Insulinresistens hos vuxna

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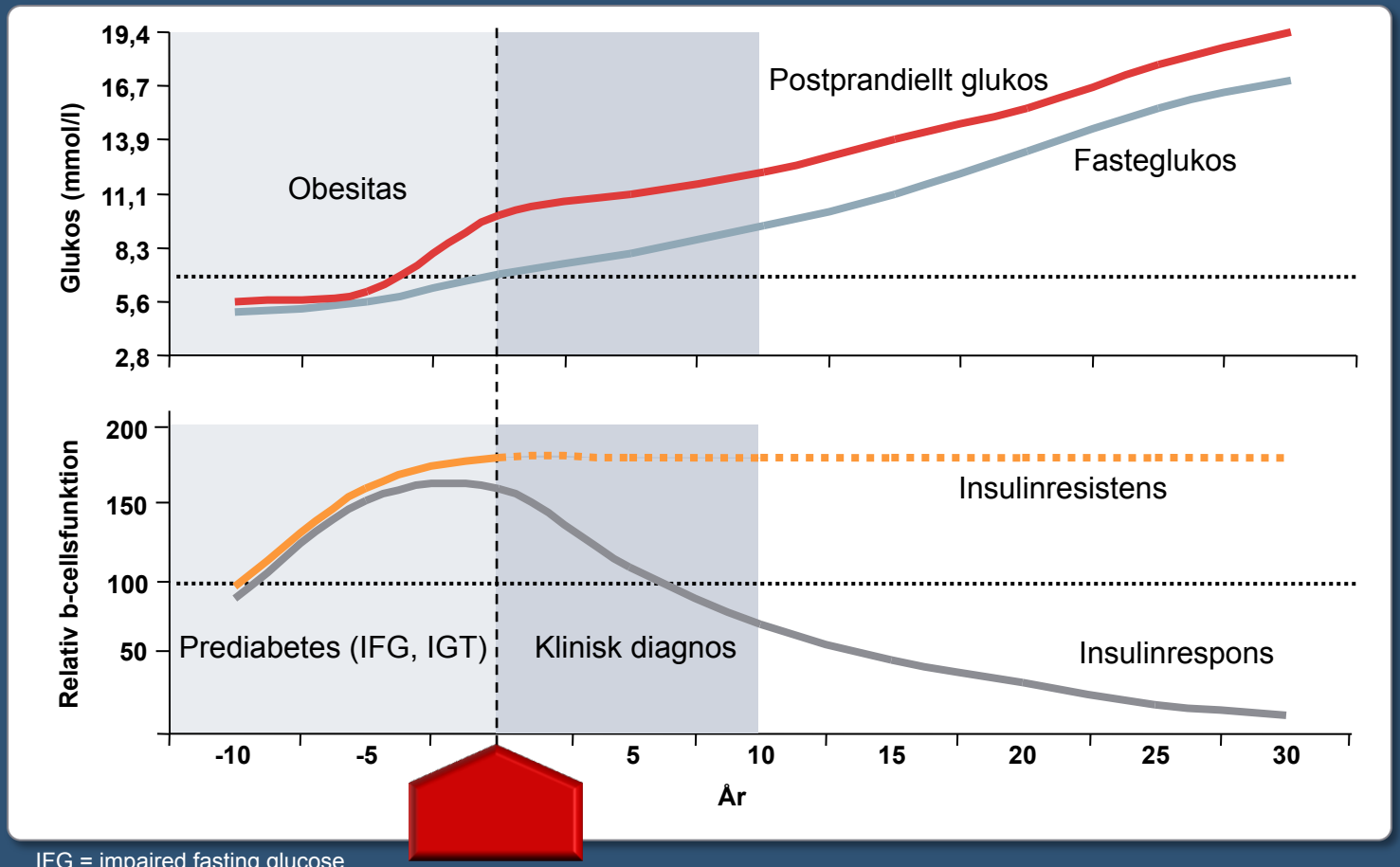
Karolinska Institutet

SÖS
SÖDERSJUKHUSET

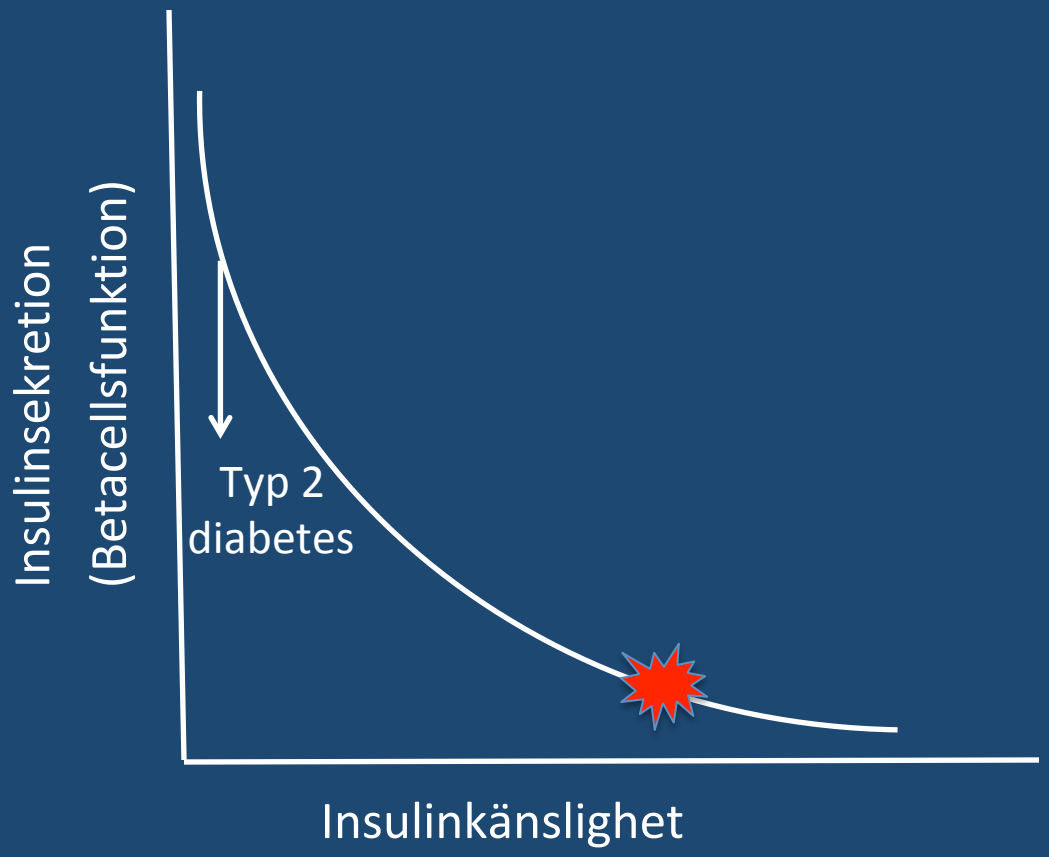
Insulinresistens och insulinrespons vid utveckling av typ 2 diabetes



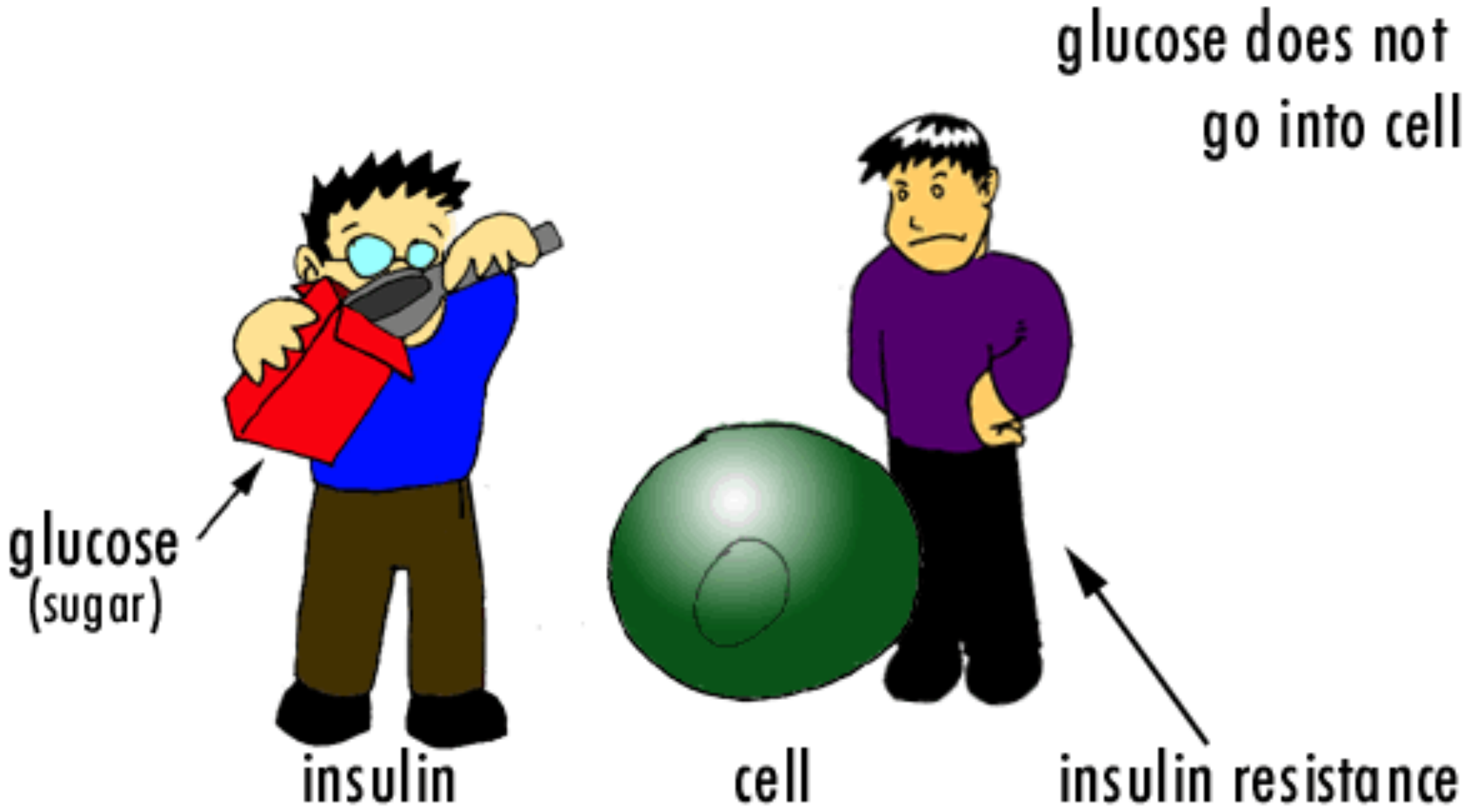
IFG = impaired fasting glucose
IGT = impaired glucose tolerance

Simonson GD, Kendall DM. *Coron Artery Dis*. 2005;16:465-472

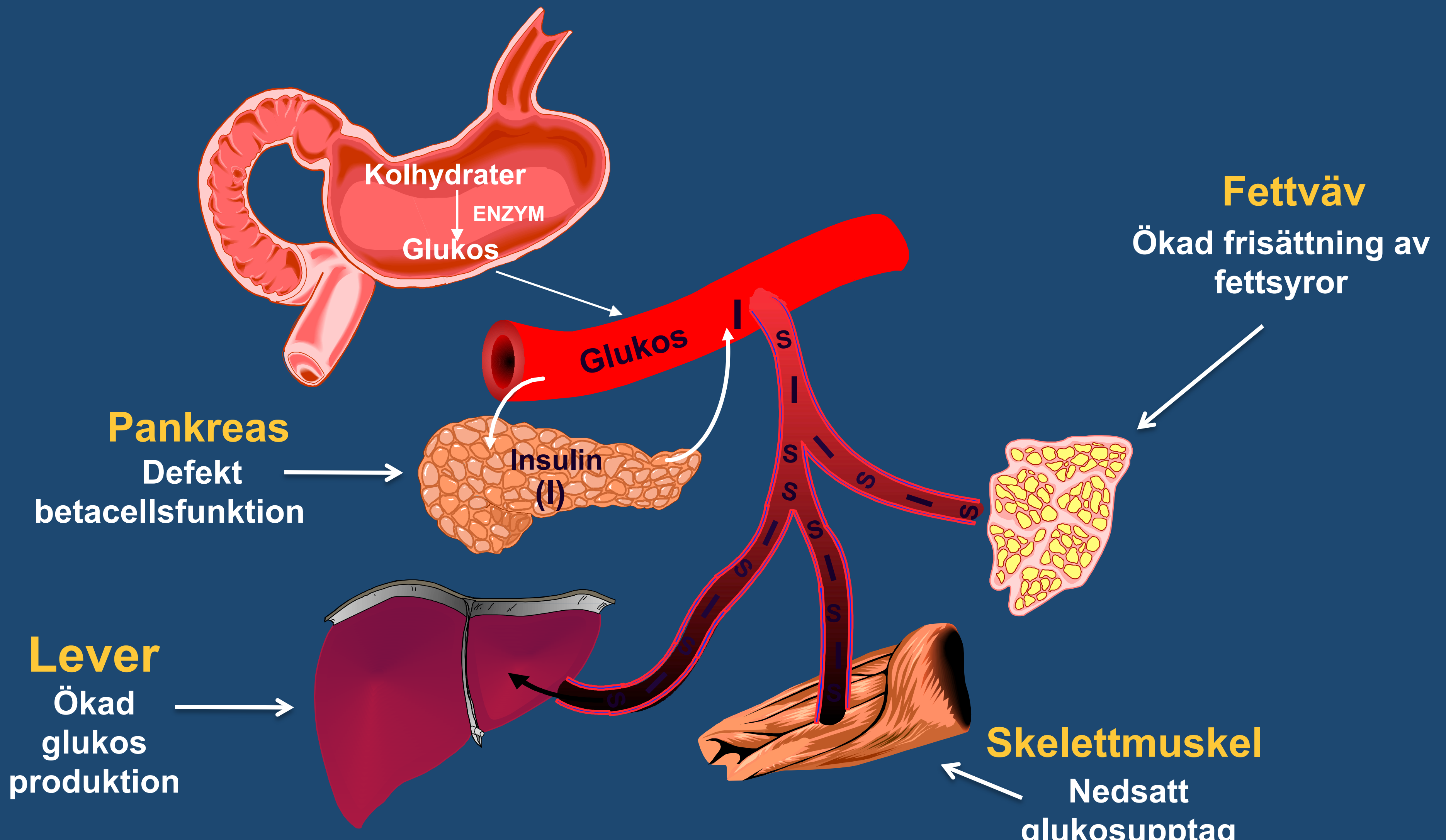
Dispositionsindex: Typ 2 Diabetes



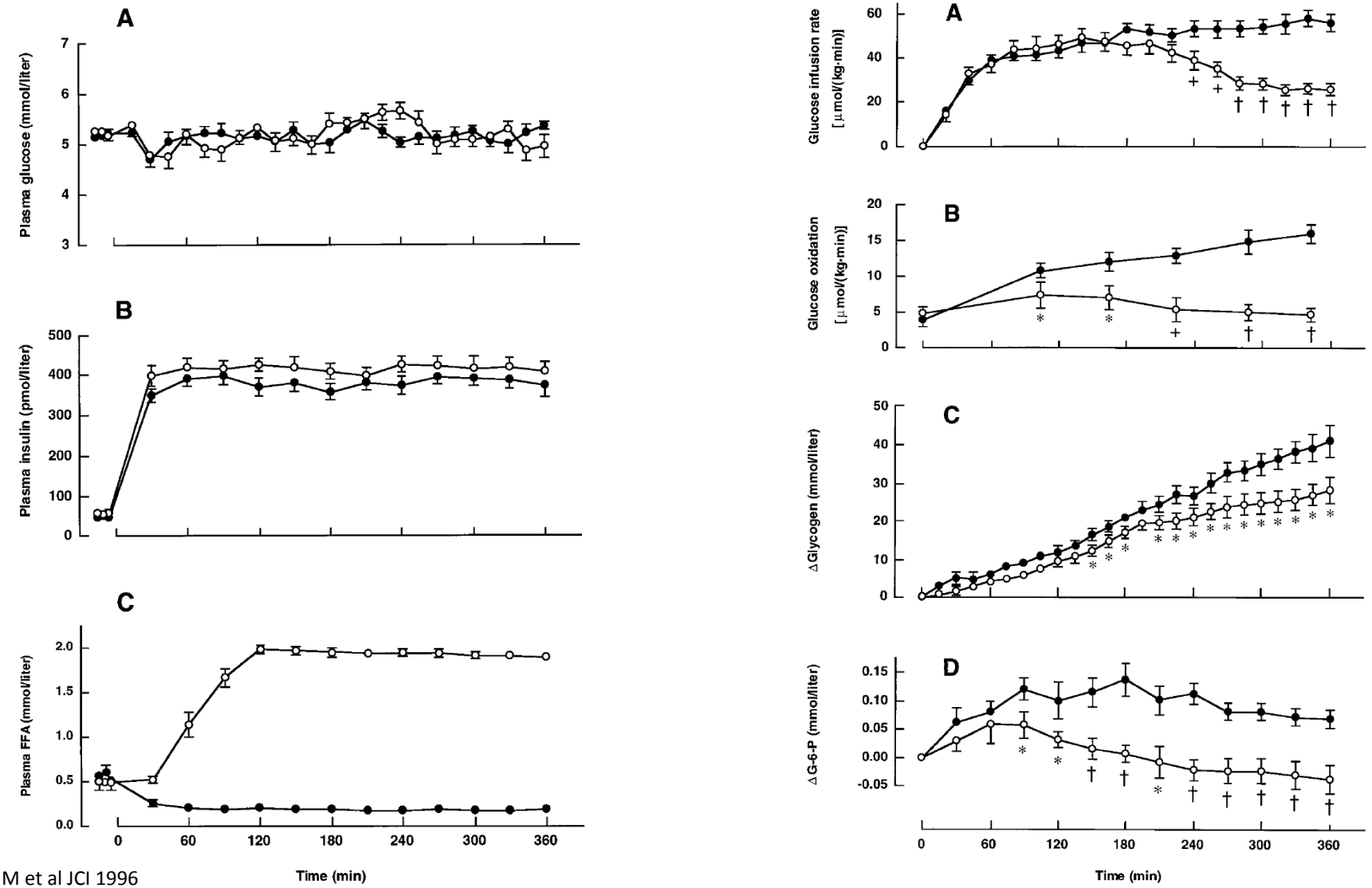
Insulinresistens



Insulinresistens

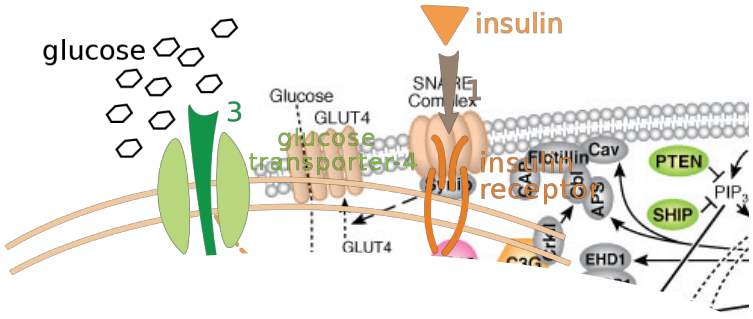


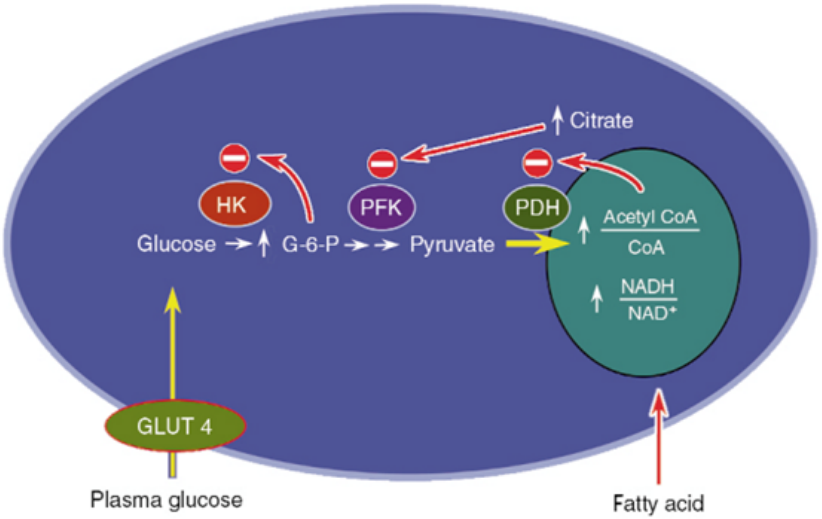
Insulinresistens utvecklas redan efter fyra timmars infusion av fria fettsyror hos människa

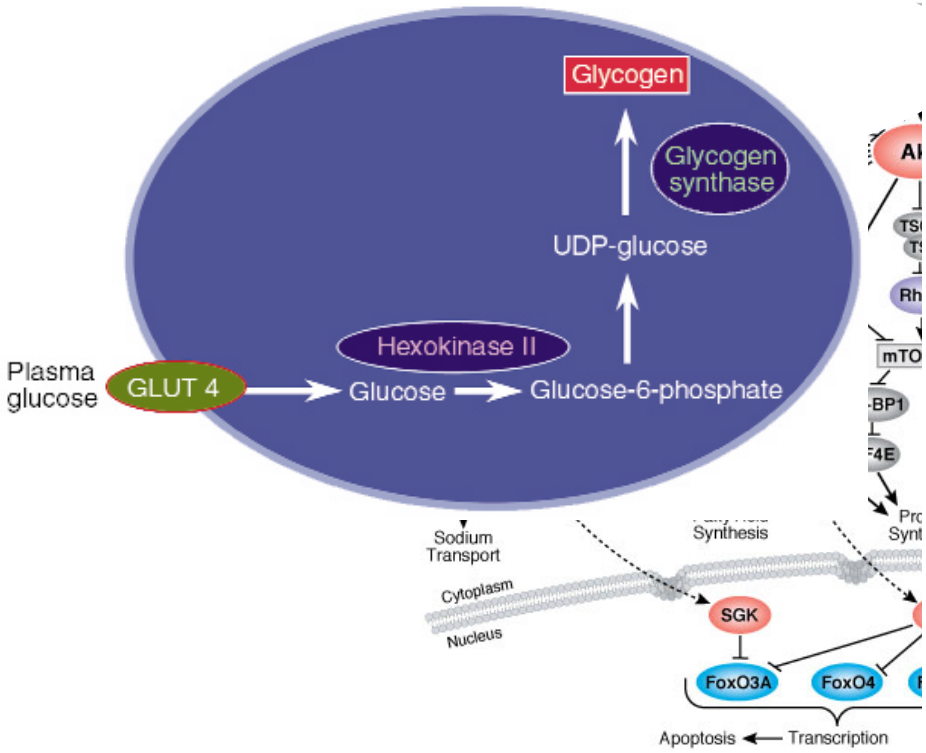


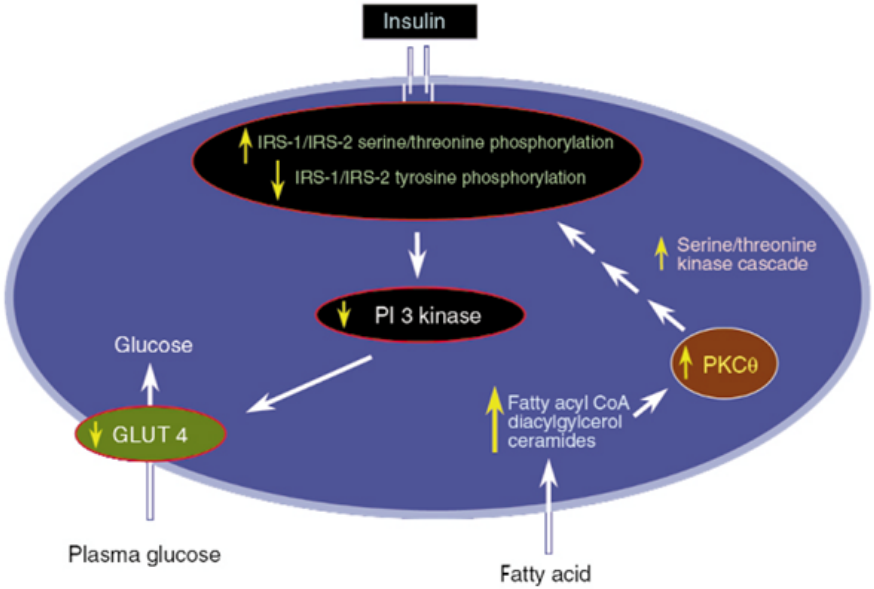
Roden M et al JCI 1996

Ökad mängd fettsyror inducerar insulinresistens i skelettmuskeln



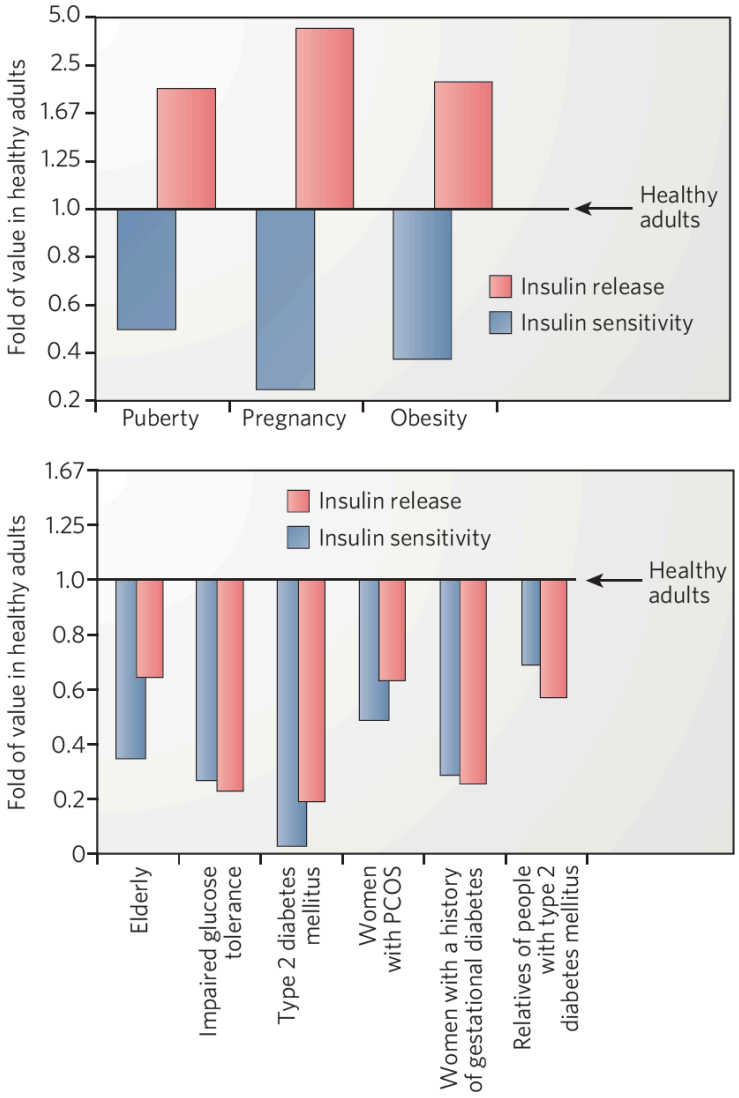






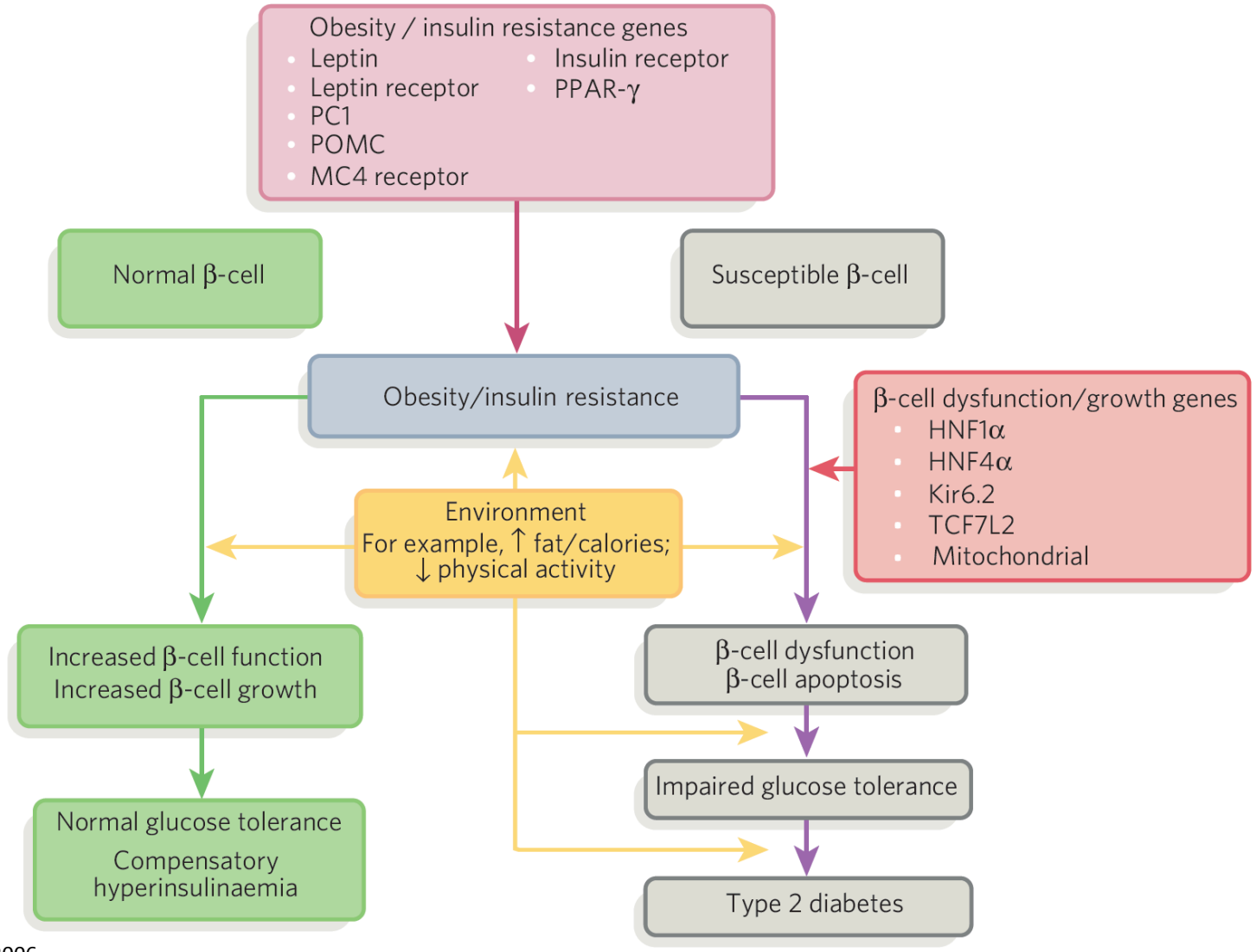
Shulman GI JCI 2000

Balans och obalans i dispositionsindex



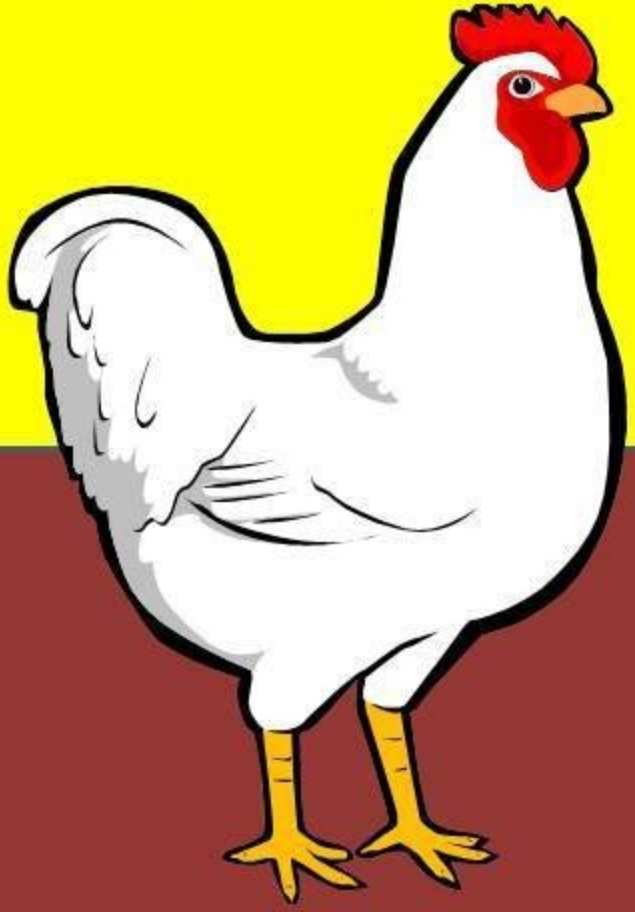
Kahn SE et al Nature 2006

Betacellsfunktionen är avgörande för utvecklingen av typ 2 diabetes: interaktion av gener och miljö



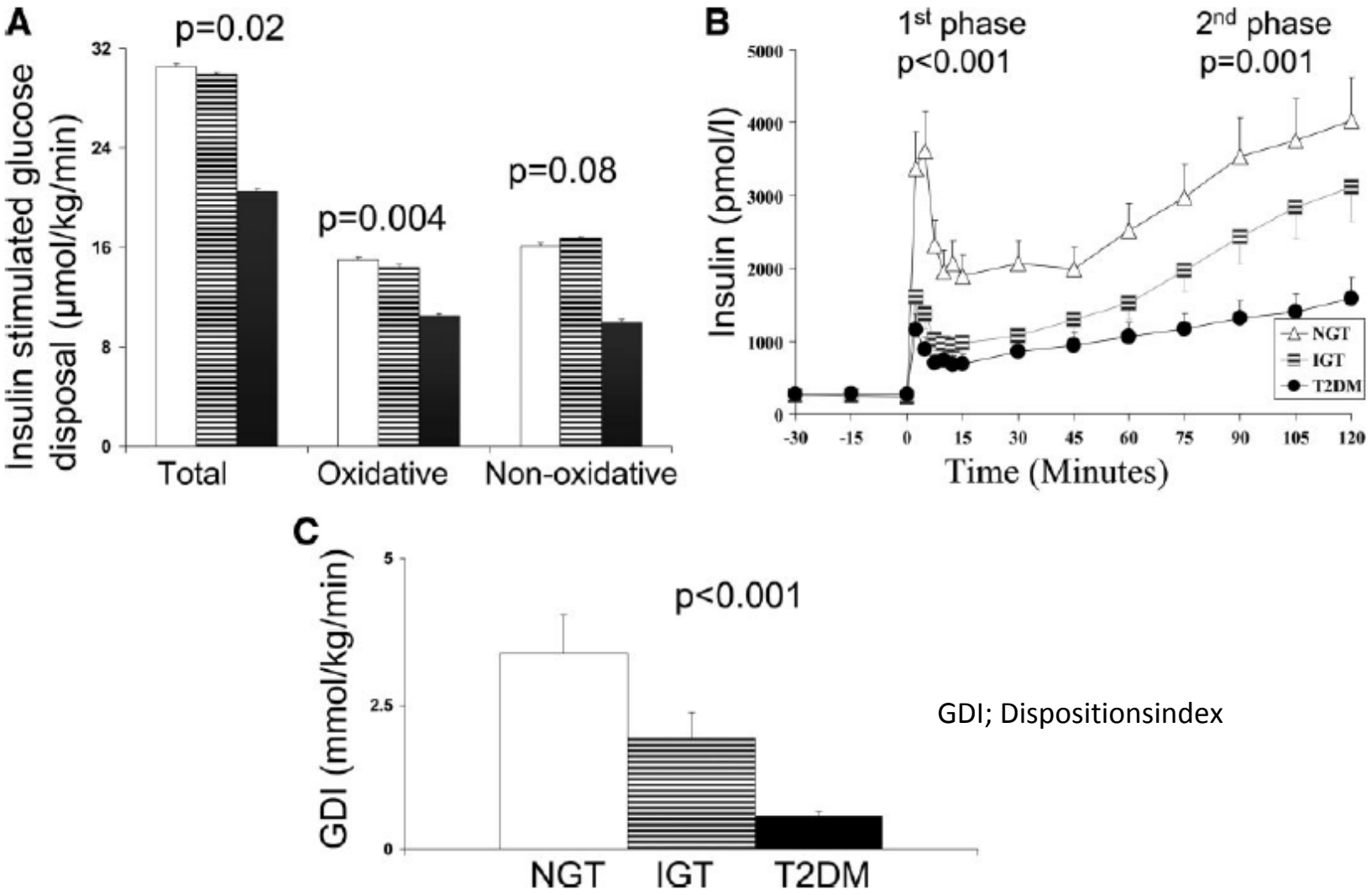
Kahn SE et al Nature 2006

Which came first?



or

Insulinsekretion, men inte insulinkänslighet, är försämrad hos unga överviktiga individer med nedsatt glukostolerans (IGT)



GDI; Dispositionsindex

Bacha et al DC 2009

For Debate

Beta cell function and its relation to insulin action in humans: a critical appraisal

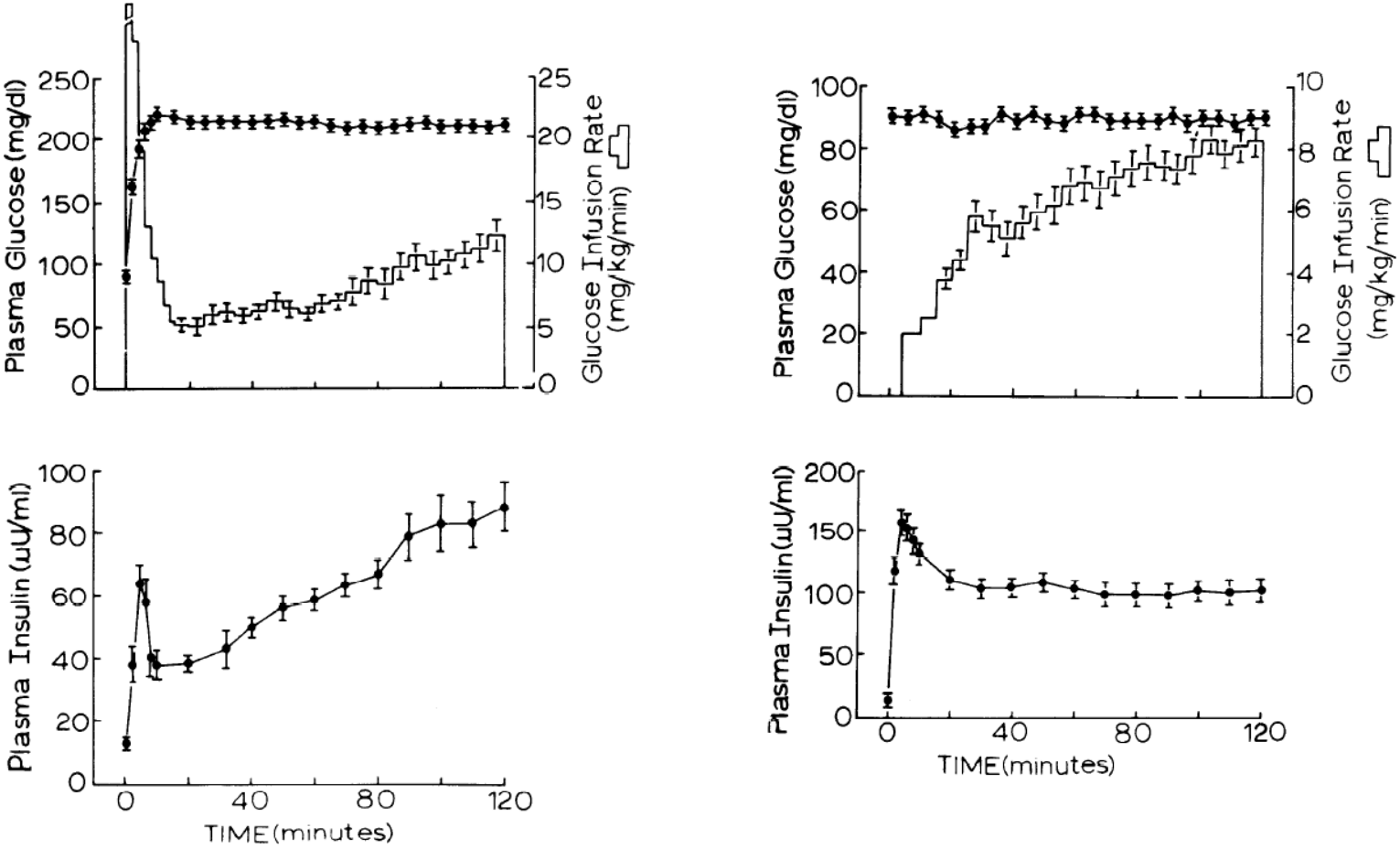
E. Ferrannini[1] · A. Mari[2]

[1] Department of Internal Medicine and CNR Institute of Clinical Physiology, University of Pisa School of Medicine, Pisa, Italy
[2] CNR Institute of Biomedical Engineering, Padova, Italy

- Betacellsfunktion
  - I relation med insulinkänslighet (dispositionsindex)
- Hur mäter vi betacellsfunktion?
  - Hur mycket av betacellsmassan och betacellsfunktionen har förlorats vid typ 2 diabetes?

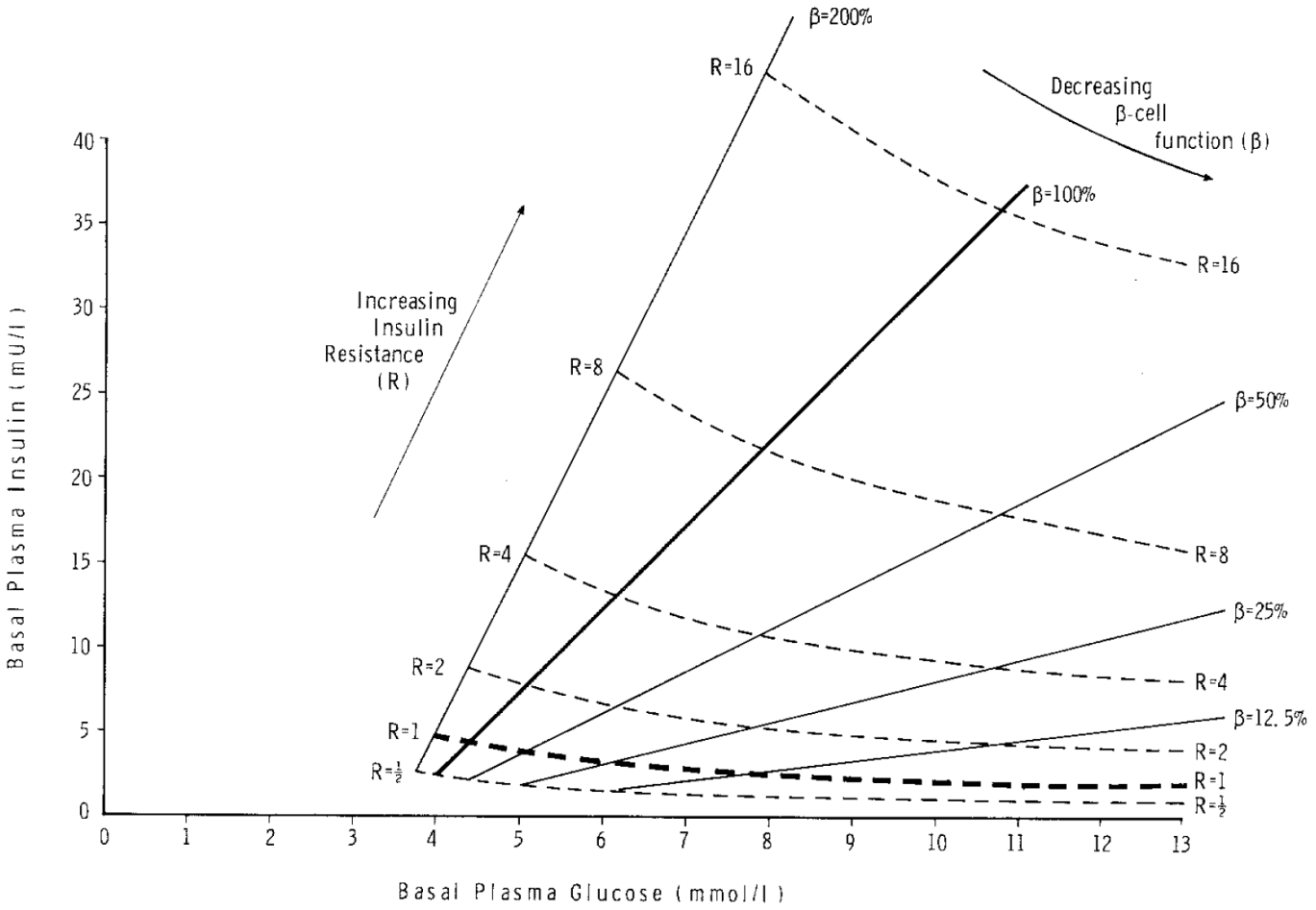
Glucose clamp technique: a method for quantifying insulin secretion and resistance

RALPH A. DEFRONZO, JORDAN D. TOBIN, AND REUBIN ANDRES
Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510; and Clinical Physiology Branch, Gerontology Research Center, National Institute of Aging, Baltimore City Hospitals, Baltimore, Maryland 20014



DeFronzo et al AJP 1979

Basal homeostasis model assessment (HOMA)



HOMA-IR = $G_b \cdot I_b / 22.5$

HOMA-BCF = $20 \cdot I_b / G_b - 3.5$

Matthews et al Diabetologia 1983

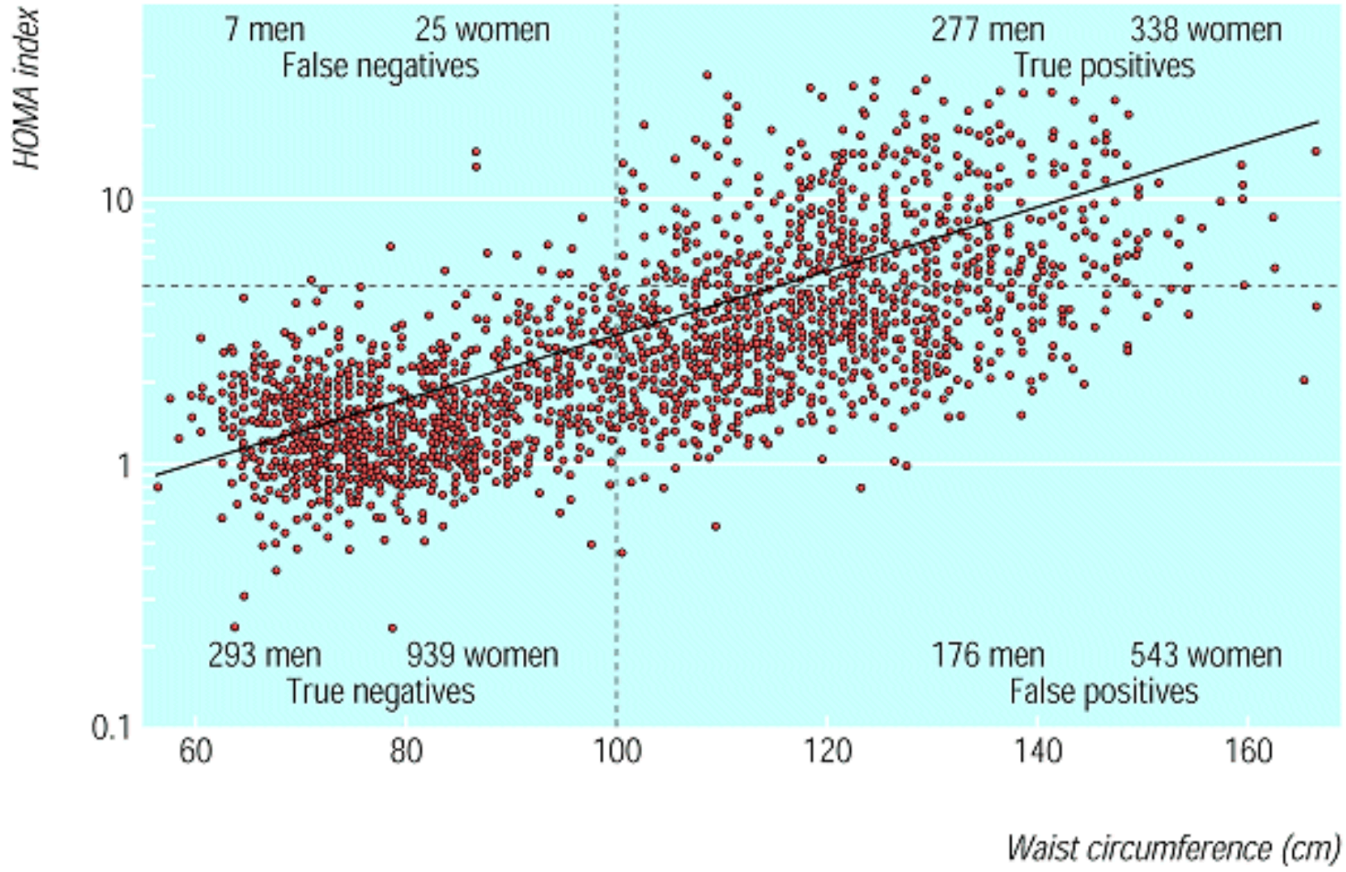
Methods for clinical assessment of insulin sensitivity and β-cell function

Best Practice & Research Clinical Endocrinology & Metabolism, 2003

Giovanni Pacini*
Andrea Mari

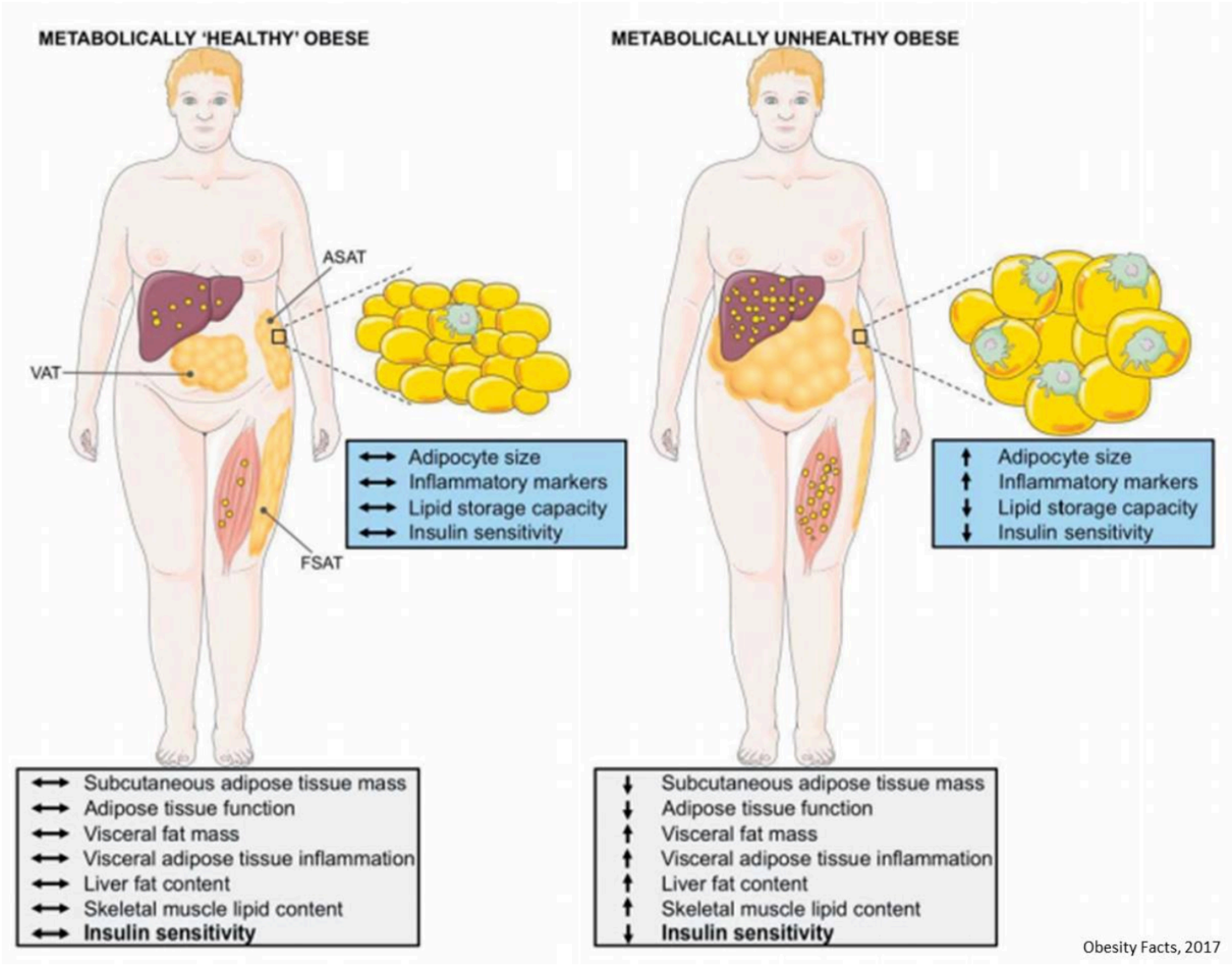
	Applicability	Informatin provided	Experimental requirments	Method	Calculation	Validation
Fasting Glucose/Insulin	Very wide	IS/BCF	1-3 samples N/A	HOMA QUICKI	Simple	Controversial
OGTT	Wide	IS/BCF	2-10 samples 2-5 hours	ISIcomp MCrest	Simple	Reasonable
IVGTT	Medium wide	BCF/IS	12-30 samples 3-5 hours	Minimal model	Computer/ Spreadsheet	Well documented
CLAMP	Medium	IS/BCF	Many samples 2-4 hours	M-value	Computer/ Spreadsheet	Reference
Graded glucose infusion	Limited	BCF	10-15 samples 6 hours		Simple	
Arginine test	Limited	BCF	>25 samples 4-5 hours		Simple	

Bukomfång: en enkel metod att utesluta insulinresistens ($HOMA_{IR}$ >3.99)



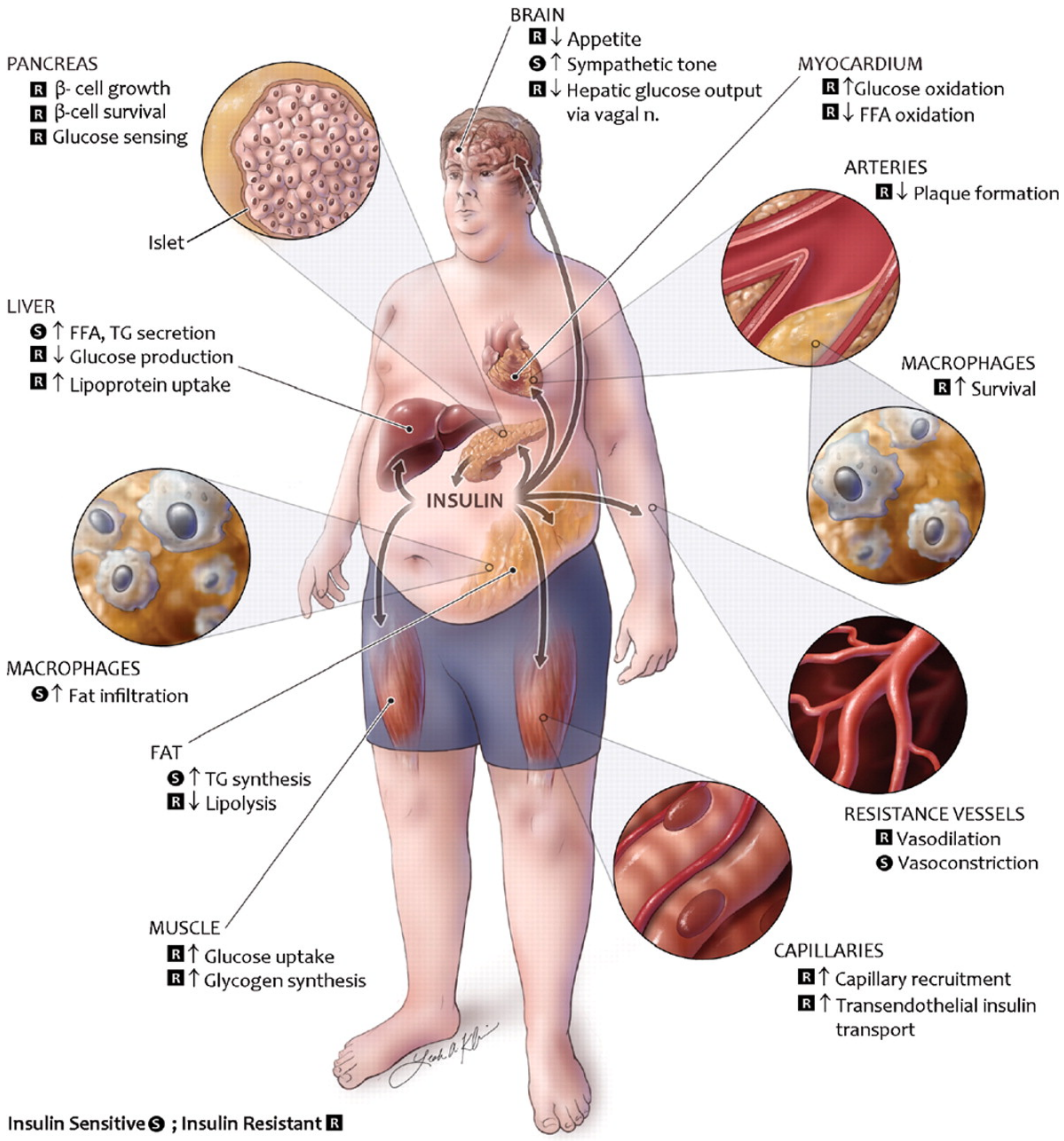
Wahrenberg et al BMJ 2005

Fettväv: ett aktivt metabolt organ



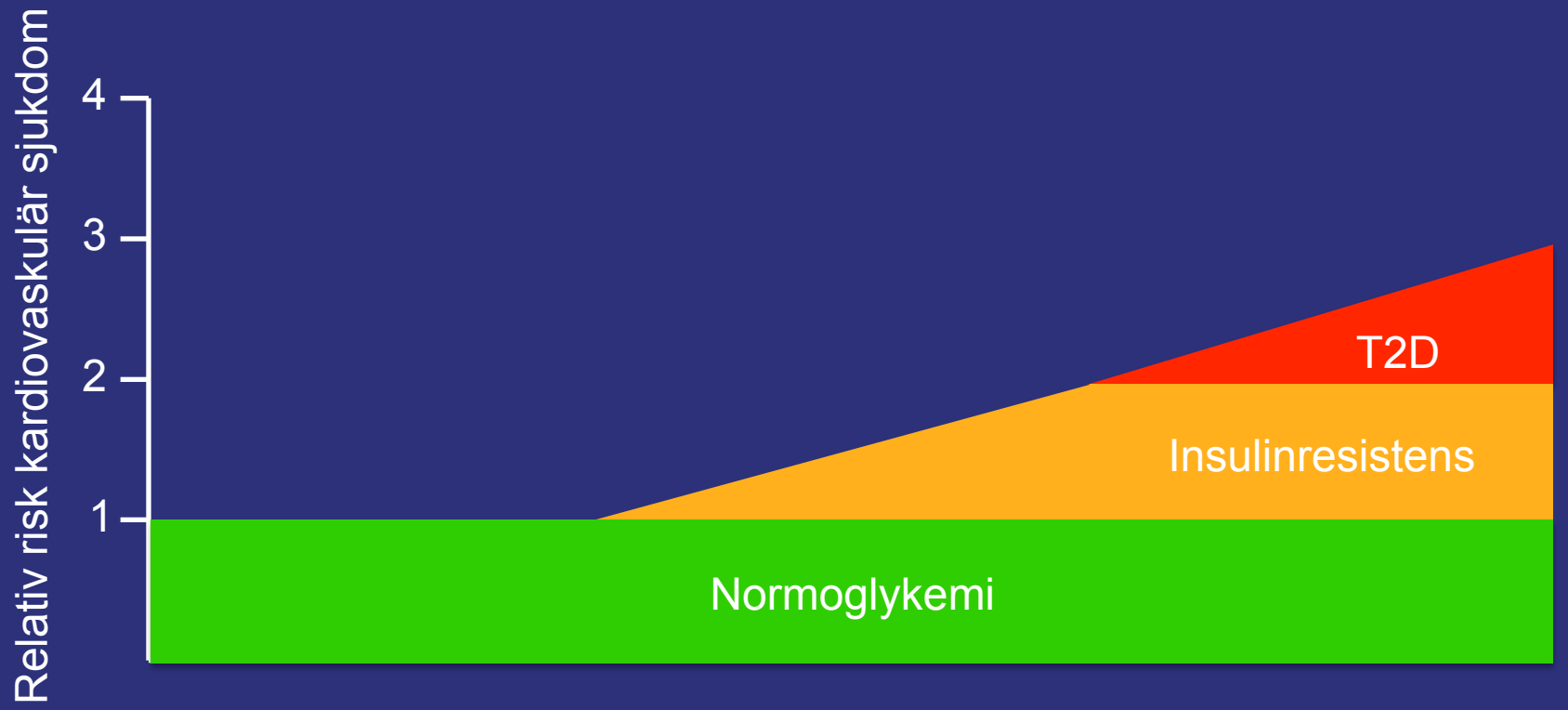
Obesity Facts, 2017

Andra av insulinets fysiologiska effekter försämras vid insulinresistens



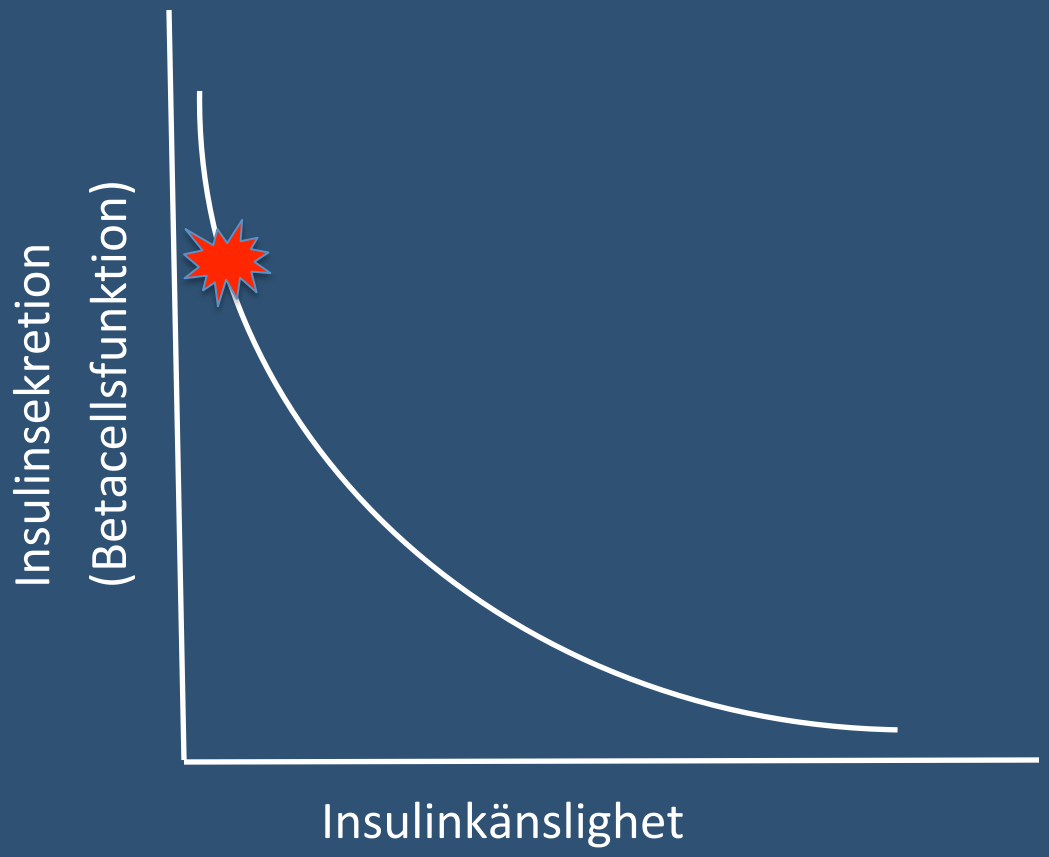
Rask-Madsen and Kahn *ATVB* 2012

Insulinresistens en oberoende riskfaktor för kardiovaskulär sjukdom



Laakso *Diabetes Care* 2010; 33: 442-449

Dispositionsindex: Motion



Effects of Diet and Exercise in Preventing NIDDM in People With Impaired Glucose Tolerance

The Da Qing IGT and Diabetes Study

The New England Journal of Medicine

VOLUME 344 MAY 3, 2001 NUMBER 18

PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

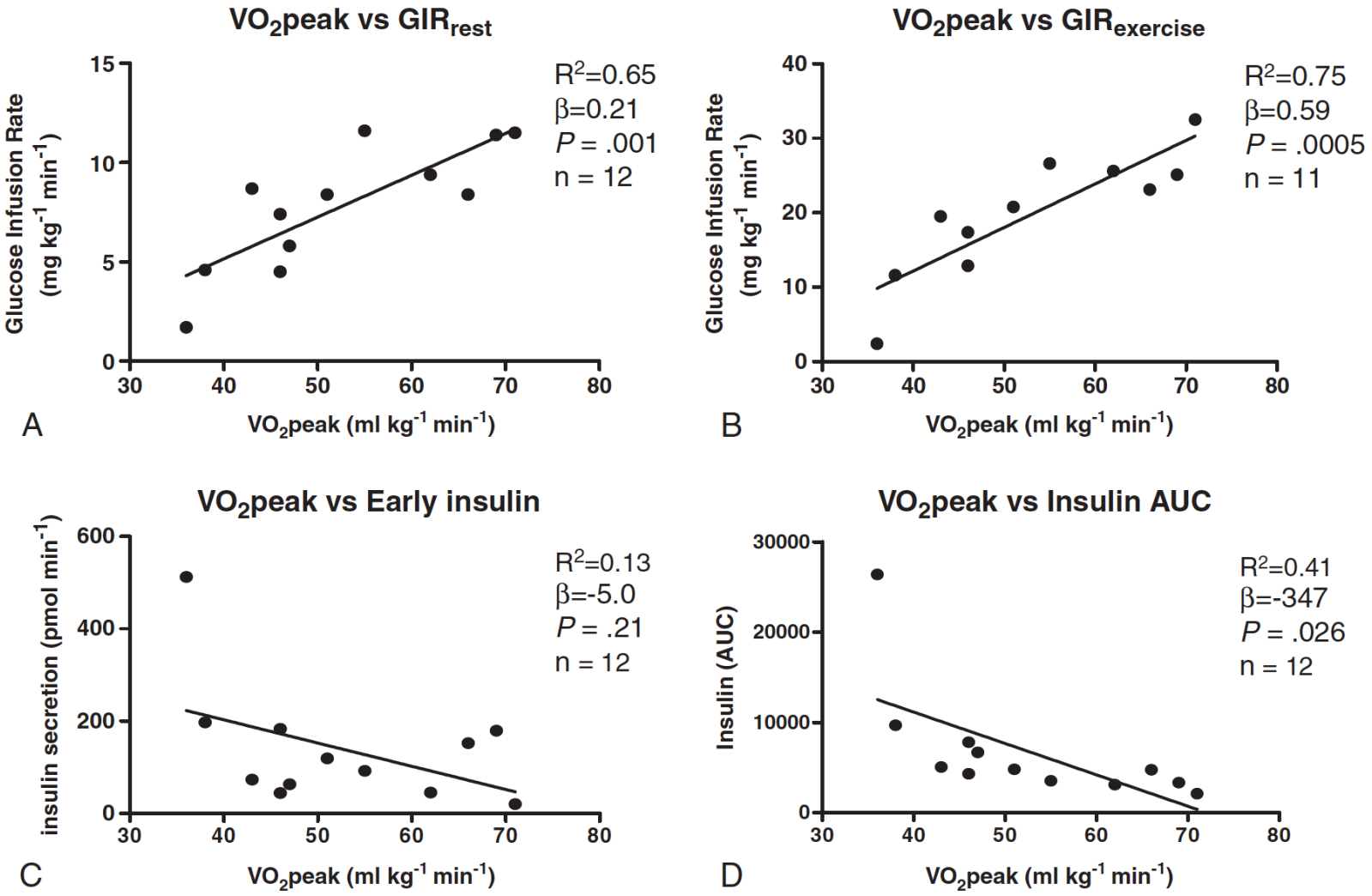
The New England Journal of Medicine

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

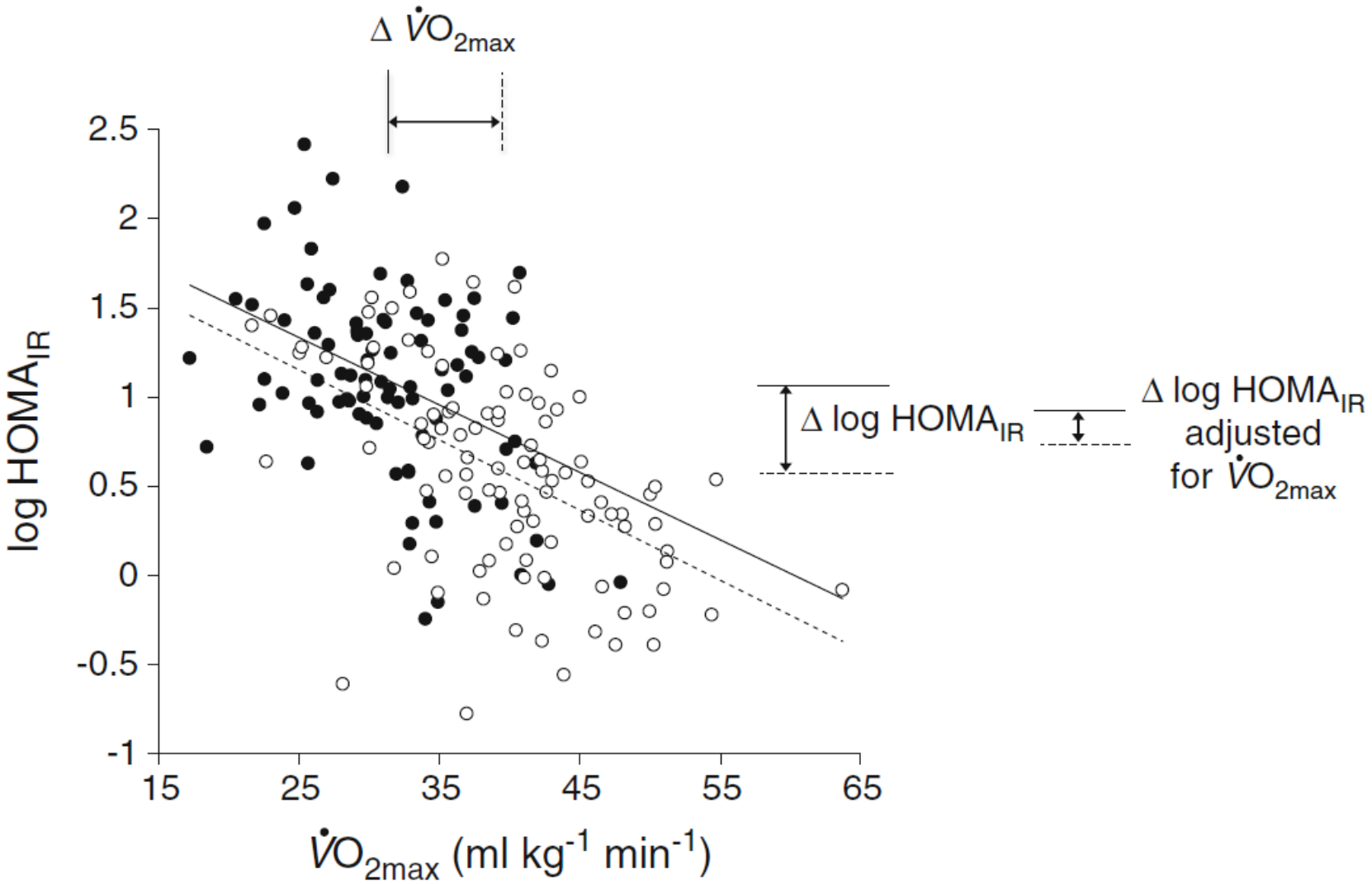
DIABETES PREVENTION PROGRAM RESEARCH GROUP*

Maximalt syreupptag i relation till insulinsekretion och insulinkänslighet hos unga individer utan diabetes



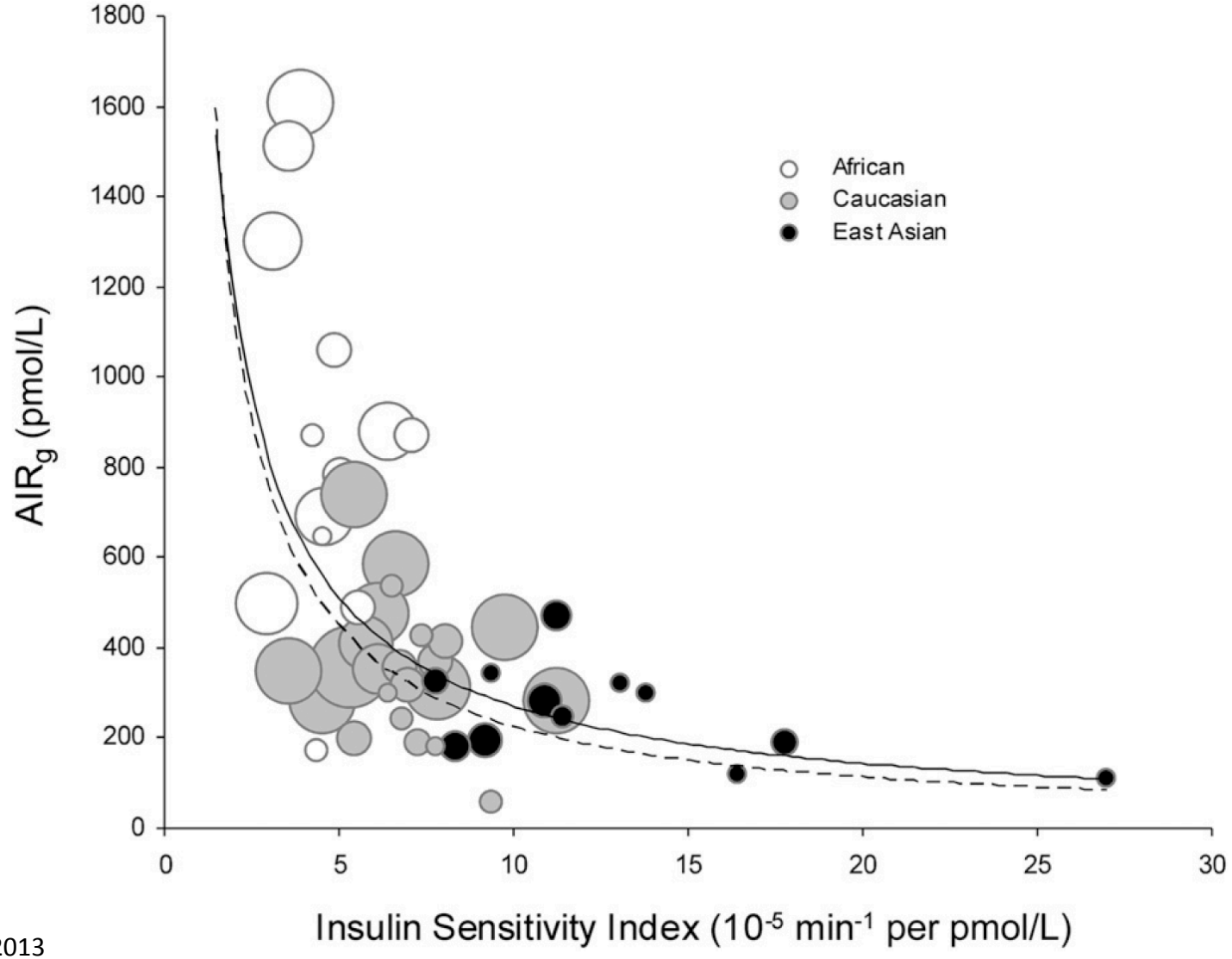
Larsen et al Metabolism 2011

Relation mellan insulinkänslighet ($HOMA_{IR}$) och maximalt syreupptag hos 100 Sydostasiater (●) jämfört med 100 Européer (○) bosatta i England



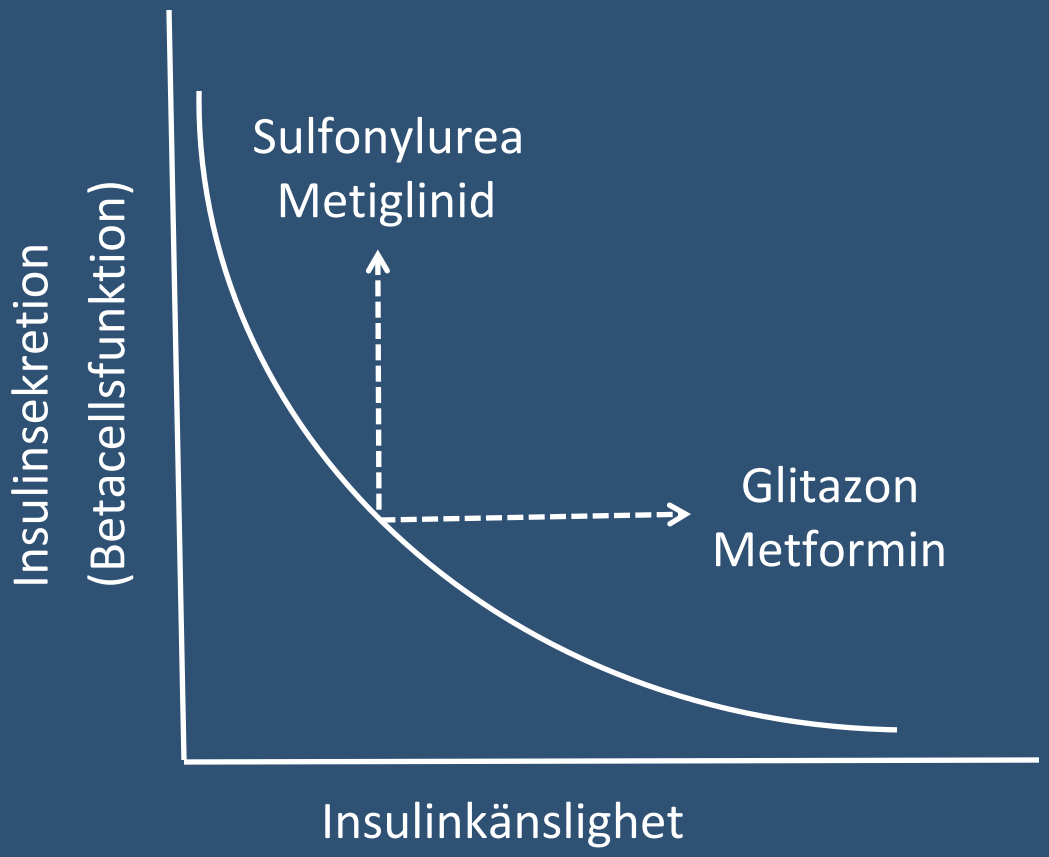
Ghouri et al Diabetologia 2013

Etnisk skillnad i förhållandet mellan insulinkänslighet och insulinsekretion hos individer utan diabetes (metaanalys)

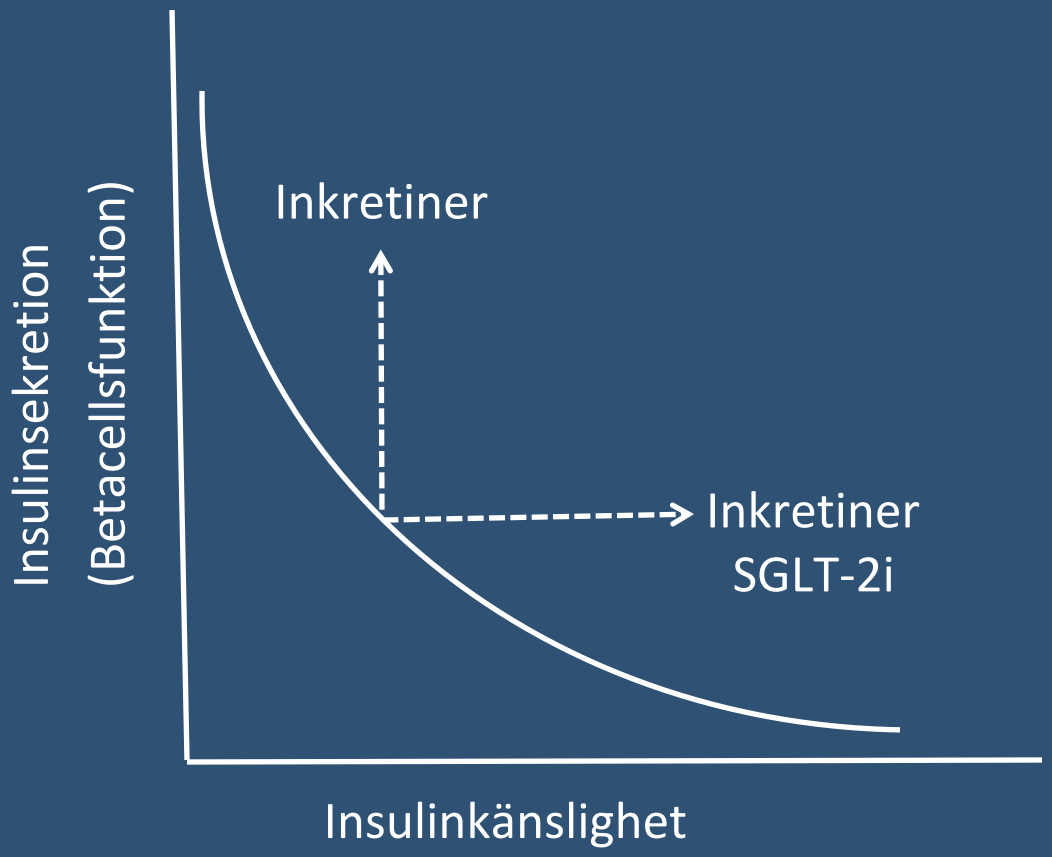


Kodama et al DC 2013

Typ 2 diabetes
Gamla verktyg i verktygslådan



Typ 2 diabetes
Nya verktyg i verktygslådan



CV Outcome Trials in T2D

	EMPA-REG	CANVAS	DECLARE**	LEADER	SUSTAIN	HARMONY
MACE*	0.86 (0.74-0.99)	0.82 (0.72-0.95)	0.85 (0.69-1.05)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.78 (0.68-0.90)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.93 (0.73-1.19)
Non-fatal MI	0.87 (0.70-1.09)	0.85 (0.69-1.05)	0.89 (0.77-1.01)	0.88 (0.75-1.03)	0.74 (0.51-1.08)	0.75 (0.61-0.90)
Non-fatal Stroke	1.24 (0.92-1.67)	0.90 (0.71-1.15)	1.01 (0.84-1.21)	0.89 (0.72-1.11)	0.61 (0.38-0.99)	0.86 (0.66-1.14)

HR (95% CI)

*Primary Outcome, CV Death + Non-fatal MI + Non-Fatal Stroke (3P-MACE)

**Primary Outcome, CV death or Hospitalization for heart failure HR 0.83 (0.73-0.95)

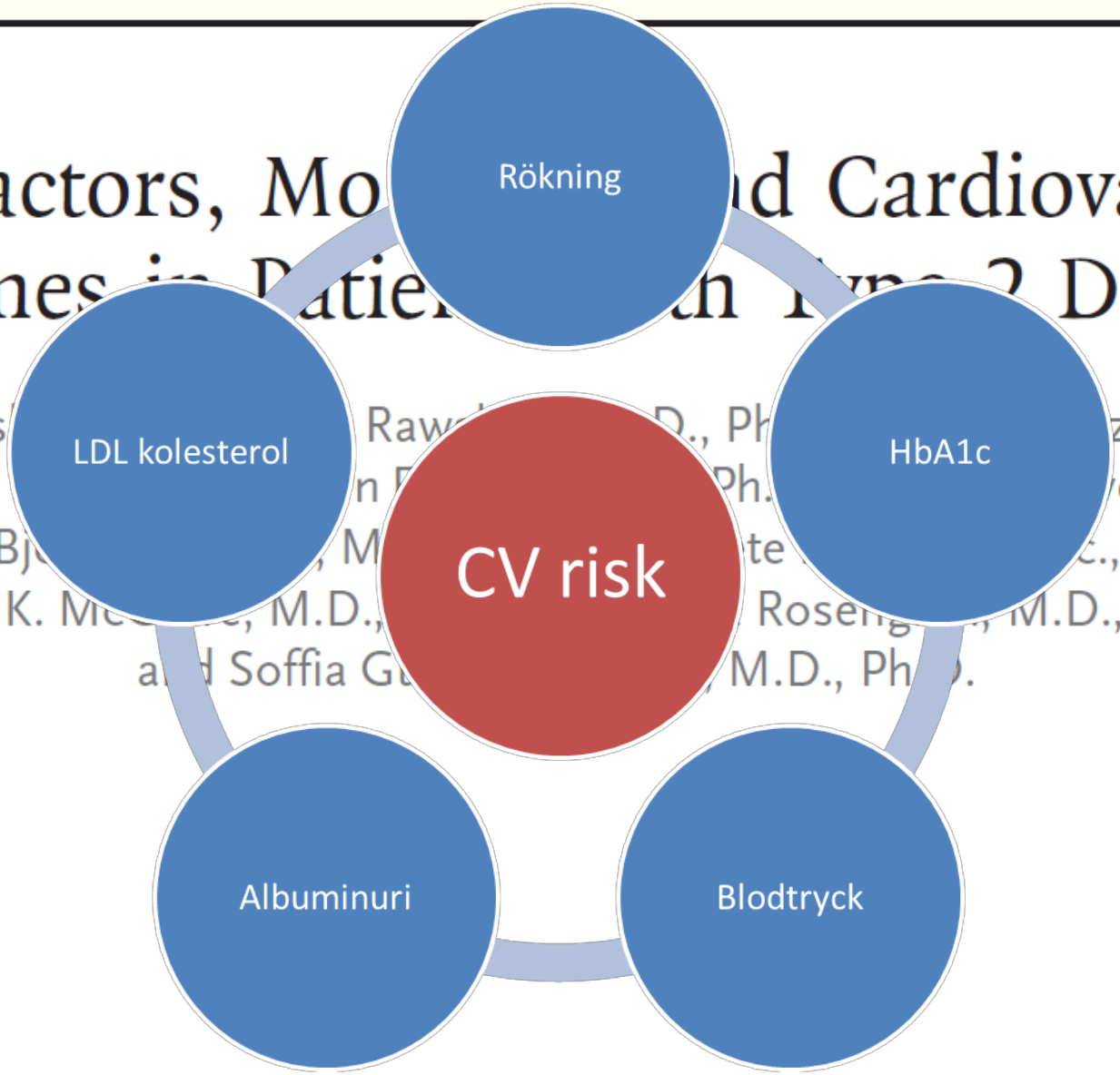
	Pat.	Age	Duration (Yrs)	Follow-up (Yrs)	BP (mmHg) Diff[1]	Weight (kg) Diff[1]	HbA1c (mean) Diff[1]
EMPA-REG OUTCOME (SGLT-2i)	7,200	63	>10	3.1	135/77 **-1.9/-0.1**	86 **-2.0**	64 mmol/mol **-2 mmol/mol**
CANVAS (SGLT-2i)	10,142	63	13.5	3.6	136/78 **-3.9/-1.4**	90 **-1.6**	66 mmol/mol **-5 mmol/mol**
DECLARE (SGLT-2i)	17,160	64	10.5	4.2	134/76 **-3.0/-0.2**	88 **-2.0**	64 mmol/mol **-2 mmol/mol**
LEADER (GLP-1)	9,340	64	12.8	3.8	136/77 **-1.2/-0.6**	92 **-2.3**	61 mmol/mol **-4 mmol/mol**
SUSTAIN-6 (GLP-1)	3,297	64	13.9	2.0	135/78 **-2.6/-1.0**	92 **-4.3**	69 mmol/mol **-10 mmol/mol**
HARMONY (GLP-1)	9,463	64	14.1	1.6	135/77 **-0.7/?**	92 **-0.8**	61 mmol/mol **-5 mmol/mol**

[1]Difference in BP/Weight/HbA1c between placebo, respectively.

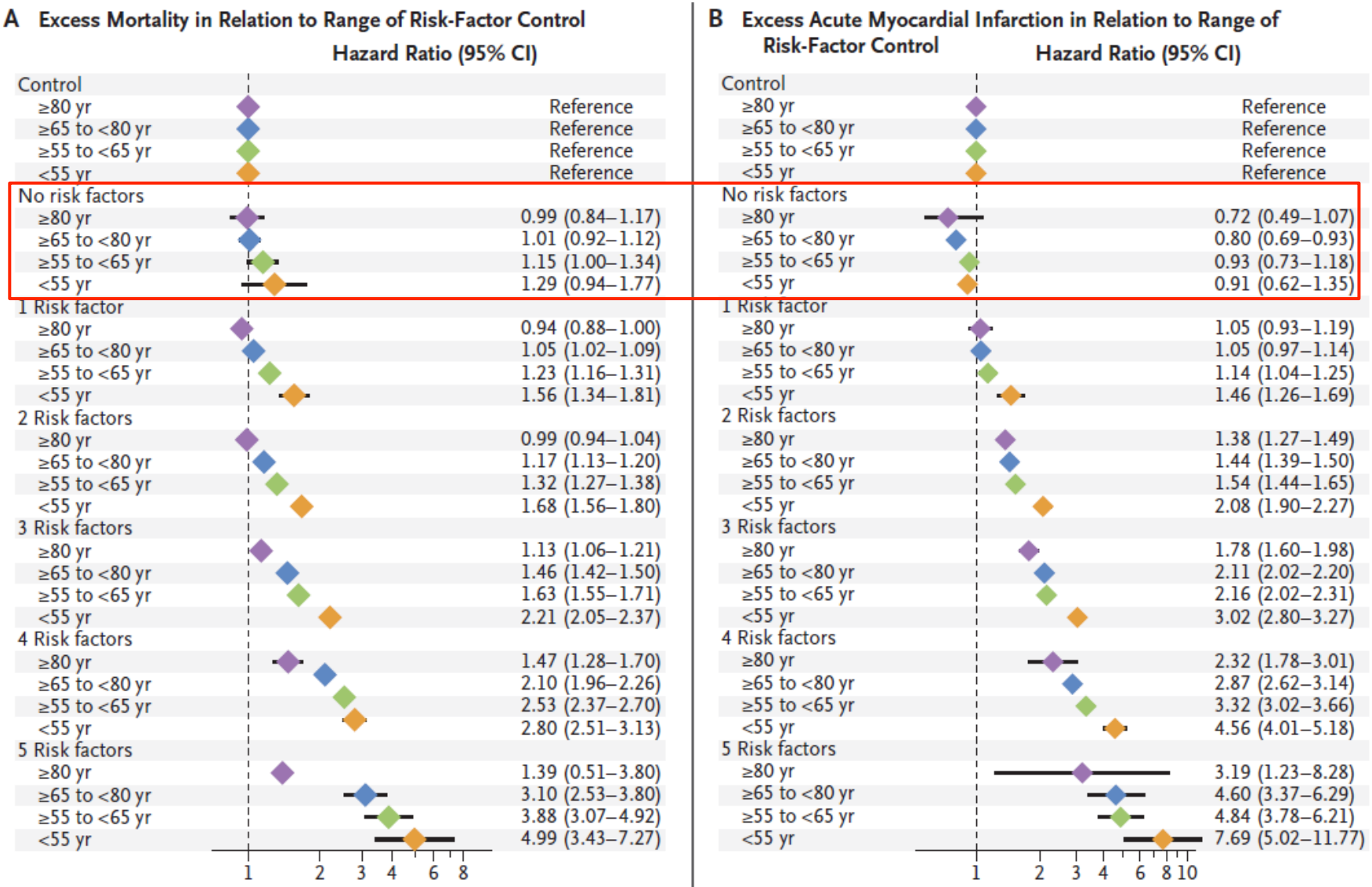
ORIGINAL ARTICLE

Risk Factors, Mo d Cardiovascular Outcomes in Patie th Type 2 Diabetes

Aidin Raws Raw D., Ph zén, Ph.D.,
Naveed Sattar, n Ph. ensson, Ph.D.,
Bj , M te c.,
Darren K. Mc , M.D., Rosen , M.D., Ph.D.,
a d Soffia G , M.D., Ph .

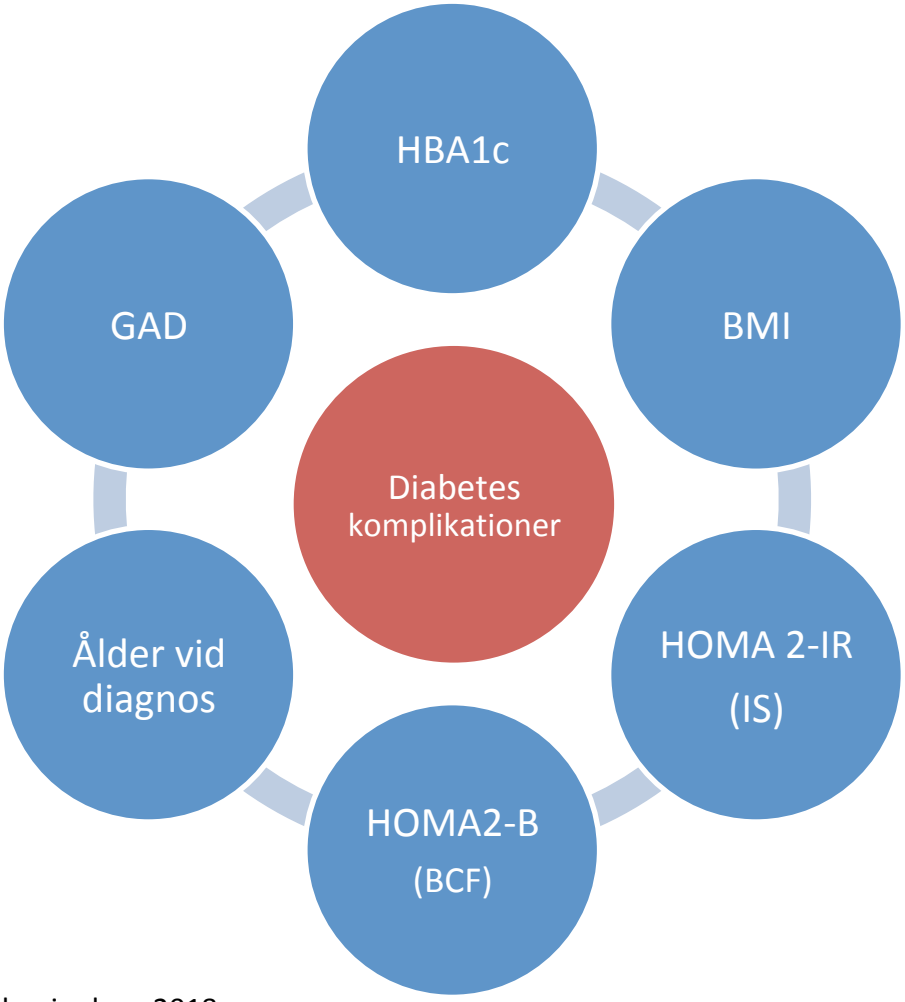


Ingen signifikant ökad mortalitet eller ökad risk för hjärtinfarkt om alla fem riskfaktorer är under kontroll



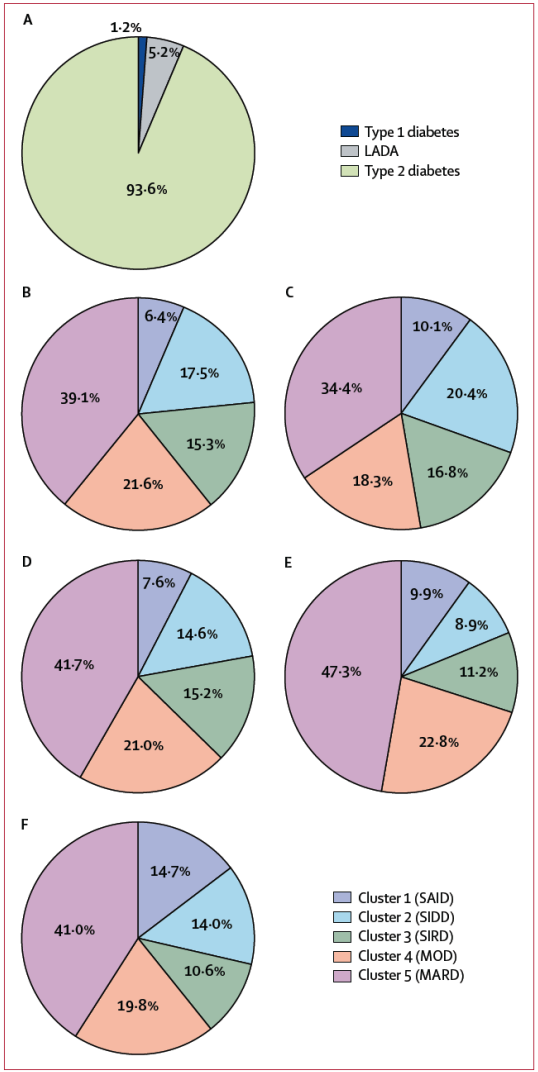
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*



Ahlqvist E et al Lancet Diabetes Endocrinology 2018

Distribution före och efter klusterindelning i samtliga kohorter



A. ANDIS (Alla nya Diabetiker i Skåne) n=8980

B. ANDIS efter klusterindelning

C. Skåne Diabetesregistret (SDR) n=1466

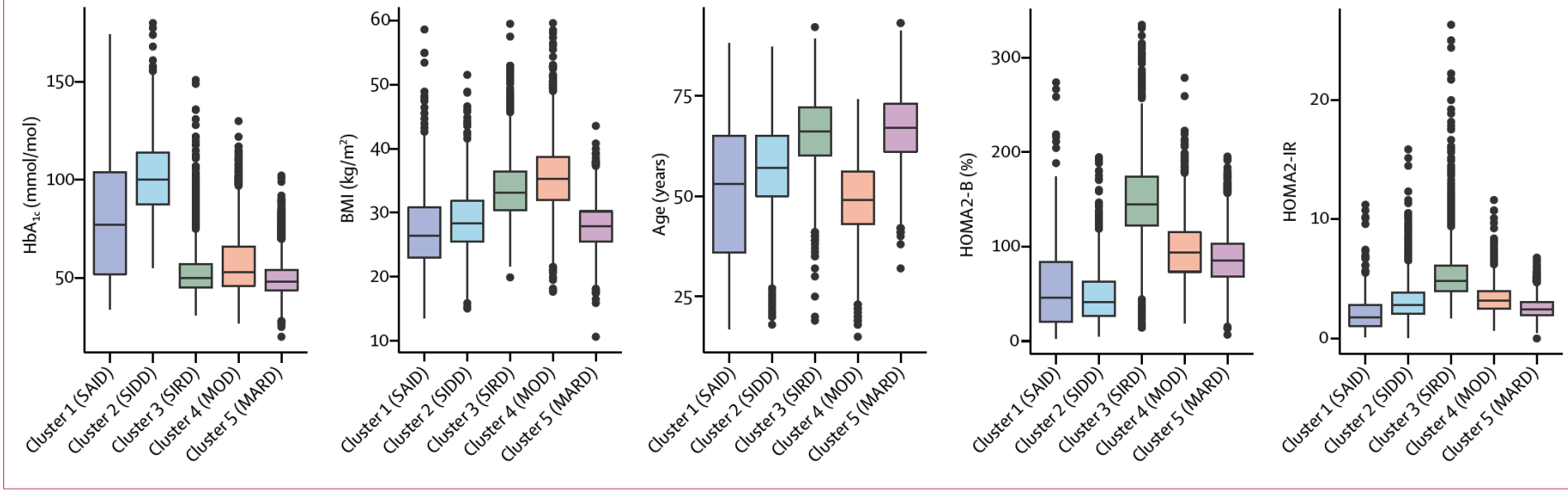
D. ANDIU (Alla nydiagnostiserade i Uppsala) n=844)

E. DIREVA (Diabetes Registry in Vasa) nydiagnostiserade (n=878)

F. DIREVA patienter med lång diabetes duration (n=2607)

1. **SAID = severe autoimmune diabetes (GAD+)**
2. **SIDD = severe insulin deficient diabetes (GAD-)**
3. **SIRD = severe insulin resistant diabetes**
4. **MOD = mild obesity related diabetes**
5. **MARD = mild age related diabetes**

Klusterindelning (6 faktorer) ur ANDIS kohorten (n=8980)



1. SAID = severe autoimmune diabetes (GAD+)
2. SIDD = severe insulin deficient diabetes (GAD-)
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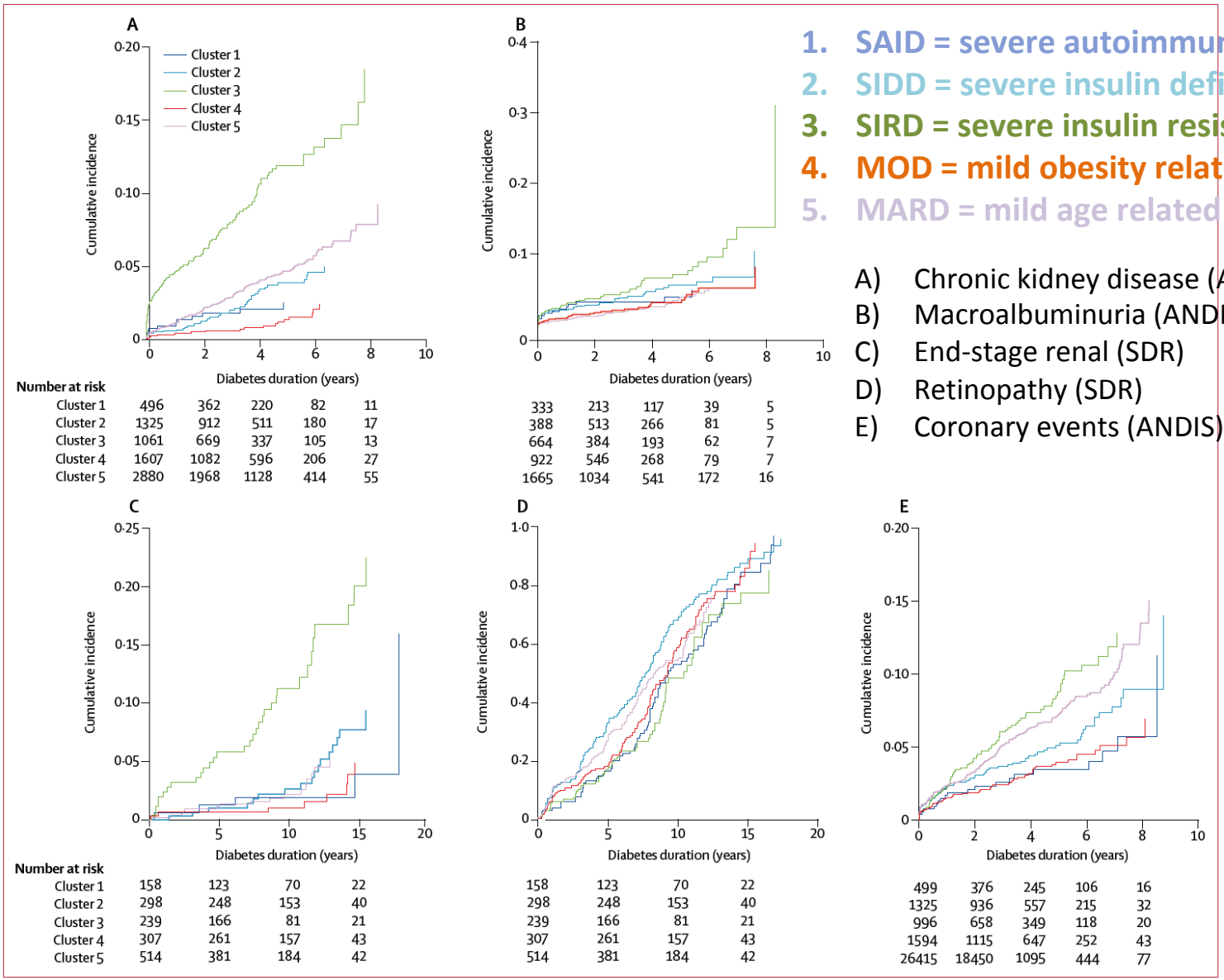
Risk för komplikationer (A-E) (ANDIS/SDR)



1. SAID = severe autoimmune diabetes (GAD+)
2. SIDD = severe insulin deficient diabetes (GAD-)
3. SIRD = severe insulin resistant diabetes
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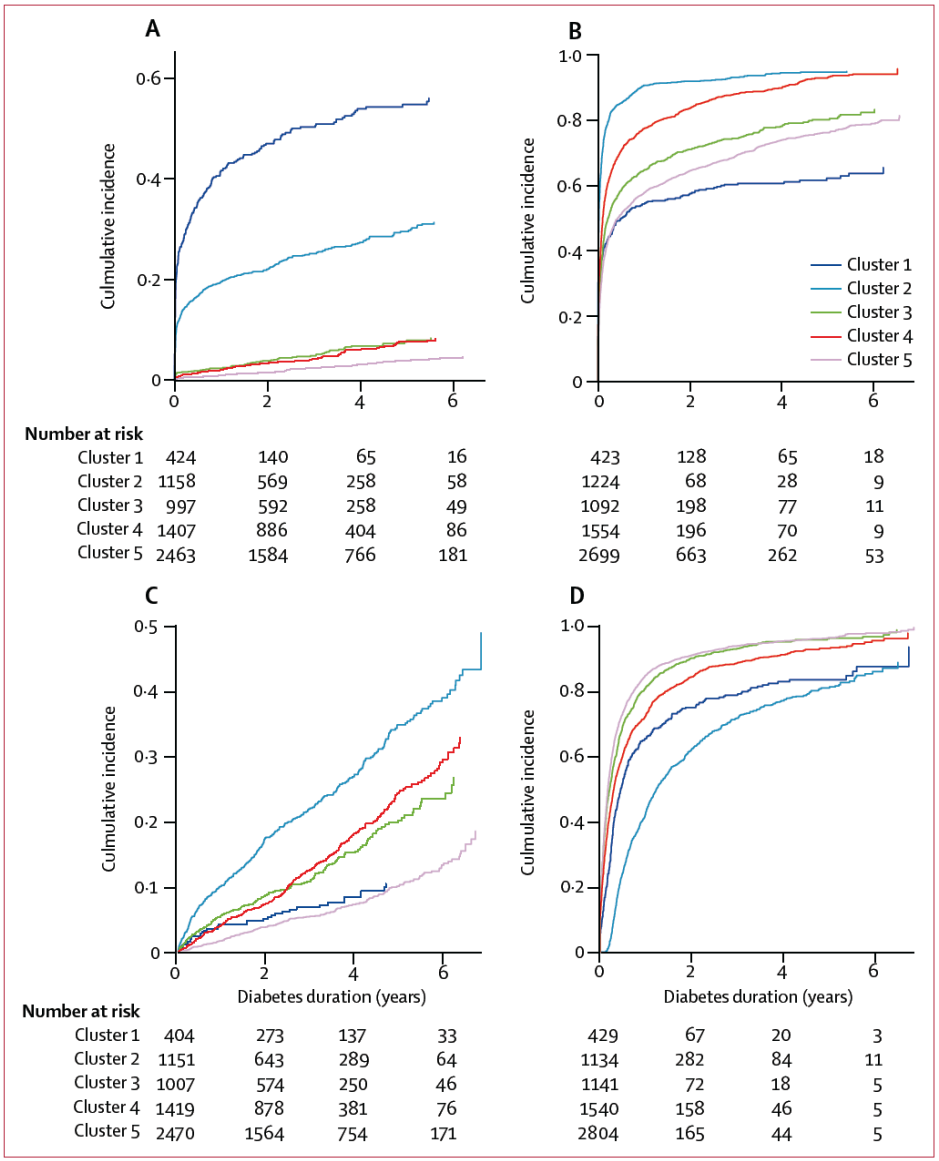
A) Chronic kidney disease (ANDIS)
B) Macroalbuminuria (ANDIS)
C) End-stage renal (SDR)
D) Retinopathy (SDR)
E) Coronary events (ANDIS)

Antidiabetiska läkemedel i ANDIS (n=8980) under uppföljningen



1. SAID = severe autoimmune diabetes (GAD+)
2. SIDD = severe insulin deficient diabetes (GAD-)
3. SIRD = severe insulin resistant diabetes
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(A) Tid till insulin
(B) Tid till metformin
(C) Tid till andra linjens orala antidiabetika (ej metformin)
(D) Tid till HbA1c<6·9% [52 mmol/mol])

Förslag till nya undergrupper och dess association till diabeteskomplikationer

- **Grupp 1, SAID (severe autoimmune diabetes):** motsvarar i princip typ 1 diabetes och LADA (latent autoimmune diabetes in the adult), och karaktäriseras av insjuknande i låg ålder, dålig metabol kontroll, försämrad insulinproduktion och förekomst av GAD-antikroppar

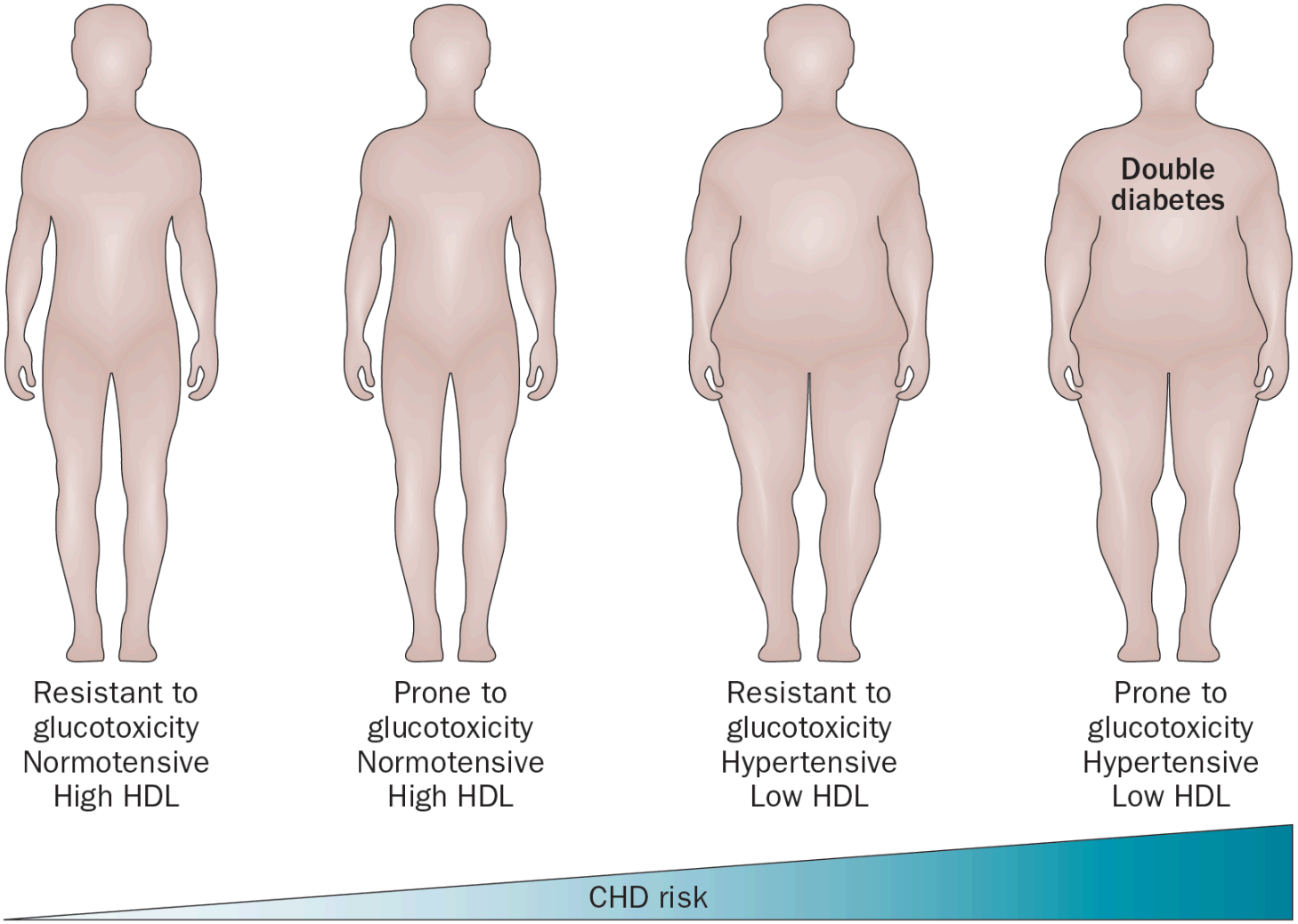
- **Grupp 2, SIDD (severe insulin-deficient diabetes):** omfattar personer utan antikroppar med högt HbA1C, försämrad insulinproduktion och måttlig insulinresistens. Grupp 2 har den högsta förekomsten av retinopati

- **Grupp 3, SIRD (severe insulin-resistant diabetes):** karaktäriseras av kraftig övervikt och allvarlig insulinresistens. Grupp 3 hade den högsta förekomsten av njurskador vilket också är den följdsjukdom som kostar samhället mest

- **Grupp 4, MOD (mild obesity-related diabetes, MOD):** omfattar kraftigt överviktiga patienter som insjuknar vid relativt ung ålder

- **Grupp 5, MARD (mild age-related diabetes, MARD):** är den största gruppen (ca 40%) och samlar de äldsta patienterna

Individer med typ 1 diabetes och med fenotyp som för typ 2 diabetes (Dubbeldiabetes) har en ökad kardiovaskulär risk



Cleland S *Nat. Rev. Endocrinol*. 2012

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WILEY

ORIGINAL ARTICLE

Estimated glucose disposal rate predicts mortality in adults with type 1 diabetes

Thomas Nyström[1,2] | Martin J. Holzmann[3,4] | Björn Eliasson[5] | Ann-Marie Svensson[6] | Ulrik Sartipy[7,8]

- Sämre glukoskontroll (HbA1c) kan inte ensamt förklara varför individer med typ 1 diabetes har en högre kardiovaskulär risk jämfört individer med bra HbA1c

- Mortalitetsrisk och dess association till olika grader av insulinkänslighet är inte tillräckligt studerat hos individer med typ 1 diabetes

Nyström et al DOM 2018

Methods

Can Clinical Factors Estimate Insulin Resistance in Type 1 Diabetes?

Katherine V. Williams, John R. Erbey, Dorothy Becker, Silva Arslanian, and Trevor J. Orchard

- Estimated Glucose Disposal Rate (eGDR)
- eGDR = 21.158−(0.09 ×WC)−(3.407 × HT)−(0.551 × HbA1c)
  - WC, Waist Circumference cm
  - HT, Hypertension 0=No, 1=Yes
  - HbA1c DCCT %
- eGDR = mg/kg/min

Williams K et al *Diabetes* 2000

Received: 20 July 2017 | Revised: 3 September 2017 | Accepted: 4 September 2017

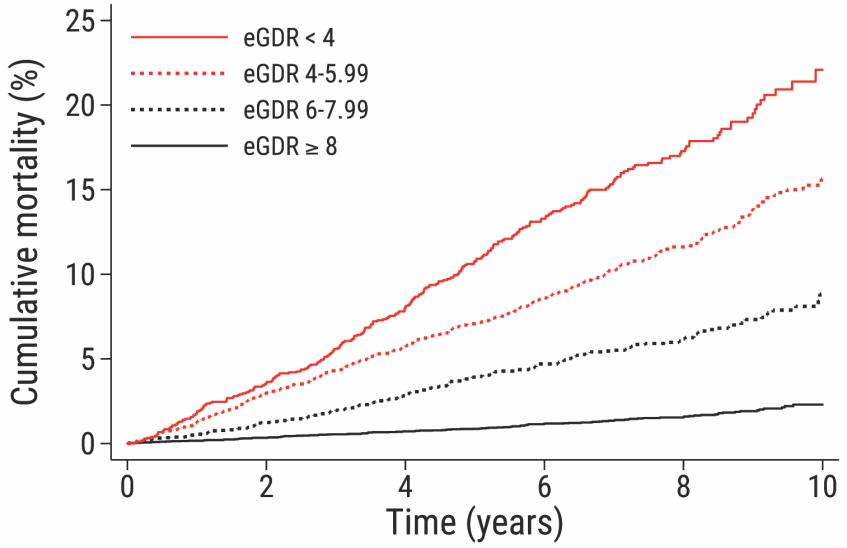
DOI: 10.1111/dom.13110

WILEY

ORIGINAL ARTICLE

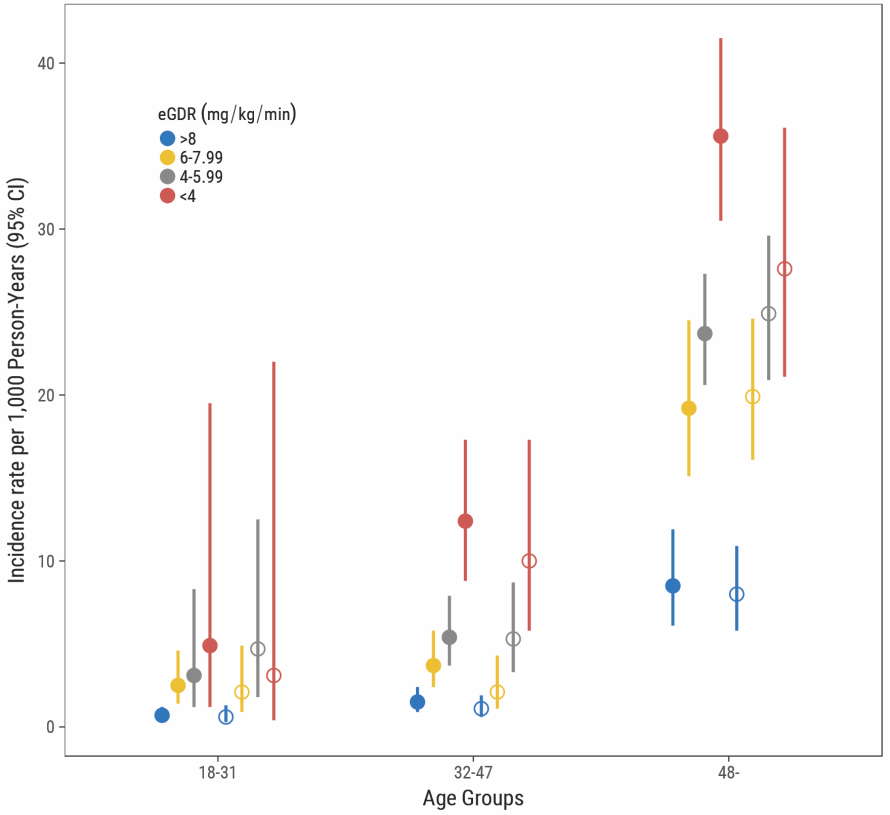
	Total (N=17050)	<4 (N=1786)	4-5.99 (N=3440)	6-7.99 (N=3487)	≥ 8 (N=8337)	% missing
Age, years, mean (SD)	40.4 (15.1)	50.7 (12.2)	50.4 (13.8)	41.1 (15.0)	33.4 (12.5)	
Women	7460 (44%)	569 (32%)	1331 (39%)	1530 (44%)	4030 (48%)	-
HbA1c, %, mean (SD)	8.1 (1.3)	9.0 (1.4)	8.2 (1.2)	8.4 (1.5)	7.7 (1.1)	-
Diabetes duration, years, mean (SD)	24.8 (15.2)	33.7 (13.0)	34.6 (14.1)	25.6 (15.2)	18.5 (12.7)	-
Body mass index, kg/m^2, mean (SD)	25.8 (4.3)	31.0 (4.7)	26.7 (4.1)	26.7 (4.3)	24.0 (3.0)	3%
Waist circumference, cm, mean (SD)	90.2 (13.0)	109.5 (11.0)	94.6 (10.3)	93.0 (12.4)	83.1 (8.4)	-
LDL, mmol/L, mean (SD)	2.6 (0.8)	2.8 (0.9)	2.6 (0.8)	2.8 (0.8)	2.6 (0.7)	21%
HDL, mmol/L, mean (SD)	1.6 (0.5)	1.4 (0.4)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	20%
Triglycerides, mmol/L, mean (SD)	1.1 (0.8)	1.7 (1.3)	1.2 (0.8)	1.2 (0.8)	0.9 (0.6)	21%
Total cholesterol, mmol/L, mean (SD)	4.7 (0.9)	4.9 (1.1)	4.8 (1.0)	4.9 (0.9)	4.6 (0.9)	17%
Lipid-lowering medication	5048 (30%)	1220 (70%)	1904 (57%)	1002 (30%)	922 (11%)	-
Blood pressure						
Systolic, mmHg, mean (SD)	127 (16)	137 (17)	135 (16)	128 (15)	121 (13)	3%
Diastolic, mmHg, mean (SD)	74 (9.1)	77 (10)	74 (9.7)	74 (9.0)	72 (8.3)	3%
Hypertension	6005 (35%)	1762 (99%)	3139 (91%)	1072 (31%)	32 (0%)	-
Smoker	2149 (13%)	226 (13%)	468 (14%)	491 (15%)	964 (12%)	-

Överlevnadskurvor, mortalitetsincidens och association till eGDR <4, 4-5.99, 6-7.99 (>8=referens)



Number at risk

eGDR < 4	1786	1723	1385	984	575	92
eGDR 4-5.99	3440	3338	2831	2218	1321	211
eGDR 6-7.99	3487	3444	2883	2189	1330	225
eGDR ≥ 8	8337	8309	6988	5416	3415	589

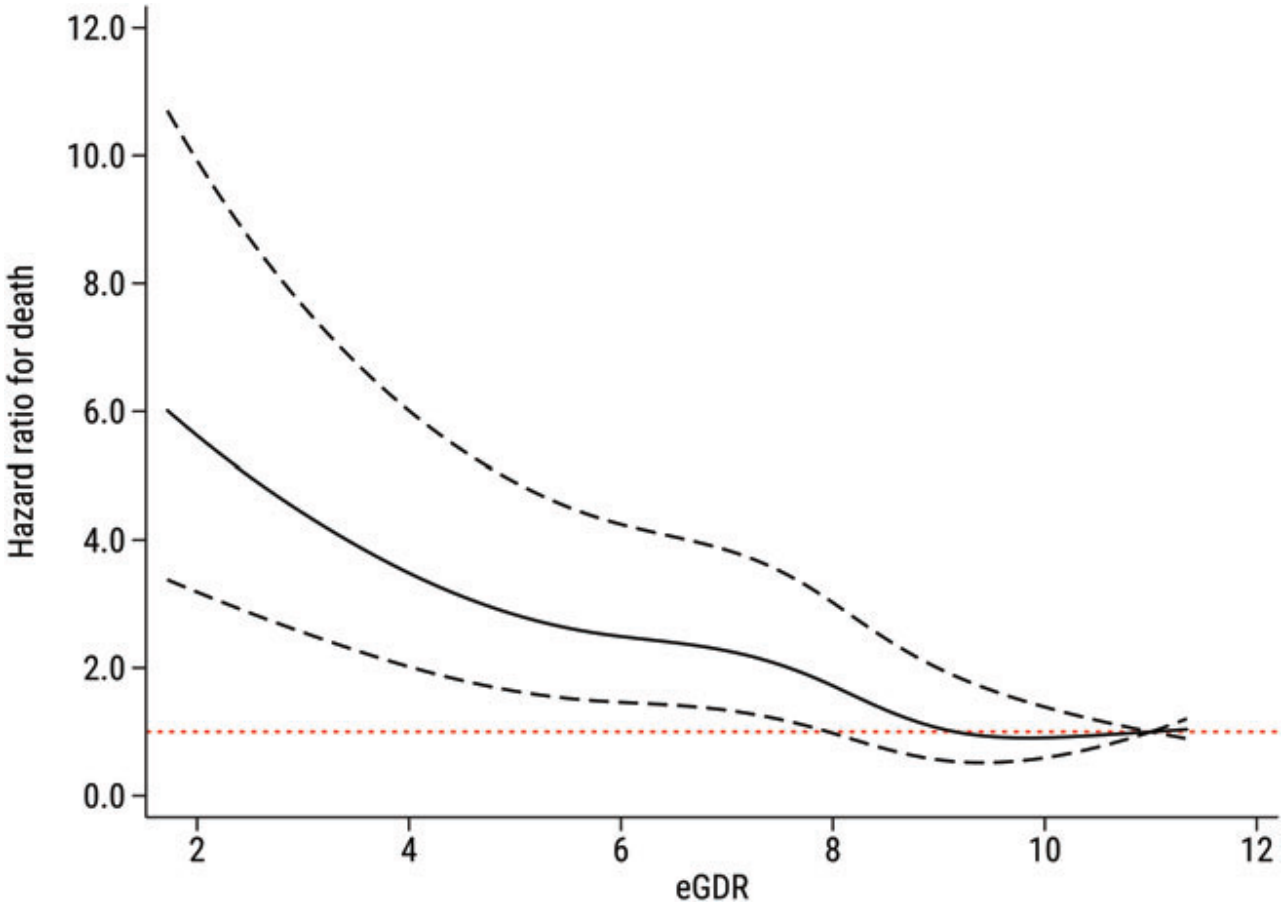


Med lägre eGDR ökar risken till förtida död och kardiovaskulära händelser

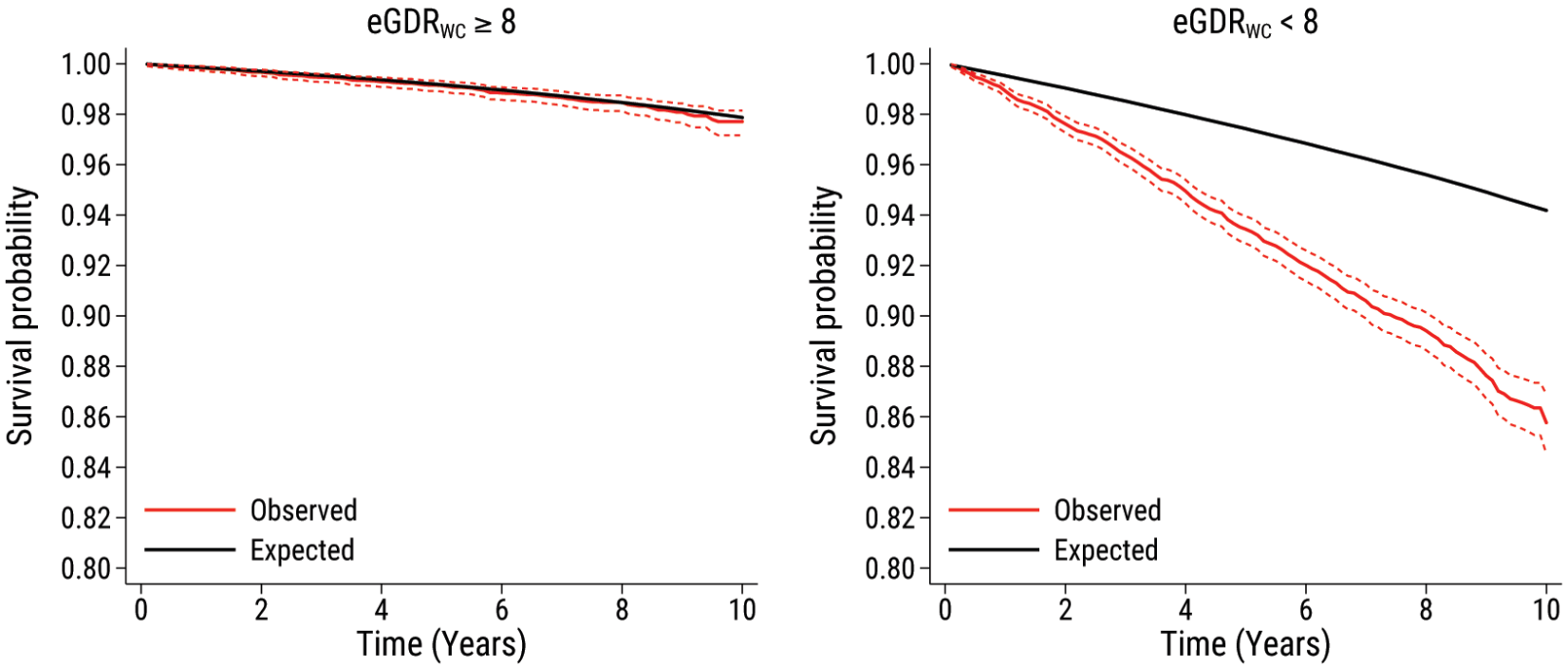
Outcome	eGDR level (mg/kg/min)	Model 1	Model 2	Model 3	Model 4
All-cause mortality	≥8.0 (ref)	1.00	1.00	1.00	1.00
	6-7.99	3.99 (3.18-5.01)	2.27 (1.80-2.87)	2.02 (1.59-2.55)	1.73 (1.34-2.21)
	4-5.99	7.64 (6.22-9.39)	2.71 (2.17-3.37)	2.29 (1.83-2.86)	1.92 (1.49-2.46)
	<4	11.4 (9.18-14.1)	4.39 (3.49-5.53)	3.34 (2.63-4.23)	2.78 (2.04-3.77)
Cardiovascular mortality	≥8.0 (ref)	1.00	1.00	1.00	1.00
	6-7.99	7.54 (4.66-12.2)	3.56 (2.19-5.78)	2.90 (1.78-4.74)	2.17 (1.30-3.64)
	4-5.99	14.6 (9.28-22.9)	3.95 (2.49-6.27)	3.11 (1.95-4.96)	2.19 (1.31-3.66)
	<4	25.0 (15.8-39.6)	7.43 (4.65-11.9)	4.97 (3.07-8.05)	3.07 (1.70-5.54)
Cardiovascular event* or death	≥8.0 (ref)	1.00	1.00	1.00	1.00
	6-7.99	3.78 (3.19-4.48)	2.16 (1.81-2.56)	2.00 (1.68-2.38)	1.52 (1.27-1.83)
	4-5.99	8.96 (7.71-10.4)	3.23 (2.75-3.78)	2.92 (2.49-3.42)	1.86 (1.55-2.22)
	<4	13.0 (11.1-15.2)	4.94 (4.18-5.83)	4.18 (3.53-4.96)	2.22 (1.79-2.75)

*A combination of acute myocardial infarction, stroke, or ischemic heart disease.
Ref = reference category
Model 1 was unadjusted, Model 2 was adjusted for age and sex, Model 3 was adjusted for age, sex, and renal function, and Model 4 was adjusted for all variables reported in Table 1, except for hypertension, HbA1c, and waist circumference because they were components of eGDR.

Hazard risk kvot (heldragen linje) 95% CI (streckad linje) för association mellan eGDR som kontinuerlig variabel (referens eGDR=11) och mortalitet



Överlevnadskurvor efter stratifiering (eGDR ≥8 och <8) hos individer med typ 1 diabetes jämfört med matchad bakgrundsbefolkning



Sammanfattning

- Insulinresistens: Samverkan mellan nedsatt insulinkänslighet och betacellsfunktion
- Insulinresistens är en oberoende riskfaktor till kardiovaskulär sjukdom
- Grad av insulinresistens har betydelse för valet av antidiabetisk behandling vid typ 2 diabetes
- Ny klassifikation av diabetes, där bl.a. graden av insulinresistens ingår, kan förutse risken för diabeteskomplikationer
- Insulinresistens förekommer även hos individer med typ 1 diabetes och associerar till ökad kardiovaskulär risk och död

Tack

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