Insulineresistentie en hyperglykemie

Bad companions voor vasculaire gezondheid

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Koolhydraten en Insulinegevoeligheid
Utrecht, 10 maart 2020

Insulineresistentie

Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants

*The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects)**

Lancet 2014;383:970

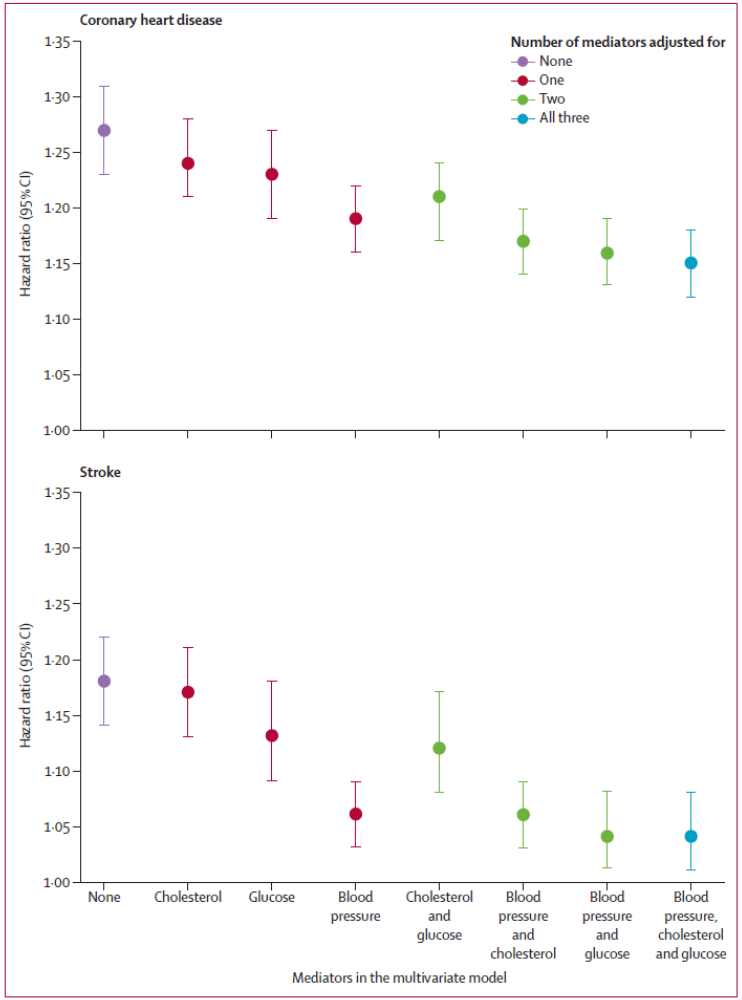


Figure 1: Hazard ratios per 5 kg/m² higher body-mass index adjusted for different combinations of mediators in coronary heart disease and stroke

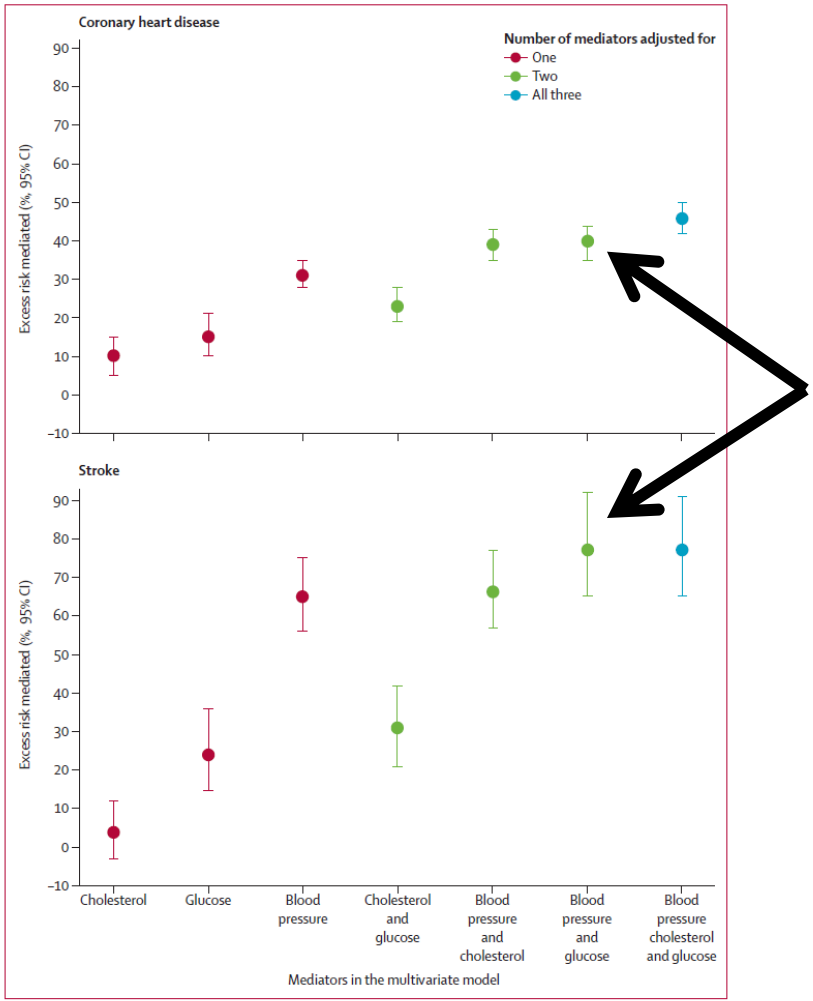


Figure 3: Percentage of excess risk per 5 kg/m² higher body-mass index mediated through different combinations of metabolic risk factors in coronary heart disease and stroke

Insulin Resistance:
Two Keys to Understanding its Role in Vascular Disease

Insulin resistance implies (induces, is accompanied by)
hyperinsulinaemia

Insulin:
not just a glucose – regulating hormone

Hypertension and Dyslipidaemia in Obesity

insulin resistance plus hyperinsulinaemia

- ↓ dilation of small and large arteries, and ↑ arterial stiffening
- ↑ activity of sympathetic nervous system and RAAS
- ↑ renal sodium retention

adipokines (RAAS, leptin)

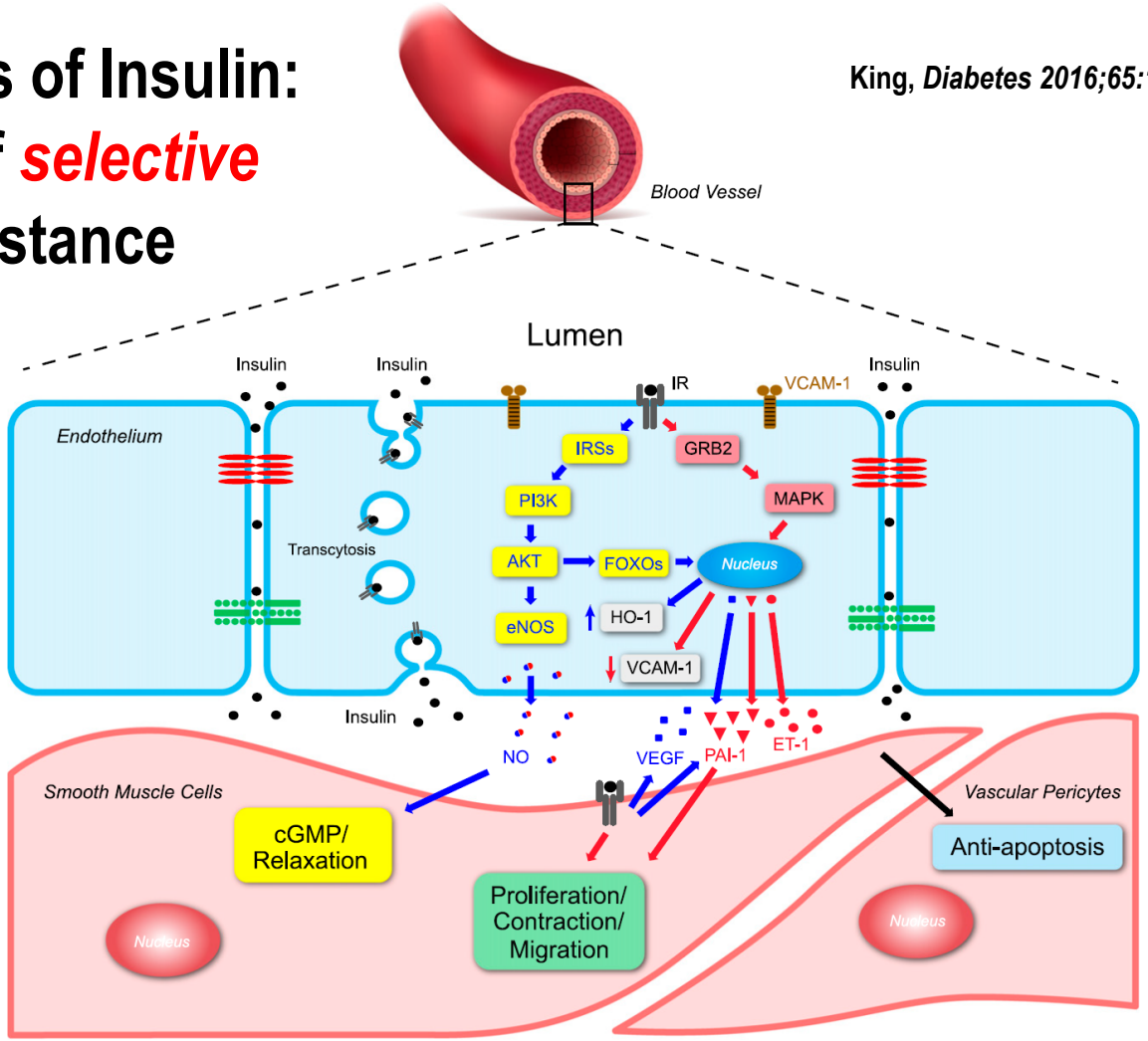
hypertriglyceridaemia: central role

- ↑ adipose tissue lipolysis
- ↑ hepatic apo B and VLDL secretion
- ↓ lipoprotein lipase

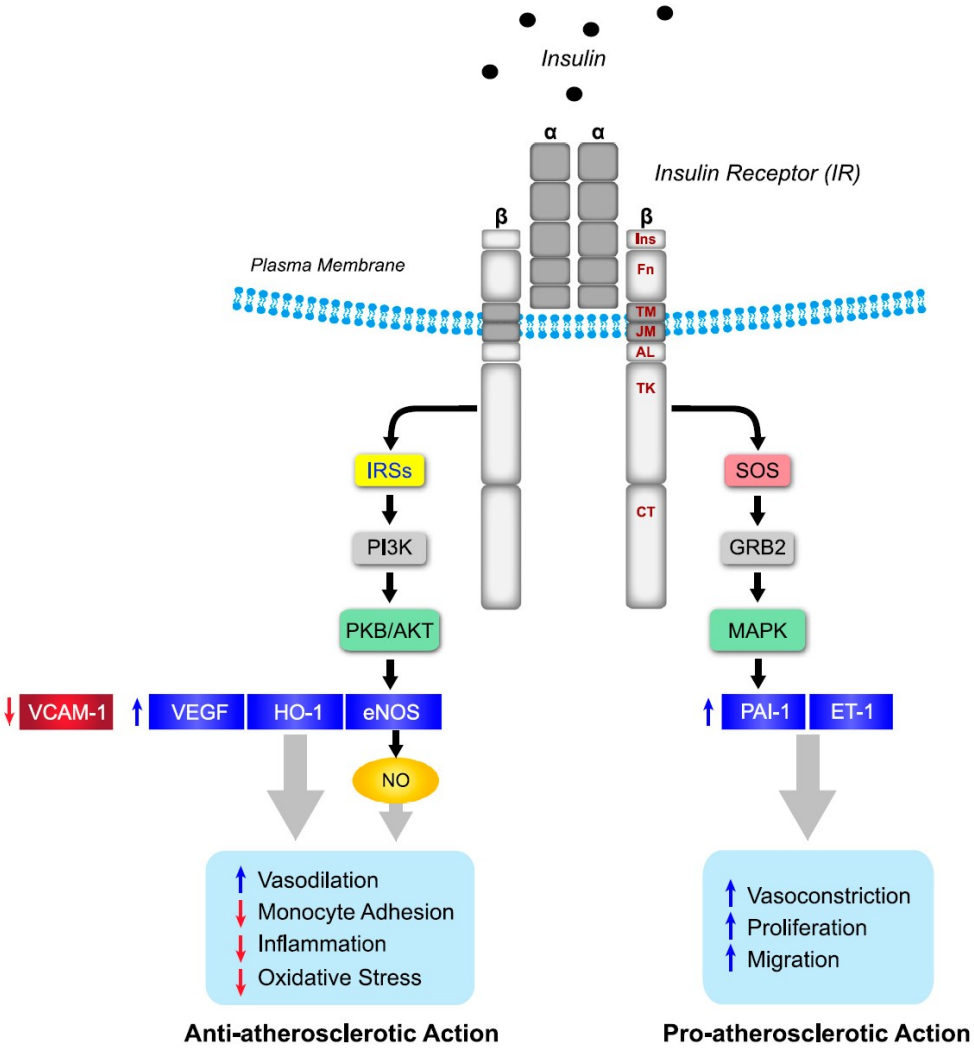
low HDL-c and high small dense LDL follow from high TGs

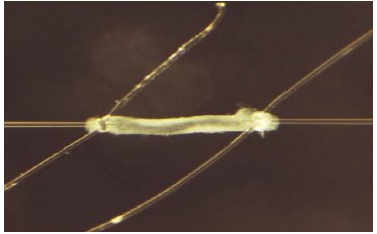
Vascular Effects of Insulin: the concept of *selective* insulin resistance

King, *Diabetes 2016;65:1462*

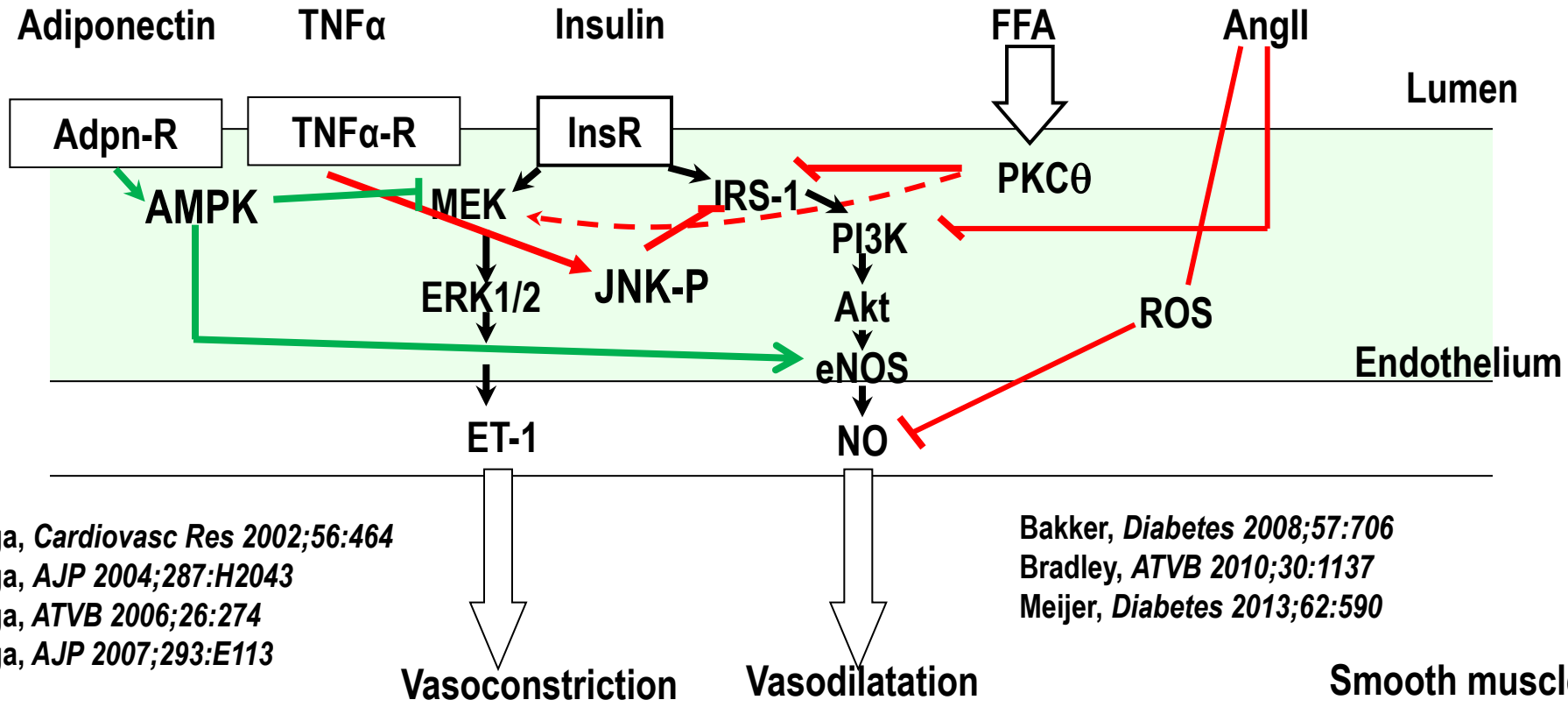


King, *Diabetes 2016;65:1462*





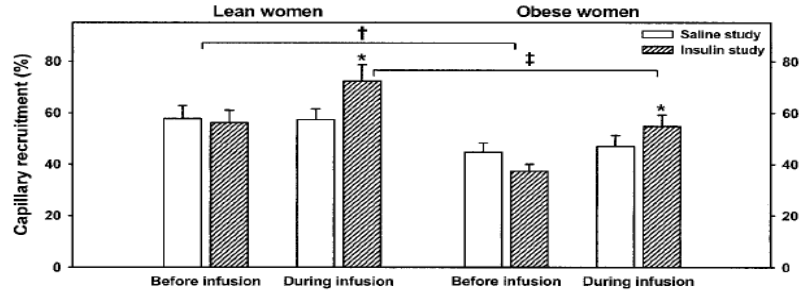
Regulation of Insulin-Mediated Vasoreactivity by Adiponectin, TNFα, FFAs and AngII

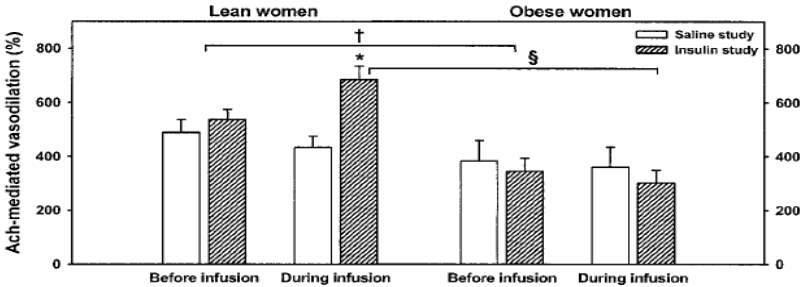


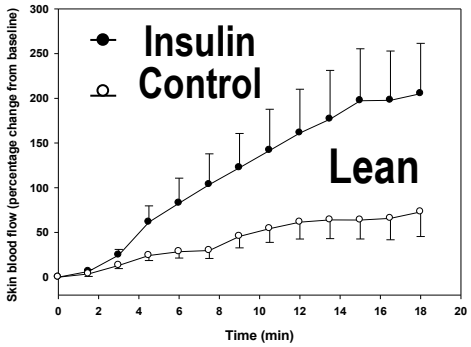
Eringa, *Cardiovasc Res 2002;56:464*
Eringa, *AJP 2004;287:H2043*
Eringa, *ATVB 2006;26:274*
Eringa, *AJP 2007;293:E113*

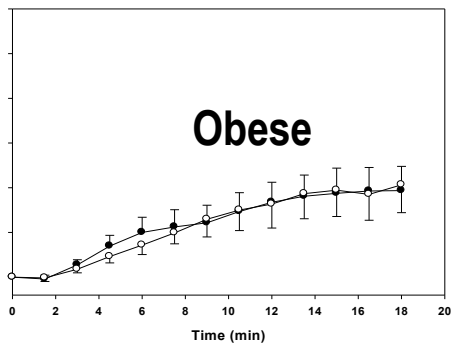
Bakker, *Diabetes 2008;57:706*
Bradley, *ATVB 2010;30:1137*
Meijer, *Diabetes 2013;62:590*

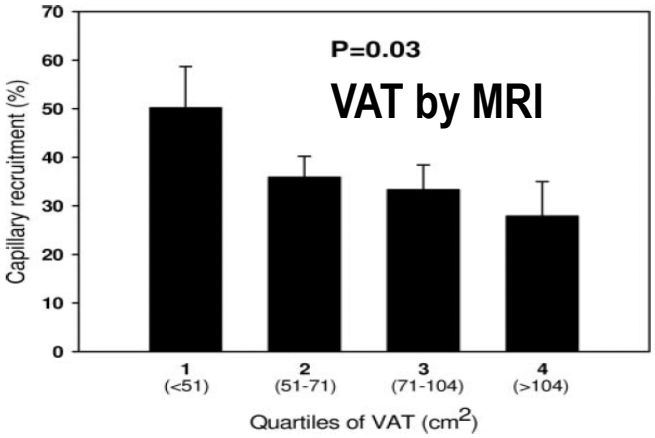
Microvascular dysfunction in obesity







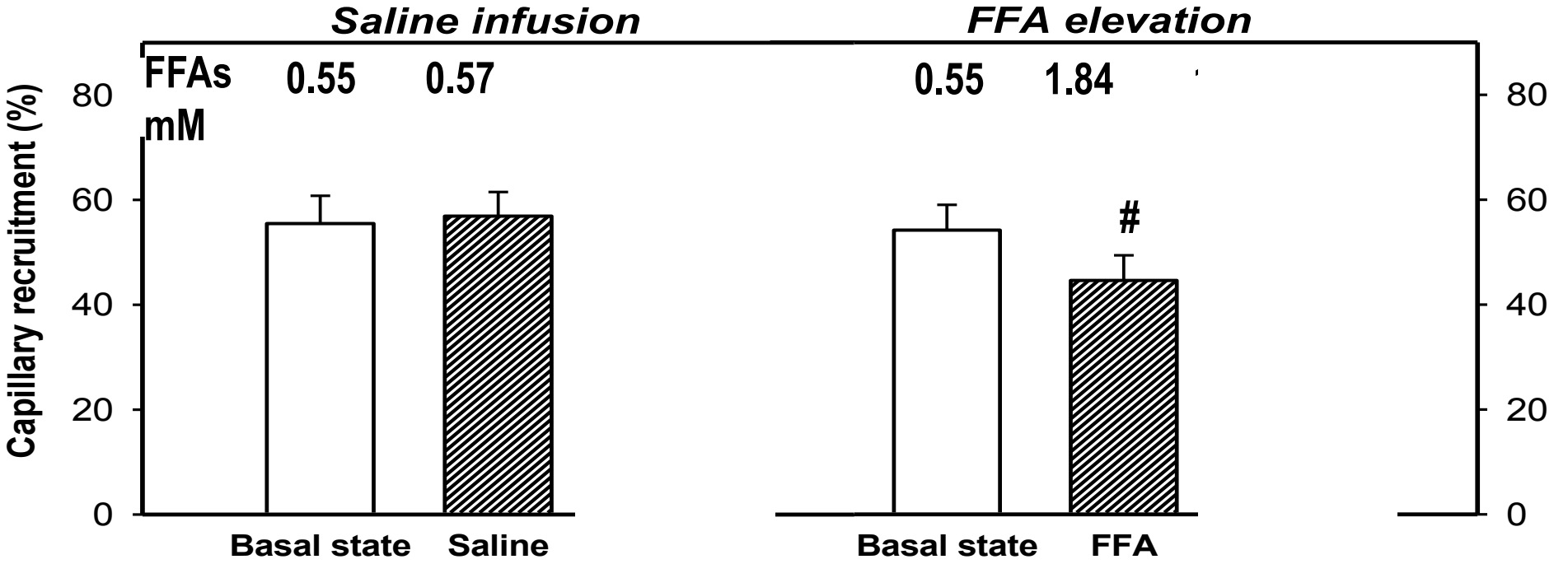




De Jongh, *Circulation 2004;109:2529*; De Jongh, *JCEM 2006;91:5100;* De Jongh, *Microvasc Res 2008;75:256*

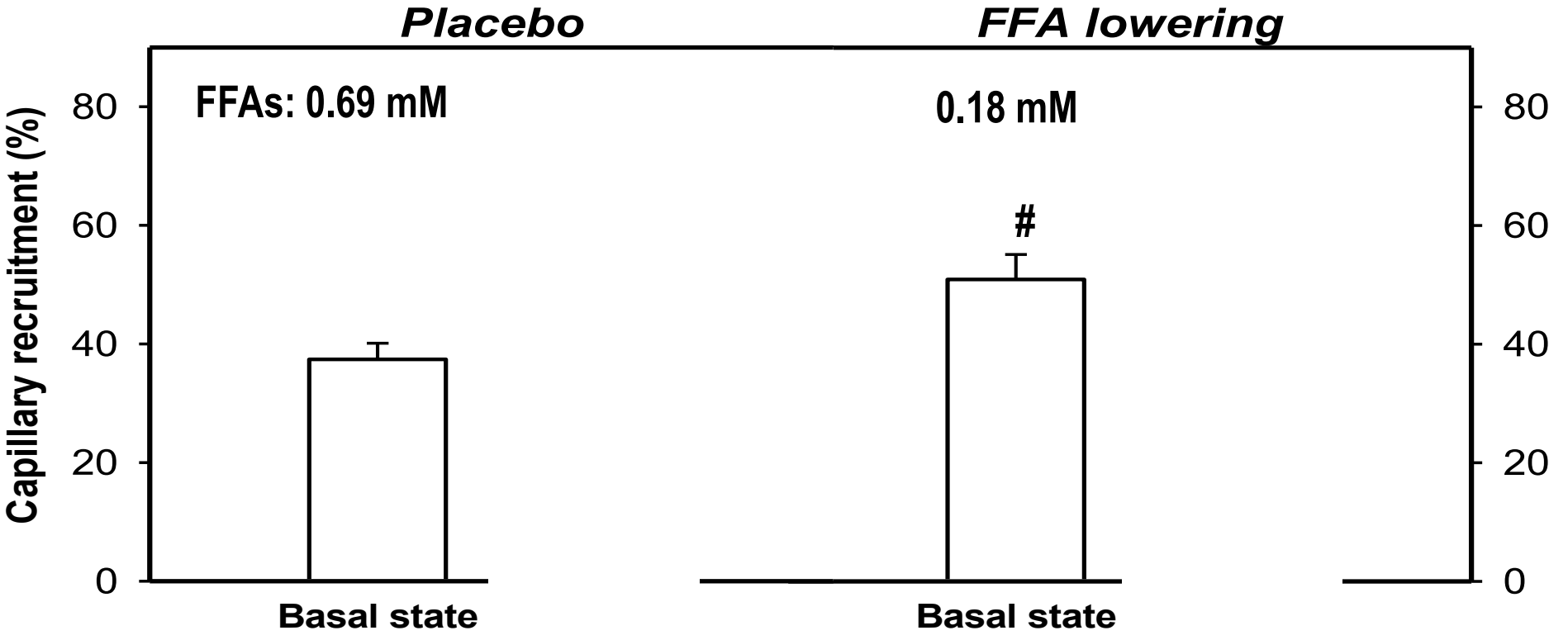
An Intralipid-Induced Acute (2 – 6h) Increase in FFAs Impairs Capillary Recruitment in Lean Women

De Jongh, *Diabetes 2004;53:2873*



An Acipimox-Induced Overnight Decrease in FFAs Improves Capillary Recruitment in Obese Women

De Jongh, *Diabetes 2004;53:2873*



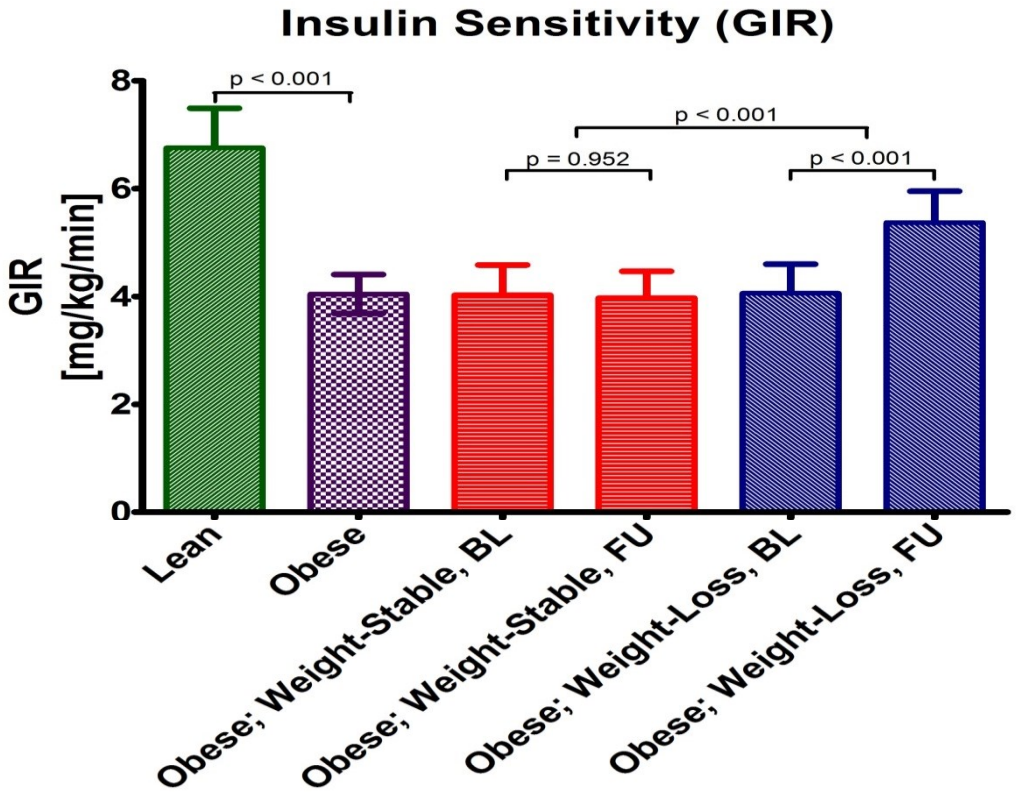
Weight loss improves whole – body glucose disposal in part through improvement of microvascular function

Lean N = 25
BMI = 23.3

Obese N = 50

Weight stable N = 26
BMI = 29.9 → 30.0

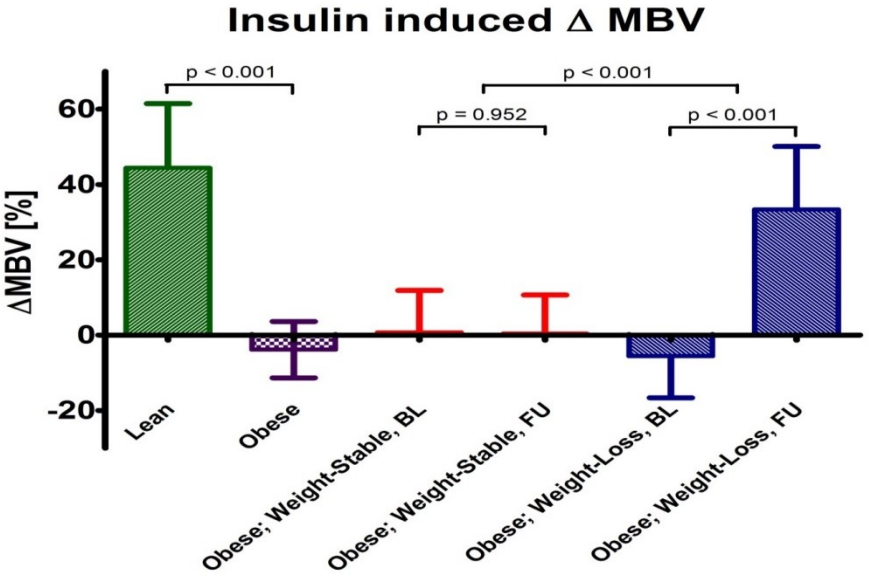
Weight loss N = 24
BMI = 30.0 → 27.0
mean 9.8 kg

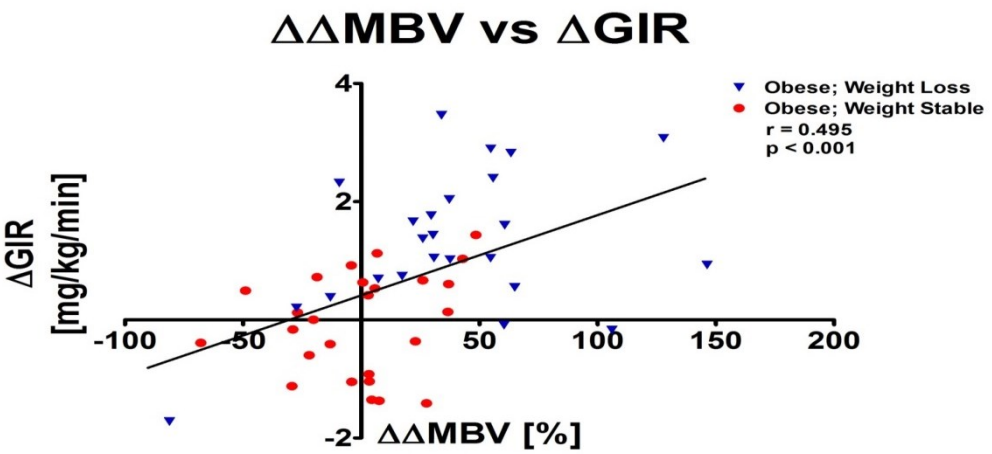


Kusters, *JCI Insight 2017;2:e89695*

Mean ± 95% CI

Weight loss improves insulin-induced muscle microvascular recruitment





Hyperglykemie

Prediabetes

Table 1. Classification criteria of glucose metabolism status (WHO 2006)

	2h post OGTT glucose (mmol/L)		
Fasting plasma glucose (mmol/L)	**< 7.8**	**7.8 - 11.1**	**≥ 11.1**
< 6.1	Normal (NGM)	IGT (Prediabetes)	Type 2 diabetes (T2DM)
6.1 - 7.0	IFG (Prediabetes)	IFG + IGT (Prediabetes)	Type 2 diabetes (T2DM)
≥ 7.0	Type 2 diabetes (T2DM)	Type 2 diabetes (T2DM)	Type 2 diabetes (T2DM)

DE MAASTRICHT STUDIE

Prediabetes affects ~ 25% of individuals 40 – 75 years of age

Lifetime risk at age 45 y is ~50%

Ligthart (Rotterdam Study),
Lancet Diabetes Endocrinol 2016;4:44

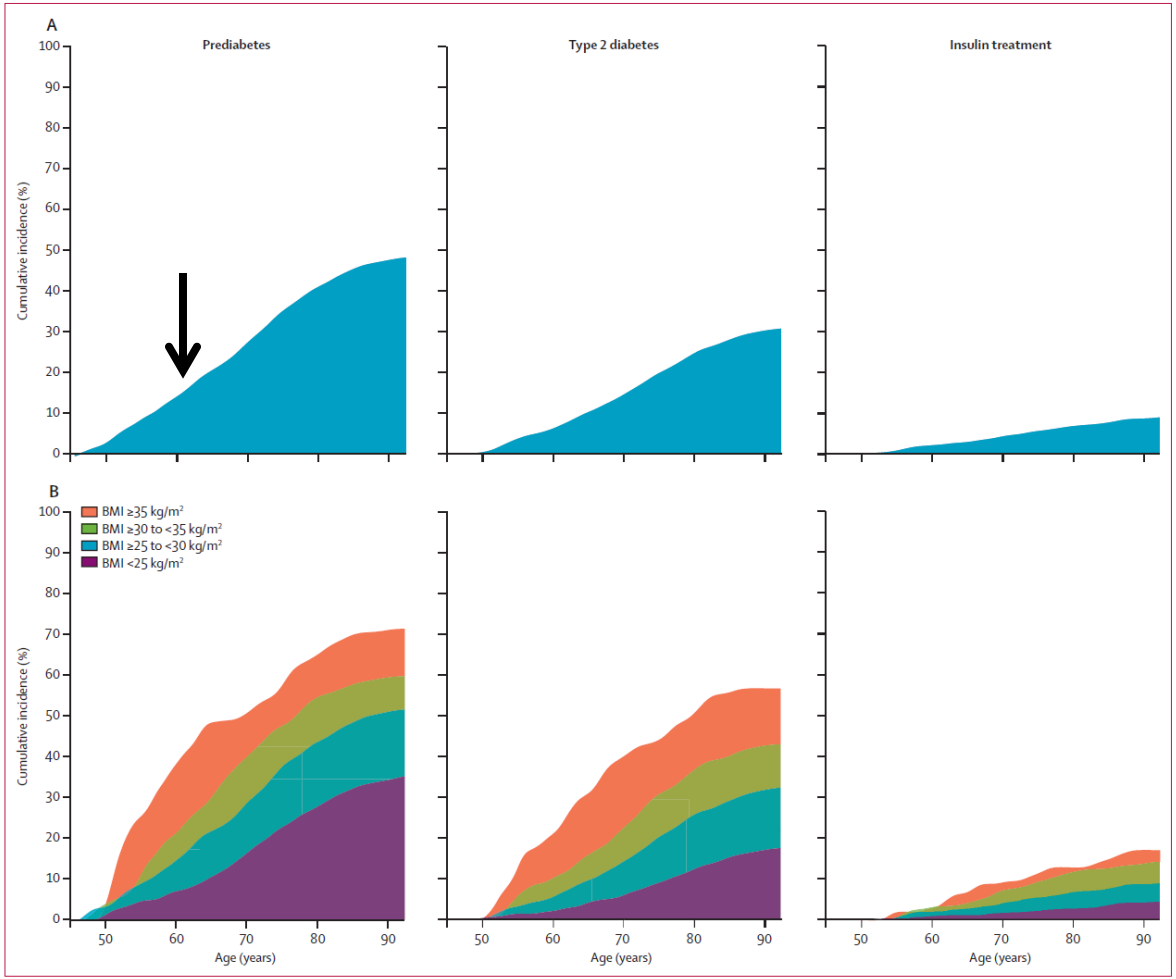
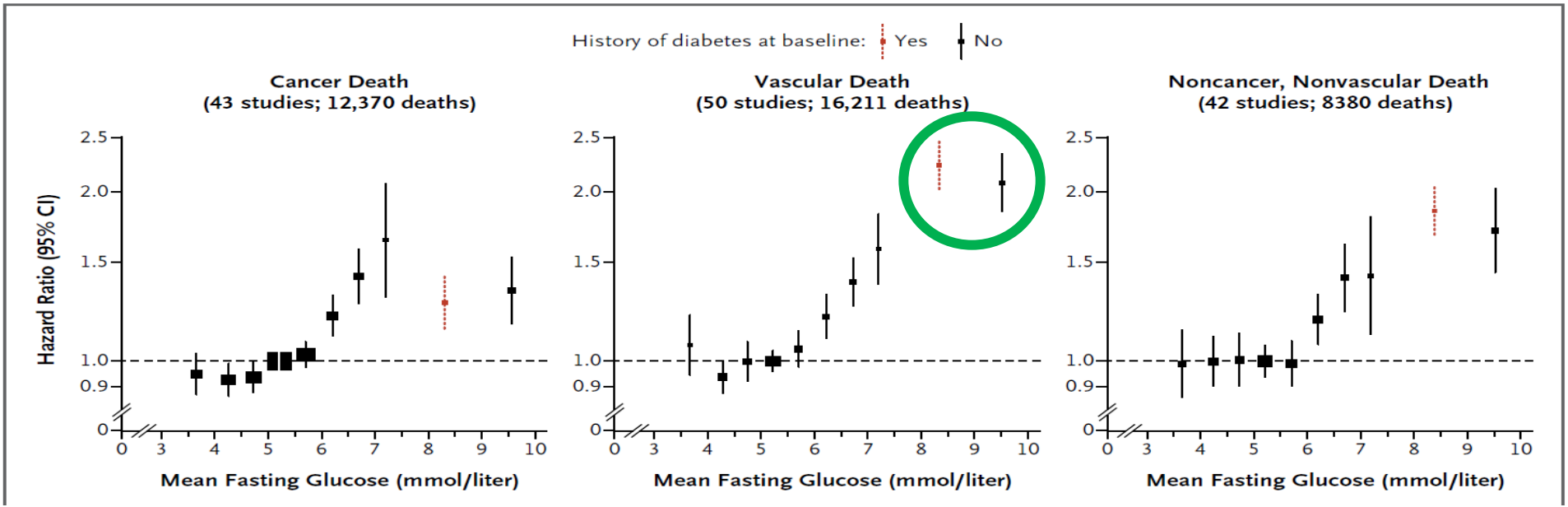
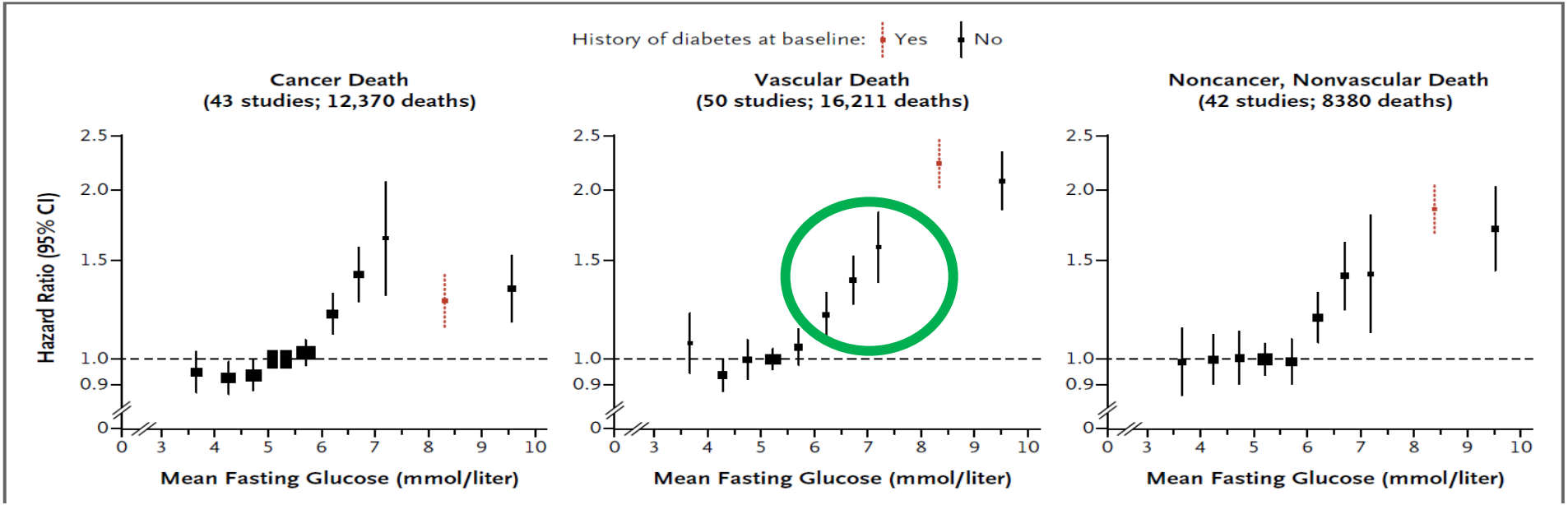


Figure 2: **Lifetime risk of prediabetes, type 2 diabetes, and use of insulin treatment in individuals aged 45 years, adjusted for the competing risk of death**
(A) Cumulative incidence of prediabetes (fasting glucose >6·0 mmol/L), type 2 diabetes (fasting glucose ≥7·0 mmol/L or use of glucose-lowering drug), and insulin use in all individuals aged 45 years, adjusted for the competing risk of death. (B) Cumulative incidences of prediabetes, type 2 diabetes, and insulin use in individuals aged 45 years, adjusted for the competing risk of death, by BMI.



Adjusted for **age, sex, systolic blood pressure, lipids, inflammation, estimated glomerular filtration rate,**
smoking, body mass index, socio-economic status, lifestyle

Emerging Risk Factors Collaboration, N Engl J Med 2011;364:829



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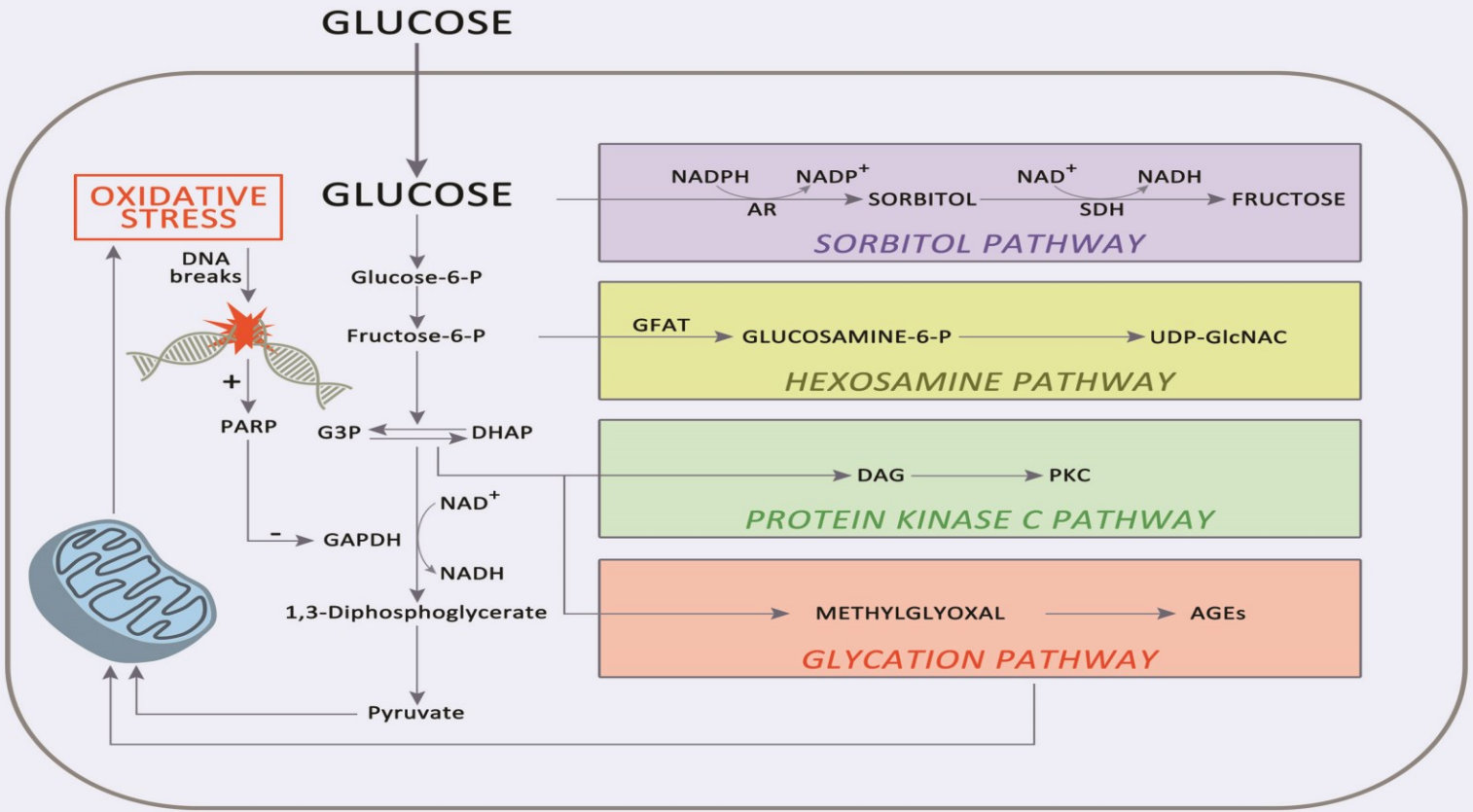
Emerging Risk Factors Collaboration, N Engl J Med 2011;364:829

Microvascular Endothelial and Neural Cells

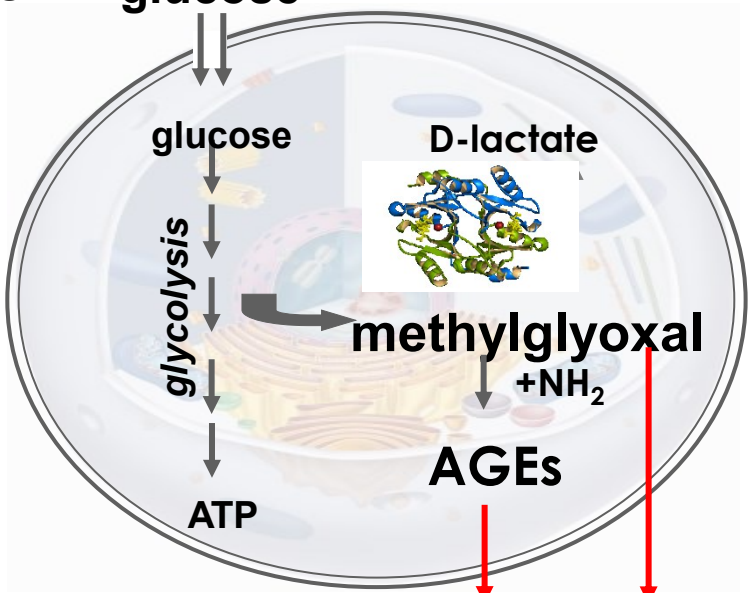


Brownlee, *Diabetes 2005;54:1615;* Schalkwijk & Stehouwer, *Physiol Rev 2020;100:407*

Targeting methylglyoxal

(pre)diabetes → glucose

Schalkwijk & Stehouwer,
Physiol Rev 2020;100:407



glyoxalase 1

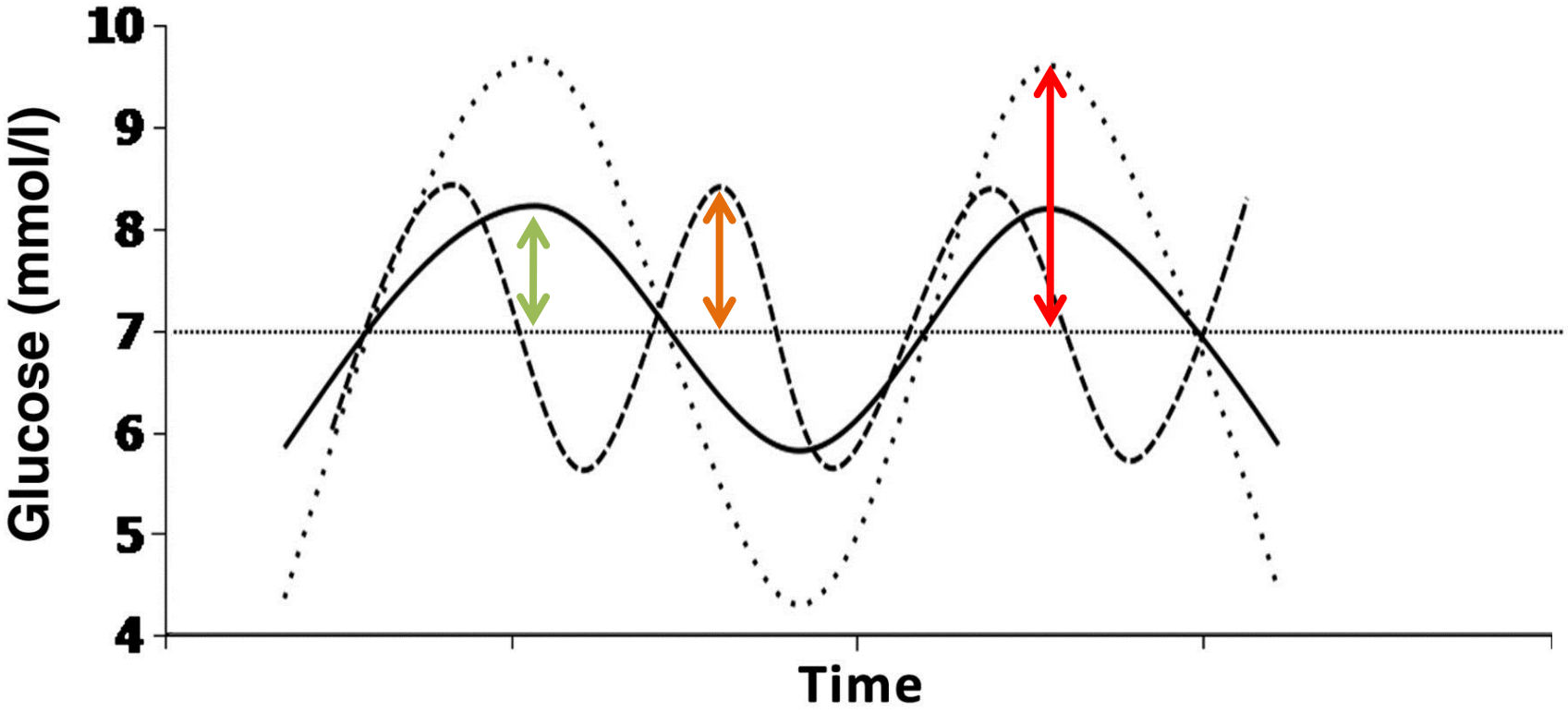
scavengers, eg pyridoxamine

Brouwers et al. Diabetologia. 2010
Brouwers et al. J Biol Chem 2011
Berner et al. Diabetologia. 2012
Van Eupen et al. Diabetologia 2013
Brouwers et al. Diabetologia 2014
Giacco F et al. Diabetes 2014

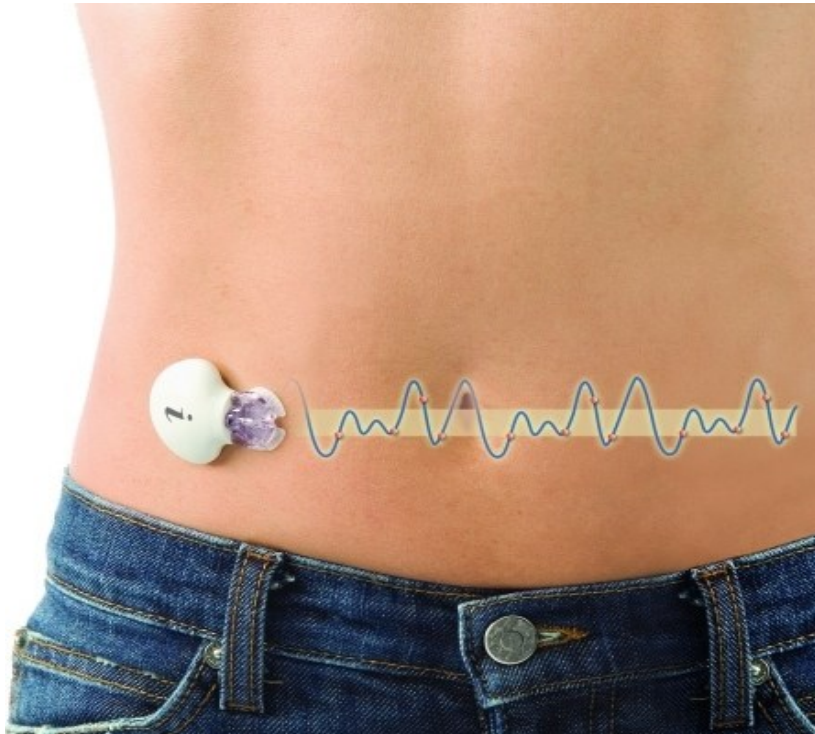
Microvascular dysfunction

Oxidative stress; reduced NO bioavailability
Protein glycation
DNA glycation

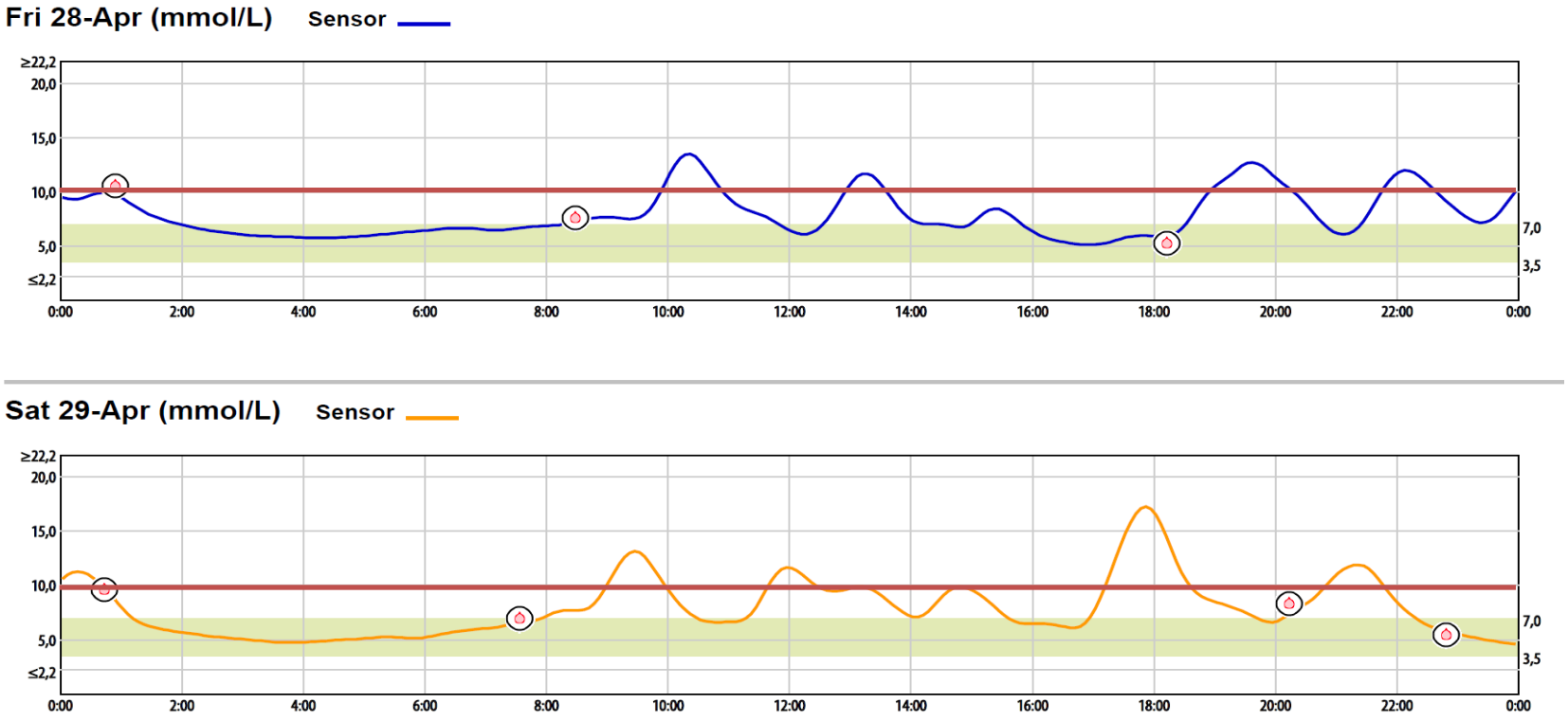
Glucose Variability



Continuous Glucose Monitoring

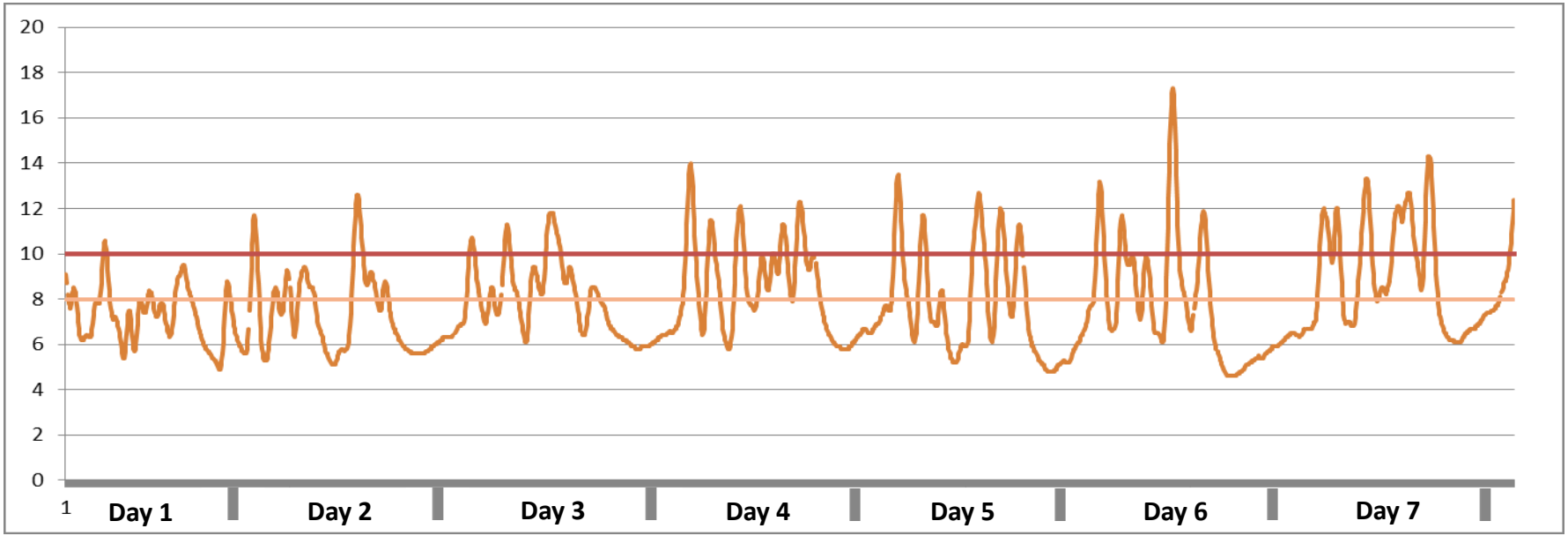


Type 2 diabetes



Fasting plasma glucose, mmol/L	7.1	**HbA_{1c}**, mmol/mol	48	**Time > 10 mmol/L**, h/day	4.4	**Mean glucose**, mmol/L	8.0	**Glucose variability (SD)**, mmol/L	2.2

Type 2 diabetes



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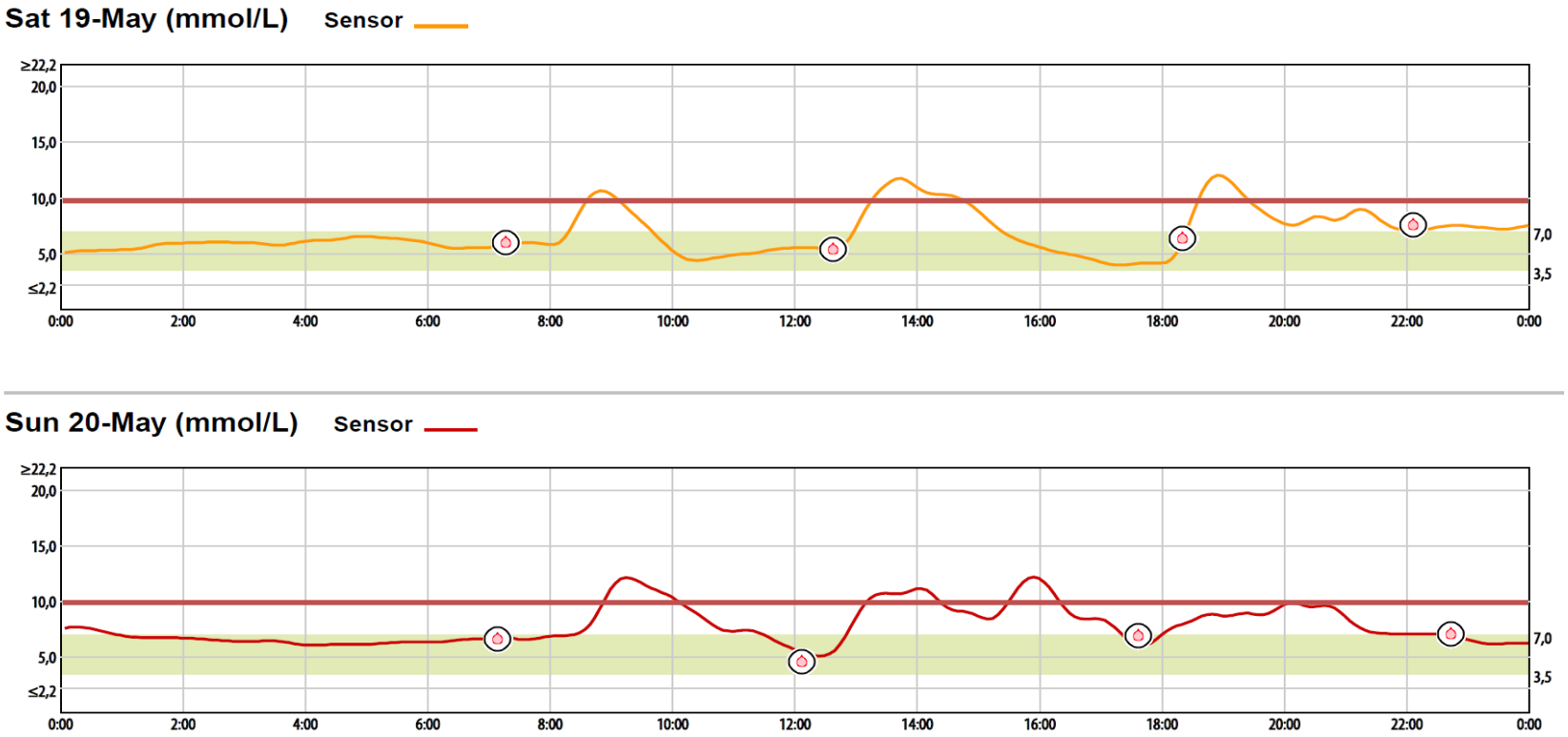
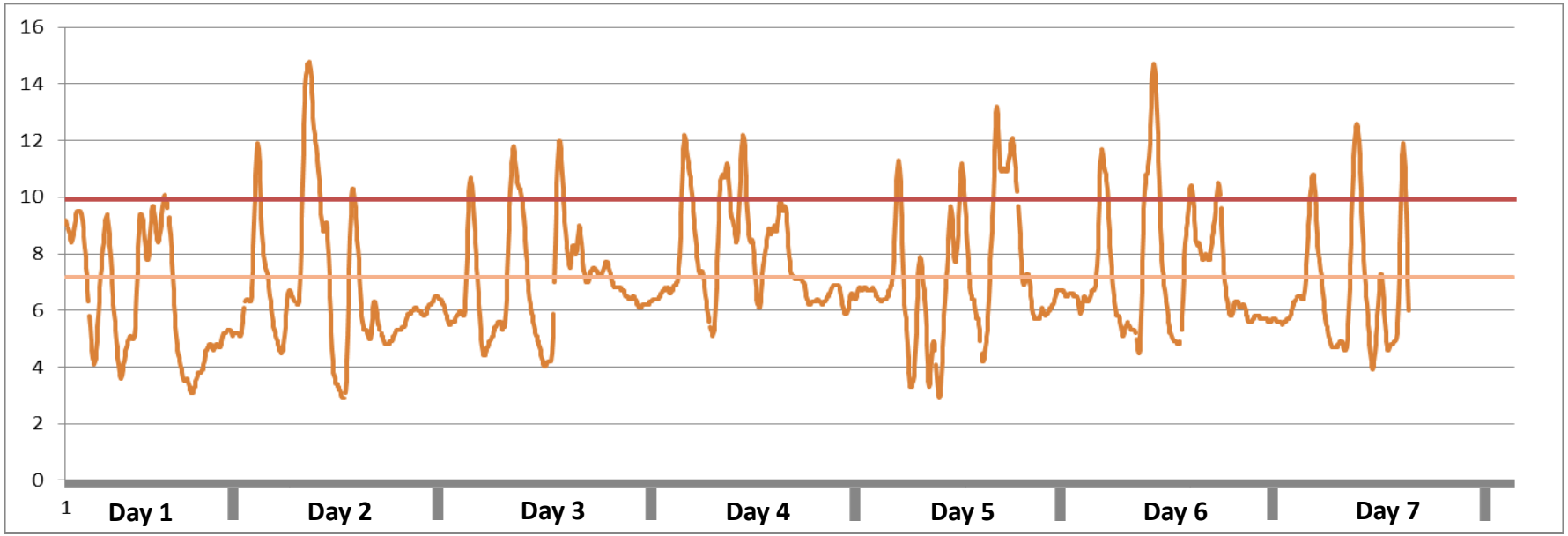
Prediabetes



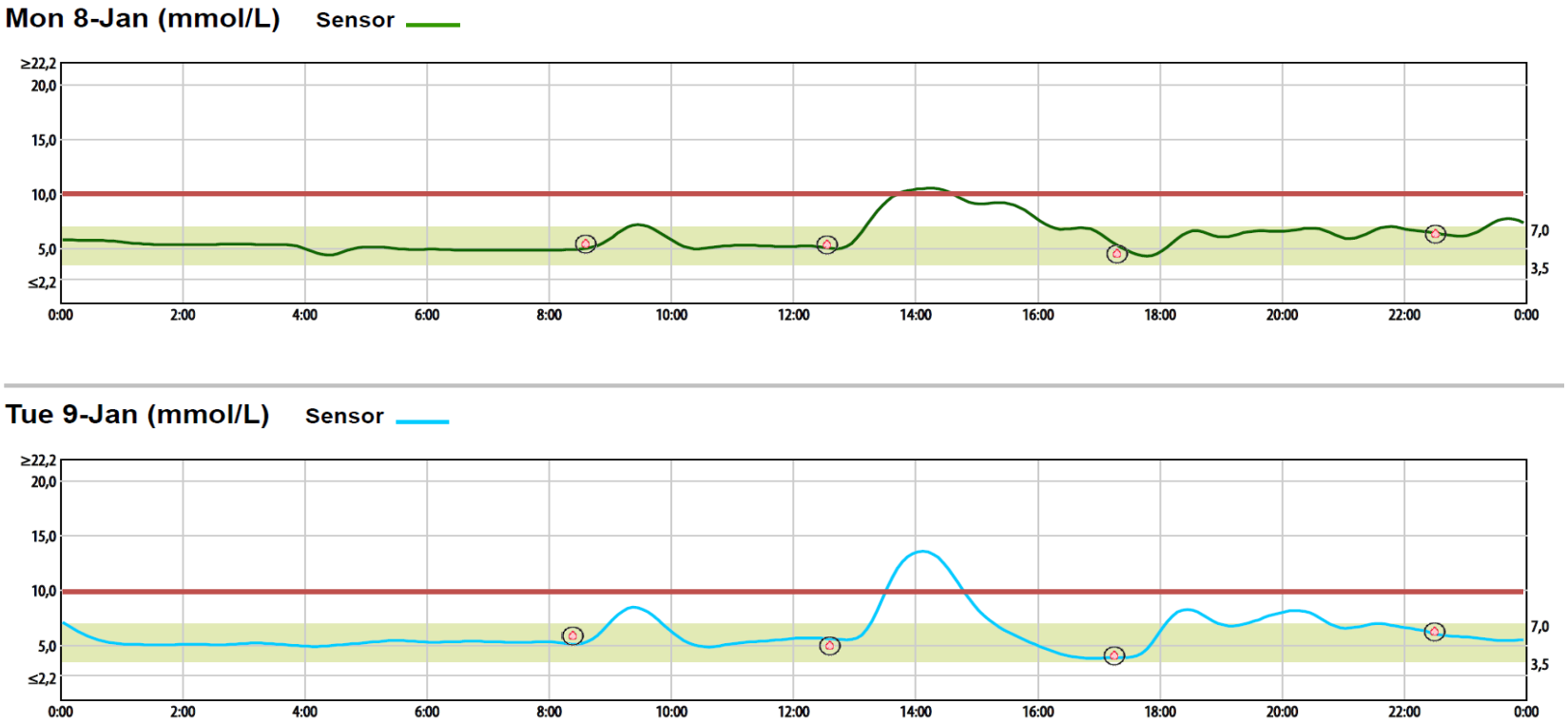
Fasting plasma glucose, mmol/L	4.8	**HbA_{1c}**, mmol/mol	37	**Time > 10 mmol/L**, min/day	136	**Mean glucose**, mmol/L	7.1	**Glucose variability (SD)**, mmol/L	1.9

Prediabetes



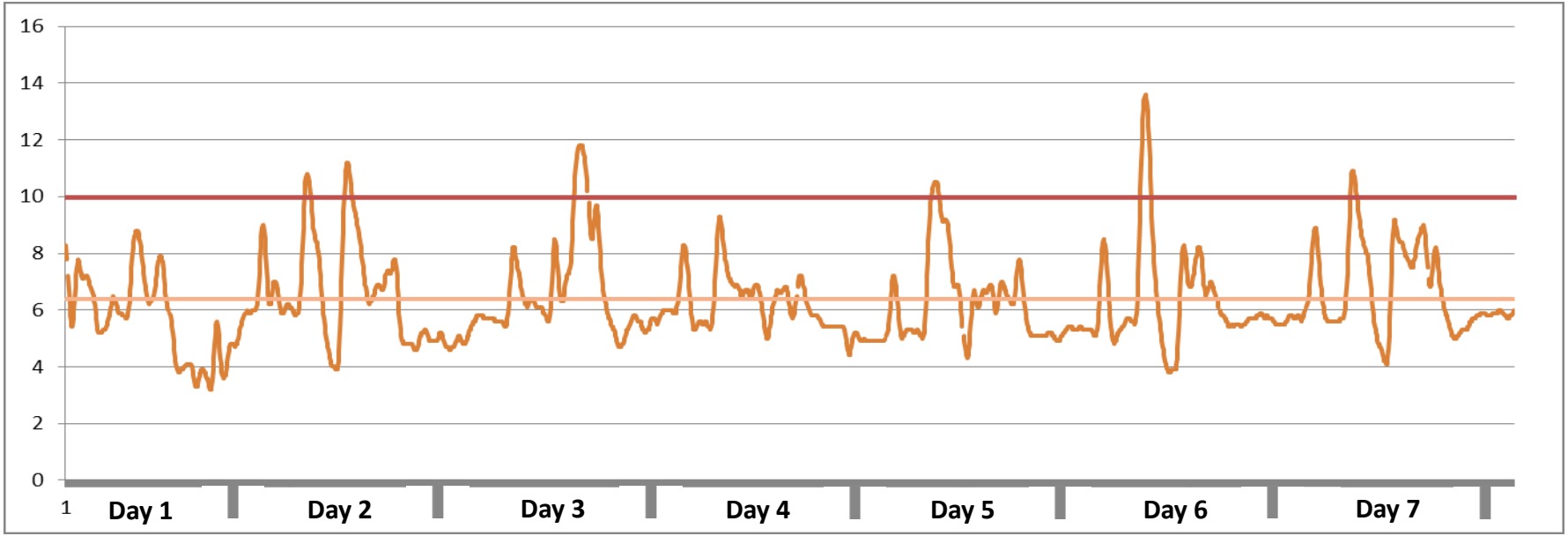
Fasting plasma glucose, mmol/L	4.8	**HbA_{1c}**, mmol/mol	37	**Time > 10 mmol/L**, min/day	136	**Mean glucose**, mmol/L	7.1	**Glucose variability (SD)**, mmol/L	1.9

Normal glucose metabolism



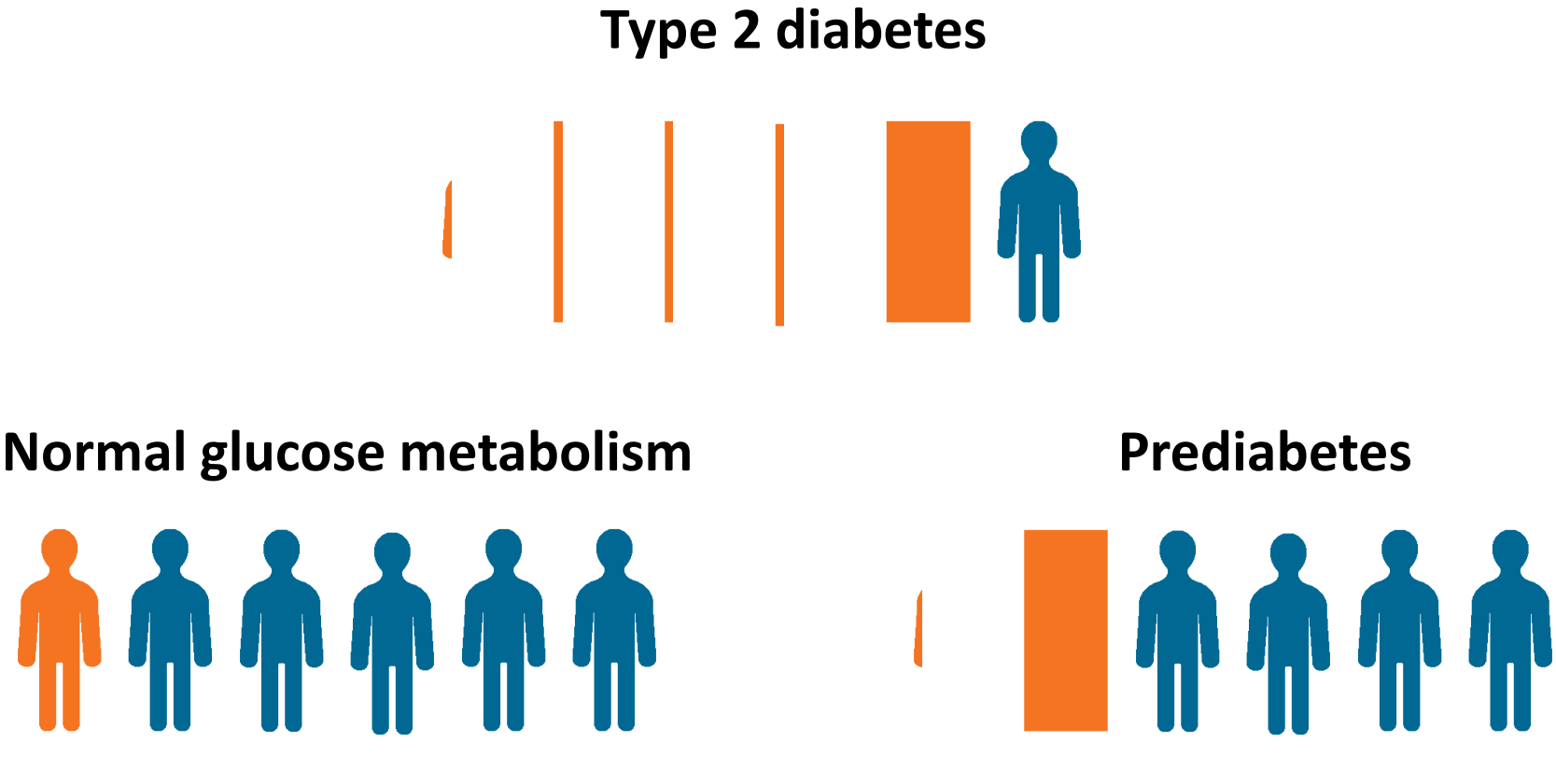
Fasting plasma glucose, mmol/L	5.4	**HbA_{1c}**, mmol/mol	38	**Time > 10 mmol/L**, min/day	60	**Mean glucose**, mmol/L	6.4	**Glucose variability (SD)**, mmol/L	1.6

Normal glucose metabolism

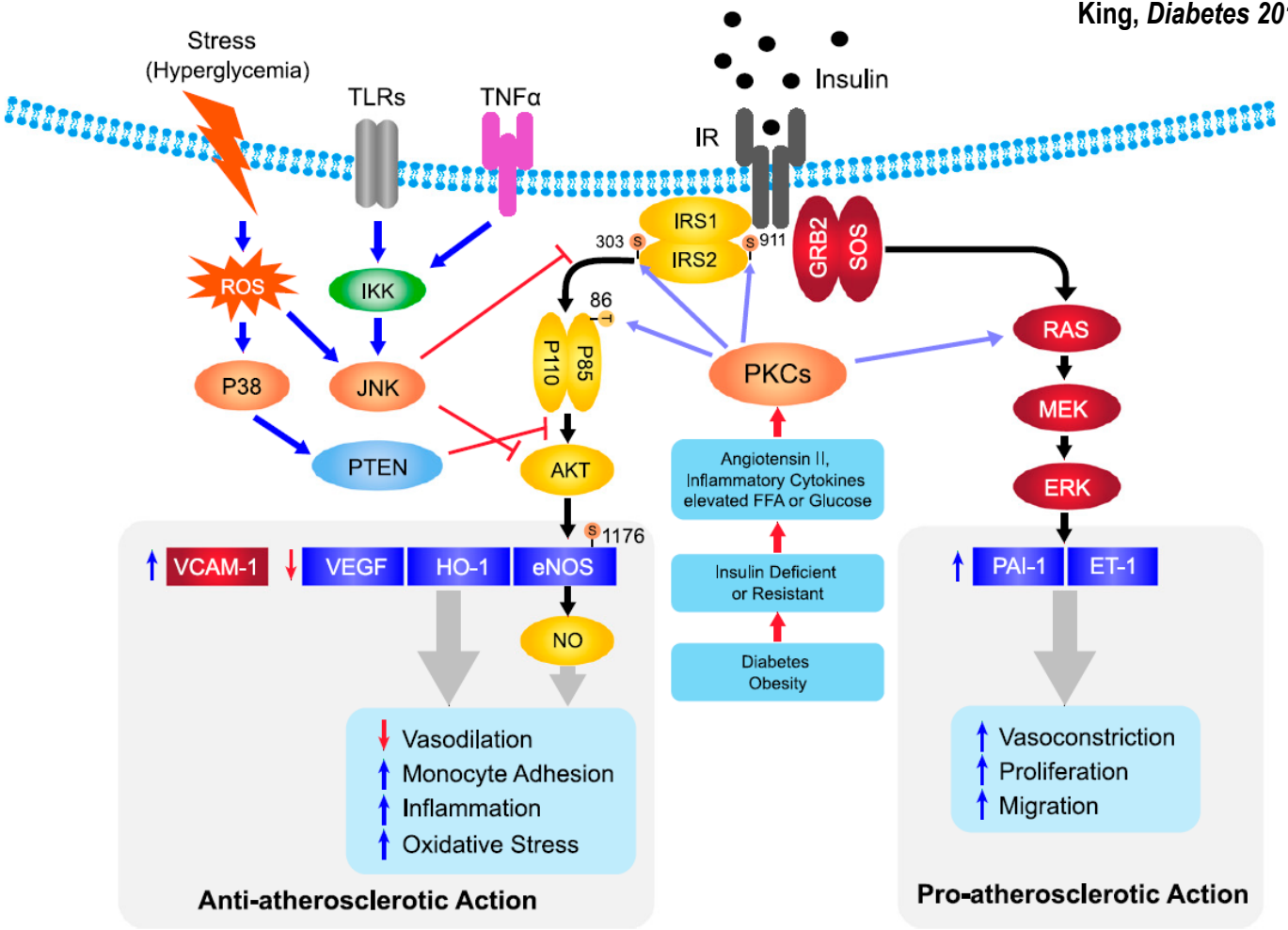


Fasting plasma glucose, mmol/L	5.4	**HbA_{1c}**, mmol/mol	38	**Time > 10 mmol/L**, min/day	60	**Mean glucose**, mmol/L	6.4	**Glucose variability (SD)**, mmol/L	1.6

Observed glucose values > 10 mmol/L



King, *Diabetes 2016;65:1462*



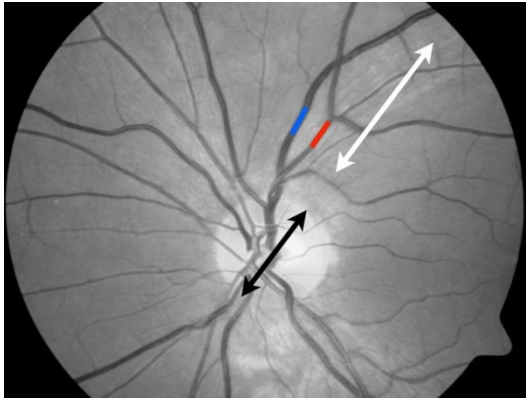
Diabetes is

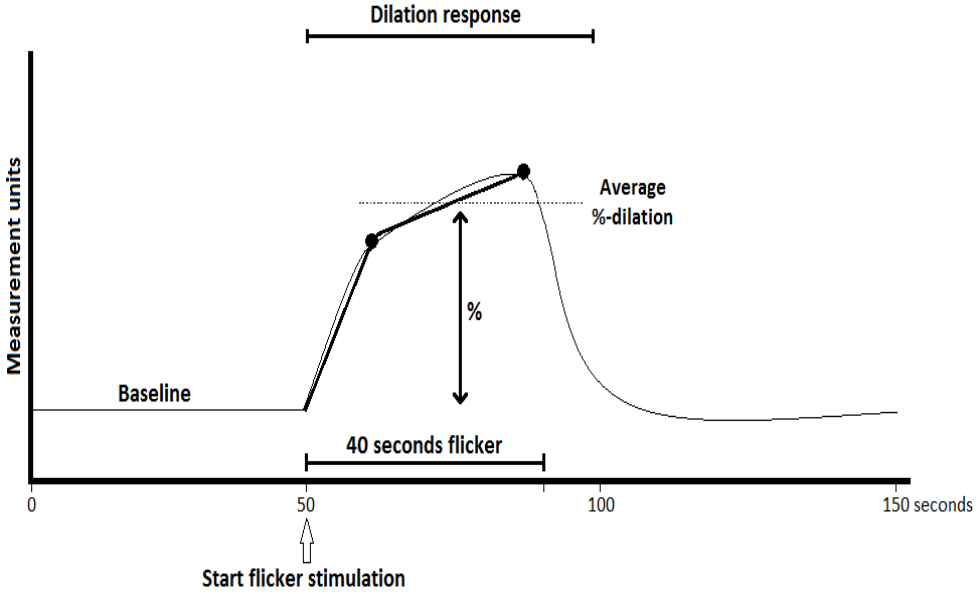
a progressive microvascular *and* neuronal disorder

that affects many (all?) organs

The ‘diabetic process’ starts in prediabetes

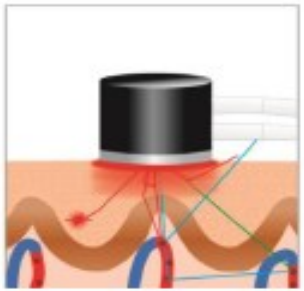
Retinal Dynamic Vessel Analysis

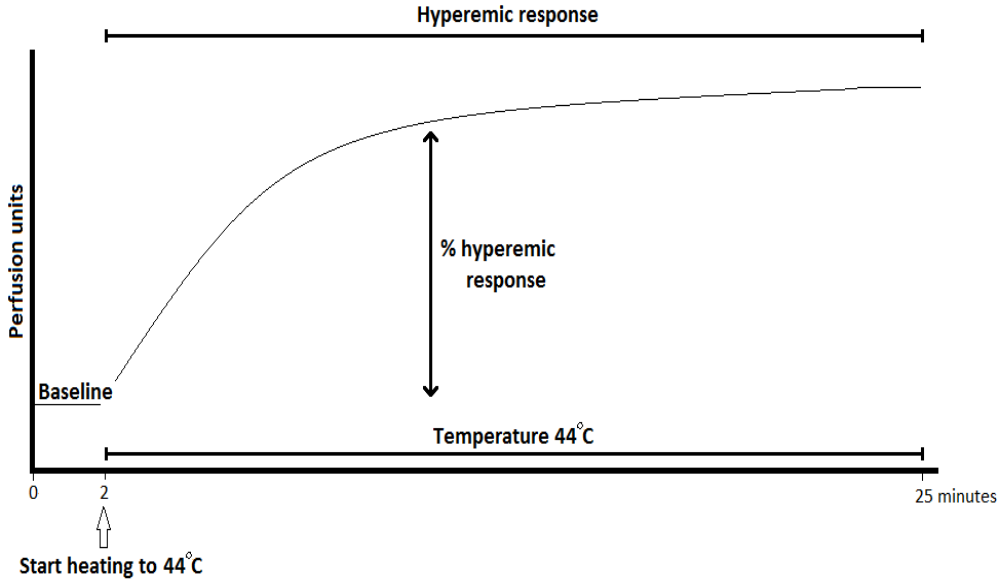




- Retinal vasodilator response to flicker light exposure
  - Increased metabolic demands of retinal neurons
  - NO–dependent response
- %–increase in diameter

Skin Laser Doppler Flowmetry

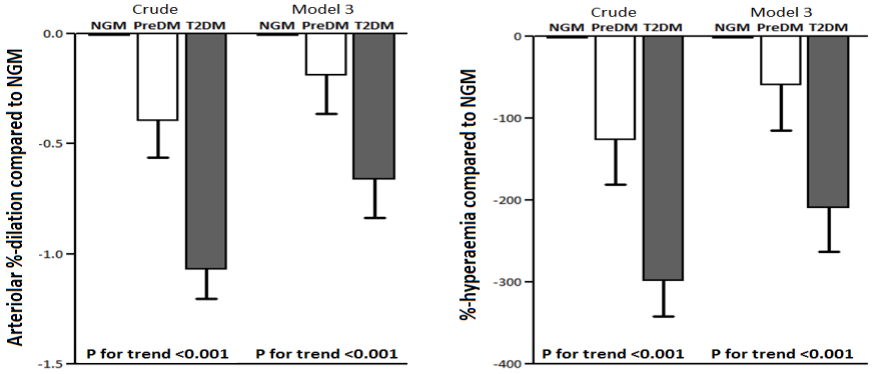




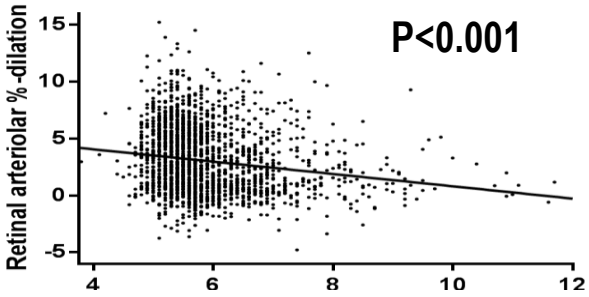
- Skin vasodilator response to heat exposure
  - Thermoregulatory function
  - NO–dependent response
- Heat–induced skin %–hyperaemia

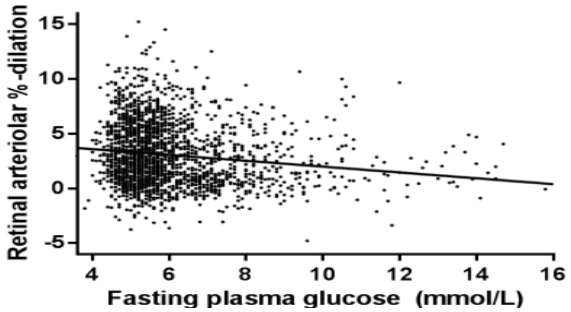
THE MAASTRICHT STUDY

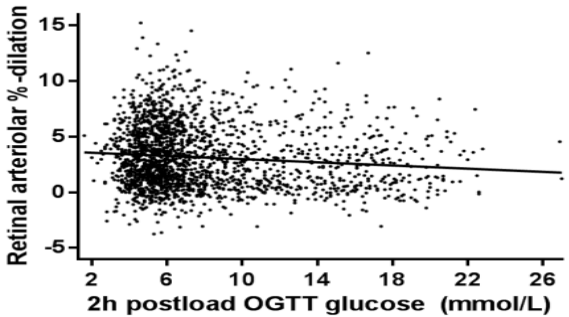
These responses are impaired in T2D *and* in prediabetes

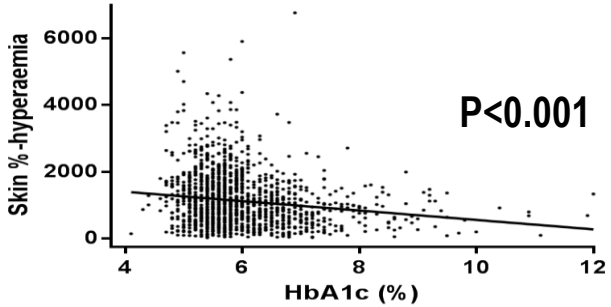


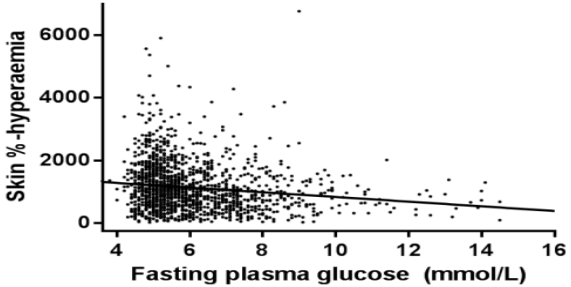
Sörensen, *Circulation 2016;134:1339*
Sörensen, *Diabetes Care 2017;40:e103*

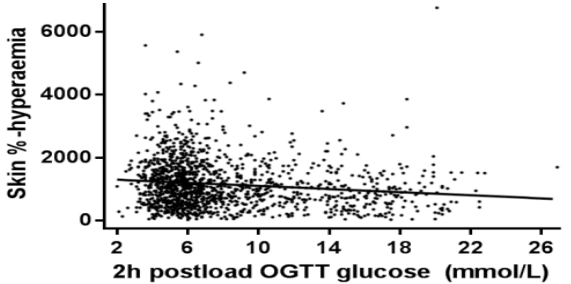








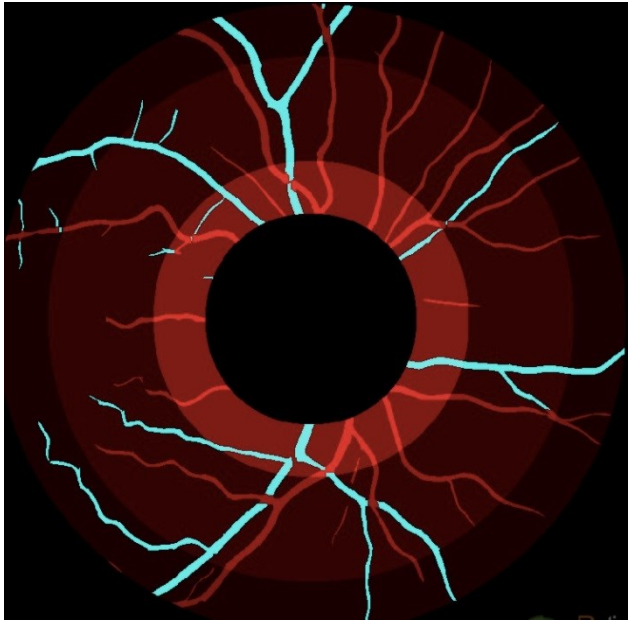




Retinal arteriolar and venular diameters

RHINO

TU/e



Original image of fundus photography

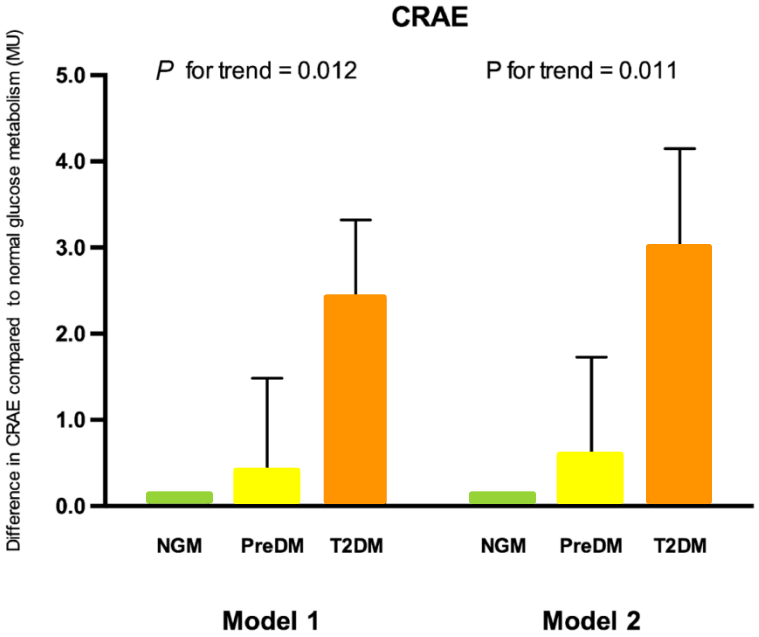
Processed image

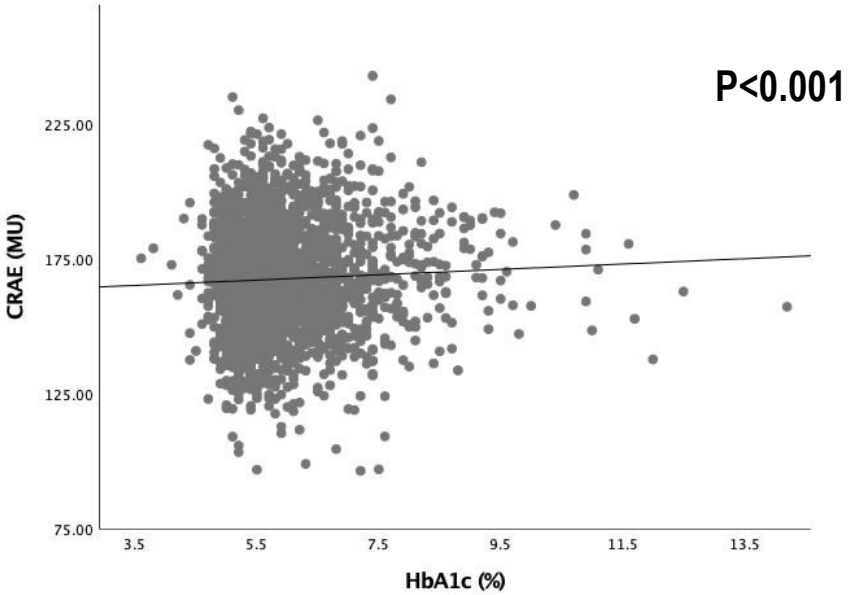
Li, *Diabetologia 2020, in press*

THE MAASTRICHT STUDY

Association of (pre)diabetes and HbA1c with retinal *arteriolar* diameter

N = 1506 NGM **404 prediabetes** **778 T2D**



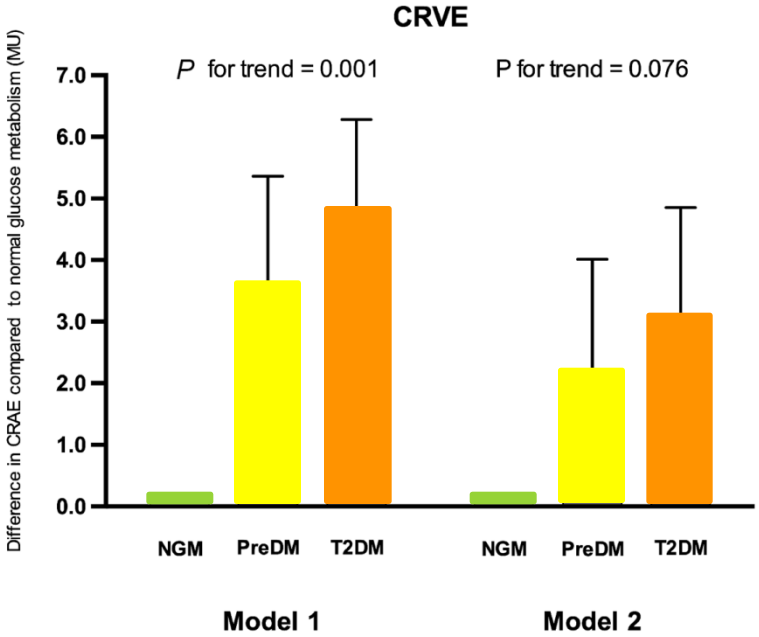


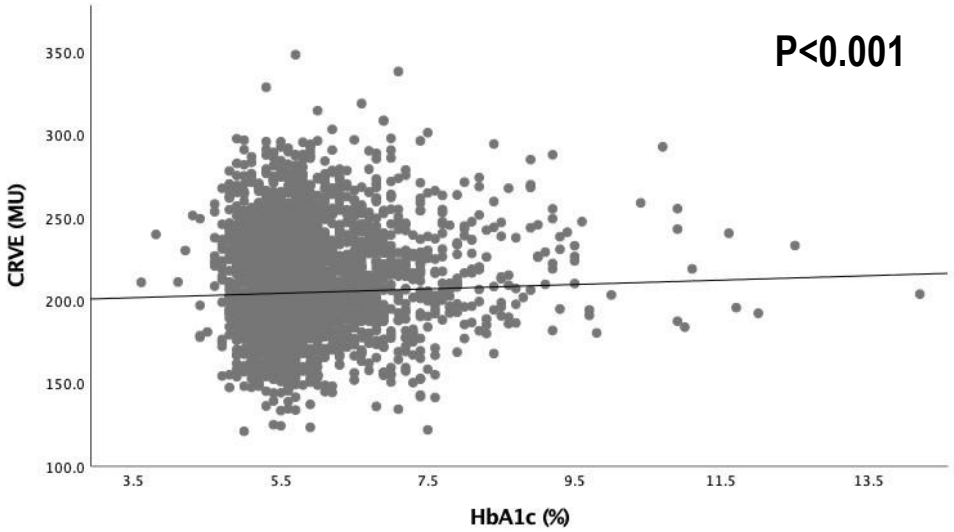
THE MAASTRICHT STUDY

Li, *Diabetologia 2020, in press*

Association of (pre)diabetes and HbA1c with retinal *venular* diameter

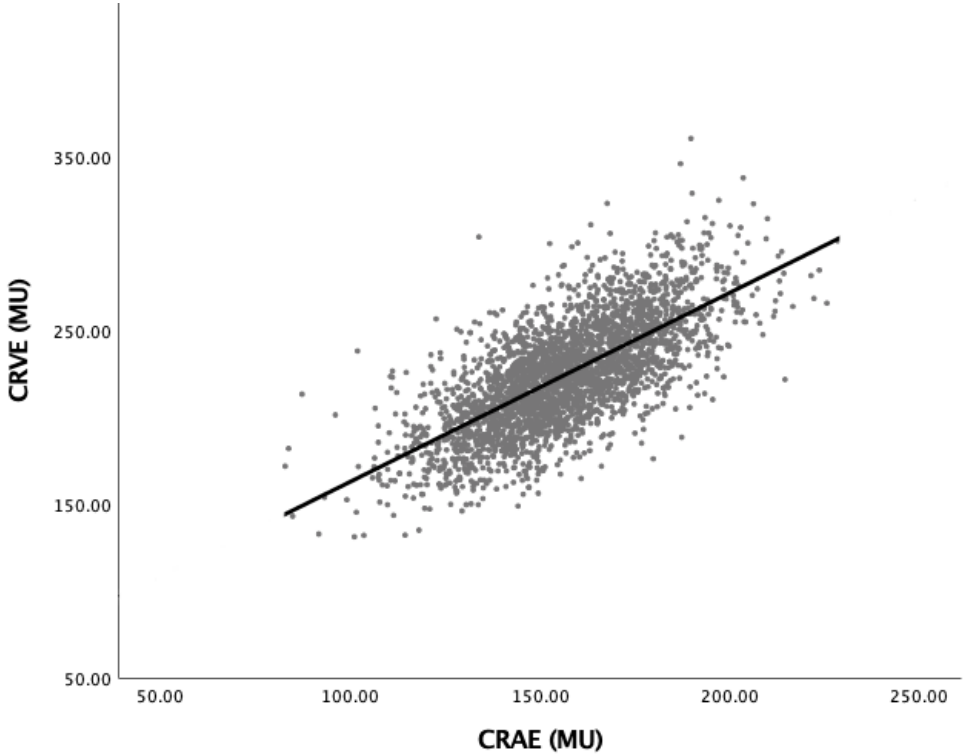
N = 1506 NGM **404 prediabetes** **778 T2D**



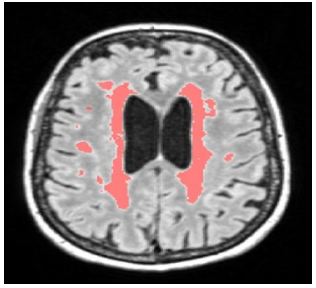


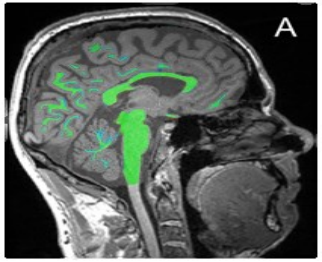
THE MAASTRICHT STUDY

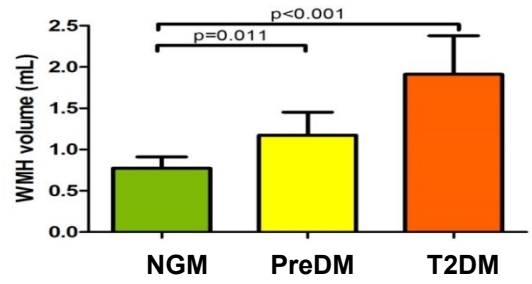
Retinal arteriolar and venular diameters are closely linked even after adjustment for age, glycaemia, blood pressure and low-grade inflammation

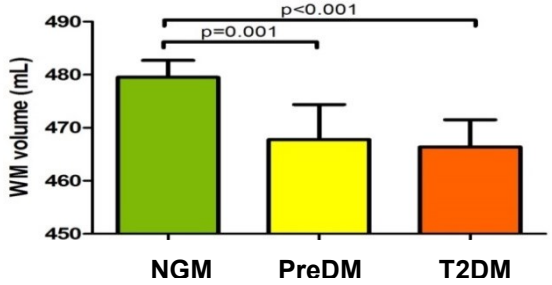


Cerebral white matter hyperintensities and volume loss ~ small vessel disease

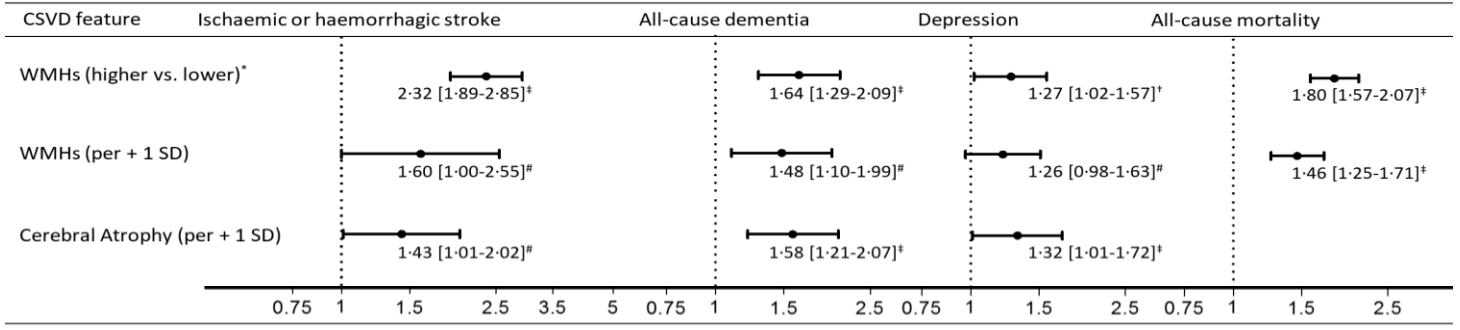








Van Agtmaal, *Diabetes Care 2018;41:2535*

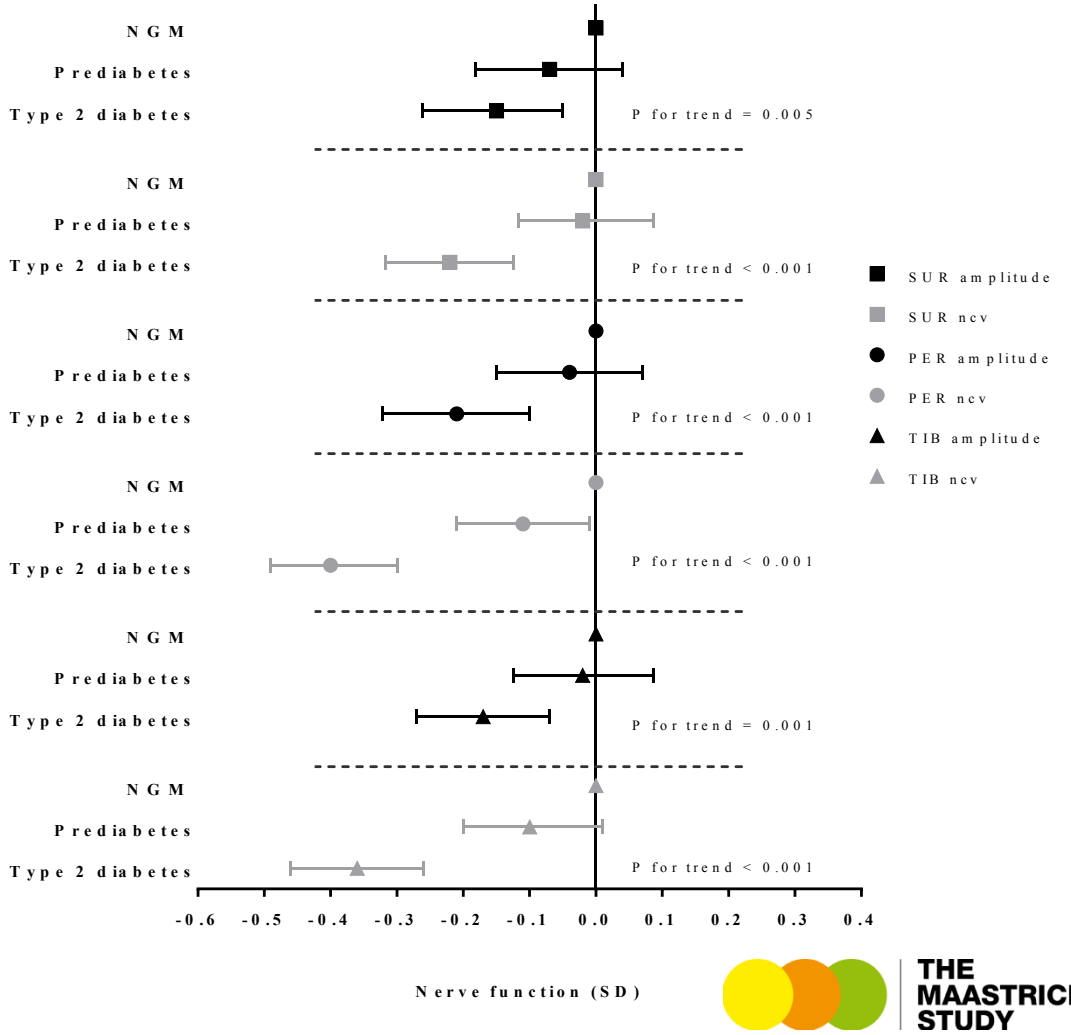


Rensma, *Neurosci Biobeh Rev 2018;90:164;* Van Agtmaal, *Jama Psych 2017;74:729;* Martens, *Am J Kidney Dis 2017;69:179;* Martens, *Nephrol Dial Transpl 2018;33:128*

Impairment of sural, peroneal and tibial nerve (ie, sensory and motor large fibre) function assessed by EMG

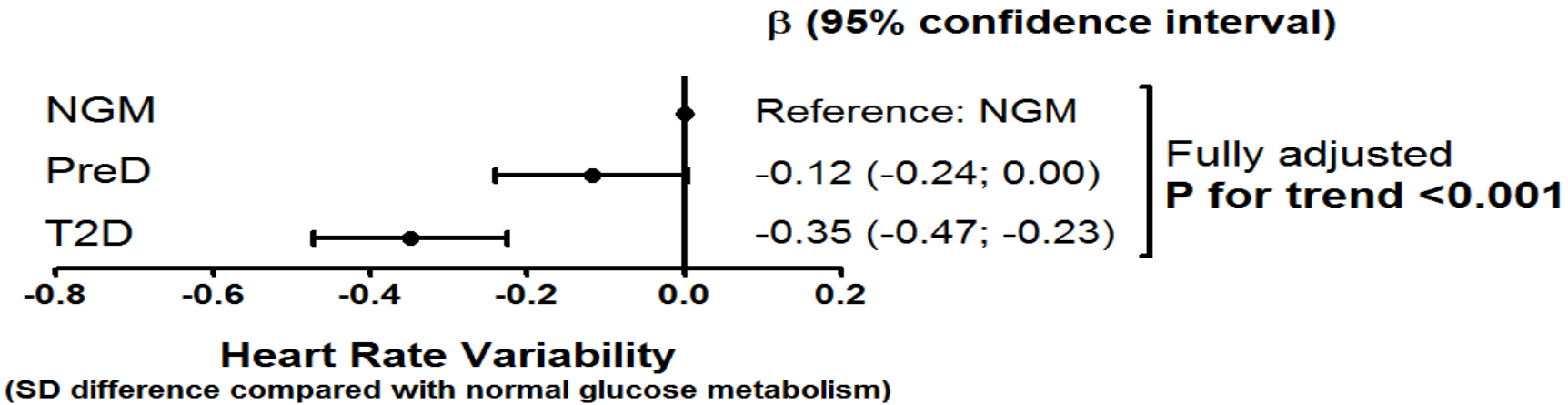
standardised associations w/ (pre)diabetes adjusted for potential confounders

Van der Velde, *submitted*



THE MAASTRICHT STUDY

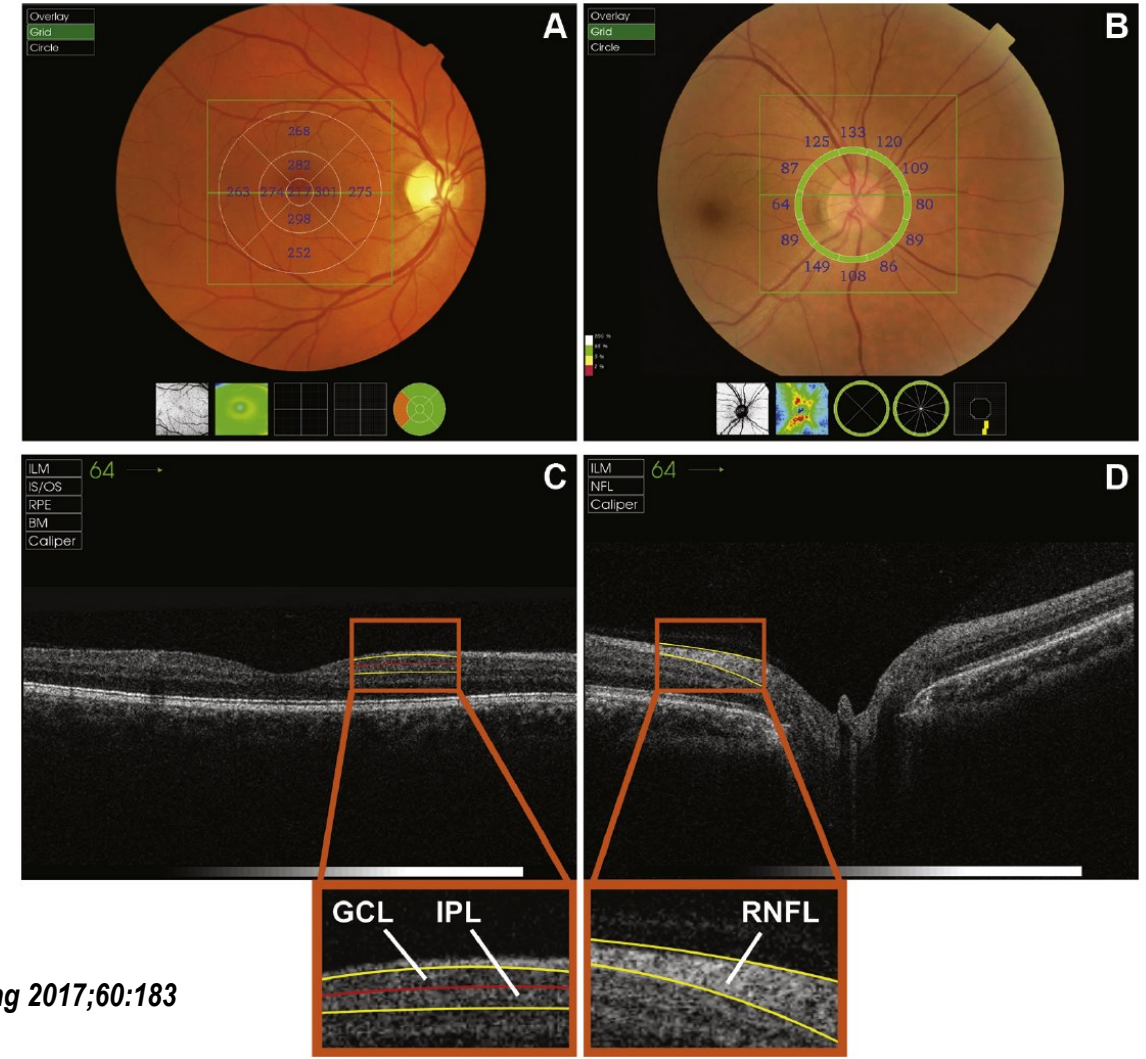
Cardiac autonomic nervous function (ie, small fibre) assessed by heart rate variability from 24h–EKG



adjusted for age, sex, body mass index, alcohol, smoking, physical activity, systolic BP, TC/HDL ratio, antihypertensive and lipid-modifying drugs, history of CVD, and eGFR

Coopmans, Zhou, *Diab Care 2020, in press*

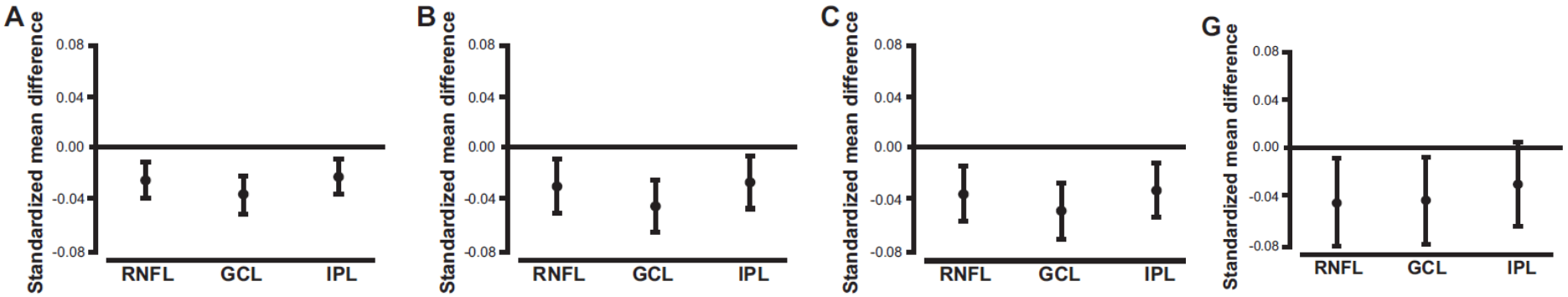
Optical coherence tomography



Mutlu, *Neurobiol Aging 2017;60:183*

Retinal Neurodegeneration is Associated with Brain Atrophy

Brain volume | Gray matter | White matter | Hippocampus



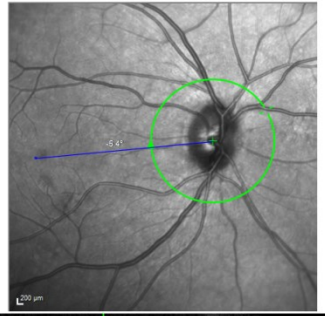
RNFL = retinal nerve fibre layer ~ axons
GCL = ganglion cell layer ~ nerve cell bodies
IPL = inner plexiform layer ~ dendrites

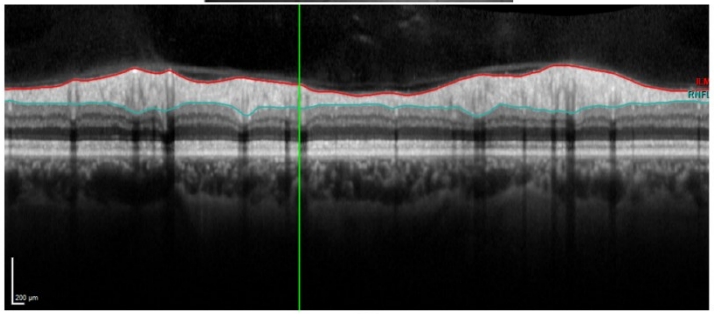
~greater risk of dementia[1]

N = 2124, Rotterdam Study

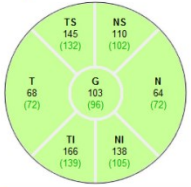
[1]Mutlu, *Jama Neurol 2018;75:1256*

De Clerck, *Invest Ophthalmol Vis Sci 2017;58:1017*

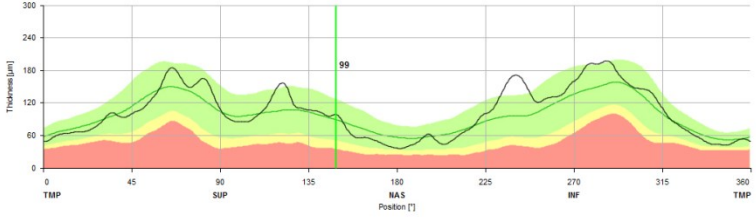


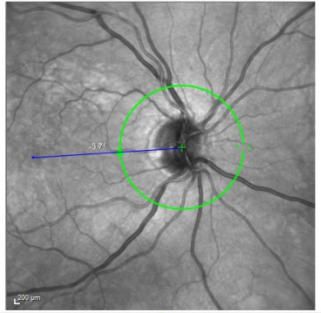


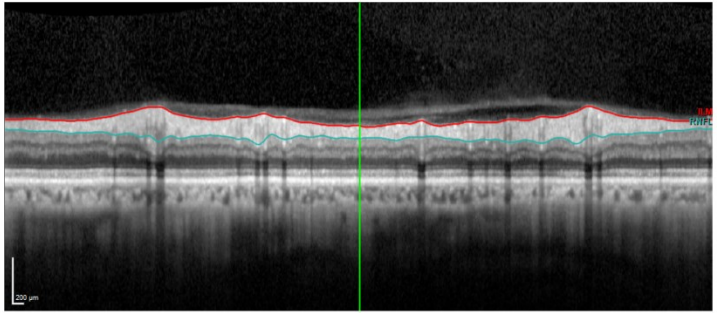
NGM



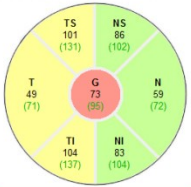
Within Normal Limits



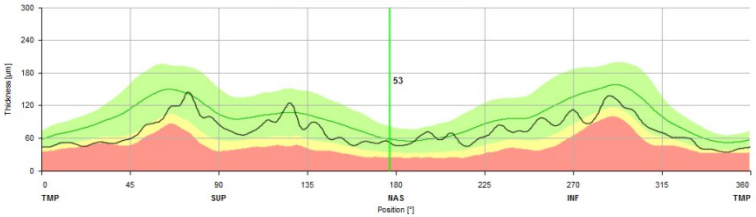




T2D

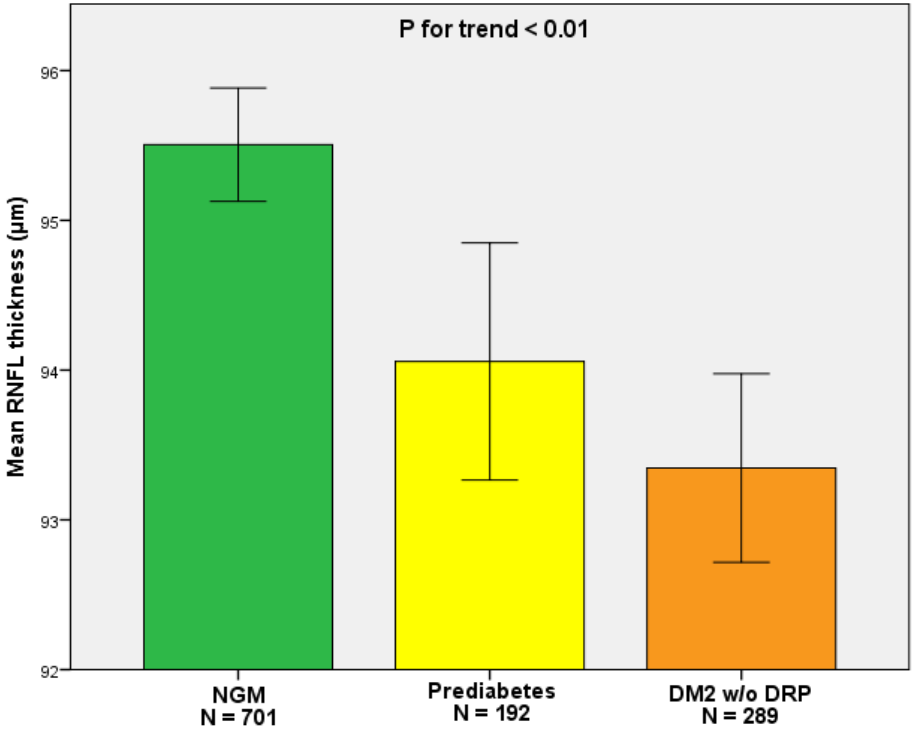


Outside Normal Limits



T2D and prediabetes are associated with thinning of the retinal nerve fibre layer

… around the optic disc …



De Clerck, *Invest Ophthalmol Vis Sci 2017;58:1017*

De Clerck, *Lancet Diabetes Endocrinol 2015;3:653 (meta-analysis)*

… and around the macula

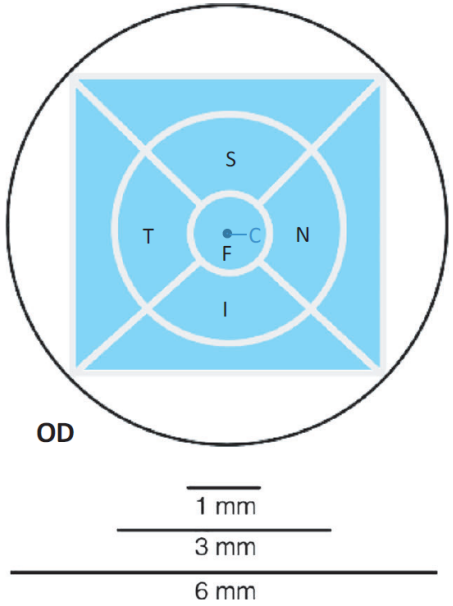
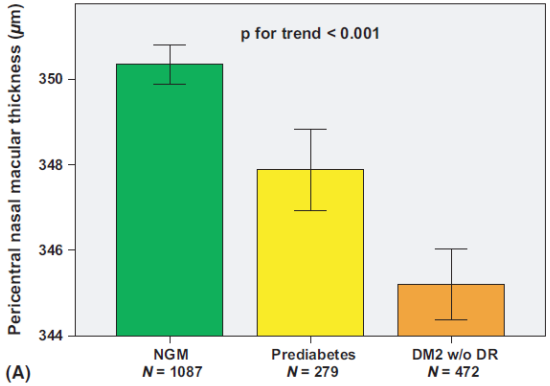
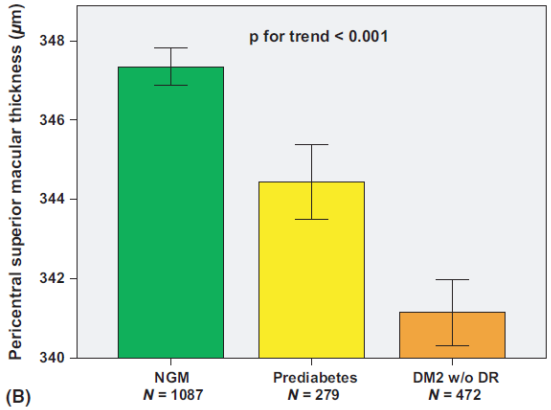
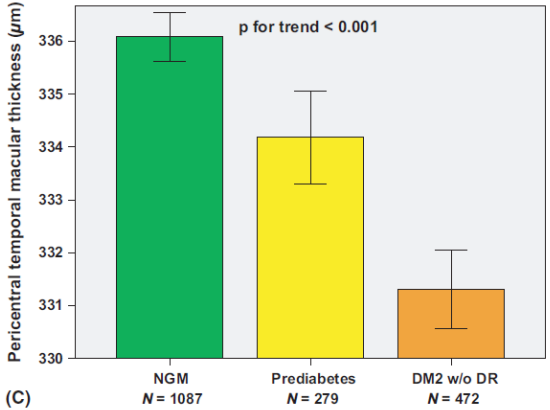
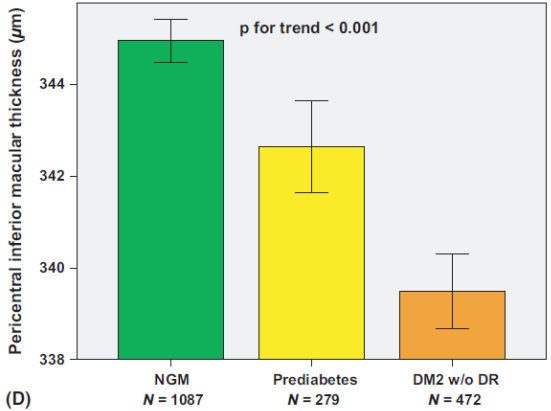


Fig. 1. Illustration of the region in the ETDRS grid from which data were gathered for the volume scan in a right eye. The blue area represents the area from which data were gathered. The two regions in the centre constitute the central macula. The four regions around the fovea constitute the pericentral macula. Point C = centre thickness, Region F = foveal thickness, Region I = pericentral inferior macular thickness, Region N = pericentral nasal macular thickness, Region, S = pericentral superior macular thickness, Region T = pericentral temporal macular thickness.



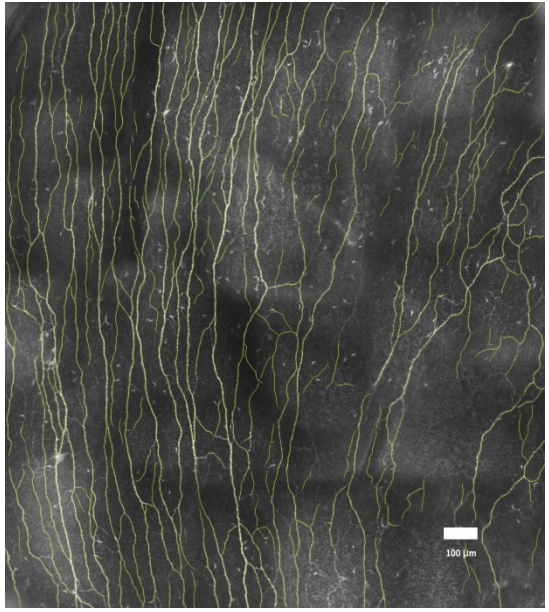


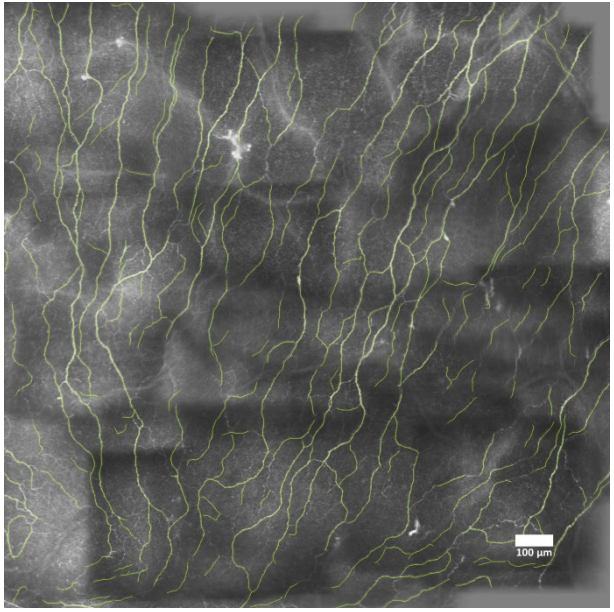


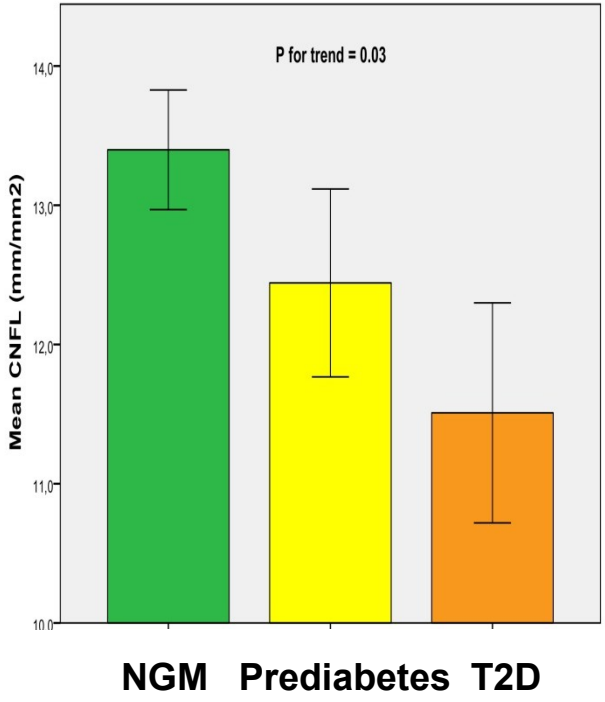


De Clerck, *Acta Ophthalmol 2018;96:174*

Corneal confocal microscopy: reduced corneal nerve fibre length in T2D and in prediabetes







De Clerck, *Lancet Diabetes Endocrinol 2015;3:653 (meta-analysis)*

De Clerck, *Acta Ophthalmol 2020 in press*

THE MAASTRICHT STUDY

White matter organisation ~ information transfer
Global network structure and intrinsic network organisation

NGM (n=1510) – prediabetes (n = 348) – T2D (n=510)

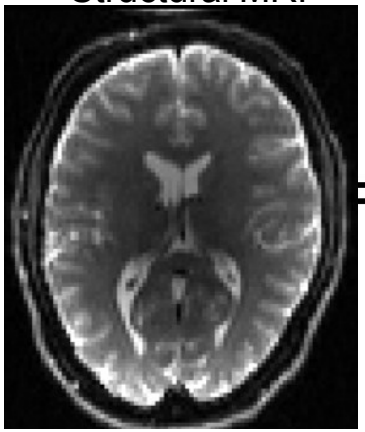
B

A

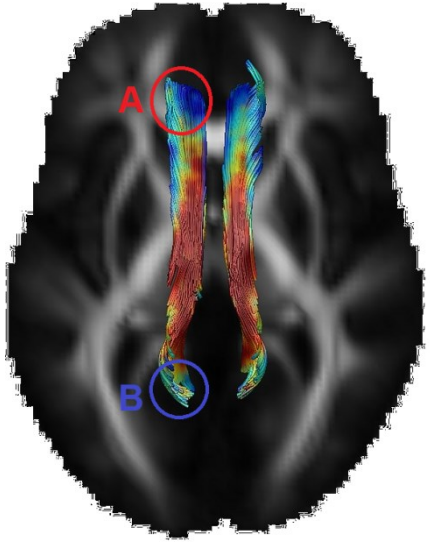
Vergoossen, *Diabetes Care 2020;43:201*

THE MAASTRICHT STUDY

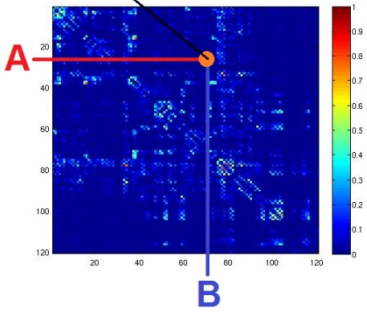
Structural MRI



Diffusion MRI
Fiber Tractography

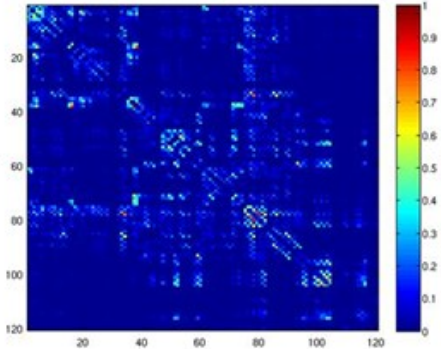


Tract Volume

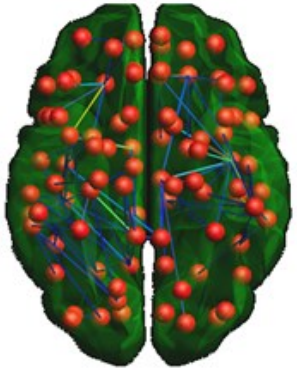


Graph theoretical analysis
→ Connectivity matrix with tract volumes

Structural Connectivity



White Matter Network

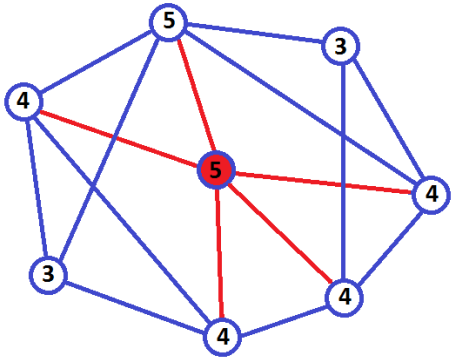


THE MAASTRICHT STUDY

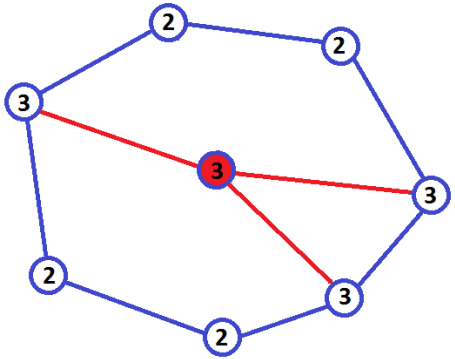
Global network structure

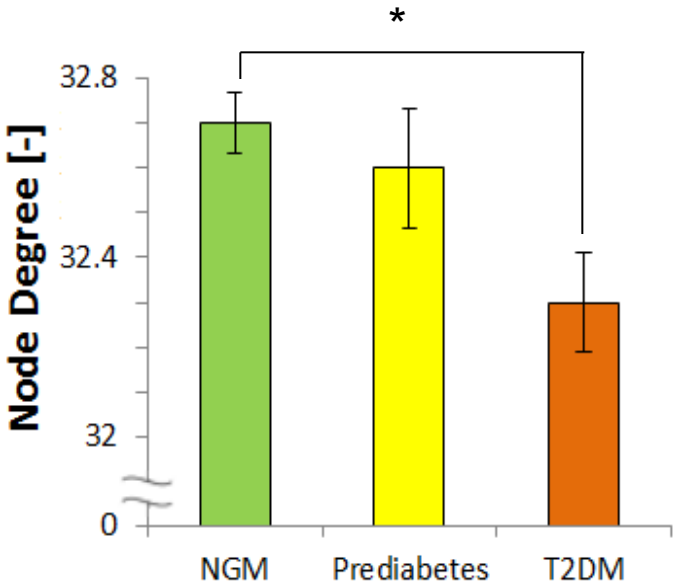
Network density (node degree)

High node degree



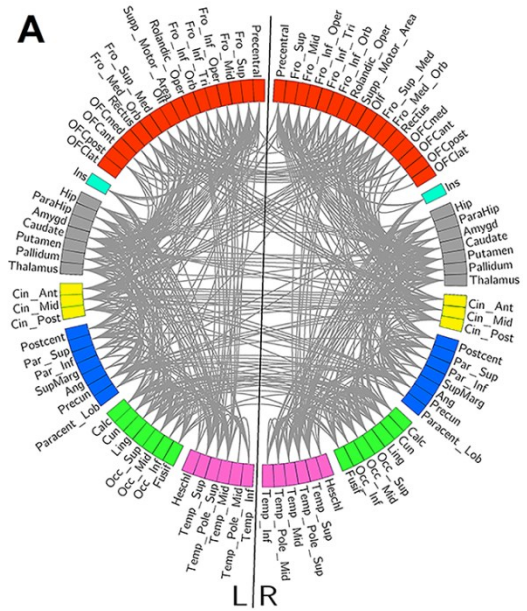
Low node degree

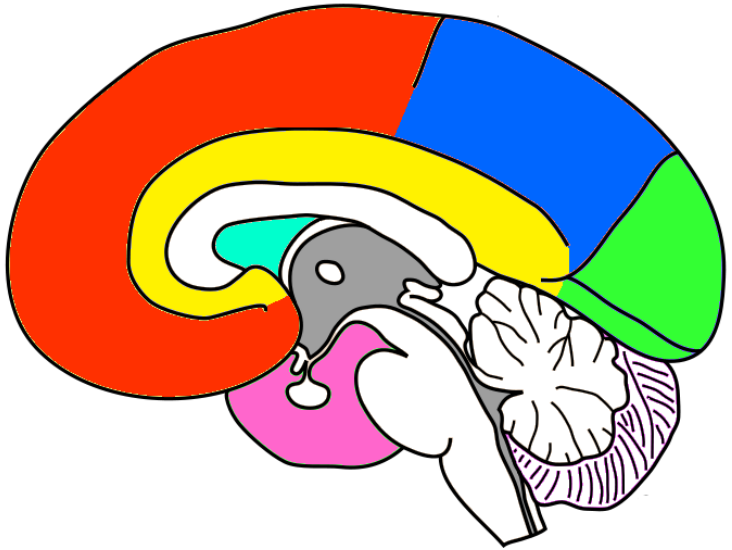




THE MAASTRICHT STUDY

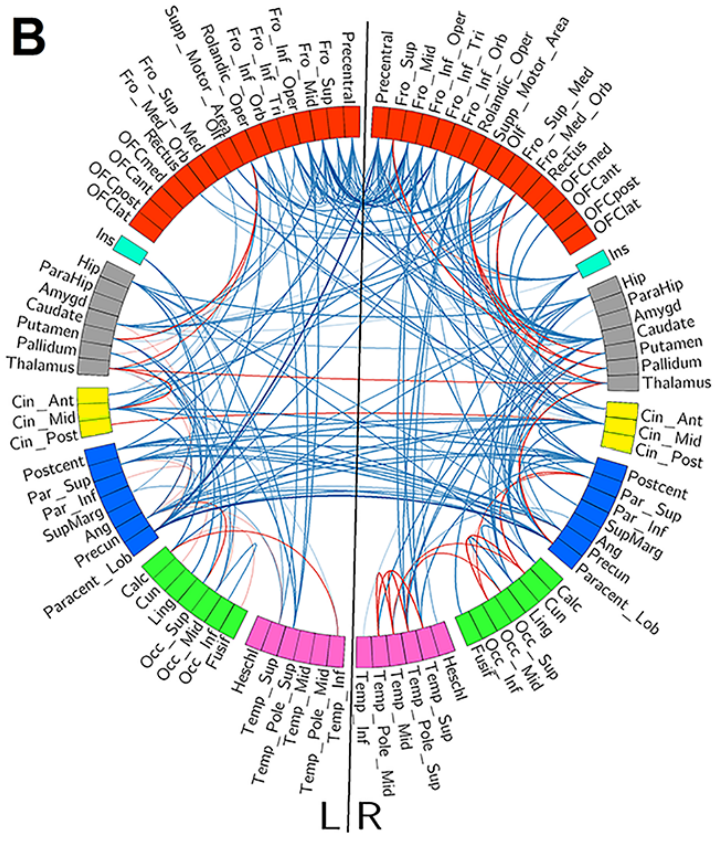
Organisation of white matter networks



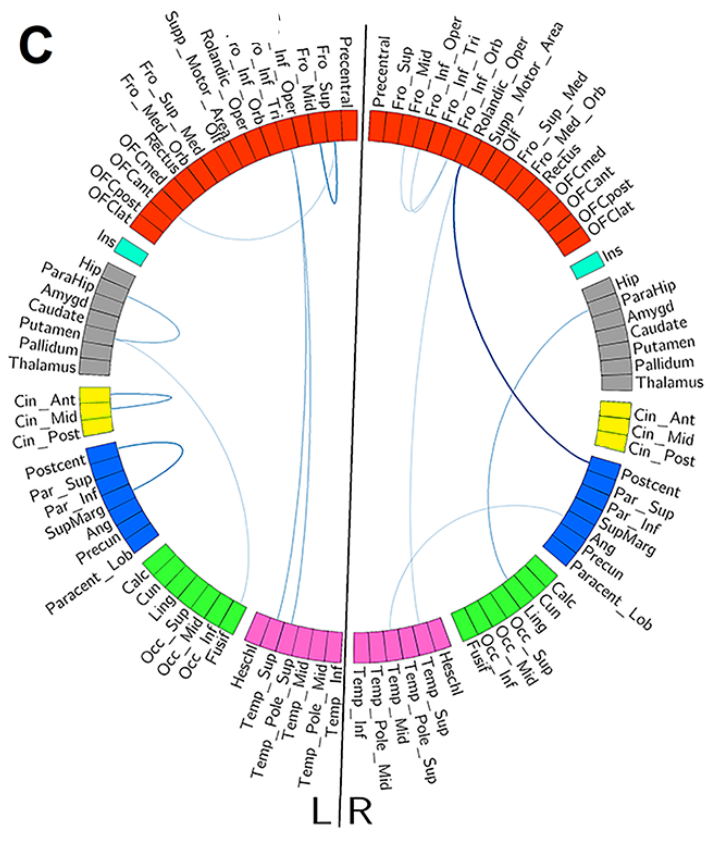


NGM

THE MAASTRICHT STUDY



T2D vs NGM



Prediabetes vs NGM

Insulineresistentie en hyperglykemie

Bad companions voor vasculaire gezondheid

Koolhydraten en Insulinegevoeligheid
Utrecht, 10 maart 2020

Thank you for your attention!