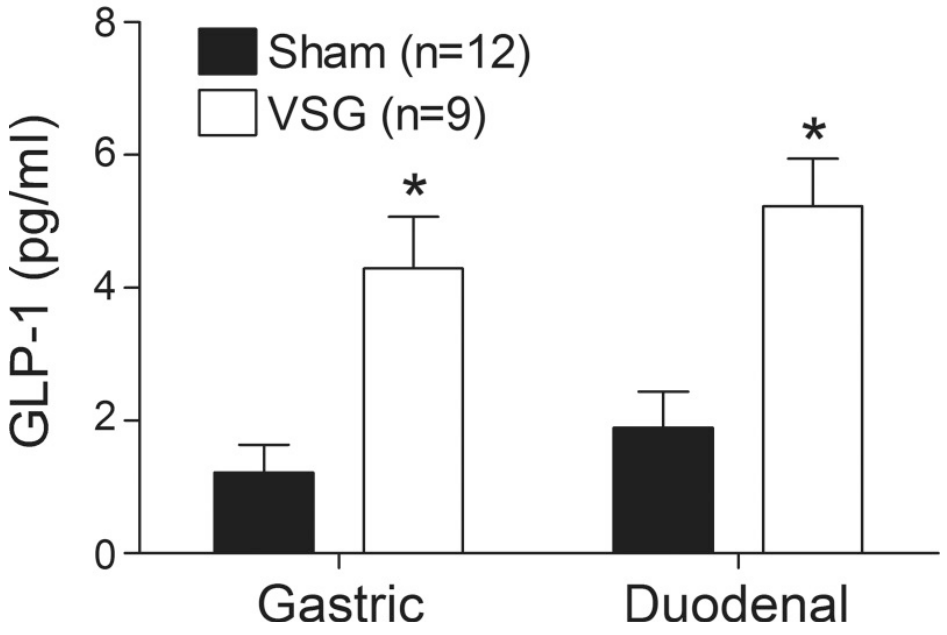
Mechanisms contributing to post-operative exaggerated L-cell responses



A: Lack of anticholinergic responsiveness indicates loss of neural regulation of gastric emptying post-VSG

B: Lack of Exenatide (Exn-4, a GLP-1 analogue) responsiveness indicates loss of paracrine regulation on gastric emptying ("ileal brake")

Isocaloric duodenal nutrient infusion



However, even when nutrients are infused directly into the intestine at an identical rate, GLP-1 secretion is greater post-VSG relative to sham

Chambers et al, Am J Physiol Endocrinol Metab. 2014 Feb 15