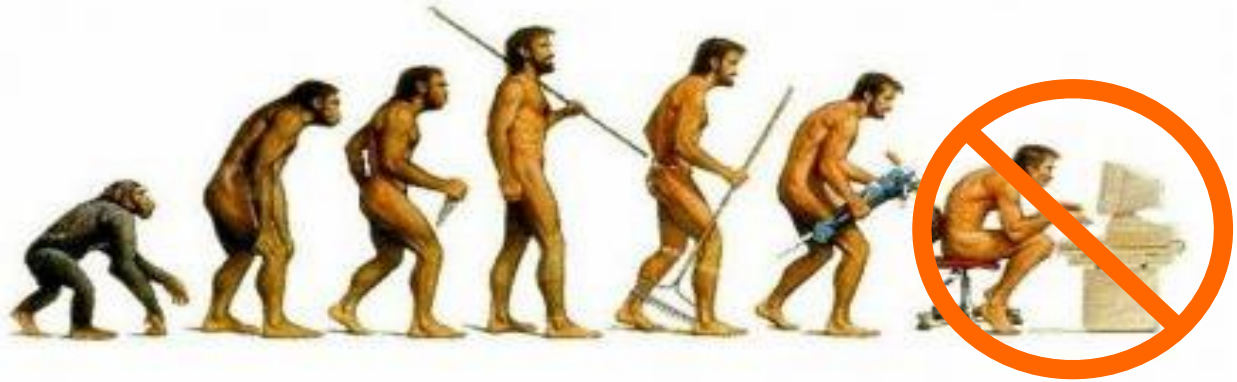


GET UP, STAND UP, STAND UP FOR YOUR HEALTH!
Prevention of sedentary behaviors to improve metabolic flexibility and metabolic health

Audrey BERGOUIGNAN, PhD

Anschutz Health and Wellness Center
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

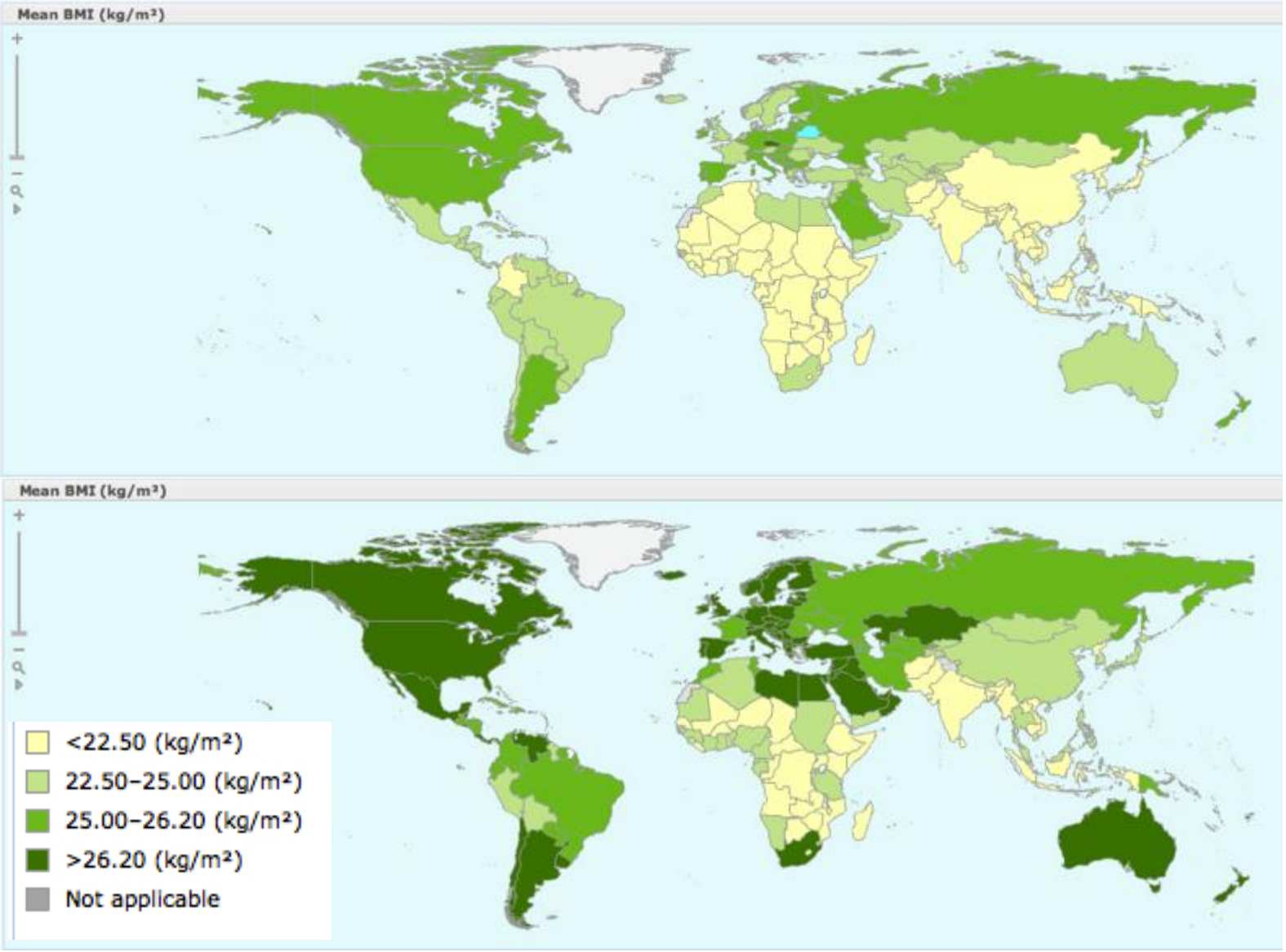
UNIVERSITÉ DE STRASBOURG

cnrs INC INEE IN2P3

iPHC
Institut Pluridisciplinaire Hubert CURIEN
STRASBOURG

The obesity and associated metabolic diseases pandemy

1980

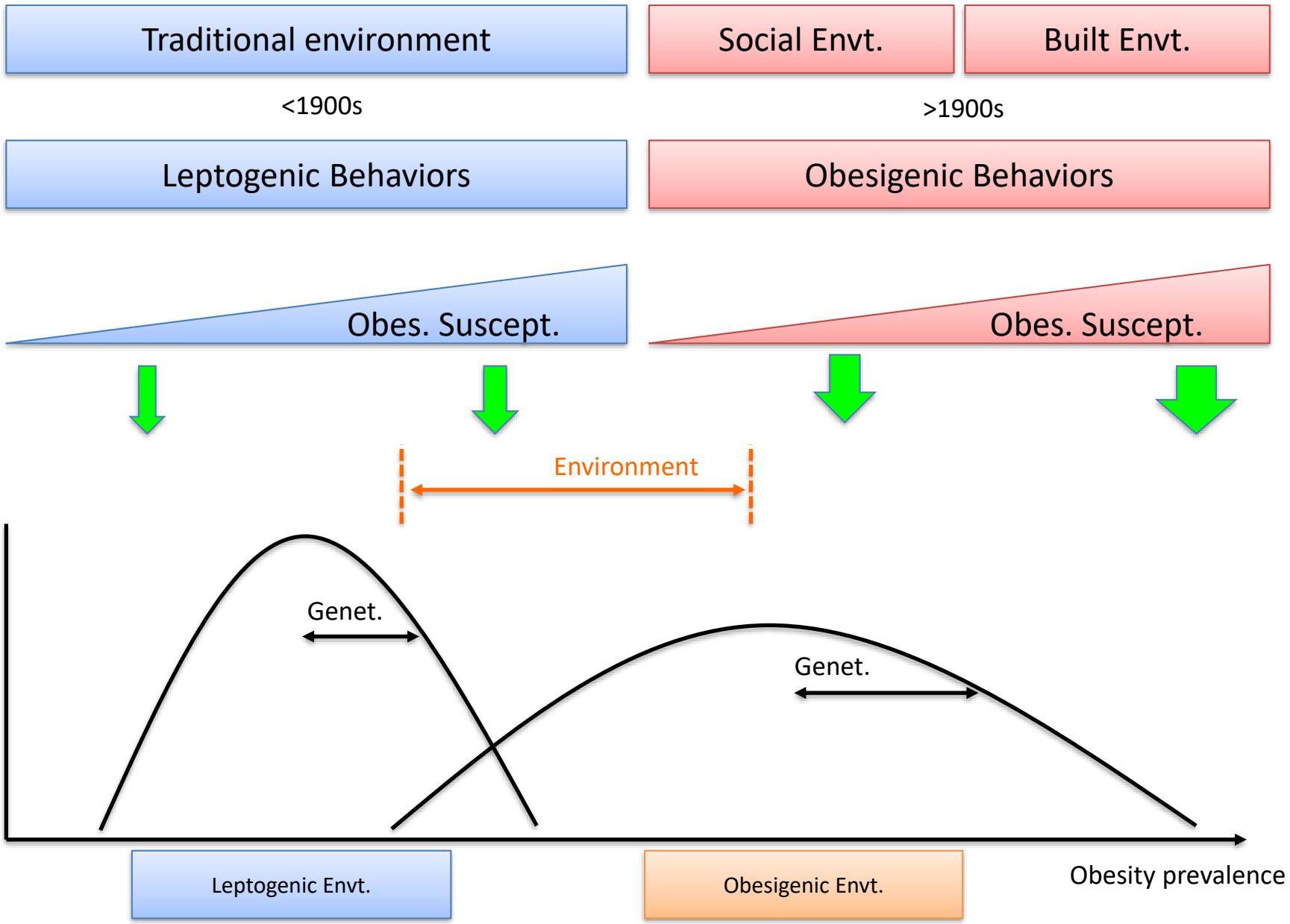


2012

http://www5.imperial.ac.uk/medicine/metabolic_risks/bmi/

Worldwide evolution of body mass index

The causes



Worldwide evolution of body mass index

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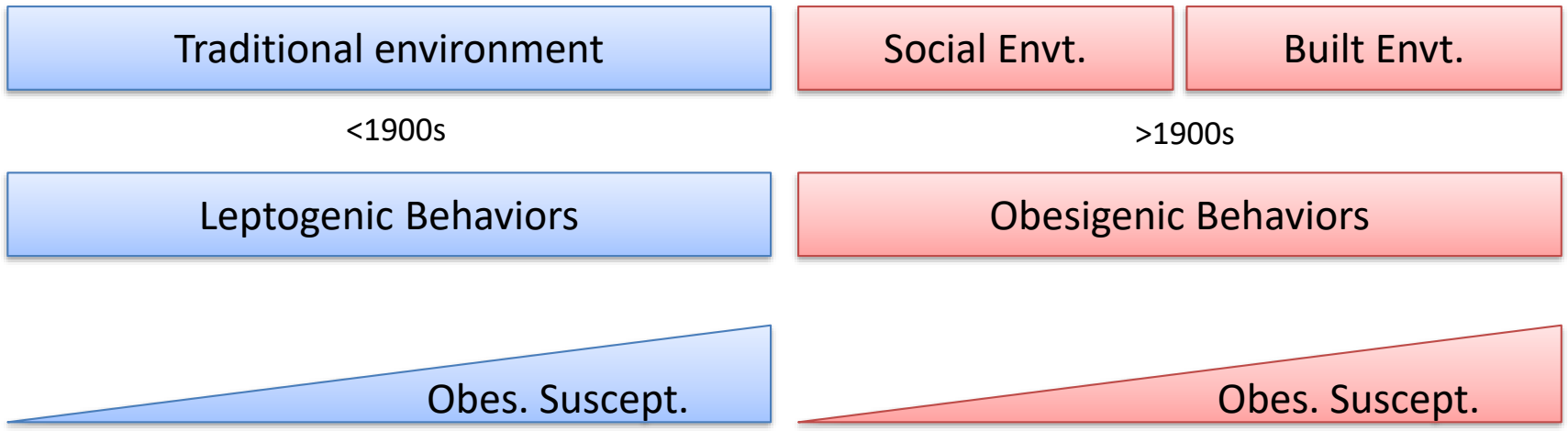
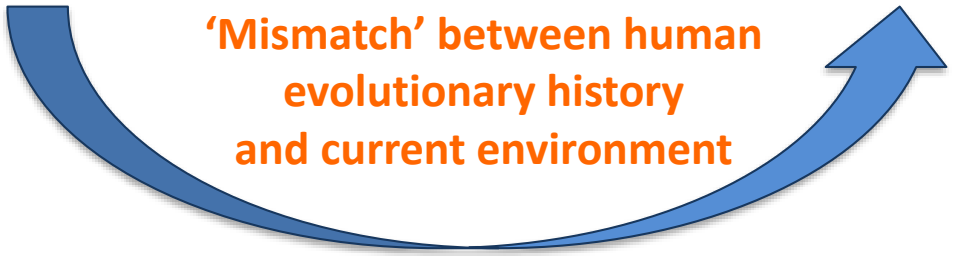
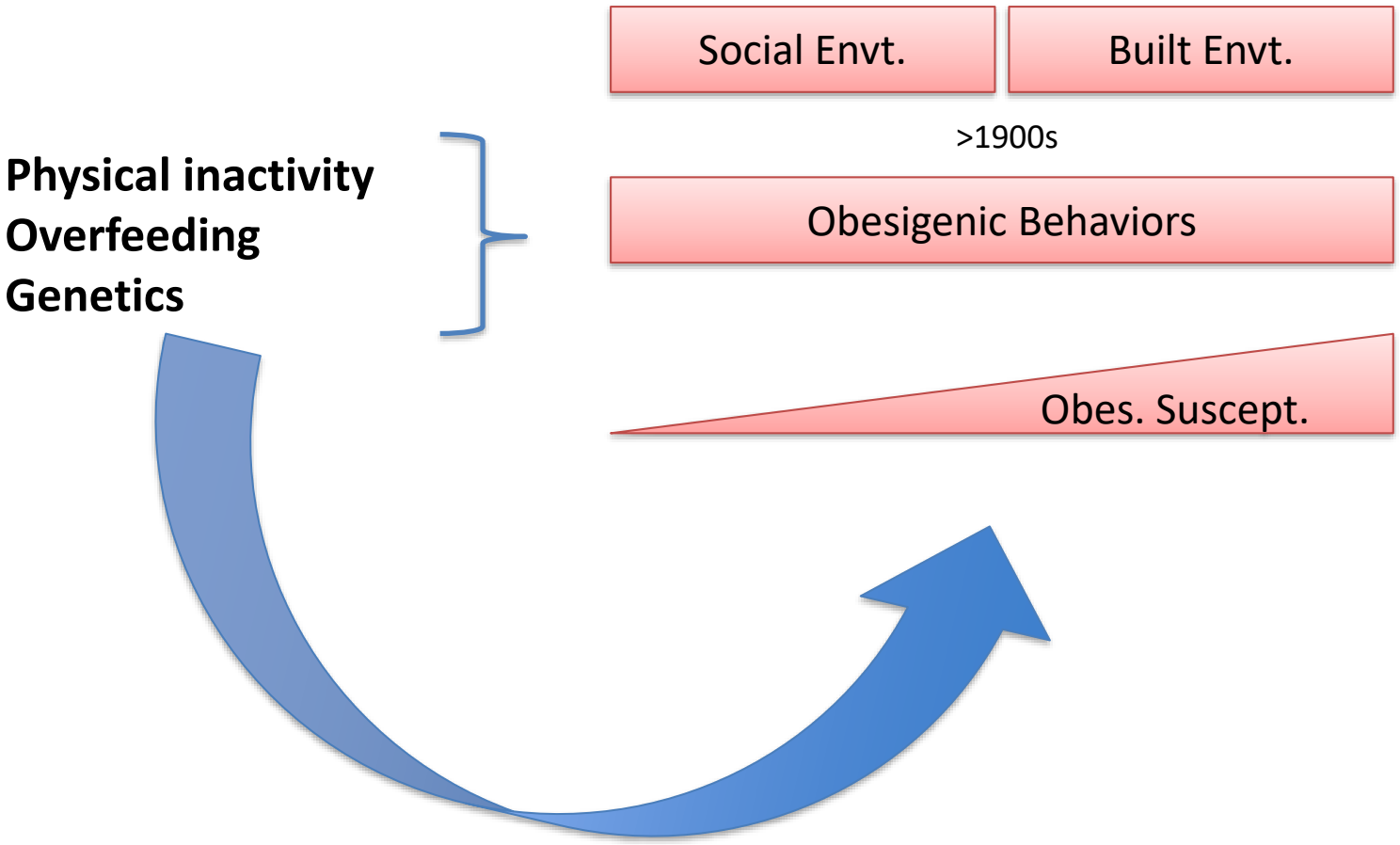




Role of physical inactivity in basic features of the obese phenotype?



Role of physical inactivity in basic features of the obese phenotype?

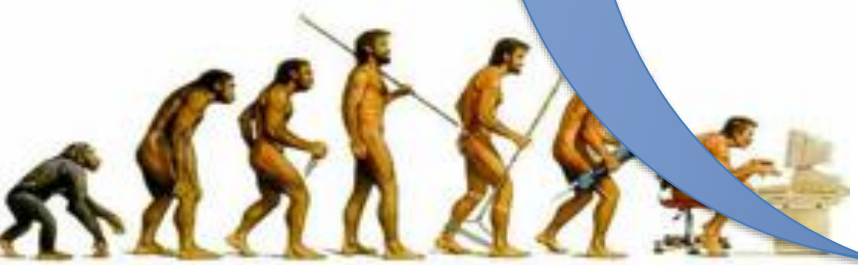
Physical inactivity
Overfeeding
Genetics

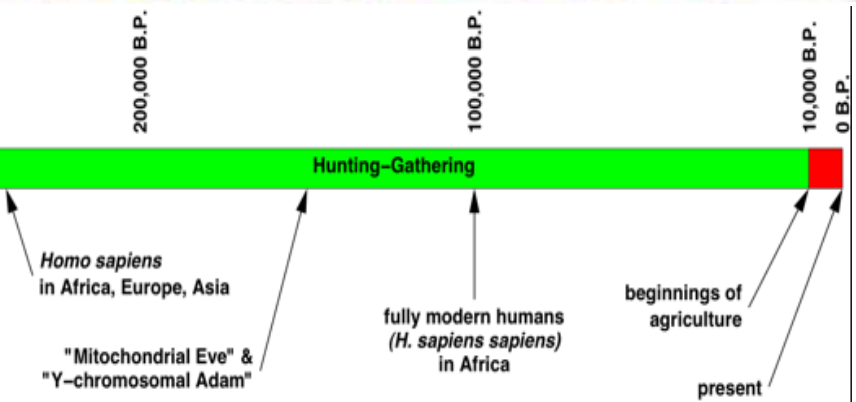
Social Envt. | Built Envt.

>1900s

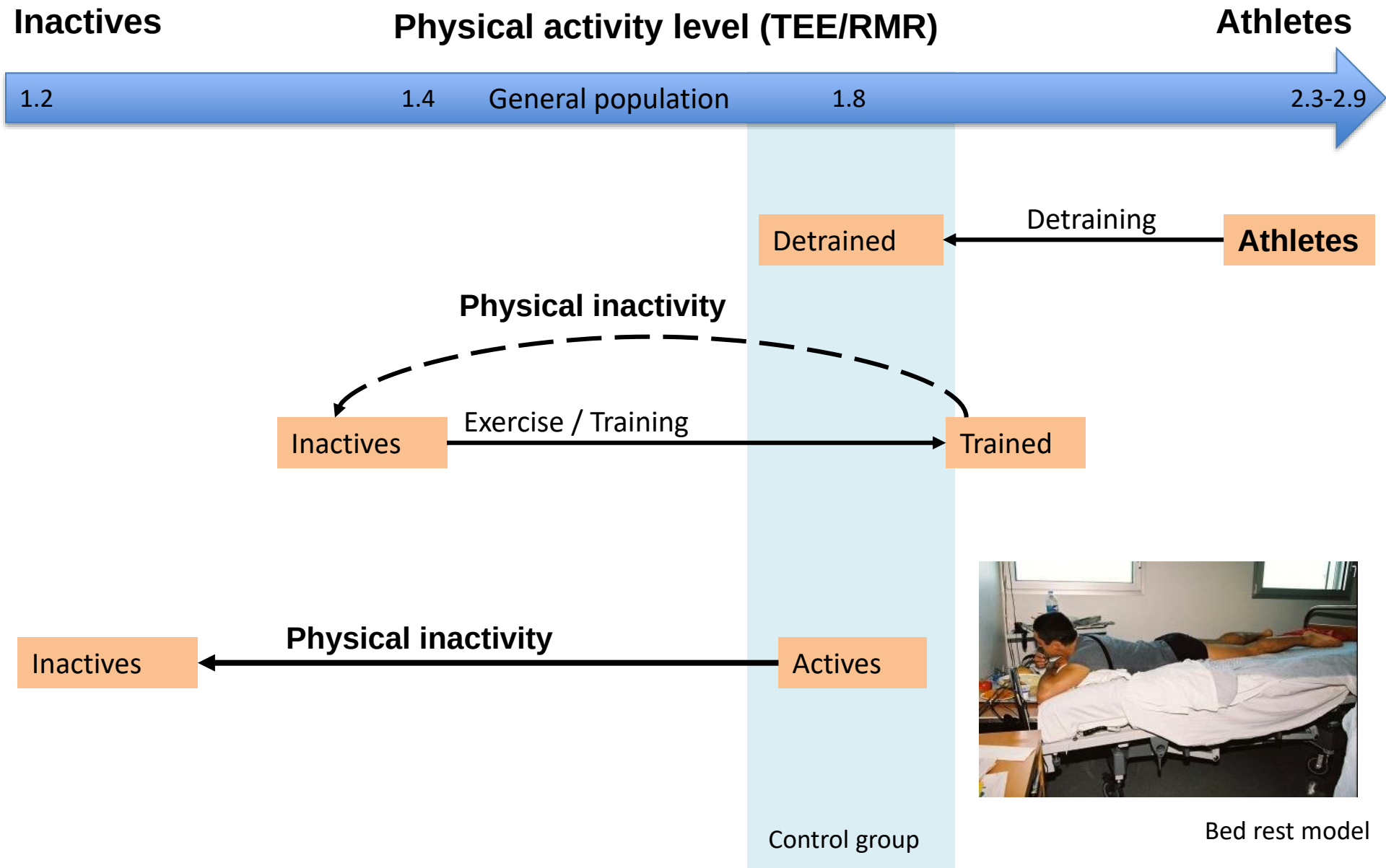
Obesigenic Behaviors

Obes. Suscept.





How can we study the direct effects of physical inactivity?



Bed rest model

Chronic physical inactivity induced by strict head down tilt bed rest in healthy humans

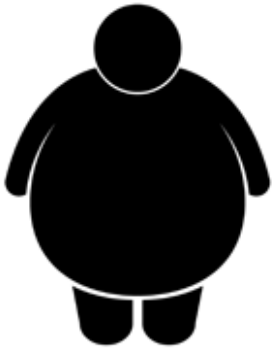
Head-down tilt bed rest

Physiological adaptations to space environment

Healthy lean active subjects

Blanc et al, J Clin Endocinol Metab 1998
Bergouignan et al, J Clin Endocinol Metab 2010

Physiology of physical inactivity

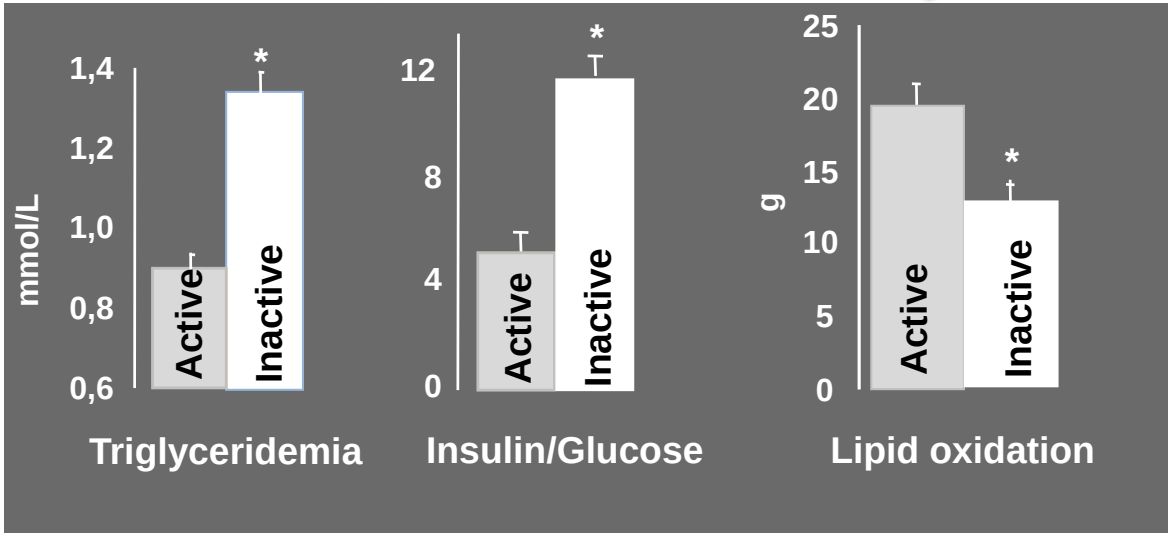


CAUSES?

Extreme inactivity

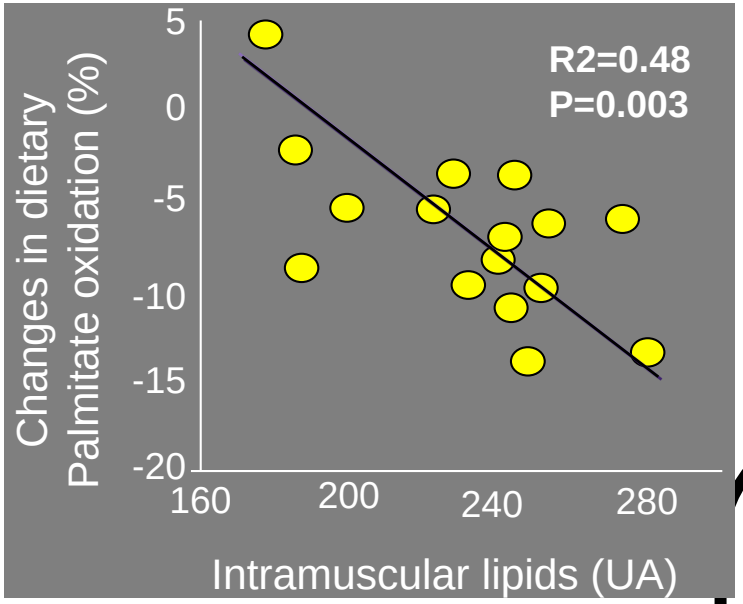
Level of physical inactivity of the general population

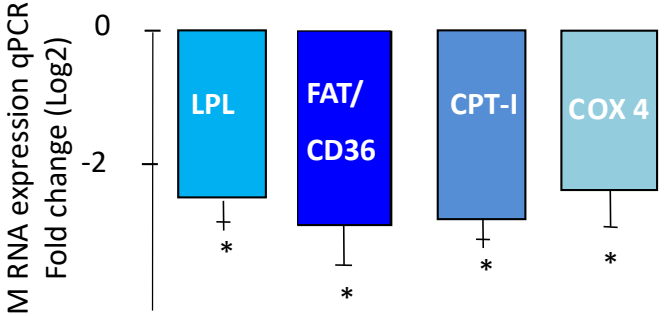
No change in fat mass

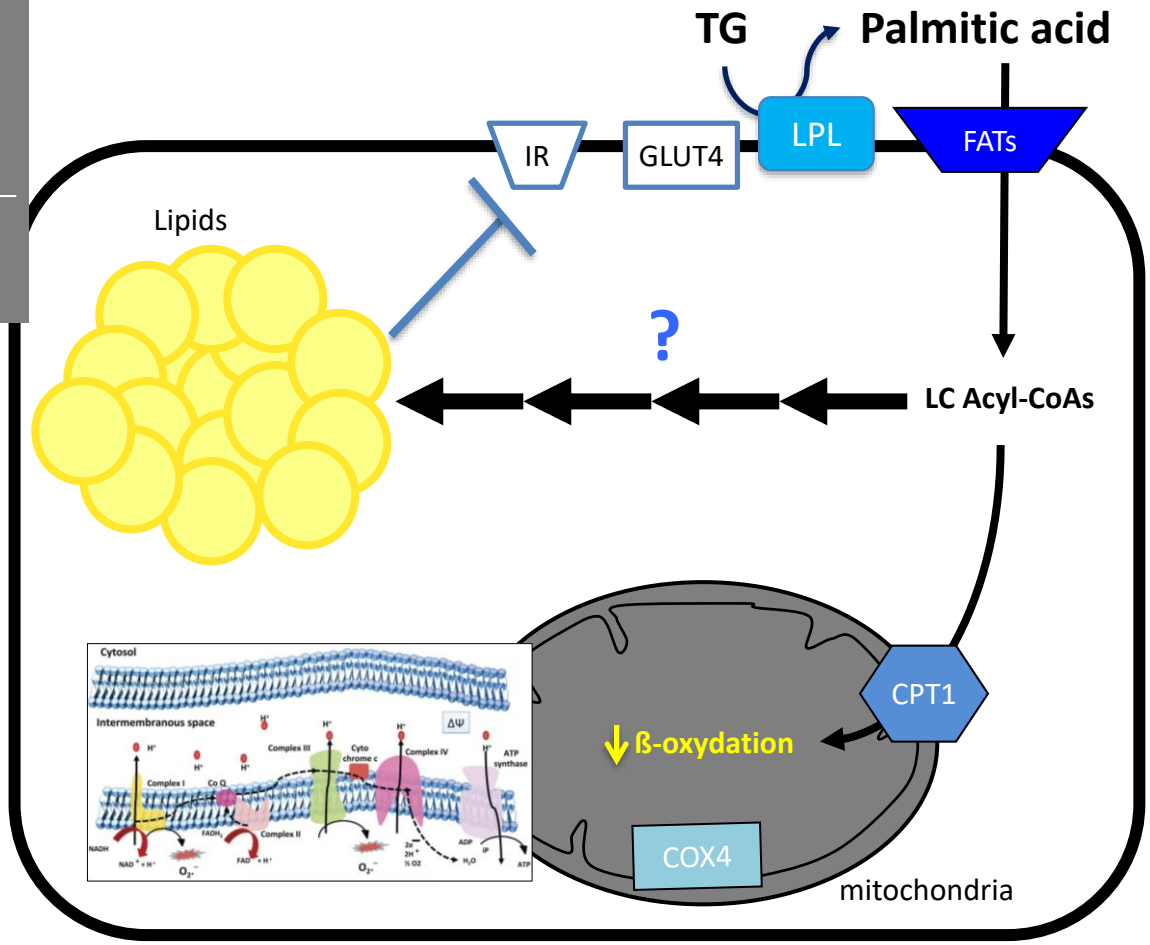


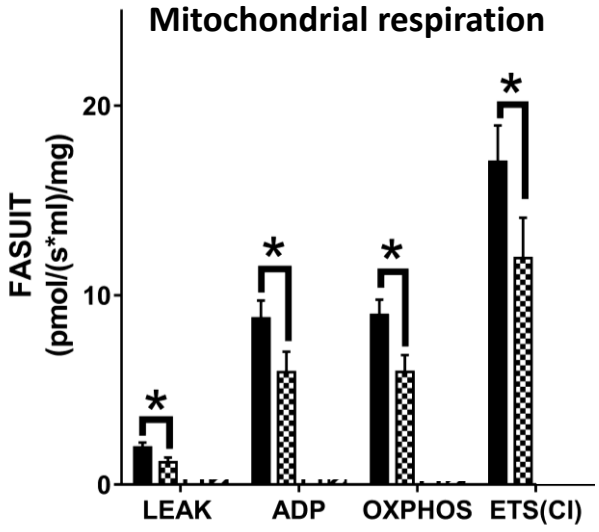
Bergouignan et al. PloS Clin Trial 2006; Diabetes 2009, J Clin Endo Metabo 2010, AJCN 2013; Rudwill et al. JCEM 2018

Physiology of physical inactivity: Mechanisms at muscle level









Kenny H et al. Diabetologia, 2017

Bergouignan et al, Diabetes 2009

Physiology of physical inactivity: Cascade of events

Physical inactivity

Low muscle energy turnover

Accumulation of
DAG, ceramides, acylcarnitine

Muscle insulin resistance

Hyperinsulinemia

Bergouignan et al J Appl Physiol, 2011

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Ectopic fat storage
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↑ Adipose tissue
(central + peripheral)

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Metabolic syndrome

Bergouignan et al J Appl Physiol, 2011

Similar metabolic features between obese and inactive individuals

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Bergouignan et al J Appl Physiol, 2011

Is metabolic flexibility playing a role in this cascade of events?

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Metabolic inflexibility

Metabolic syndrome

?

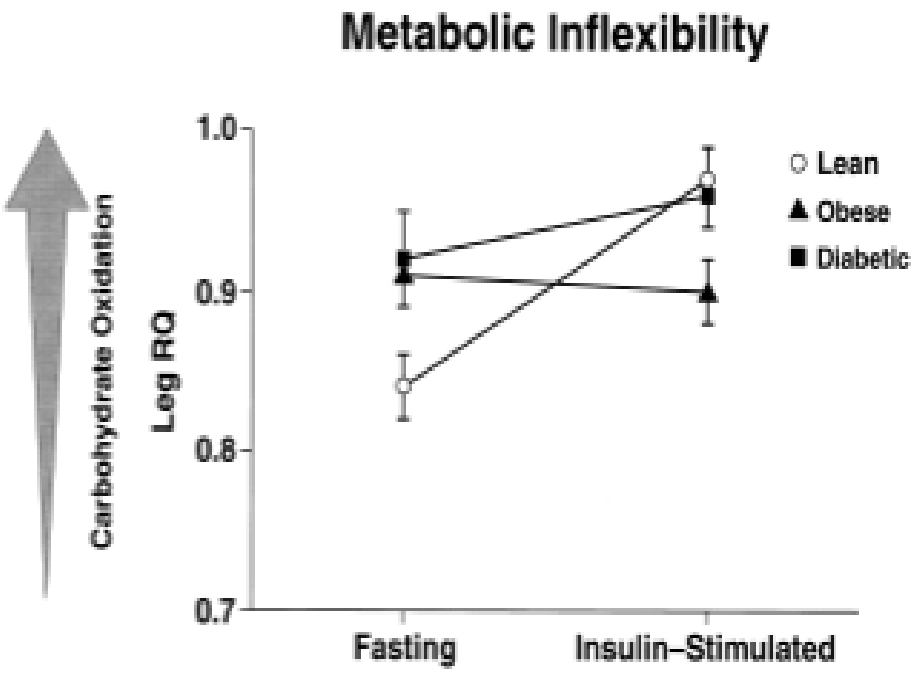
Bergouignan et al J Appl Physiol, 2011

Metabolic flexibility, the early definition

Metabolic flexibility = The ability of the body to adjust substrate oxidation to changes in substrates availability and energy demand

Δ Substrate Availability → *Regulator(s)* → Δ Substrate Oxidation

Glucose Infusion → *↑ Insulin* → *Δ Leg RQ*



Kelley and Mandarino, J Clin Invest 1990

Metabolic flexibility, our broader paradigm

Regulator ⟷ ***Effector***

Metabolic "Stressor"

Meal

Diurnal Fluctuations

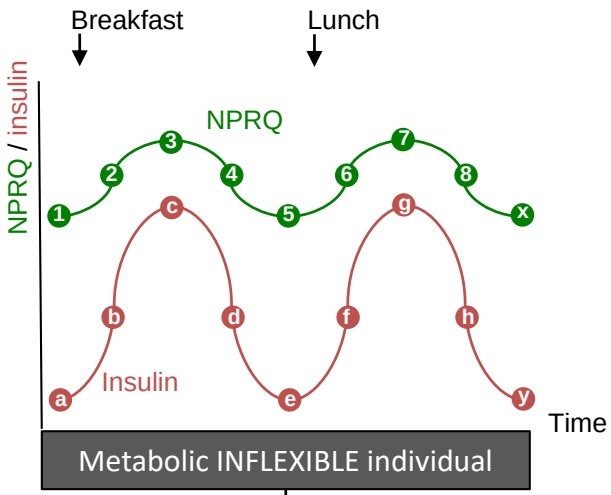
Δ Substrate Availability

↑ Glucose

↑ Insulin

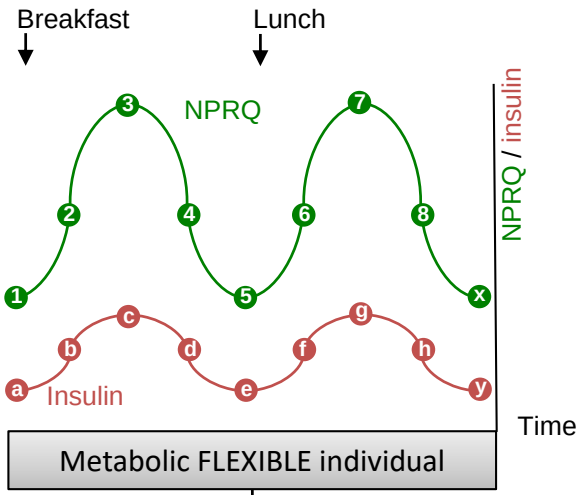
Δ Substrate Oxidation

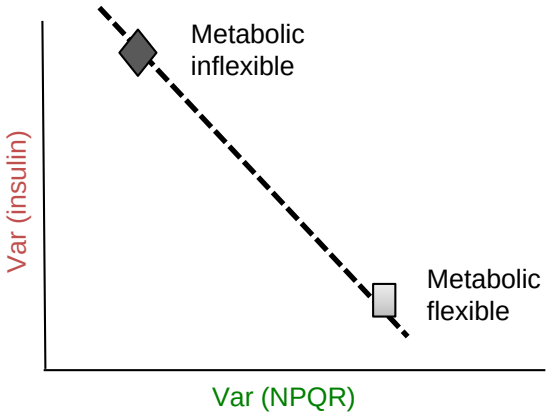
Δ NPRQ



$$\text{Var (NPQR)} = \Sigma_1^{x}\ [(NPQR_{1,x} - NPQR_{mean})]^2$$

$$\text{Var (Ins.)} = \Sigma_a^{y}\ [(Ins._{a,y} - Ins._{mean})]^2$$





Bergouignan et al J Appl Physiol, 2011;
Rynders CA, J Physiol 2018

Metabolic inflexibility, a direct consequence of physical inactivity

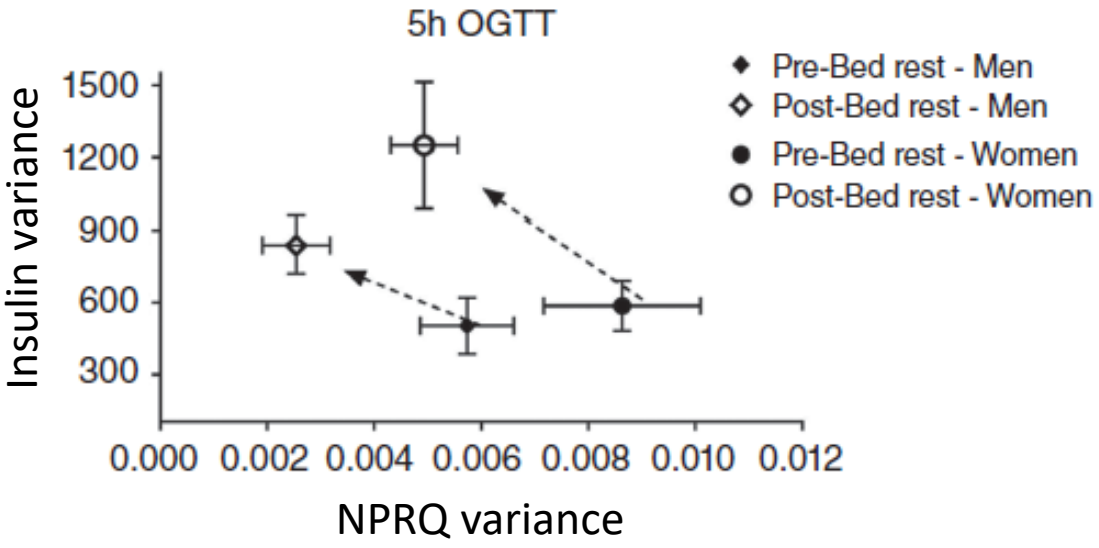
Regulator ⟷ *Effector*

Metabolic "Stressor"
Glucose Load (OGTT)

Δ Substrate Availability
↑ Glucose

↑ Insulin

Δ Substrate Oxidation
Δ NPRQ



Blanc et al. JCEM 1998; Rynders A et al J Physiol, 2018

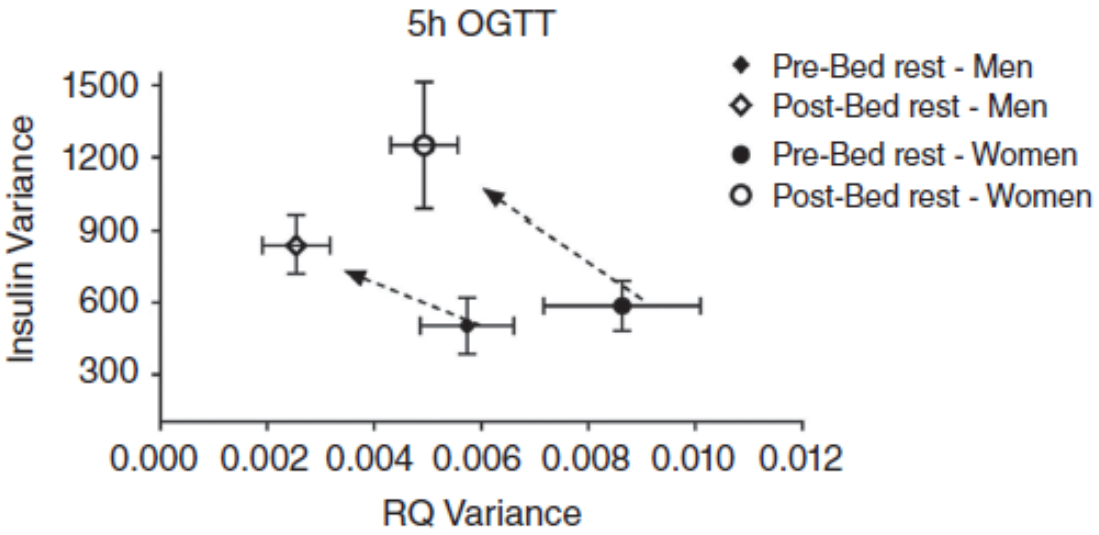
Metabolic inflexibility, a direct consequence of physical inactivity, that precedes the development of other metabolic alterations

https://academic.oup.com/jcem J Clin Endocrinol Metab, May 2018, 103(5):1910–1920 doi: 10.1210/jc.2017-02267

CLINICAL RESEARCH ARTICLE

Metabolic Inflexibility Is an Early Marker of Bed-Rest–Induced Glucose Intolerance Even When Fat Mass Is Stable

Floriane Rudwill,[1]* Donal O'Gorman,[2,3]* Etienne Lefai,[4] Isabelle Chery,[1] Alexandre Zahariev,[1] Sylvie Normand,[5] Allan F. Pagano,[6] Angèle Chopard,[6] Anthony Damiot,[1] Claire Laurens,[1] Leanne Hodson,[7] Emmanuelle Canet-Soulas,[4] Martina Heer,[8] Petra Frings Meuthen,[9] Judith Buehlmeier,[9,10] Natalie Baecker,[9] Laure Meiller,[4,5] Guillemette Gauquelin-Koch,[11] Stéphane Blanc,[1]* Chantal Simon,[4,5]* and Audrey Bergouignan[1,12,13]*



Blanc et al. JCEM 1998; Rynders A et al J Physiol, 2018; Rudwill F et al 2018

Metabolic inflexibility, a direct consequence of physical inactivity, that precedes the development of other metabolic alterations

Physical inactivity

Low muscle energy turnover

Accumulation of DAG, ceramides, acylcarnitine

Decreased mechanical workload

Remodeling of the muscle

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↑ Adipose tissue (central + peripheral)

Metabolic inflexibility

Metabolic syndrome

?

Bergouignan et al J Appl Physiol, 2011

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Bergouignan et al J Appl Physiol, 2011

What is the impact of these alterations on body weight regulation?

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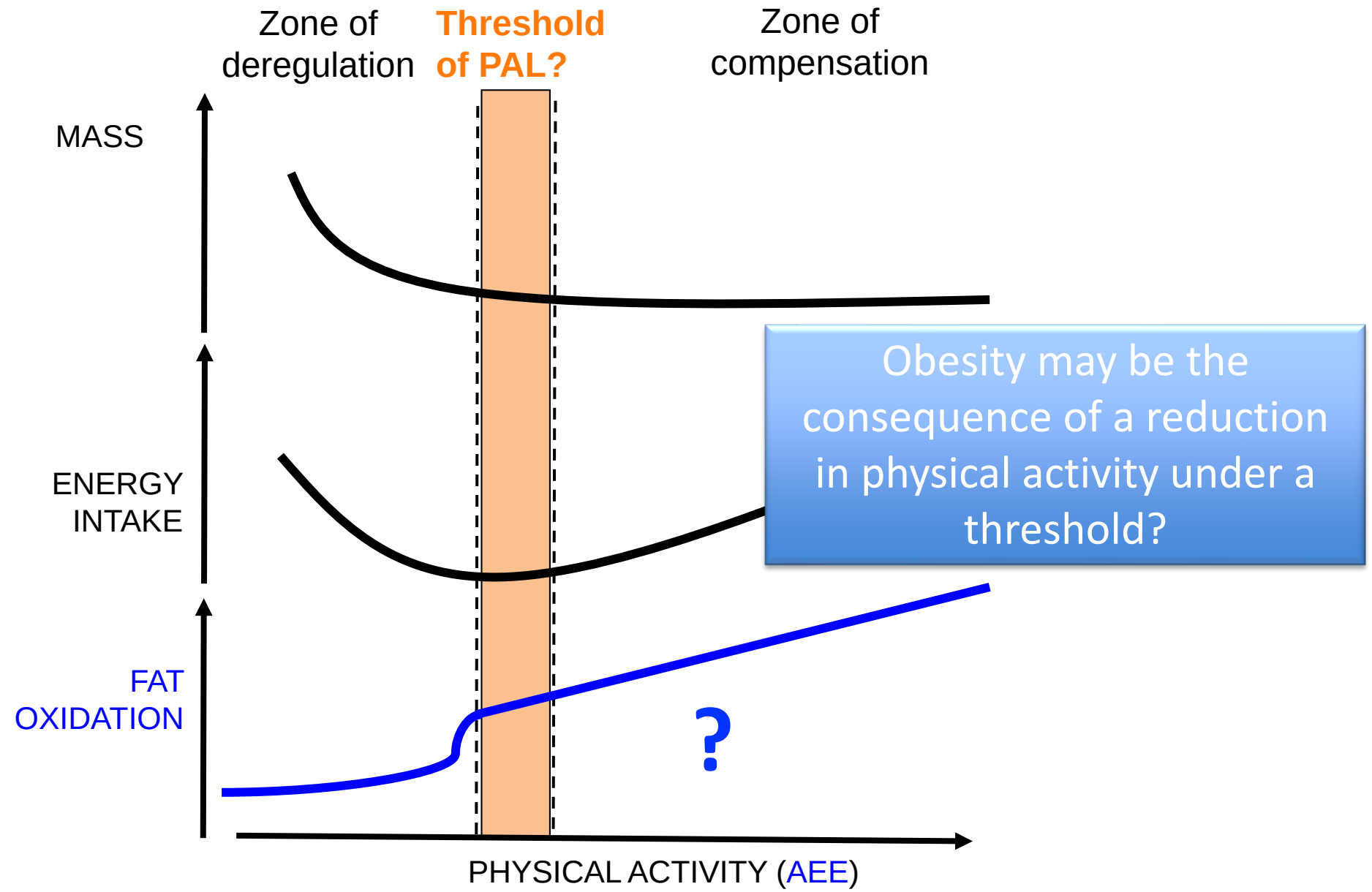
Metabolic inflexibility

Weight gain ?

Bergouignan et al J Appl Physiol, 2011

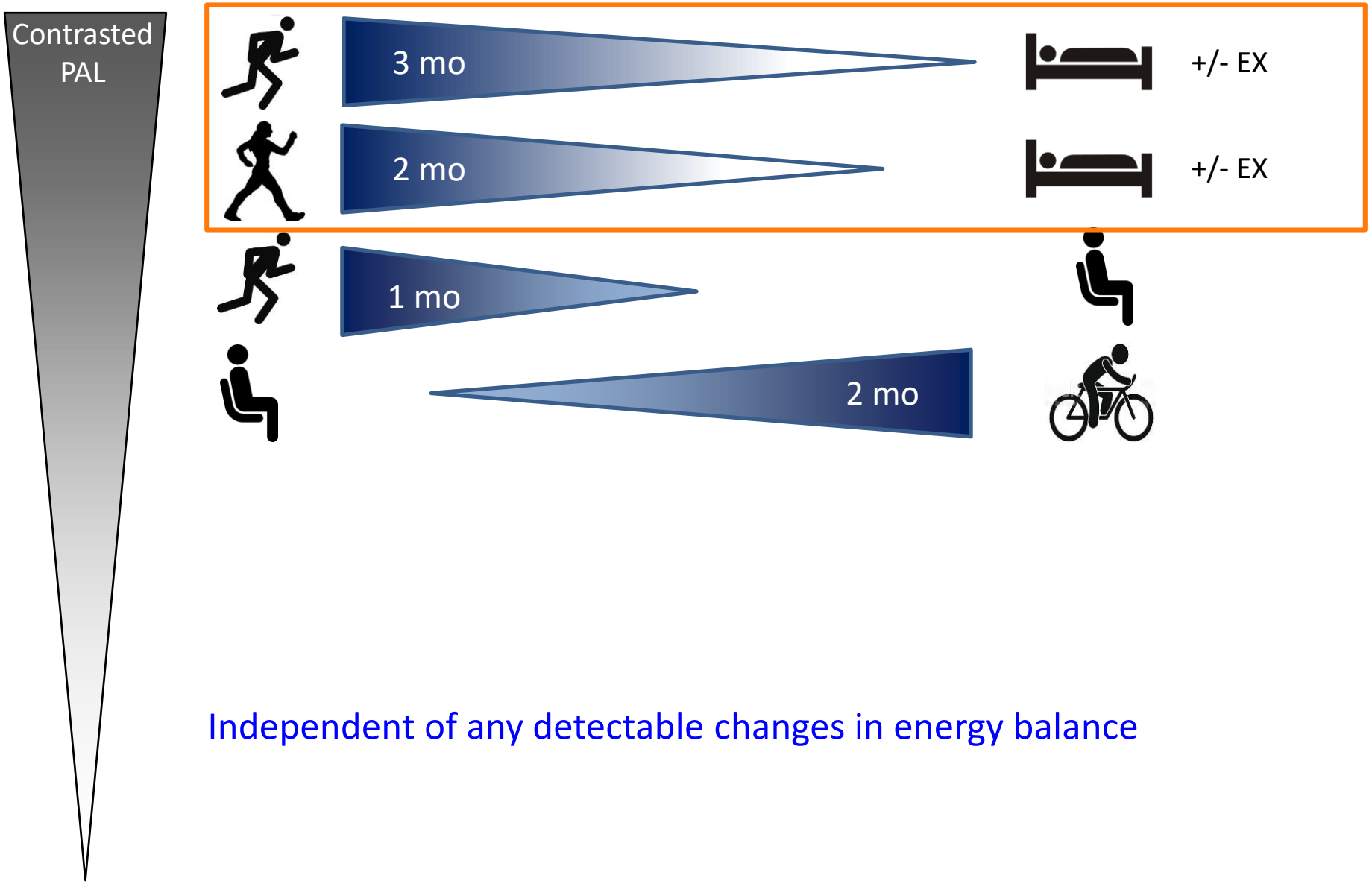
The old Mayers's hypothesis on body weight regulation, 1954



Obesity may be the consequence of a reduction in physical activity under a threshold?

Adapted from Mayer et al, AJP 1954

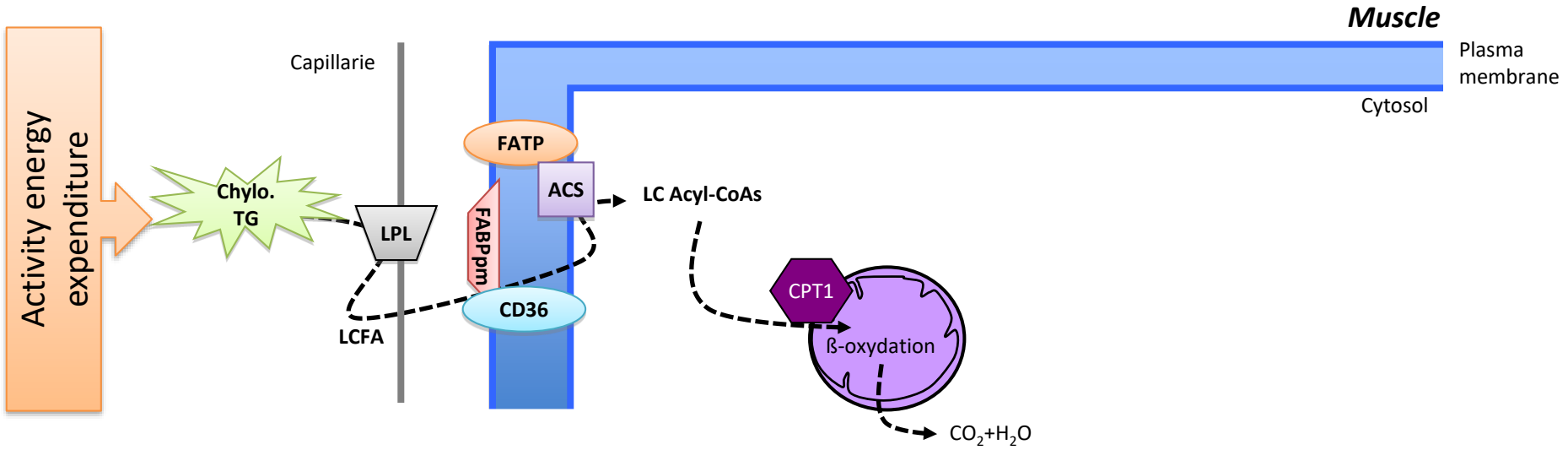
Relationship between physical activity and fat oxidation?

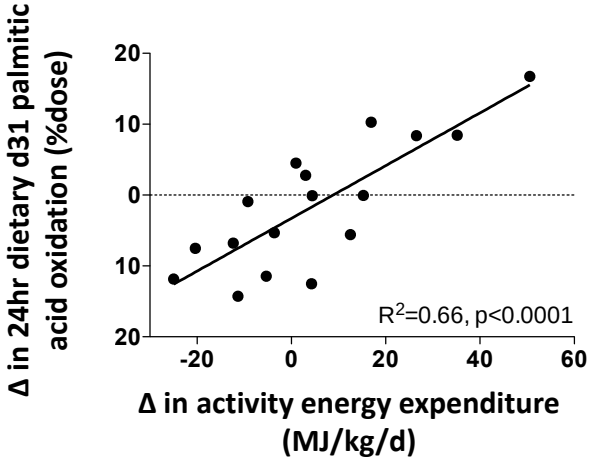


Independent of any detectable changes in energy balance

Effects of physical activity level variations on a key parameter of body weight regulation

Activity energy expenditure predicts dietary fat oxidation

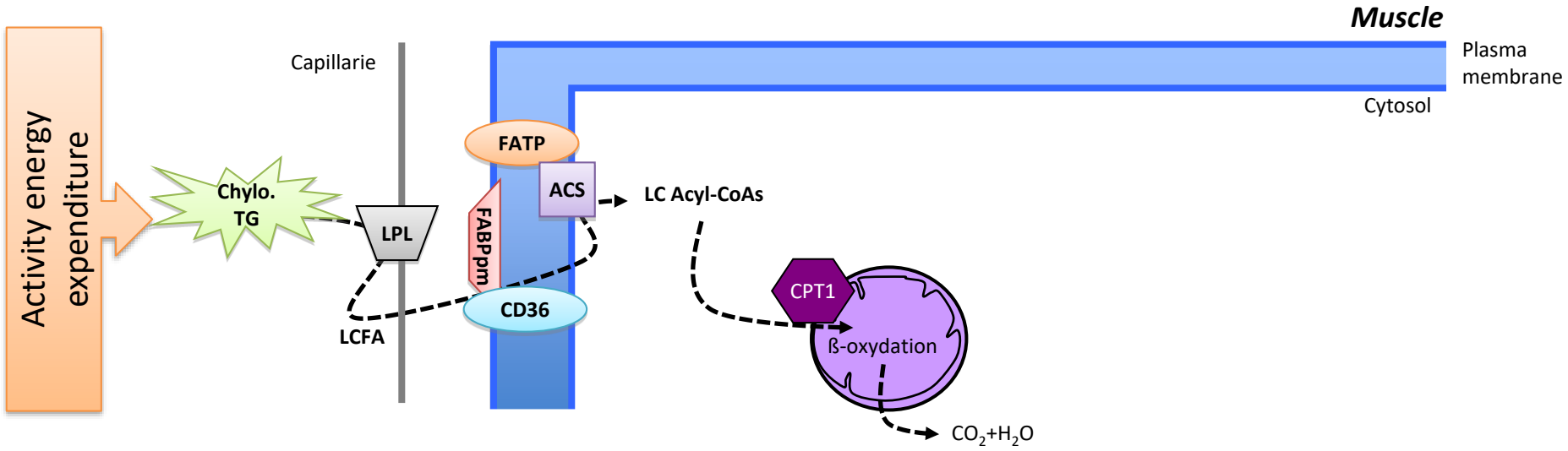


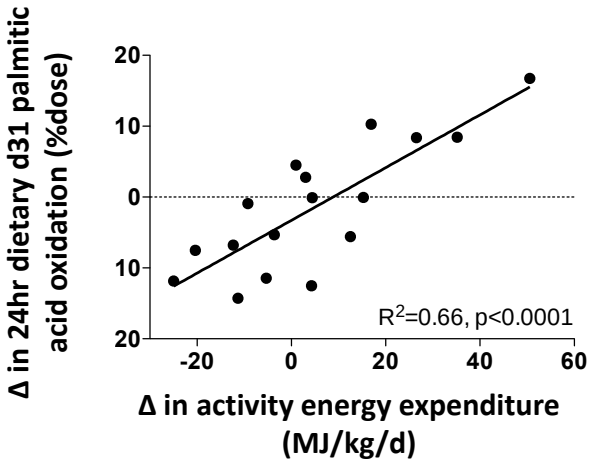


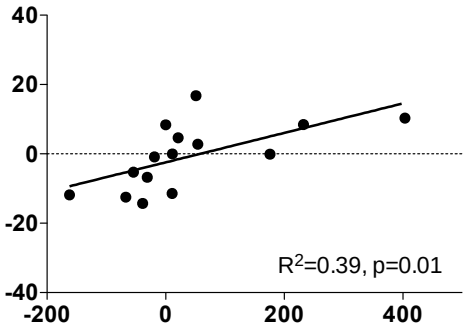
Bergouignan et al. AJCN 2013

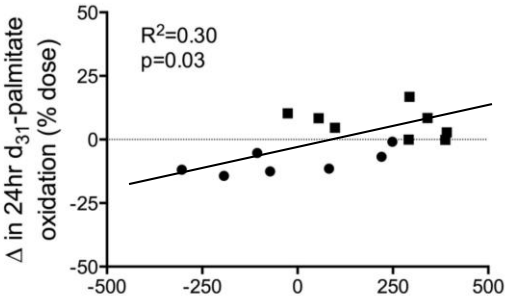
Effects of physical activity level variations on a key parameter of body weight regulation

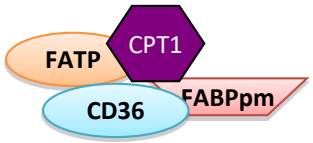
Activity energy expenditure predicts dietary fat oxidation through coordinated changes in plasma trafficking and muscle handling









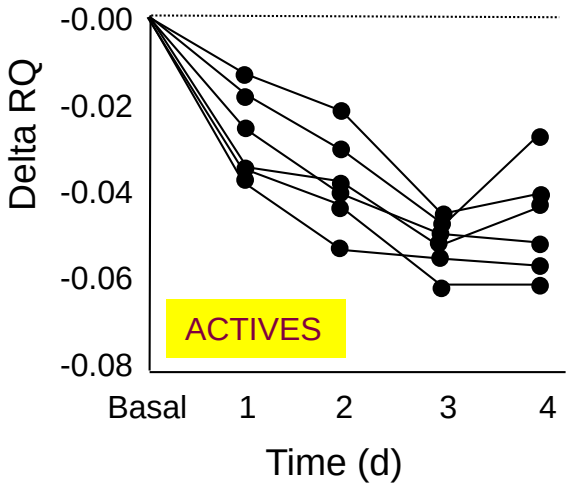


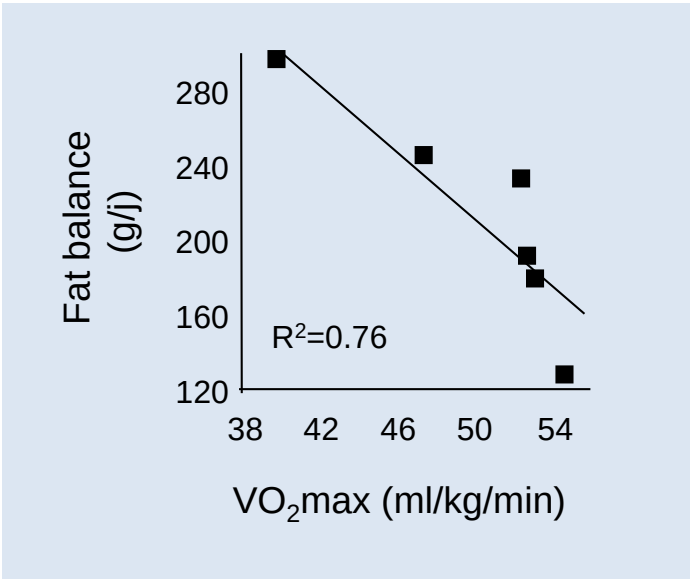
Bergouignan et al. AJCN 2013

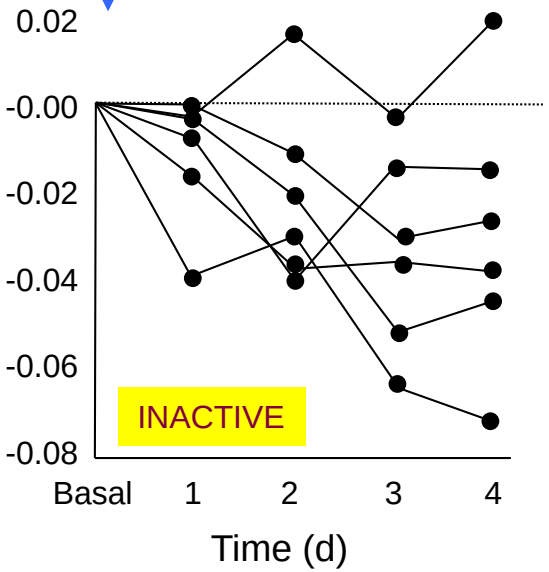
Physically inactive individuals are unable to adjust fat oxidation to an increase in fat intake (metabolic inflexibility)

Eucaloric high fat diet

Lipid oxidation

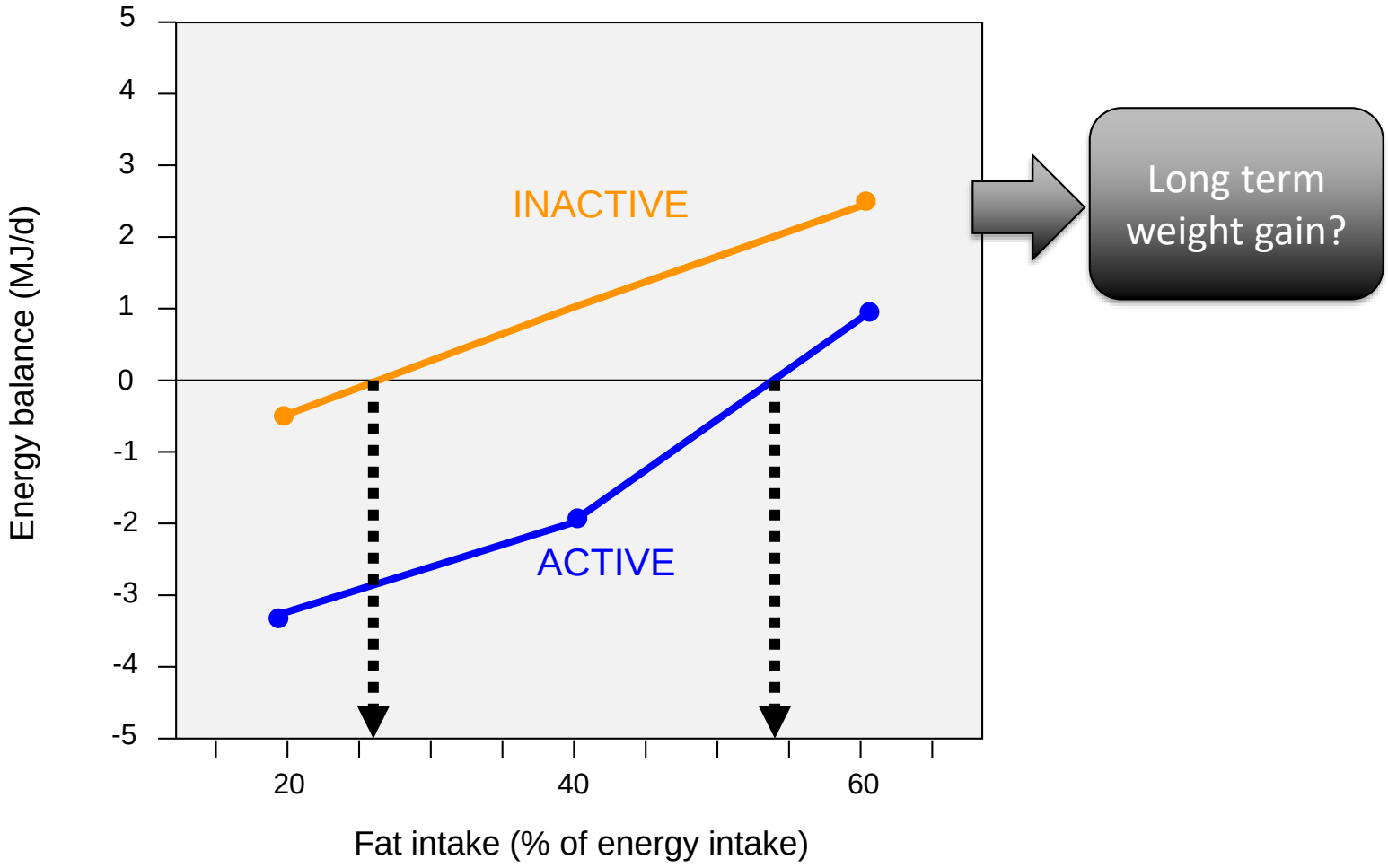






Smith et al. Am J Clin Nutr, 2000 -> men
Hansen et al. Am J Clin Nutr, 2008 -> women

Metabolically inflexible, inactive individuals are more vulnerable to high fat diet



Adapted from Stubbs et al. 1995

Sedentary behaviors, metabolic inflexibility and longitudinal weight gain

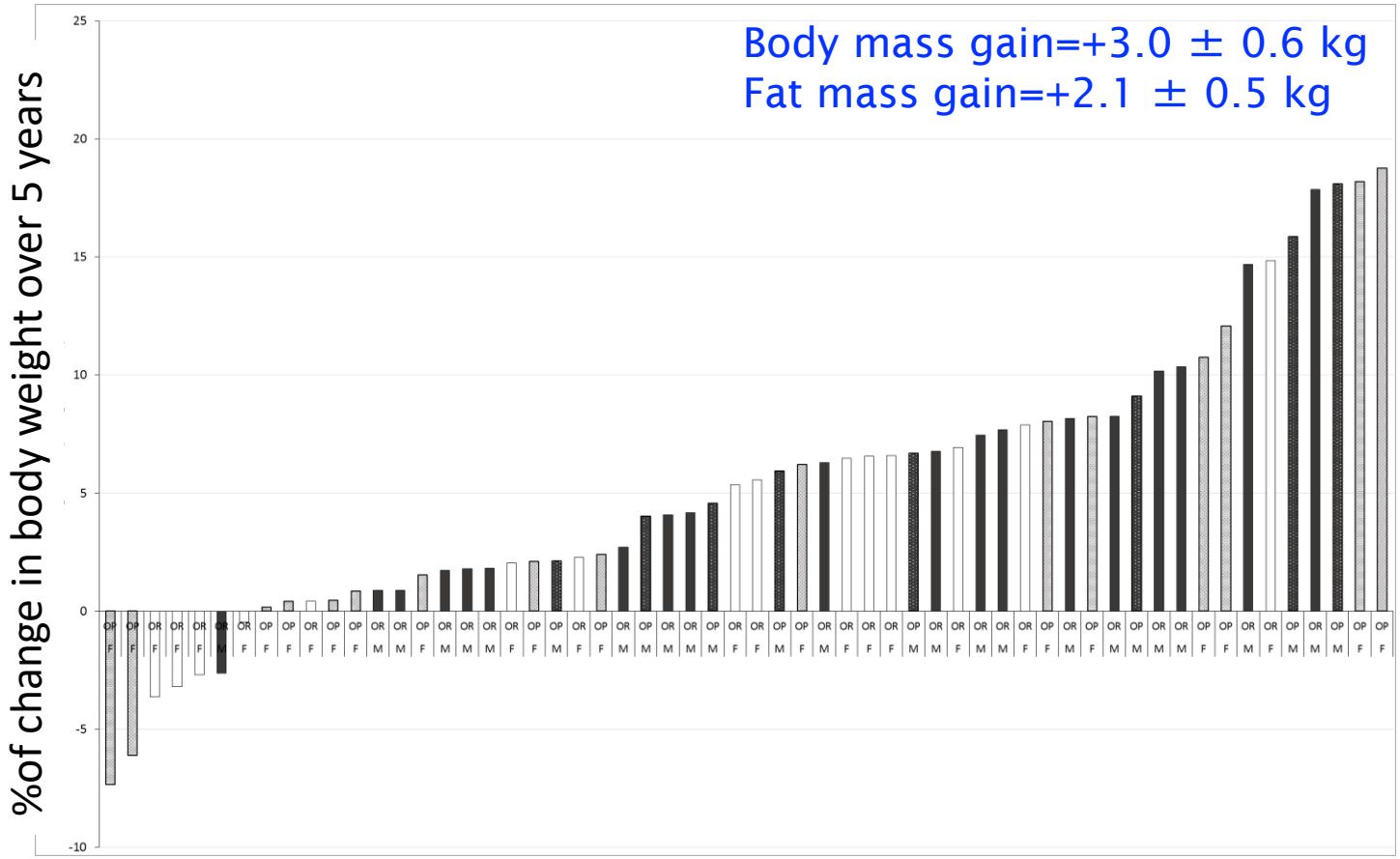
Energy Adaptations to Time Study

Daniel Bessesen, MD
Univ. of Colorado

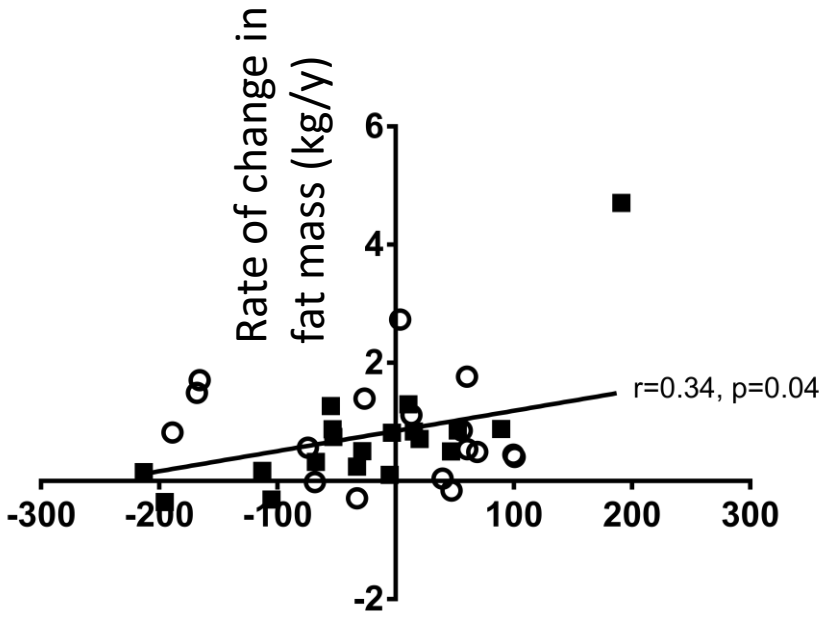
At baseline: 3 days overfeeding:

- Changes in energy expenditure & physical activity
- Changes in 24h nutrient metabolism

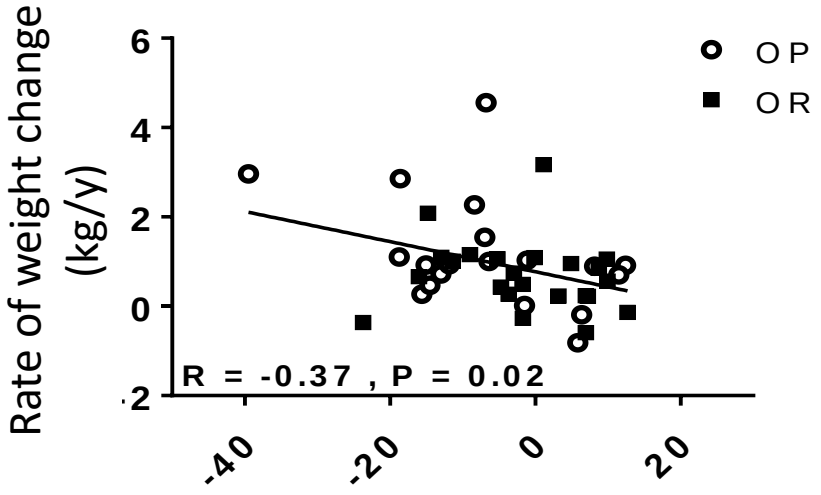
5-year follow-up: body weight and composition



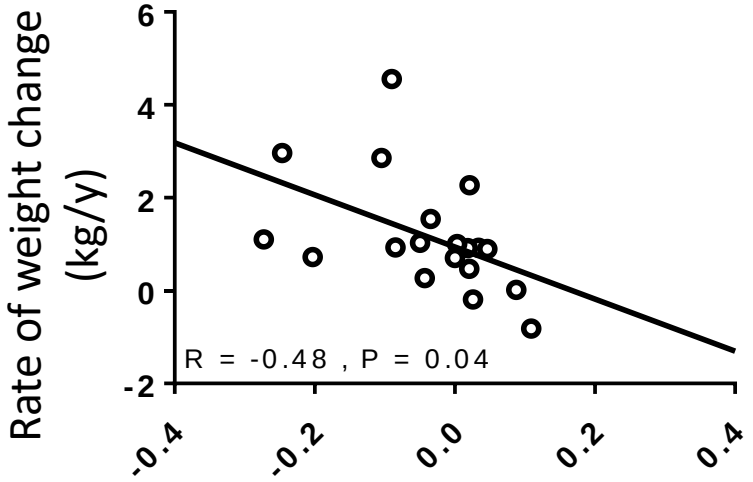
Sedentary behaviors, low sleep fat oxidation and metabolic inflexibility are predictors of longitudinal weight gain



Change in time spent sedentary (min/day)



Change in sleep fat oxidation (g/8h)

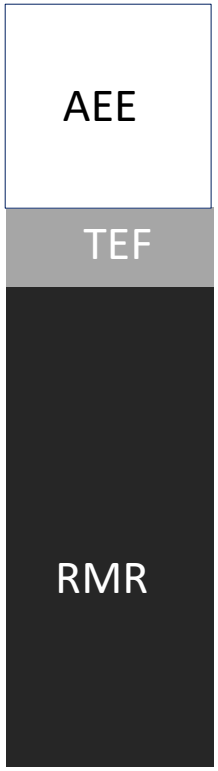


Change in metabolic flexibility (sleep-day RQ)

Rynders CA et al. Obesity 2017; Creasy SA et al. Obesity 2018; Rynders CA et al. Obesity, in press

How to directly study sedentary behaviors?

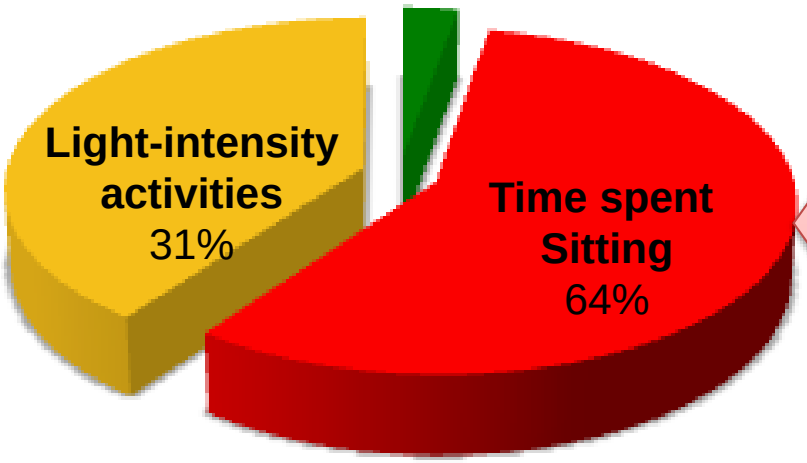
Total energy expenditure



Ambulatory period

RECOMMENDATIONS
150 min / week of moderate-to-vigorous physical activity
Very low volume

Large volume
Main determinant of total energy expenditure

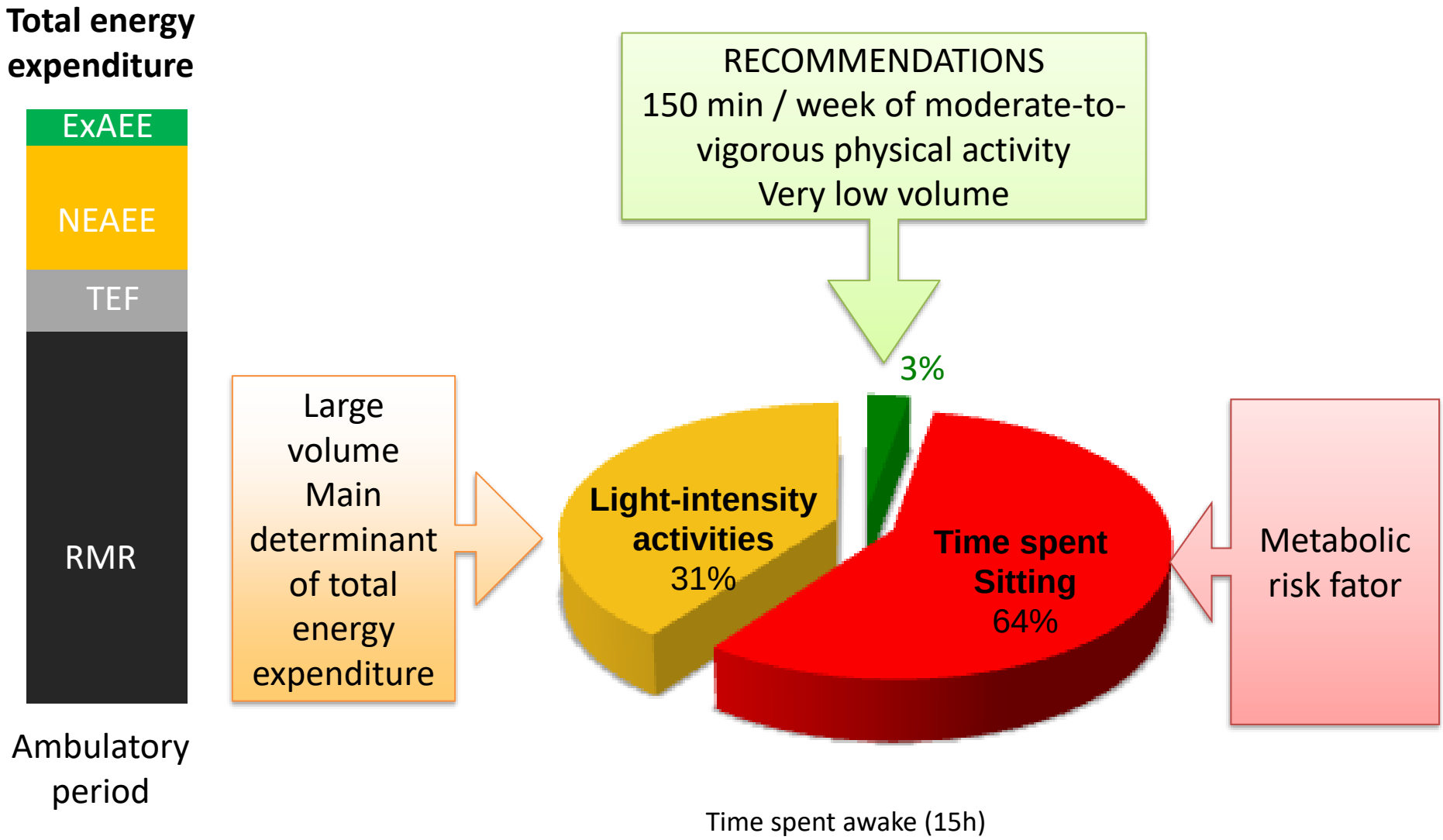


Metabolic risk fator

Time spent awake (15h)

NHANES 2003-2006

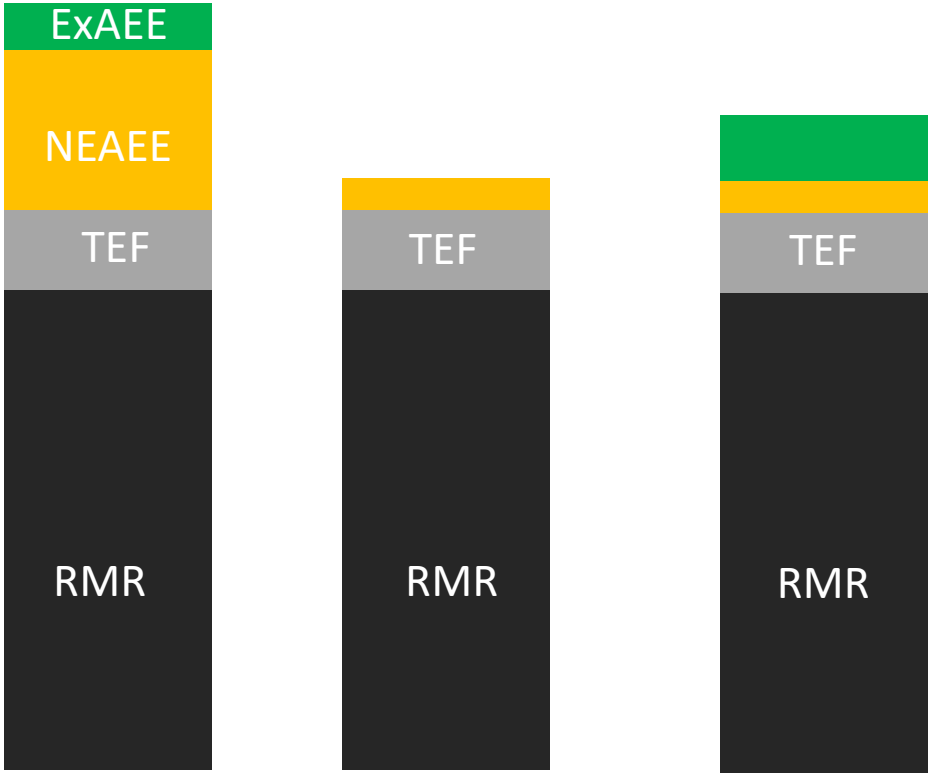
How to directly study sedentary behaviors?



NHANES 2003-2006

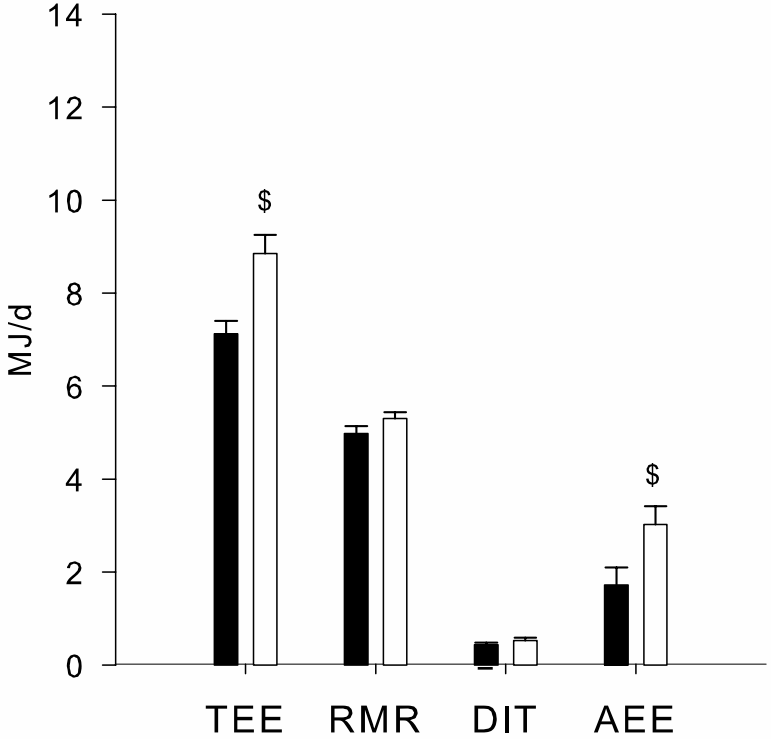
How to directly study sedentary behaviors?

Total energy expenditure



Ambulatory period

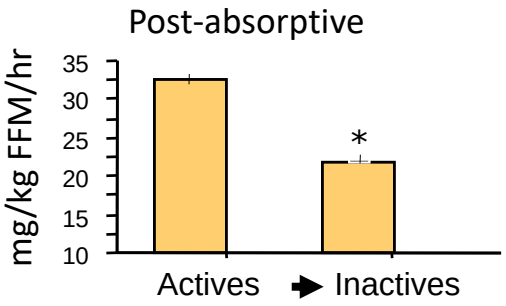
Bed-rest period

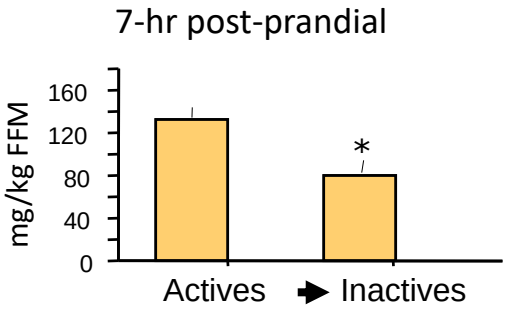


Bergouignan et al. JCEM 2010

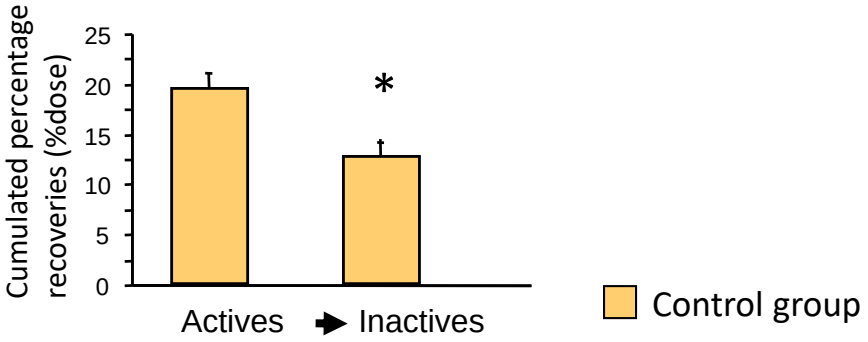
Can exercise offset the physical inactivity induced metabolic alterations?

Total lipid oxidation





Dietary fatty acid oxidation



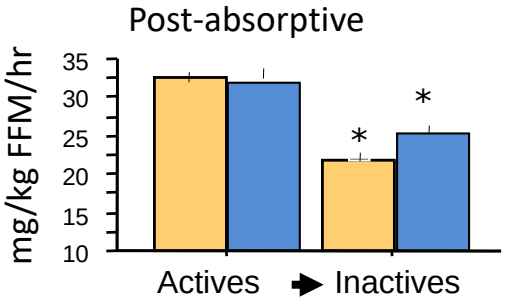
* P<0.05 vs ambulatory period

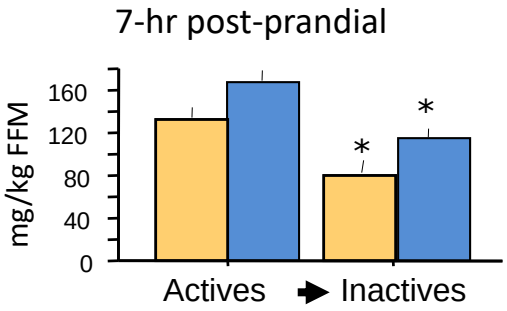
Bergouignan et al. PLoS Clin Trials, 2006; Diabetes 2009

Can exercise offset the physical inactivity induced metabolic alterations?

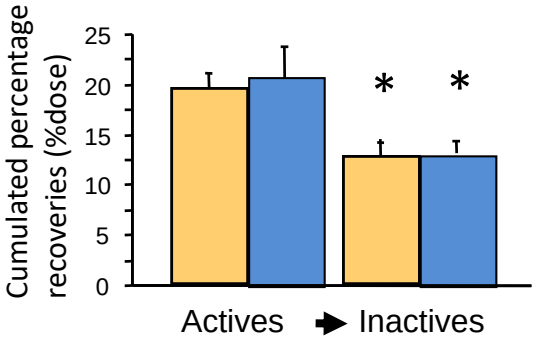
Surprisingly, it does not…

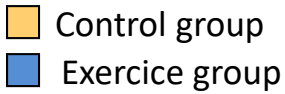
Total lipid oxidation





Dietary fatty acid oxidation





* P<0.05 vs ambulatory period

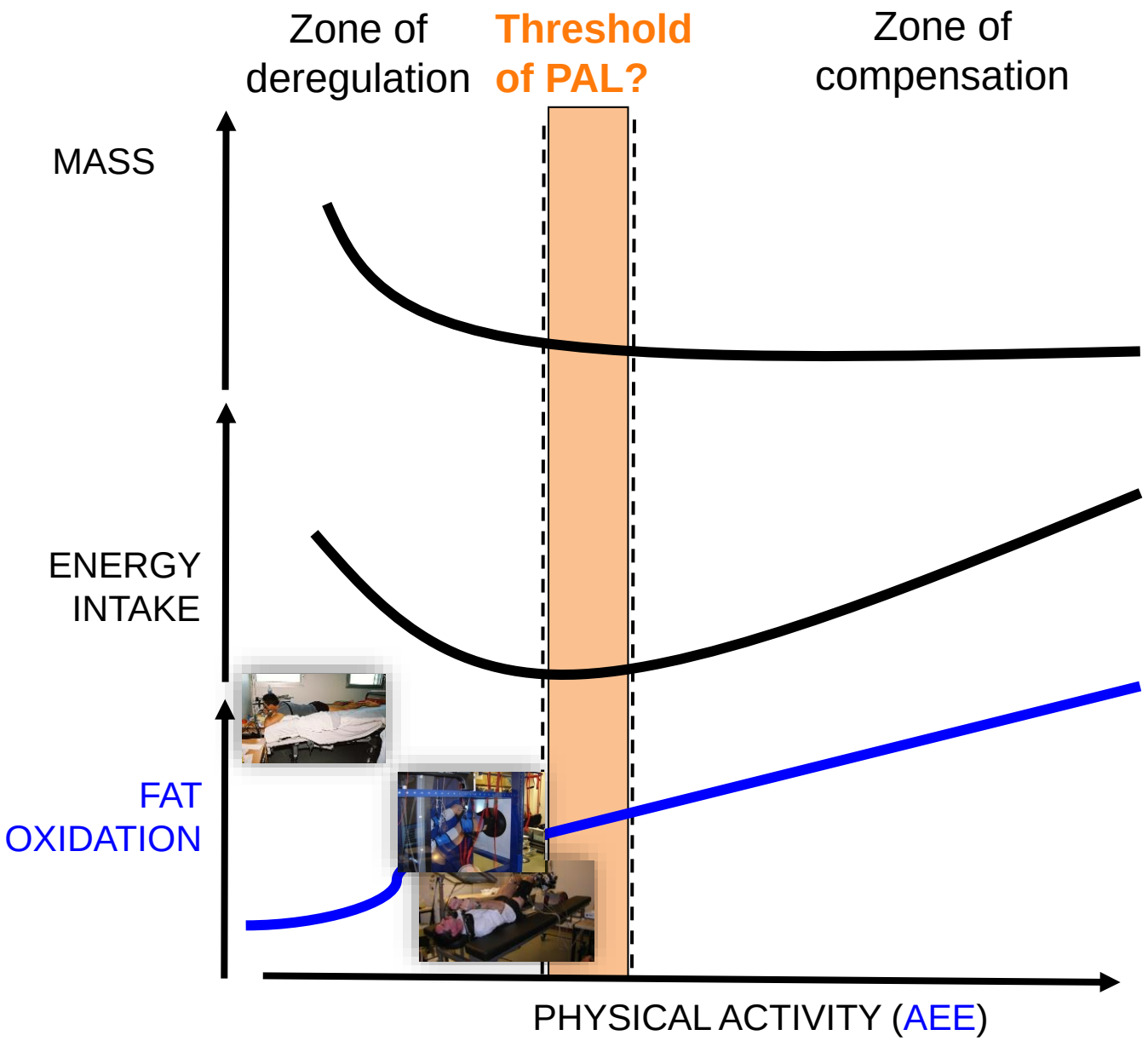
Resistive exercise
3 days / week
35 min per session

\+

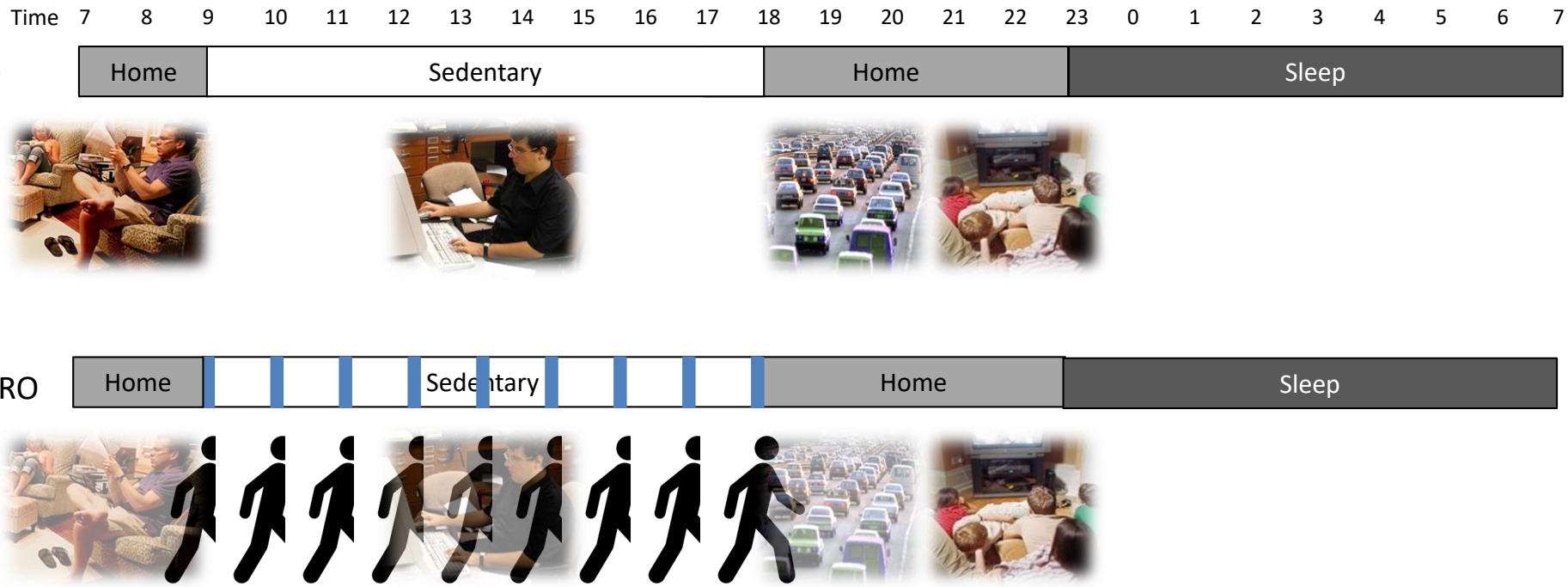
Aerobic exercise
3-5 days / week
45 min per session
40-80%VO2peak

Bergouignan et al. PLoS Clin Trials, 2006; Diabetes 2009

Benefits of exercise only if we reach a certain level of activity energy expenditure?



Breaking up sedentary time paradigm



↓ postprandial insulin concentration
↓ postprandial glucose concentration

Breaking up sedentary time versus increase in energy expenditure?

Dunstan D et al. Diabetes Care, 2012, Dempsey Diab Care 2018; Bailey D et al. J Sc Med Sp; Blankenship J et al. APNM 2014

Breaking up sedentary time paradigm

Randomized control trial

10F and 10M overweight sedentary adults - 4 days

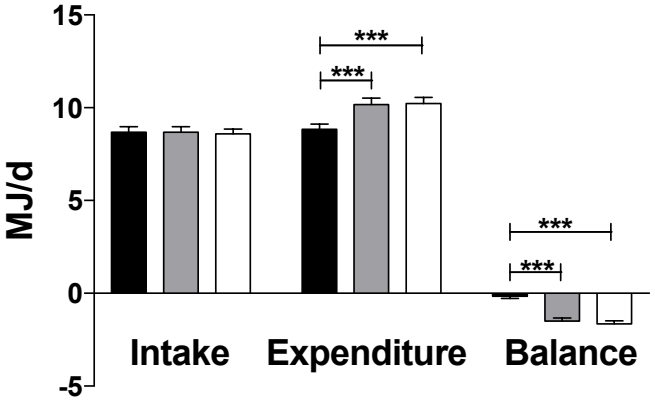
Diet, caffeine, alcohol, physical activity fully controlled


Bally
the Hotel CALORIEfor
over!

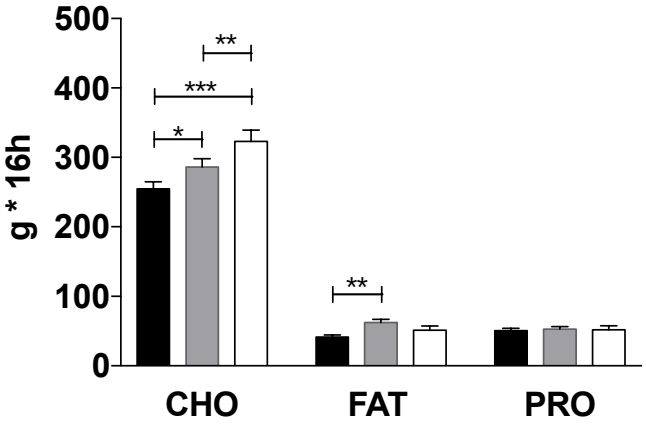
At same energy expenditure and deficit, a differential use of nutrient

Both interventions:
↓ postprandial insulin concentration
No change in postprandial glucose concentration

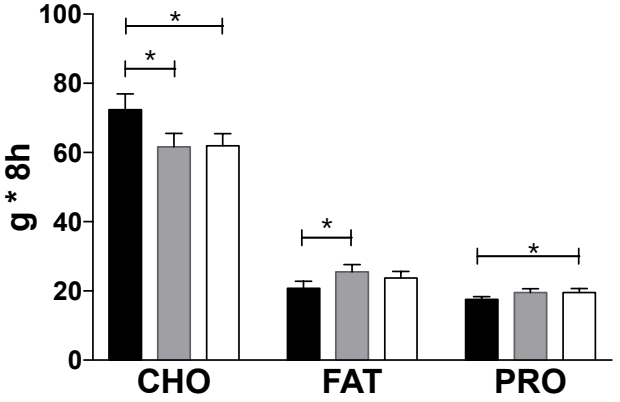
24hr energy intake, expenditure and balance



Waking nutrient oxidation

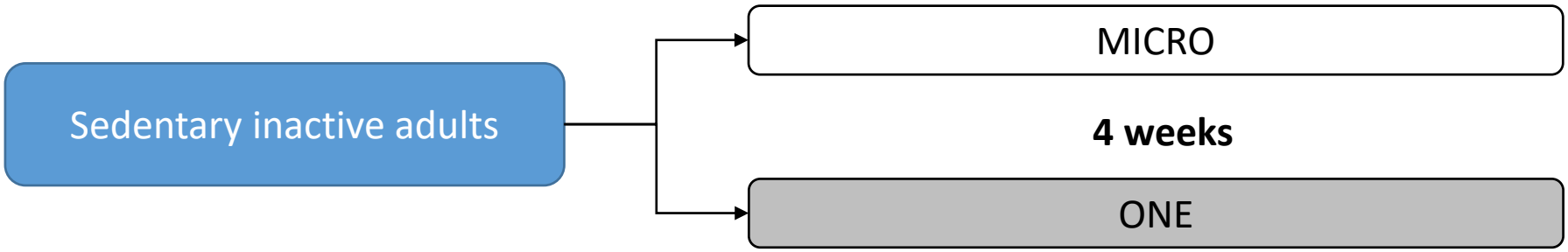


Sleeping nutrient oxidation



Does breaking up sedentary behavior improve metabolic flexibility?

Medium-term metabolic effects?



Sedentary behaviors and profile of physical activity
Total energy expenditure and metabolic rate
Insulin sensitivity and glycemic control
24hr nutrient metabolism
Mitochondrial function
Molecular mechanisms

Medium-term metabolic effects?

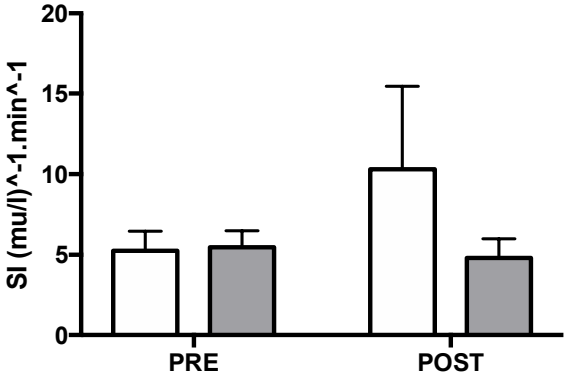
Sedentary inactive adults

MICRO (n=8)

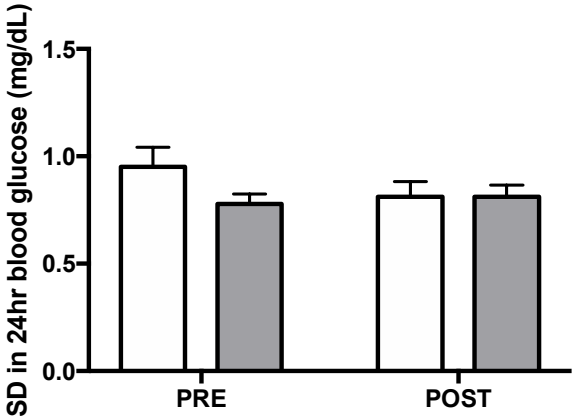
4 weeks

ONE (n=8)

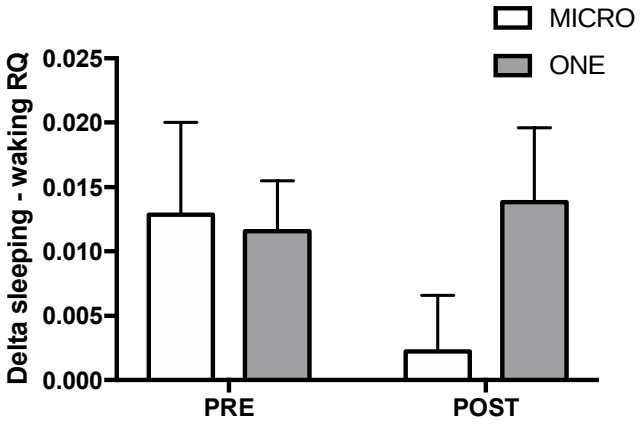
Insulin sensitivity (IVGTT)



24hr glycemic variability



Metabolic flexibility

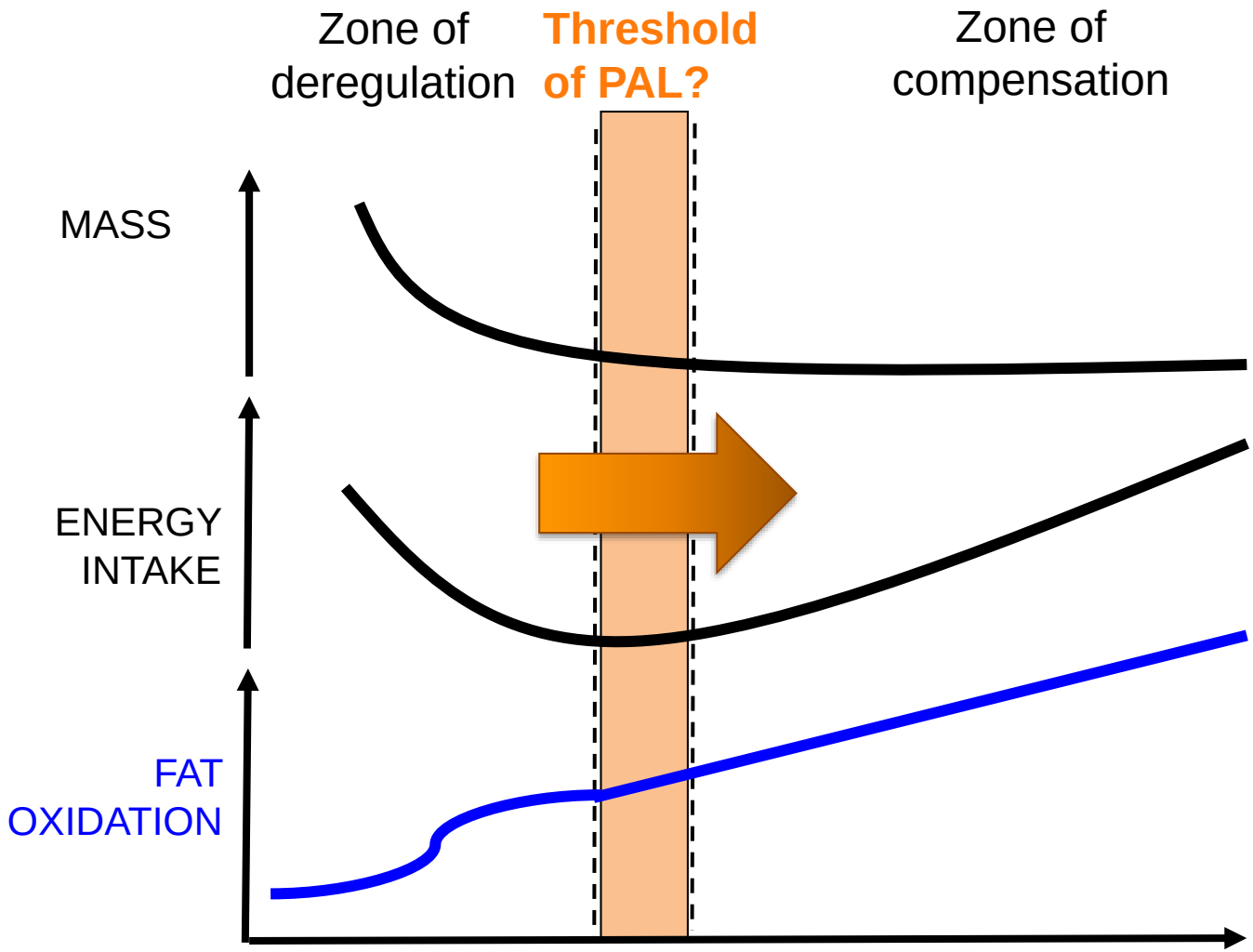


Breaking up sedentary time may have further health benefits than those associated with energy expenditure

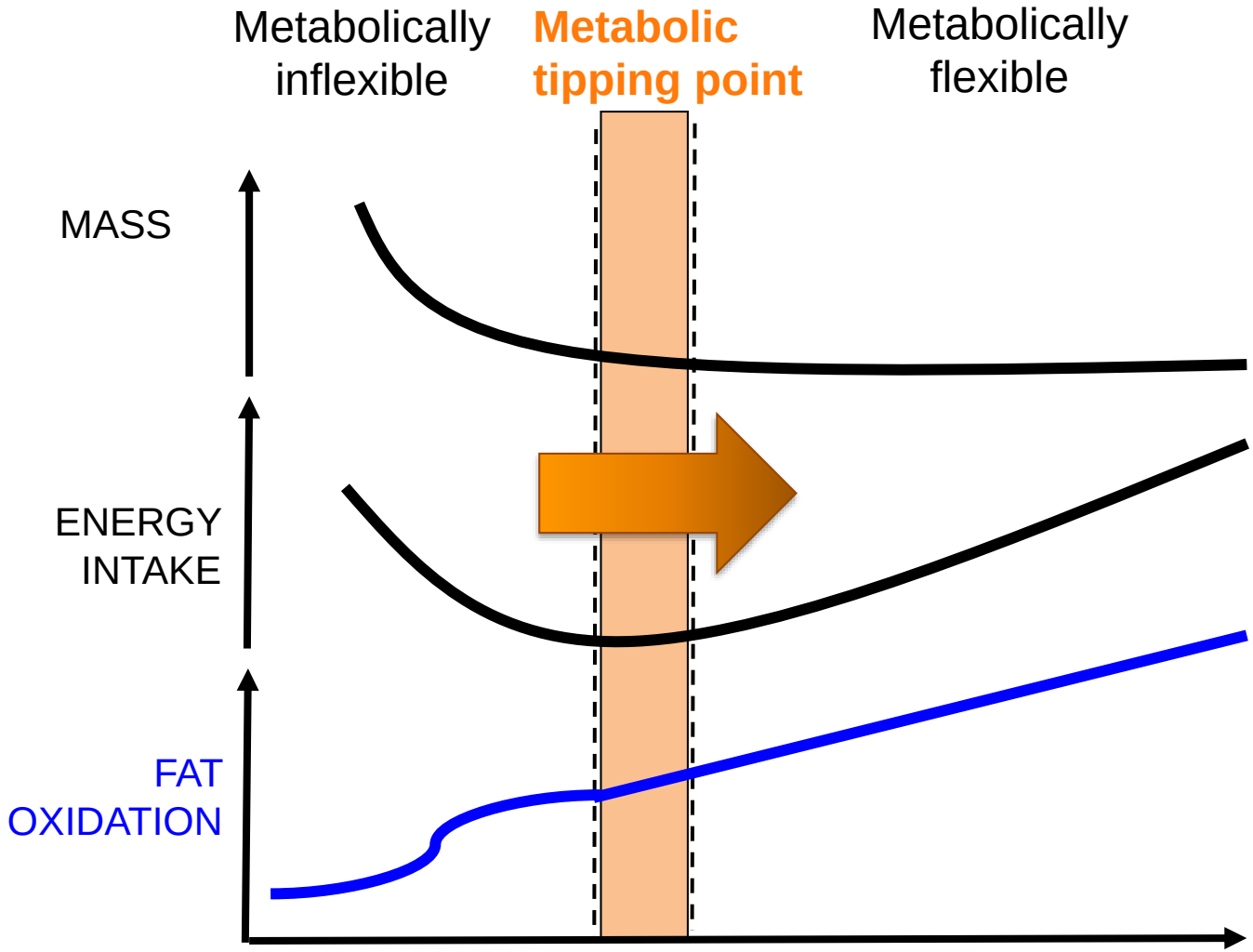
Conclusions

- Sedentary behavior is a key predictor of metabolic flexibility
- Metabolic inflexibility contributes to the development of physical inactivity induced metabolic alterations
- Exercise alone, without reaching a certain level of physical activity level or energy expenditure, does not offset the physical activity induced metabolic alterations
- Non-exercise activities likely play a key role in the regulation of metabolism
- In addition to the effects of energy expenditure, breaking up sedentary time may confer health benefits including the improvement of metabolic flexibility

Revisiting the old Mayer's hypothesis

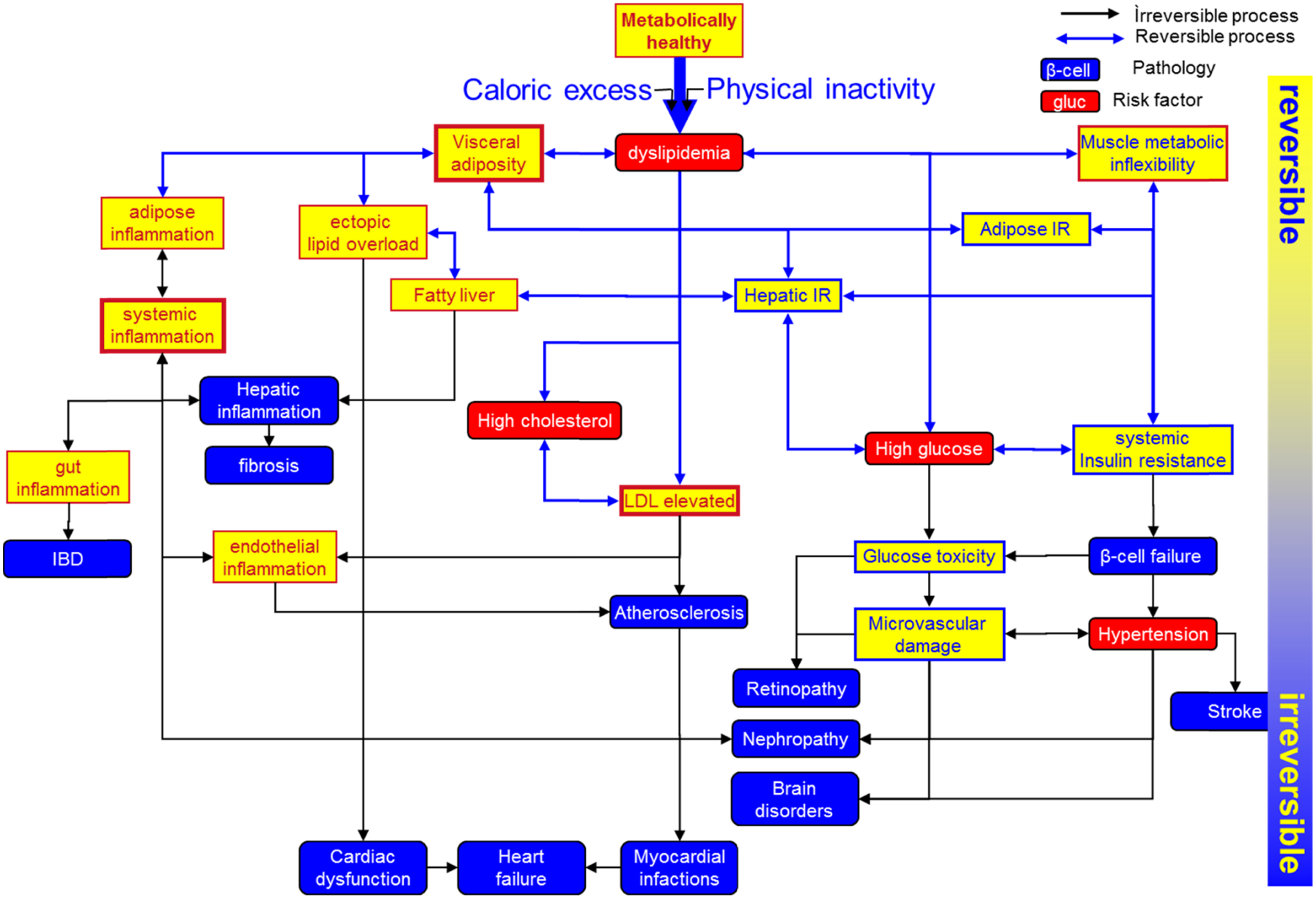


Revisiting the old Mayer's hypothesis



Physiopathology of metabolic inflexibility

Metabolic flexibility is a core component of metabolic health and diseases



Van Ommen B. Gens Nutr, 2014

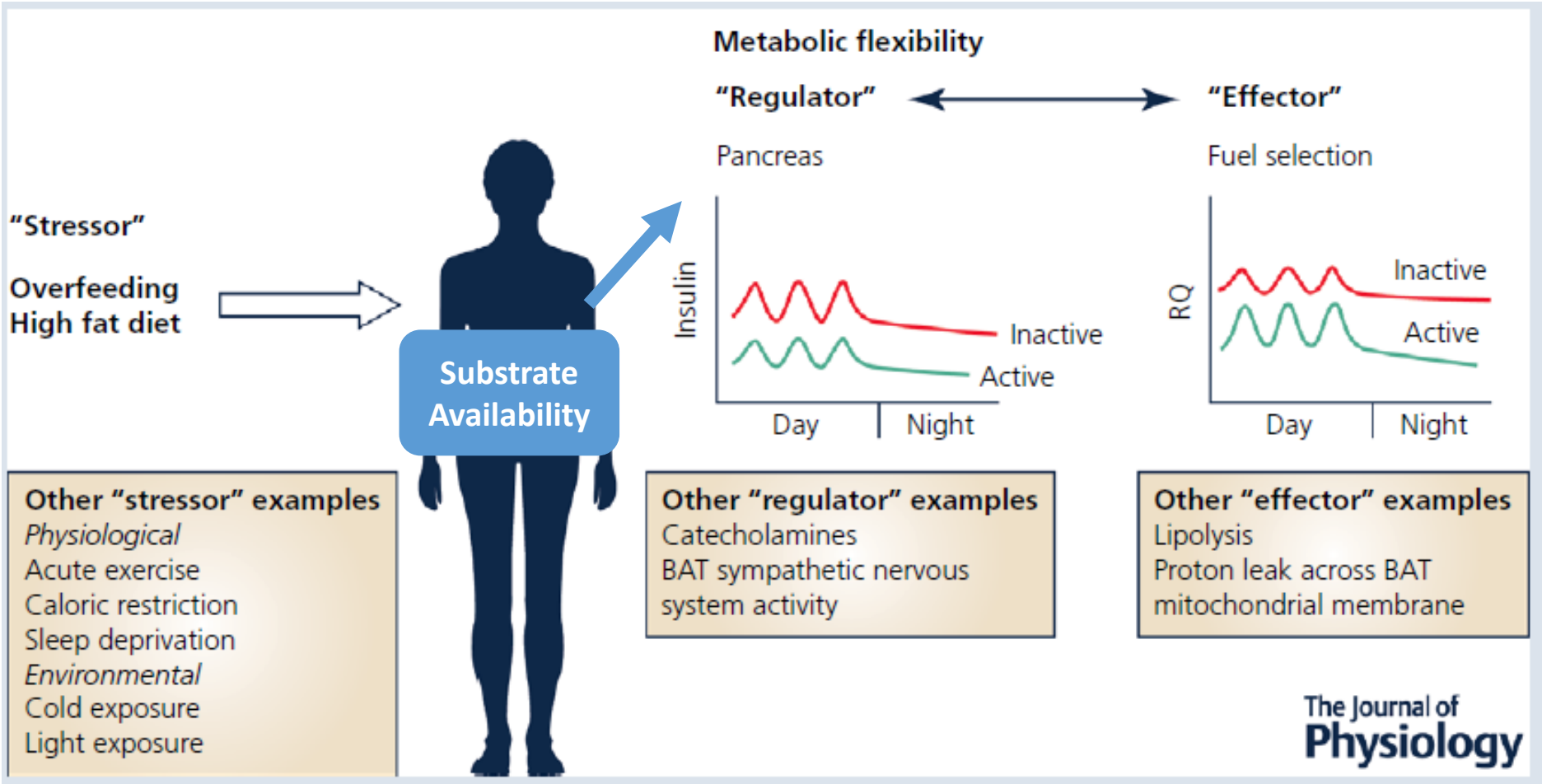
ACKNOWLEDGEMENTS

University of Strasbourg/CNRS
Stéphane Blanc, PhD
Alexandre Zahariev
Isabelle Chery
Floriane Rudwill, PhD
Anthony Damiot
Edwina Antoun, PhD
Iman Momken, PhD

University of Lyon/CRNHL
Chantal Simon, MD, PhD
Etienne Lefai, PhD
Sylvie Normand, PhD
Laure Gabert

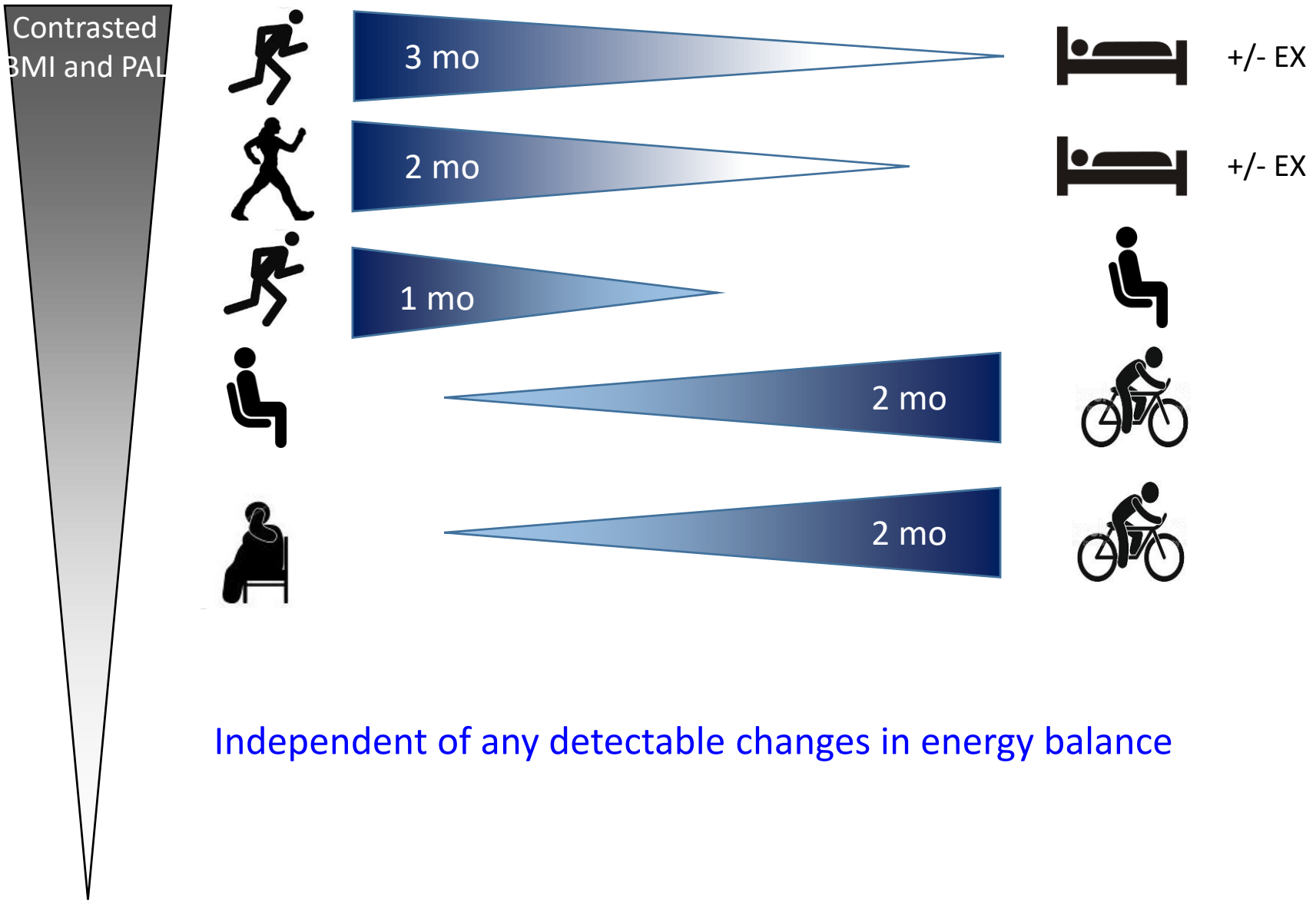
University of Colorado
Anschutz Health & Wellness Center
Division of Endocrinology
James Hill, PhD
Daniel Bessesen, MD
Nathan De Jong, MPH
Andrew Lange, MPH
Carlos Mendez
Laura Schreck
Corey Rynders CA, PhD
Elizabeth Kealey, RD
David Goldstrohm, PhD
Paul MacLean, PhD
Matthew Jackman, PhD
Ginger Johnson
Ed Melanson, PhD
Zhaoxing Pan, PhD

Sedentary behavior is a key predictor of metabolic inflexibility



Rynders C et al. J Physiol 2018

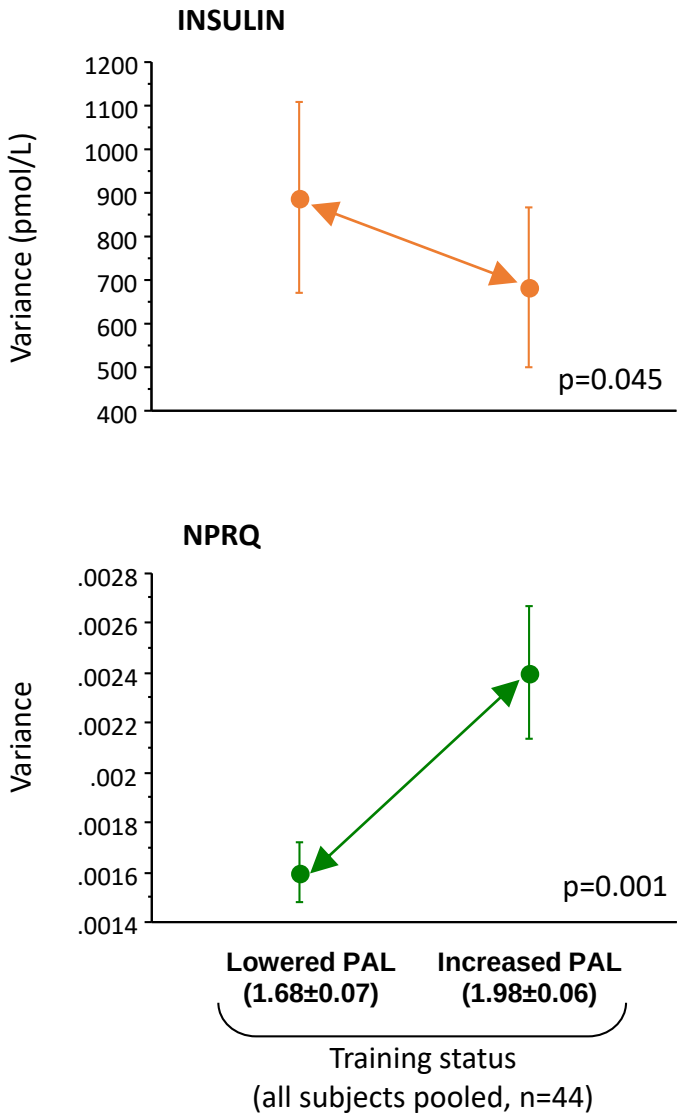
Is metabolic flexibility determined by levels of physical activity?



Independent of any detectable changes in energy balance

Is metabolic flexibility determined by levels of physical activity?

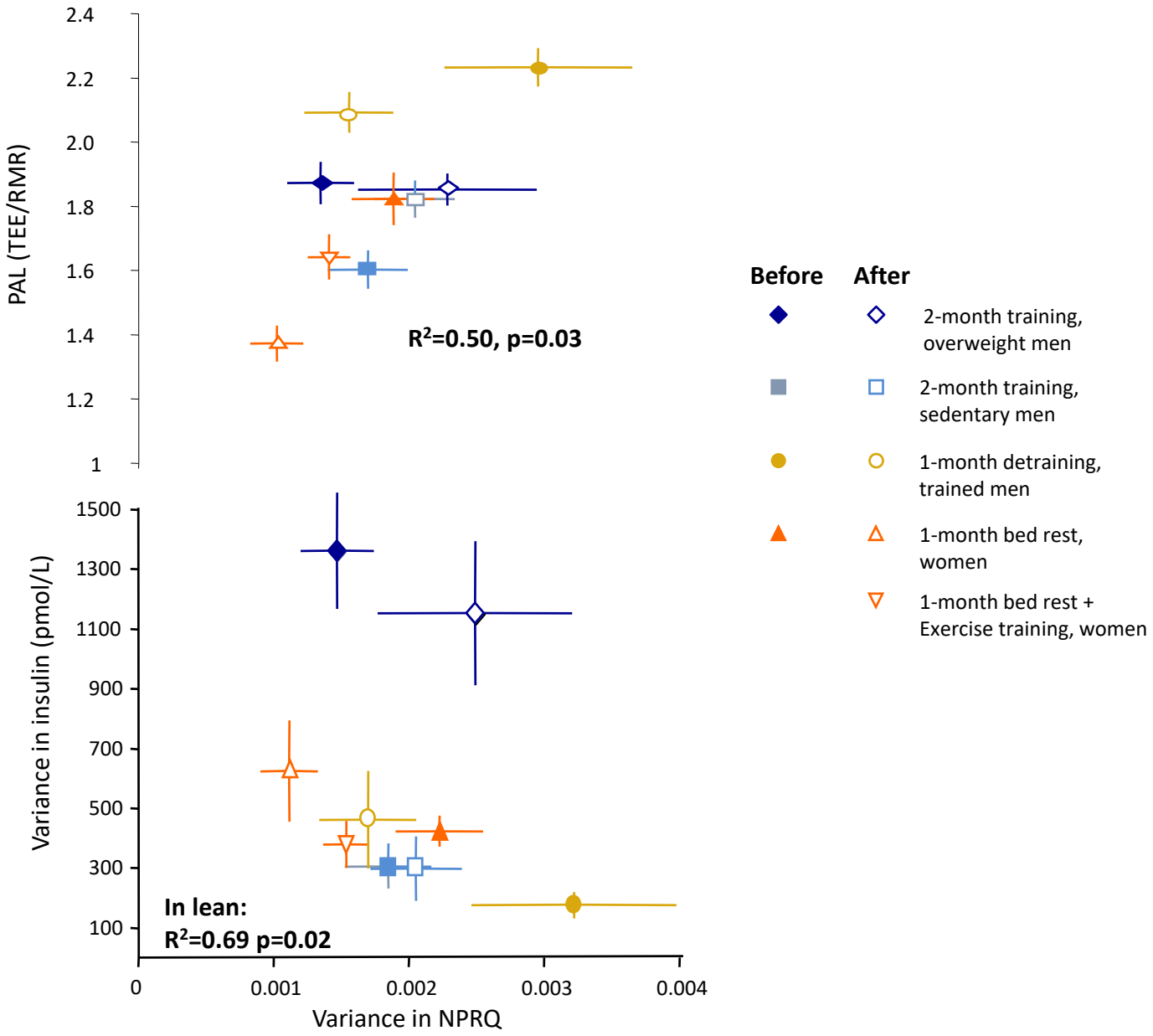
An increase in physical activity level improves metabolic flexibility



Bergouignan et al JAP, 2011

Is metabolic flexibility determined by levels of physical activity?

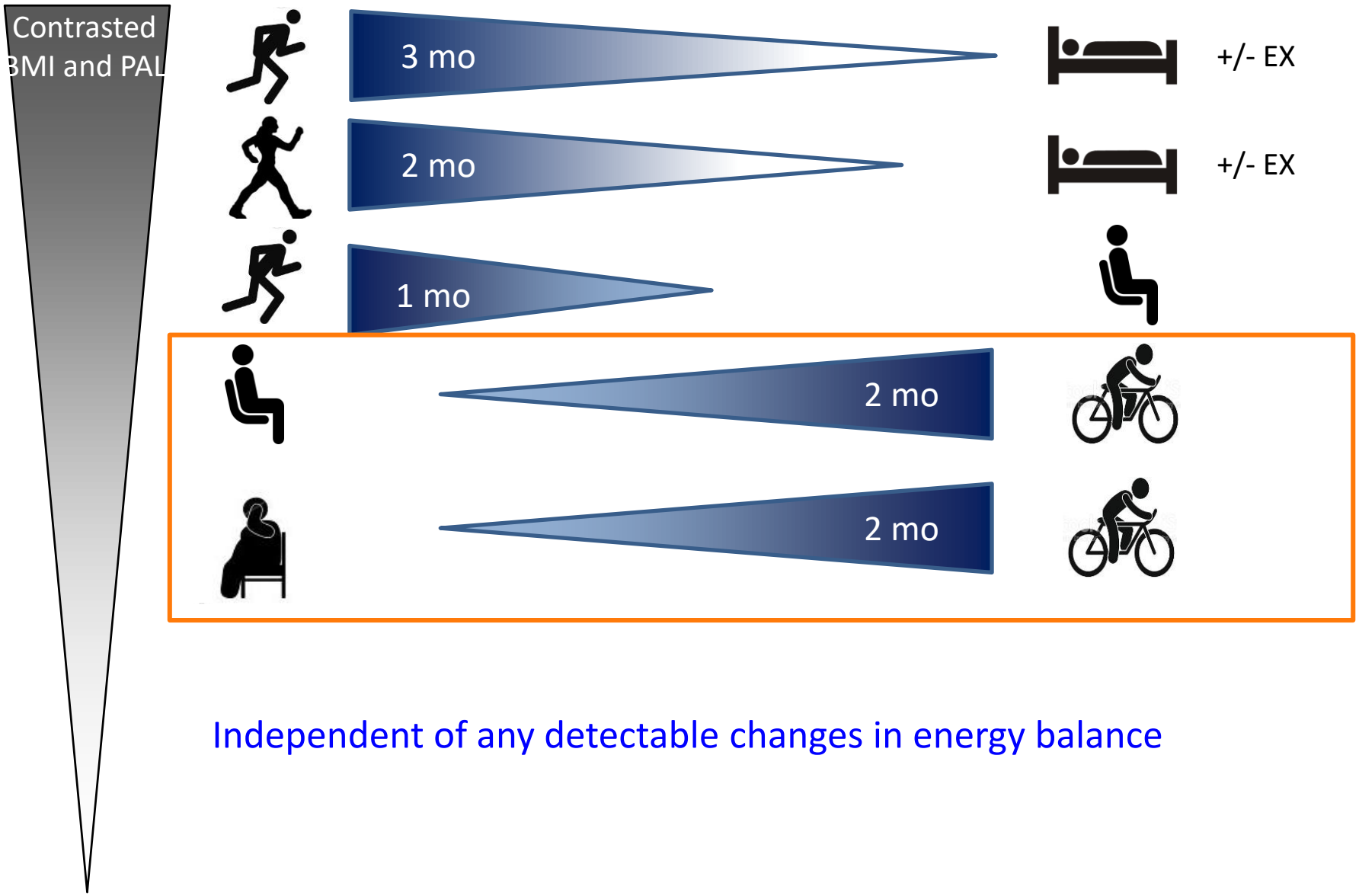
Physical activity predicts metabolic flexibility



Bergouignan et al JAP, 2011

How to examine the relationship between AEE and fat oxidation?

Effect of adiposity?

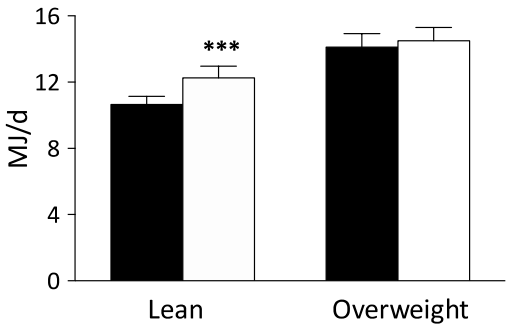


Independent of any detectable changes in energy balance

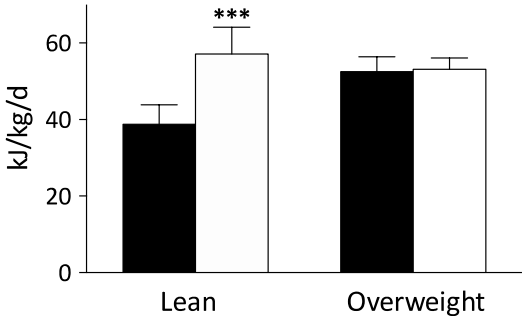
Effect of exercise training on AEE and fat oxidation in lean and obese

A spontaneous compensation in response to exercise training

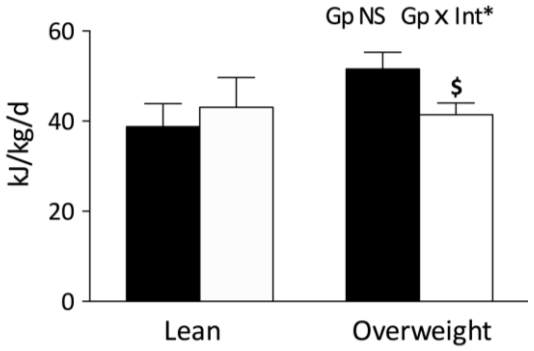
24hr total energy expenditure



24hr activity energy expenditure



24hr non-exercise activity energy expenditure



Intervention:

Before

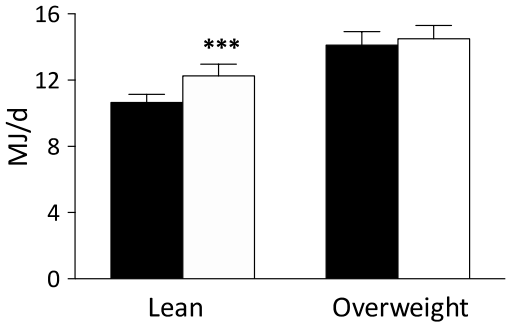
After

Lefai E et al. Int J Obes 2016

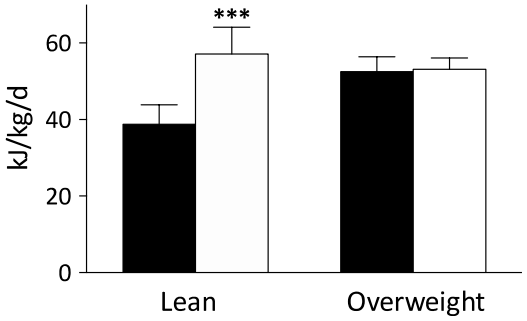
Effect of exercise training on AEE and fat oxidation in lean and obese

Even when no increase in TEE and AEE, exercise training increases 24hr total and dietary fat oxidation

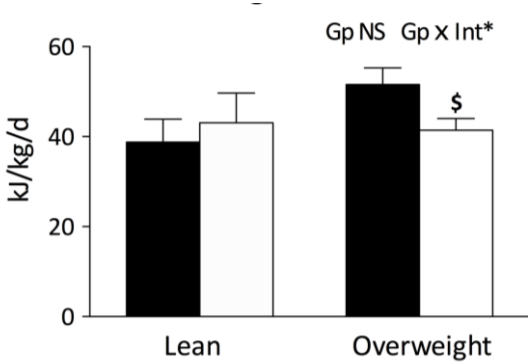
24hr total energy expenditure



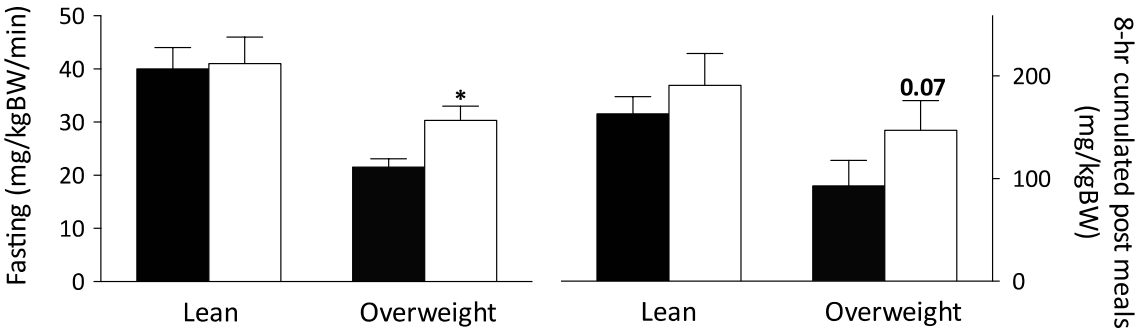
24hr activity energy expenditure



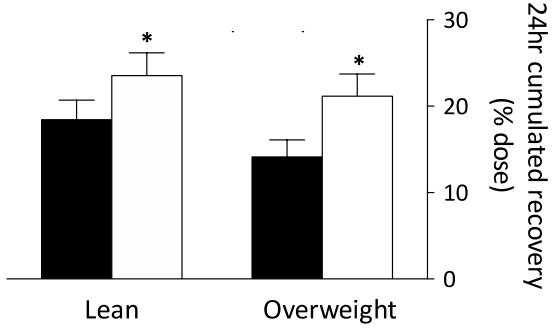
24hr non-exercise activity energy expenditure



Total fat oxidation



24hr dietary fat oxidation

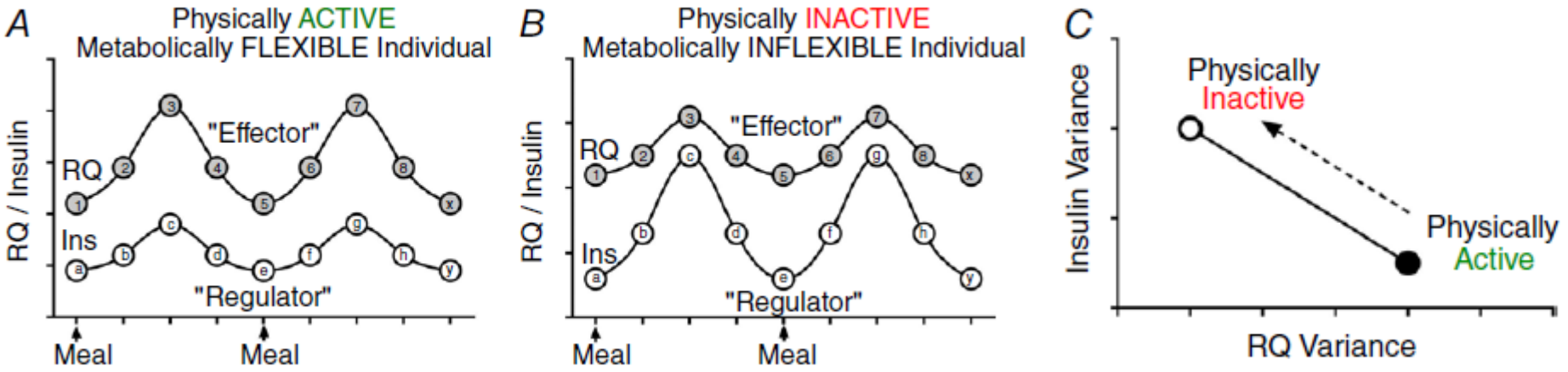


*p<0.05 vs before training
***p<0.001 vs. before training

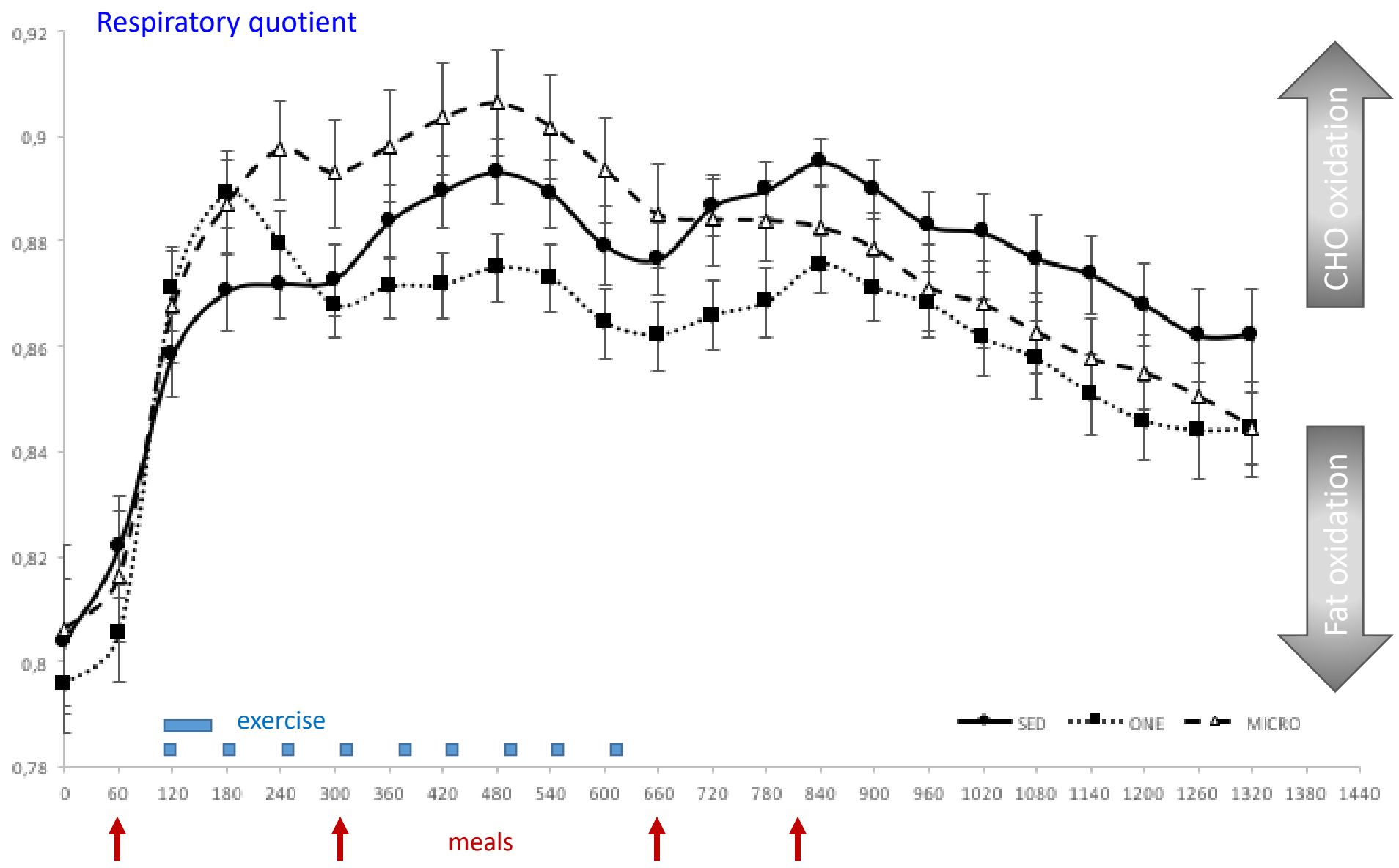
Intervention:
Before
After

Lefai E et al. Int J Obes 2016

Physical inactivity is a predictor of metabolic inflexibility



24h measurement of amount of fat and carbohydrate being used as fuel



DeJong N et al. JAP, under review