De circadiane klok en insuline resistentie

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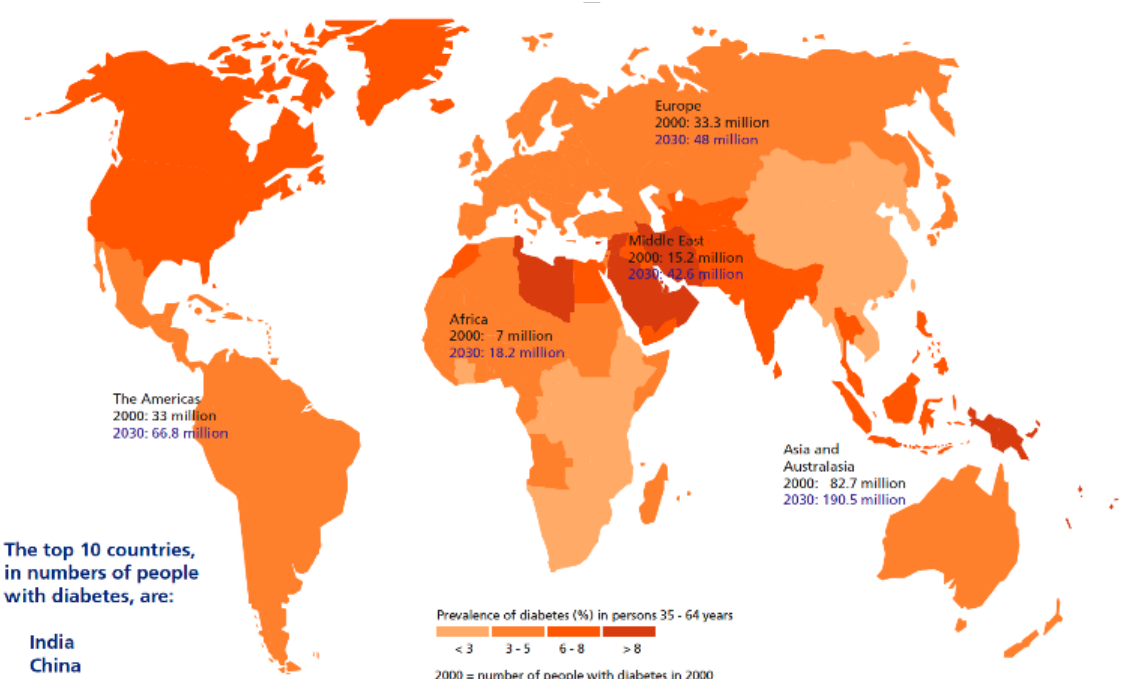
Prevalentie van diabetes

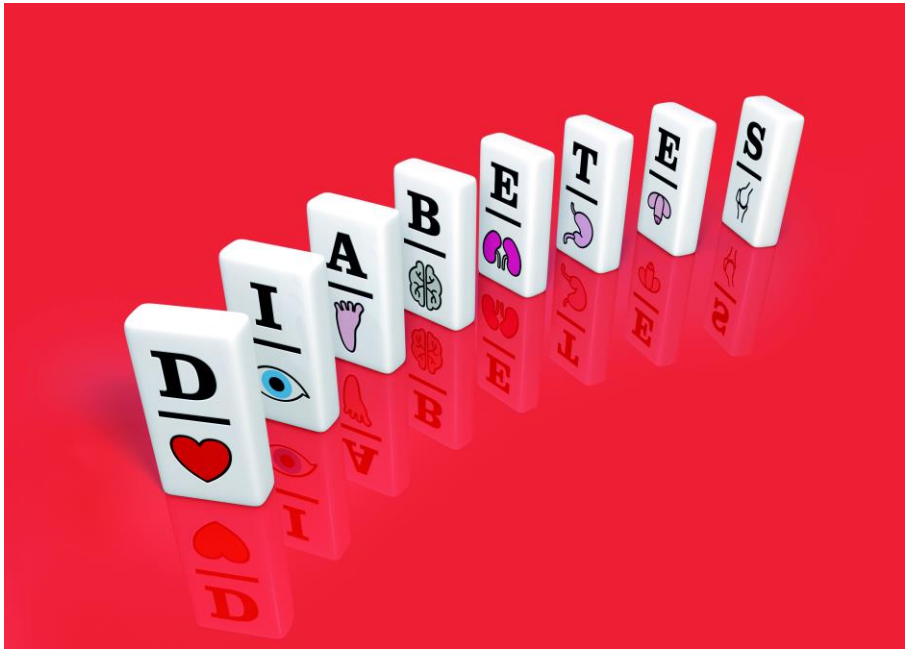


The top 10 countries, in numbers of people with diabetes, are:

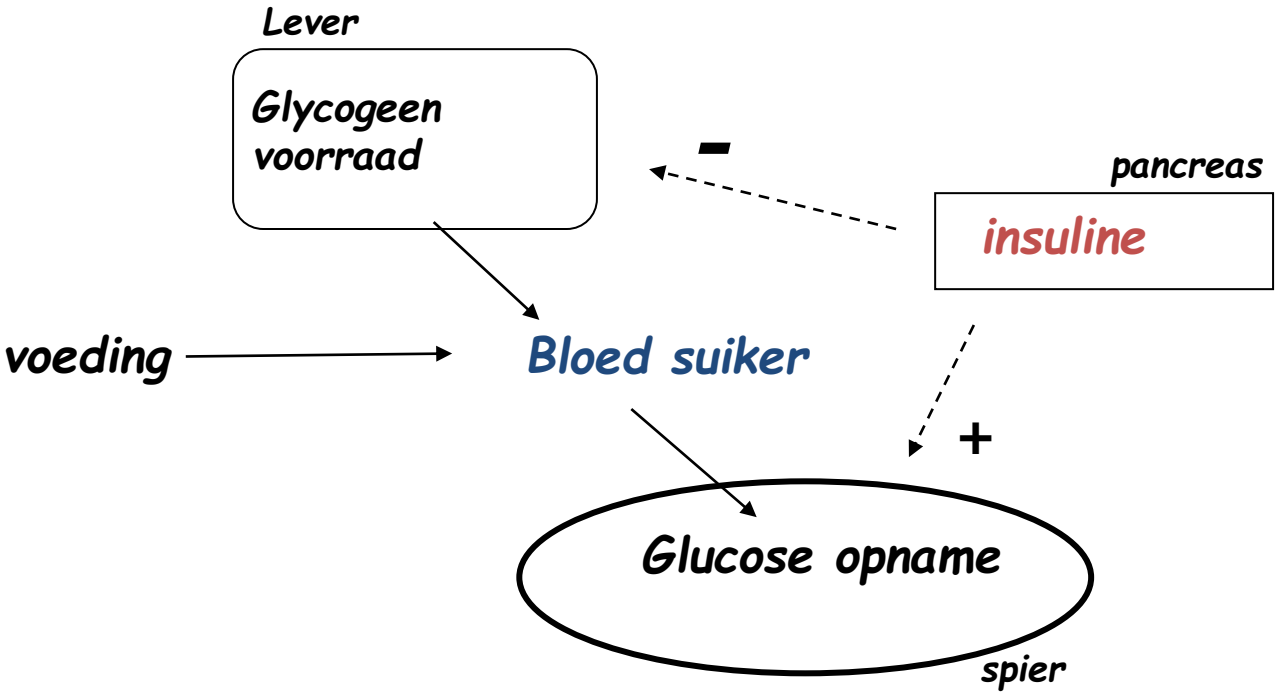
India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh

Year		2000	2030
Ranking	*Country*	*People with diabetes (millions)*	
1	India	31.7	79.4
2	China	20.8	42.3
3	United States of America	17.7	30.3

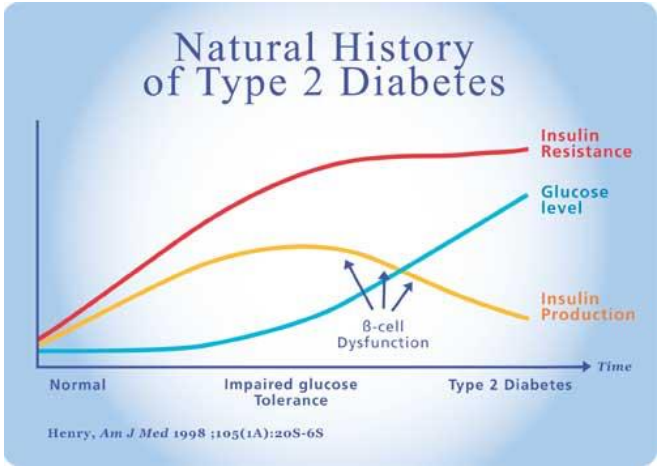
Domino effect:
diabetes verhoogt risico op complicaties

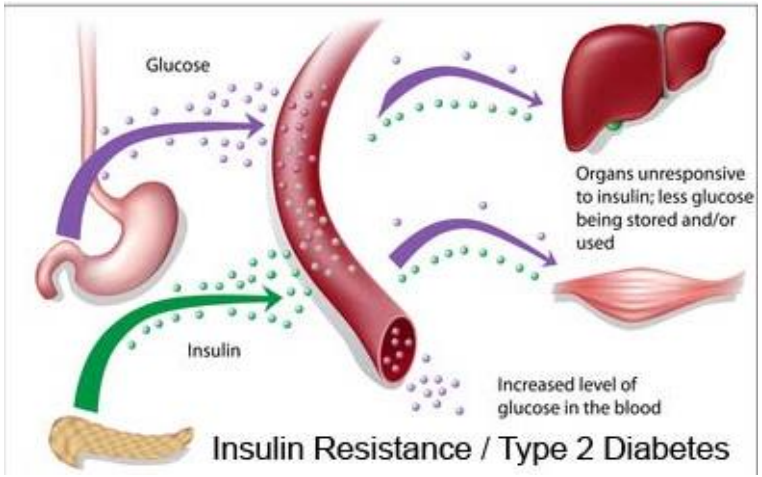


Bloed glucose regulatie



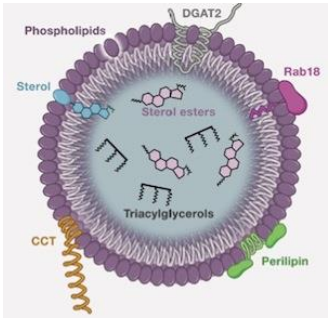
Focus op insuline resistentie





(spier) insuline resistentie ontstaat door vetstapeling in de spier

Dietary fat

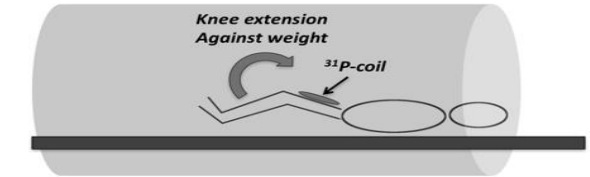


Lipolysis (ATGL, hsl)

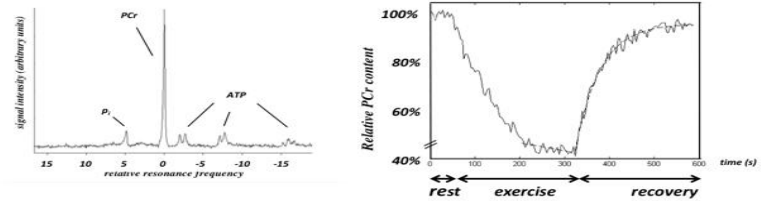
Fatty acid

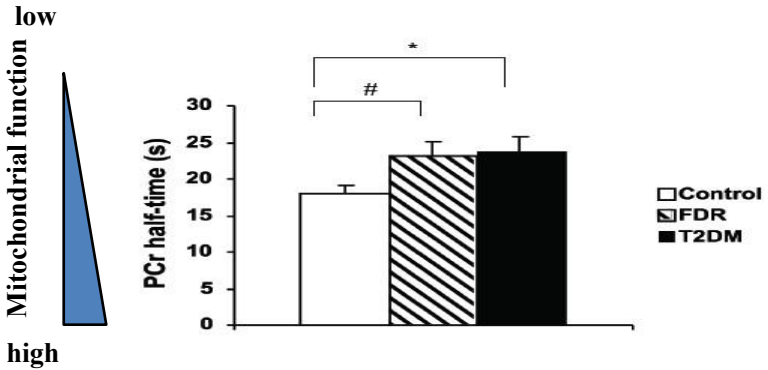
Storage (DGAT, perilipins)

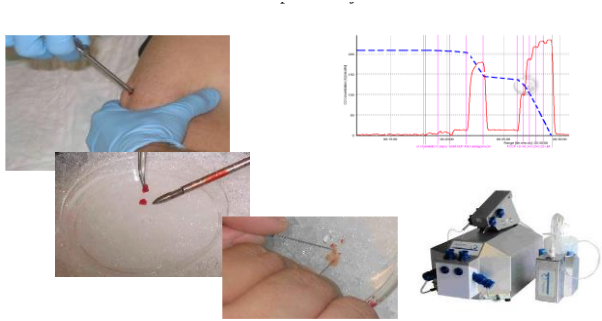
mitochondriele functie is verlaagd in type 2 diabetes mellitus en prediabeten

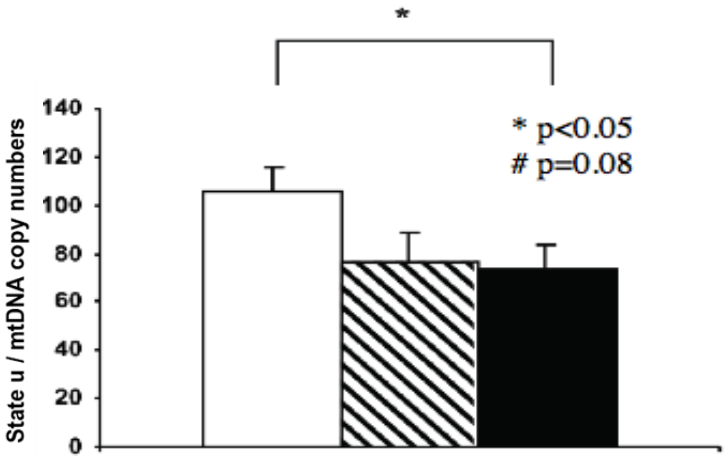


Exercise is performed in MRI scanner during 31P-MRS measurement







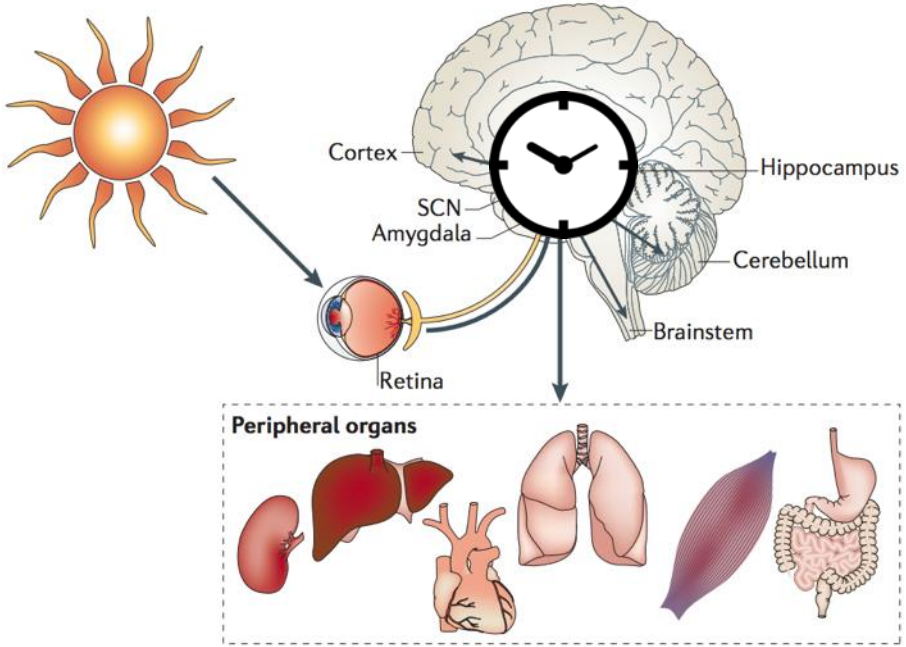


31P-coil, 31-phosphorus coil; 31P-MRS, 31 phosphorus magnetic resonance spectroscopy; FDR, first degree relatives; MRI, magnetic resonance imaging; mtDNA, mitochondrial deoxyribonucleic acid; PCr, polymerase chain reaction; State u, maximal respiratory capacity; T2DM, type 2 diabetes mellitus.

1. Schrauwen-Hinderling VB et al. Diabetologia. 2007;50(1):113-20. 2. Phielix E, el at. Diabetes. 2008;57(11):2943–9.

Waarom?

De biologische klok reguleert lichaamsfuncties



Kondratova et al. Nat Rev Neurosc, 2012


Circadian
Misalignment


McDonald's
open 24 hours

Shift werk verhoogt het risico op diabetes

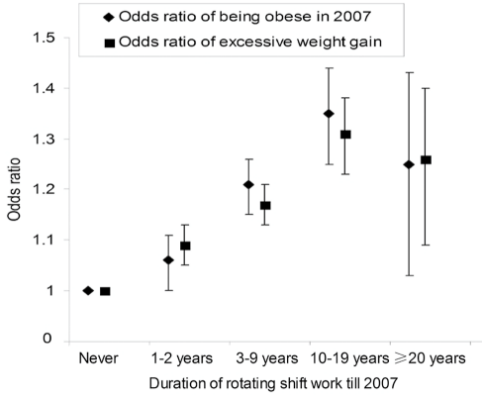


Table 2. Hazard ratio of type 2 diabetes by years of working rotating night shifts.

Studies	Duration of Rotating Night Shift Work					*p*-Value for Trend	Hazard Ratio per 5 y of Shift Work
	Never	1–2 y	3–9 y	10–19 y	≥20 y		
NHS I (1988–2008)							
Cases/person-years	2,322/519,988	1,388/311,468	1,534/292,014	549/86,844	372/50,380	—	—
Incidence rate (per 1,000 person-years)	4.5	4.5	5.3	6.3	7.4	—	—
Age-adjusted model	1.00	0.99 (0.93–1.06)	1.17 (1.10–1.25)	1.42 (1.29–1.55)	1.64 (1.46–1.83)	<0.001	1.14 (1.12–1.17)
Multivariate-adjusted model 1	1.00	1.01 (0.95–1.08)	1.15 (1.08–1.23)	1.32 (1.20–1.45)	1.47 (1.32–1.64)	<0.001	1.11 (1.08–1.13)
Multivariate-adjusted model 2	1.00	1.00 (0.94–1.07)	1.06 (0.99–1.13)	1.09 (0.99–1.20)	1.20 (1.07–1.34)	<0.001	1.05 (1.02–1.07)
NHS II (1989–2007)							
Cases/person-years	1,000/584,808	1,053/540,270	1,377/599,813	449/128,835	82/11,593	—	—
Incidence rate (per 1,000 person-years)	1.7	2.0	2.3	3.5	7.1	—	—
Age-adjusted model	1.00	1.13 (1.04–1.23)	1.34 (1.23–1.45)	1.76 (1.57–1.96)	2.50 (2.00–3.14)	<0.001	1.23 (1.19–1.27)
Multivariate-adjusted model 1	1.00	1.12 (1.02–1.22)	1.28 (1.18–1.39)	1.54 (1.38–1.73)	2.13 (1.70–2.67)	<0.001	1.18 (1.14–1.22)
Multivariate-adjusted model 2	1.00	1.07 (0.98–1.16)	1.05 (0.97–1.14)	1.11 (1.00–1.25)	1.44 (1.15–1.80)	0.026	1.05 (1.01–1.08)
Pooled results[a]							
Age-adjusted model	1.00	1.04 (0.99–1.10)	1.24 (1.18–1.30)	1.55 (1.45–1.66)	1.78 (1.61–1.96)	<0.001	1.17 (1.15–1.20)
Multivariate-adjusted model 1	1.00	1.05 (1.00–1.11)	1.20 (1.14–1.26)	1.40 (1.30–1.51)	1.58 (1.43–1.74)	<0.001	1.13 (1.11–1.14)
Multivariate-adjusted model 2	1.00	1.03 (0.98–1.08)	1.06 (1.00–1.11)	1.10 (1.02–1.18)	1.24 (1.13–1.37)	<0.001	1.05 (1.04–1.06)

Multivariate-adjusted model 1: adjusted for age (continuous), alcohol consumption (0, 0.1–4.9, 5.0–14.9, ≥15 g/d), physical activity level (<3, 3–8.9, 9–17.9, 18–26.9, ≥27 MET-h/wk), smoking status (never, past, current 1–14/d, current 15–24/d, current ≥25/d), race (white, nonwhite), menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users), oral contraceptive use (yes, no; in NHS II), family history of diabetes (yes, no), current aspirin use (yes, no), quintiles of total calorie, diabetes dietary score. Multivariate-adjusted model 2: model 1 plus updated BMI category (<23, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2).

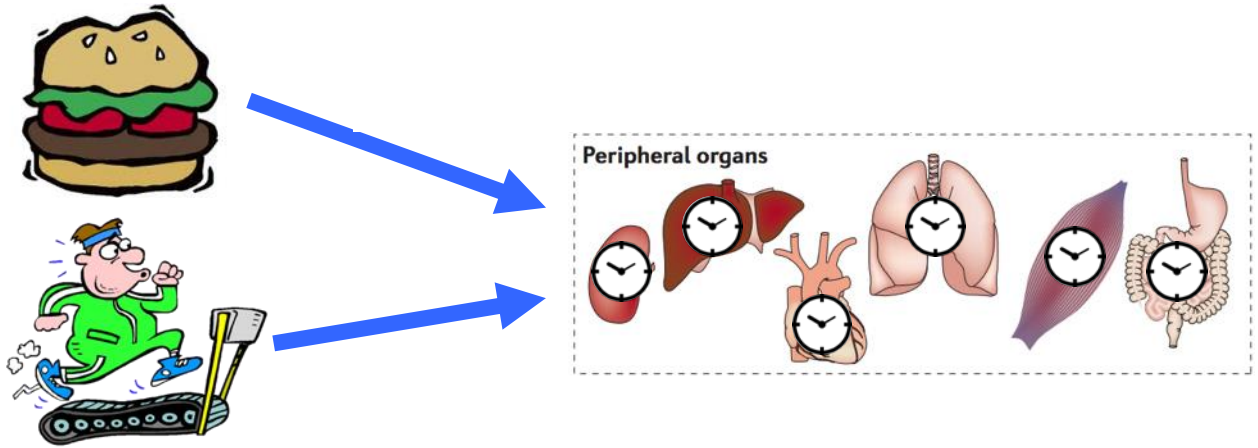
[a]The results were pooled using fixed-effect models.

doi:10.1371/journal.pmed.1001141.t002

Pan et al., 2011, PlosMedicine

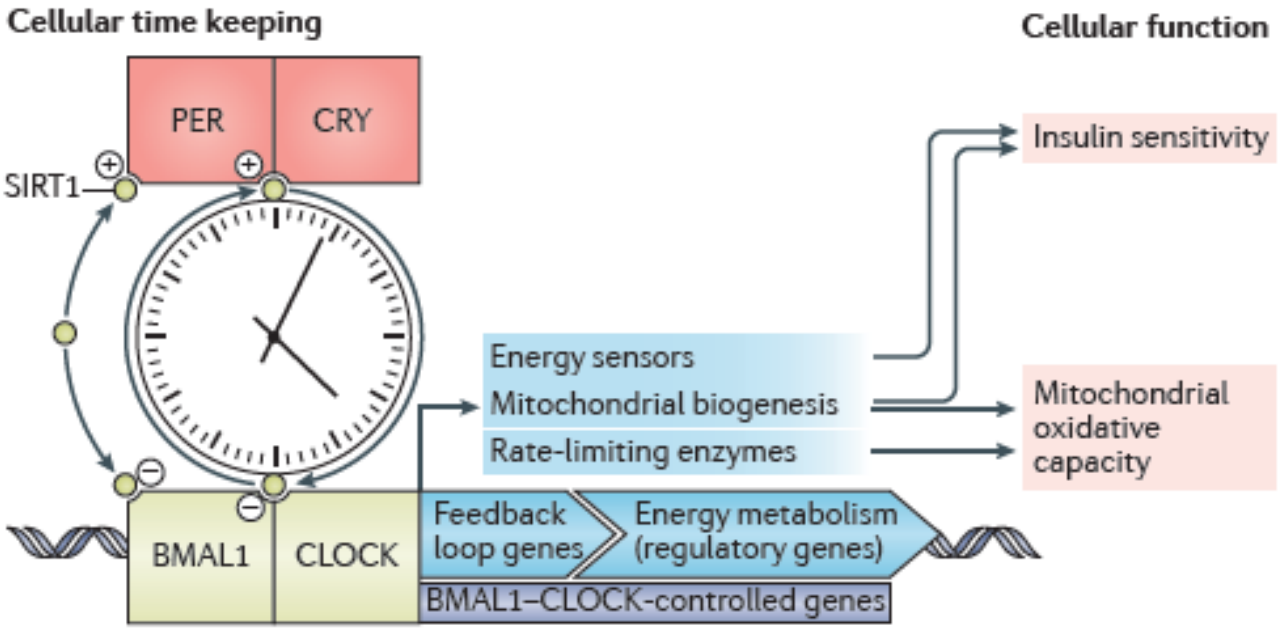
Wat is de rol van de biologische klok in de etiologie van type 2 diabetes ?

Het lichaam heeft meerdere biologische klokken



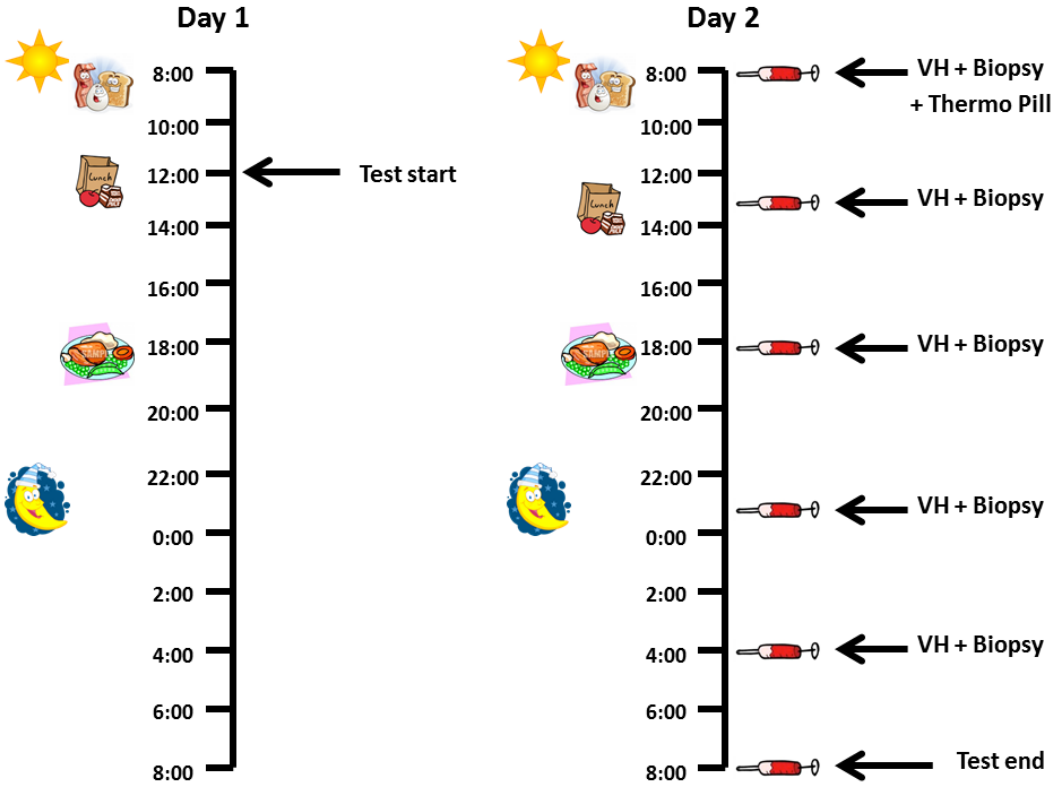
Kondratova et al. Nat Rev Neurosc, 2012

Mitochondria worden gereguleerd door de biologische klok



Hesselink, Schrauwen-Hinderling, Schrauwen,
Nature Rev Endo, 2016

Q: Is het (mitochondrieel) metabolism van de spier ritmisch bij de mens?

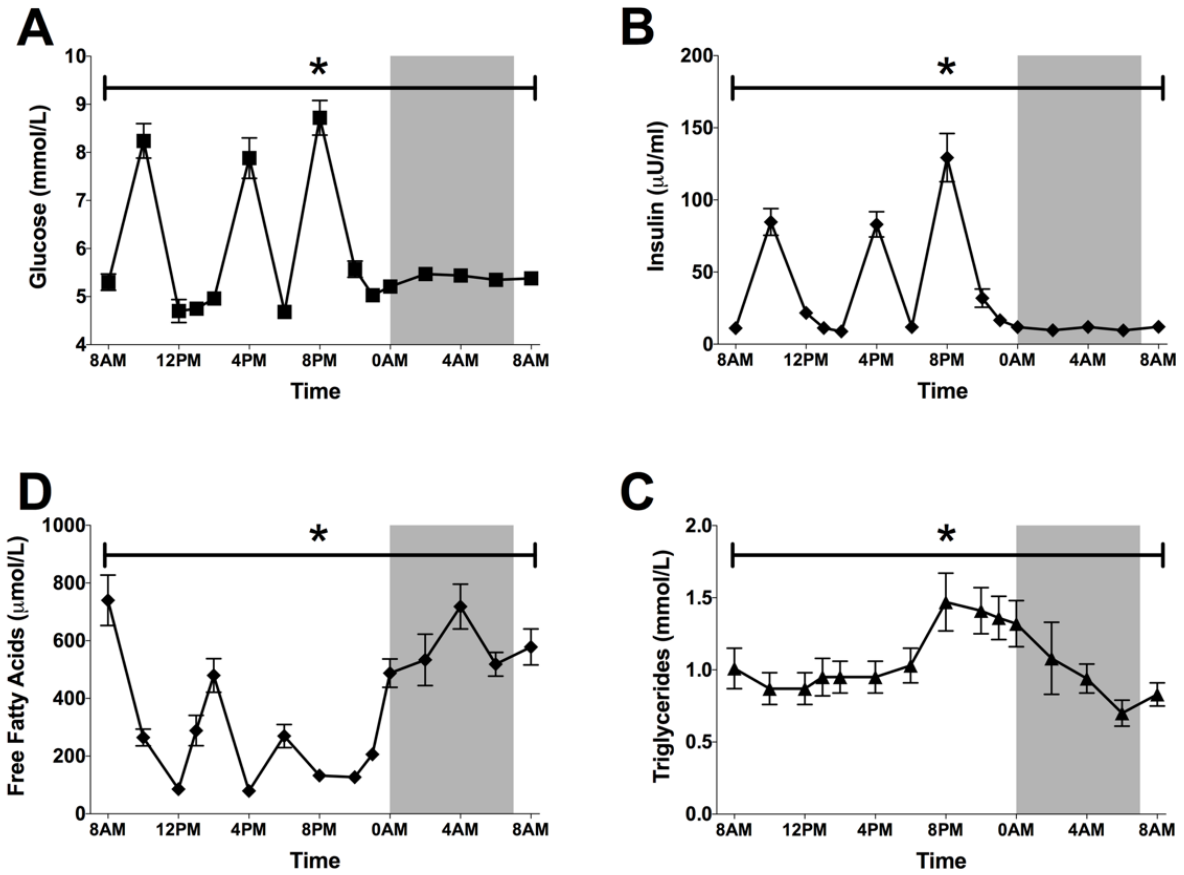

Day 1
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
0:00
2:00
4:00
6:00
8:00
Test start
Day 2
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
0:00
2:00
4:00
6:00
8:00
VH + Biopsy
+ Thermo Pill
VH + Biopsy
VH + Biopsy
VH + Biopsy
VH + Biopsy
Test end


Start day
Start night
Breakfast
Lunch
Dinner
VH = Ventilated Hood
Biopsy = Skeletal Muscle Biopsy

Proefpersoon karakteristieken

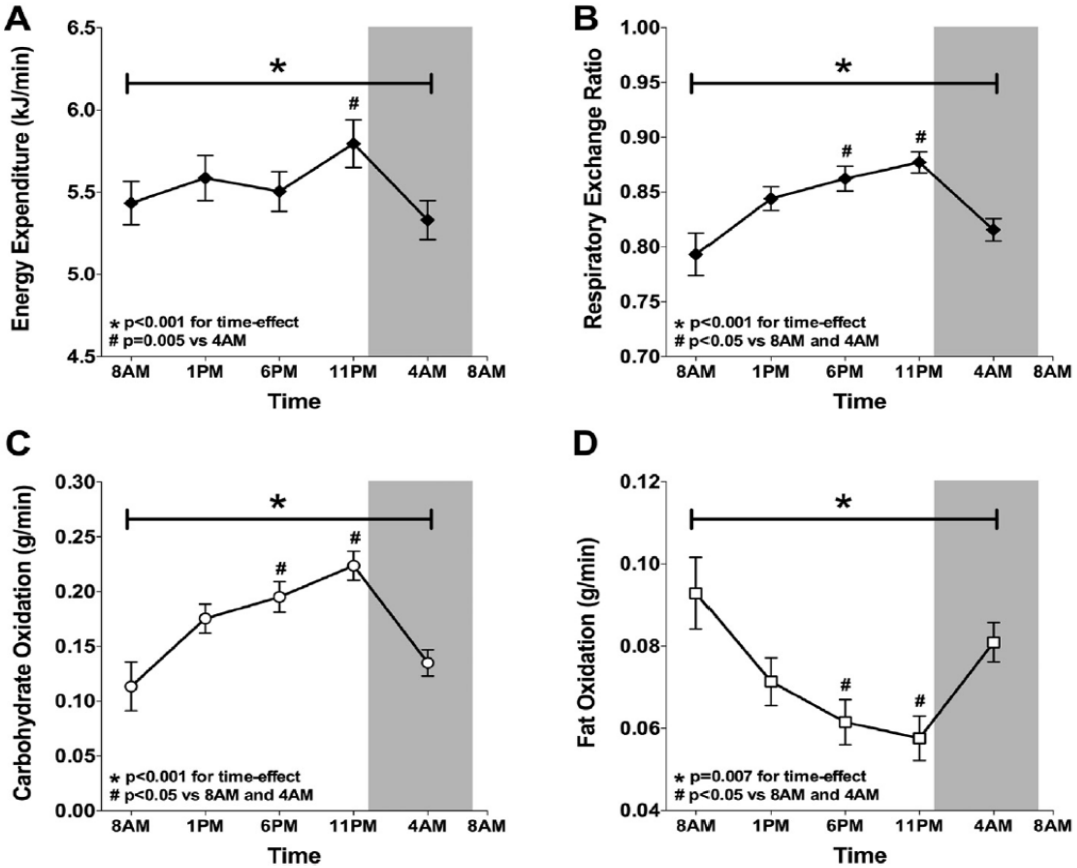
- Gezonde mannen
- 18-35 jaar
- Normaal slaap patroon
- Sedentaire leefstijl

“24 uurs ritme” in bloed parameters



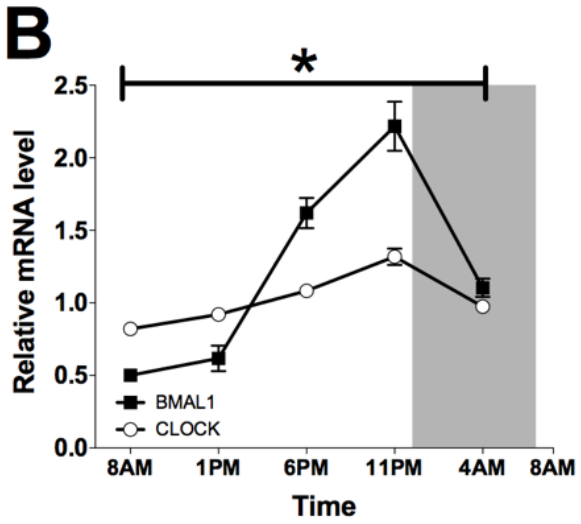
van Moorsel et al., Mol Metab 2016

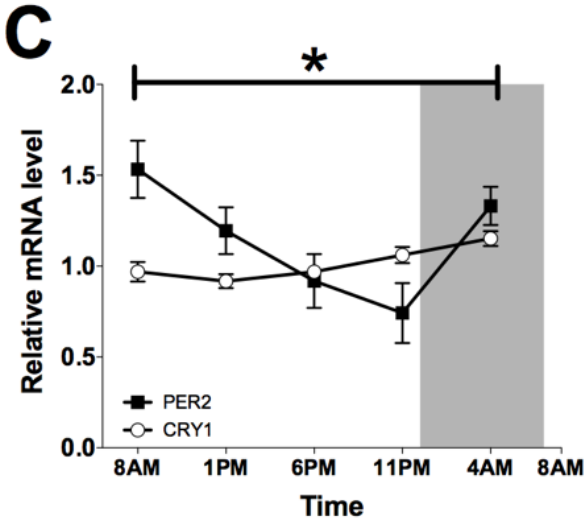
Rust energiegebruik is het hoogst laat in de avond, het laagst in de nacht

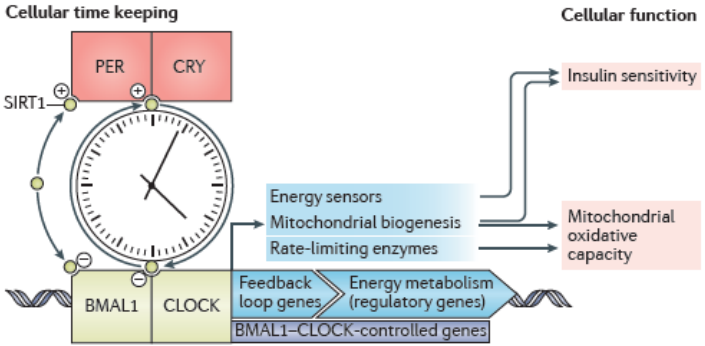


van Moorsel et al.,
Mol Metab 2016

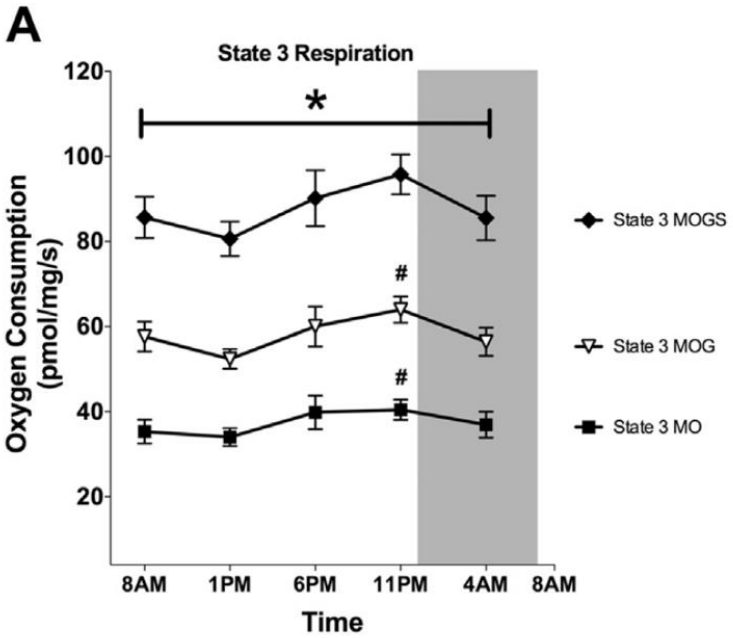
Biologische klok in de spier bij de mens

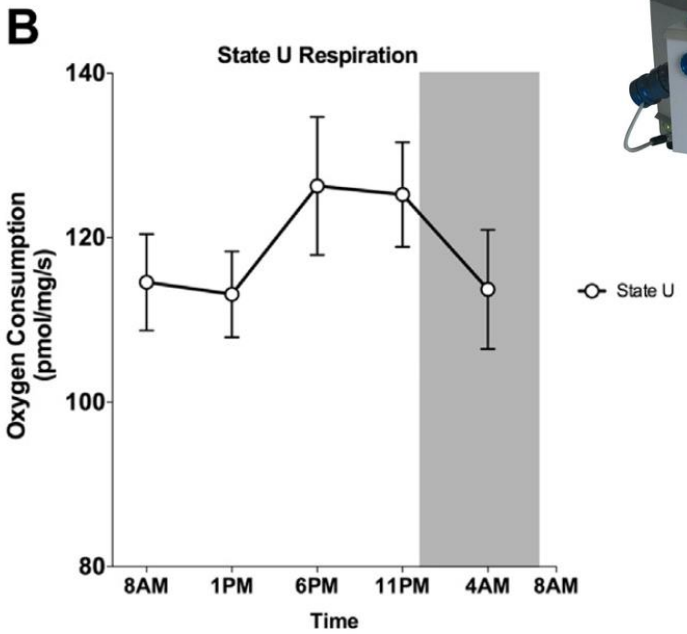






Mitochondriele functie in de spier heeft 24 uurs ritmiek





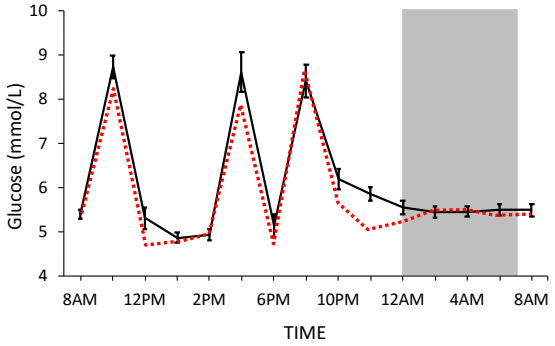
van Moorsel et al., Mol Metab 2016

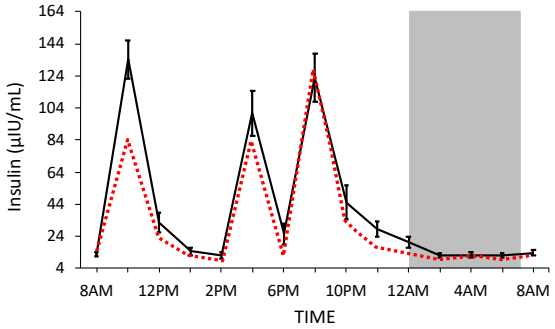
Q: Is het spier metabolism verstoord in mensen met verhoogd risico op diabetes?

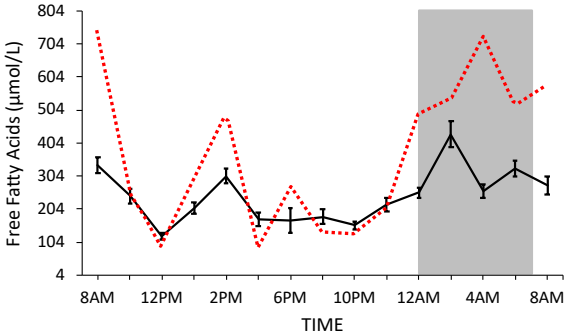
Proefpersoon karakteristieken

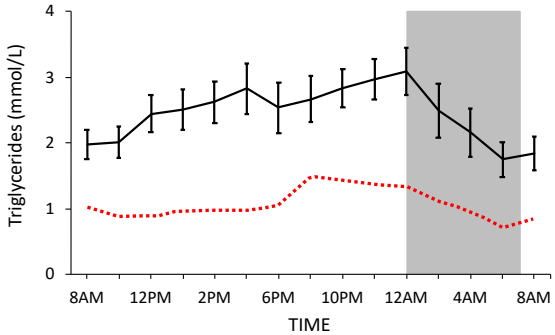
Parameter	Mean ± SD
Age (years)	65 ± 9
Height (m)	1.78 ± 0.05
Body weight (kg)	96 ± 12
BMI (kg/m^2)	30.3 ± 2.7
Body fat (%)	33 ± 4
Fasting plasma glucose (mmol/L)	5.7 ± 0.4
Fasting plasma insulin (µIU/mL)	13.8 ± 8.5
2-h plasma glucose (mmol/L)	7.3 ± 1.5
HbA_{1c} (%)	5.3 ± 0.5
Glucose clearance (ml/kg/min)	327 ± 38

24 uur ritme in bloed parameters is verstoord in ‘prediabeten’



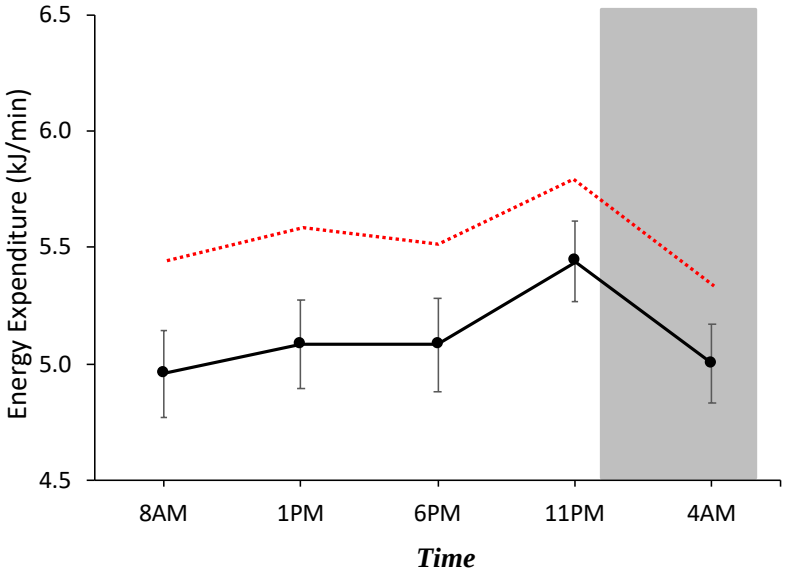






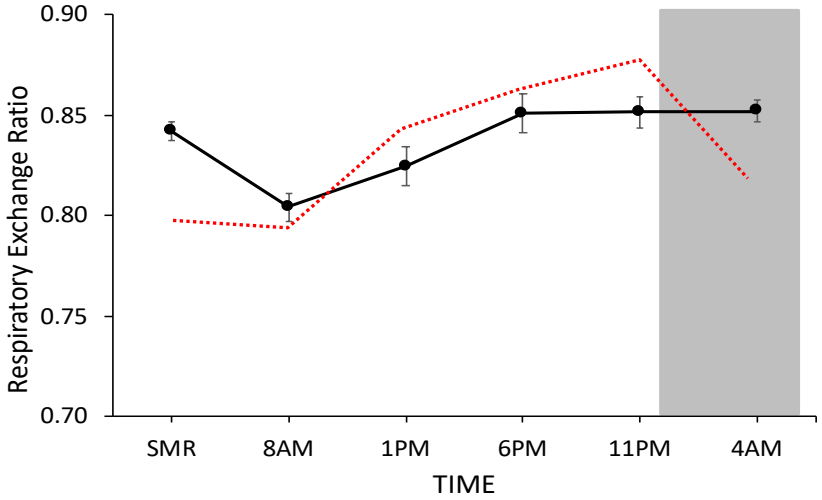
Wefers et al., Mol Metab 2020

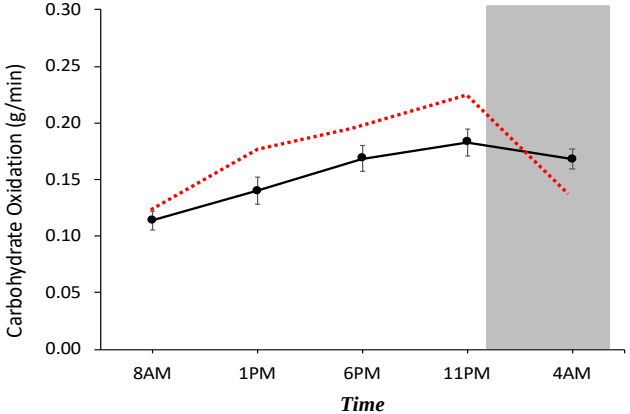
Rust energiegebruik is identiek

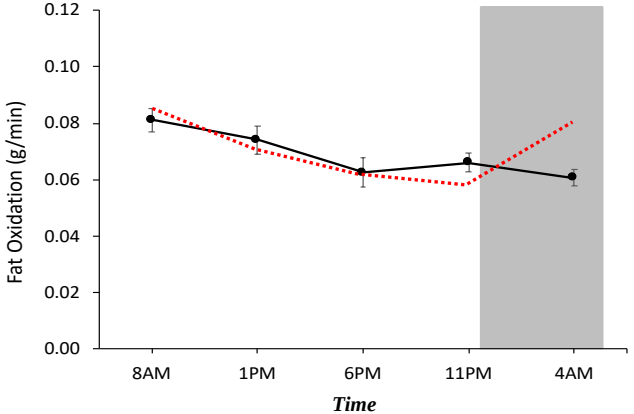


Held et al., Mol Metab 2020

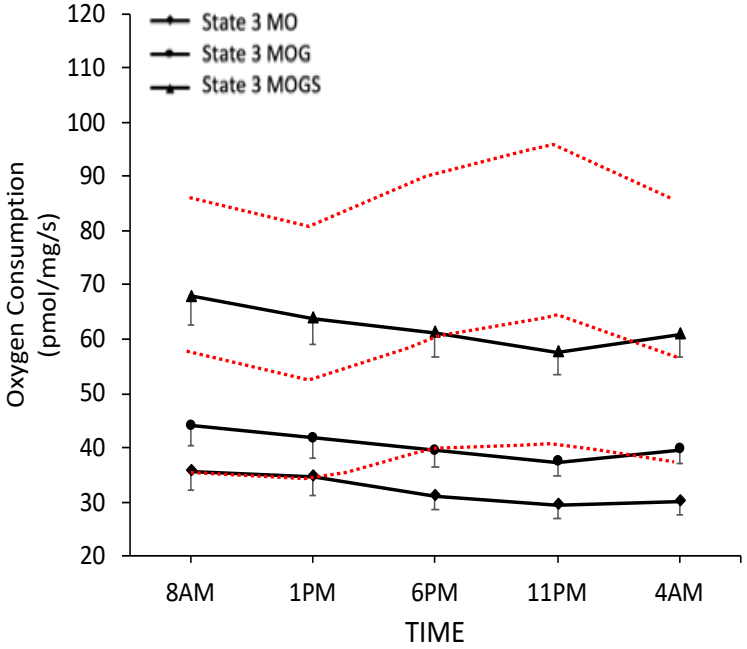
24h ritme in substraat metabolisme is verstoord in ‘prediabeten’

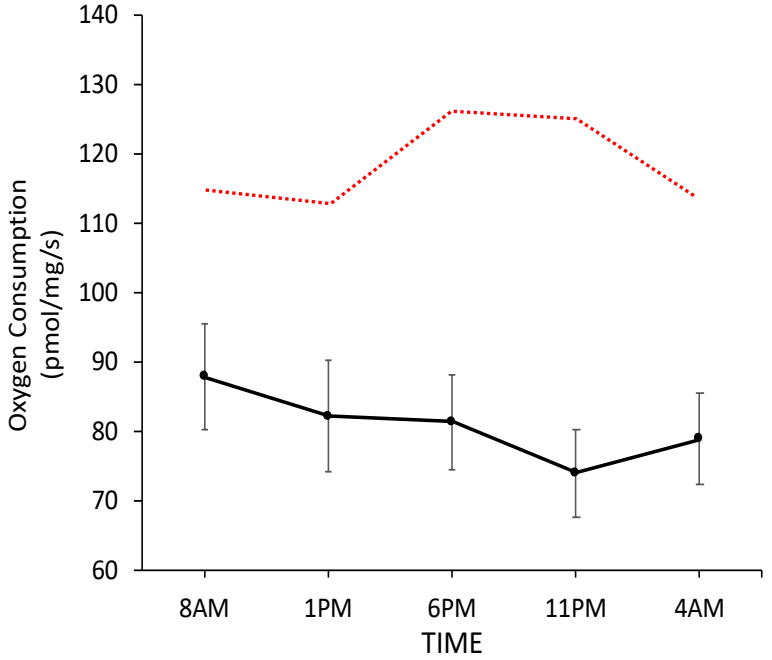






Mitochondriele functie is NIET rhytmisch in prediabeten



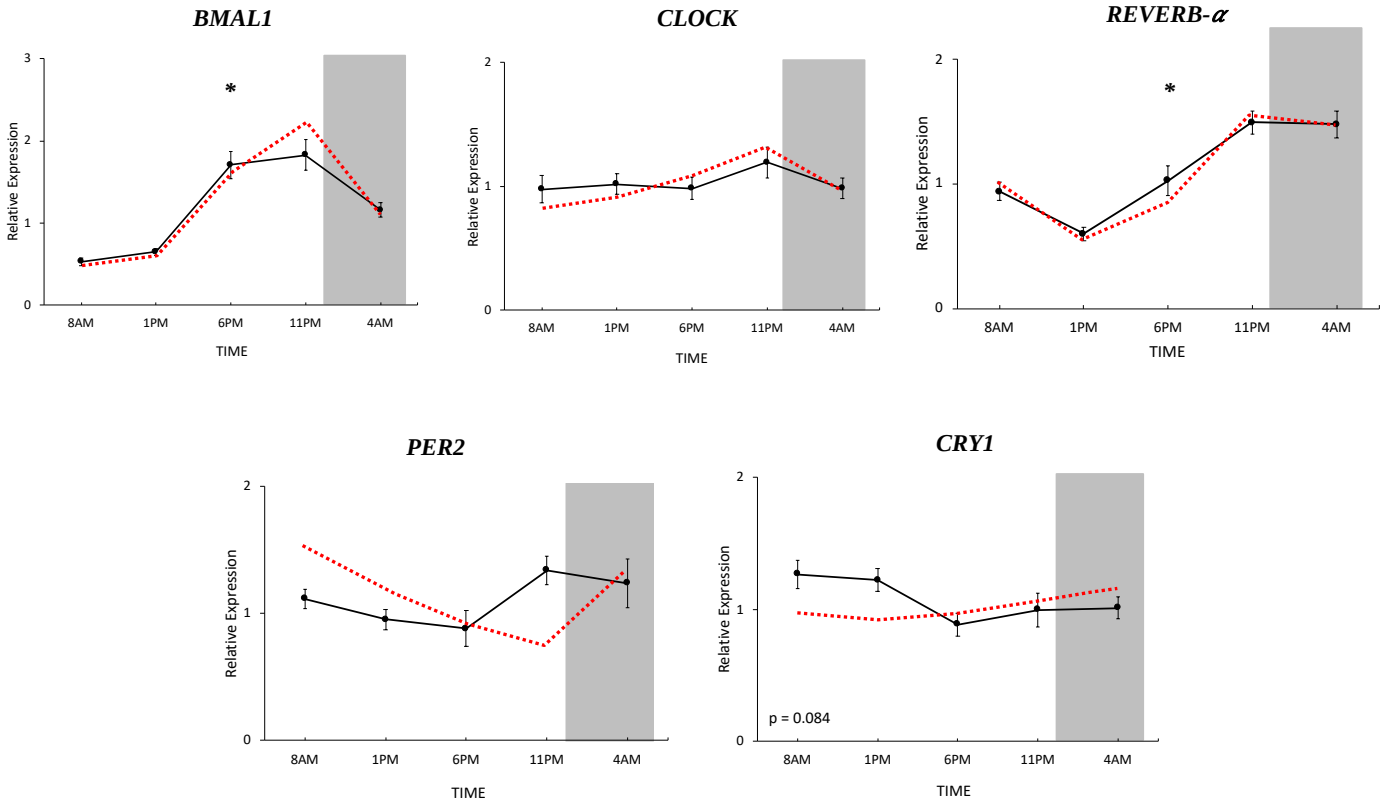


Slanke, jonge vrijwilligers

prediabetes

Held et al., Mol Metab 2020

Biologische klok in de spier is verstoord in prediabeten

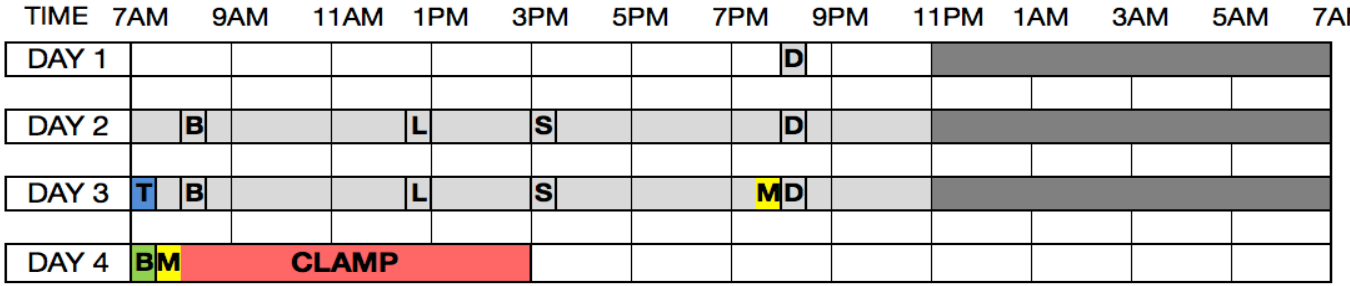


Held et al., Mol Metab 2020

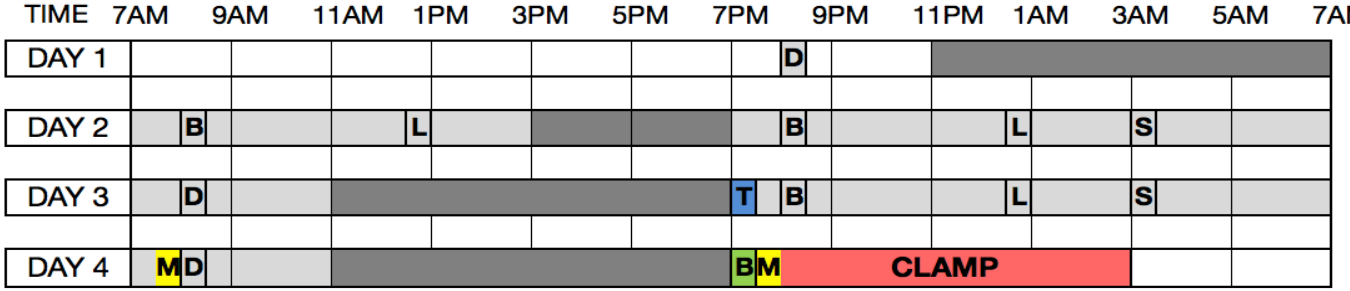
Q: leidt een verstoring van de biologische klok tot insuline resistentie in gezonde, jonge mannen?

Dag-nacht shift protocol

Control Condition



Circadian Misalignement Condition



4 lux 0 lux **B** Breakfast **L** Lunch **S** Snack **D** Dinner

Clamp **T** Ingestion Thermometer **M** Muscle Biopsy **B** Blood Draw, Resting Metabolic Rate

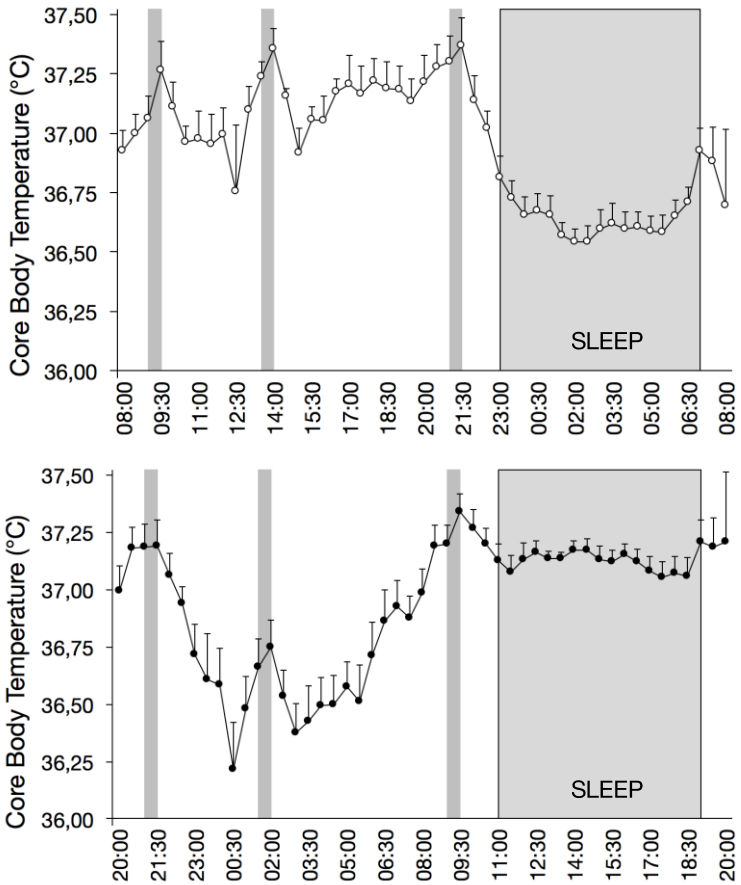
Proefpersoon karakteristieken

	Mean (n=14)	±SD
Age (years)	22.4	2.8
Height (meter)	1.82	0.08
Weight (kg)	74.5	11.1
BMI (kg/m^2)	22.3	2.1
Score MEQ	53.8	6.8

Na dag-nacht shift: energie metabolisme is laag gedurende de dag

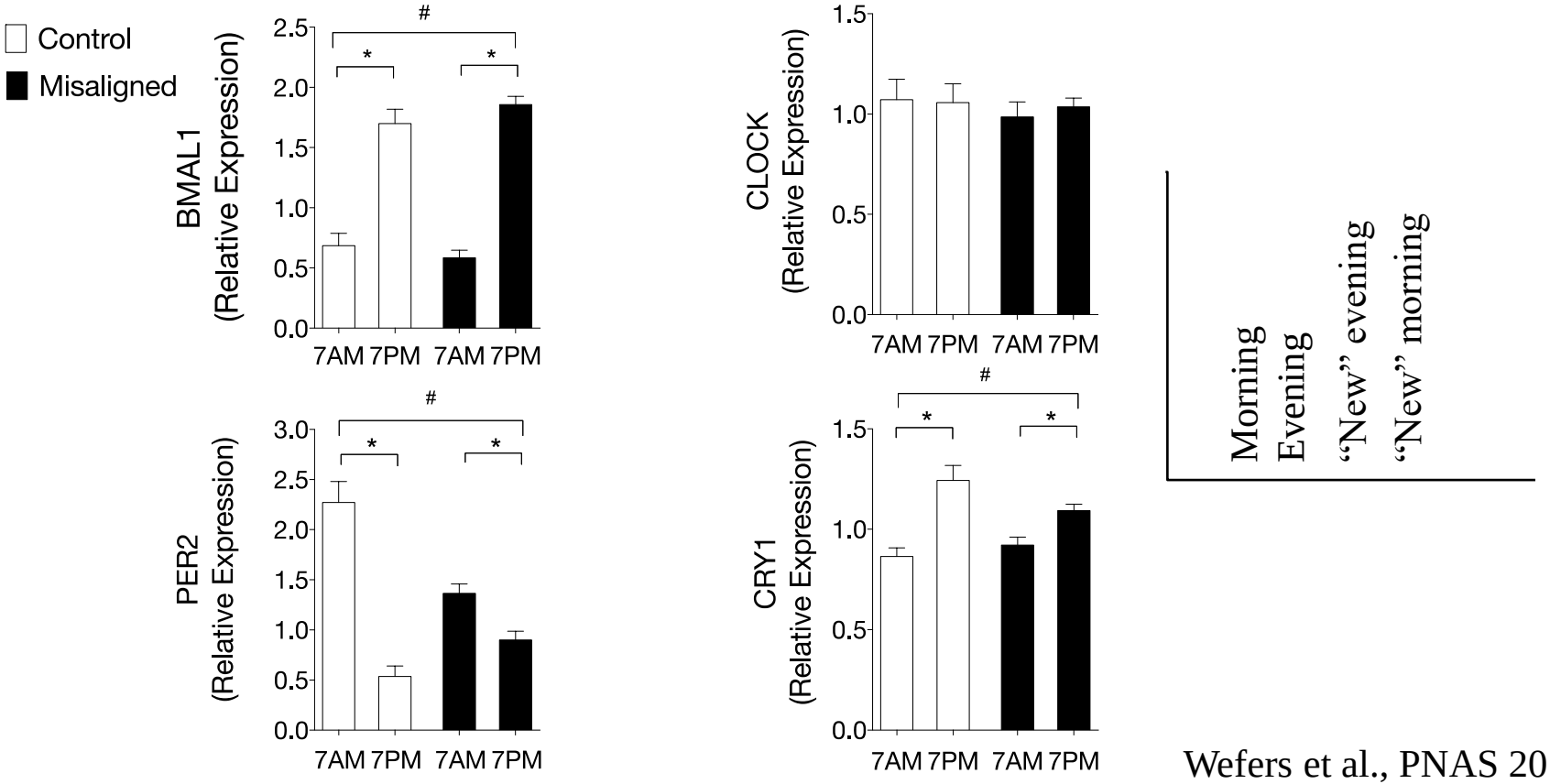
Control condition

Circadian misalignment



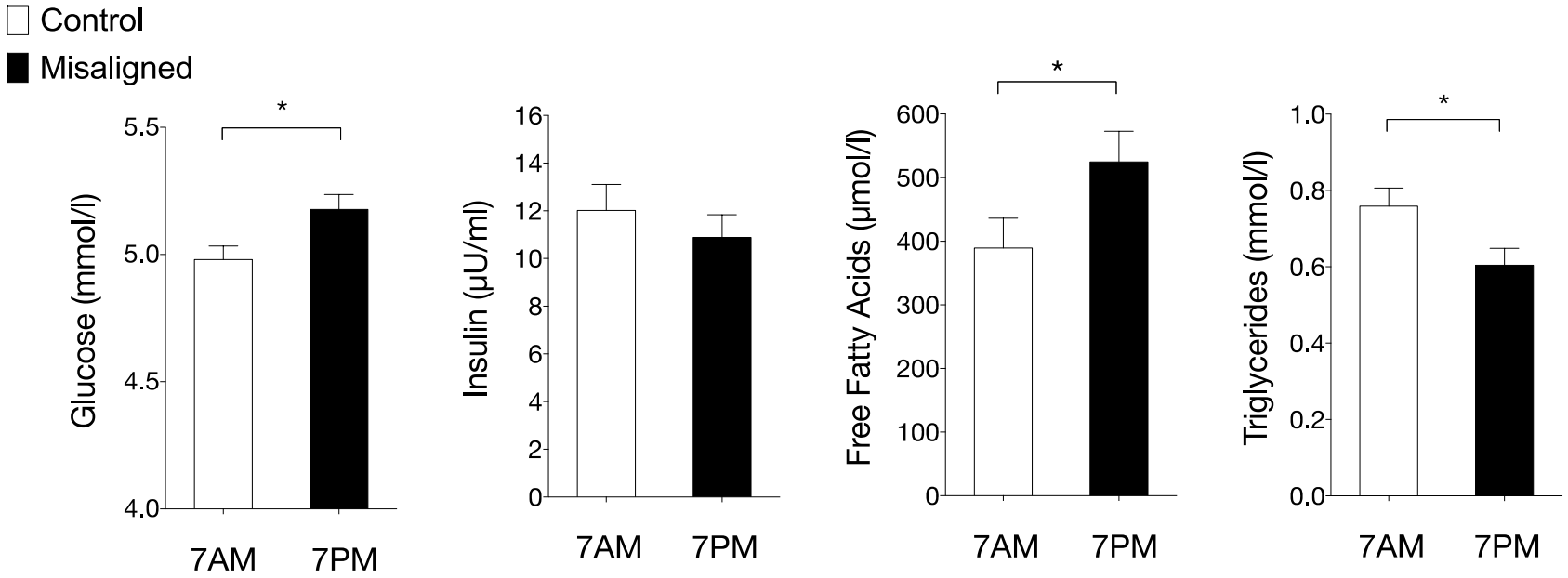
As start bij de ‘ochtend’

Biologische klok in de spier past zich niet aan de dag-nacht shift aan (na 2 dagen)



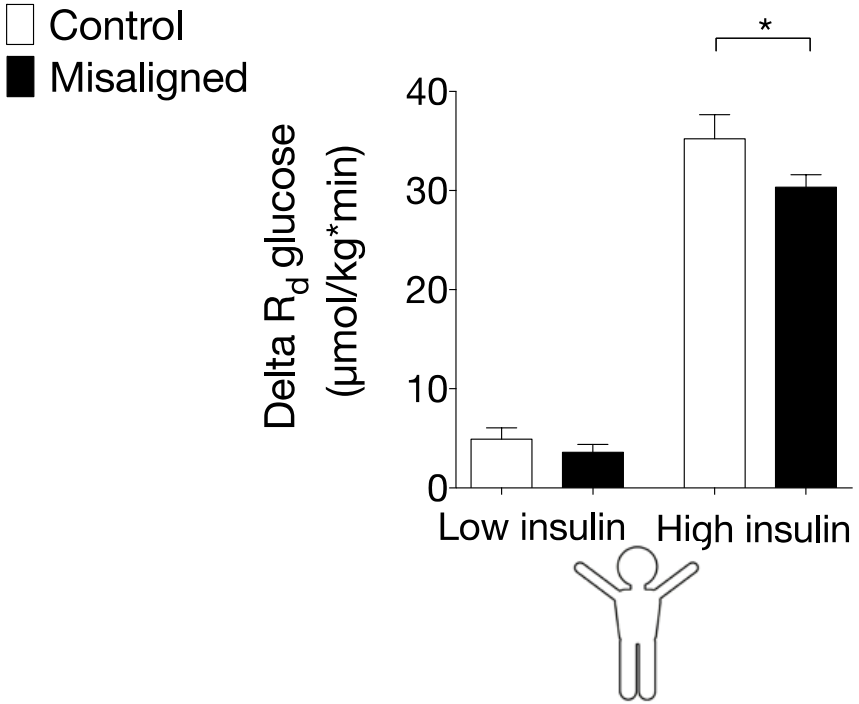
Wefers et al., PNAS 2018

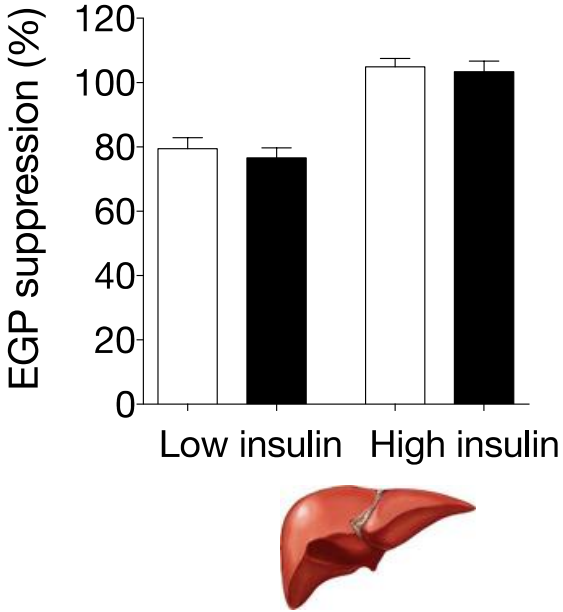
Bloed parameters zijn verstoord na dag-nacht shift



Wefers et al., PNAS 2018

Insuline gevoeligheid is verlaagd na 2 dagen dag-nacht shift

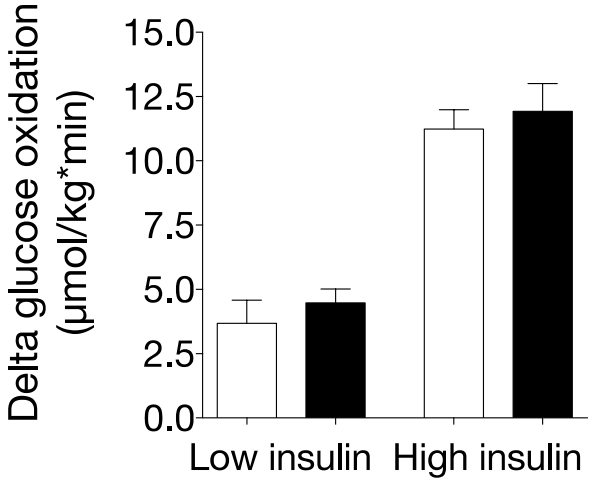




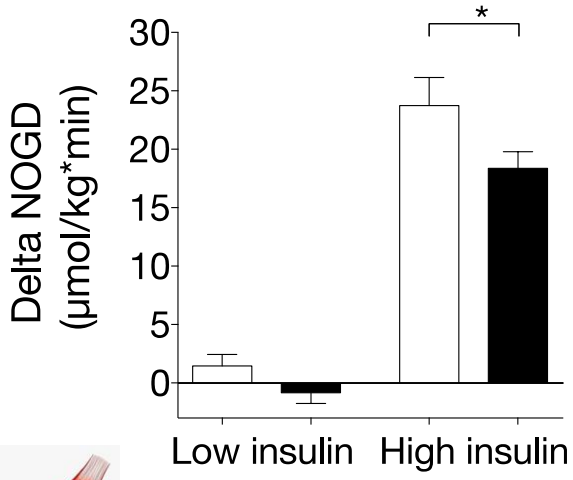
Wefers et al., PNAS 2018

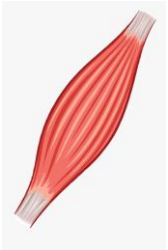
Vooral glycogen opslag is verstoord

Control
Misaligned



~ 23% decrease

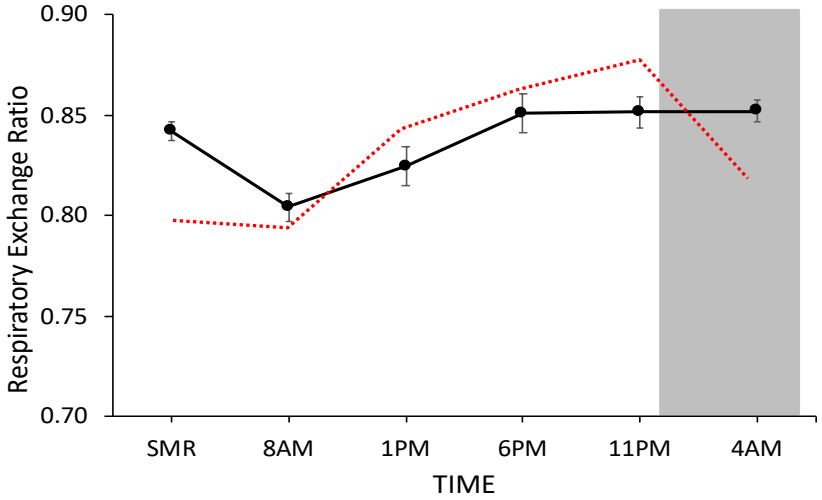


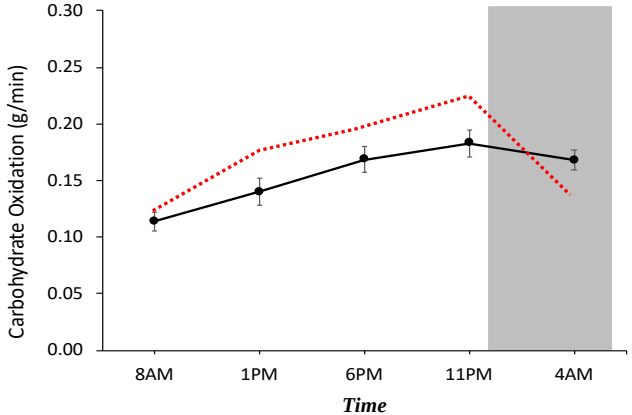


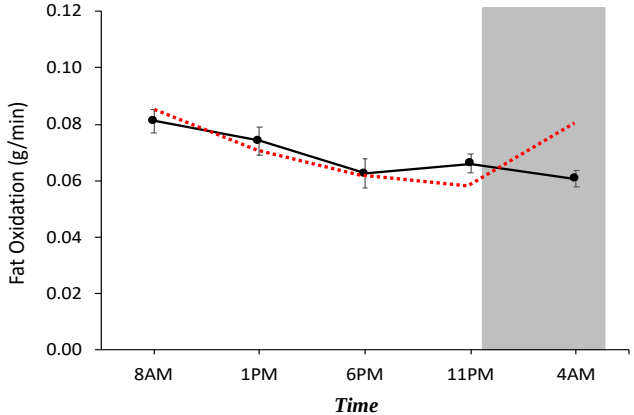
Wefers et al., PNAS 2018

Q: Kunnen we de biologische klok ’gebruiken’ om gezondheid te verbeteren?

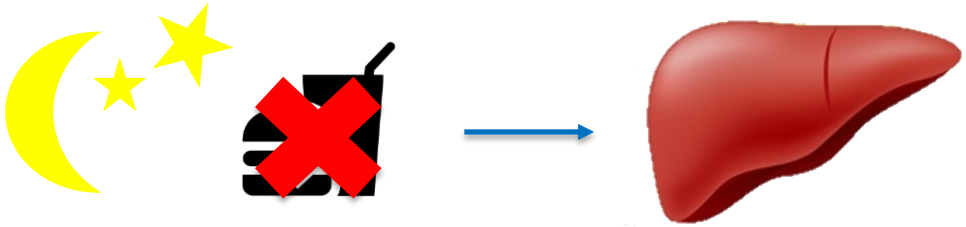
Met name het metabolism in de nacht is verstoord in prediabeten







Leverglycogeen is belangrijk in de nacht



A long overnight fasting period may be of great importance in maintaining metabolic health.

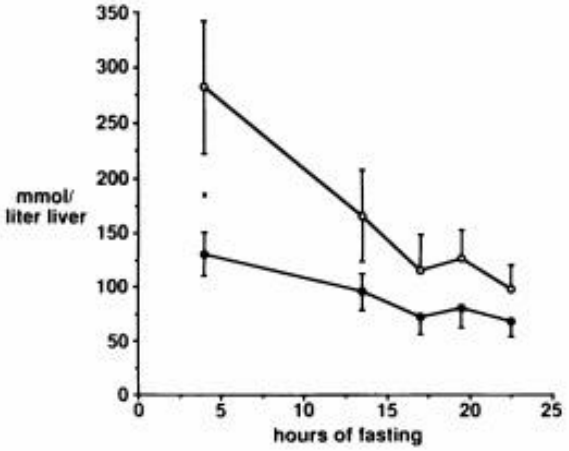


Figure 2. Time course for the mean liver glycogen concentration in the diabetics (●) and controls (○).

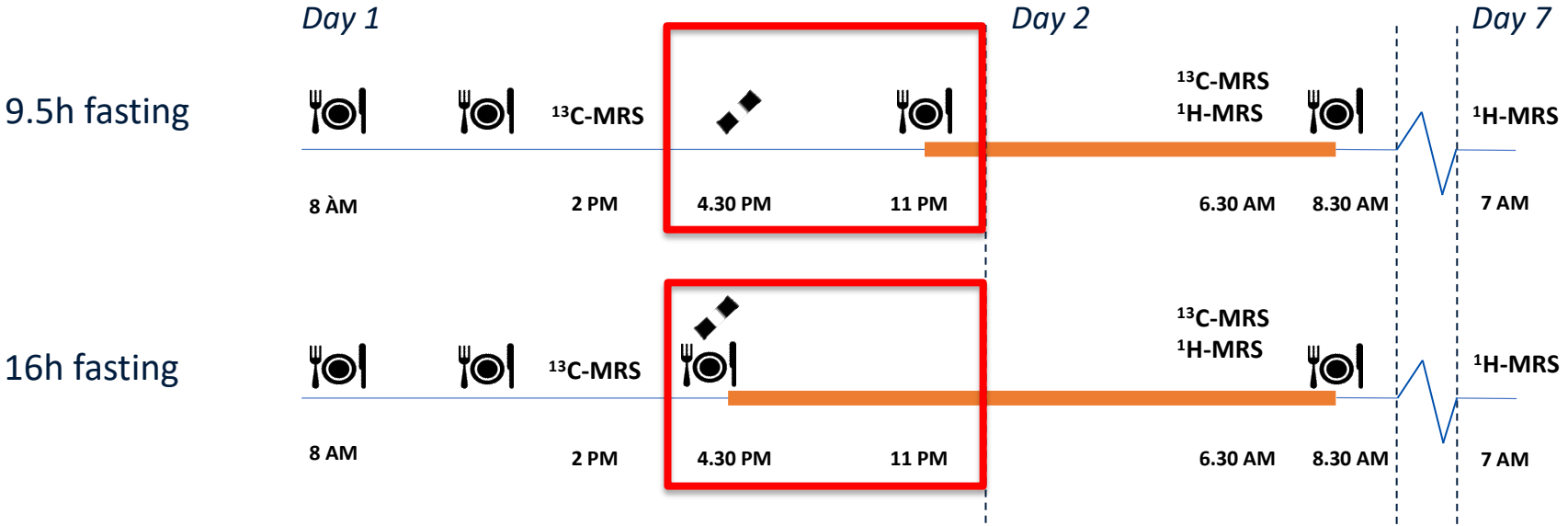
Magnusson et al. J. Clin. Invest. 1992

Q: kunnen we het metabolisme verbeteren door de vastentijd binnen een dag te verlengen?

Study opzet

Insulin resistente patienten met vervette lever

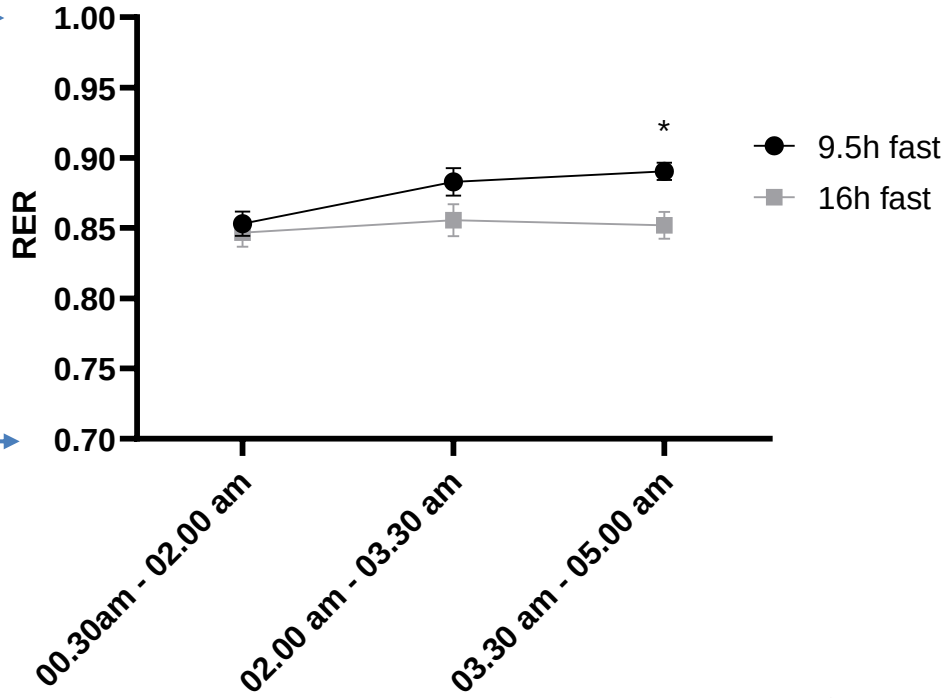
- Randomized, cross over trial



Geen acuut effect van verlengde vasten periode op het nachtelijk substraat gebruik

suiker verbranding

Vet verbranding



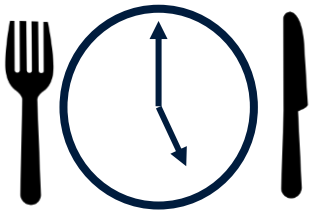
** p<0.05*

Data are presented as mean ± SEM

Roumans et al., unpublished

Q: wat zijn de langere termijn effecten van ‘time restricted eating’?

Beperken van de voedselinname naar ~ 6 uur/dag voor 2-4 weken heeft positieve effecten



Energy balance

- Blood pressure
- Postprandial insulin
- Insulin sensitivity
- Beta cell function

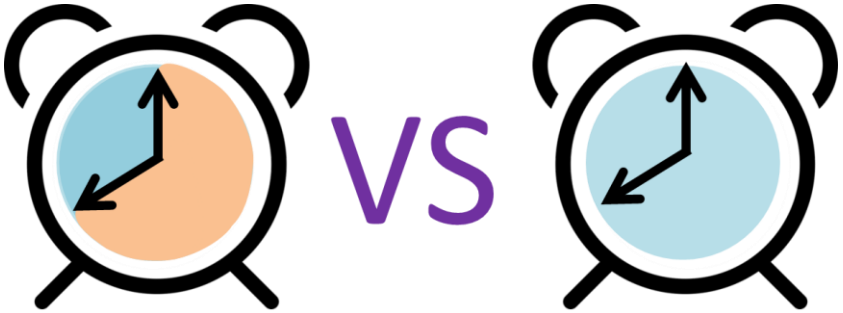
more pronounced fasting state

Hepatic glycogen

Wat als we 3 weken lang voedselinname beperken tot ~ 10 uur/dag? (haalbare aanpak?)

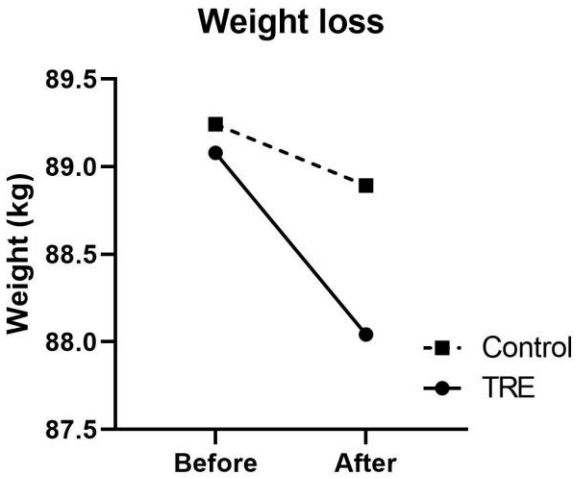
- Randomized controlled cross-over study
- n = 14 (M/F) patients with type 2 diabetes

3 weeks **Wash-out ≥ 4 weeks** **3 weeks**



10 hrs eating window **≥14 hrs eating window**

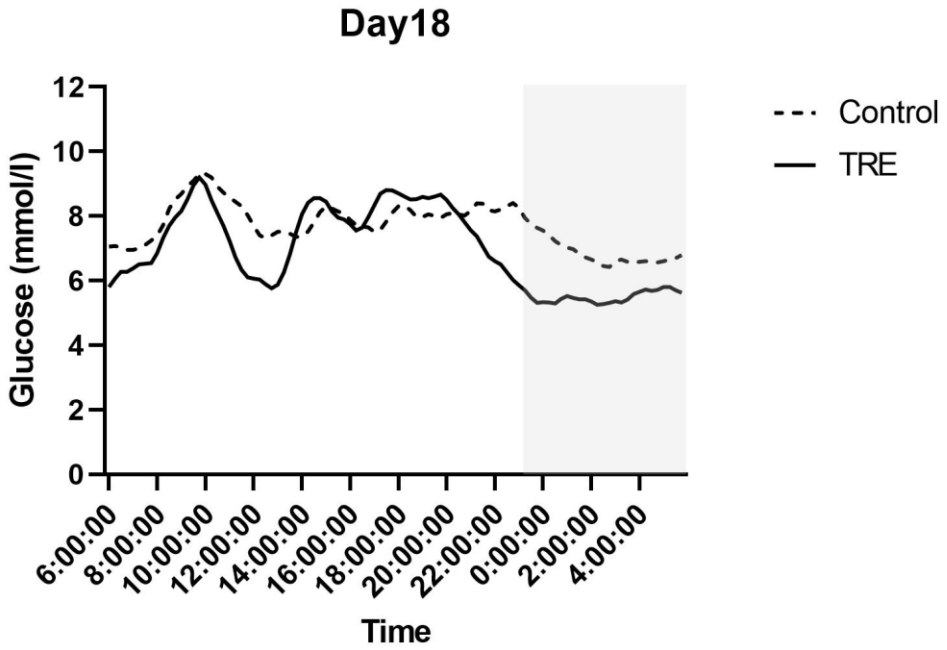
3 weken TRE resulteert in gewichtsverlies



- TRE (-1.0 kg)
- Controle (-0.3 kg)

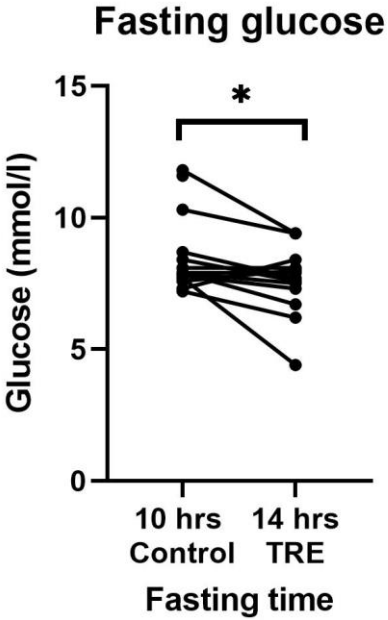
Andriessen et al., Diabetologia in press

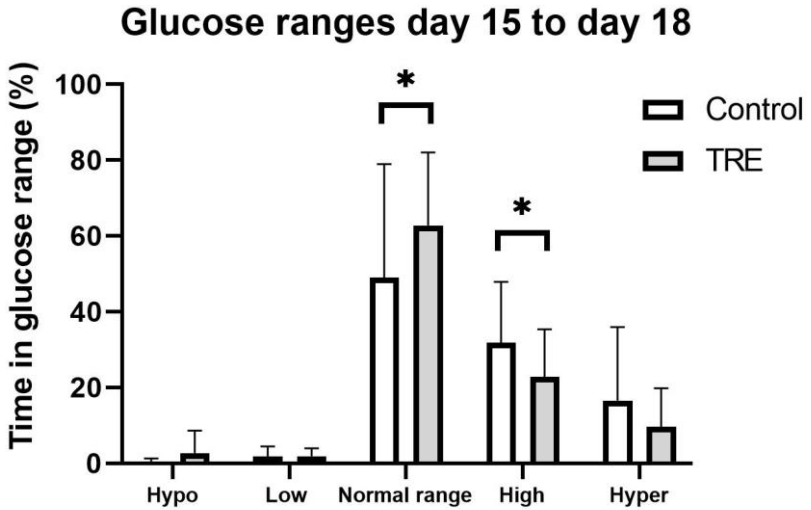
TRE heeft positief effect op 24 uurs glucose



Andriessen et al., Diabetologia in press

Bloed glucose daalt door TRE





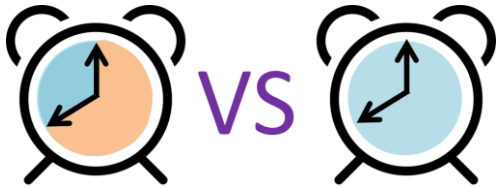
Andriessen et al., Diabetologia in press

Conclusie

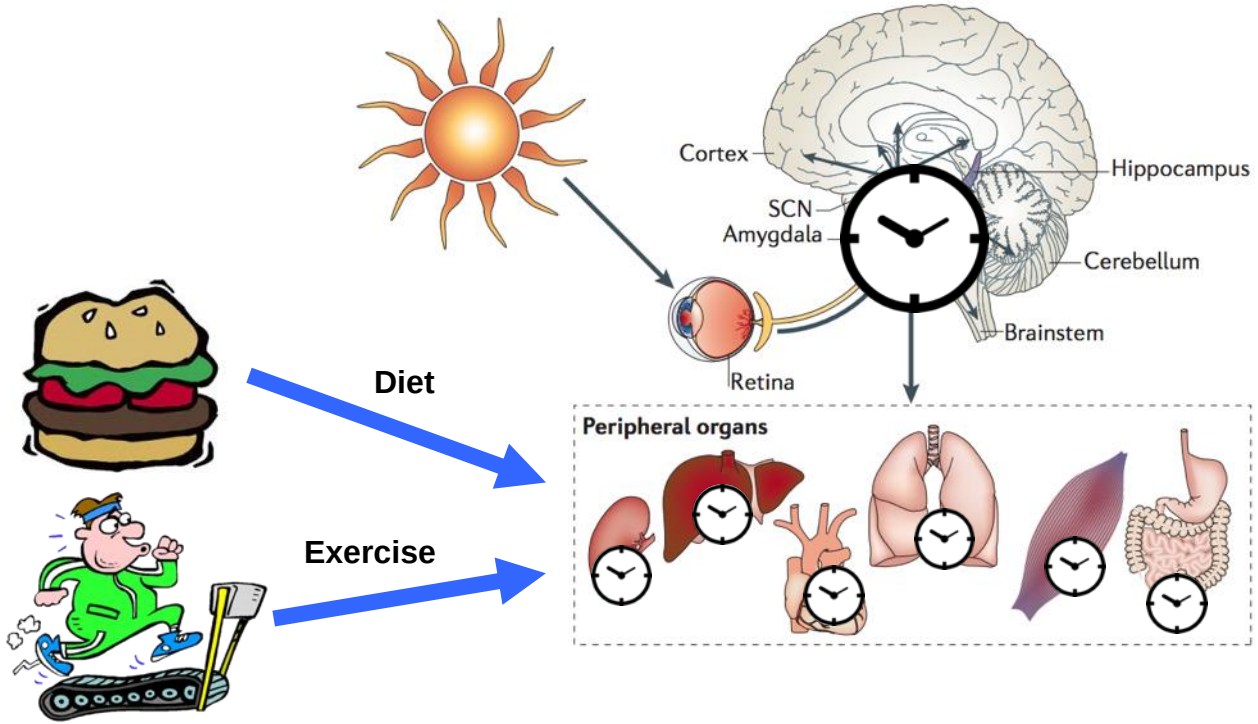
- Drie weken beperken van de voedselinname tot 10 uur /dag is effectief in het verlagen van bloedsuikerspiegel in type 2 diabetes patienten

- TRE leidt tot gewichtsverlies

- De interventie was haalbaar voor alle deelnemers



Inspanning kan ook een invloed hebben op de biologische klok



SCN, suprachiasmatic nucleus.

Kondratova A, et al. Nat Rev Neurosci. 2012;13(5):325–335.

Q: is er een verschil in de effecten van trainen in de ochtend versus de middag?

- Twaalf weken training programma, combinatie van duur en kracht training
- 32 mannen met BMI > 26 kg/m2
- 12 deelnemers trainden tussen 08:00 en 10:00 (AM groep)
- 20 deelnemers trainden tussen 15:00 en 18:00 (PM groep)
- Compliantie ~ 98%.

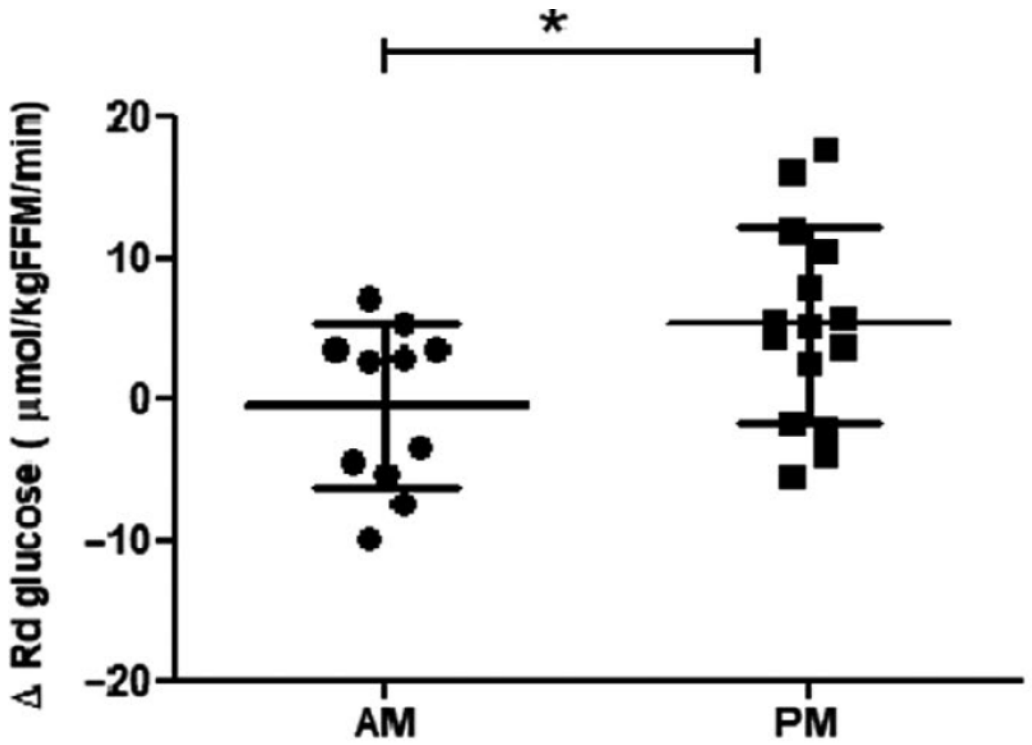
Mancilla et al., Physiol Rep 2020

Geen verschillen vóór 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

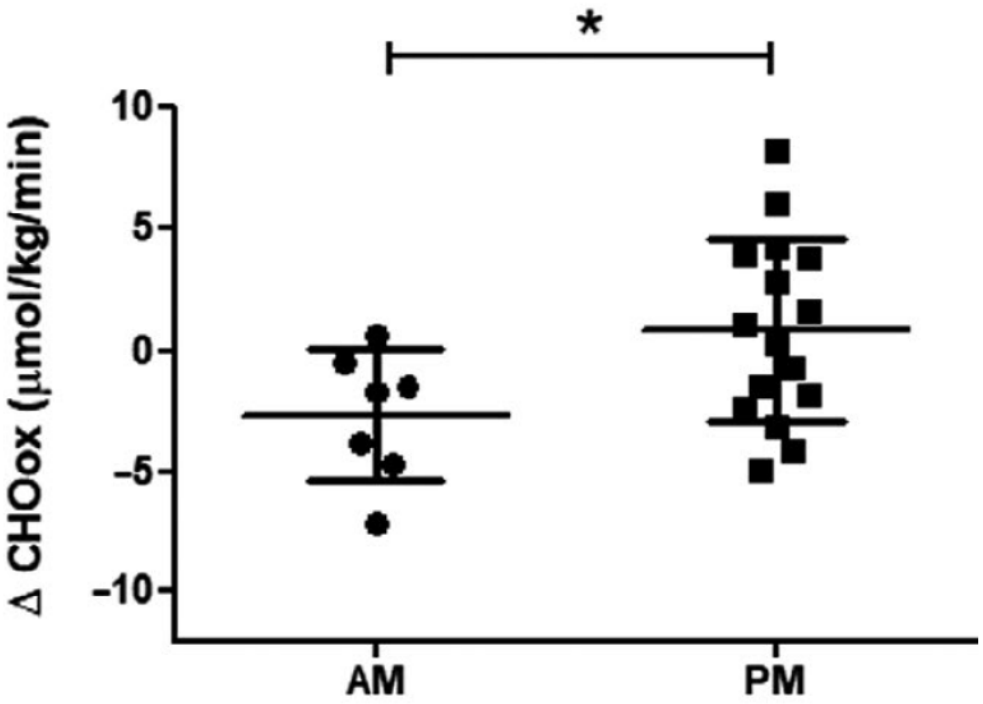
Mancilla et al., Physiol Rep 2020

Middag training verbetert de insuline gevoeligheid meer dan ochtend training



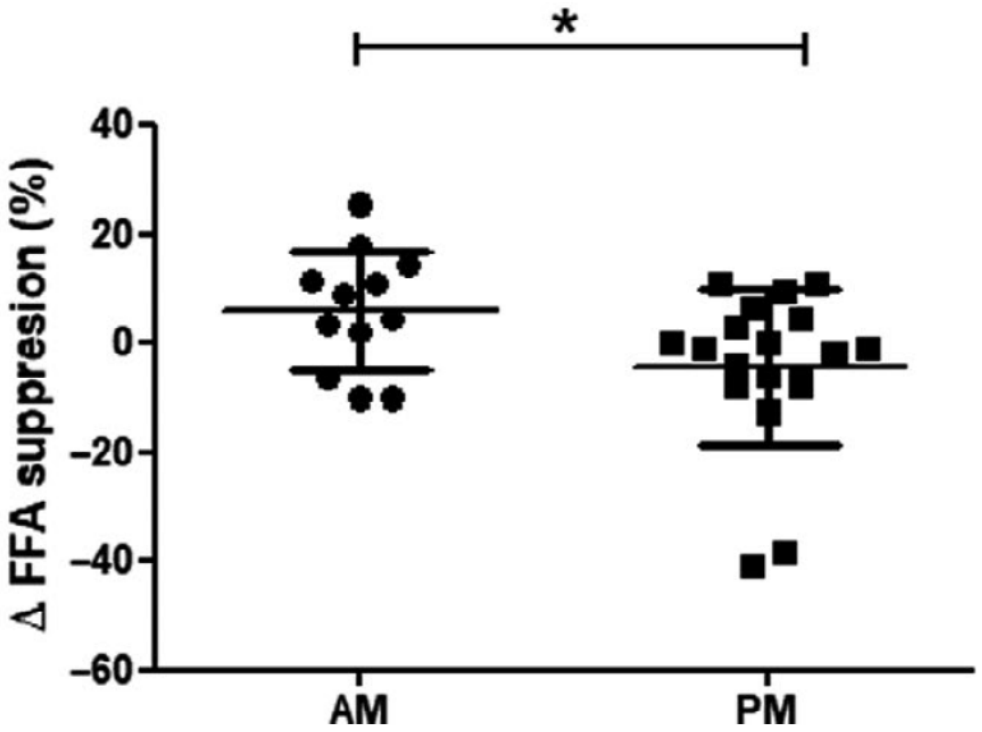
Mancilla et al., Physiol Rep 2020

Middag training verbetert de glucose oxidatie meer dan ochtend training



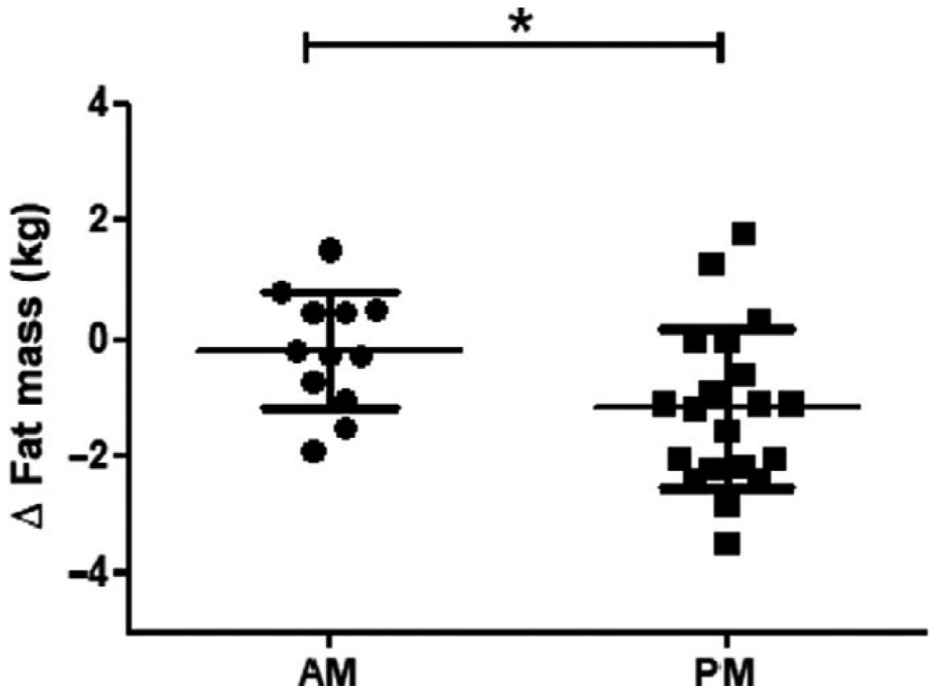
Mancilla et al., Physiol Rep 2020

Middag training verbetert de insuline gevoeligheid van vetweefsel meer dan ochtend training



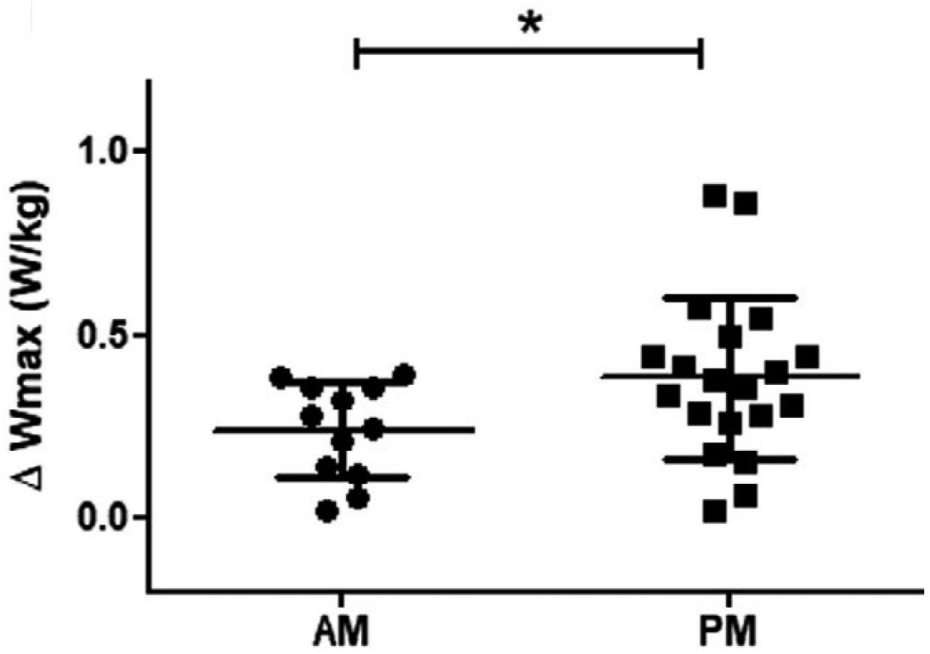
Mancilla et al., Physiol Rep 2020

Middag training verlaagd de hoeveelheid vetmassa meer dan ochtend training



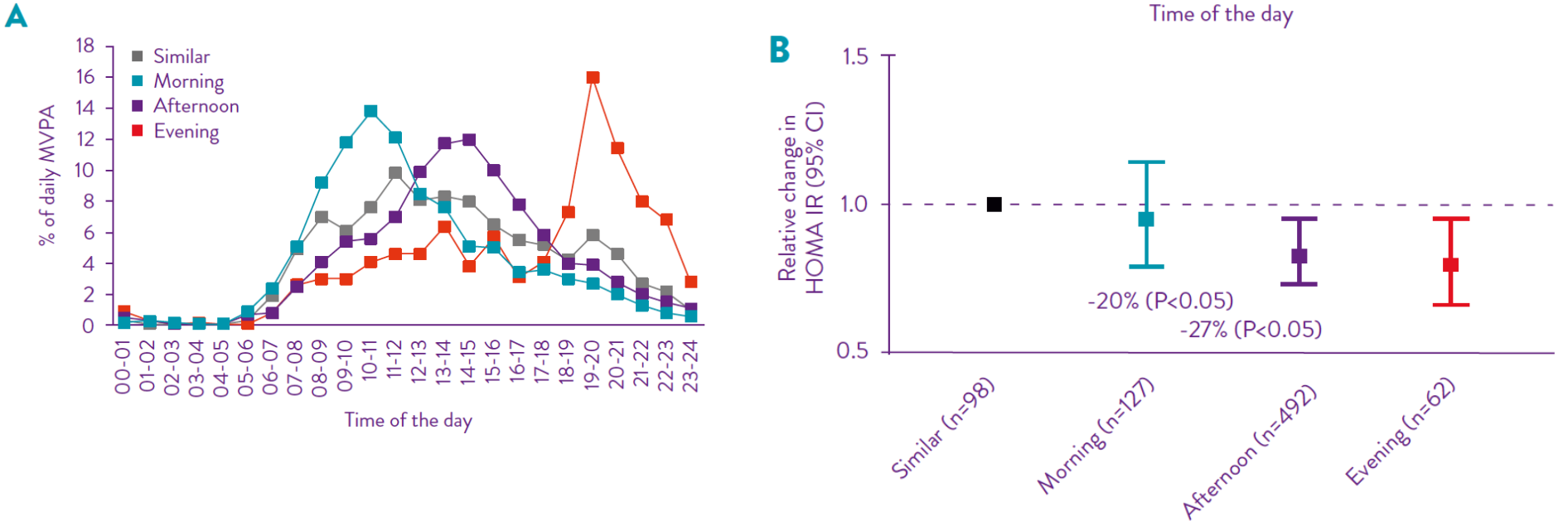
Mancilla et al., Physiol Rep 2020

Middag training verbetert het prestatie vermogen meer dan ochtend training



Mancilla et al., Physiol Rep 2020

Activiteit later op de dag is geassocieerd met betere insuline gevoeligheid



Van de Velde et al., unpublished

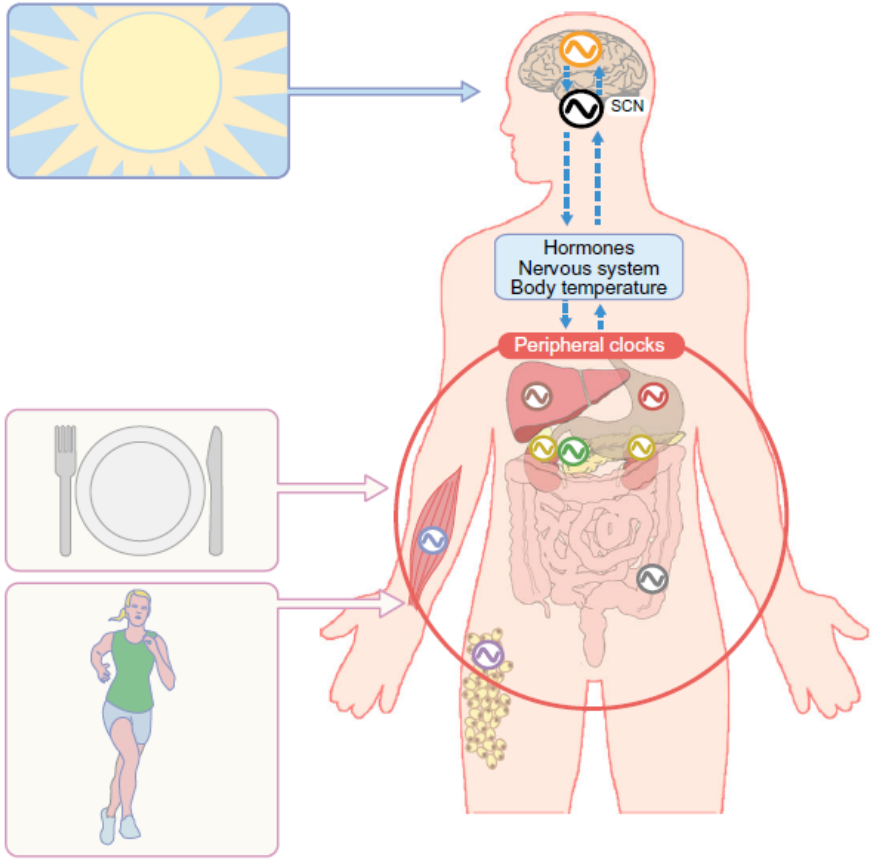
The New York Times

PHYS ED

The Best Time of Day to Exercise

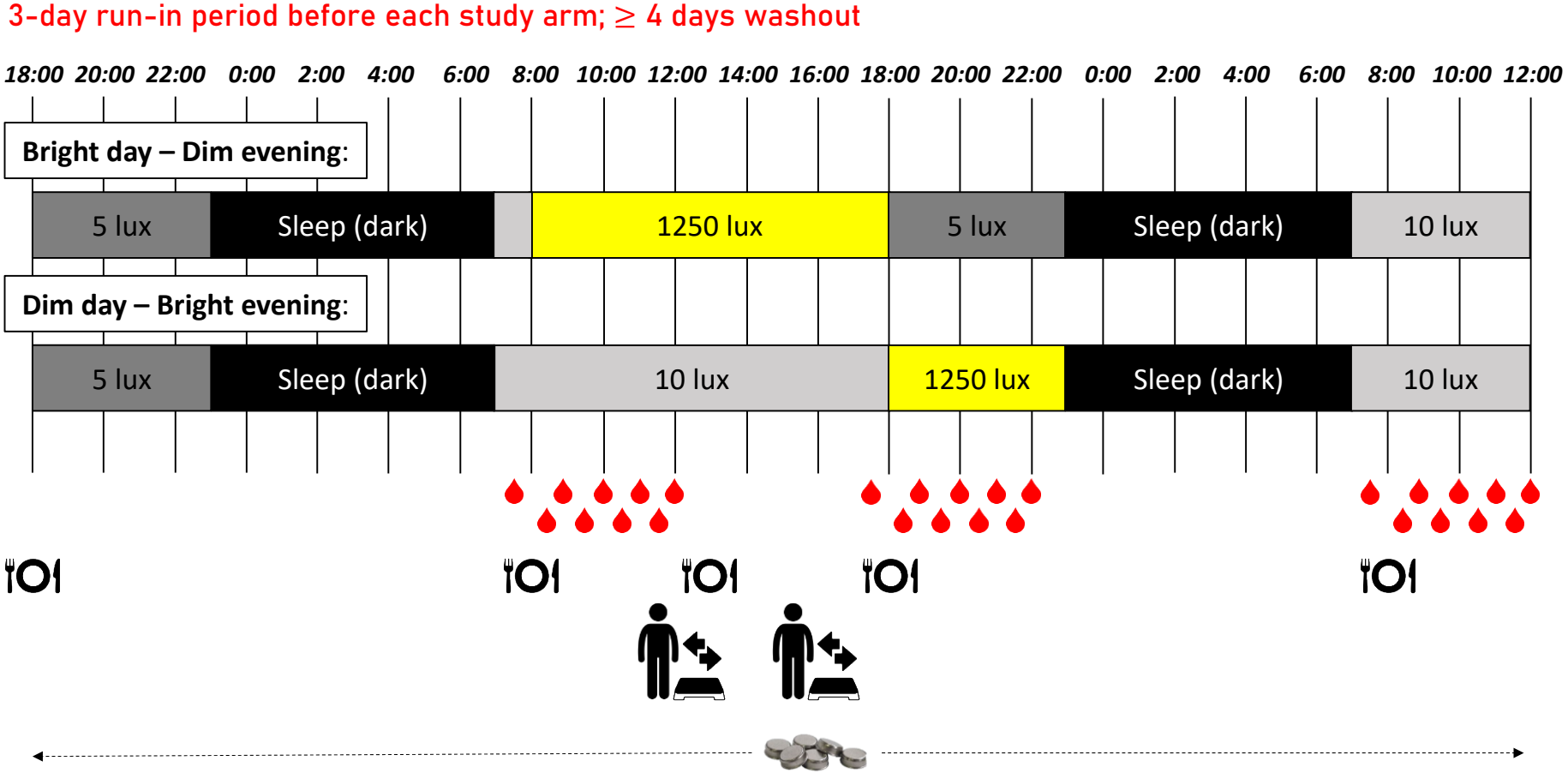
Men at risk for diabetes had greater blood sugar control and lost more belly fat when they exercised in the afternoon than in the morning.

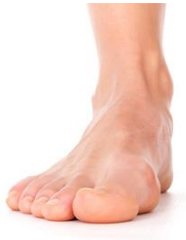
Mancilla et al., Physiol Rep 2020

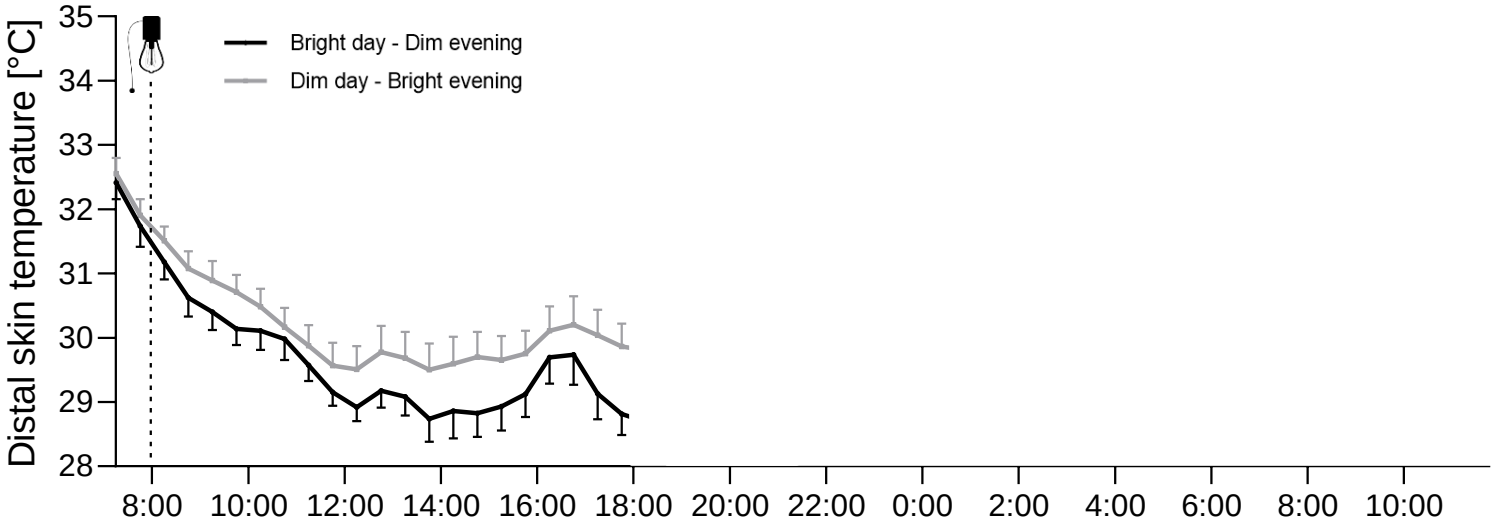


Mason et al. Diabetologia 2020

Q: Effect van optimale licht omstandigheden op energie metabolisme

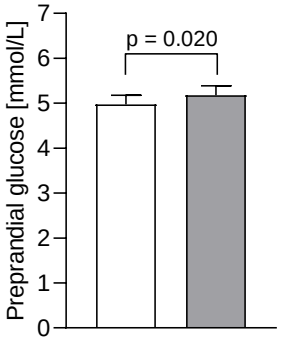




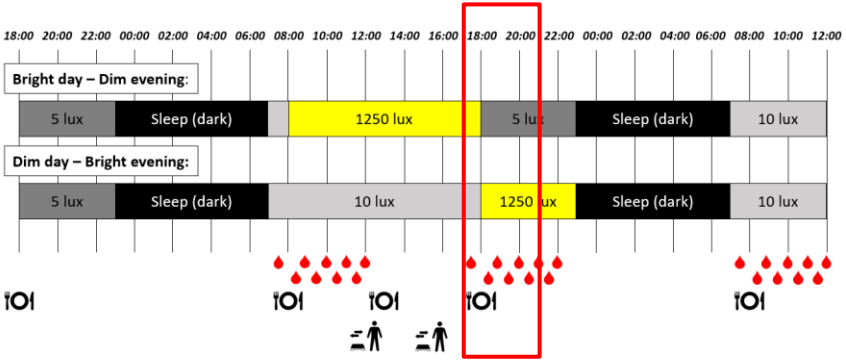


Huid temperatuur van de extremiteiten verandert door licht

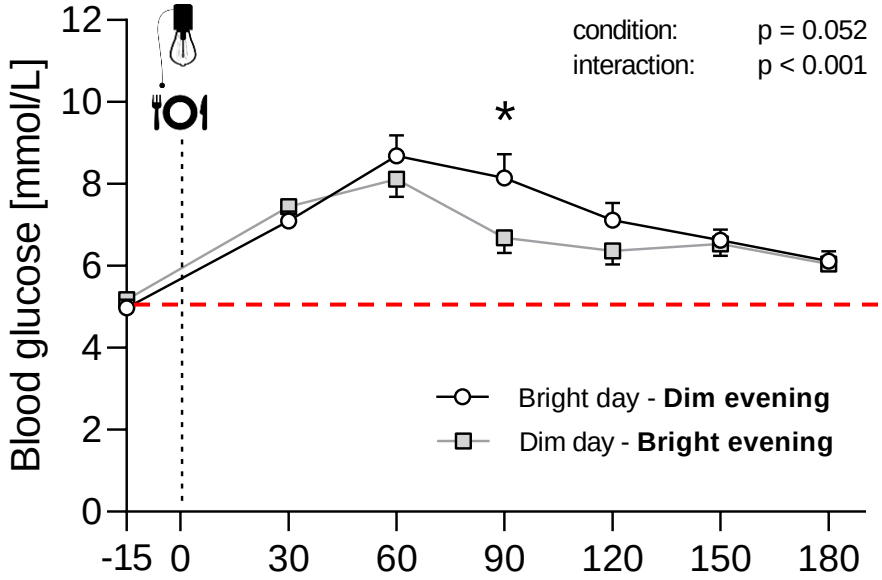
Harmsen et al., Diabetologia 2022

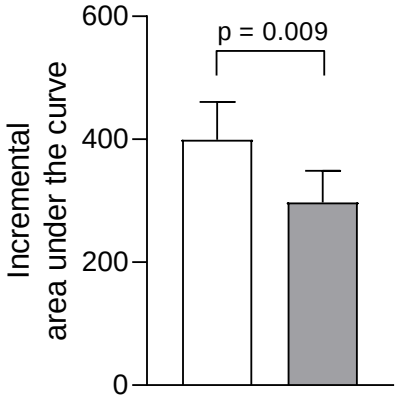


Bright day - Dim evening
Dim day - Bright evening



Dinner





Harmsen et al., Diabetologia 2022

Conclusies

- Mitochondriele functie en substrate metabolisme vertonen 24 uurs ritme in gezonde, maar niet in pre-diabete volwassenen
- Een snelle dag-nacht shift (jet lag/ night shift) resulteert in insuline resistentie
- Beperken van de voedselinname tot ~ 10 uur/dag heeft gunstige effecten op bloedsuikerspiegel in type 2 diabetes
- Inspanning in de middag/avond verbetert het metabolisme meer dan inspanning in de ochtend
- Blootstelling aan licht heeft een invloed op onze stofwisseling

The stars