# Just Do it!
# Physical exercise & glucose homeostasis; the effect of exercise modalities

*Matthijs Hesselink*
*Maastricht University*
*www.DMRG.nl*

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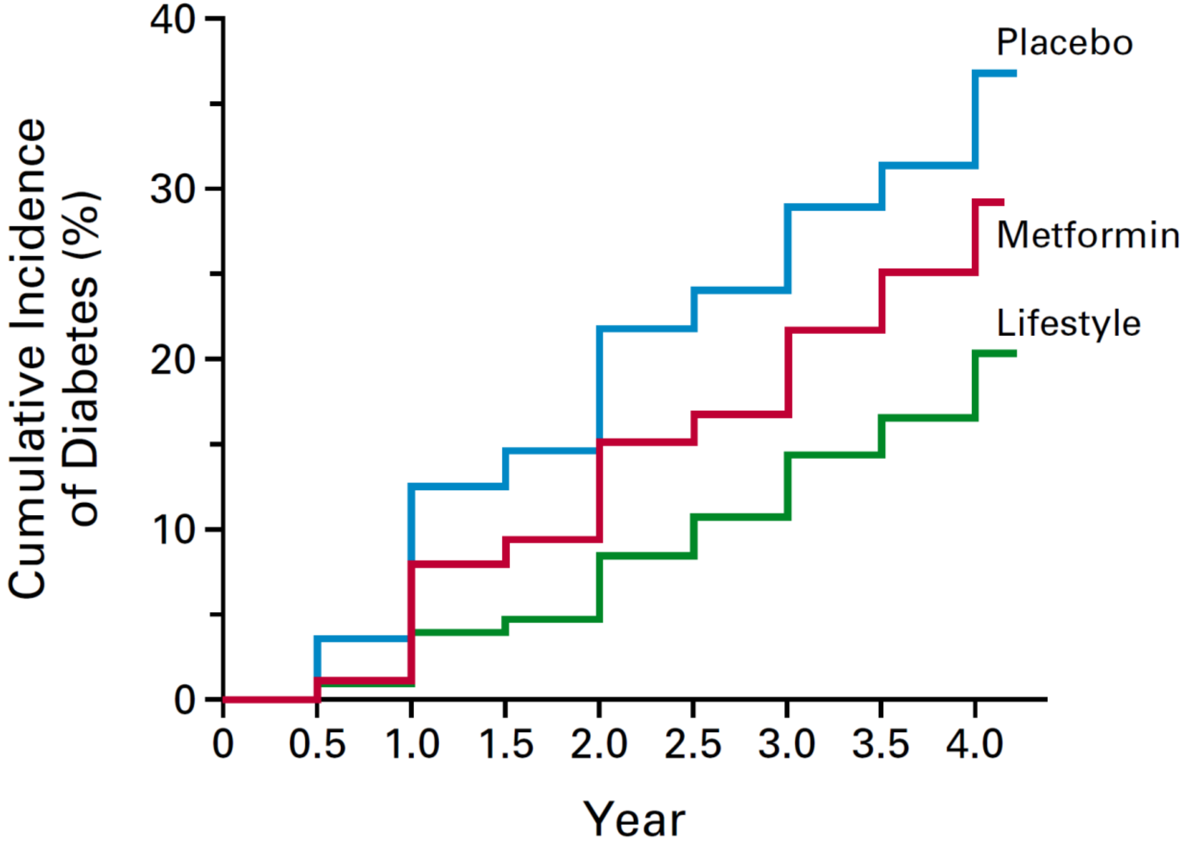
# Glucose homeostasis and insulin resistance?

- In a healthy human body plasma glucose levels are maintained at ~5.5 mmol/l
- Insulin regulates peripheral glucose uptake and endogenous glucose production
- Hence insulin is key in regulating glucose homeostasis

- Unresponsiveness of target organs to insulin, disrupts glucose homeostasis
- Insulin stimulates glucose uptake in muscle, liver and adipose issue (and inhibits hepatic glucose production and adipose tissue lipolysis and proteolysis)

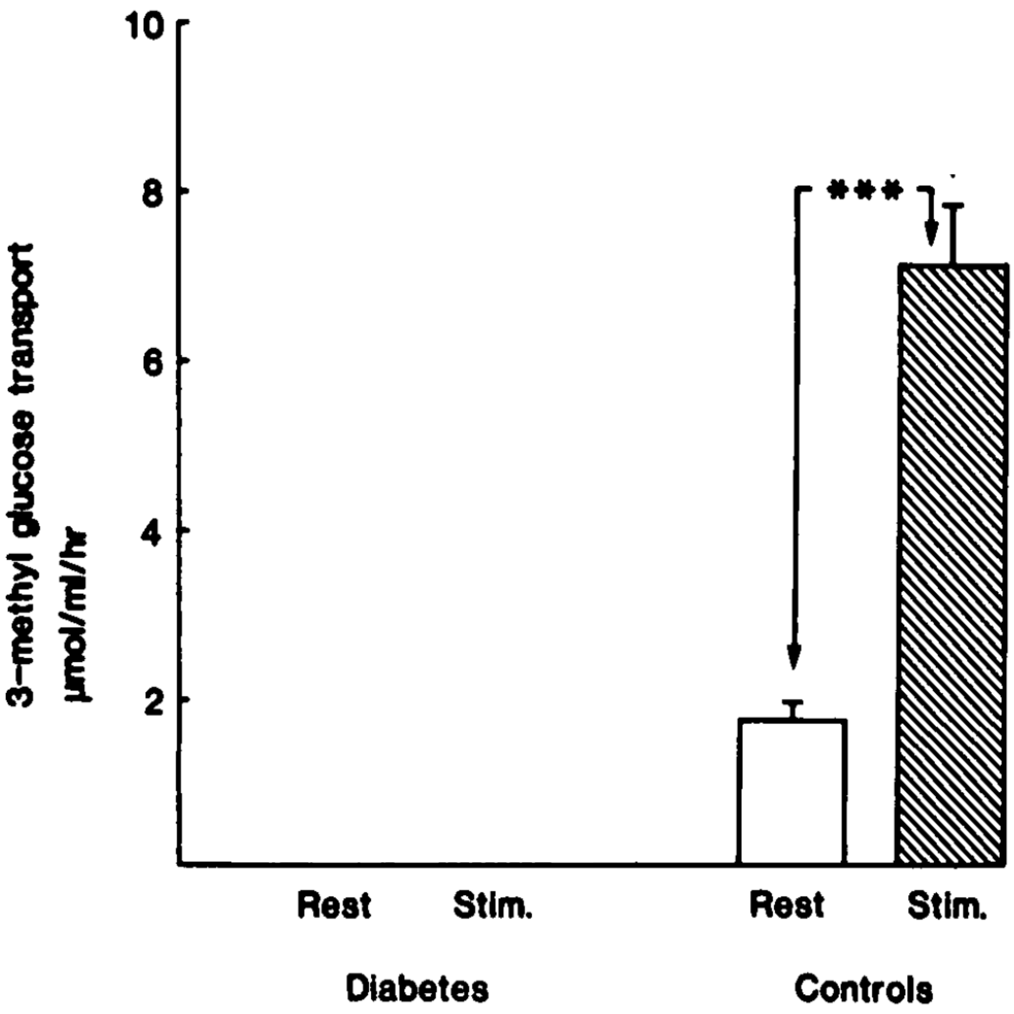
# Lifestyle interventions blunt progressive T2D incidence






DPPRG., NEJM 2002

# Contractile activity increases glucose uptake

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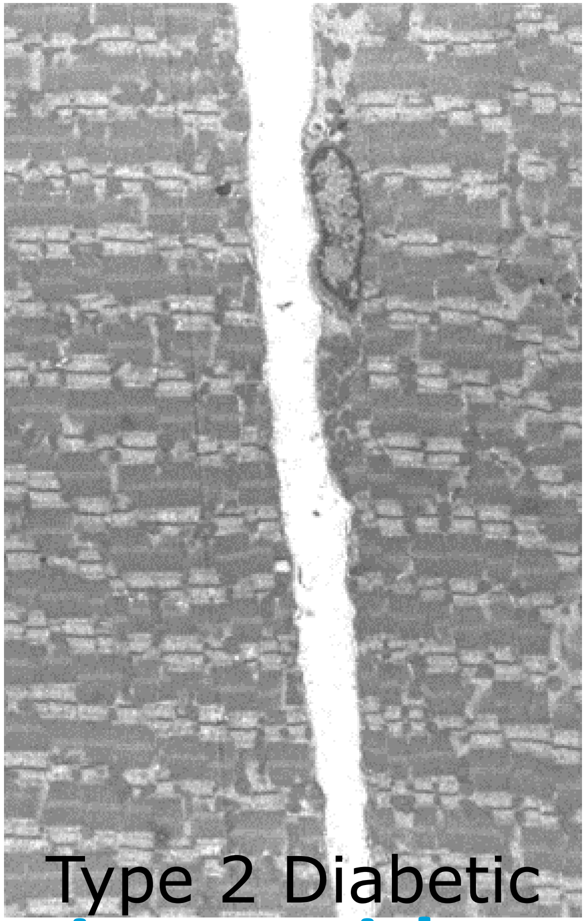
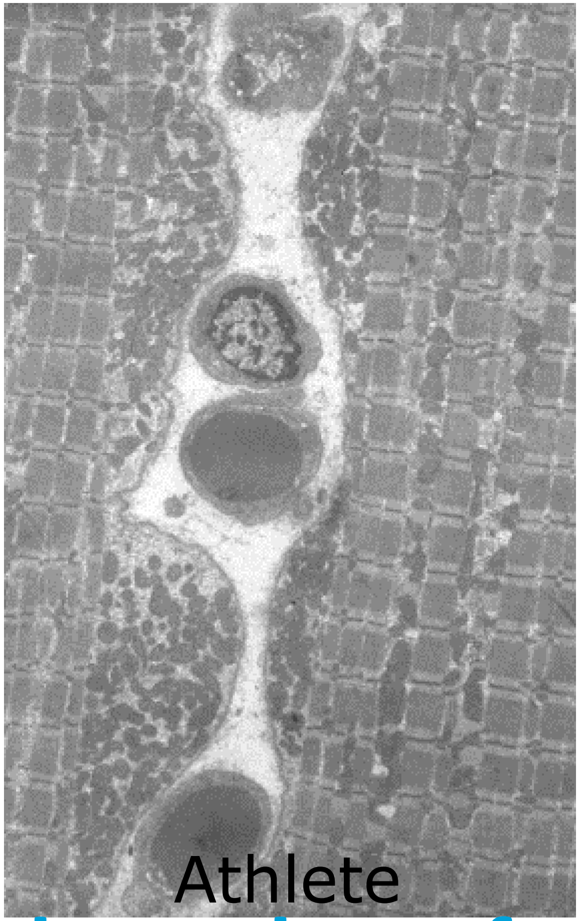
Wallberg-Henriksson, Diabetes Care 1992

# Skeletal muscle is responsible for ~80% of glucose uptake after a meal

- Myocellular insulin resistance is central in the development of type 2 diabetes mellitus
- Muscle can burn glucose and fat in mitochondria

# …however…




**Patients with type 2 diabetes have fewer mitochondria, which also work poorly…**

**Q: What is the effect of exercise training on mitochondrial function and insulin sensitivity?**



Meex et al., Diabetes 2010

# Subject characteristics…

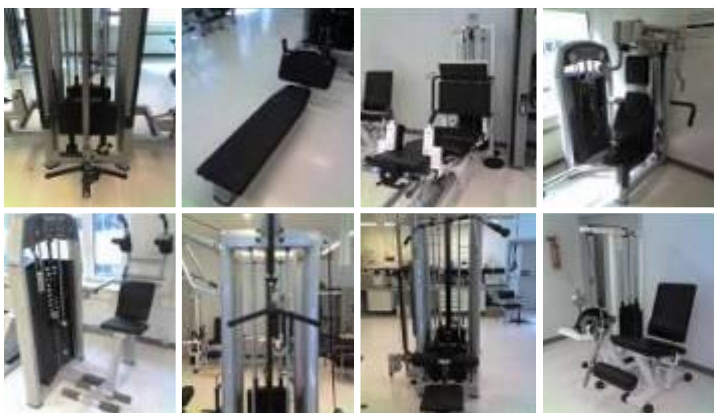
20 control subjects (fasting glucose level < 7.0; 2-hours glucose < 7.8)
18 type 2 diabetics (fasting glucose level > 7.0; 2-hours glucose > 11.1)

| | Controls (n = 20)<br>At baseline | Diabetics (n = 18)<br>At baseline |
|---|---|---|
| Age (Years) | 59 ± 1 | 59 ± 1 |
| Weight (kg) | 95 ± 3 | 94 ± 3 |
| Length (cm) | 179 ± 1 | 177 ± 1 |
| BMI (kg/m$^2$) | 30 ± 1 | 30 ± 1 |



Meex et al., Diabetes 2010

Screening | Baseline measurements | Training 12 weeks | Post intervention measurements



<u>Resistance training:</u> 1x/week, 8 exercises
1 set, 8 repetitions, 50% of MVC
2 sets, 8 repetitions, 75% of MVC

<u>Endurance training:</u> 2x/week.
30 minutes on 55% of max power output


- Progressive training program
- 5 minutes of warming up and cooling down before and after every training session on 45% of max power output on the ergometer
- Supervised training and heart rate monitored

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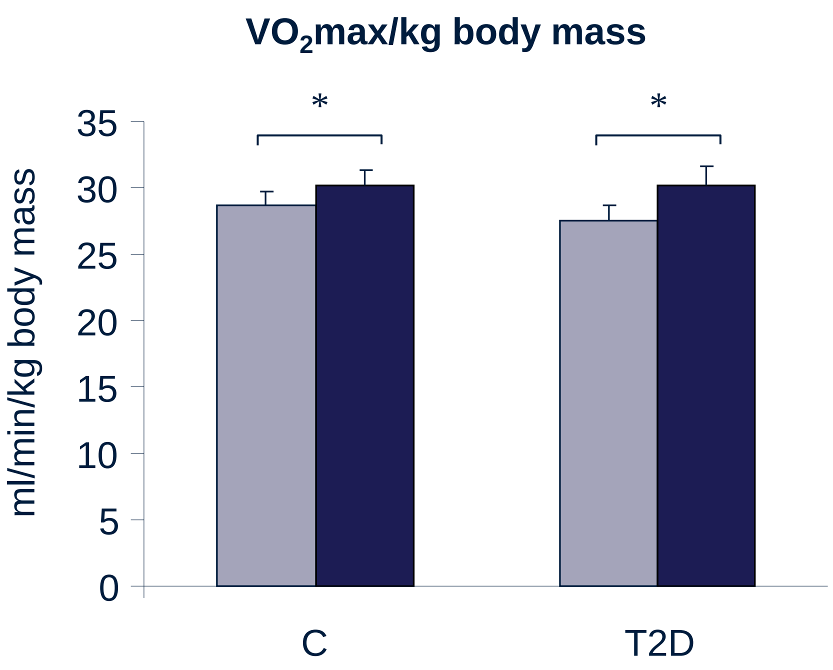
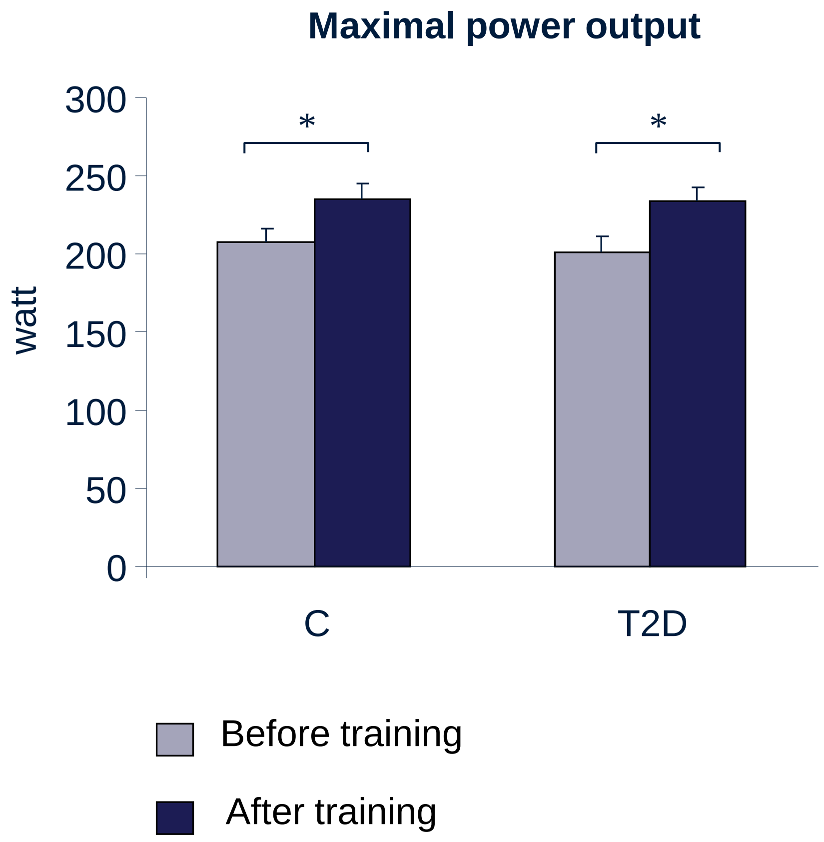
Meex et al., Diabetes 2010

# Training improves fitness




Data are means ± SE

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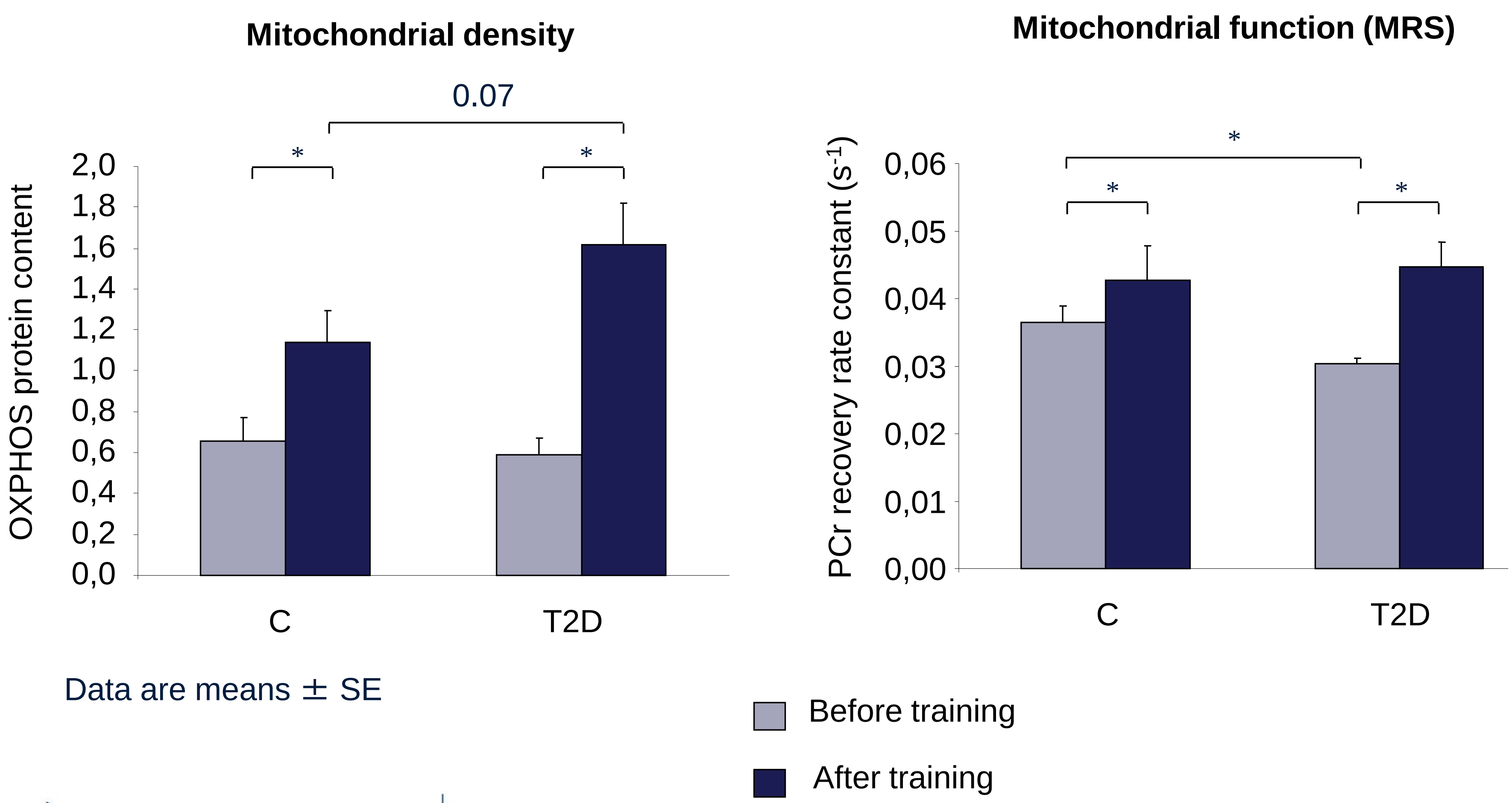
Meex et al., Diabetes 2010

# Training restores mitochondrial density and function




Data are means ± SE

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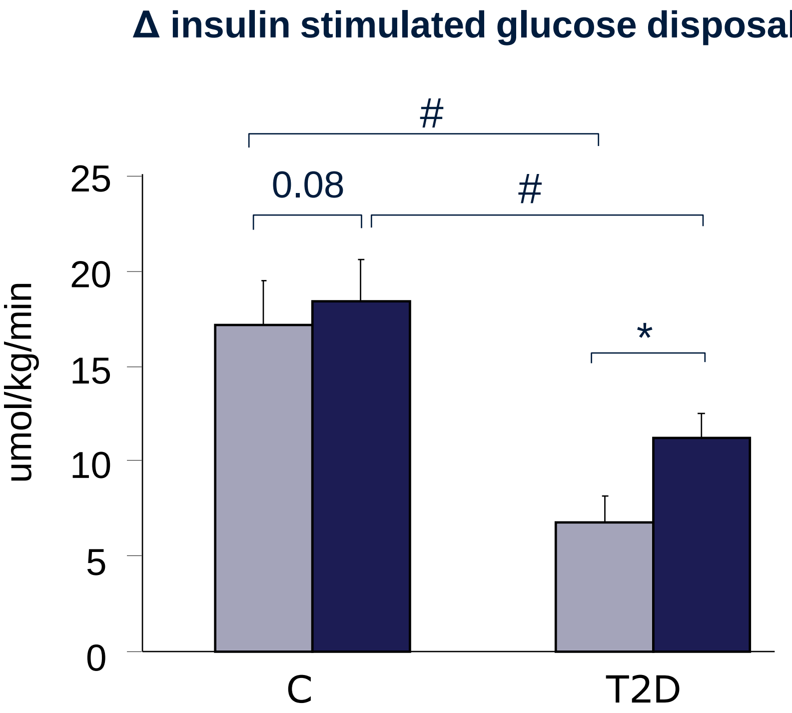
Meex et al., Diabetes 2010

# Training improves (but not restores) insulin sensitivity in T2D




Data are means ± SE

# significant different from C

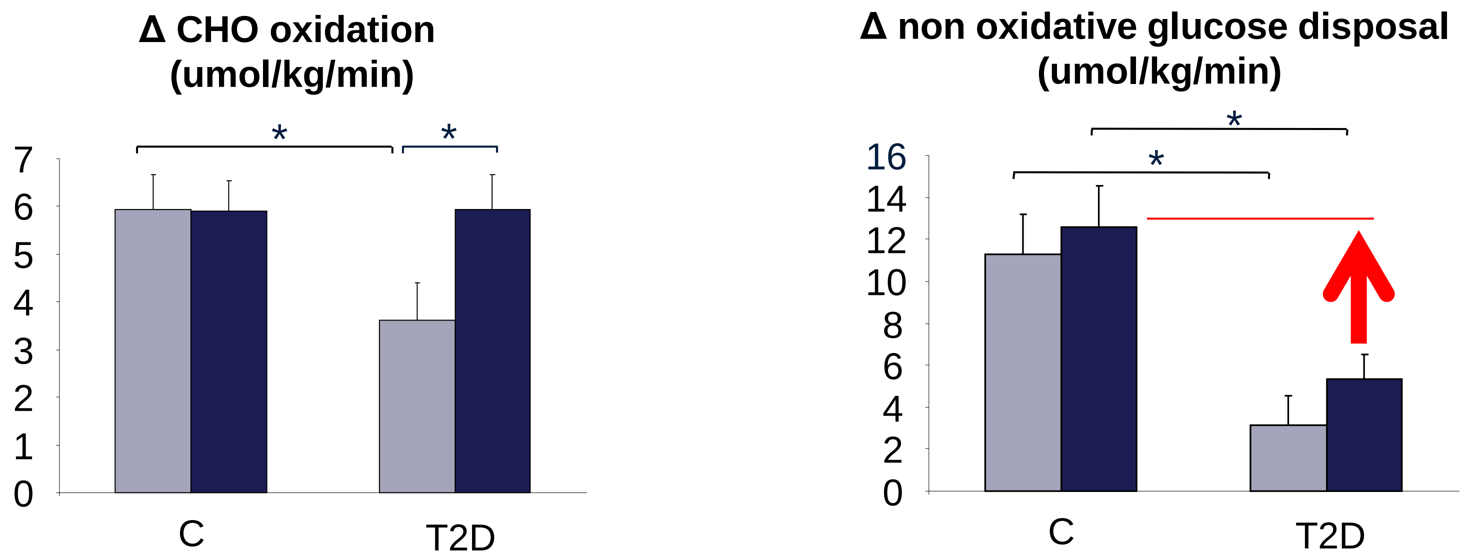
Before training

After training



Meex et al., Diabetes 2010

# Improvement in insulin sensitivity entirely due to improved oxidative glucose disposal




Data are means ± SE

Before training After training

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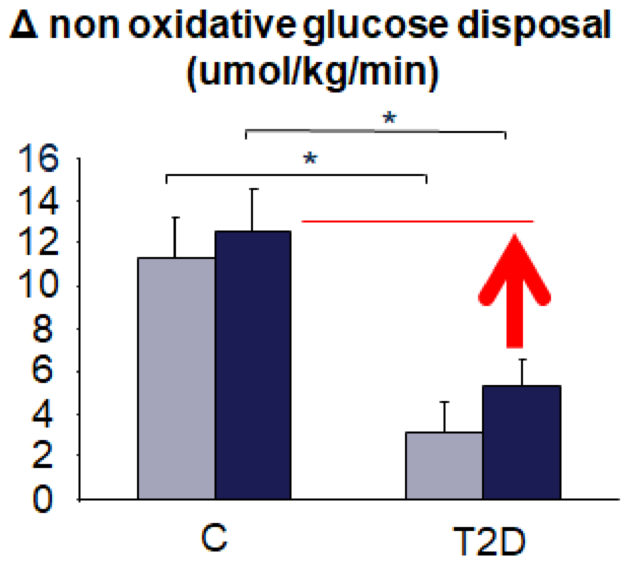
Meex et al., Diabetes 2010

# Summary

- Insulin sensitivity improves by training
- This is due to increased oxidative glucose disposal
- Improvements in non-oxidative glucose disposal are warranted for complete restoration of insulin sensitivity
- Exercise training improves insulin sensitivity of adipose tissue and liver (data not shown)
- Exercise training improves metabolic flexibility

- All these favorable changes occur without major changes in body mass (modest albeit significant increase in lean mass)

**Q: Can we adjust the training program to also hit the non-oxidative glucose disposal?**



# HIIT it hard....

Background

- Repeated high intensity interval training (HIIT) is ‘the conventional way’ to augment glycogen (re)synthesis
- Insulin-mediated non-oxidative glucose disposal (glycogen synthesis) is insufficiently affected by ‘conventional’ exercise training

# HIIT it hard….

Aim

- Can a supervised HIIT period (12 weeks) improve NOGD and 24 hour glucose profile in insulin-resistant subjects.

*Sub aims*

- *Examine if timed -post-HIIT- ingestion of a PH-CHO drink throughout a supervised HIIT period (12 week) prevents adverse effects on blood glucose levels, energetic feelings and mood state*

# Study design

N = 25
Males/females
BMI= 28-35 kg/m$^2$
Sedentary
No T2DM

Randomization
2 Paired training groups

Group 1

3/w
1m cycling at
~80-90% Wmax,
2m resting,
10 times

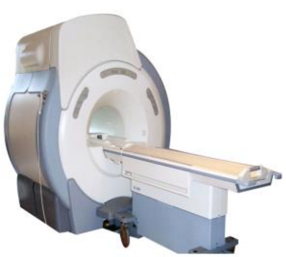

Group 2

3/w
1m cycling at
~80-90% Wmax,
2m resting,
10 times

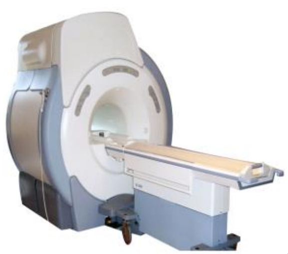

Pre and Post training tests

Hyperinsulinemic-euglycemic clamp:
Rd, CHOox, NOGD, EGP

$^1$H-MRS
Liver fat content and composition



$^{31}$P-MRS
Skeletal muscle oxidative capacity



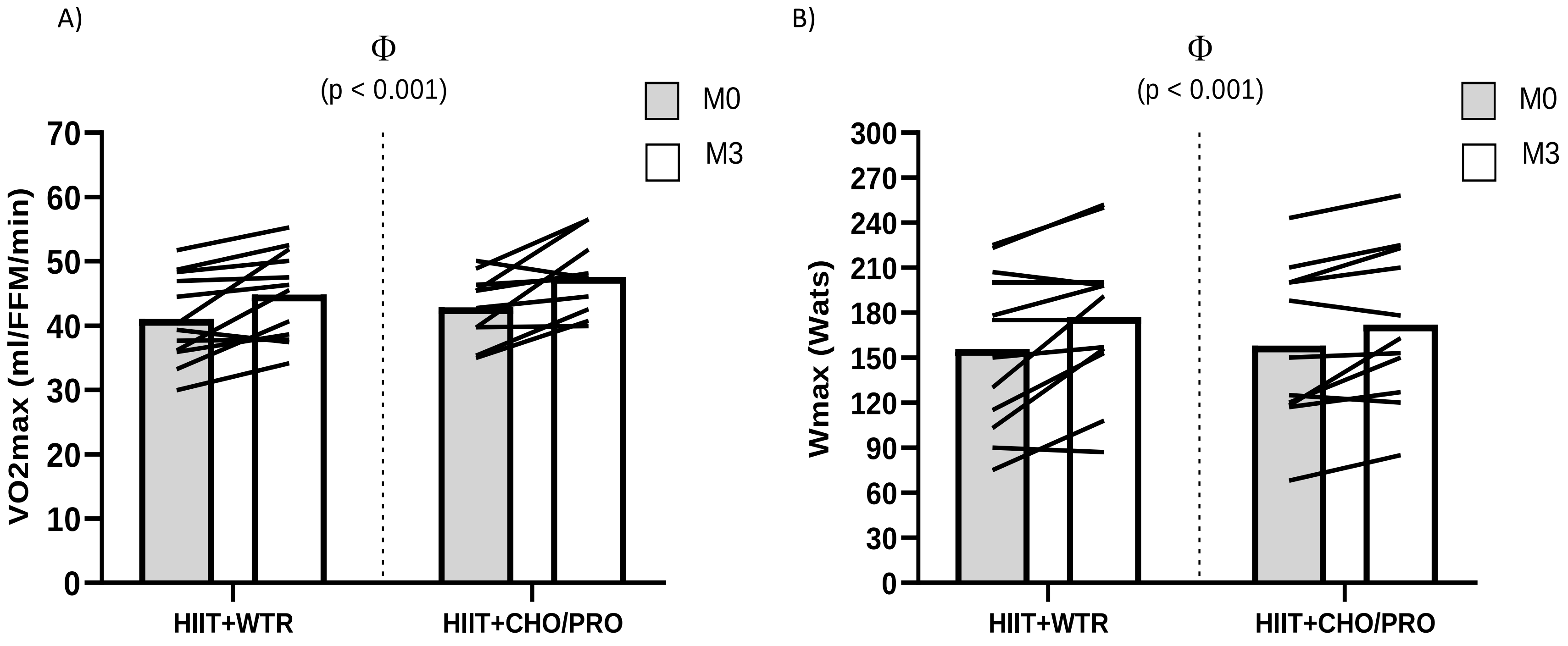
Body composition and VO2max

# Participants characteristics

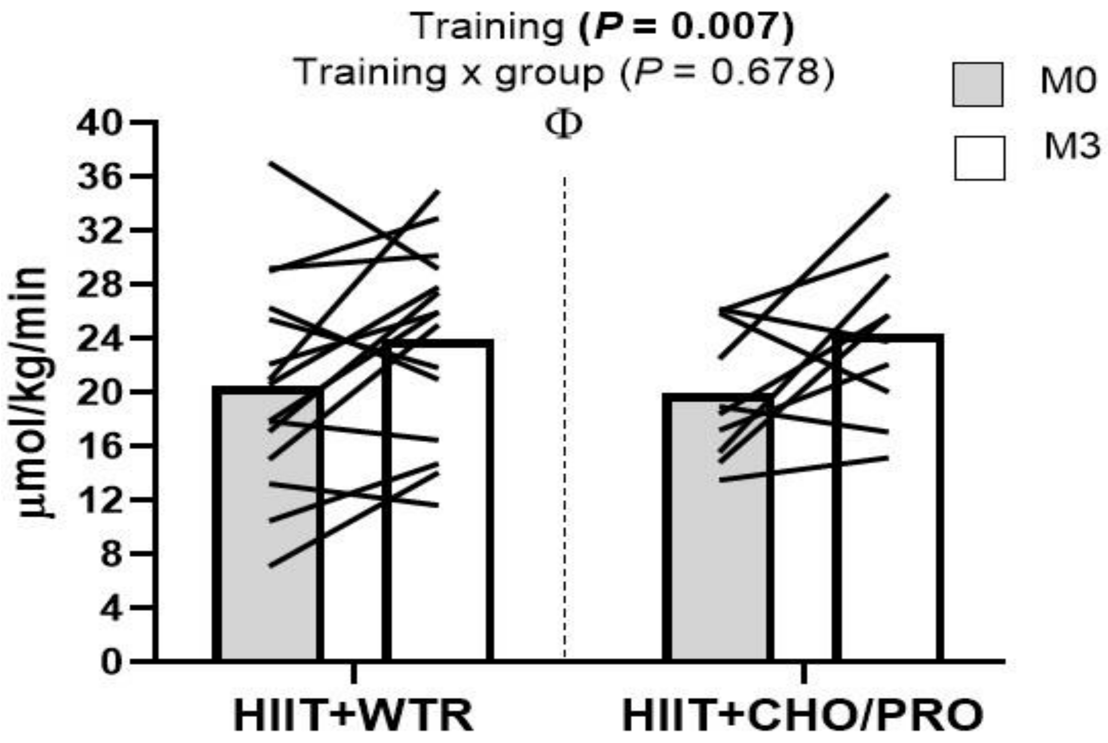
| | HIIT + WTR | HIIT + CHO/PRO | P value |
|---|---|---|---|
| Sample size (f/m) | 8/6 | 6/5 | 0.85 |
| Age (yr) | 61 ± 8 | 65 ± 7 | 0.22 |
| Body weight (kg) | 92.6 ± 15 | 86.3 ± 13 | 0.29 |
| BMI ($kg/m^2$) | 32.4 ± 3.2 | 31.0 ± 3.3 | 0.34 |
| Fat mass (Kg) | 39.4 ± 7.6 | 36.8 ± 11 | 0.54 |
| FFM (Kg) | 53.2 ± 14 | 49.5 ± 9 | 0.45 |
| VO2max (ml/FFM/min) | 41 ± 7 | 43 ± 5.3 | 0.50 |
| Fasting Glucose (mmol/L) | 5.5 ± 0.3 | 5.3 ± 0.3 | 0.25 |
| M value (µmol/min/FFM) | 54.6 ± 5 | 53.4 ± 5 | 0.80 |
| Training compliance (%) | 99.5 ± 1.6 | 97.2 ± 4.1 | 0.09 |

WTR: Water, CHO/PRO: Carbohydrate + Protein

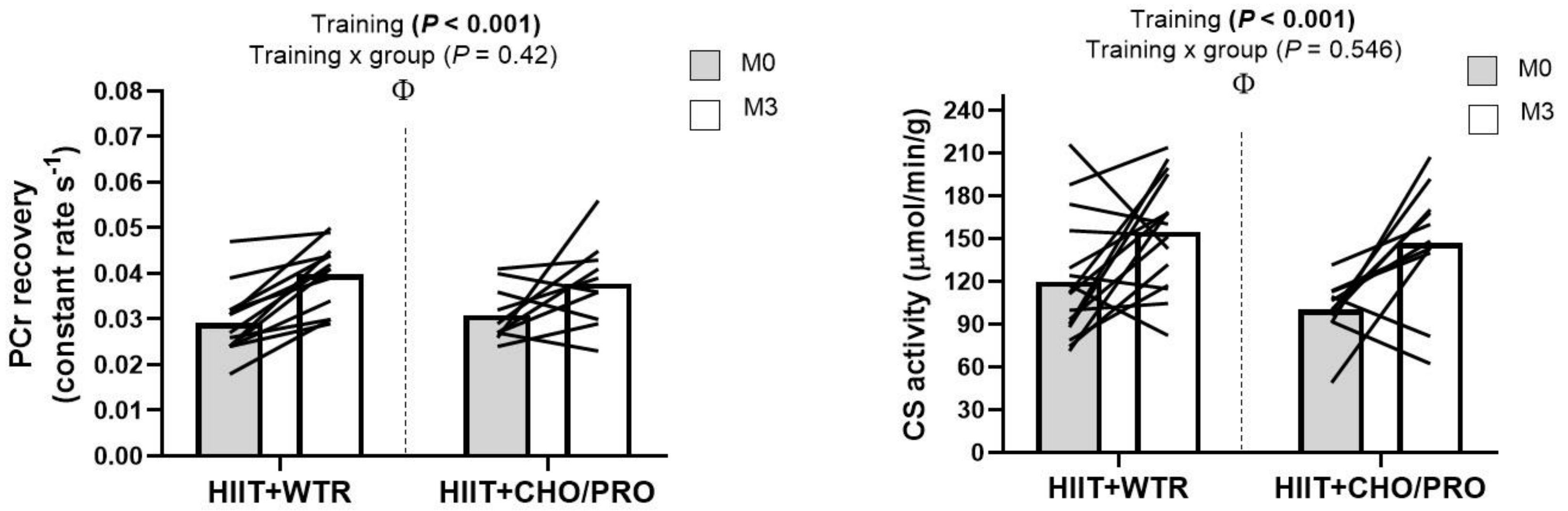
# HIIT improves fitness



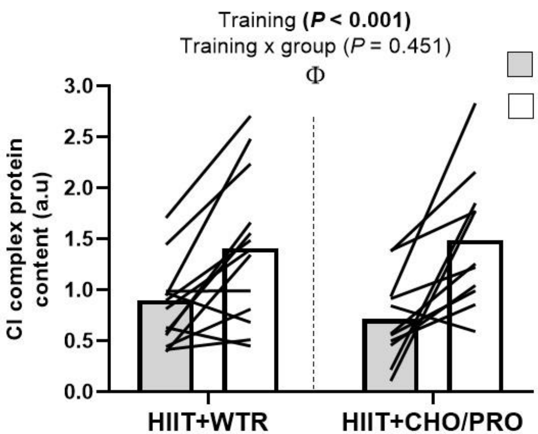
# HIIT improves oxidative glucose disposal

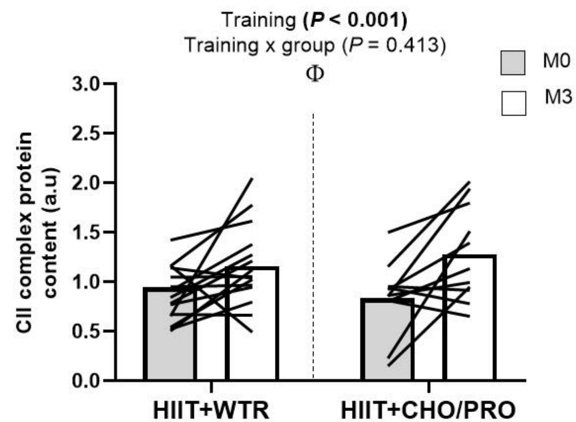


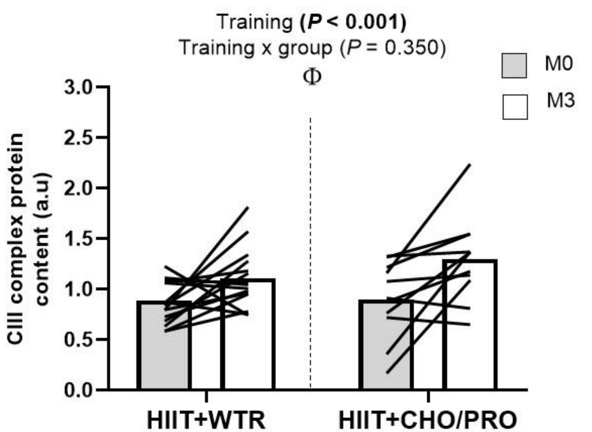
# HIIT improves mitochondrial function and capacity

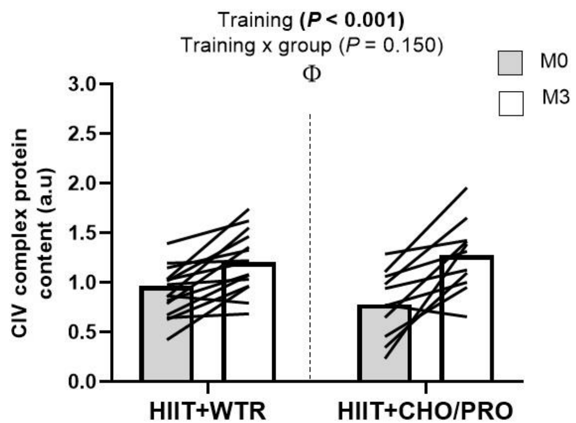


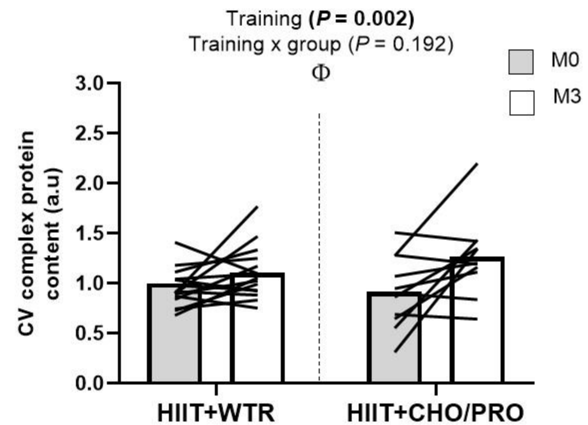
# HIIT increases mitochondrial density

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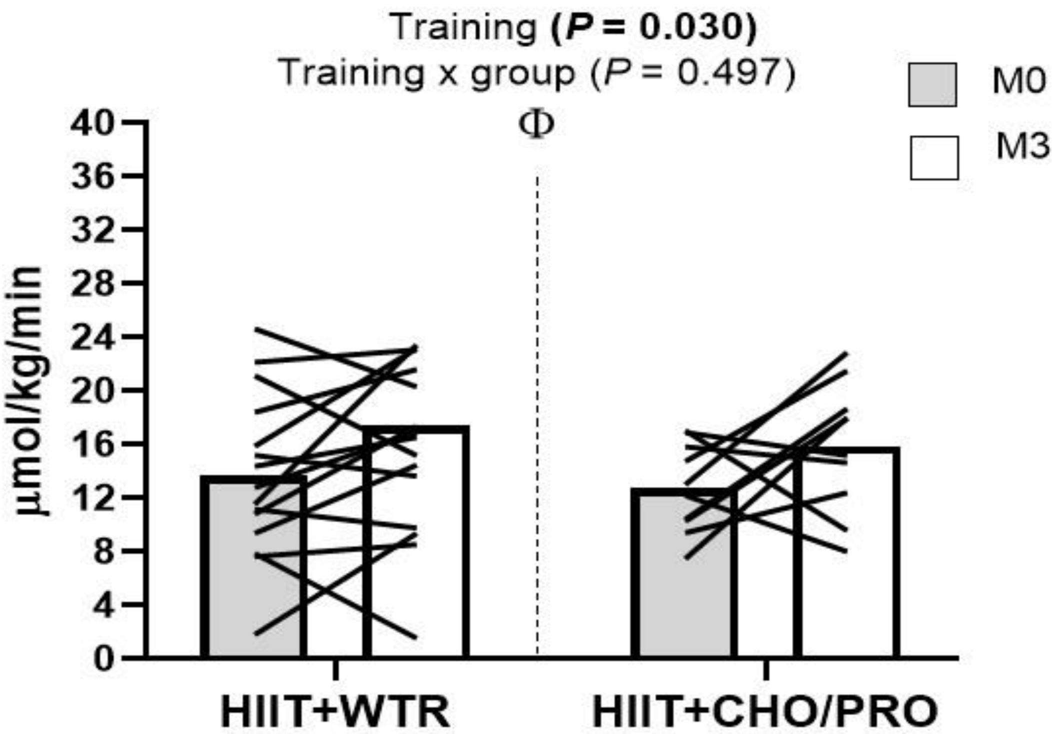
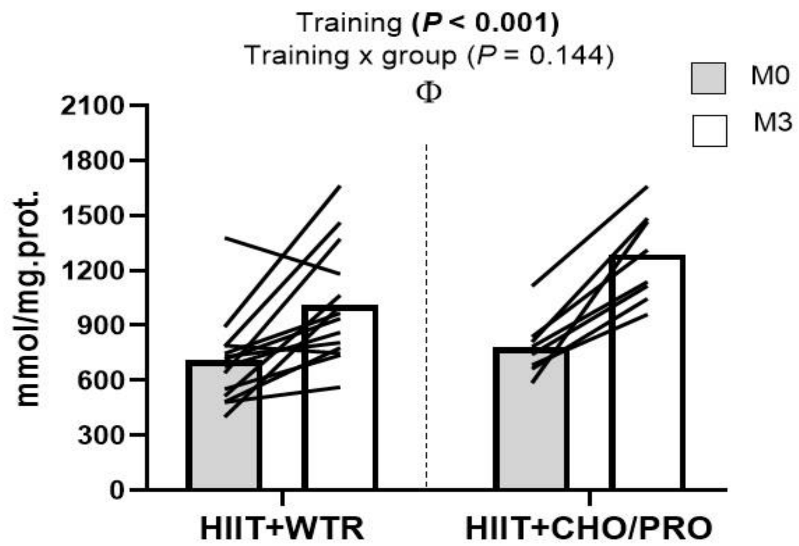
Thesis defense by Rodrigo Mancilla, Feb 10, 16.00, 2022

# HIIT improves non-oxidative glucose disposal

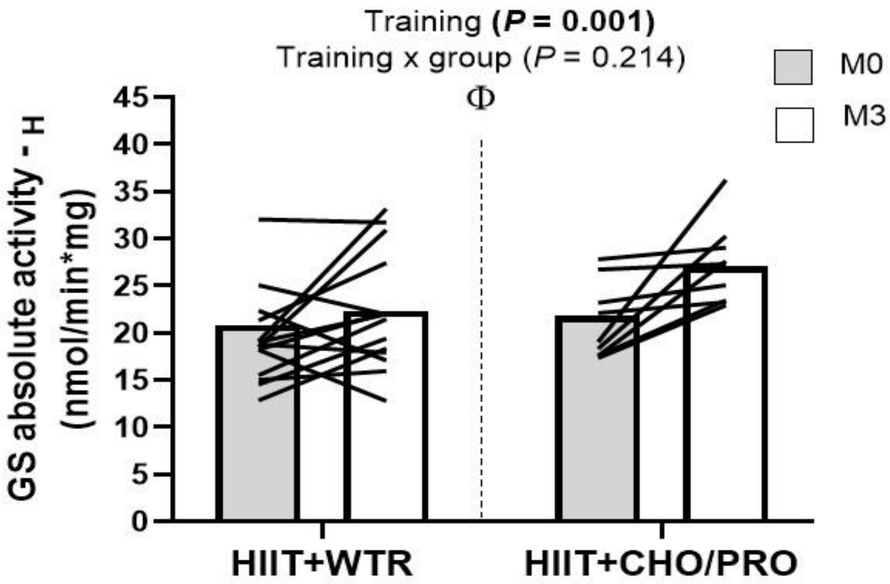


# HIIT increases glycogen synthesis capacity in skeletal muscle

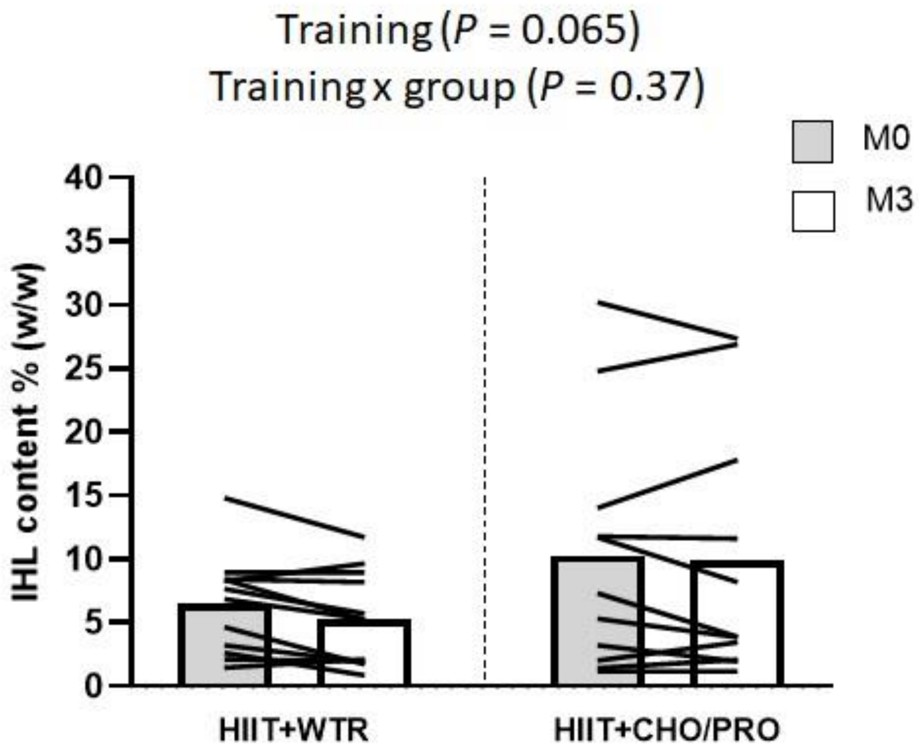
Glycogen content - Insulin stimulation



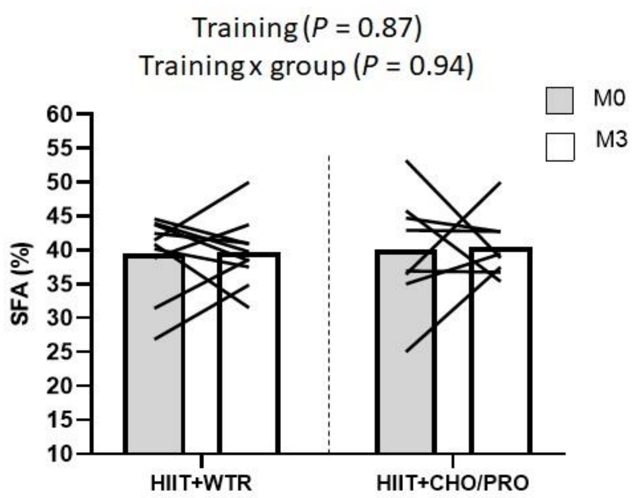

GS activity – Insulin stimulaton

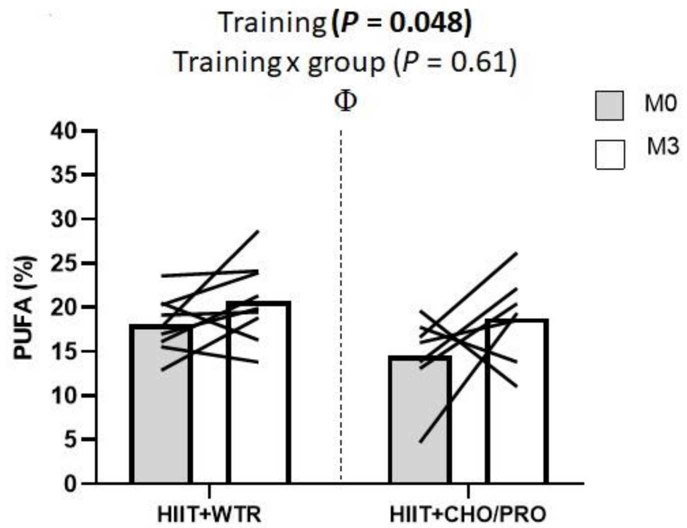


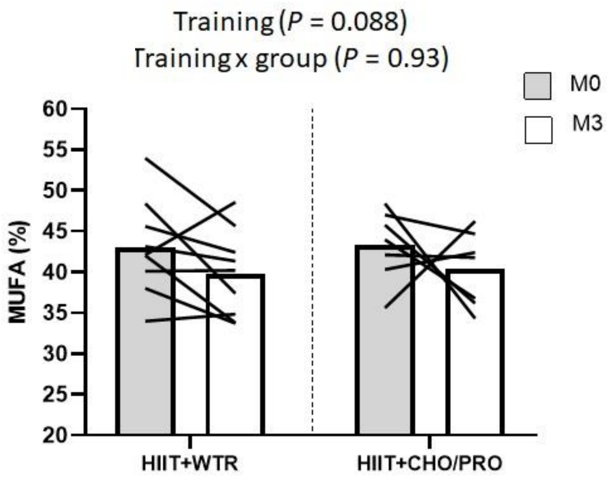
# HIIT does not affect total intrahepatic fat content…



# … but does affect intrahepatic fat composition

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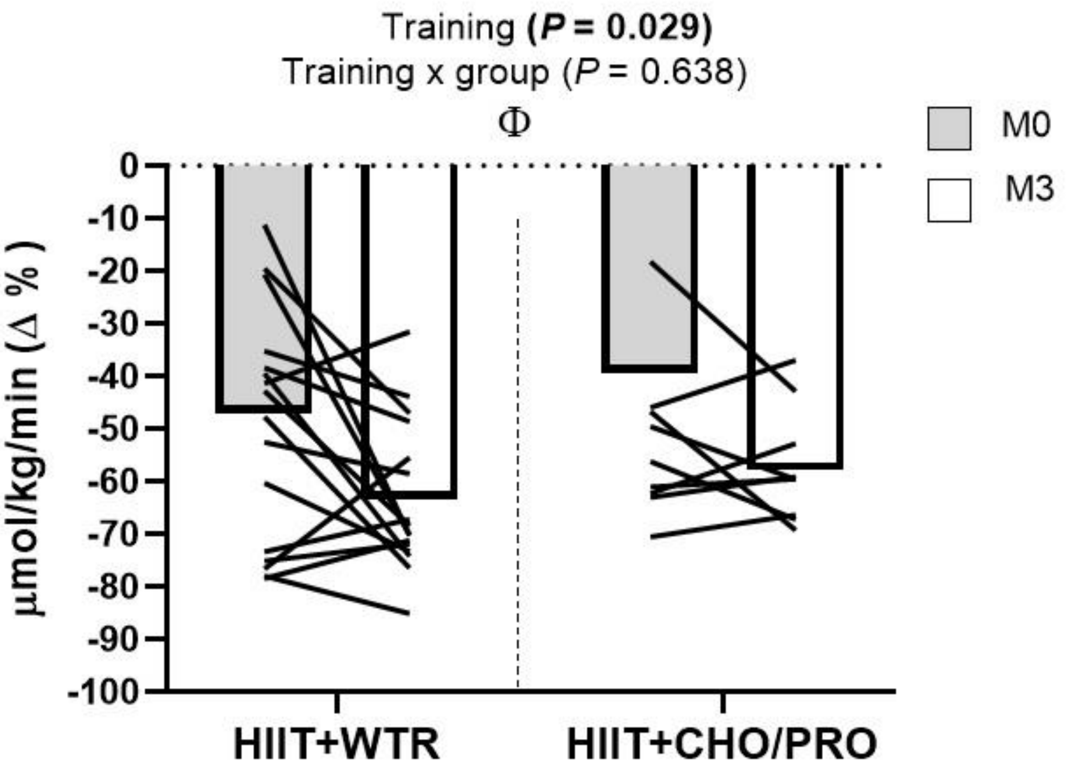
# HIIT improves hepatic insulin sensitivity



# Summary

- HIIT is less time consuming and highly appreciated by the participants (might be selection bias)…
- HIIT improves Insulin sensitivity, **also non-oxidative glucose disposal**
- HIIT improves mitochondrial function, capacity and density
- HIIT improves metabolic flexibility
- HITT favorably changes liver fat content (change towards a higher fraction PUFA/MUFA) no change in SFA (data not shown)
- HIIT improves hepatic insulin sensitivity
- HIIT improves adipose tissue insulin sensitivity **(only water condition!)**

- All these favorable changes occur without changes in body mass

**Q: But hey, I hate to exercise… can't you come up with something more appealing?**

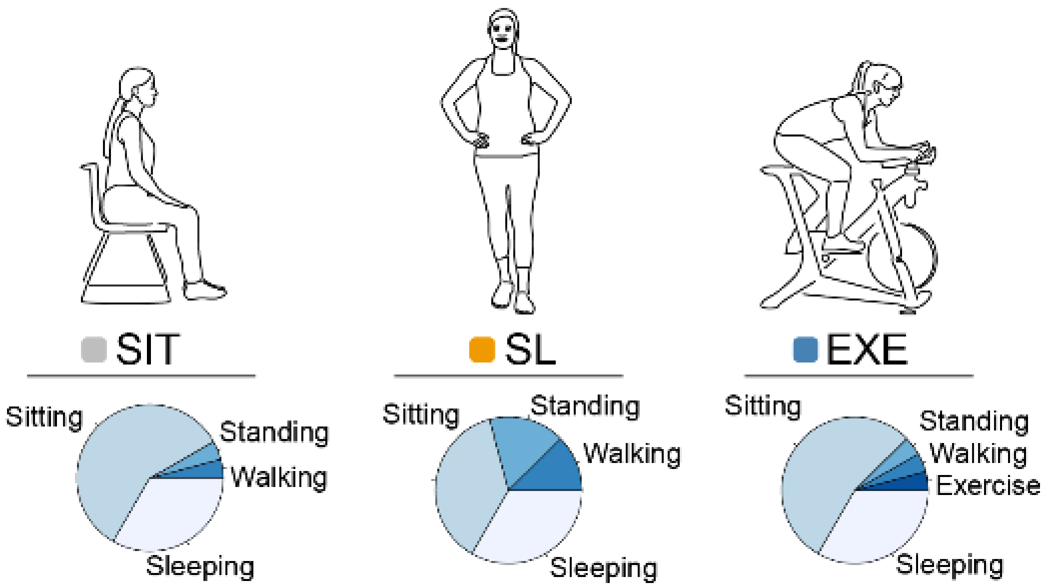
# Dutch Physical Activity Guidelines (2017)

- Physical activity is good for you – the more, the better
- **Engage in physical activity of moderate intensity for at least 150 minutes every week, spread over several days (often interpreted as 5*30 minutes)**
- Engage in activities that strengthen your muscles and bones at least twice a week. Older people should combine these with balance exercises
- **Avoid long periods sitting down**



Weggemans et al., Int J of Behav Nutr and Phys Act, 2018

# We sit way more than we move.
# How about reducing time spent sitting?

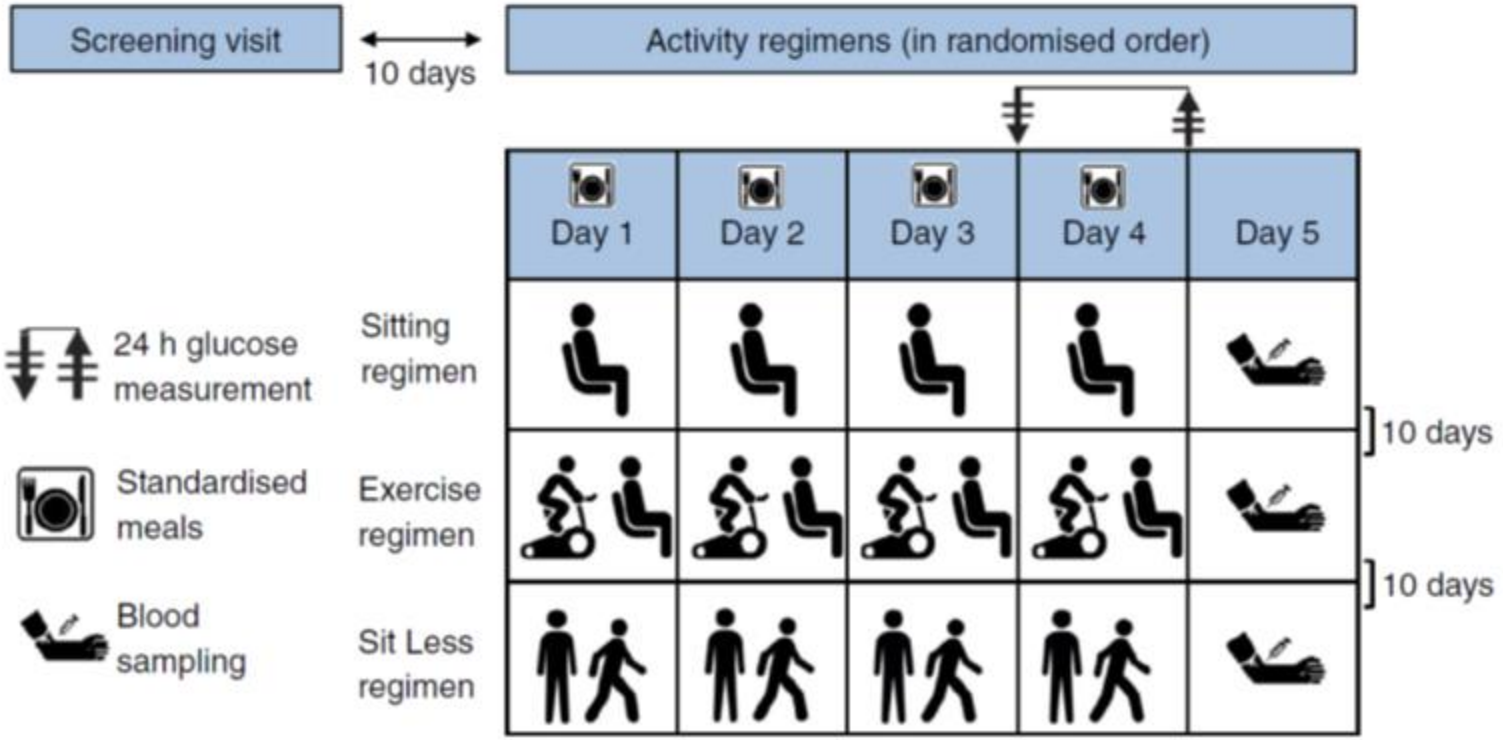



- Keep sleep constant throughout all conditions
- Adhere to the 30’ exercise /day guideline
- Reduced sitting time in the sit less (SL) condition and increased ambulatory time (standing and sitting) energetically equal to 30’ exercise (EXE)
- 4 consecutive days



Duvivier et al., Diabetologia 2017

# Design

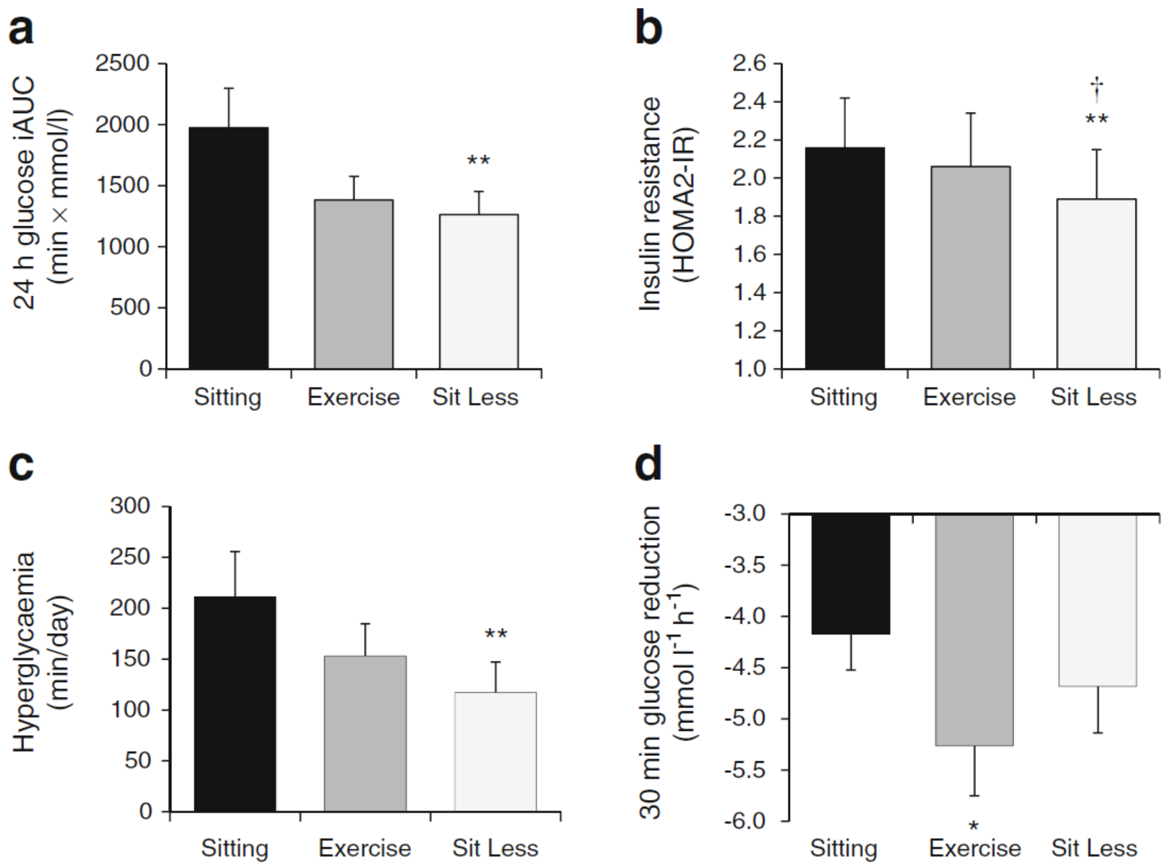





Duvivier et al., Diabetologia 2017

# Sit-less improves 24 hours glucose control

## in individuals with type 2 diabetes (Duvivier, Diabetologia 2017) and in young healthy lean (Duvivier, Plos One 2013)

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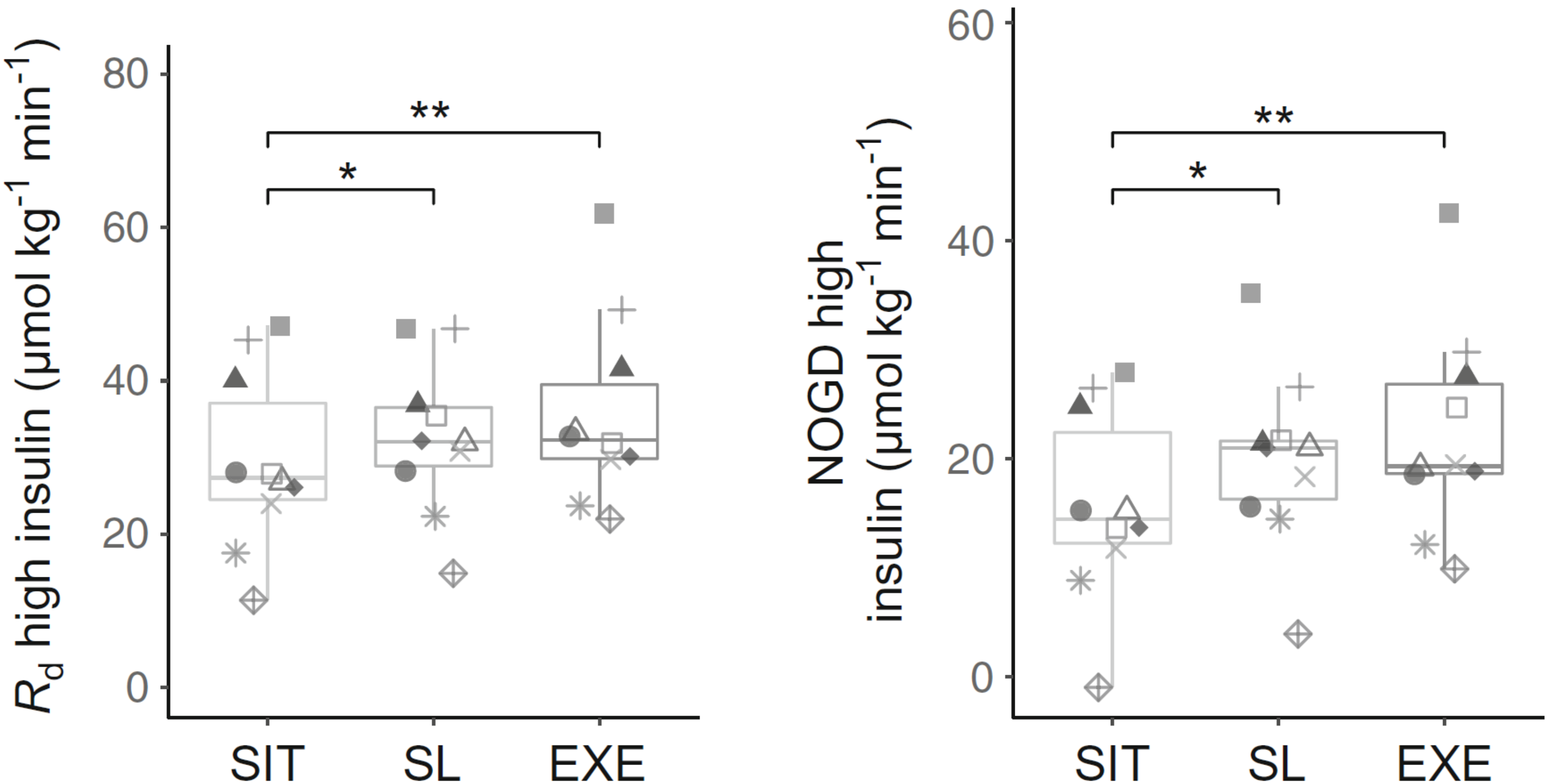
Duvivier et al., Diabetologia 2017

# Q: How about insulin sensitivity?

# Sit-less improves insulin stimulated glucose uptake

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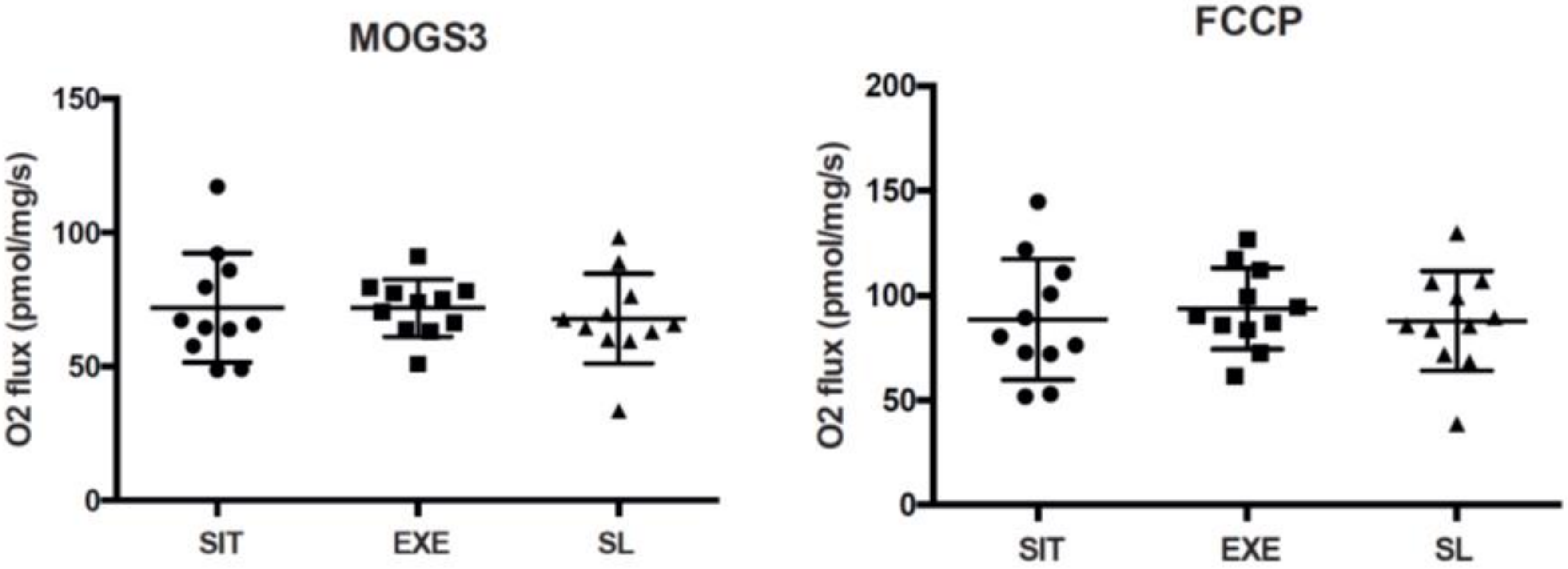
Remie et al., Diabetologia 2021 in press

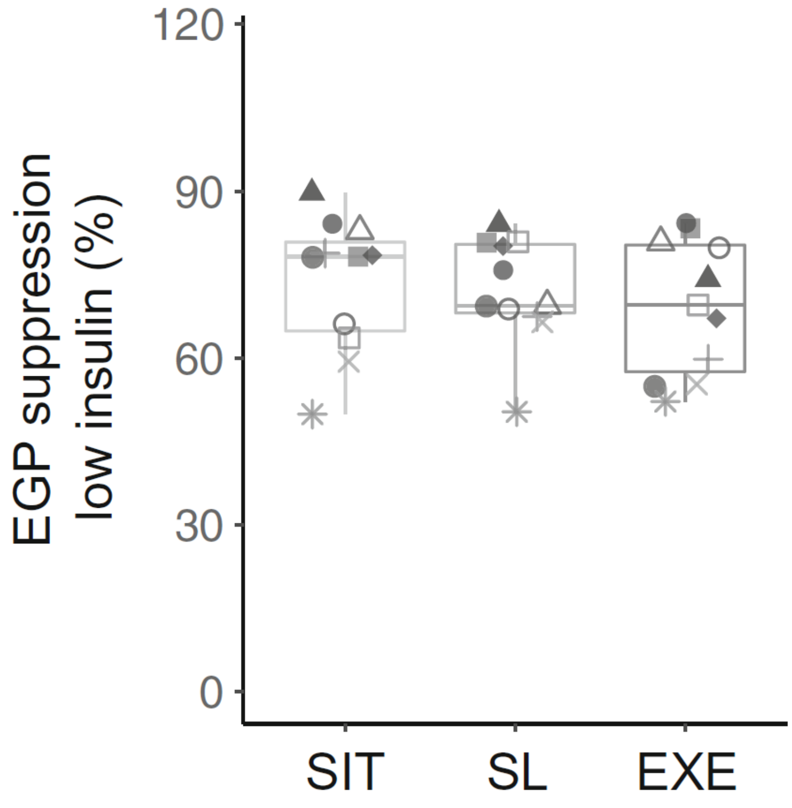
# No effect on mitochondrial function

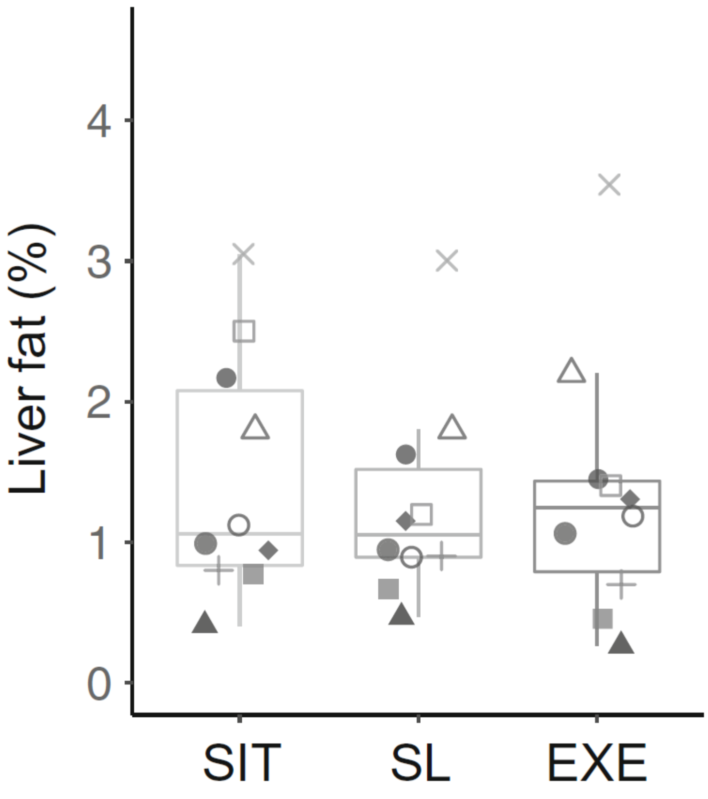





Remie et al., unpublished

# No effect on liver fat or liver insulin sensitivity

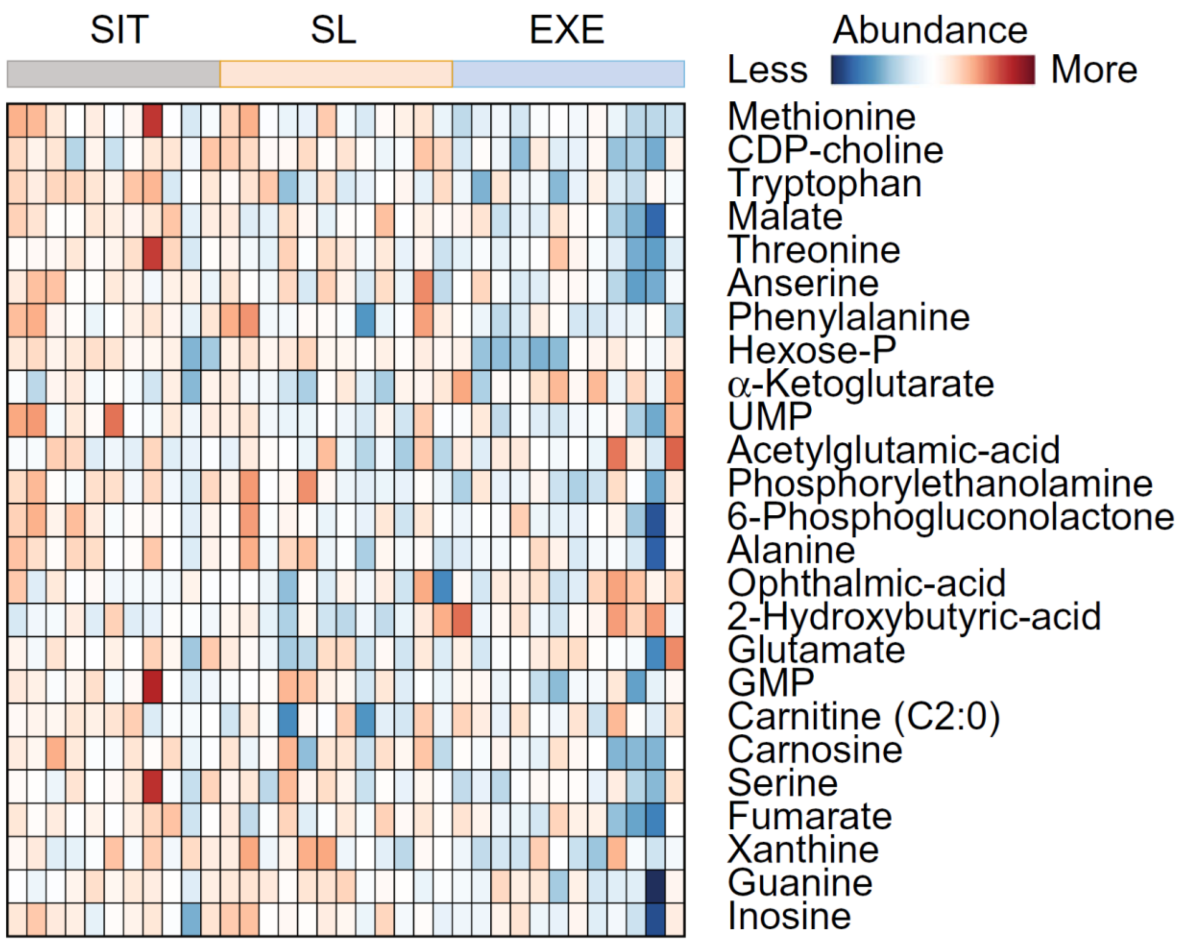





Remie et al., Diabetologia 2021 in press

# Myocellular metabolite responses to sit-less are similar to exercise-mediated responses

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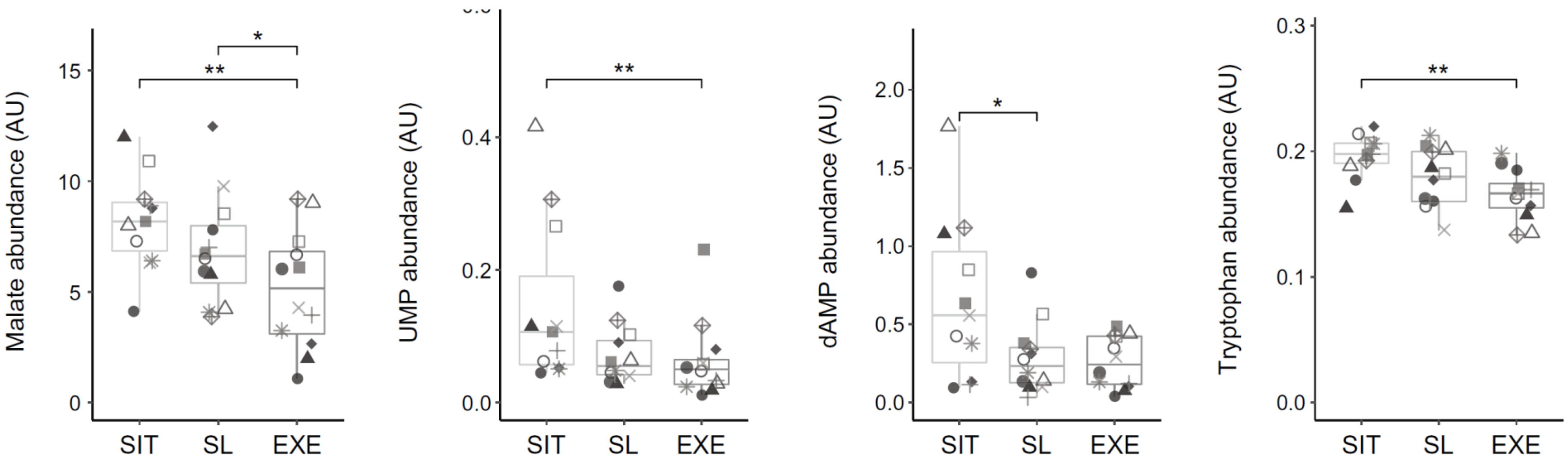
Remie et al., Diabetologia 2022

# Myocellular metabolite responses to sitting less are similar to those produced by exercise

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Remie et al., Diabetologia 2022

# Summary

- Exchanging sedentary time standing and walking for 4 days improves peripheral insulin sensitivity
- Exercise and sitting less revealed similar physiological effects on insulin sensitivity
- Exercise and sitting less revealed similar underlying molecular metabolic changes in skeletal muscle
- Sit less induces a shift in muscle metabolites similar to what is being observed after exercise

- Sustained replacement of sitting time by standing and walking can be an alternative to moderate to vigorous exercise to improve metabolic health

# Conclusion

- A wide range of exercise modalities improve glucose homeostasis partly via distinct mechanism
- Exercise-mediated improvements in parameters other than glucose homeostasis have not yet been extensively been analysed, but are likely to be more modality dependent (e.g. cardiac output and related cardiometabolic health and muscle mass are unlikely improve upon sit-less)

# Take home message

- A run in the park… will help
- Going ‘all-out’ for just a couple of minutes per day… will help
- Breaking the day by walking the dog… will help

# Thanks to the DMRG team

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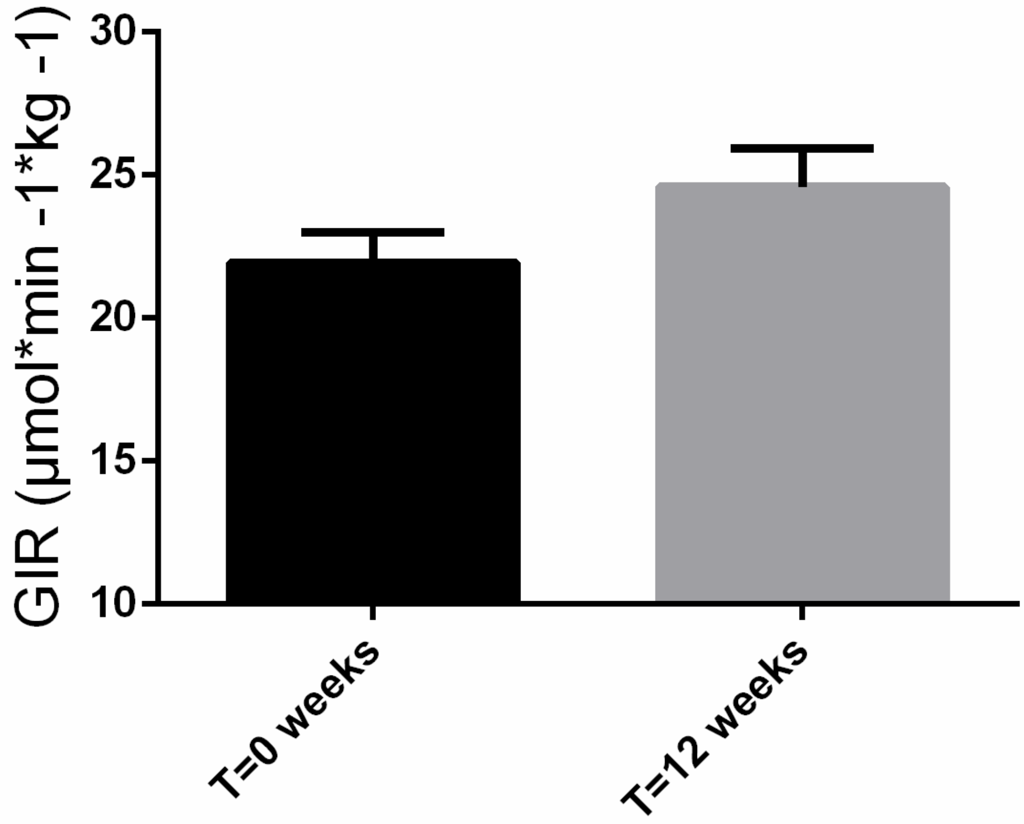
# Q: Do we all benefit?

# Exercise improves insulin sensitivity

**mean improvement in glucose infusion rate:**

**13% in 71 individuals**

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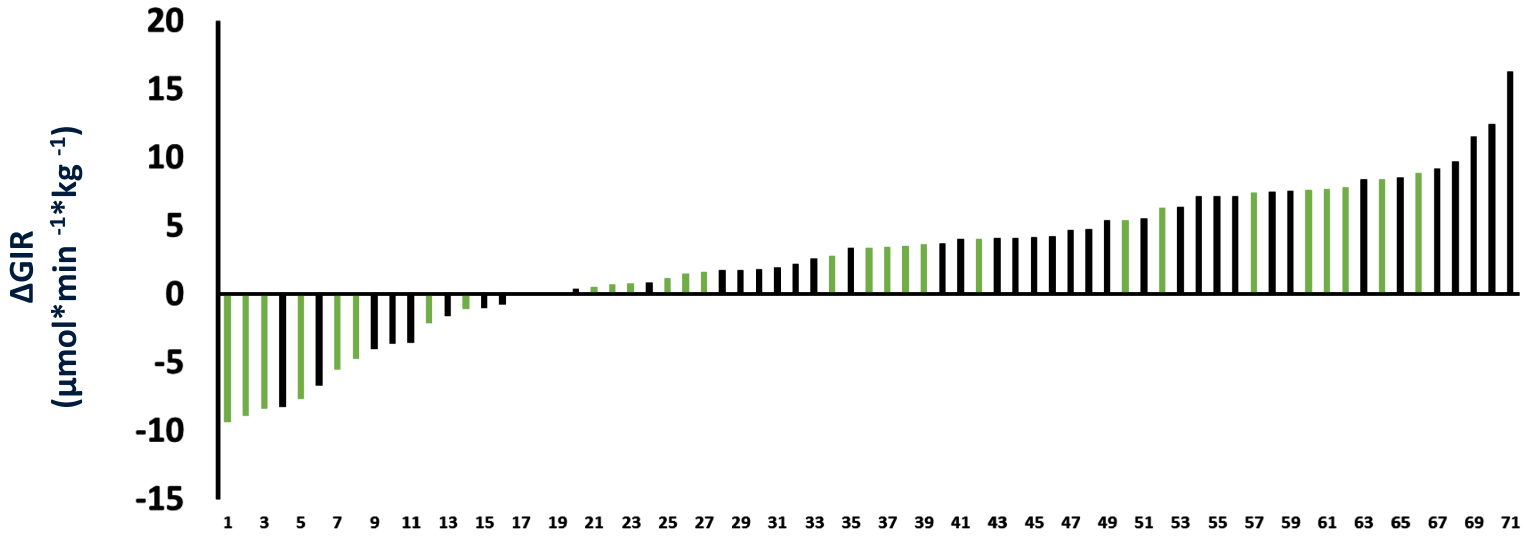
# Individual responses in GIR of the 71 participants




Green bars T2DM, black bars normoglycemic individuals

www.dmrg.nl unpublished

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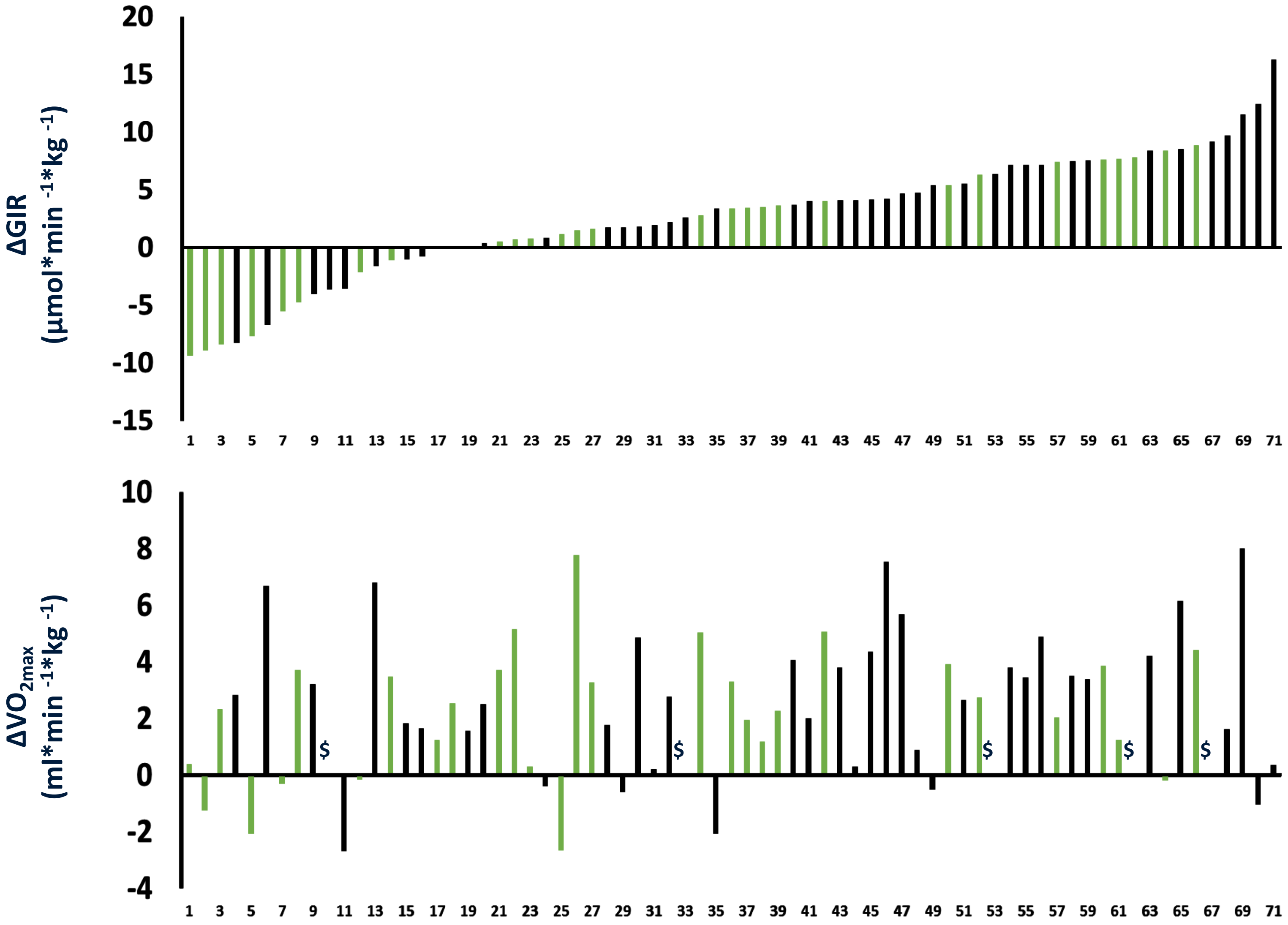
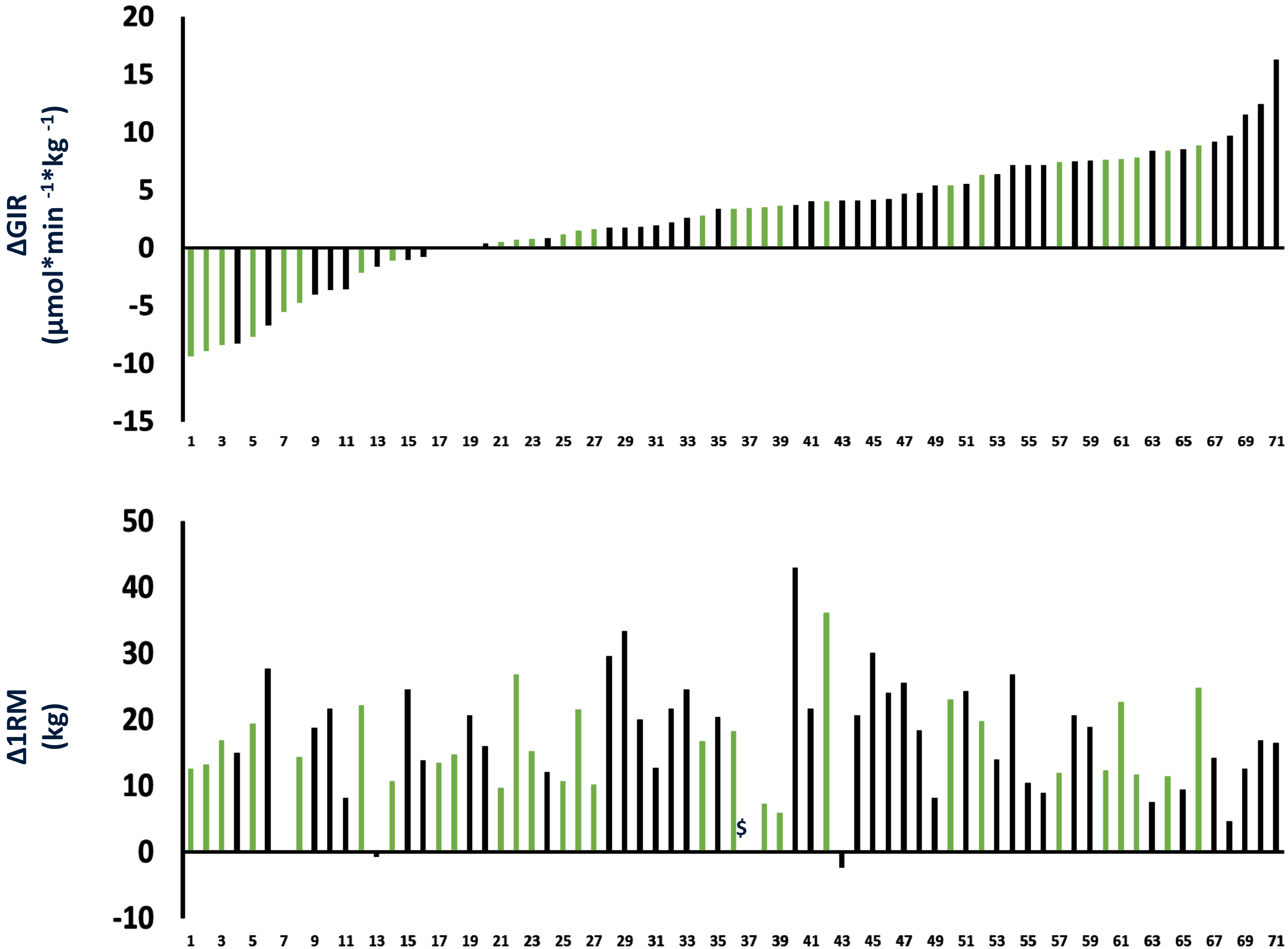
# Response heterogeneity not due to change in $VO_2$ max



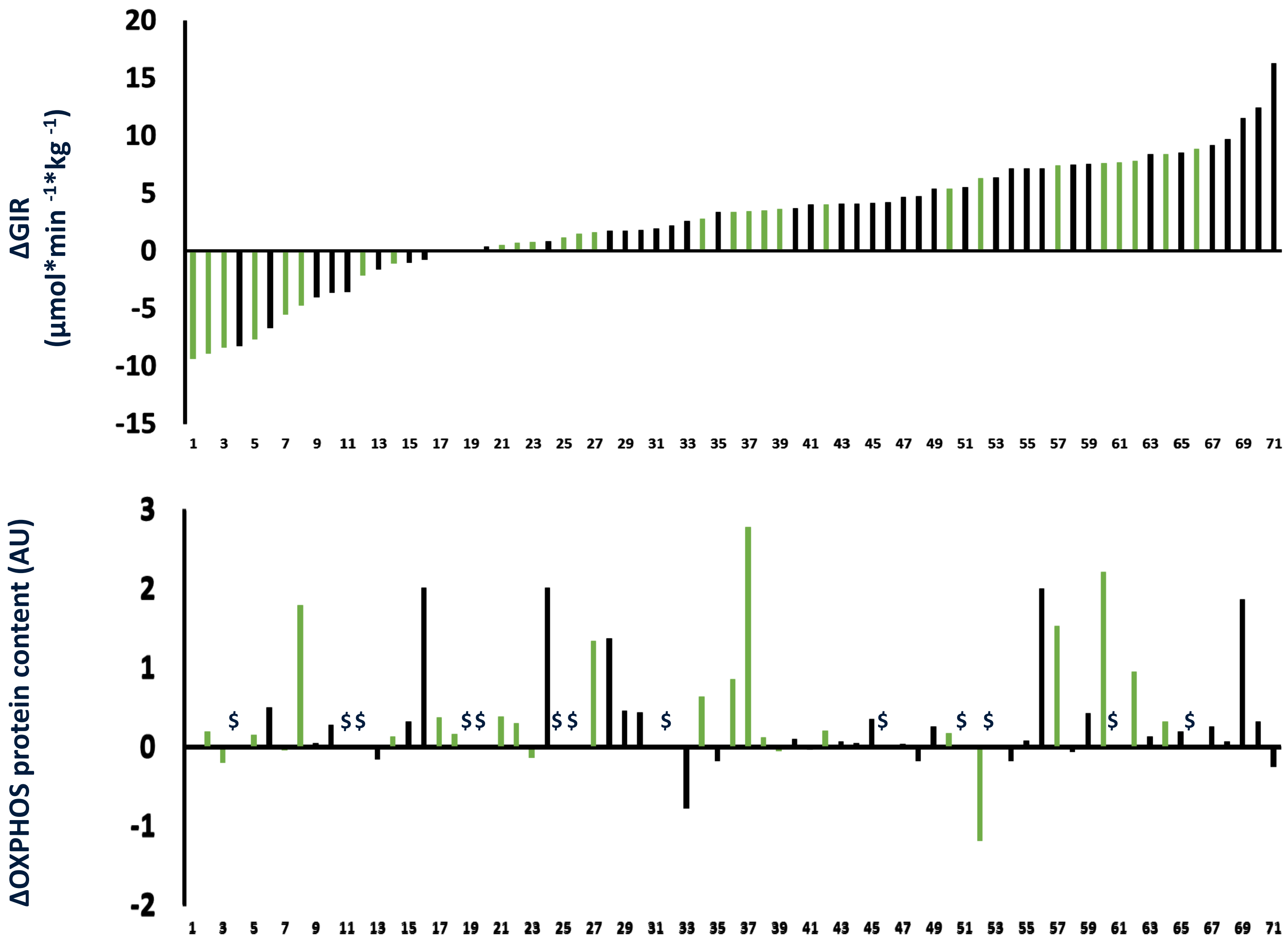

Maastricht University | Maastricht UMC+

www.dmrg.nl unpublished

# Response heterogeneity not due to change in strength



# Response heterogeneity not due to change in OXPHOS



# Summary

- Response on insulin sensitivity upon exercise training is rather heterogeneous
- Seventeen individuals (23.9%) did not -or responded negatively- on GIR upon 12 weeks of training (not taken TE into account)
- Baseline characteristics were similar for ‘responders’ and ‘non-responders’
- ‘Non-responders’ on GIR were responsive on other classical markers for training response, so they did train!
- Factors (yet) unidentified may contribute to exercise response heterogeneity.

# Q: Morning or afternoon training for optimal benefit?

# Retrospective analysis of previous studies

- Twelve weeks combined aerobic resistance exercise
- Thirty-two males at risk for or diagnosed with type 2 diabetes (BMI > 26 $kg/m^2$)
- Twelve individuals did all their training sessions between 08:00 and 10:00 (AM group)
- Twenty individuals did all their training sessions between 15:00 and 18:00 (PM group)
- Compliance with the exercise training averaged 98%.
- Two step hyperinsulinemic euglycemic clamp



Mancilla et al., Physiol Rep 2020

# Similar baseline characteristics prior to training

| | AM | PM |
|---|---|---|
| Sample size | 12 | 20 |
| T2D subjects | 4 | 8 |
| NAFL subjects | 3 | 6 |
| Healthy obese subjects | 5 | 6 |
| Age (year) | 61 ± 5 | 57 ± 7 |
| Body weight (kg) | 94.7 ± 11.7 | 98.1 ± 10 |
| BMI (kg/m$^2$) | 30.3 ± 2.6 | 29.8 ± 2.3 |
| Fat mass (kg) | 27.4 ± 4.3 | 28.8 ± 5.6 |
| Fat percentage (%) | 28.6 ± 2.3 | 29 ± 3.2 |
| Trunk fat mass (kg) | 16.0 ± 2.5 | 16.2 ± 3.4 |
| Fat-free mass (kg) | 65.4 ± 7.2 | 67.1 ± 5.1 |
| $VO2_{max}$ (ml/kg/min) | 26 ± 4.0 | 26.5 ± 4.5 |
| $W_{max}$ (W/kg) | 1.9 ± 0.4 | 2.0 ± 0.3 |
| Fasting glucose (mmol/l) | 6.7 ± 2.1 | 6.8 ± 2.1 |
| Fasting-free fatty acids (μmol/l) | 566 ± 171 | 615 ± 169 |



Mancilla et al., Physiol Rep 2020

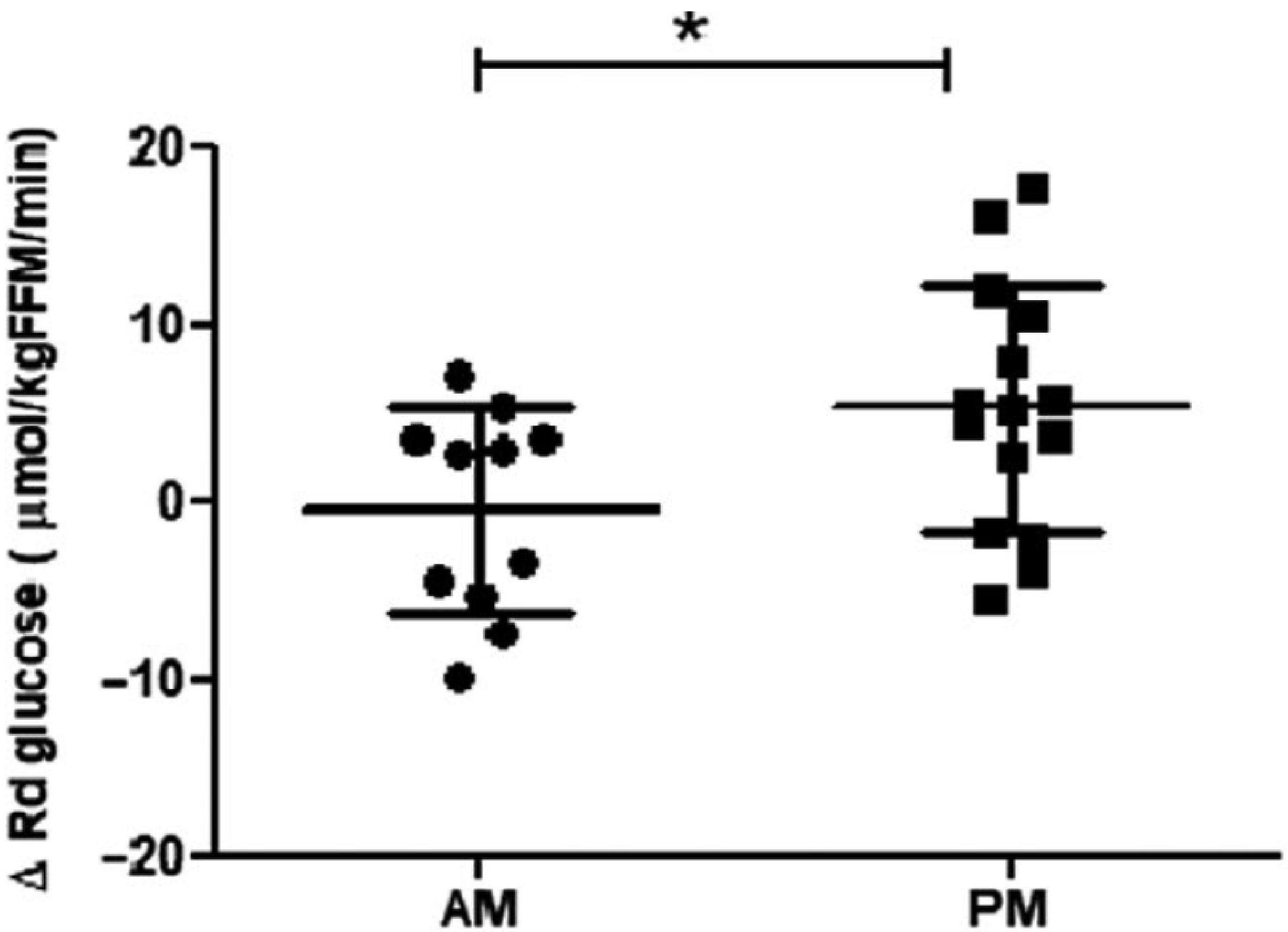
# Similar baseline insulin sensitivity prior to training

| | AM | PM |
|---|---|---|
| Clamp data | | |
| Basal EGP (μmol/min/kgFFM) | 7.4 ± 1.5 | 8.1 ± 3.5 |
| Basal $R_d$ (μmol/min/kgFFM) | 7.8 ± 1.8 | 7.9 ± 3.6 |
| Basal $CHO_{ox}$ (μmol/min/kgFFM) | 5.9 ± 3.9 | 5.3 ± 2.6 |
| Insulin-induced suppression of plasma FFA (%) | −62.6 ± 9.5 | −61.6 ± 16.0 |
| Insulin-induced suppression of EGP (%) | −41.8 ± 26.3 | −32.2 ± 28.9 |
| Delta $R_d$ (μmol/min/kgFFM) | 16.9 ± 11.2 | 15.2 ± 9.0 |
| Delta NOGD (μmol/min/kgFFM) | 8.9 ± 7.2 | 8.2 ± 6.2 |



Mancilla et al., Physiol Rep 2020

# Training-mediated improvement in insulin stimulated glucose uptake more profound after afternoon training

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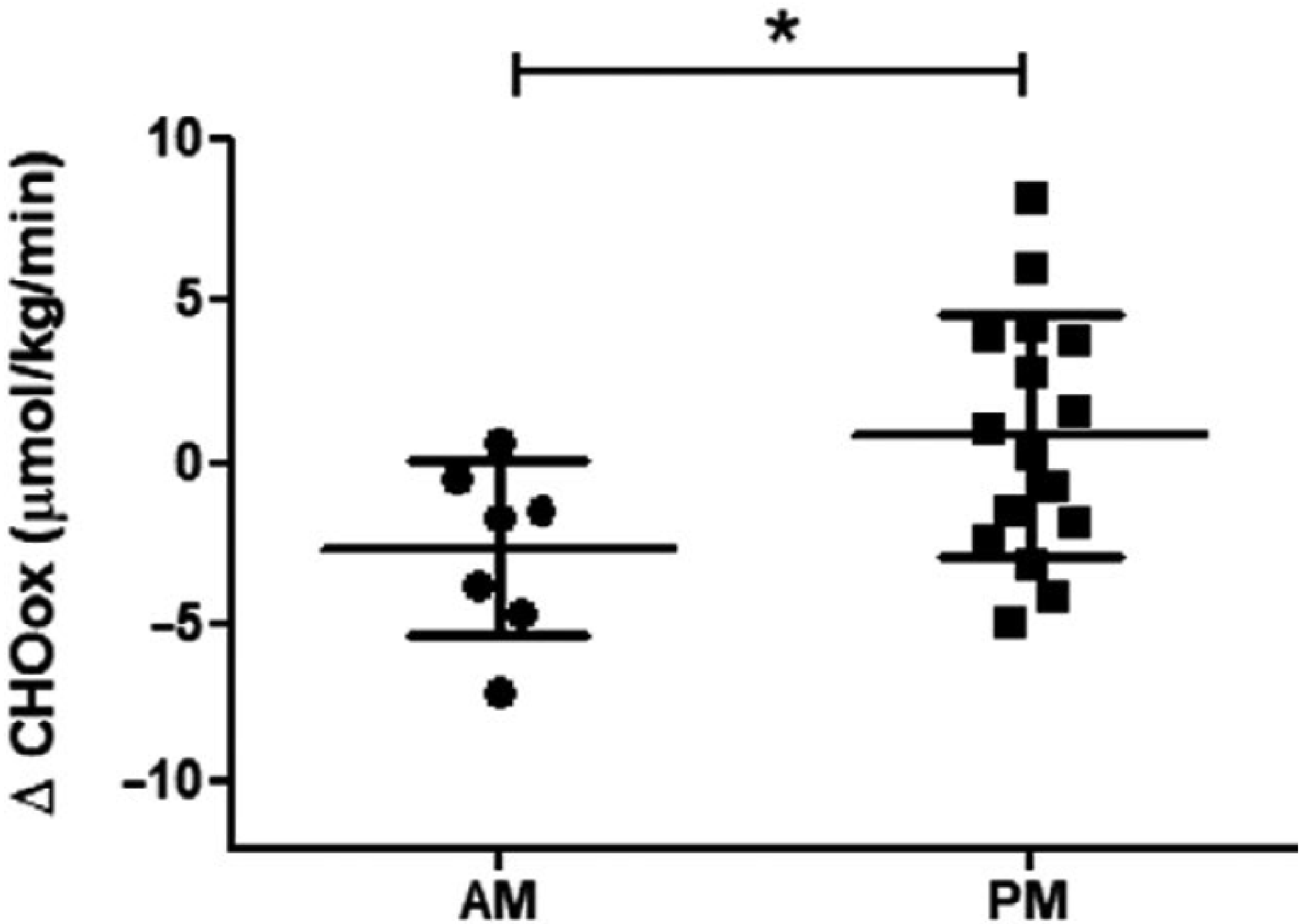
Mancilla et al., Physiol Rep 2020

# Training-mediated improvement in insulin stimulated glucose oxidation more profound after afternoon training

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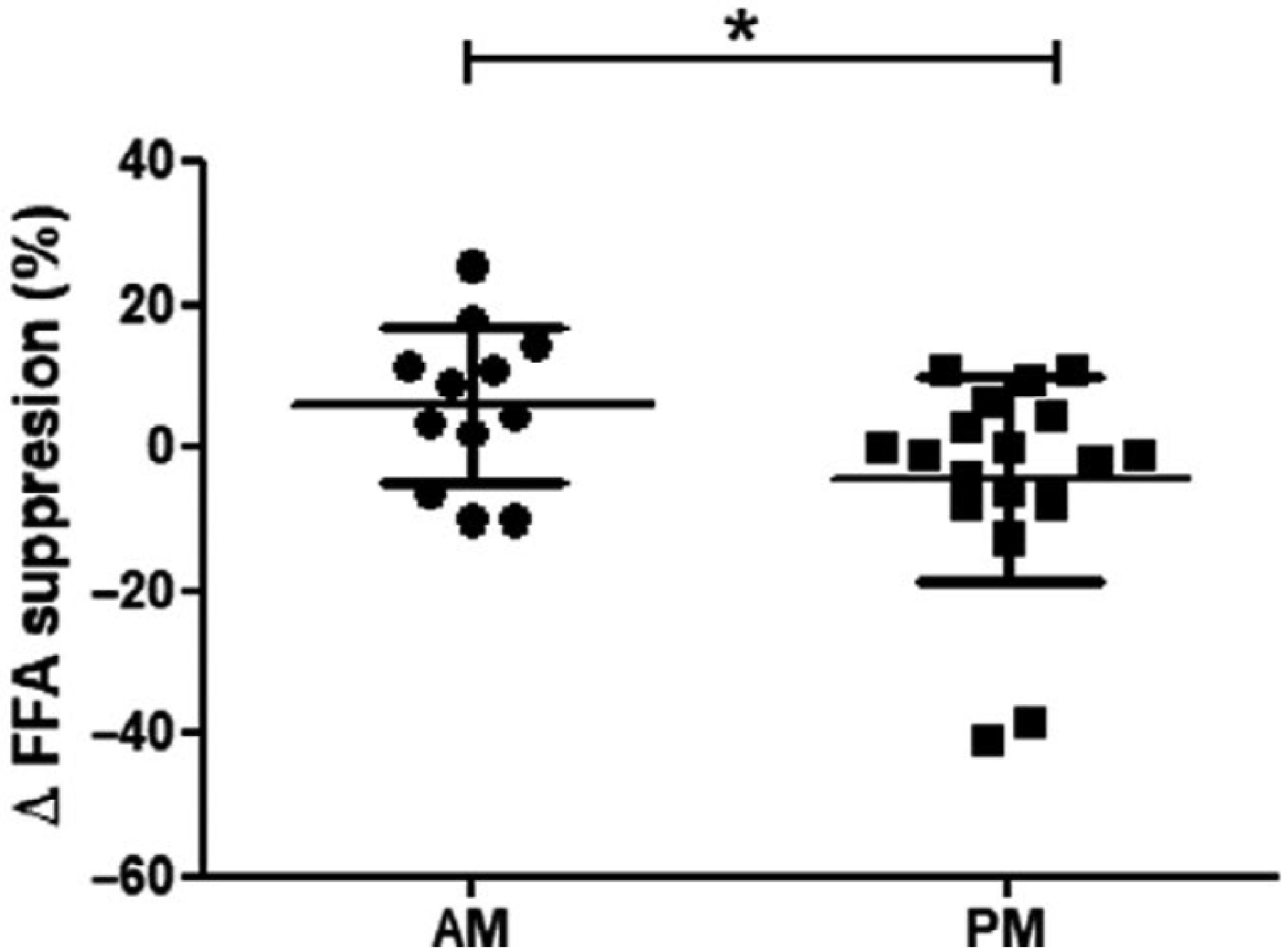
Mancilla et al., Physiol Rep 2020

# Training-mediated improvement inhibition of AT lipolysis is more profound after afternoon training

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Mancilla et al., Physiol Rep 2020

# Timing matters!




Mancilla et al., Physiol Rep 2020

# Thanks to the DMRG team

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# Questions?

# Sit-less improves 24 hours glucose control

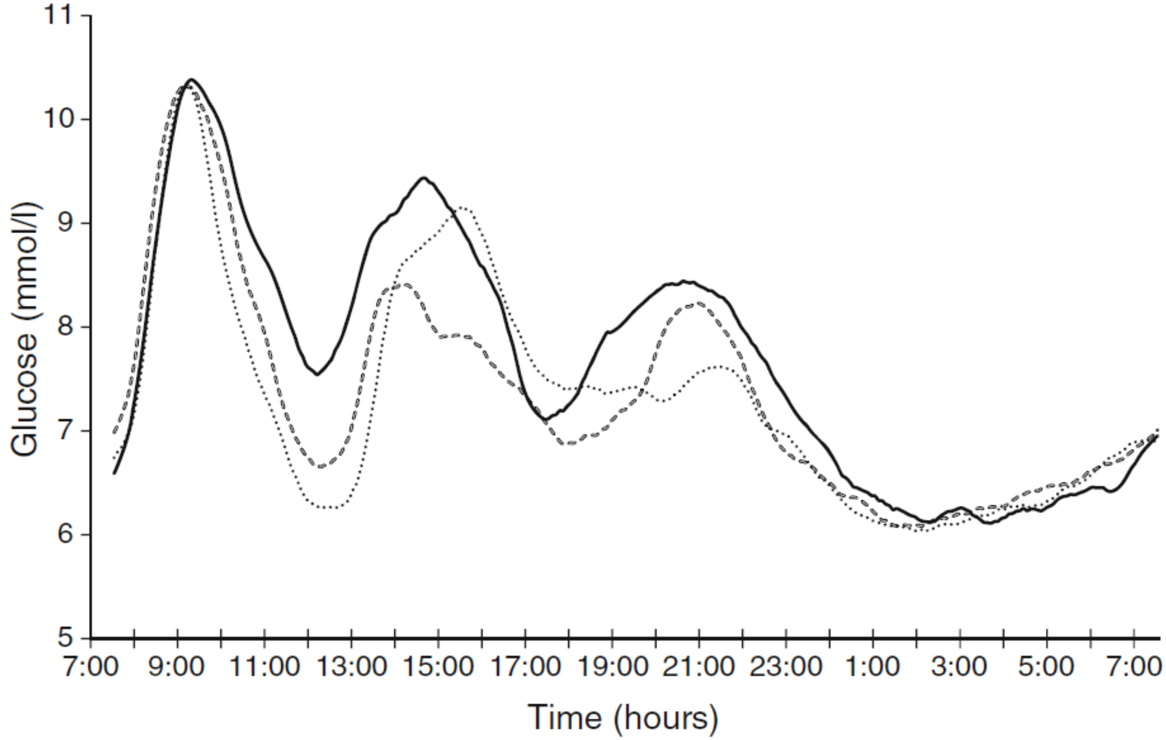
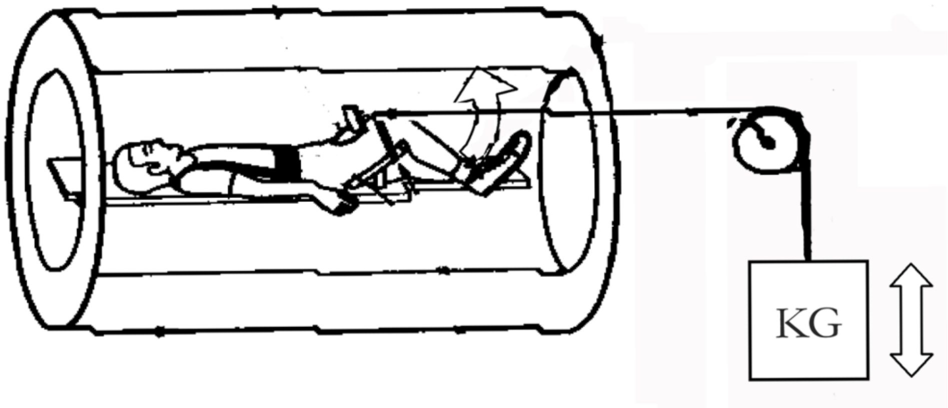


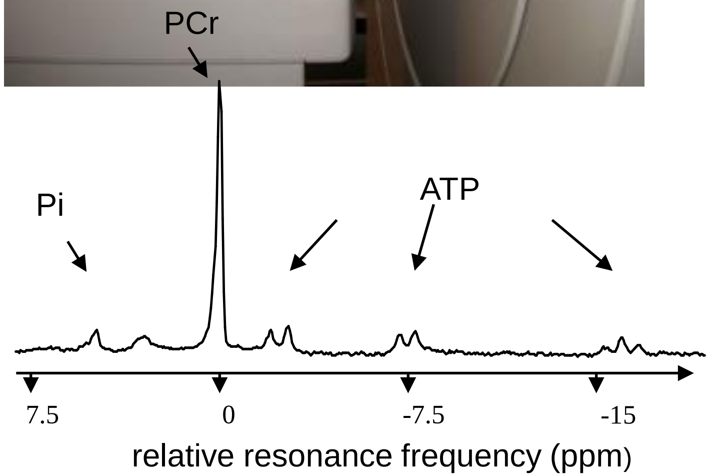

**Fig. 2** Mean 24 h glucose profiles during the last day of each activity regimen (*n* = 19 individuals). Solid line, Sitting regimen; dashed line, Sit Less regimen; dotted line, Exercise regimen



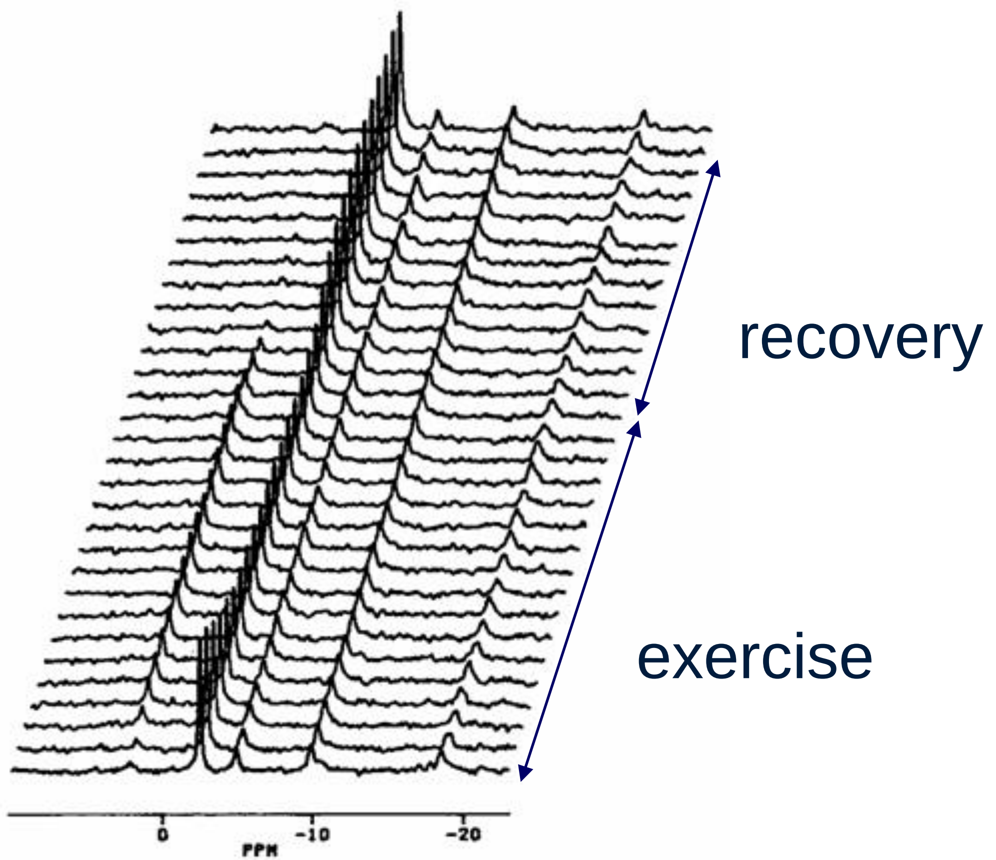
Duvivier et al., Diabetologia 2017

# Muscle mitochondrial function *in vivo* by $^{31}$P NMR Spectroscopy



# Muscle mitochondrial function *in vivo* by $^{31}P$ NMR Spectroscopy

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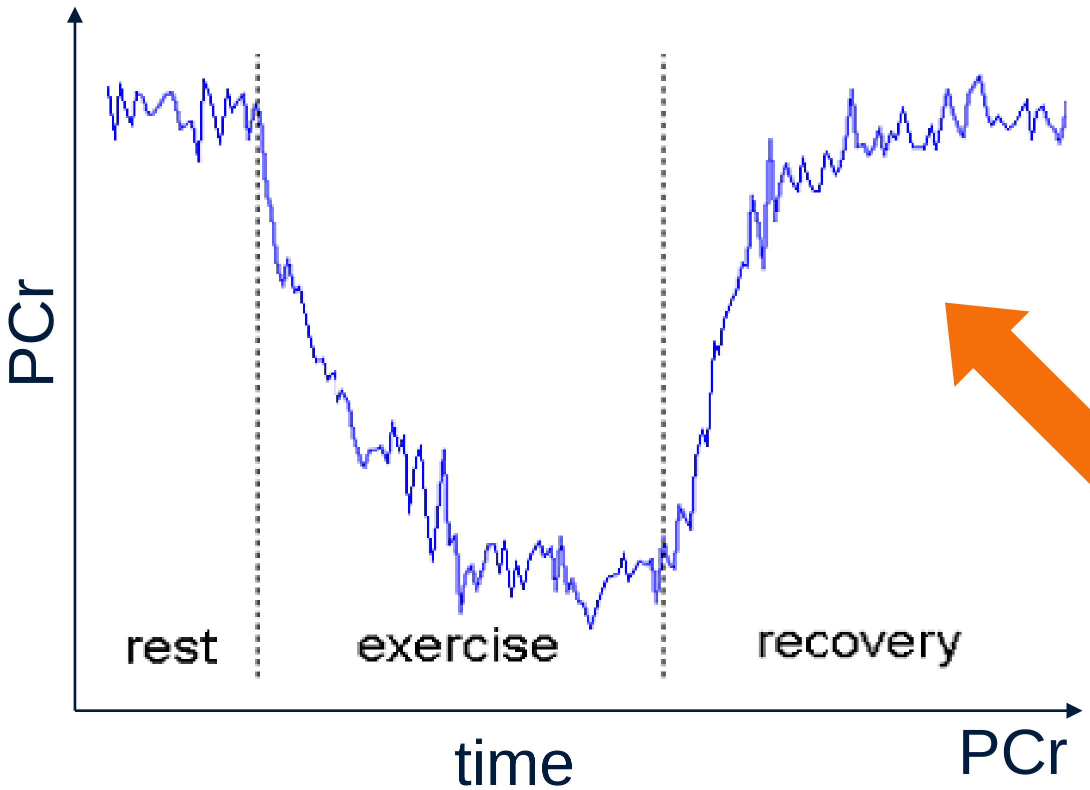
# Muscle mitochondrial function *in vivo* by $^{31}$P NMR Spectroscopy




PCr resynthesis is almost purely aerobic

PCr recovery half-time reflects mitochondrial function