The way to man’s heart is through the stomach

Dr Tommy Wood, BA (Cantab), BM BCh (Oxon), PhD

Low Carb Breckenridge 2017

nourish
balance
thrive

Conflicts of Interest

- None to declare

A note on context

- Nourish Balance Thrive
  - Athletes
  - Chronic and autoimmune diseases
  - Cognitive decline

  - Well-informed
  - Multiple practitioners
  - “Have tried everything” (including low carb diets)

Why is a low carb diet not “working”?

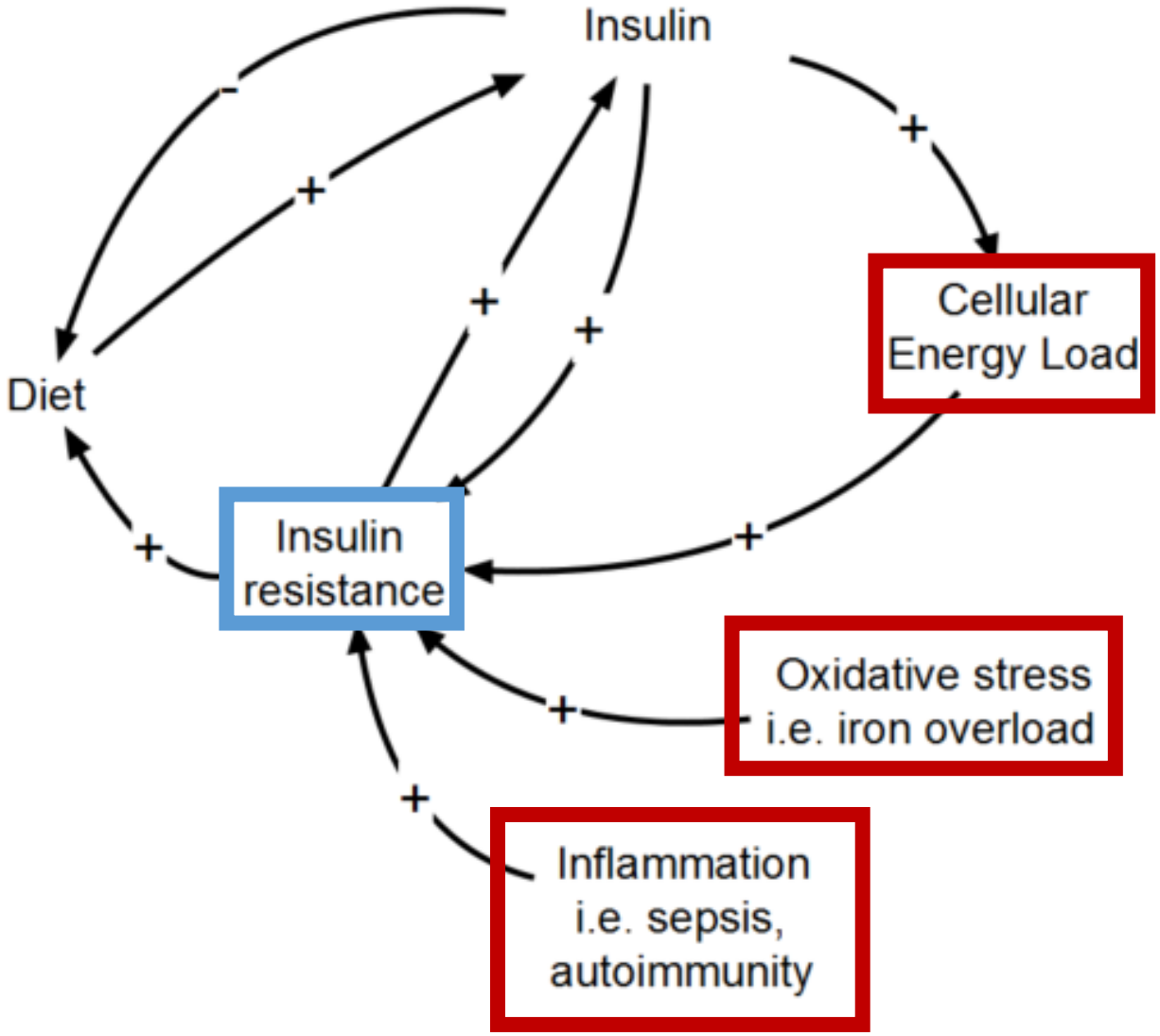
Why is a low carb diet not working?

- Carb restriction is first-line treatment for metabolic disease
  - Obesity
  - (Type 2) diabetes
  - Insulin resistance

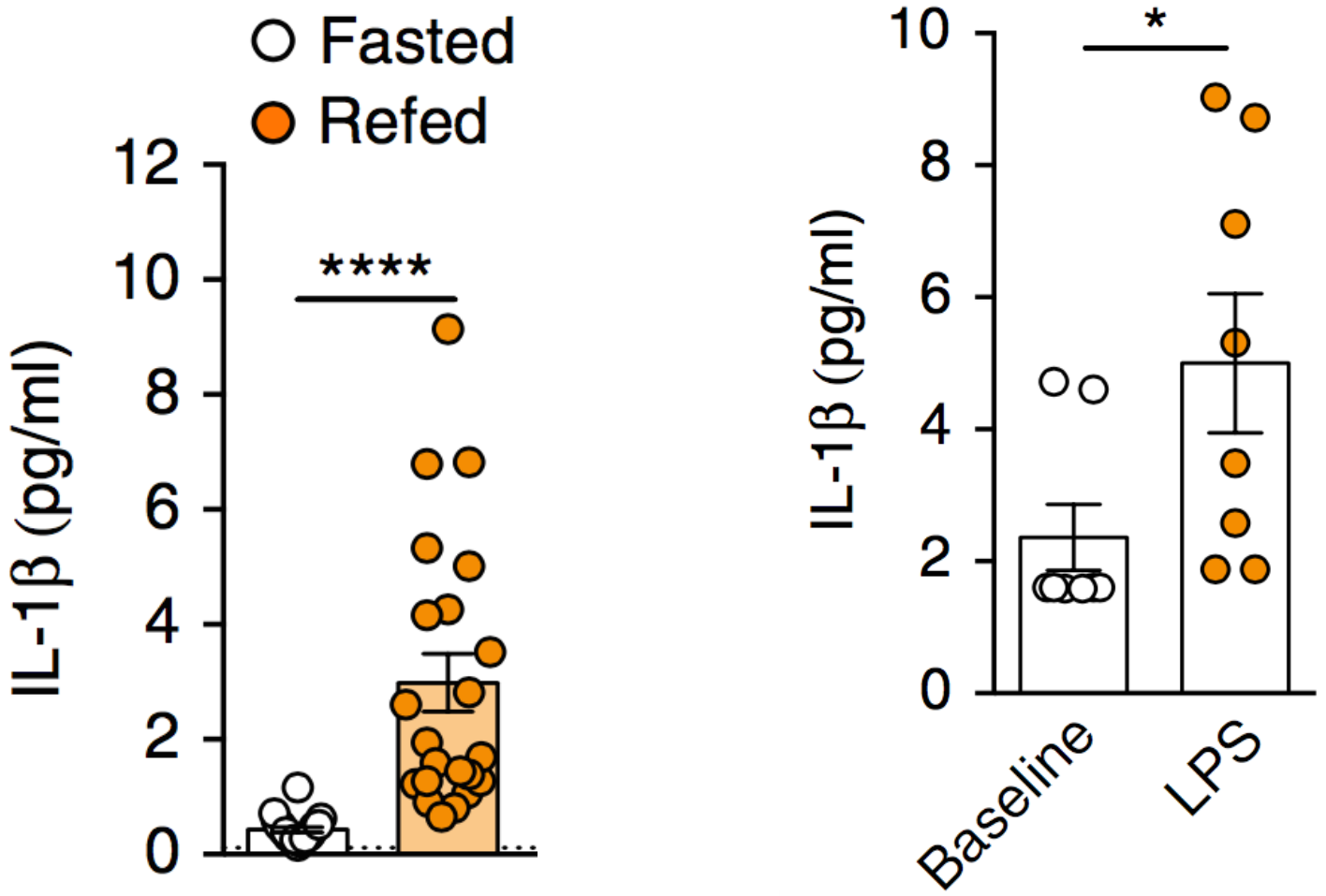
High fat diets may continue to drive one of the main underlying causes of insulin resistance:

Gut-derived endotoxaemia

Modifiable factors controlling insulin resistance



“Every meal stimulates inflammation”

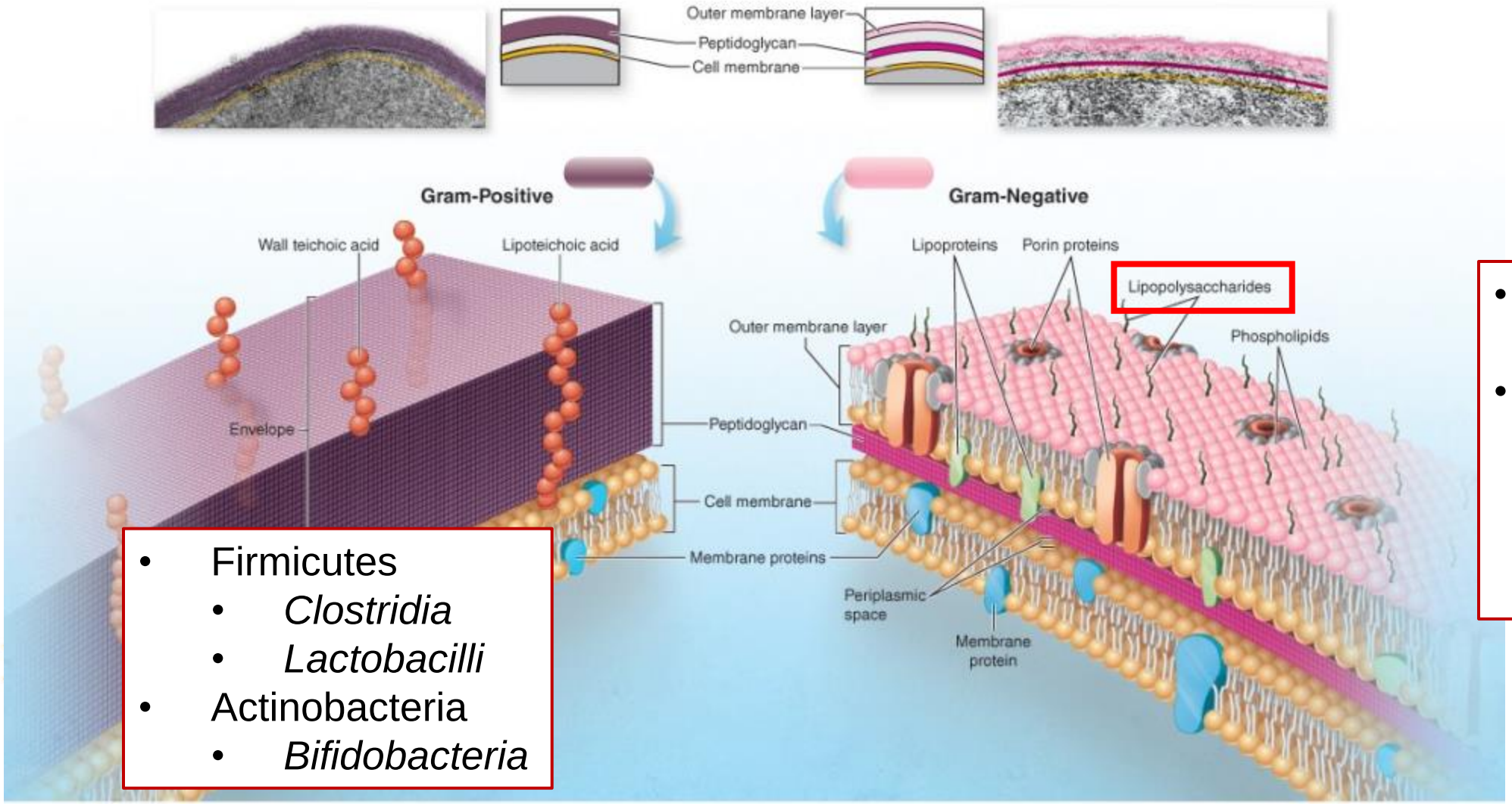


“feeding stimulated immunosurveillance, possibly to limit the dissemination of microorganisms contained in food”

From Dror *et al*., Nature Immunology 2017

Lipopolysaccharides (LPS)

- Constituent of outer membrane of Gram-negative bacteria



- Firmicutes
  - *Clostridia*
  - *Lactobacilli*
- Actinobacteria
  - *Bifidobacteria*

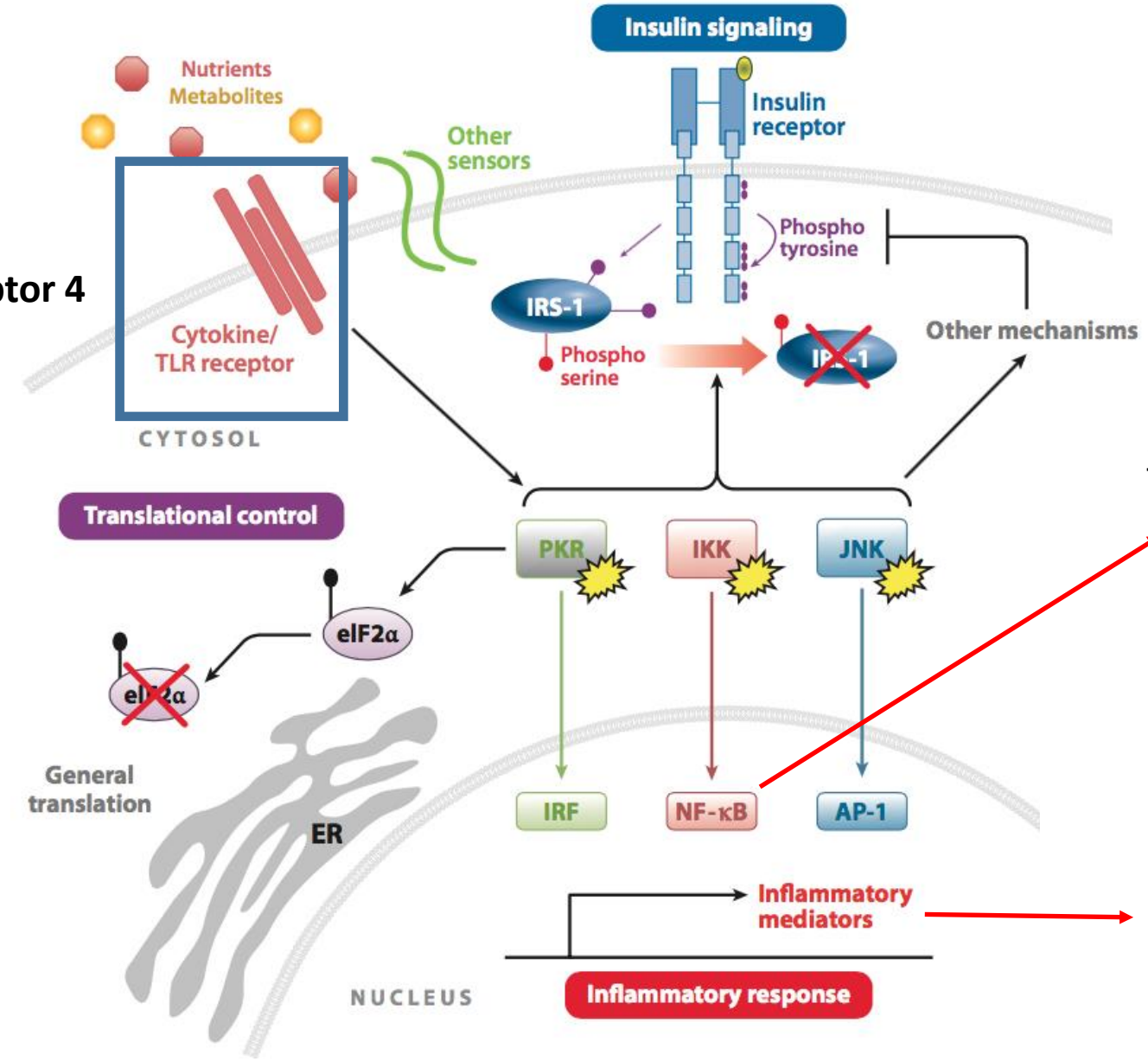
- Bacteroidetes
  - *Prevotella*
- Proteobacteria
  - *E. coli*
  - *Enterobacter*
  - *Helicobacter*
  - *Citrobacter*

E. coli LPS as a model of inflammation

- Brain injury
- Sepsis
- Metabolic disease
  - “Metabolic endotoxaemia”

Endotoxaemia Drives Insulin Resistance

LPS → Toll-like receptor 4 (TLR-4)



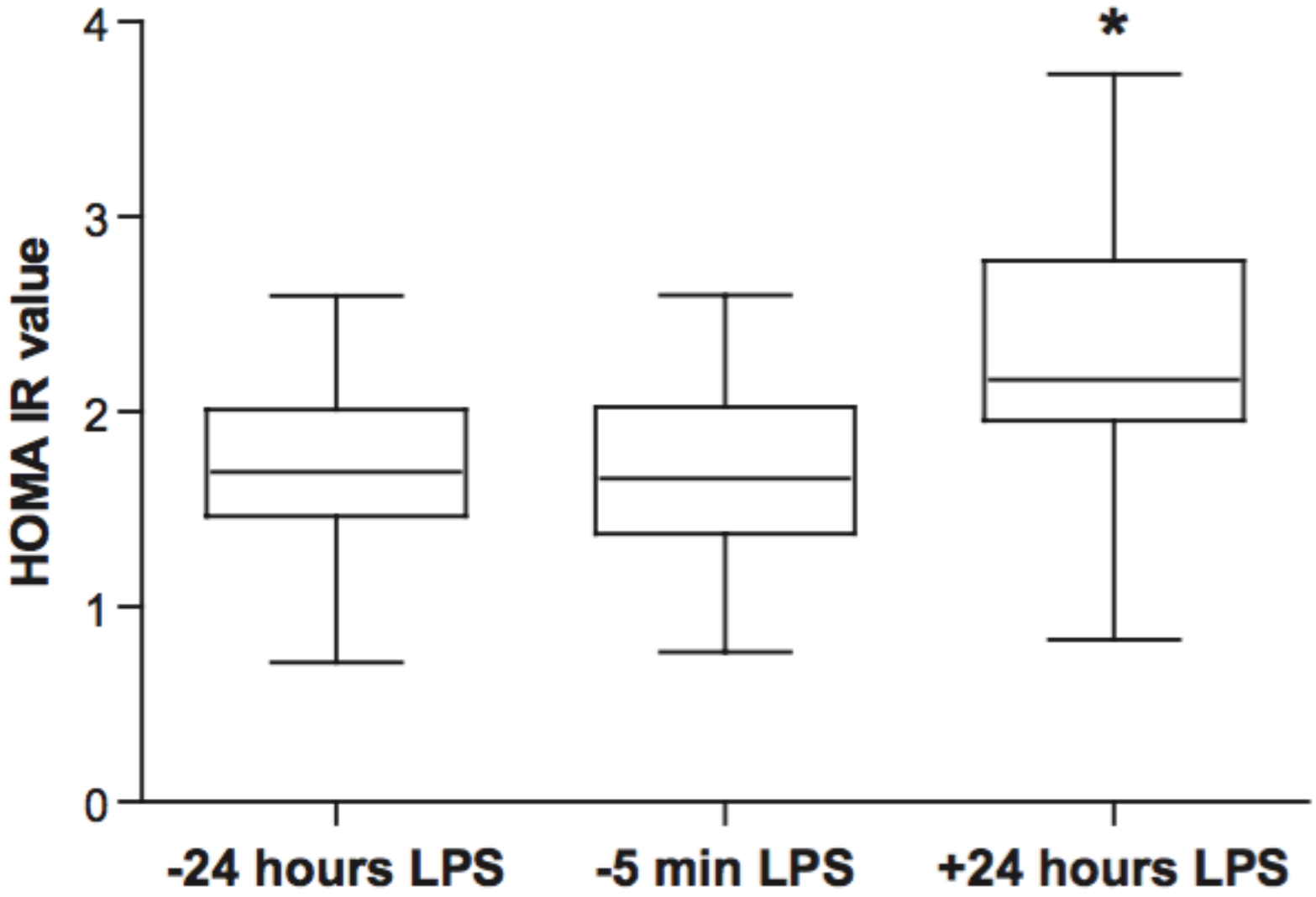
Chronic NF-κB signalling:

Inhibition of autophagy

↑ Leptin Resistance
↓ Adiponectin

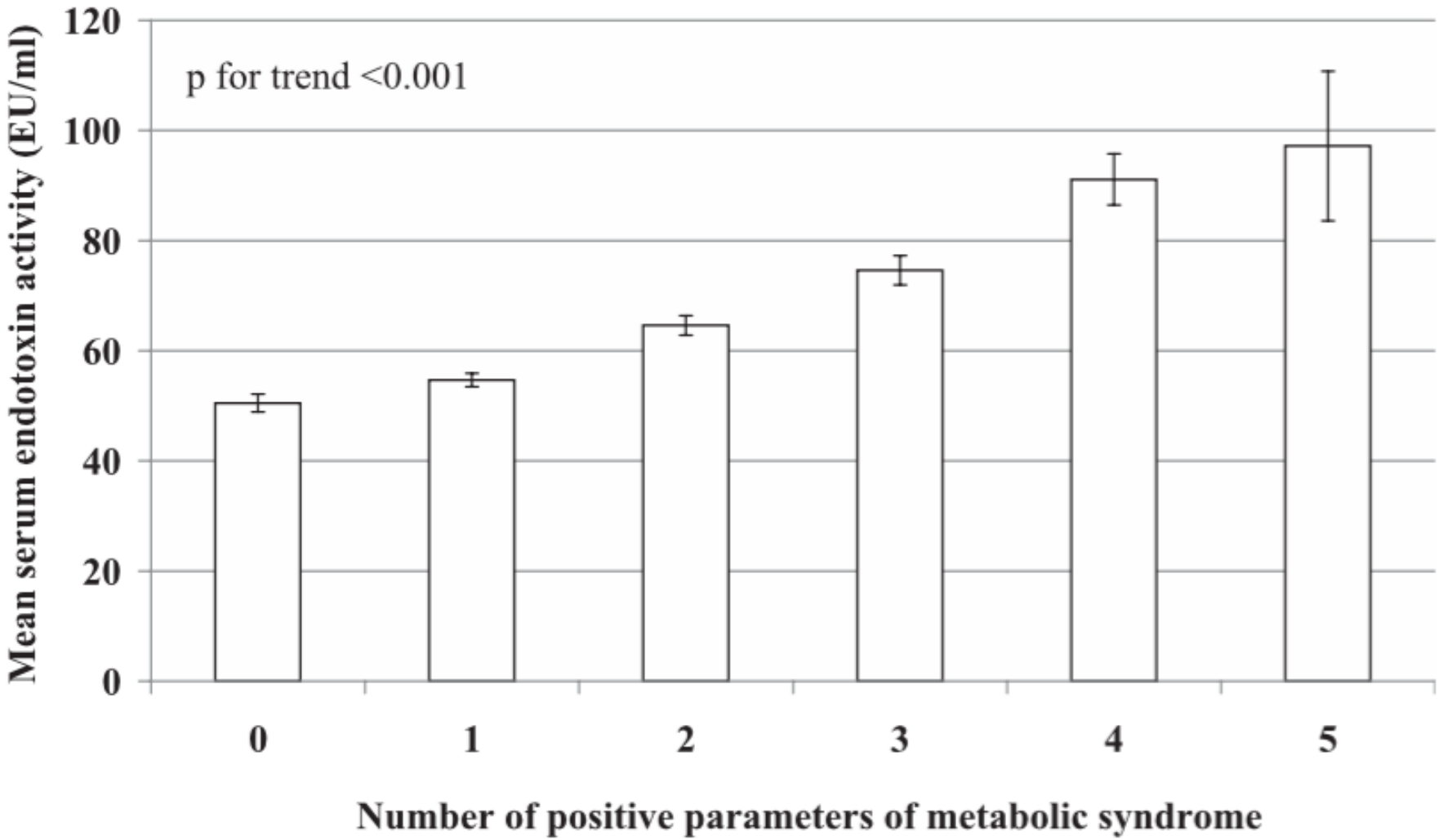
e.g. IL-6 and TNF-α

Acute endotoxaemia causes insulin resistance



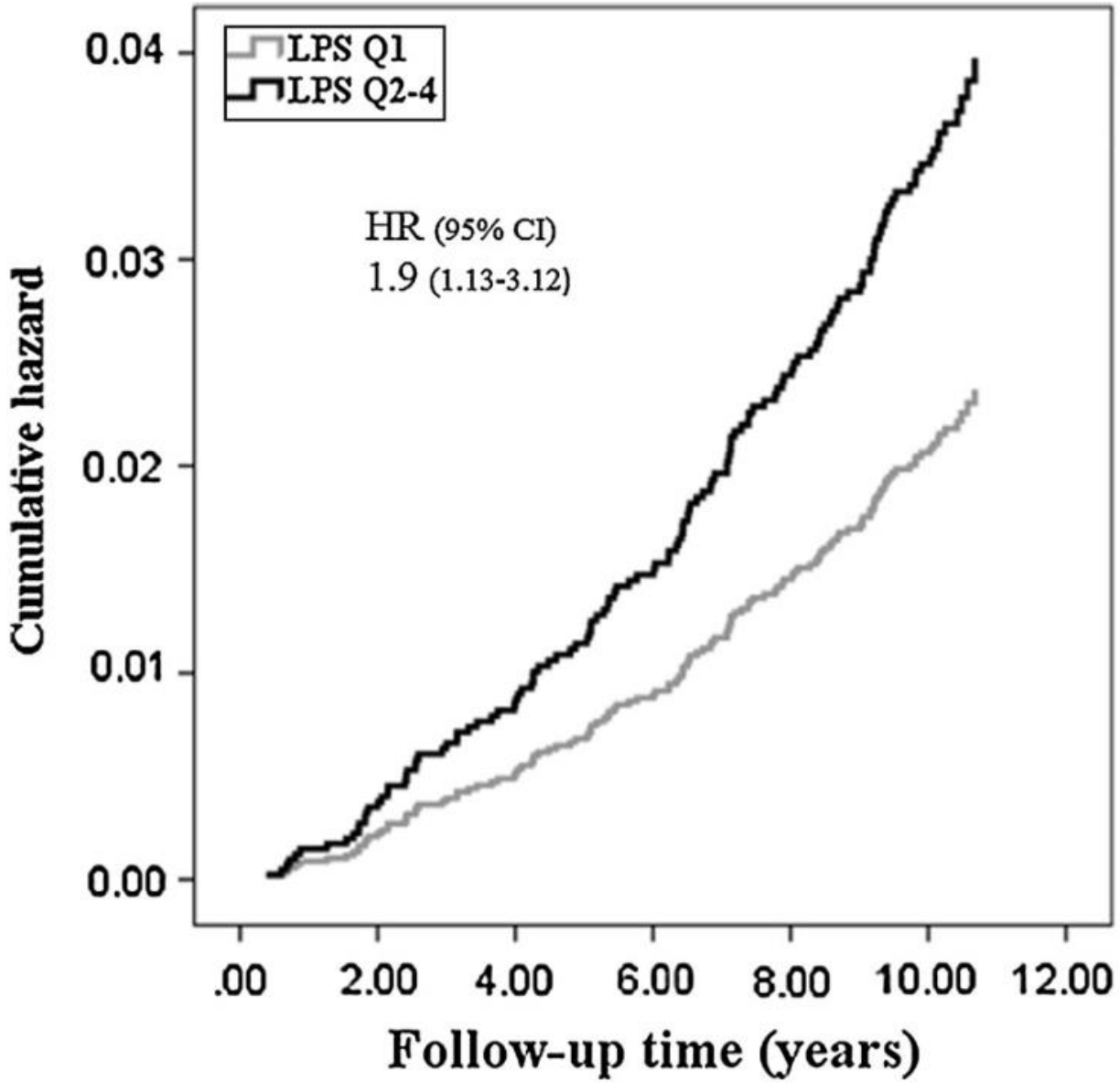
From Mehta *et al.*, Diabetes 2010

Endotoxaemia and metabolic disease



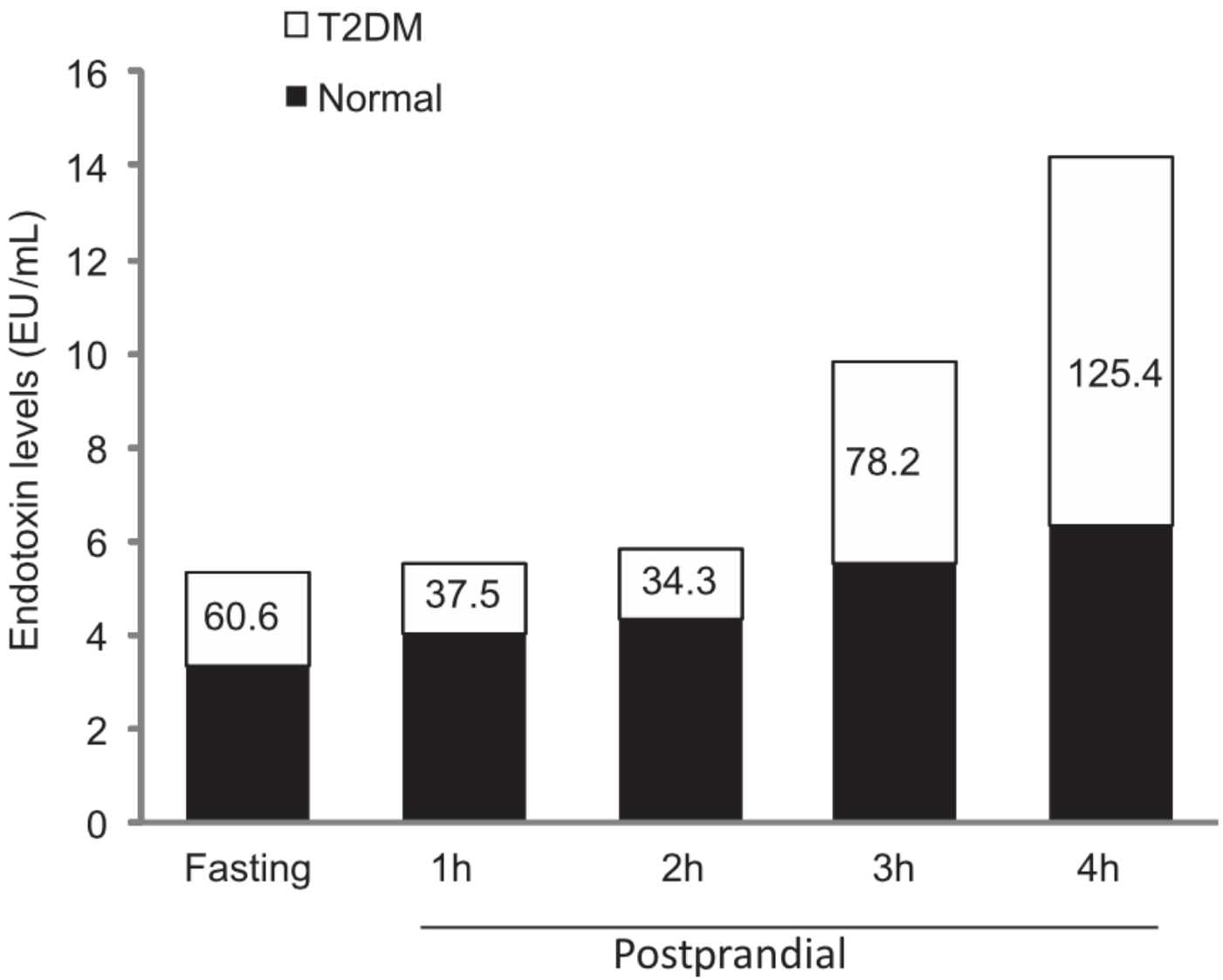
From Pussinen *et al.*, Diabetes Care 2011

Endotoxaemia and incident heart disease



From Kalli *et al*., Acta Diabetol 2015

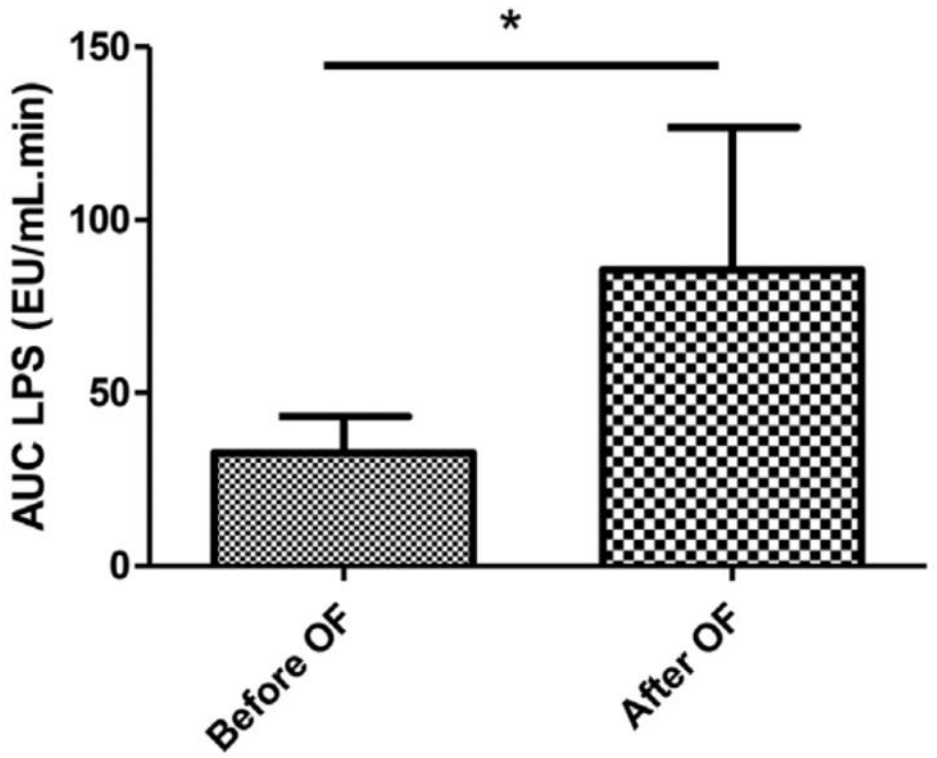
Postprandial endotoxaemia in metabolic disease



From Harte *et al.*, Diabetes Care 2012

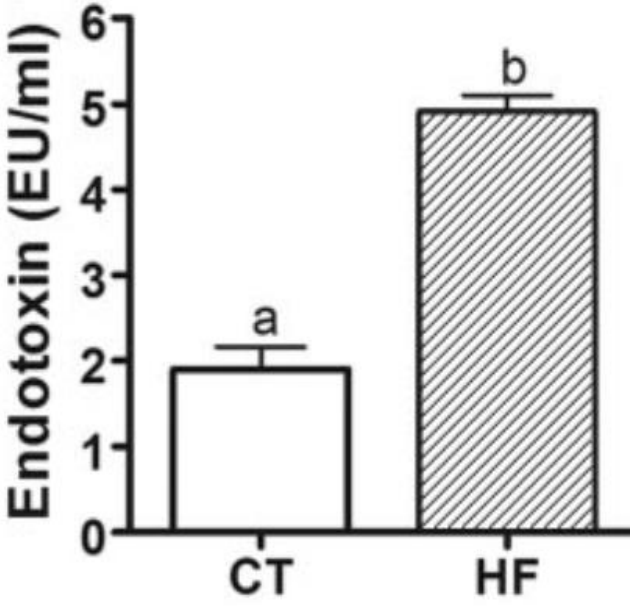
Does endotoxaemia *cause* metabolic disease?

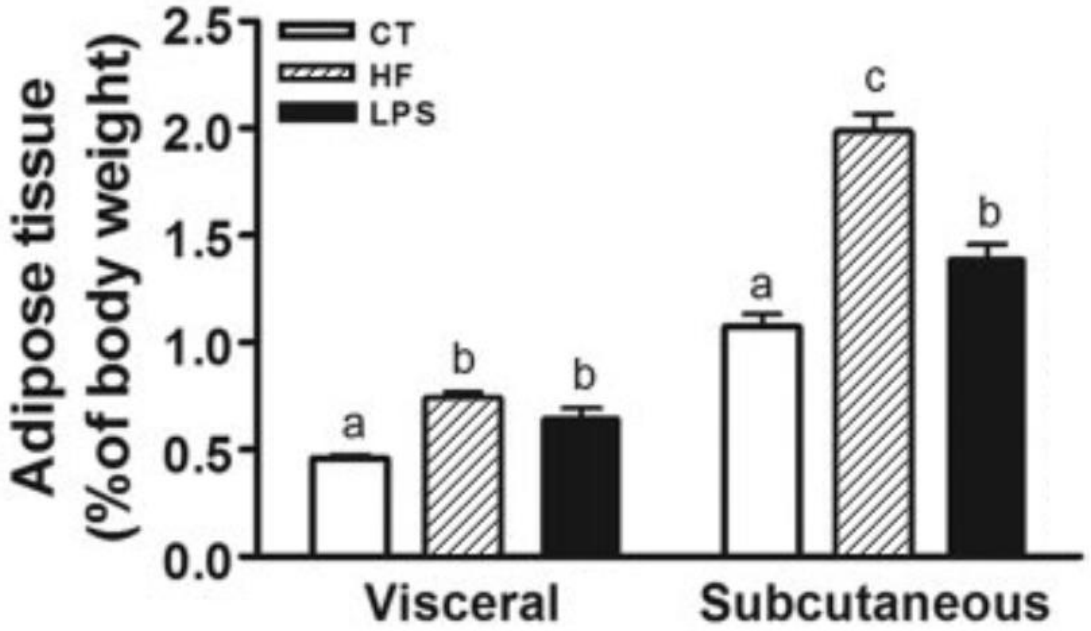
- Overfeeding studies (mixed/Western diet)
  - Fastest way to produce insulin resistance
  - Within 1-7 days
- Overfeeding increases endotoxaemia

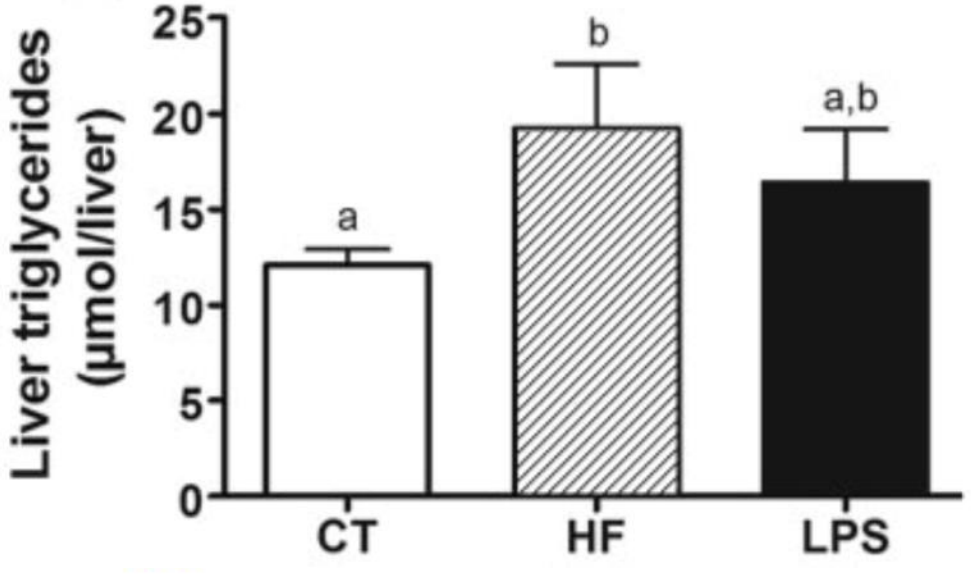


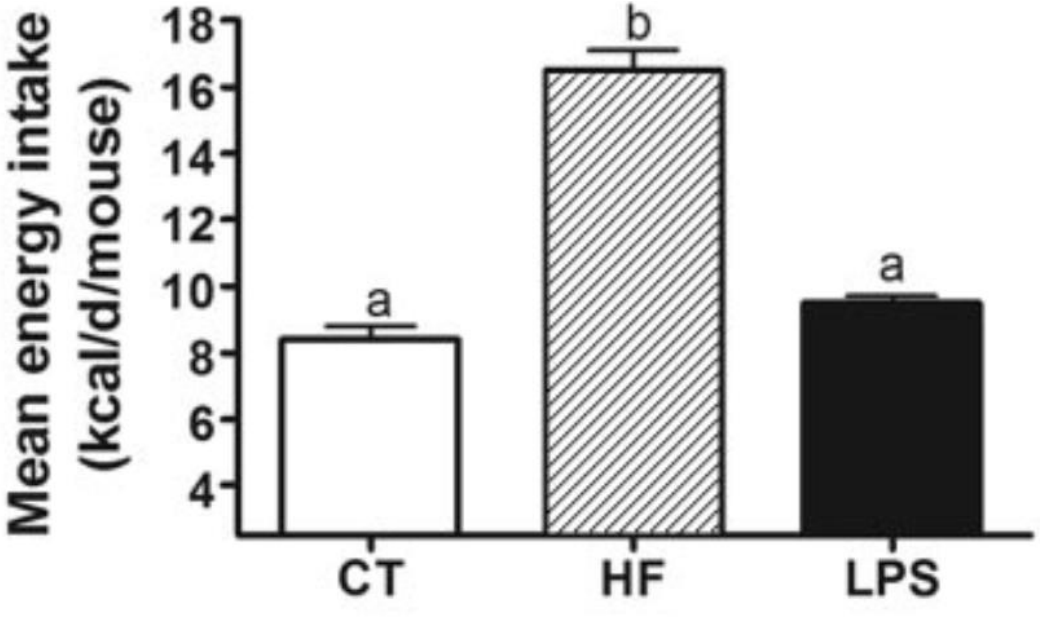
From Laugerette *et al.*, Mol Nutr Food Res 2014

“Endotoxaemia initiates obesity and IR”



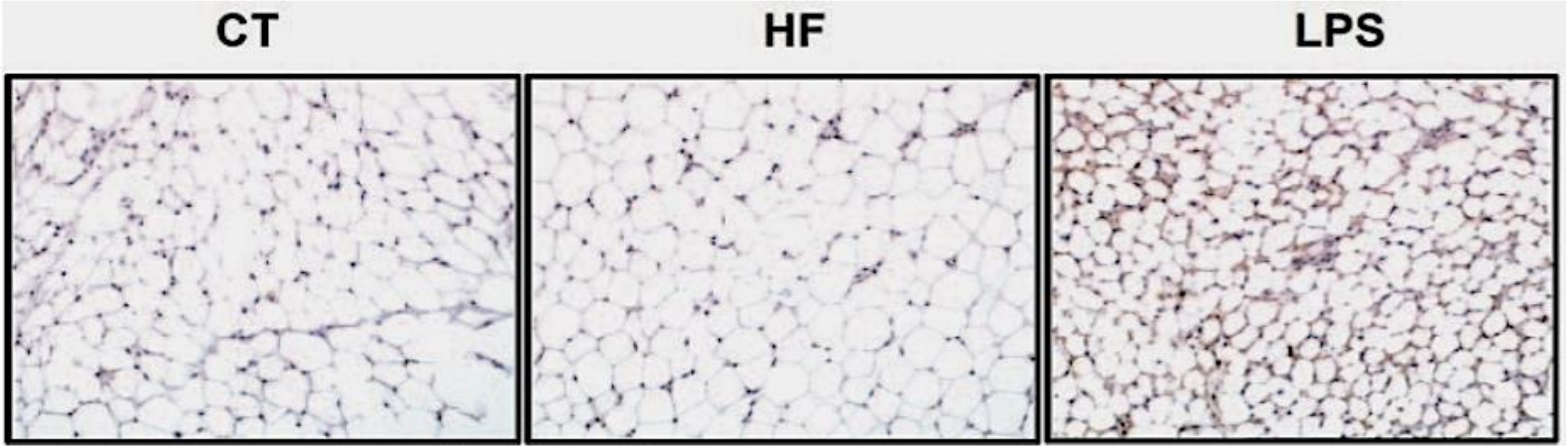






Adapted from:
Cani *et al.*,
Diabetes 2007

LPS suppresses lipogenesis



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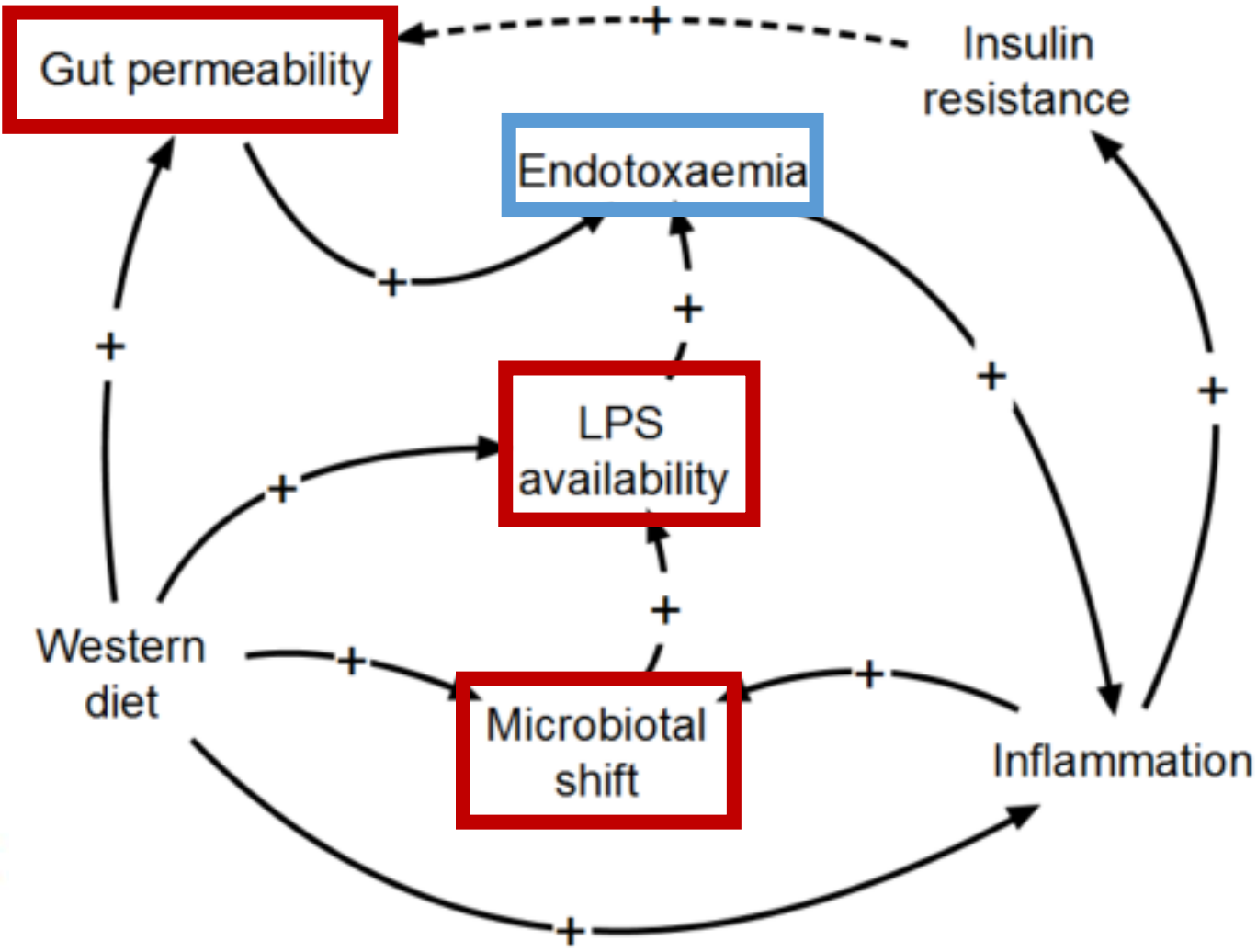
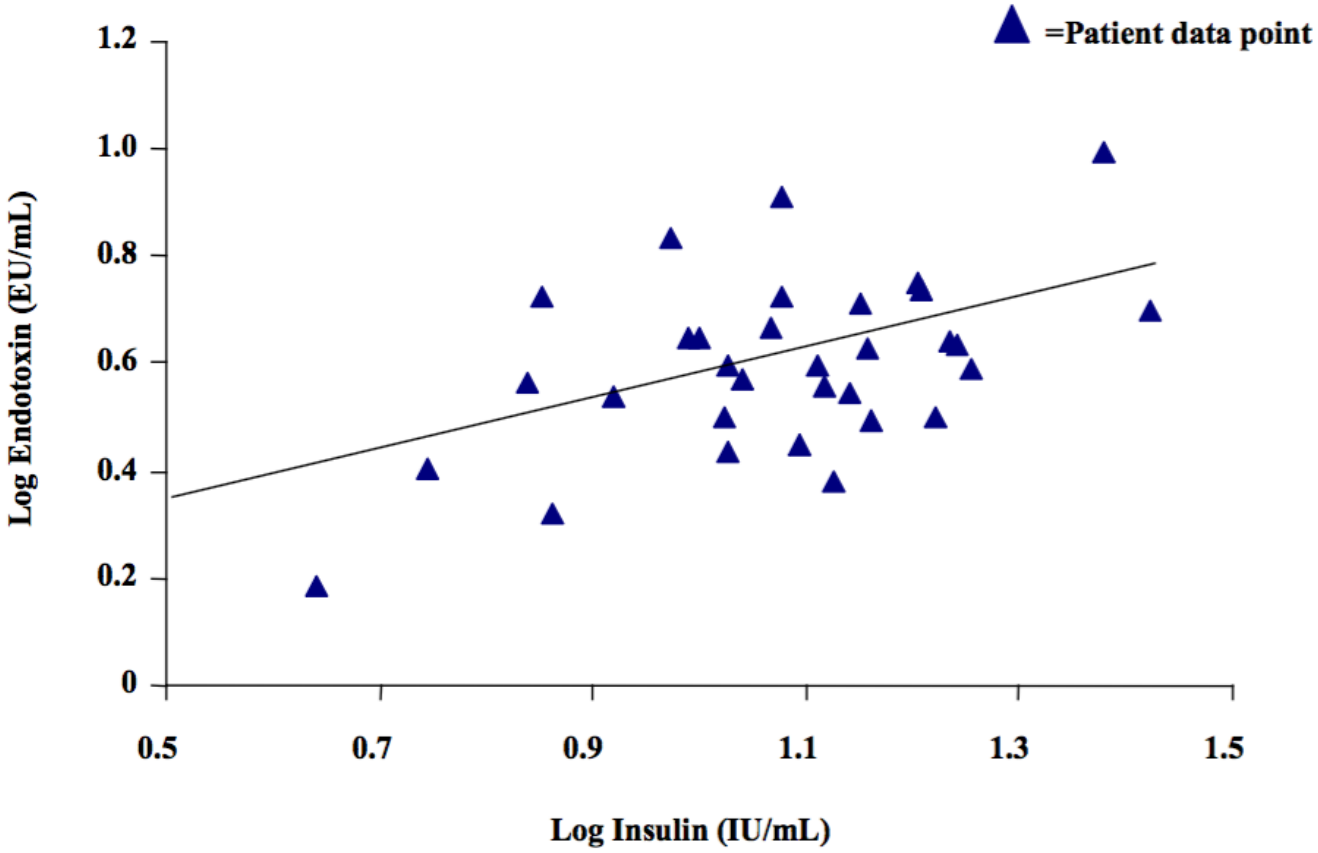
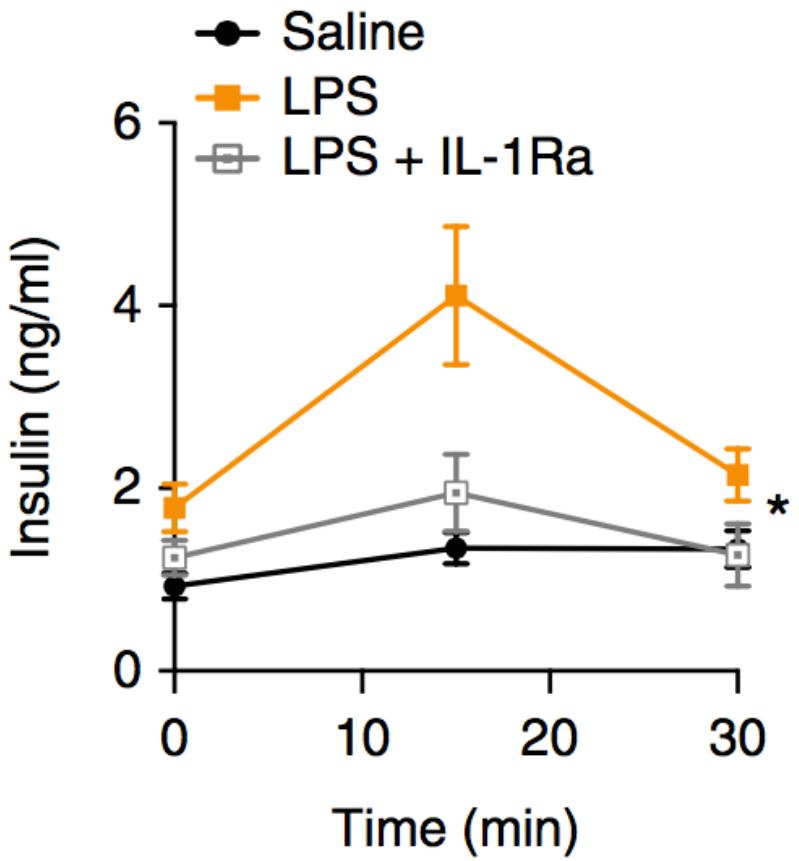


Microbiotal changes in metabolic disease

- Increased
  - Pathogenic proteobacteria
    - Imbalanced *E. coli*
    - Citrobacter
- Decreased
  - Bifidobacteria
  - Akkermansia (mucin layer)
  - Roseburia (butyrate producers)

LPS *directly* increases insulin secretion



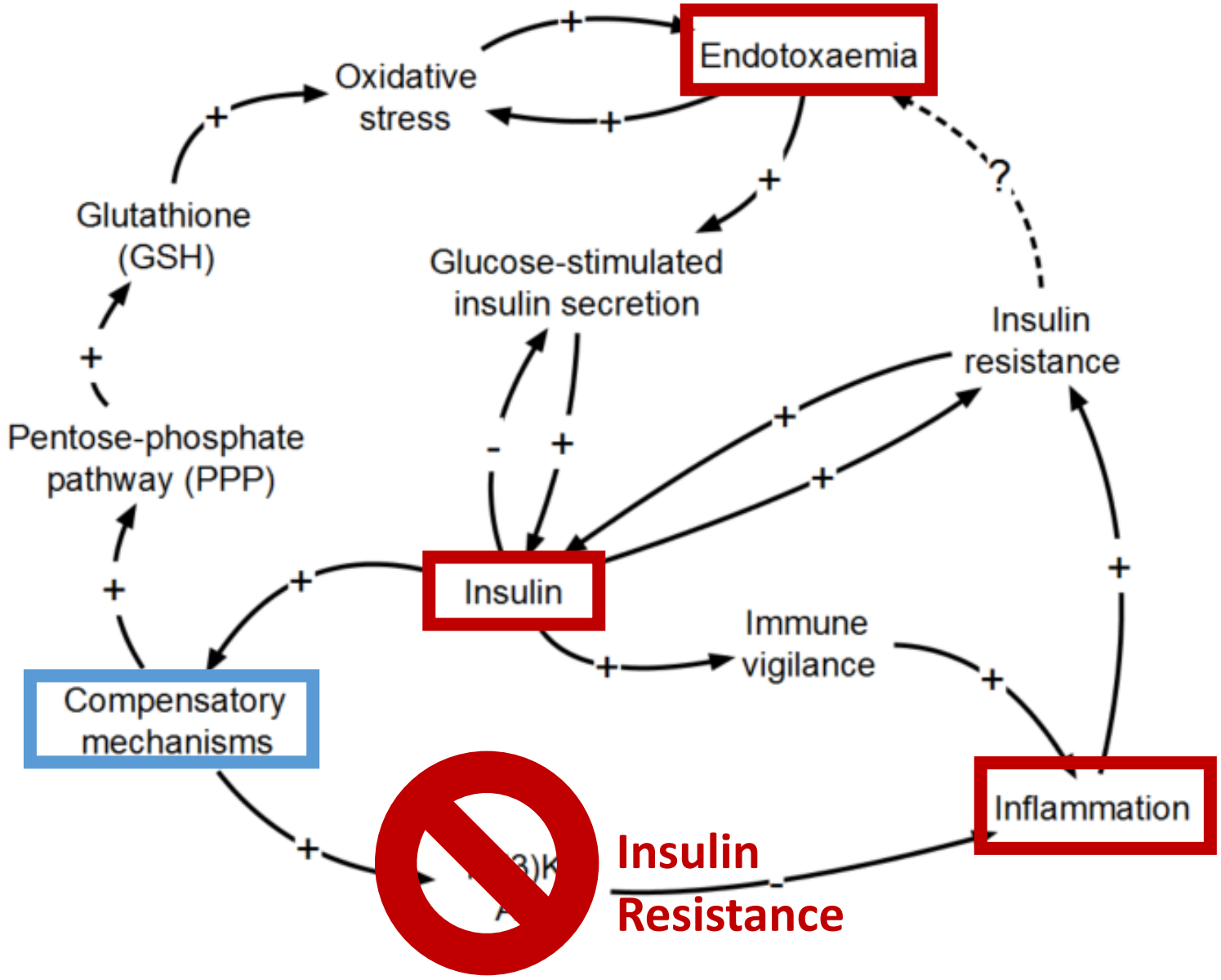


Hyperinsulinaemia diverts resources to the immune system in the setting of endotoxaemia

From Creely *et al*., Am J Physiol Endocrinol Metab 2006

From Dror *et al*., Nature Immunology 2017

Benefits of insulin become maladaptive over time



Cellular responses determine risk

	MetS	
	OR (95 % CI)	*p* value
Age (year)	1.03 (1.02–1.04)	0.001
Male	2.03 (1.65–2.51)	<0.001
Education (year)	0.96 (0.94–0.99)	0.008
Current smoking	0.88 (0.70–1.11)	0.281
Hypertension	–	–
Cholesterol (mmol/l)	1.23 (1.13–1.35)	<0.001
CRP (mg/l)	1.07 (1.04–1.09)	<0.001
Energy (418 kJ or 100 kcal)	0.98 (0.96–0.99)	0.005
High LPS*	**2.56 (1.97–3.32)**	**<0.001**

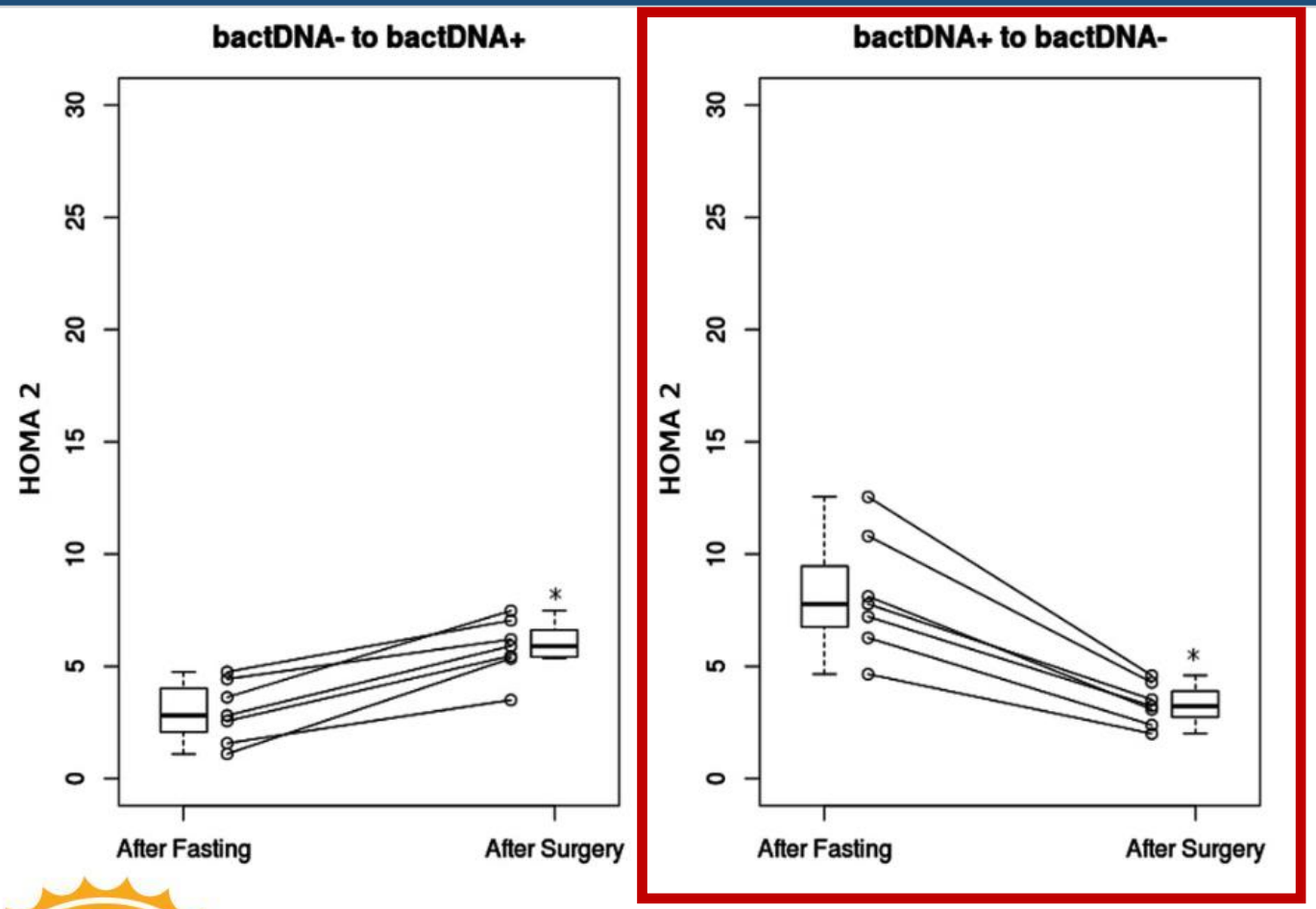
"elevated markers of inflammation are reliably detected on leukocytes… not consistently raised in plasma"

Herieka and Erridge, Mol Nutr Food Res. 2014

Strategies

Things that fix insulin resistance fix endotoxaemia.
Or vice versa?

Gastric Bypass

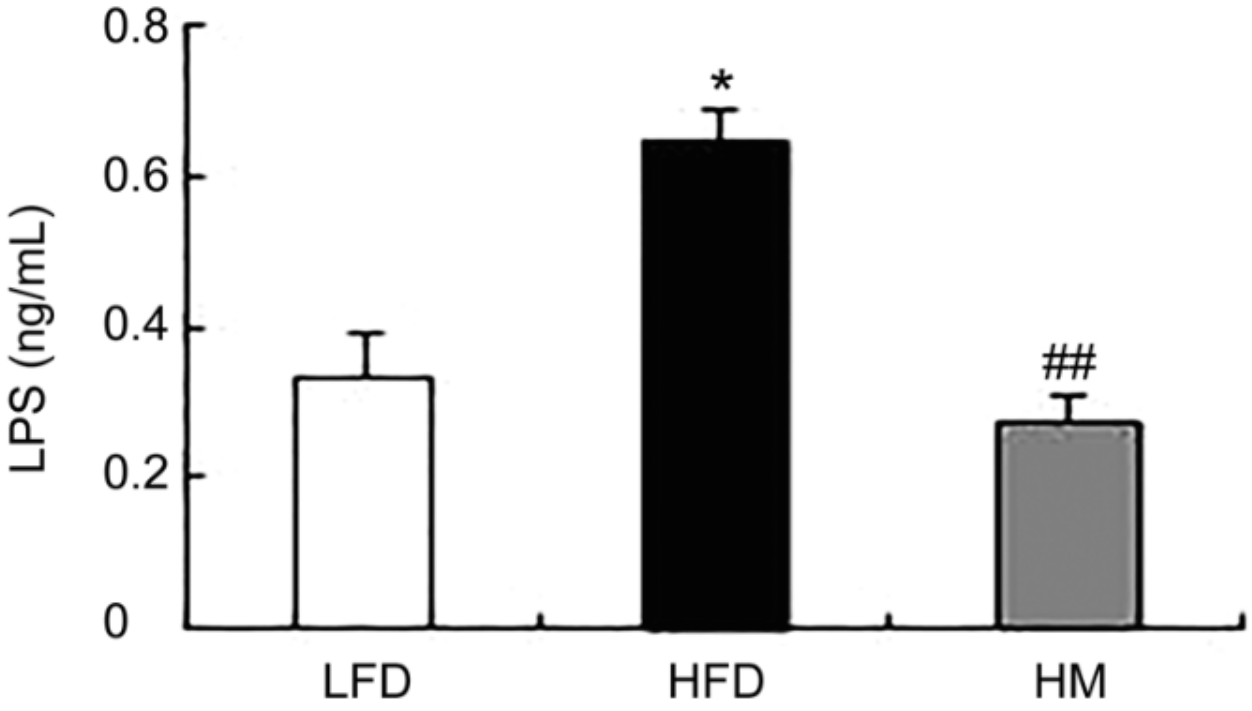


- Increases microbiotal diversity
  - *Akkermansia*
- Decreases gut permeability
  - ↑ Tight-junction proteins
  - ↑ GLP-2
- Decreases endotoxaemia

From Ortiz *et al.*, J Clin Endocrinol Metab, 2014

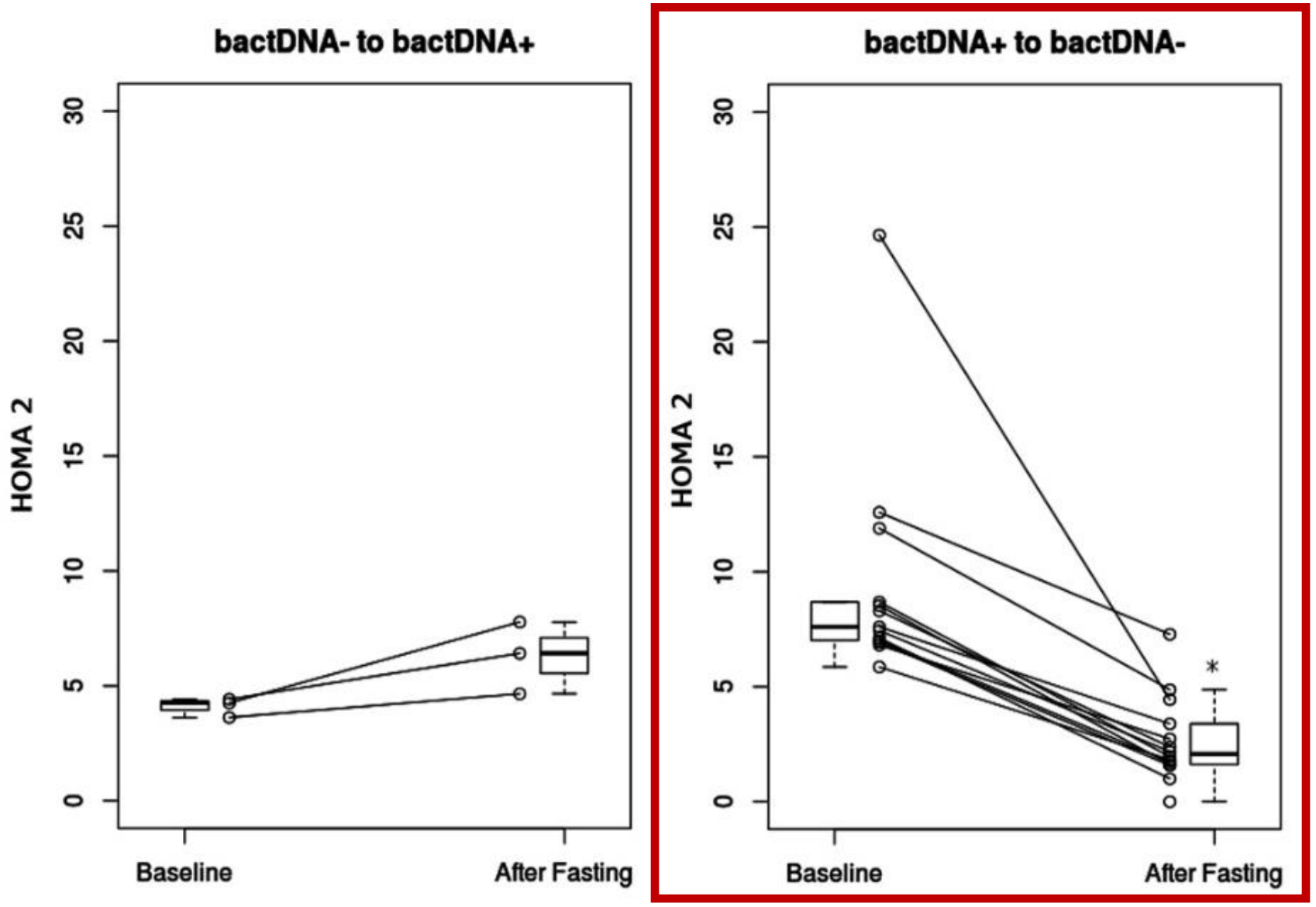
Metformin

- Increases beneficial gut bacteria in T2DM
  - *Akkermansia*, *Bifidobacteria,* Butyrate producers
- Suppresses TLR-4 signalling
- Decreases endotoxaemia



Zhou *et al*., Acta Pharmacologica Sinica 2016

Fasting



From Ortiz *et al*., J Clin Endocrinol Metab, 2014

Eat real food

- Low carb bars, emulsified “fatbombs”, and protein chips?

Nutritional Facts

Serving Size: 1 Roll (115g)

Amount/Serving	
Calories 530	Calories from Fat 450
	%Daily Value*
Total fat 50g	77%
Saturated fat 42g	210%
Trans fat 0.5g	
Polyunsaturated fat 0.5g	
Monounsaturated fat 2.5g	
Cholesterol 85mg	28%
Sodium 410mg	17%
Total Carbohydrate 26g	9%
Dietary Fiber 12g	48%
Sugars 2g	
Sugar Alcohol 10g	
Protein 11g	

Description

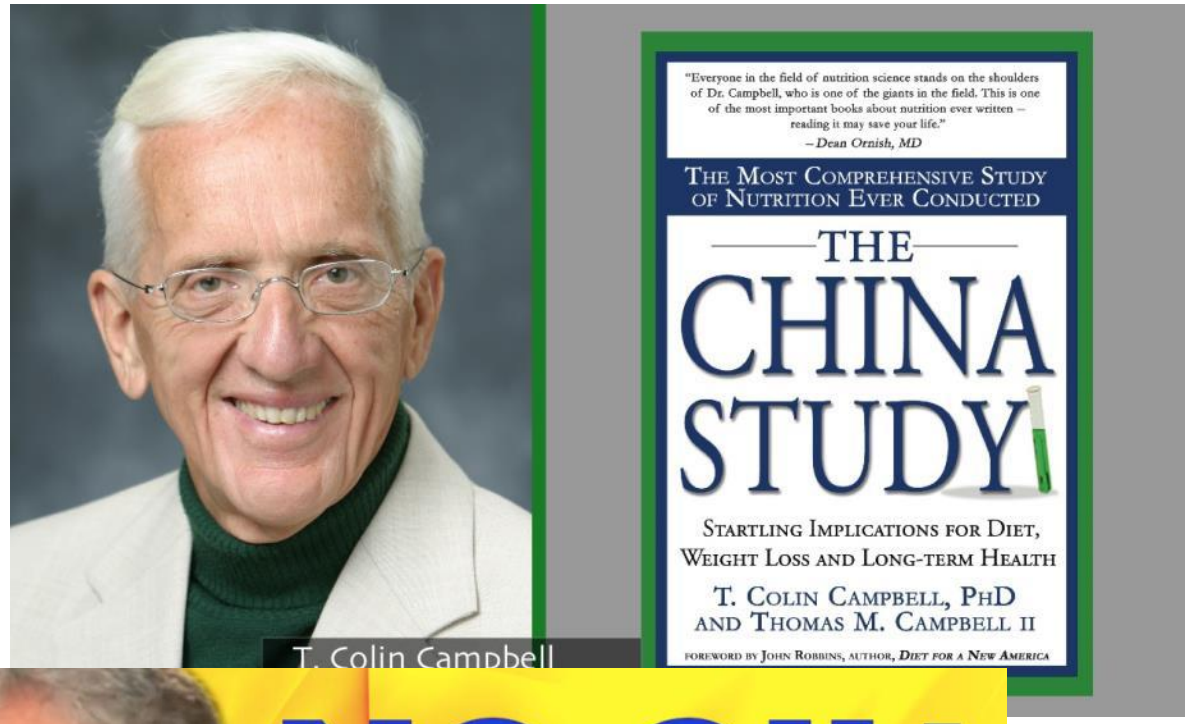
designed to keep you in ketosis with a 2:1 ratio of Fat to Protein plus Carbohydrates (F:P+C). All Quest Keto Meals are 480-510 calories and under 4 Net Carbs.** Enjoy all the indulgence and take the guesswork out of Keto.

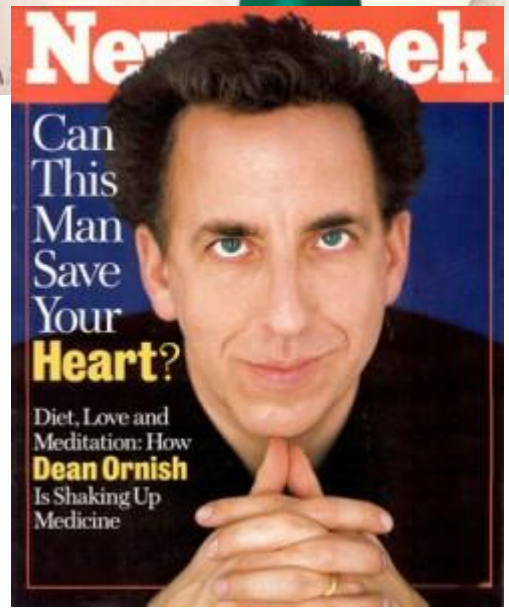
**Total Carbs – Fiber – Erythritol = Net Carbs

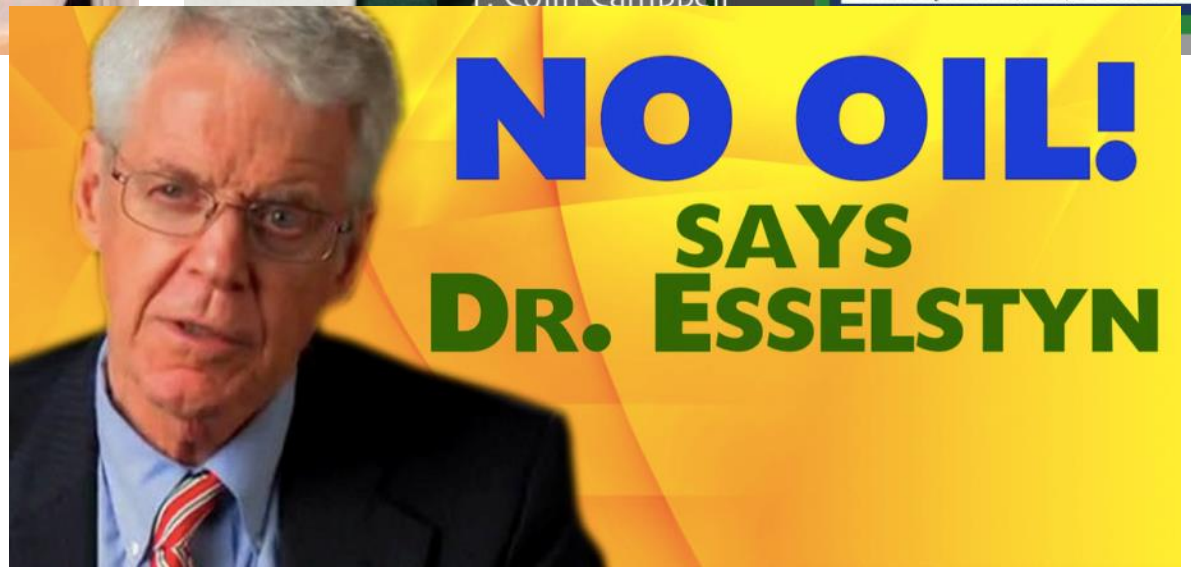
Ingredients

COCONUT OIL POWDER (COCONUT OIL, SOLUBLE CORN FIBER, SODIUM CASEINATE [A MILK DERIVATIVE], SUNFLOWER LECITHIN), CREAM CHEESE (PASTEURIZED MILK AND CREAM, CHEESE CULTURE, SALT, STABILIZERS [CAROB BEAN AND/OR XANTHAN AND/OR GUAR GUMS]), WHOLE EGG, SWEETENER BLEND (ERYTHRITOL, STEVIOL GLYCOSIDES), UNSALTED BUTTER (SWEET CREAM), WHEY PROTEIN ISOLATE, CELLULOSE, VINEGAR, NATURAL FLAVOR, SODIUM CASEINATE, SOLUBLE CORN FIBER, BAKING POWDER (MONOCALCIUM PHOSPHATE, POTATO STARCH, POTASSIUM BICARBONATE), CINNAMON, WATER, XANTHAN GUM, LOCUST BEAN GUM, BAKING SODA (SODIUM BICARBONATE), SUCRALOSE

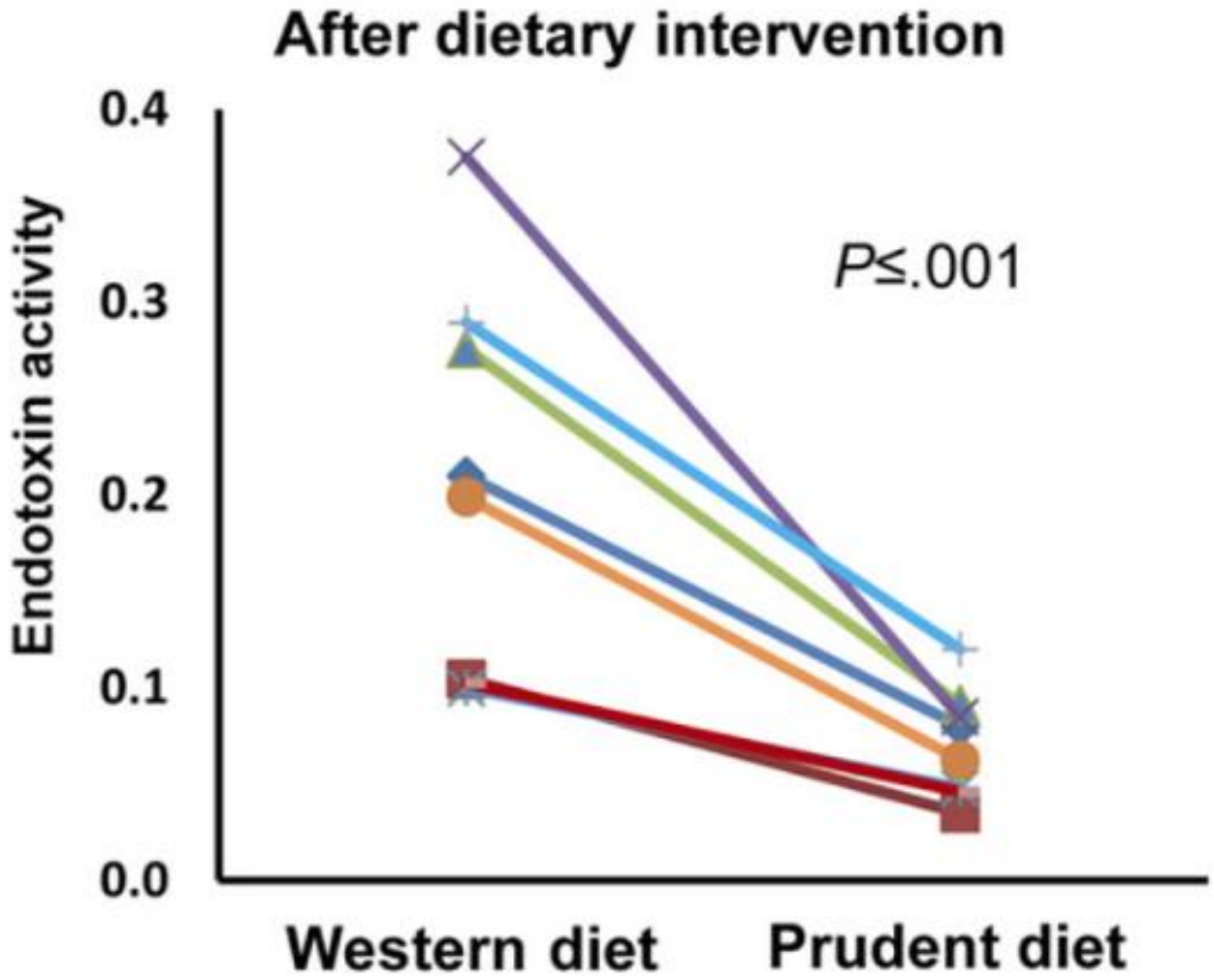
“Extreme” measures







Dietary fat drives endotoxin absorption



From Pendyala *et al*., Gastroenterology 2012

Test and treat the gut

- 48 y/o Oncologist - competitive figure skater
- Fatigue and dramatic decrease in performance on LCHF

BACTERIOLOGY CULTURE		
Expected/Beneficial flora	**Commensal (Imbalanced) flora**	**Dysbiotic flora**
4+ Bacteroides fragilis group	2+ Beta strep, group B	
NG Bifidobacterium spp.	2+ Citrobacter freundii complex	
NG Escherichia coli	2+ Gamma hemolytic strep	
NG Lactobacillus spp.	1+ Staphylococcus aureus	
NG Enterococcus spp.		

- Failure of LCHF diet:
  - Identify and treat pathogens
  - Support a better gut microbiota
  - Fuel appropriately
    - Both activity *and* co-morbidities
  - Fix the environment!

Summary

- Endotoxaemia contributes to metabolic disease
  - Western diet
  - Shifts in gut function and microbiota
  - Heart disease in athletes
- Interventions that reduce endotoxaemia improve metabolic health
- High fat intake can exacerbate endotoxaemia
  - May contribute to “failure” of LCHF diet
  - Depends on initial and current gut health and genetics

Acknowledgements

- Endotoxin project
  - Dr. Guðmundur Jóhannsson
  - Dr. Robert Hansen
- Chief Engineer
  - Prof. Elizabeth Nance
- Nourish Balance Thrive
- Thanks to you all!

The way to man’s heart is through the stomach

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Low Carb Breckenridge 2017

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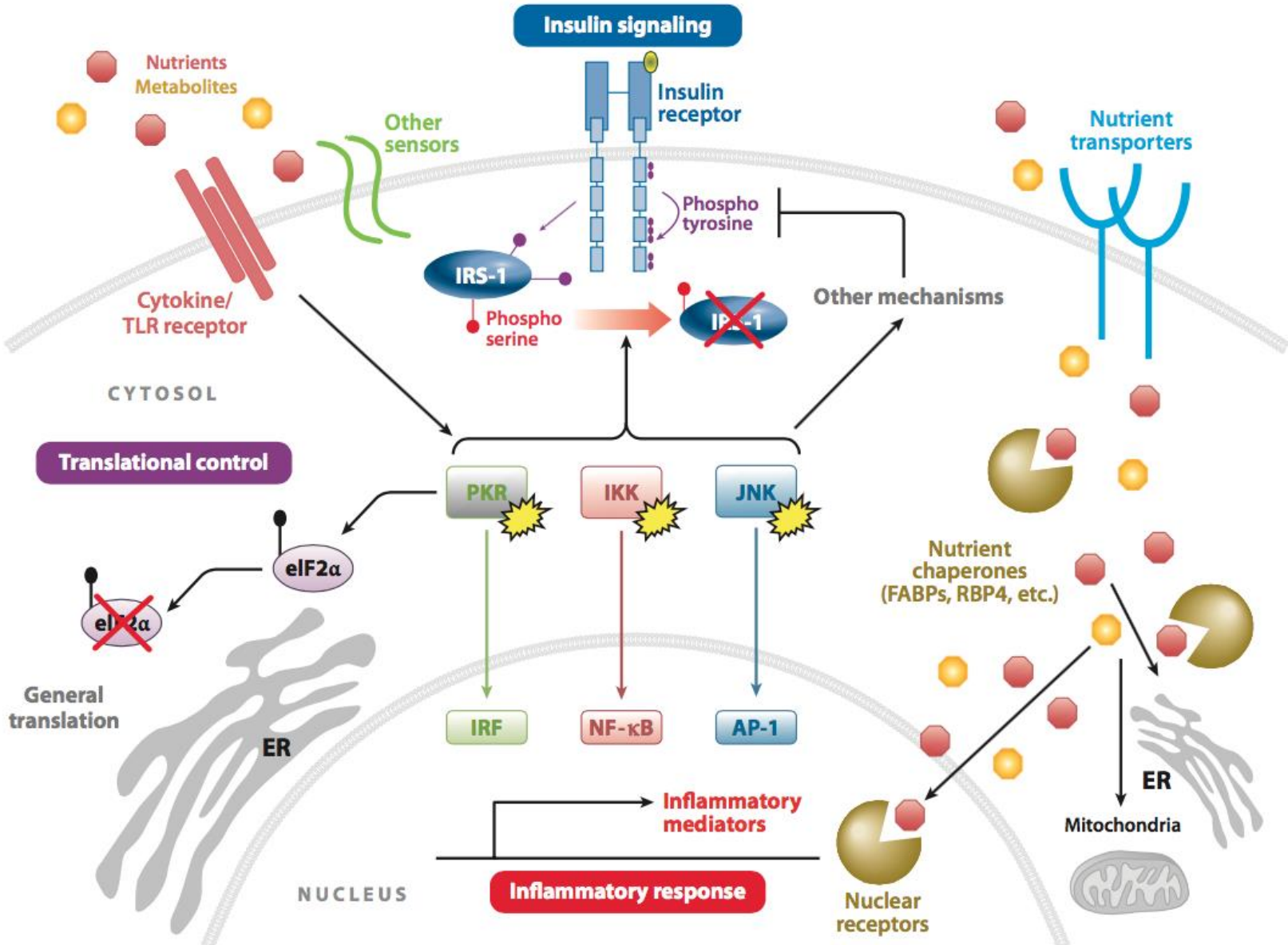

Insulin signaling
Nutrients
Metabolites
Other
sensors
Insulin
receptor
Nutrient
transporters
Phospho
tyrosine
IRS-1
Phospho
serine
Cytokine/
TLR receptor
Other mechanisms
CYTOSOL
Translational control
PKR
IKK
JNK
eIF2α
Nutrient
chaperones
(FABPs, RBP4, etc.)
General
translation
ER
IRF
NF-κB
AP-1
Inflammatory
mediators
ER
Mitochondria
NUCLEUS
Inflammatory response
Nuclear
receptors

TLR-4 signalling in obesity/T2DM

- Higher TLR-4 signalling in obese etc

- Best way to induce IR – overfeed a Western diet
  - Directly affects endotoxaemia

- Potentially the best way to reverse IR in the scientific literature?
  - Gastric bypass

What about the insulin??

- Anti-inflammatory
  - Rodents
  - Humans
  - Increases immune-system vigilance (diverts nutrients to immune system)
- May help drive production of visceral fat
  - If this is prevented (or inflammation fully suppressed), results in peripheral ectopic fat and inflammation

Factors affecting LPS translocation

- Fat intake (via chylomicrons)
- Sugar intake (fructose)
- Gut permeability
  - Gut microbiota
- Metabolic disease
  - Feed-forward effect
  - Weight loss reduces endotoxaemia

Eat real food

M.E.A.L. Diet

for rapid fat loss

M — **Meat** — any animal product

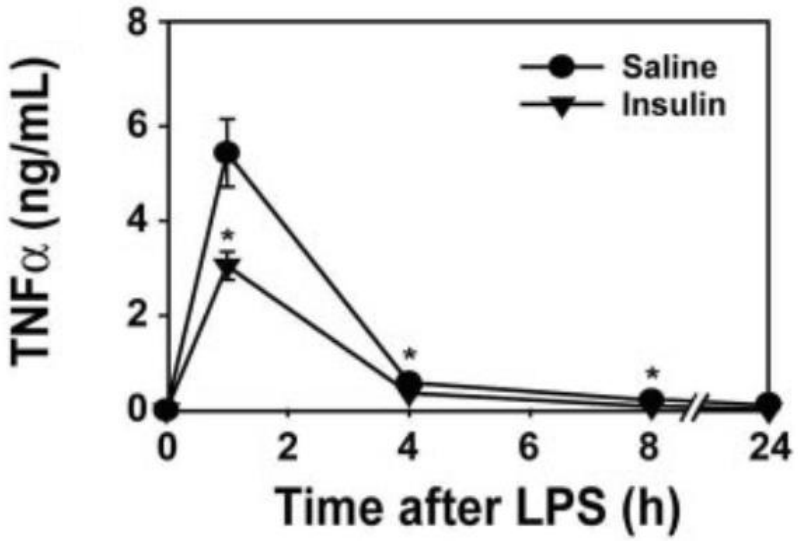
E — **Eggs**

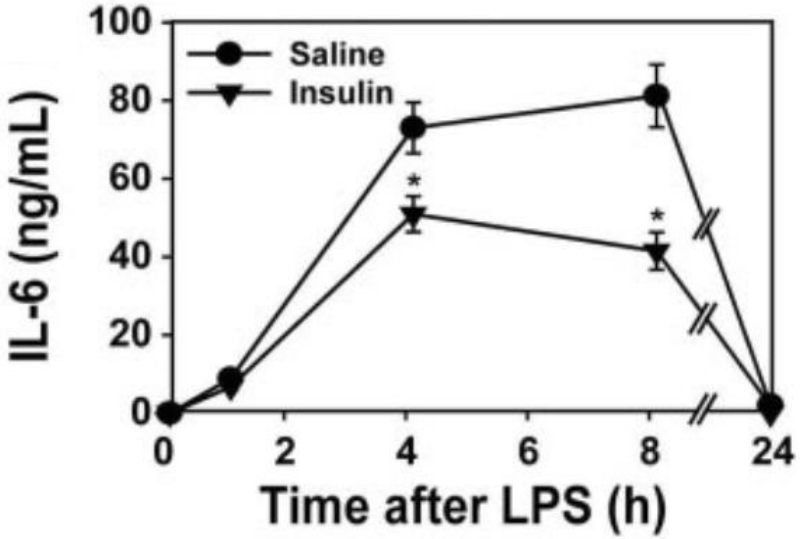
A — **Added** — fats for cooking

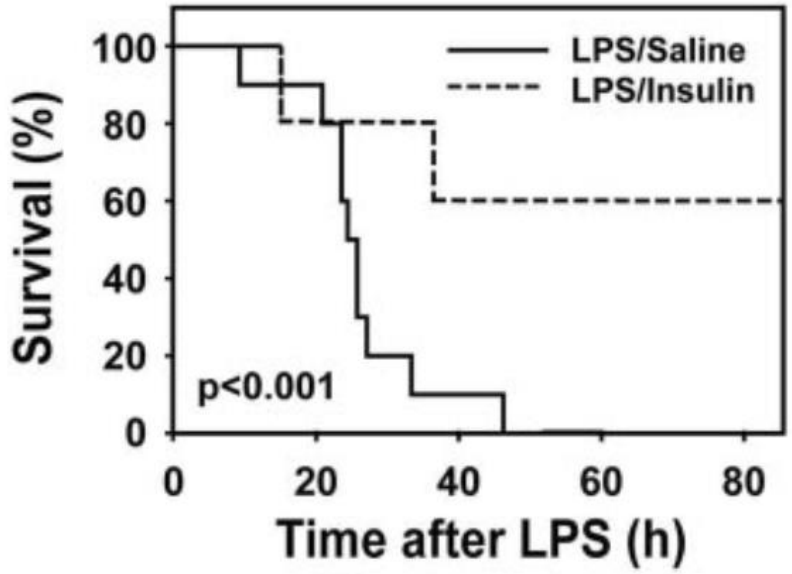
L — **Leaves** — non-starchy vegetables

Probiotics

Insulin is protective during endotoxaemia

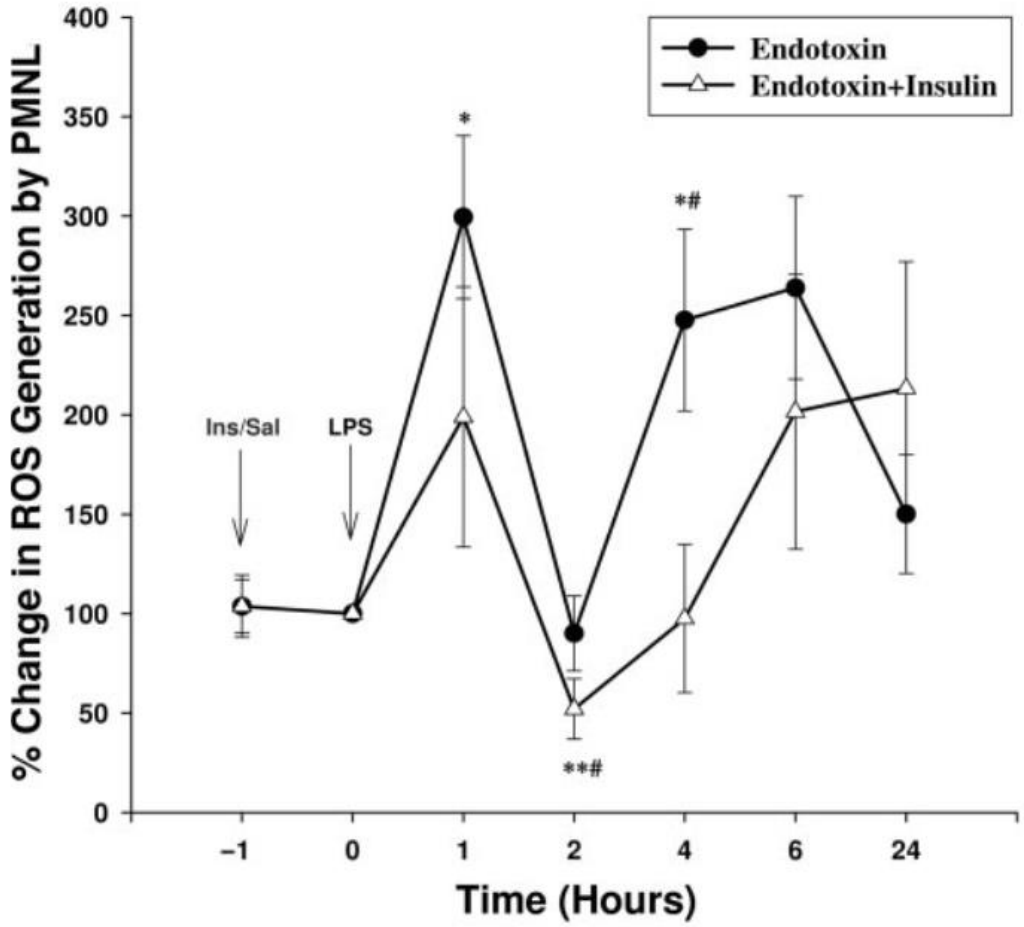


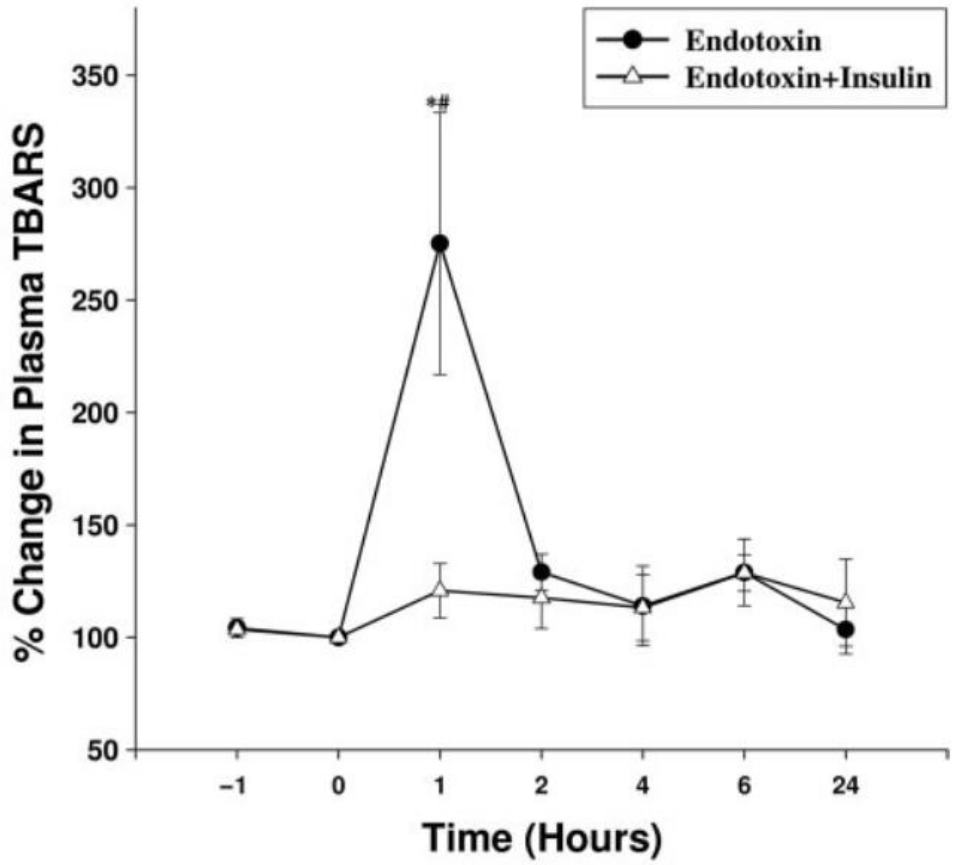




From Kidd *et al.*, JPET 2008

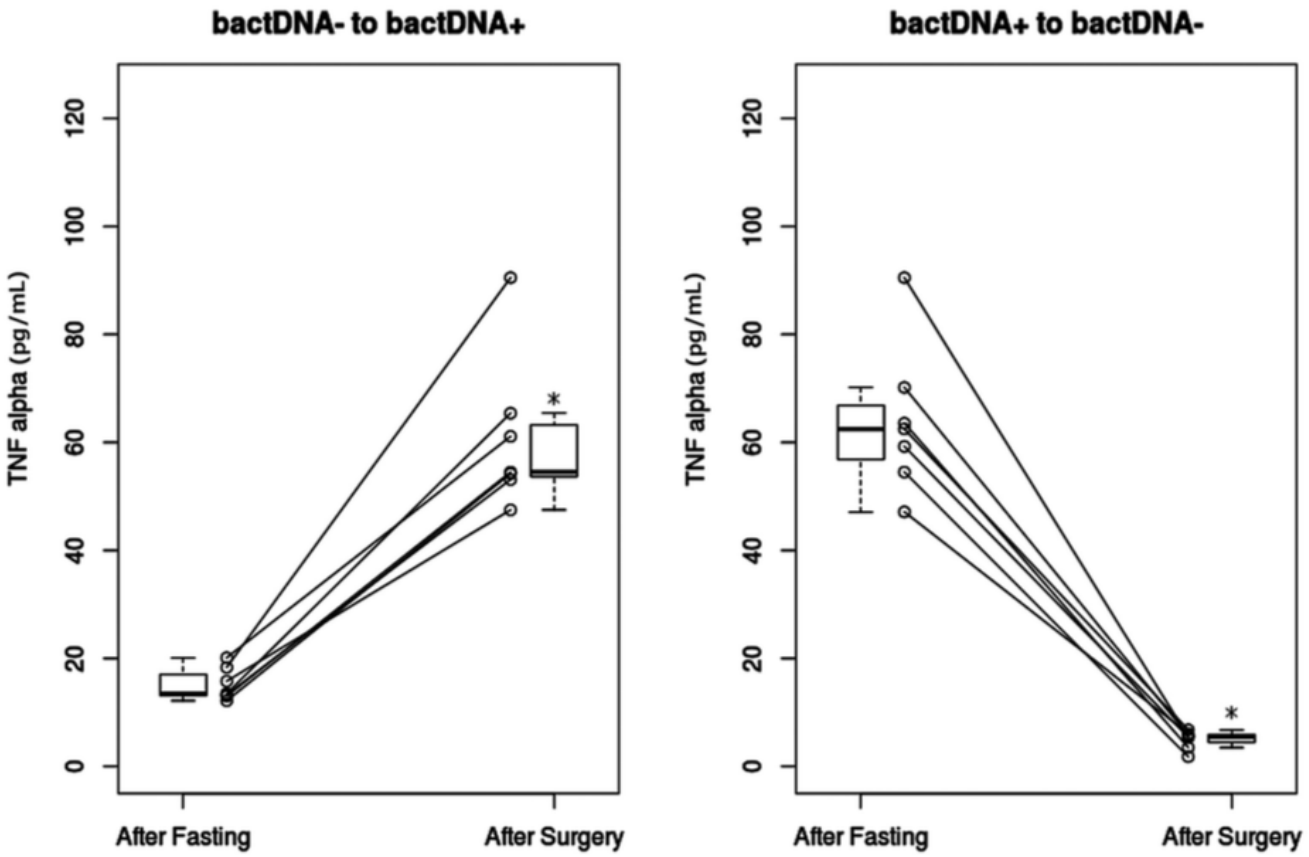
Insulin is protective during endotoxaemia

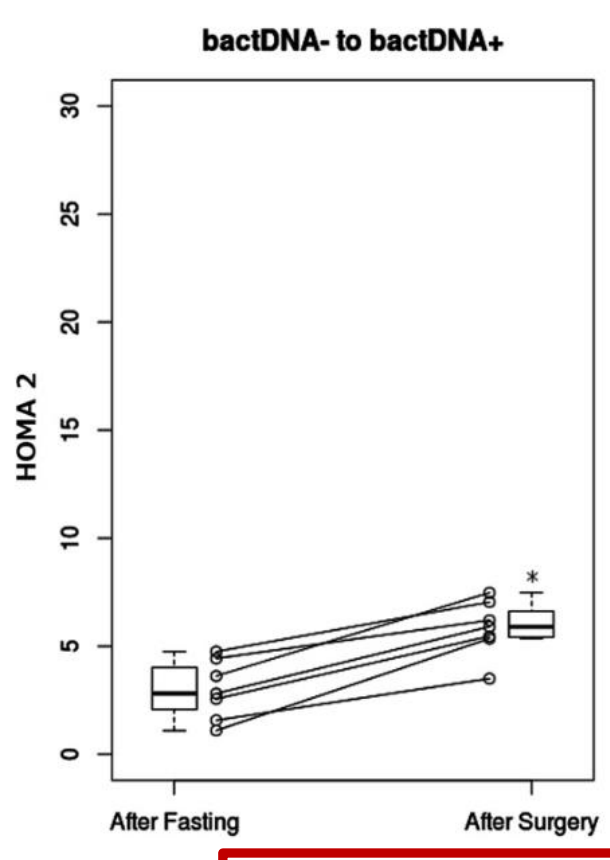


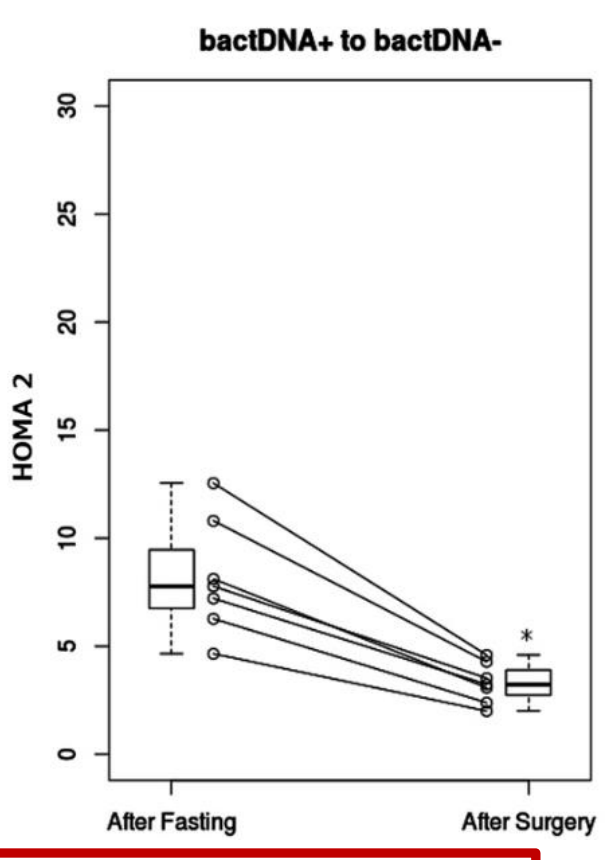


From Dandona *et al.*, Diabetes Care 2010

Gastric Bypass



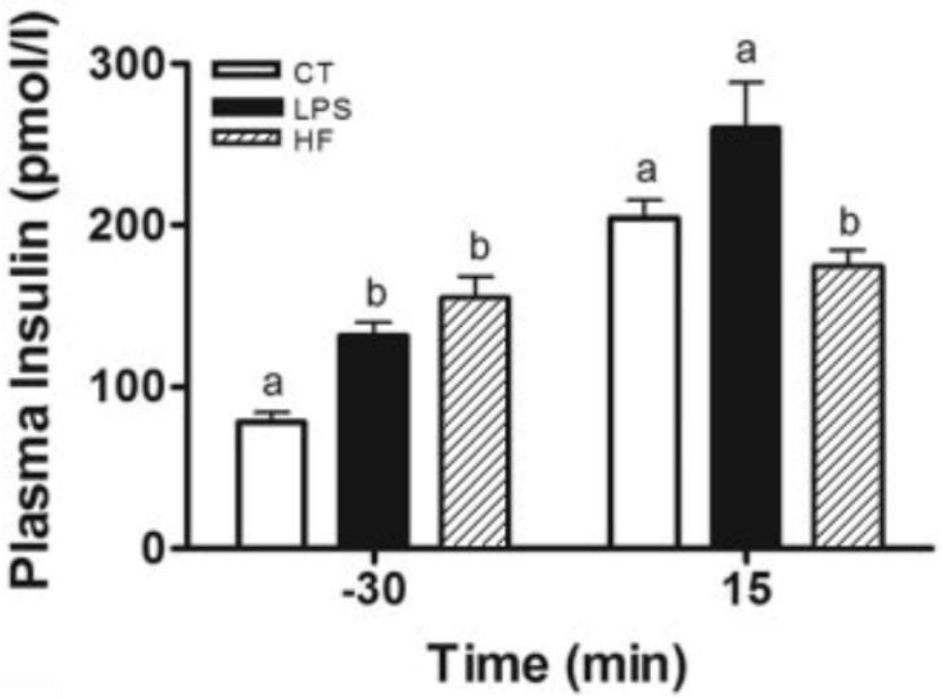




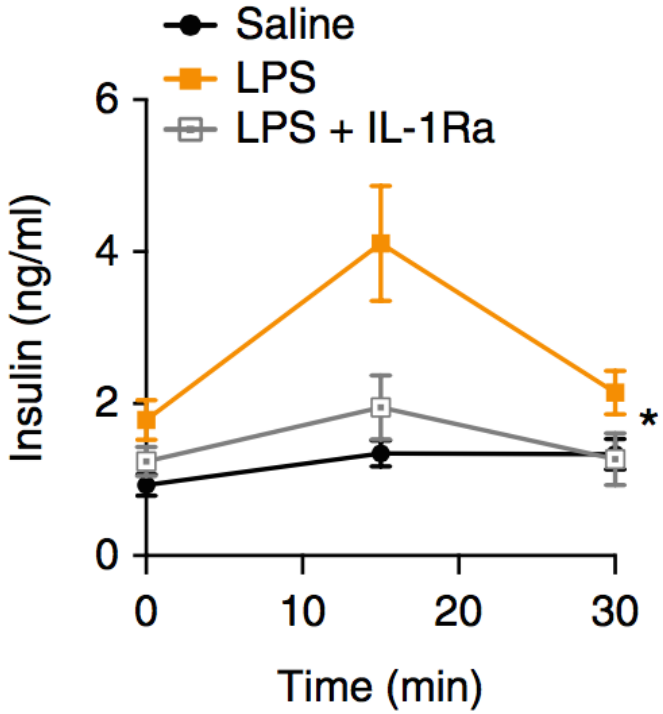
From Ortiz *et al.*, J Clin Endocrinol Metab, 2014

- Increases microbiotal diversity
- Decreases gut permeability
  - ↑ Tight-junction proteins
  - ↑ GLP-2
- Decreases endotoxaemia

LPS stimulates GSIS



From Cani *et al*., Diabetes 2007



From Dror *et al*., Nature Immunology 2017

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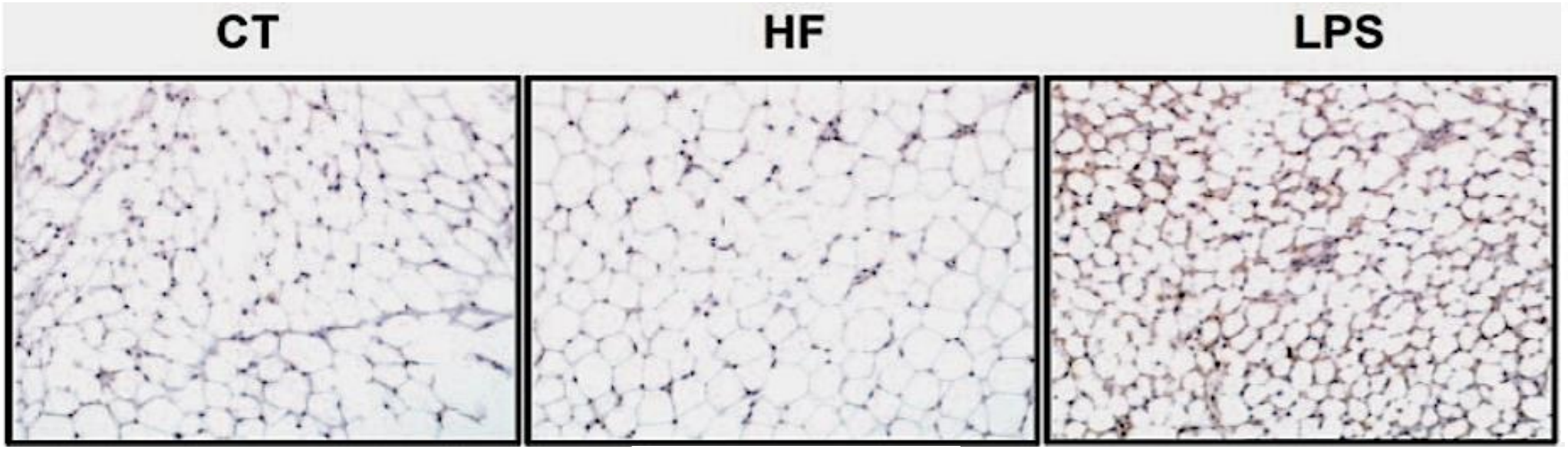

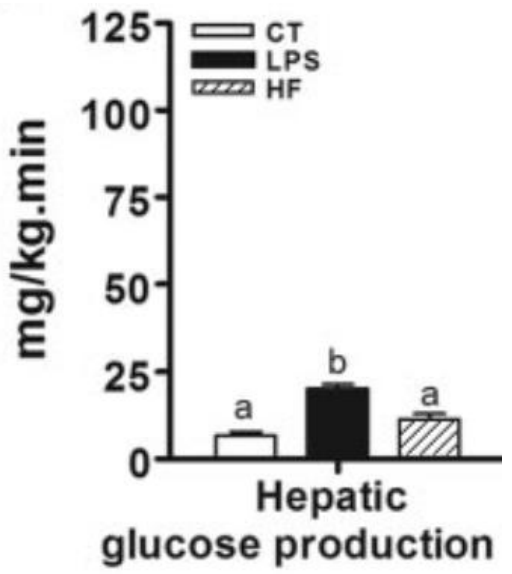

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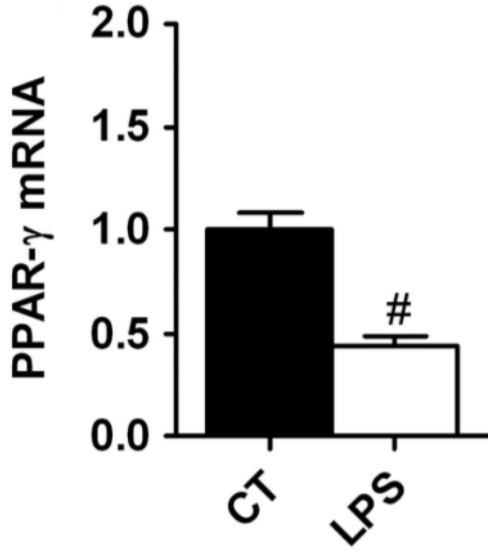
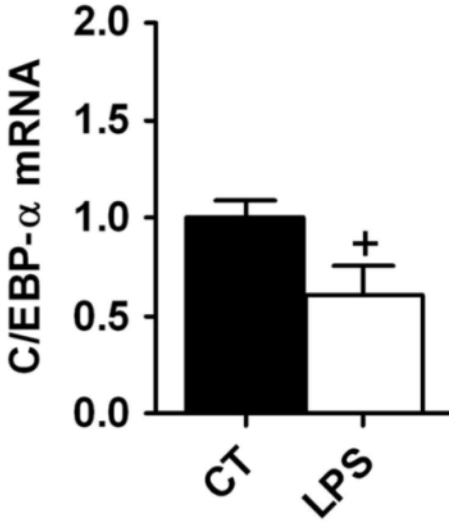
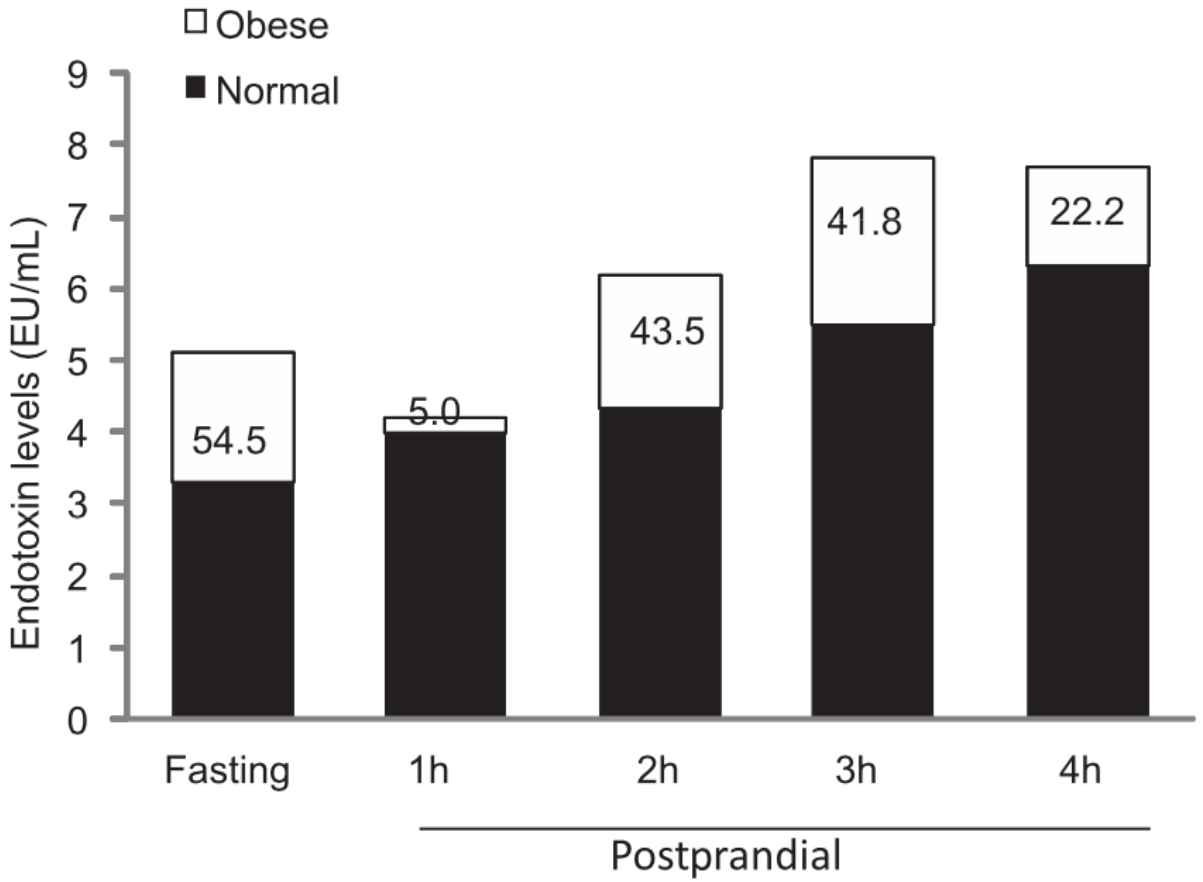
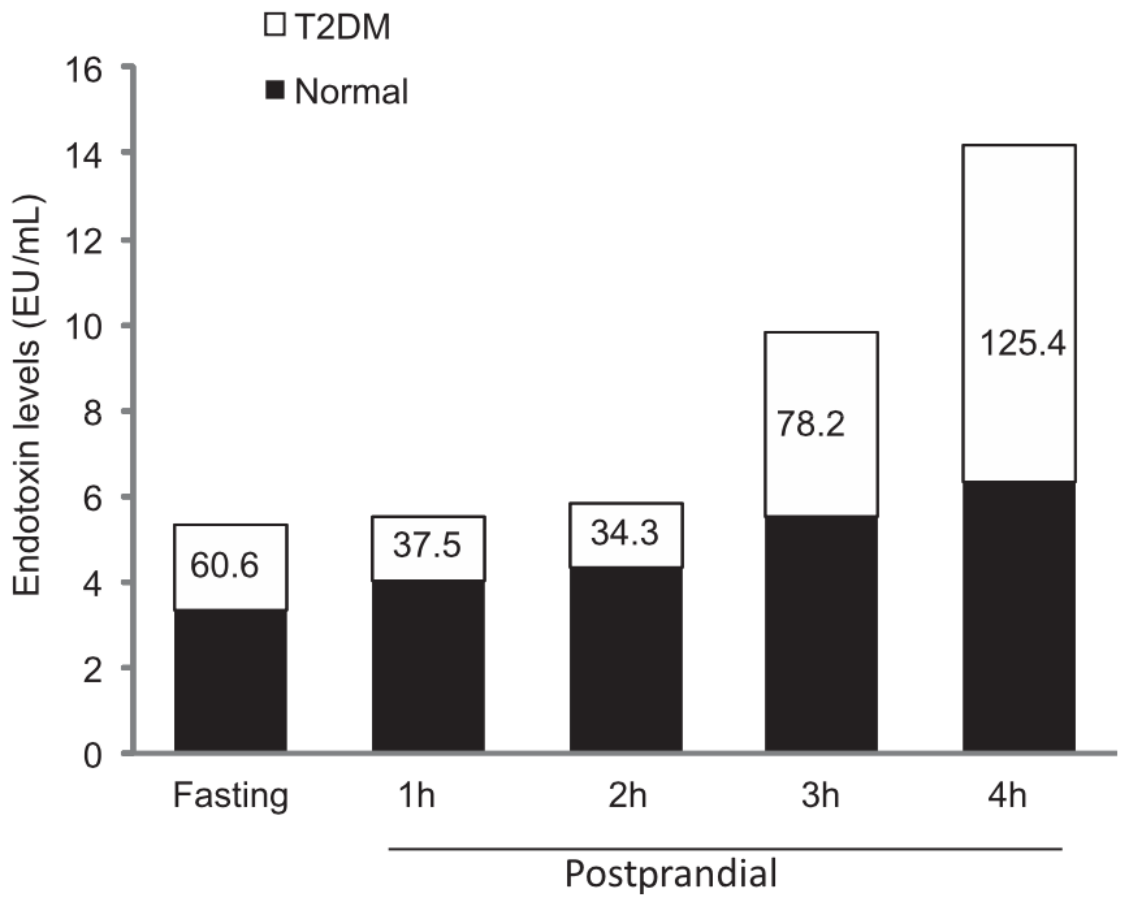




From: Muccioli *et al*., Molecular Systems Biology 2007

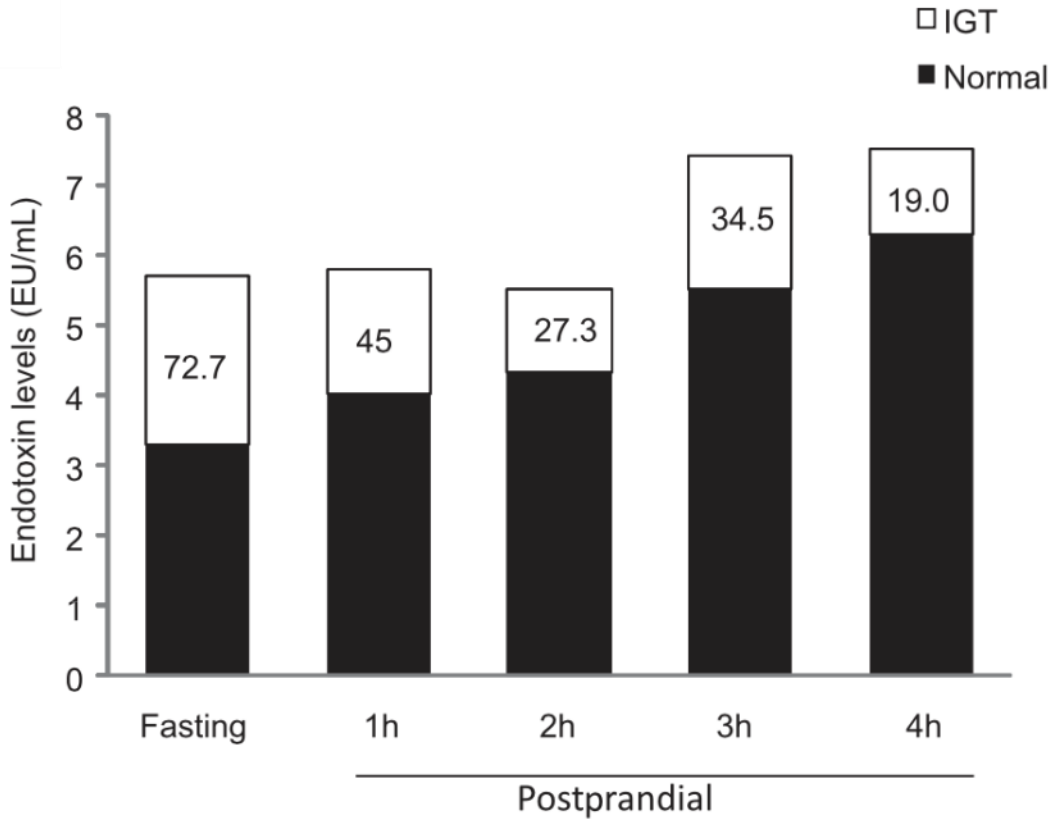
Postprandial endotoxaemia in metabolic disease



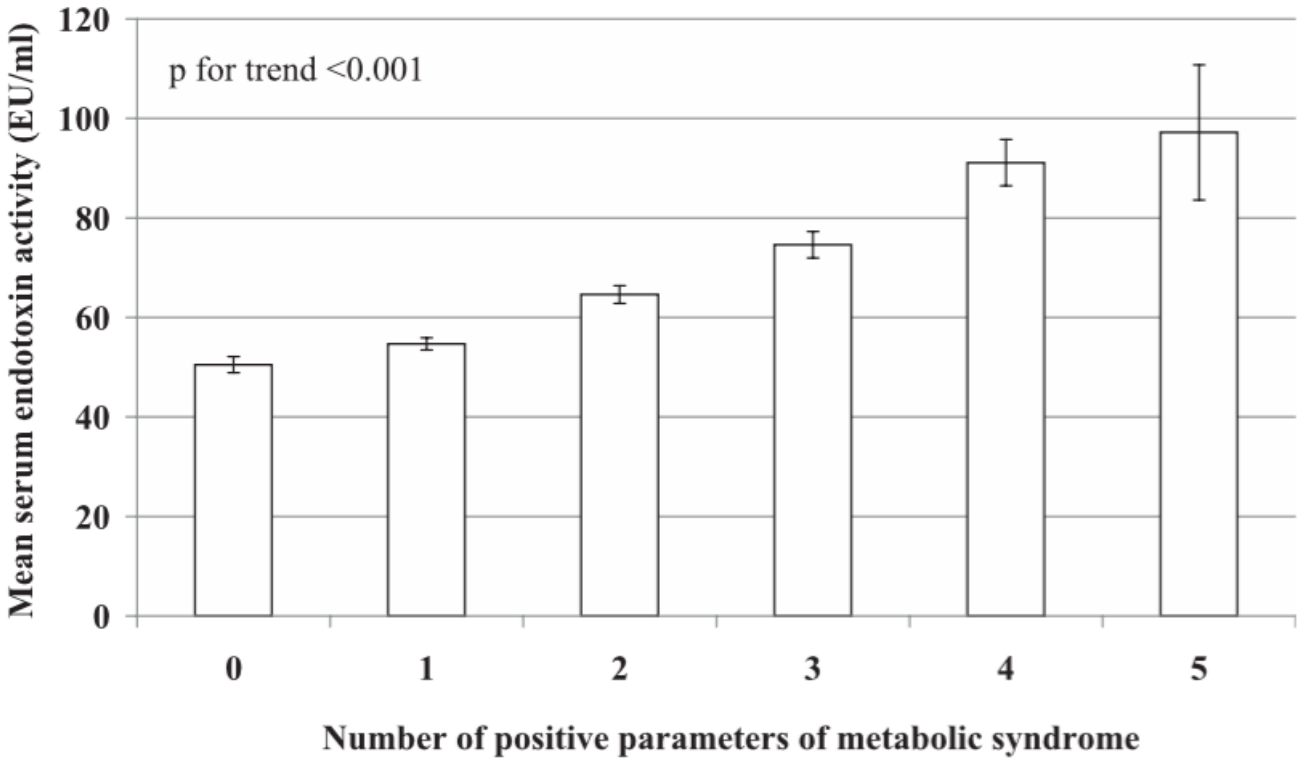


From Harte *et al.*, Diabetes Care 2012

Endotoxaemia and metabolic disease

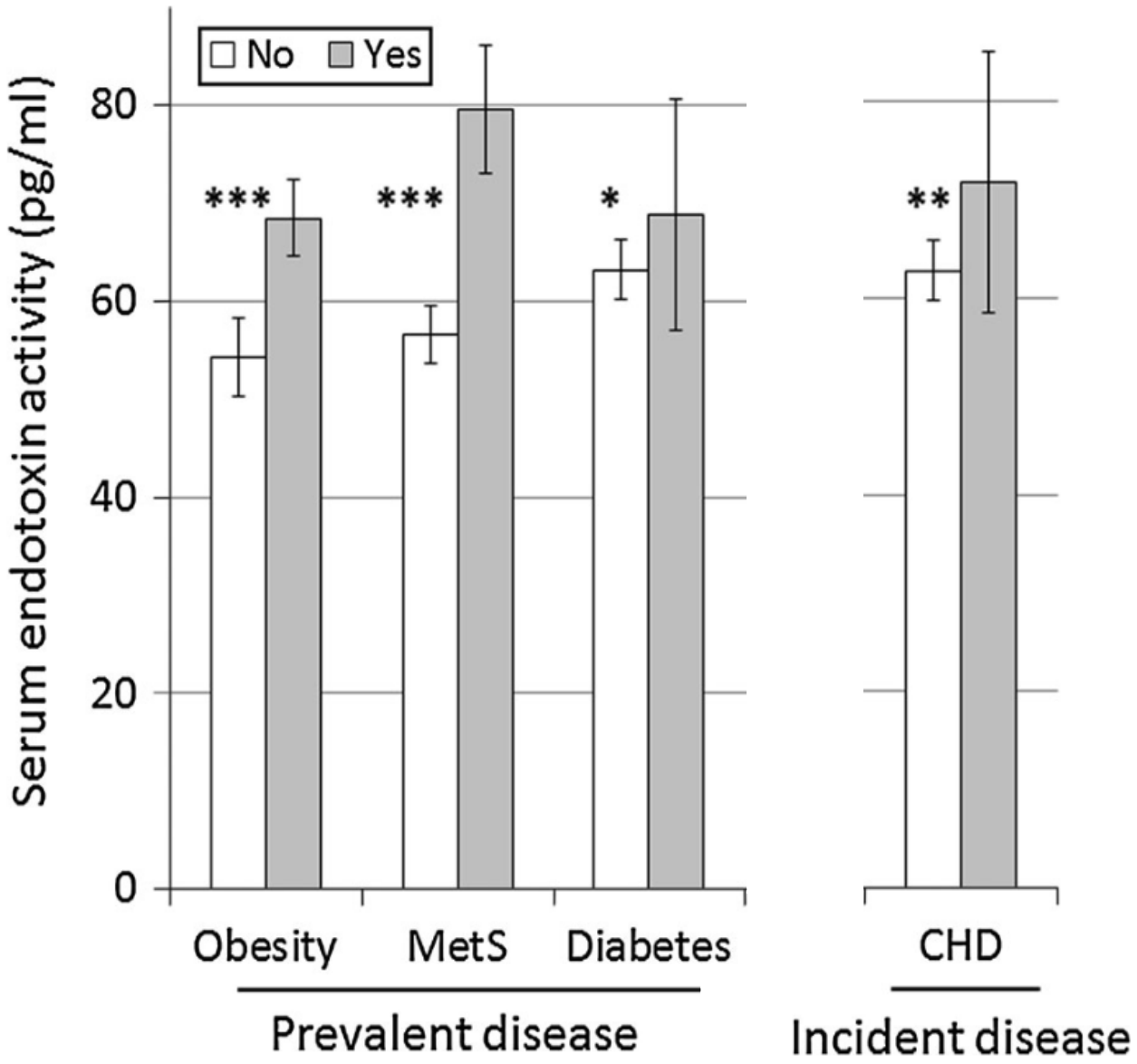


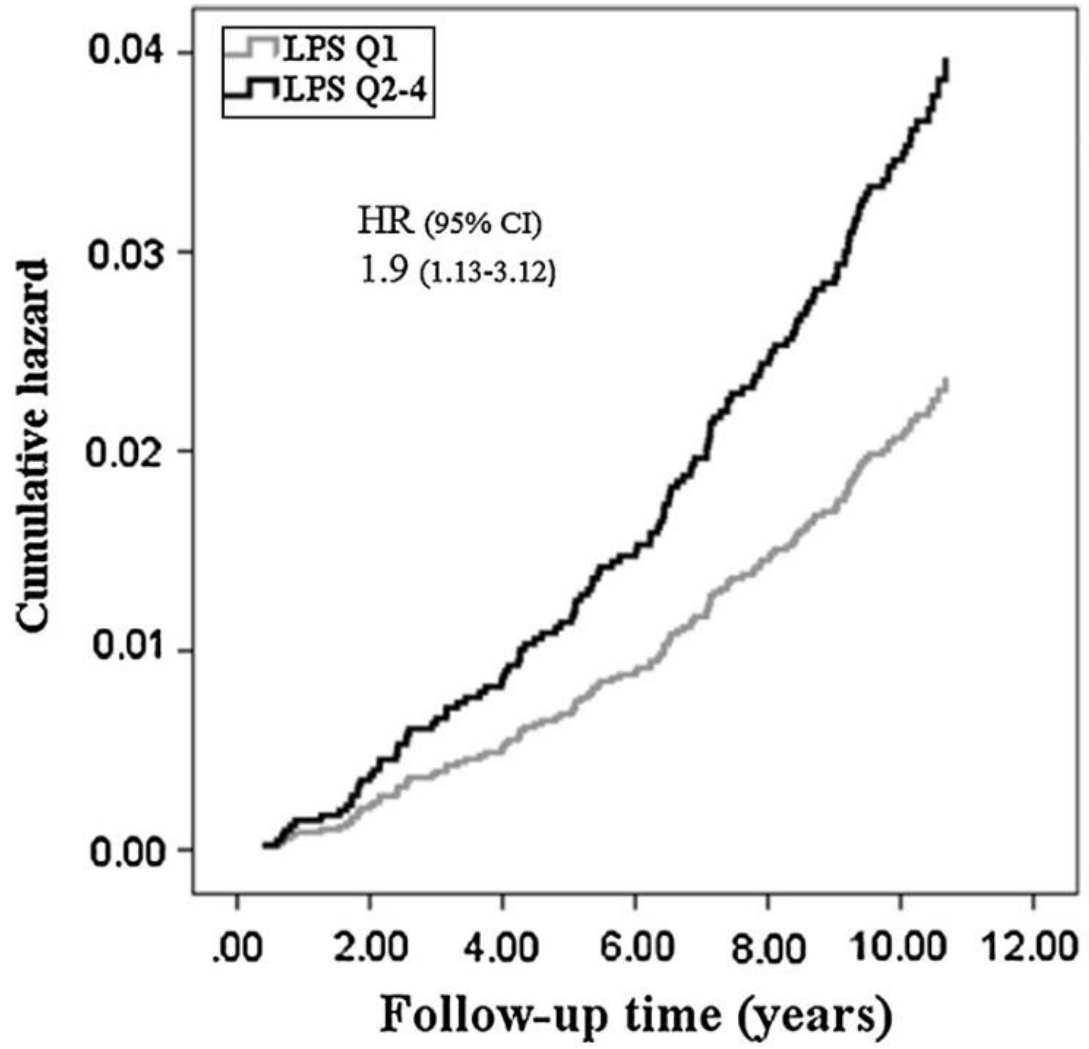
From Harte *et al*., Diabetes Care 2012



From Pussinen *et al*., Diabetes Care 2011

Endotoxaemia in the FINRISK study

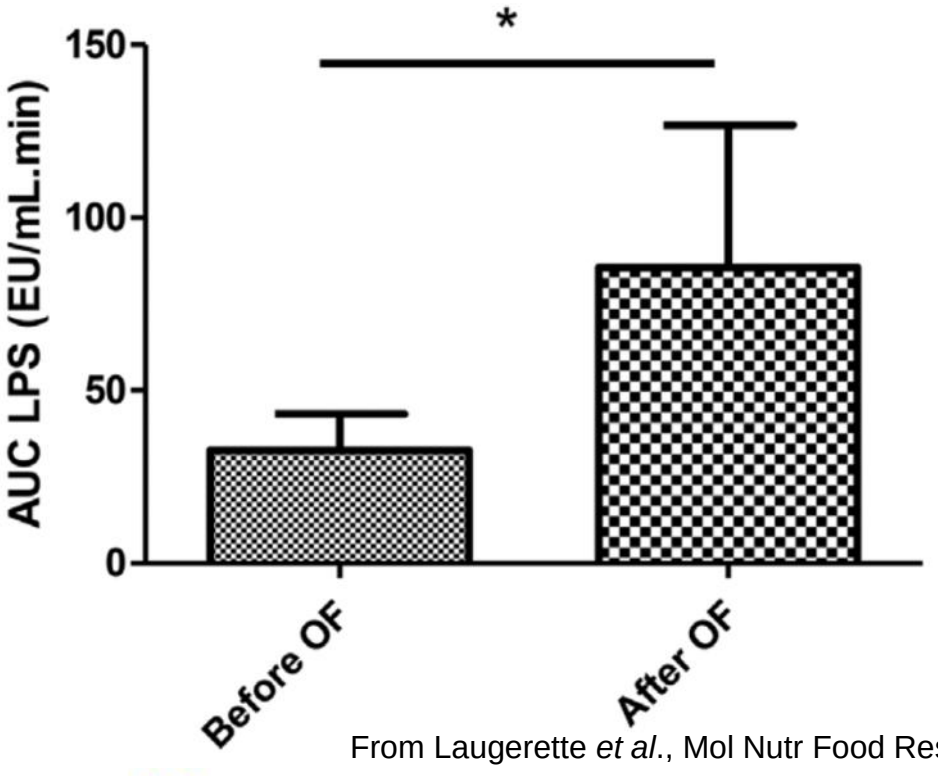




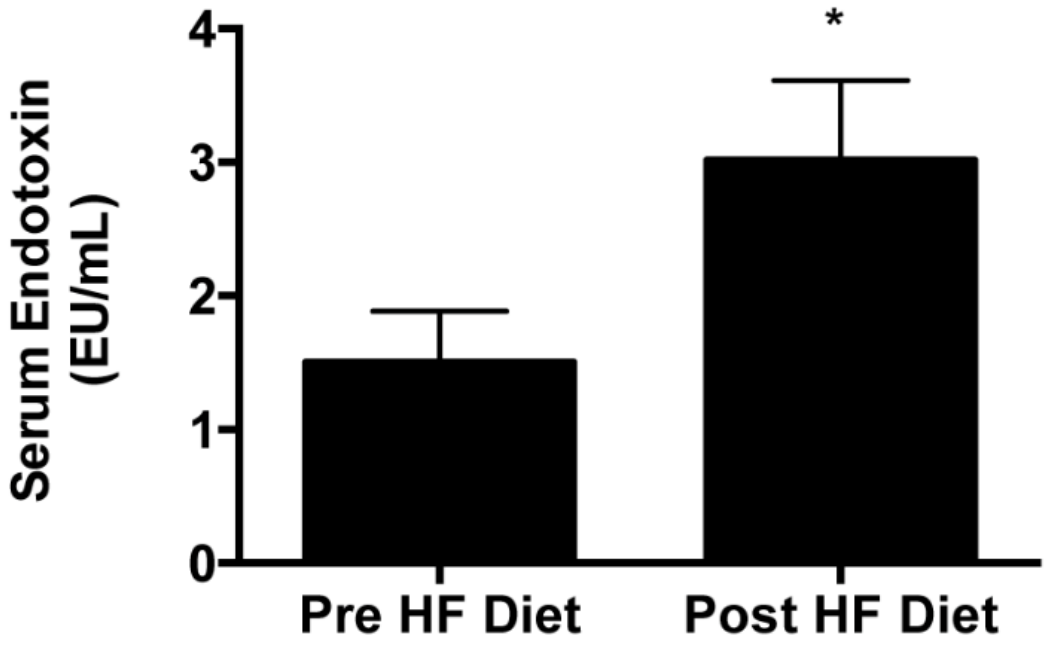
From Kalli *et al.*, Acta Diabetol 2015

Is endotoxaemia relevant in metabolic disease?

- Overfeeding studies (mixed/Western diet)
  - Fastest way to produce IR (check REFS)
  - Within XXX days
- Overfeeding increases endotoxaemia

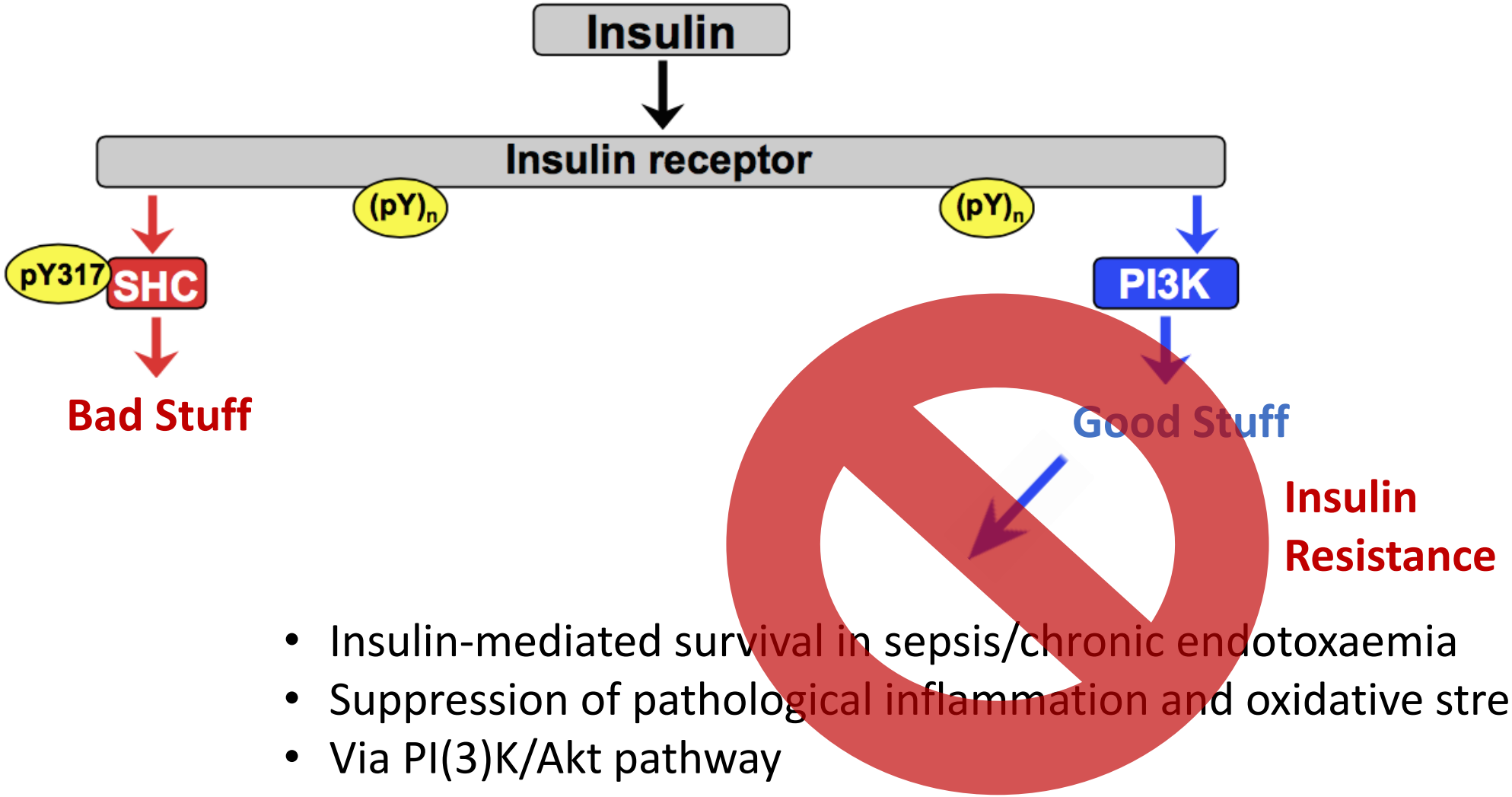


From Laugerette *et al*., Mol Nutr Food Res 2014



From Anderson *et al*., Obesity 2015

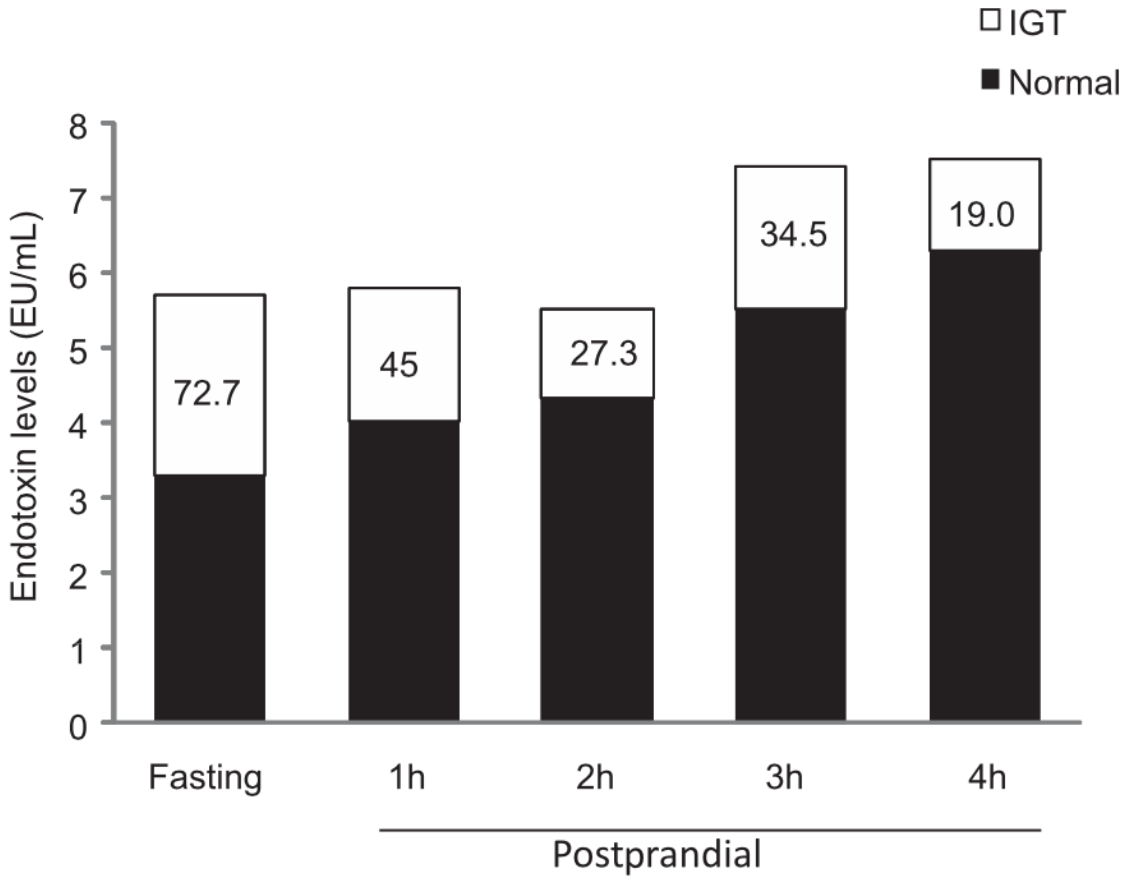
IR abolishes inflammatory modulation of insulin



Adapted from:
Williams and Wu,
Atherosclerosis 2016

- Insulin-mediated survival in sepsis/chronic endotoxaemia
- Suppression of pathological inflammation and oxidative stress
- Via PI(3)K/Akt pathway

Low carb LPS delivery systems



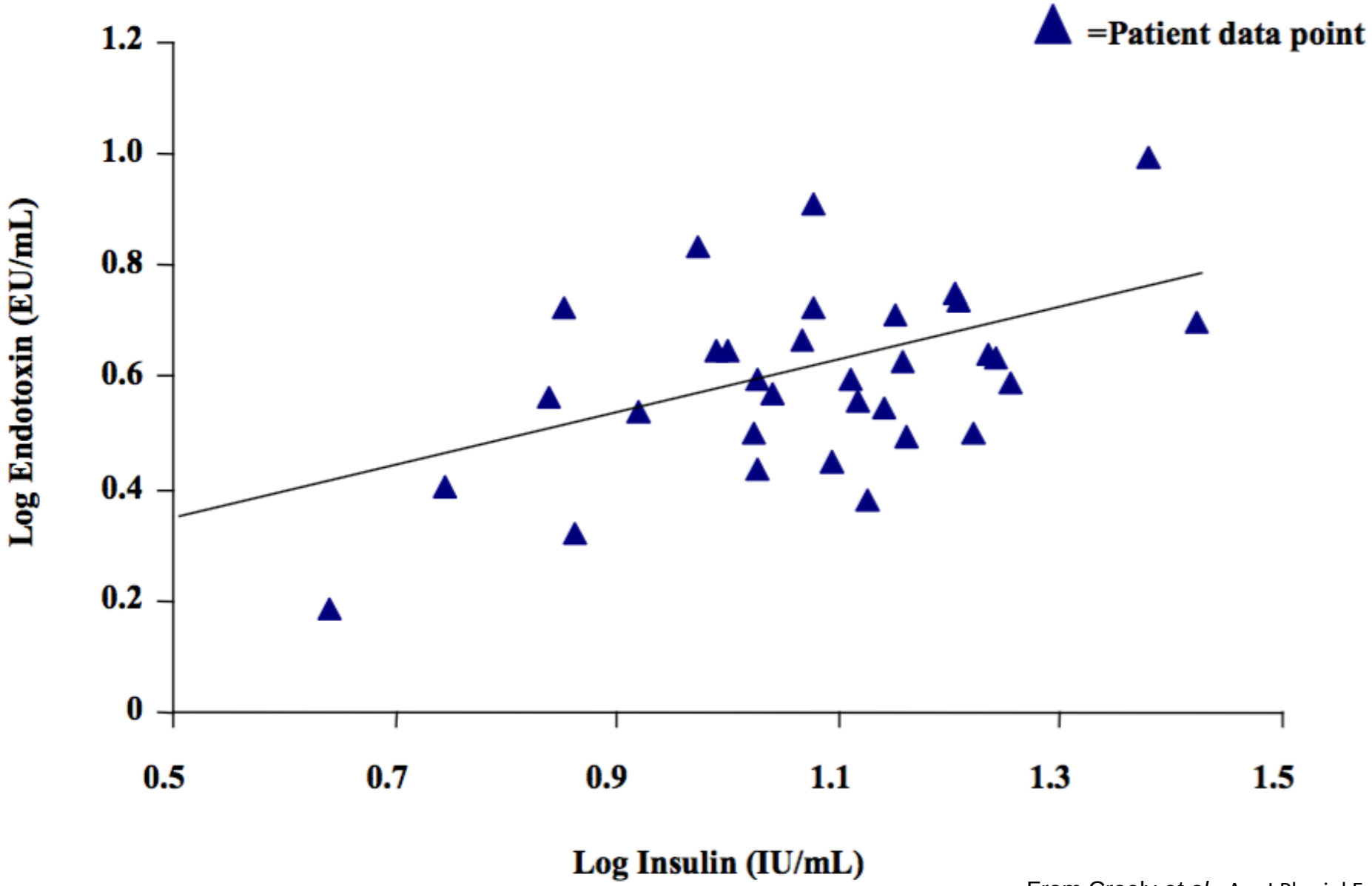
- Photo of BPC

From Harte *et al*., Diabetes Care 2012

LPS integrates models of cardiovascular disease

- Healthy gut makes IAP, which neutralises LPS
- Also defensins and antimicrobial peptides

Endotoxin increases insulin levels



From Creely *et al.*, Am J Physiol Endocrinol Metab 2006

Fasting