EndoDiabetes Mötet
Linköping 26-28 mars 2025

ESCAPERS - varför undgår vissa T1D patienter komplikationer trots lång diabetesduration?

Peter M Nilsson, seniorprofessor/expert

Inst. Kliniska vetenskaper Malmö

Lunds universitet

Inga jäv att deklarera för denna presentation

Den kliniska utmaningen – gåtan med långtids-T1D utan tecken till allvarliga komplikationer – varför?

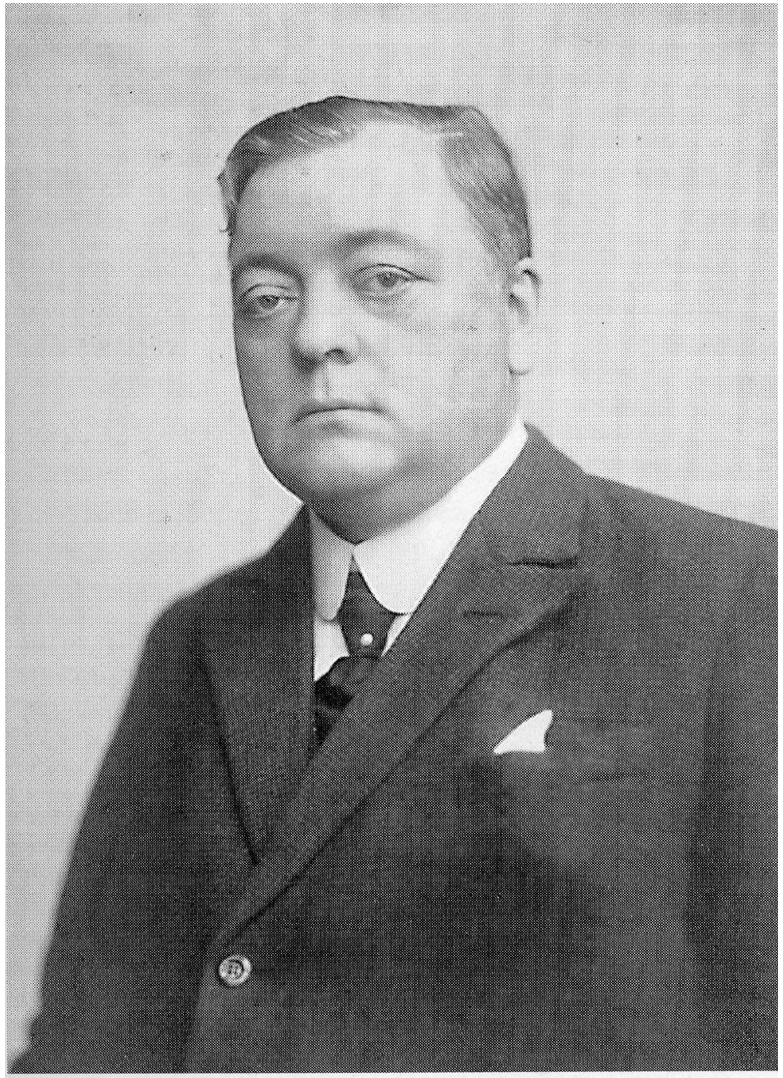
- Epidemiologi – tidstrender?
- Mekanismer?
- Finns sanna skyddsfaktorer, eller inte?
- Behandlingsrelaterat?
- Personlighet – psykologi – coping strategier?
- Sociala nätverk, stöd, pedagogik?

Den kliniska utmaningen – gåtan med långtids T1D utan tecken till allvarliga komplikationer – varför?

- Epidemiologi – tidstrender?
- Mekanismer?
- Finns sanna skyddsfaktorer, eller inte?
- Behandlingsrelaterat?
- Personlighet – psykologi - coping?
- Sociala nätverk, stöd, pedagogik?

- Slumpen?

Svensk diabetologi i ett historiskt perspektiv



Karl Petrén

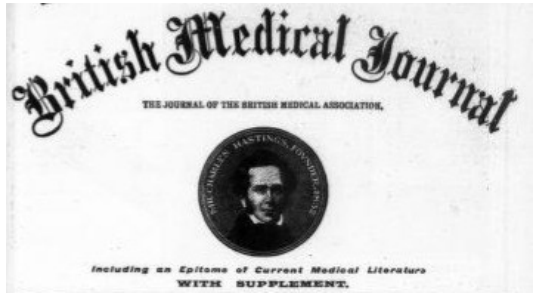
- **Karl Petrén** (1868-1927) var professor i internmedicin i Lund, samt sin samtids störste svenske auktoritet inom diabetesvården
- Han genomförde noggranna försök med en fettrik, kolhydrat-fattig kost på diabetespatienter
- Resultaten publicerades i en monografi 1923; *”Översikt över behandlingen av diabetes”*
- Samma år introducerades **insulin** i kliniken då Petrén startade insulinbehandling av diabeteskoma vid lasarett i Lund (*BMJ* 1927)

Karl Petrén
Lund

STATISTICAL EVIDENCE OF THE VALUE OF INSULIN.*

BY

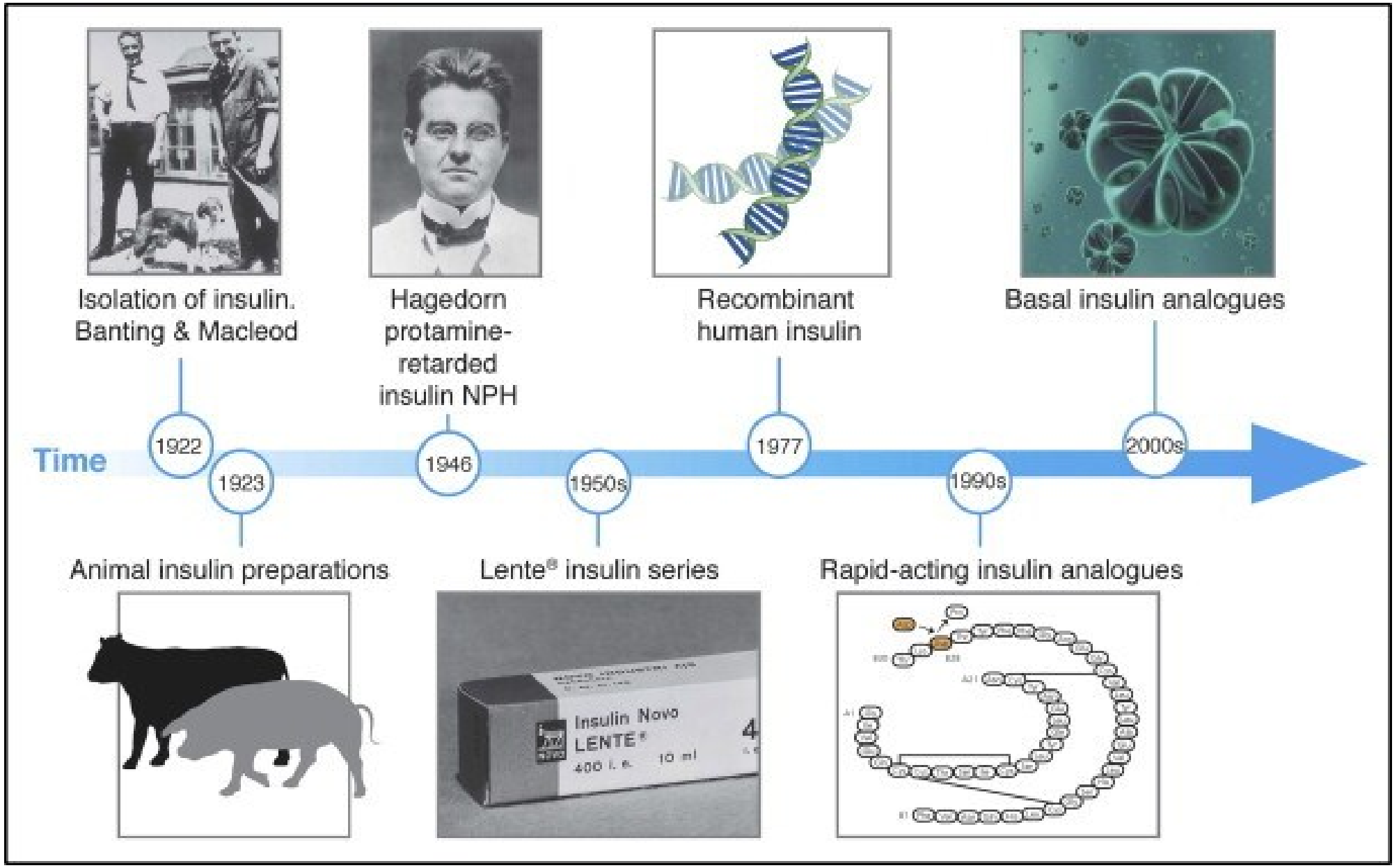
THE LATE PROFESSOR K. A. PETRÉN,
University of Lund, Sweden.



Seventy-three Attacks of Coma in 57 Cases (May, 1923 to July, 1927).

Year.	No. of Cases.	Living.	Fatal Issue.		
			In Coma.		Other Diseases.
			In Hospital.	At Home.	
1923	10	6	—	—	4 (3 tuberculosis)
1924	15	9	1	4	1
1925	10	10	—	—	—
1926	17	14	1	—	2 (sepsis)
1927	5	3	2 (?1)	—	—
Total ...	57	42	4 (?3)	4	7

Petrén K. *Brit Medical J* 1927 Dec 3;2(3491):1019-20.



Hirsch IB, *et al*. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. *Endocr Rev.* 2020; 41:733–55.

Fallbeskrivning av en typ 1 diabetes ”escaper”

- 87-årig kvinna av svensk (norrländsk) etnicitet, diabetesheredität okänd
- Insjuknade 1941 (vid 3 års ålder) i insulinkrävande diabetes
- Aldrig använt tobak/alkohol
- Personlighet: Noggrann och bestämd, men ej pedantisk, alltid varit mycket noga med att sköta insulinbehandling och glukoskontroll
- Klinik: Alltid mycket god glykemisk kontroll, HbA_{1c} 33-49 mmol/mol senaste 15 åren. Ingen mikroalbuminuri och normal njurfunktion (eGFR 74 ml/min 2024). BMI 22.3 kg/m^2
- Autoantikroppar x 3 (GAD65, IA2, ZnT8) negativa. C-peptid fastande och måltidsstimulerad < 0.10 nmol/L
- På äldre dagar fått behandling mot dyslipidemi och hypertoni (båda välreglerade)
- Komplikationer: Endast mild-måttlig diabetesretinopati **trots 84 års diabetesduration**
- Insulinbehandling: Humulin NPH x 2, Humalog inför måltid

Prof/öl Åke Sjöholm, 2025

Internationella studier

50 years ago!

Juvenile Diabetes Mellitus After Forty Years

Aldo T. Paz-Guevara, M.D., Tah-Hsiung Hsu, M.D., and Priscilla White, M.D., Baltimore and Boston

Forty-year survivors with juvenile diabetes

A. Nephropathy

	Patients	%
No renal involvement	43	58.9
Normotensive: Proteinuria	15	20.5
Hypertensive: + BUN	6	8.2
Hypertension without proteinuria	9	12.3
Totals	73	99.9

B. Cardiac Complications

	Sex			
	M	F	Totals	%
Myocardial infarction	2	10	12	16.4
Angina pectoris	1	2	3	4.1
No involvement	29	29	58	79.4
Totals	32	41	73	99.9

"This group of patients demonstrates that juvenile diabetics can *survive forty or longer years without crippling complications*. **We don't know precisely the reasons for their long survival**. Multiple factors are probably involved, but a meticulous day-by-day care of their illness might have been an important one."

Diabetes **1975** Jun;24(6):559-65.

In 1970, the **Joslin Diabetes Clinic** team began awarding a 50-Year Bronze Medal. Then Joslin presented the first 75-Year Medal in 1996 and the first 80-Year Lifetime Achievement Award in 2013

High Concentration of Medium-Sized HDL Particles and Enrichment in HDL Paraoxonase 1 Associate With Protection From Vascular Complications in People With Long-standing Type 1 Diabetes

Diabetes Care 2020;43:178–186 | https://doi.org/10.2337/dc19-0772

George L King
Joslin Diabetes Clinic

Residual β cell function and monogenic variants in long-duration type 1 diabetes patients

Marc Gregory Yu,[1,2] Hillary A. Keenan,[1,2] Hetal S. Shah,[1,2] Scott G. Frodsham,[3] David Pober,[1] Zhiheng He,[1,2] Emily A. Wolfson,[1] Stephanie D'Eon,[1] Liane J. Tinsley,[4] Susan Bonner-Weir,[1,2] Marcus G. Pezzolesi,[1,2,3] and George Liang King[1,2]

J Clin Invest. 2019 Jul 2;129(8):3252-3263.

N= approx. 1000 TID Joslin Medalists with more than 50 year´s diabetes duration

Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort)

Diabetes, UK

- **400 T1D subjects** (54% male)
- Mean age was 68.9 years and mean age-at-onset of diabetes 13.7 years. Features of long duration diabetes in this cohort include **normal body mass** (mean BMI 25.0 kg m−2 **), low insulin dose** (mean 0.52 units kg−2) and **greatly elevated HDL-cholesterol** (mean 1.84 mmol/l)
- Mean HbA1c was 7.6% (normal range 3.8–5.0%) and no patient had a normal HbA1c at the time of sampling
- In all, 29% were taking anti-hypertensive medication. Screening for micro- and macroalbuminuria was positive in 35.7%

Bain SC, *et al.* Diabet Med. 2003;20(10):808-11

Diabetologia (2009) 52:559–567
DOI 10.1007/s00125-009-1275-1

EDITORIAL

How to survive diabetes

E. A. M. Gale

How to survive type 1 diabetes

- Choose long-lived parents
- Stay lean
- Have a normal blood pressure
- Keep your HbA_{1c} about 7%
- Have low insulin requirements
- Have a high HDL-cholesterol level
- Exercise regularly
- Be a survivor

Presence and Determinants of Cardiovascular Disease and Mortality in Individuals With Type 1 Diabetes of Long Duration: The FinnDiane 50 Years of Diabetes Study

- From 5,396 individuals included in the Finnish Diabetic Nephropathy Study (FinnDiane), **729** diagnosed in 1967 or earlier **survived with T1D for >50 years**

- In individuals with diabetes duration of >50 years, the 60-year cumulative incidence of CVD from the diagnosis of diabetes was **64.3%**

- **15.0% had no advanced diabetic complications at all**

Harjutsalo V, *et al*. The FinnDiane 50 Years of Diabetes Study. Diabetes Care. 2021; 44(8):1885-1893

Cohort profile: the ‘Biomarkers of heterogeneity in type 1 diabetes’ study - a national prospective cohort study of clinical and metabolic phenotyping of individuals with long-standing type 1 diabetes in the Netherlands

- A cross-sectional cohort included participants with **≥35 years of T1D duration** (currently n=**160**; median age 64 years; median diabetes duration 45 years; 45% female.
- Mean HbA1c was 58 mmol/mol (7.4%); 51% on insulin pump; 83% on CGM), recruited from five centers and measurements. Samples and 5-year retrospective data were collected
- **Research groups are invited to consider the use of these data and the sample collection.** Future work will include additional hormones, beta-cell-directed autoimmunity, specific immune markers, microRNAs, metabolomics and gene expression data, combined with glucometrics, anthropometric and clinical data, and additional markers of residual beta-cell function

Aanstoot HJ, *et al*. BMJ Open. 2024;14(6):e082453.

Svenska studier

Retinopathy and Nephropathy in Diabetes Mellitus

Comparison of the Effects of Two Forms of Treatment

Sven Johnsson, M.D., Malmö

TABLE 7

Incidence of retinopathy in the two series (only living patients)

	Series I		Series II	
Duration of diabetes in years	21-35	(26.5)	10-21	(15.9)
Number of patients	33		97	
Normal ocular fundi	14	(42%)	49	(51%)
Retinopathy degree I	13	(40%)	16	(16%)
II	5	(15%)	14	(14%)
III	—	(3%)	9	(19%)
IV	1		9	

Series 1: Pts. <40 years with a DM diagnosis in 1922 to 1935
Series 2: Pts. <40 years with a DM diagnosis in 1936 to 1945

Johnsson S. *Diabetes* 1960 Jan-Feb;9:1-8.

Diabetes of Excessively Long Duration with Only Minor Manifestations of Long-Term Diabetic Complications

Folke Lithner

ABSTRACT. A male patient with ketosis-prone diabetes of 55 years' duration is described. To our knowledge, this is the longest duration of diabetes reported. His daughter also has a ketosis-prone diabetes. The low degree of long-term diabetic complications in both father and daughter is remarkable.

"The low degree of long-term diabetic complications in both father and daughter is remarkable and so is the fact that the father's **diabetes was not well regulated**".

Lithner F. *Acta Med Scand*. 1978;203(1-2):143-4.

Insulin-Requiring Diabetes Mellitus of Sixty Years' Duration without Significant Late Manifestations

Carl Brechter and Jörgen Malmquist

From the Departments of Medicine, Trelleborg Hospital, Trelleborg, and University of Lund, Malmö General Hospital, Malmö, Sweden

ABSTRACT. The report concerns a man with onset of diabetes in 1921 and treated with insulin since 1922. In 1981, at the age of 75, he is in excellent health, with no signs of significant diabetic organ injuries. Among other factors, this benign course may be due to retention, until now, of some endogenous insulin production.

Brechter C, Malmquist J. *Acta Med Scand* 1981;210(3):239-40.

In **1972** the patient travelled in USA and visited **Joslin Clinic in Boston**. He was examined and found to qualify for the **Joslin 50-year medal**, which he was awarded in the following year together with nine other Swedish diabetics.

In **1979** the plasma C-peptide concentration was measured after a breakfast meal, employing radioimmunoassay reagents from the Novo Research Institute, Copenhagen, Denmark.

The sample contained a low concentration of **C-peptide, 0.08 nmol/L** (detection limit 0.06 nmol/L). The immunoreactivity may be due to the presence of small amounts of either C-peptide or proinsulin. **In either case, it would seem that a low level of B-cell secretory activity has been retained.**

Brechter C, Malmquist J. *Acta Med Scand* 1981;210(3):239-40.

The Southern Sweden Diabetes in Conscripts Study (SSDCS)

PI: Sven E Nilsson, Kristianstad-Jönköping

Image: Armémuseum

18-year old Swedish military recruits (men):

- Born 1934 to 1943
- Military conscript testing in 1959-1961
- Followed in national registers until 2018 for morbidity and mortality outcomes

Type 1 diabetes group

N = 154 identified in hospital and/or military registers

N = 34 lost to follow-up

N=120 ♂

Control group(s)

A: Family history of diabetes n=237
B: Randomly selected n=238

N = 6 excluded (type 1 diabetes)

N=469 ♂

Dybjer E, *et al*. Type 1 diabetes, cognitive ability and incidence of cardiovascular disease and death over 60 years of follow-up time in men.
Diabet Med. 2022; 39(8):e14806.

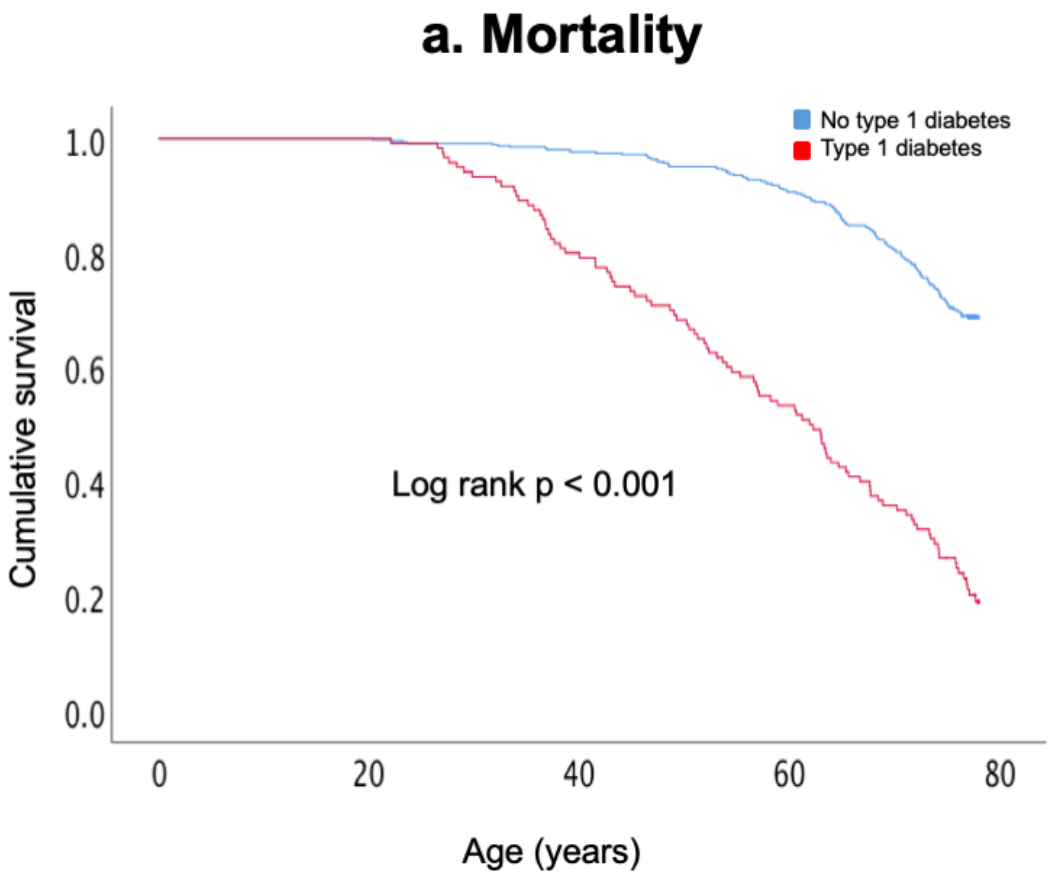
Methods

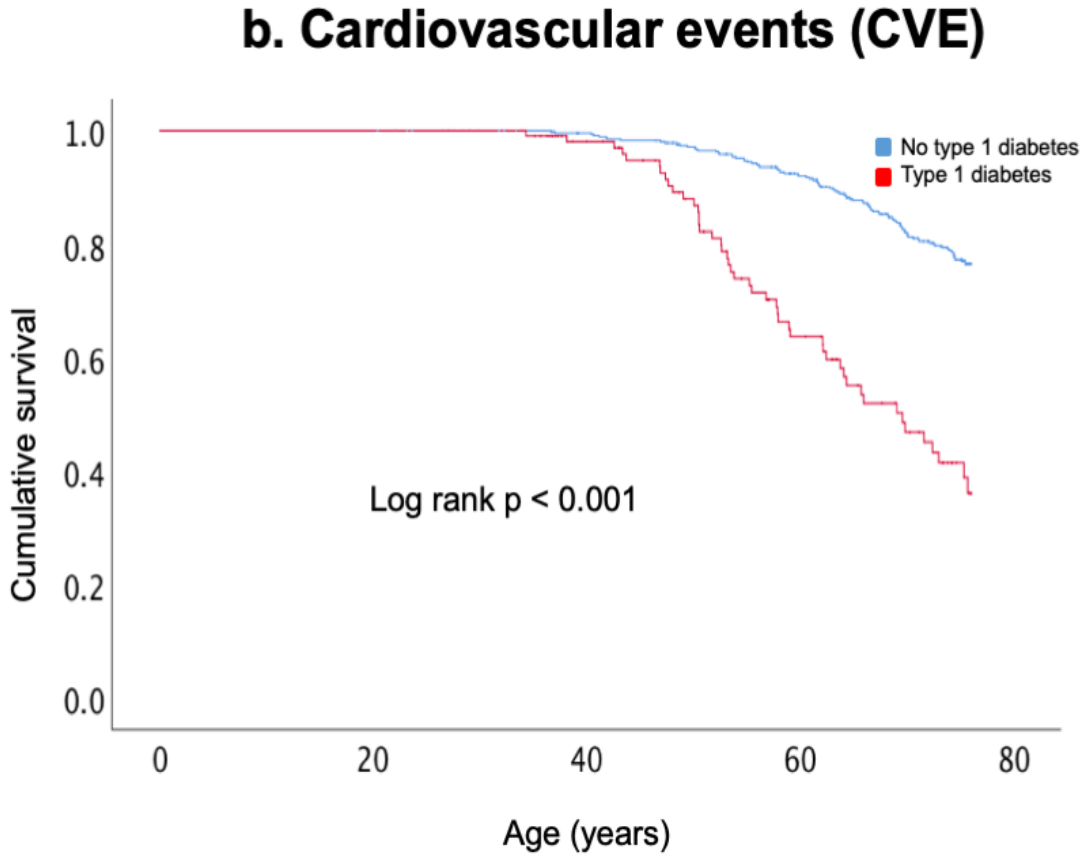
- SSDCS: Prospective cohort study with 65 years of follow-up time
- 120 men with type 1 diabetes and 469 controls
- Cognitive ability (g-factor) at age 18
- Mortality, cardiovascular events and diabetes complications (national registry data)

Elin Dybjer. MD, PhD
ST-allmänläkare, Göteborg
Avhandling: Diabetes och hjärnan
Lunds universitet 2022

Image: Armémuseum

Mortality and cardiovascular events in groups of men with and without type 1 diabetes until 2018

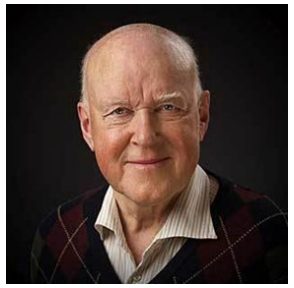




Cox regression analyses:

Type 1 diabetes: **4.6** times higher HR of all-cause mortality, **5.6** times higher HR of cardiovascular mortality and **4.0** times higher HR of cardiovascular events, p<0.001

Diabet Med. 2022; 39(8):e14806.



Sven E Nilsson
1927-2009

Långtidsöverlevnaden vid diabetes har successivt förbättrats

Lång sjukdomsduration kan ge information om protektiva möjligheter

- Att studera patienter som haft diabetes under lång tid utan förekomst av allvarliga komplikationer kan lära oss något om **protektiva faktorer** som har betydelse för sjukdomen och dess behandling.

- I en longitudinell studie (**JÖNDI) från Jönköping** beskrivs långtidsöverlevnaden för diabetiker från olika tidsperioder efter införande av insulinbehandling.

- Sedan den förste patienten med 50 års diabetesduration (DD) registrerades 1973 har denna kategori successivt ökat. Av de patienter som insjuknade under 1940-talet har cirka en tredjedel överlevt i 50 år. Antal patienter >50 års DD var **28**, och **50** >45 års DD

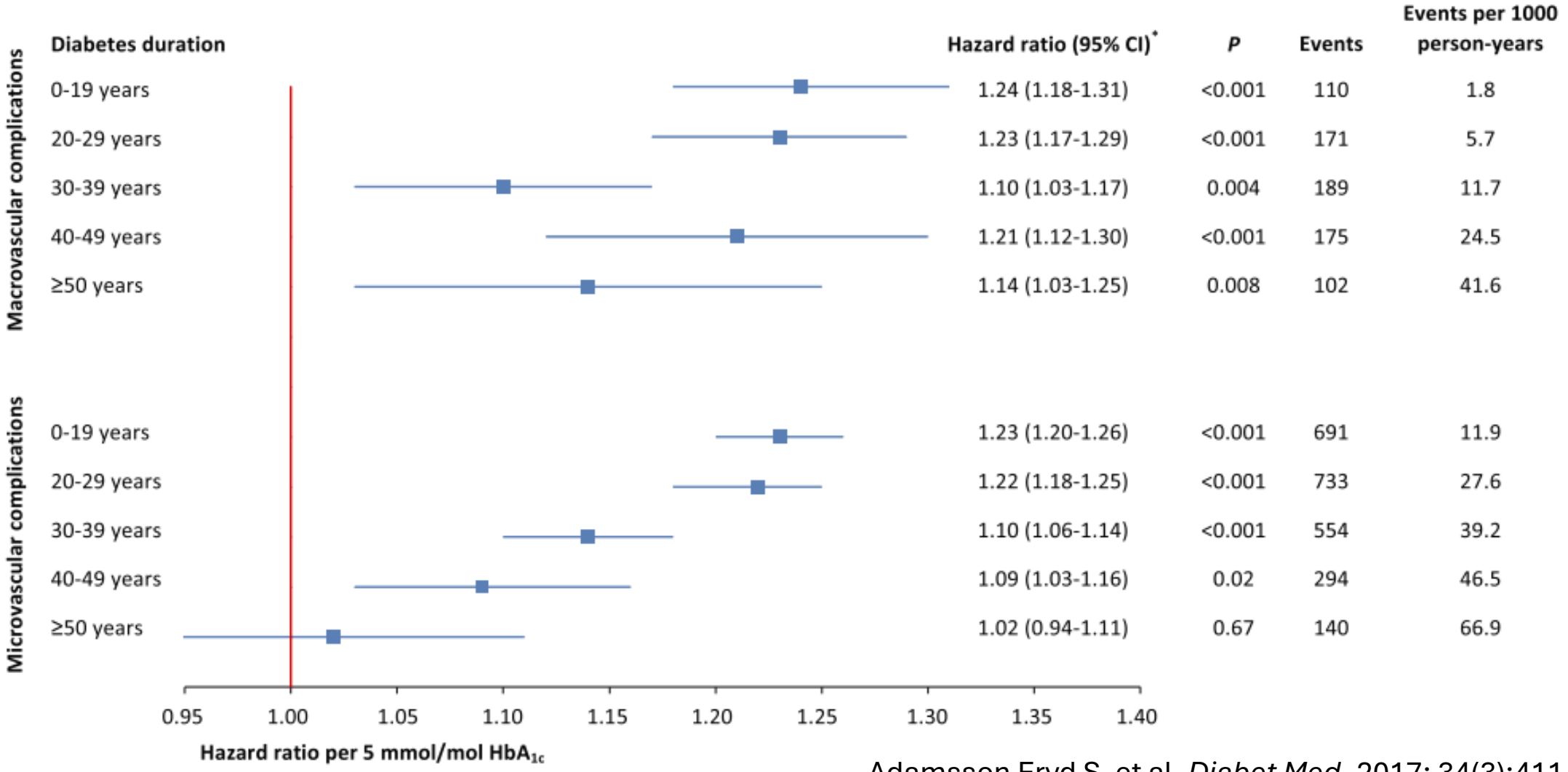
- Endast **16 procent** **(män 12 procent, kvinnor 20 procent)** av diabetikerna **har efter 50 år inga mera uttalade förändringar i ögon, perifera nerver eller njurar**. Av dessa hade **ingen heller haft hjärtinfarkt, angina pectoris eller stroke.**

Nilsson SE, Nilsson ED, Nilsson MS, Nilsson PM. *Läkartidningen* 2005; 102:2066-70

NDR NATIONELLA DIABETESREGISTRET

Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up

For T1D > 50 years (n= 1023) in all **31%** (n= 319) did not have any signs of major complications

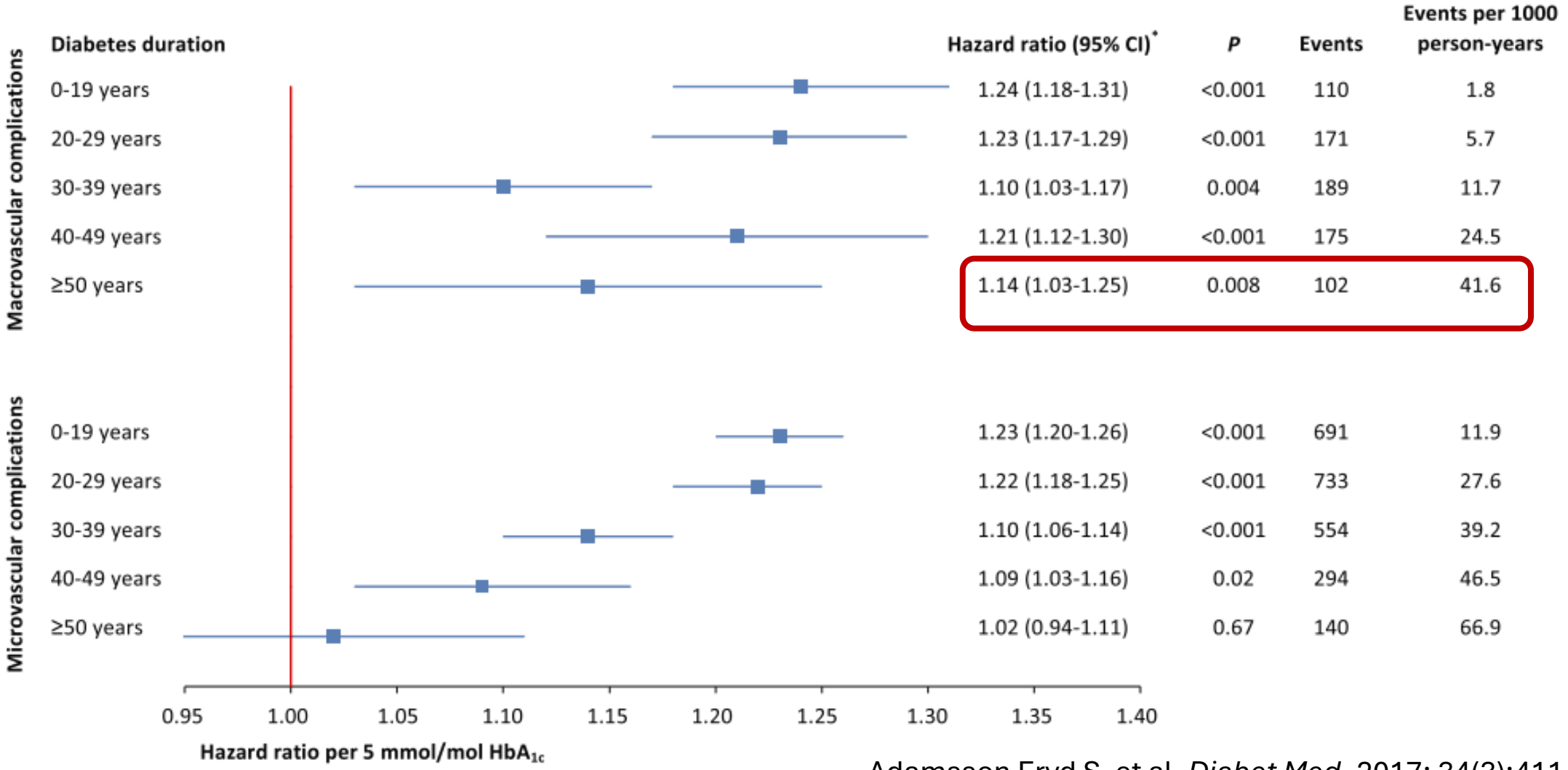


Adamsson Eryd S, et al. *Diabet Med*. 2017; 34(3):411-418.

NDR NATIONELLA DIABETESREGISTRET

Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up

For T1D > 50 years (n= 1023) in all **31%** (n= 319) did not have any signs of major complications



Adamsson Eryd S, et al. *Diabet Med*. 2017; 34(3):411-418.

Liver nucleotide biosynthesis is linked to protection from vascular complications in individuals with long-term type 1 diabetes

Jain R, *et al*. Sci Rep. 2020;10(1):11561.

Valeriya Lyssenko
Bergen University,
LUDC, Malmö

PROLONG
N= 385

DIALONG
N= 71

Phenotype	NP	RP	*p* value$_a$	*p* value$_b$
Age [years]	61.1 (7.1)	61.5 (6.7)		
Age at diagnosis [years]	12.3 (6.0)	10.4 (6.2)	0.17*	
T1D duration [years]	48.8 (3.5)	51.1 (5.2)	0.02	0.07
Sex (male)	16 (39%)	13 (43%)	0.90*	
Smoking, current	2 (5%)	1 (3%)	1.00*	
Hypertension	26 (63%)	16 (53%)	0.54*	
Waist [cm]	85.6 (10.4)	95.0 (13.2)	<0.001	3.9e−03
Systolic BP [mmHg]	144.8 (19.5)	144.5 (17.2)	0.93	0.79
Diastolic BP [mmHg]	75.7 (8.6)	73.0 (6.6)	0.12	0.31
BMI [kg/m^3]	24.6 (3.1)	27.4 (3.8)	1.7e−03	0.01

NP: **Non-progressor**, no diabetes complication over 30 years duration of type 1 diabetes
RP: **Rapid-progressors**, diabetes complications before 25 years duration of type 1 diabetes

Liver nucleotide biosynthesis is linked to protection from vascular complications in individuals with long-term type 1 diabetes

Jain R, *et al*. Sci Rep. 2020;10(1):11561.

Valeriya Lyssenko
Bergen University,
LUDC, Malmö

PROLONG
N= 385

DIALONG
N= 71

Phenotype	NP	RP	*p* value$_a$	*p* value$_b$
Age [years]	61.1 (7.1)	61.5 (6.7)		
Age at diagnosis [years]	12.3 (6.0)	10.4 (6.2)	0.17*	
T1D duration [years]	48.8 (3.5)	51.1 (5.2)	0.02	0.07
Sex (male)	16 (39%)	13 (43%)	0.90*	
Smoking, current	2 (5%)	1 (3%)	1.00*	
Hypertension	26 (63%)	16 (53%)	0.54*	
Waist [cm]	85.6 (10.4)	95.0 (13.2)	<0.001	3.9e−03
Systolic BP [mmHg]	144.8 (19.5)	144.5 (17.2)	0.93	0.79
Diastolic BP [mmHg]	75.7 (8.6)	73.0 (6.6)	0.12	0.31
BMI [kg/m^3]	24.6 (3.1)	27.4 (3.8)	1.7e−03	0.01

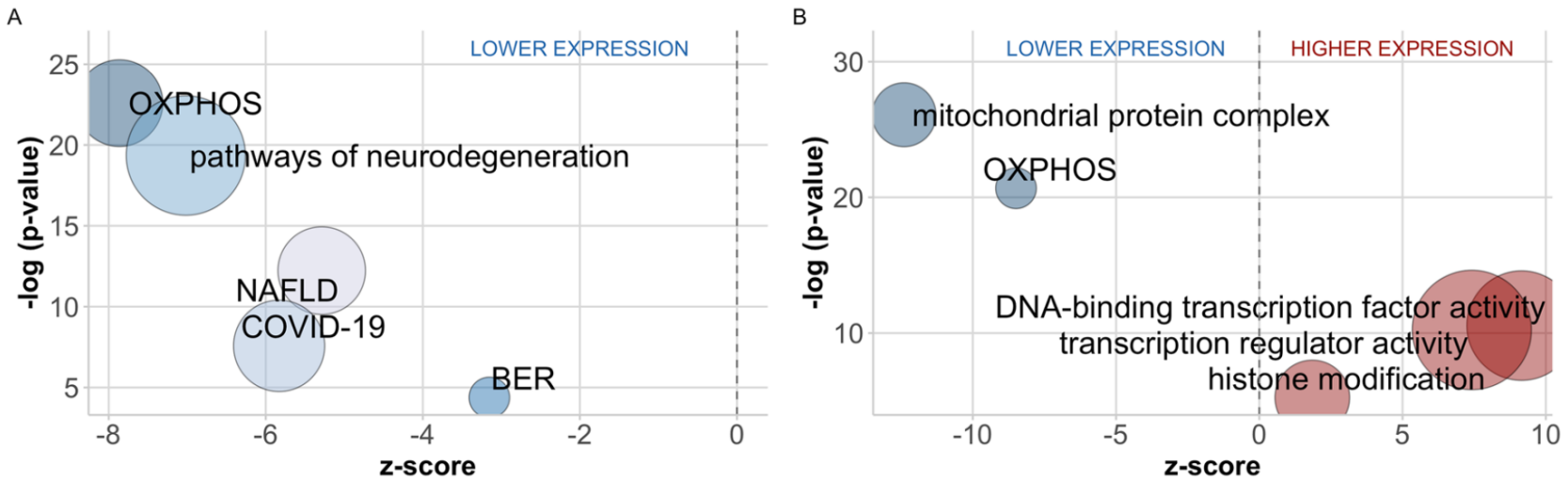
NP: **Non-progressor**, no diabetes complication over 30 years duration of type 1 diabetes
RP: **Rapid-progressors**, diabetes complications before 25 years duration of type 1 diabetes

			Mean (SD)			
Metabolite	NP	RP	NP	RP	p value$_a$	p value$_b$
APOC3 [mg/dl]	318	59	11.6 (3.9)	12.6 (5.9)	2.5e−03	0.02
Pyruvate [µM]	312	64	95.2 (28.9)	102.5 (27.9)	0.01	0.06
IGF1 [µg/L]	333	78	123.2 (42.3)	150.6 (48.4)	ns	0.1
IGFBP1 [µg/L]	330	75	93.3 (44.5)	72.9 (40.8)	3.6e−03	ns
Glucagon [pg/ml]	312	64	15.3 (12.8)	15.0 (9.6)	ns	ns
Alanine [µM]	313	64	322.0 (58.1)	325.0 (68.0)	ns	ns
Lactate [µM]	311	64	916.1 (380.0)	909.3 (393.3)	ns	ns

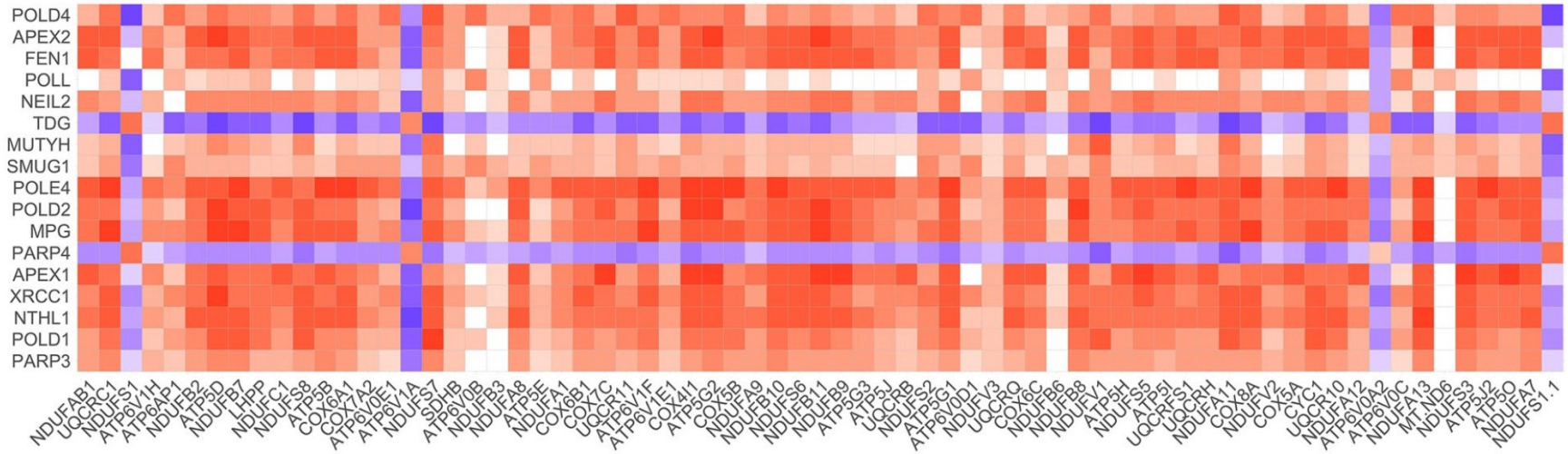
Table 3. Directly measured metabolites in the PROLONG cohort. Data were winsorized before analyses, and statistical tests performed on log2-transformed data. *NP* non-progressors, *RP* rapid progressors. *ns* non-significant ($p > 0.05$). Linear regression models: P_a (adjusted for center/storage, sex, age), P_b (adjusted for center/storage, sex, age, HbA_{1c}).

Jain R, et al. Sci Rep. 2020;10(1):11561.

Blood gene expression in PROLONG escapers (non-progressors: NP) and Neanderthals: same genes…



Synchronized expression of OXPHOS and DNA damage genes in NP



Ozgumus et.al. Sci Reports, 2021

SCIENCE ADVANCES | RESEARCH ARTICLE

CELL BIOLOGY

Longer metaphase and fewer chromosome segregation errors in modern human than Neanderthal brain development

Felipe Mora-Bermúdez[1,2]*, Philipp Kanis[2]†, Dominik Macak[2]†, Jula Peters[1]†, Ronald Naumann[1], Lei Xing[1], Mihail Sarov[1], Sylke Winkler[1], Christina Eugster Oegema[1], Christiane Haffner[1], Pauline Wimberger[3], Stephan Riesenberg[2], Tomislav Maricic[2], Wieland B. Huttner[1]*‡, Svante Pääbo[2,4]*‡

Since the ancestors of modern humans separated from those of Neanderthals, around 100 amino acid substitutions spread to essentially all modern humans. The biological significance of these changes is largely unknown. Here, we examine all six such amino acid substitutions in three proteins known to have key roles in kinetochore function and chromosome segregation and to be highly expressed in the stem cells of the developing neocortex. When we introduce these modern human-specific substitutions in mice, three substitutions in two of these proteins, KIF18a and KNL1, cause metaphase prolongation and fewer chromosome segregation errors in apical progenitors of the developing neocortex. Conversely, the ancestral substitutions cause shorter metaphase length and more chromosome segregation errors in human brain organoids, similar to what we find in chimpanzee organoids. These results imply that the fidelity of chromosome segregation during neocortex development improved in modern humans after their divergence from Neanderthals.

Lyssenko V (unpublished) 2024

ESCAPER studien

- Typ 1 DM-patienter med lång duration (>30 år) men utan betydande komplikationer (MACE, DN) inbjuds för fenotypning och omik analys

- Jämförs med (a) ålders- och könsmatchade T1DM med komplikationer (PROLONG), och (b) ålders- och könsmatchade individer utan diabetes från lokala befolkningsstudier

- **116 T1D patienter** har undersökts (november 2024) i Malmö; MRT av hjärta och aorta i en undergrupp, biobanksprover för OLINK proteomik

- Anders Gottsäter (PI), Peter M Nilsson (co-PI)

Hjärt-Lungfonden

Linköping Diabetes Complications Study


J. Ludvigsson

- Rekrytering av **269 T1D patienter** för långtidsuppföljning (PI: Johnny Ludvigsson, LiU), diagnosticerade före 15 års ålder mellan 1961-1985

- Fokus på utveckling av komplikationer, gynnsamma trender över tid
  - Nordwall M, *et al*. Diabetologia. 2004 Jul;47(7):1266-1272.

- Aktuell registerlänkning (2024) med Patientregistret och NDR

- Sammanlagt har cirka **33 patienter (15.8%)** av **209 överlevande** klarat sig utan allvarliga diabeteskomplikationer trots i medeltal 40 års diabetesduration

Maria Nordwall, Hans Arnqvist, Ola Ekström, Peter M Nilsson, Johnny Ludvigsson, 2025

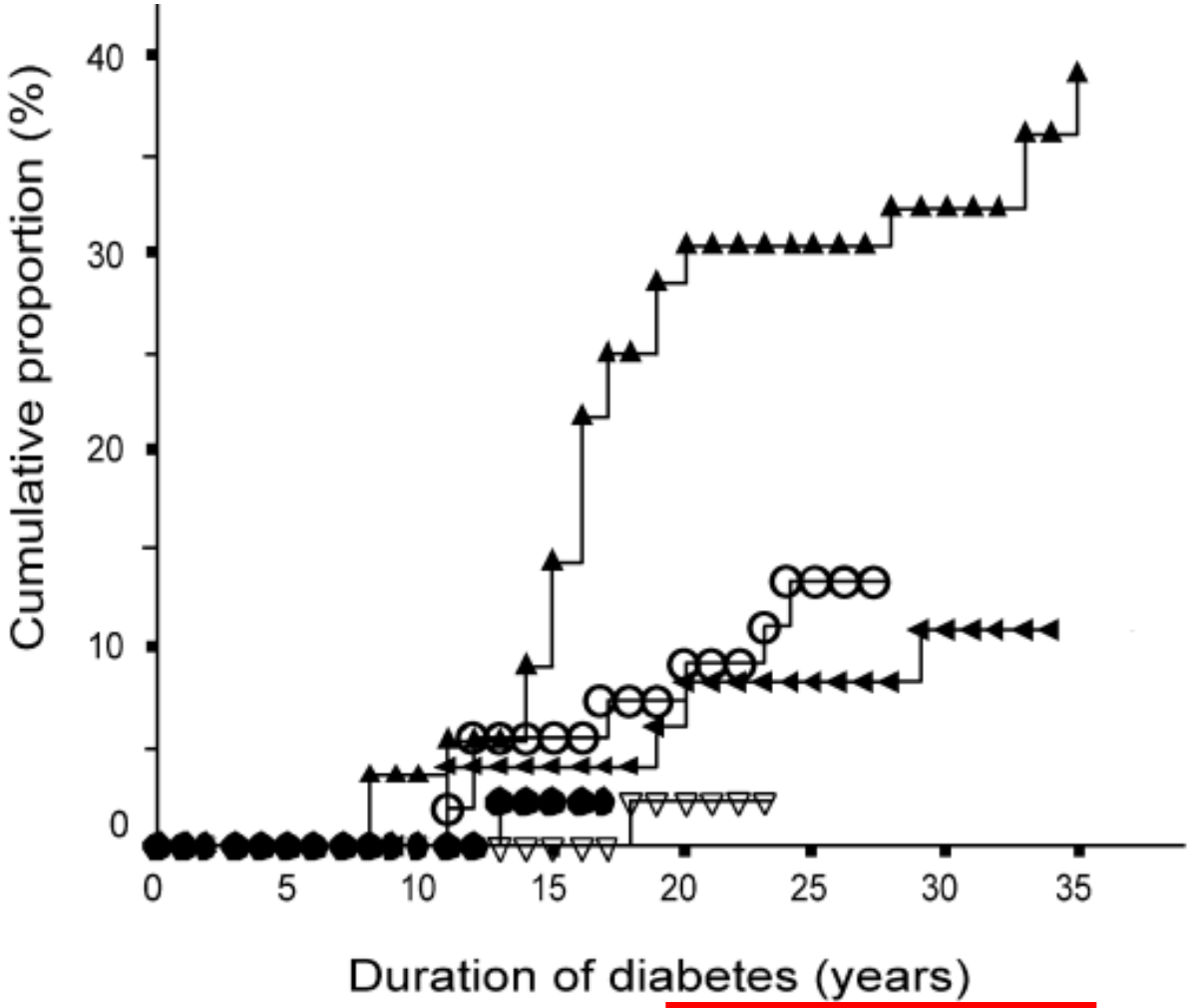
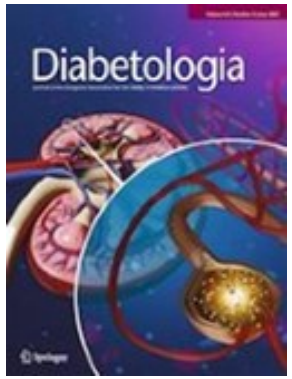


Fig. 3. Cumulative proportion of diabetic nephropathy in a population of patients with Type 1 diabetes diagnosed before the age of 15 years, according to the year of onset of diabetes. Onset of diabetes: 1961–1965 ▲, 1966–1970 ◀ (p=0.005), 1971–1975 ○ (p=0.02), 1976–1980 ▽ (p<0.001), 1981–1985 ● (p=0.02). p<0.001 for overall comparison of all groups. The p values between the oldest cohort (onset 1961–1965) and the following cohorts are indicated in brackets

Nordwall M, Bojestig M, Arnqvist HJ, Ludvigsson J. Declining incidence of severe retinopathy and persisting decrease of **nephropathy** in an unselected population of Type 1 diabetes-the Linköping Diabetes Complications Study. Diabetologia. 2004 Jul;47(7):1266-1272.

Protektiva mekanismer



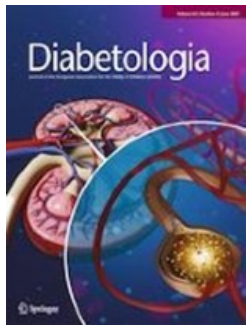
Discoveries from the study of longstanding type 1 diabetes

Bruce A. Perkins [1,2] · Leif Erik Lovblom [1,2] · Sebastien O. Lanctôt [1,2] · Krista Lamb [1] · David Z. I. Cherney [3]

To date, findings imply that the following mechanisms exist:

- Strategies to maintain or recover beta cells and their function
- Activation of specific glycolytic enzymes such as pyruvate kinase M2
- Modification of AGE production and processing
- Novel mechanisms for modification of renin–angiotensin–aldosterone system activation, in particular those that may normalize afferent rather than efferent renal arteriolar resistance
- Activation and modification of processes such as retinol binding and DNA damage checkpoint proteins

Diabetologia (2021) 64:1189–1200

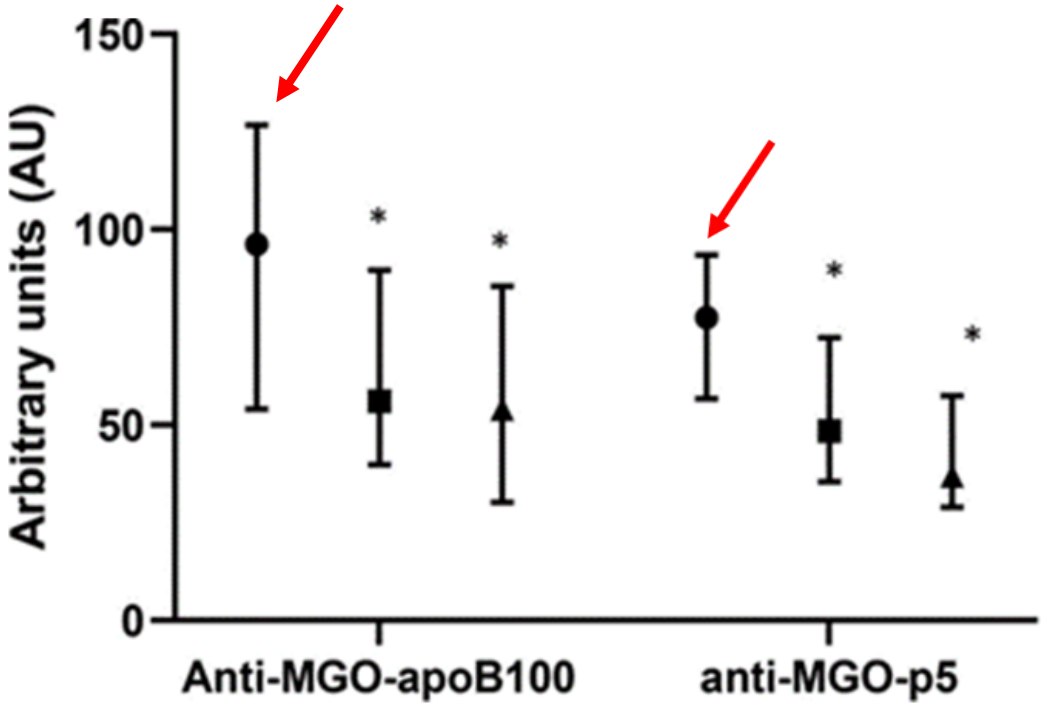


Discoveries from the study of longstanding type 1 diabetes

Among the many clinical and public health insights, research into this special study population has identified *putative mechanisms* that may in future serve as *therapeutic targets*, knowledge that likely could not have been gained without studying long-term survivors.

Diabetologia (2021) 64:1189–1200

Autoantibodies Against Methylglyoxal-Modified Apolipoprotein B100 and ApoB100 Peptide Are Associated With Less Coronary Artery Atherosclerosis and Retinopathy in *Long-Term Type 1 Diabetes*

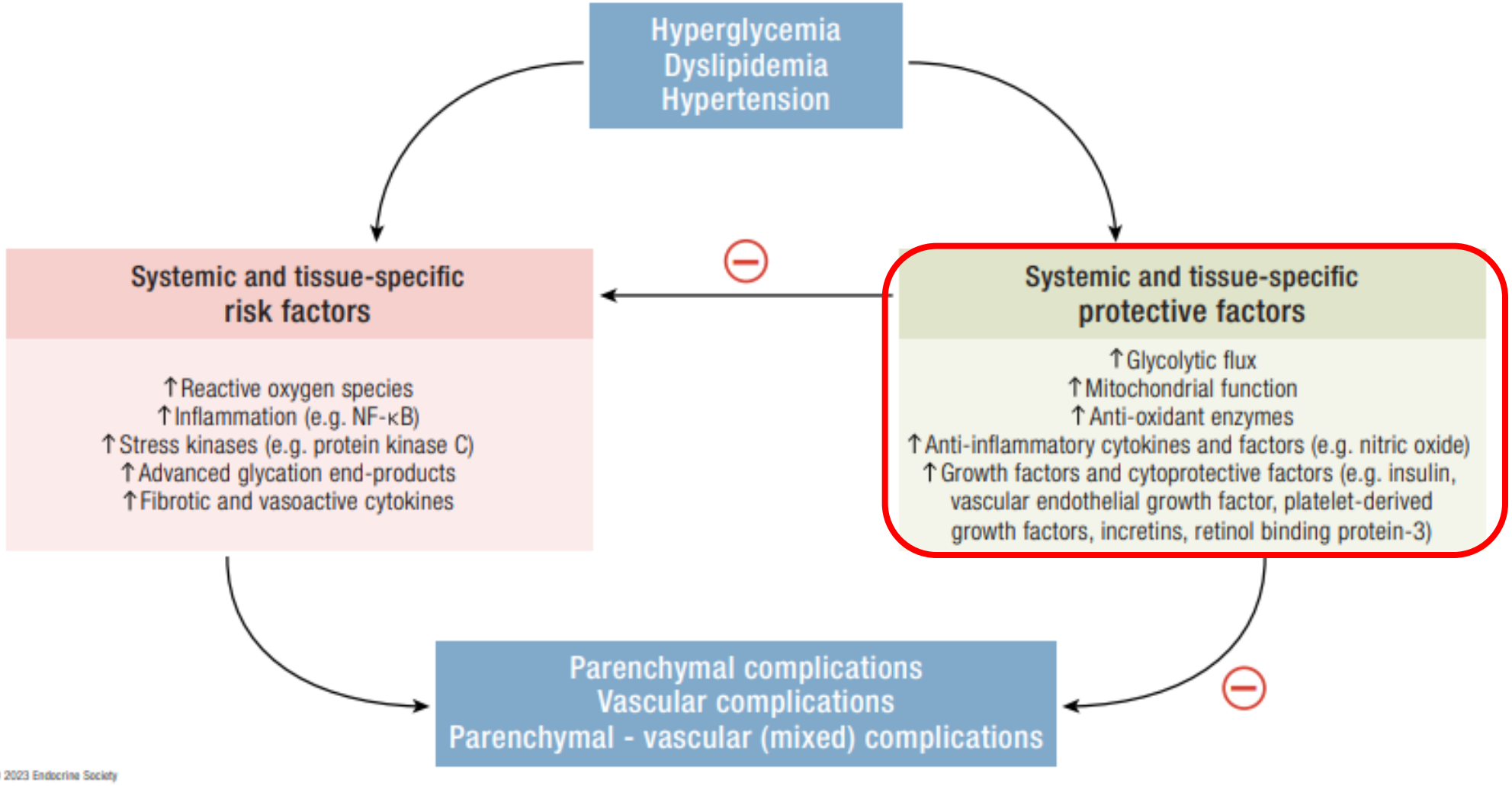


- ● No stenosis (n=14)
- ■ <50% stenosis (n=50)
- ▲ >50% stenosis (n=21)

Eva Bengtsson, docent
Aterosklerosforskning, CRC

Sveen KA, *et al* Diabetes Care. 2021;44:1402-1409.

Protective Factors and the Pathogenesis of Complications in Diabetes



Yu MG, Gordin D, Fu J, Park K, Li Q, King GL. Protective Factors and the Pathogenesis of Complications in Diabetes. Endocr Rev. 2024 Mar 4;45(2):227-252.

ESSENTIAL POINTS

- Chronic complications of diabetes should be reclassified from using the microvascular and macrovascular categories to those of vascular, parenchymal, and hybrid (vascular and parenchymal) origin
- The pathogenesis of diabetes complications often involves an interplay between systemic and tissue-specific risk and protective factors
- Endogenous protective responses may help explain the differential severity of diabetes complications, and even the lack of pathologies in some tissues, organs, and individuals
- An important limitation in the study of protective factors is the definition of the "protected" phenotype, and more extensive analysis are clearly needed in order to identify new protective pathways and elucidate additional mechanisms for those already identified

Endocr Rev. 2024 Mar 4;45(2):227-252

ESSENTIAL POINTS

- Chronic complications of diabetes should be reclassified from using the microvascular and macrovascular categories to those of vascular, parenchymal, and hybrid (vascular and parenchymal) origin
- The pathogenesis of diabetes complications often involves an interplay between systemic and tissue-specific risk and protective factors
- Endogenous protective responses may help explain the differential severity of diabetes complications, and even the lack of pathologies in some tissues, organs, and individuals
- An important limitation in the study of protective factors is the definition of the "protected" phenotype, and more extensive analysis are clearly needed in order to identify new protective pathways and elucidate additional mechanisms for those already identified

Endocr Rev. 2024 Mar 4;45(2):227-252

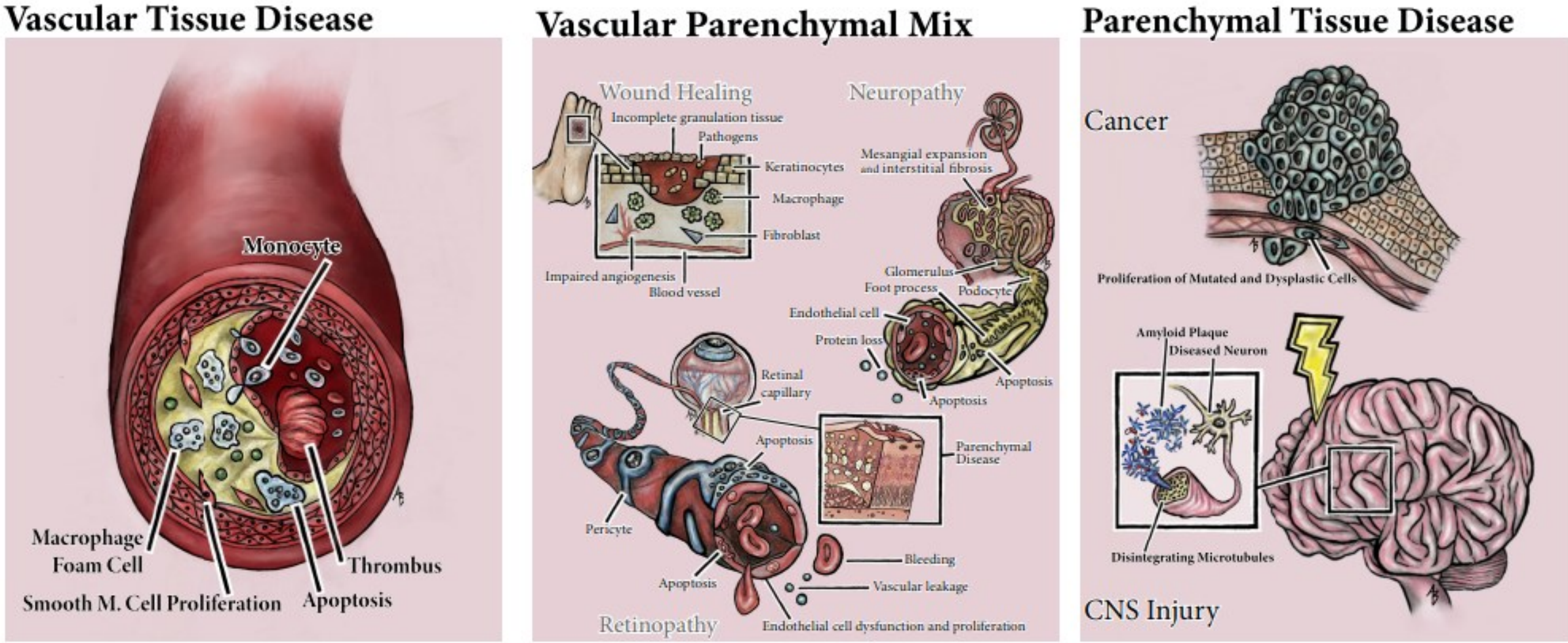


Figure 1. Vascular and tissue pathologies of complications in diabetes. ECM, extracellular matrix; Smooth M. Cell, smooth muscle cell; CNS, central nervous system.

Endocr Rev. 2024 Mar 4;45(2):227-252

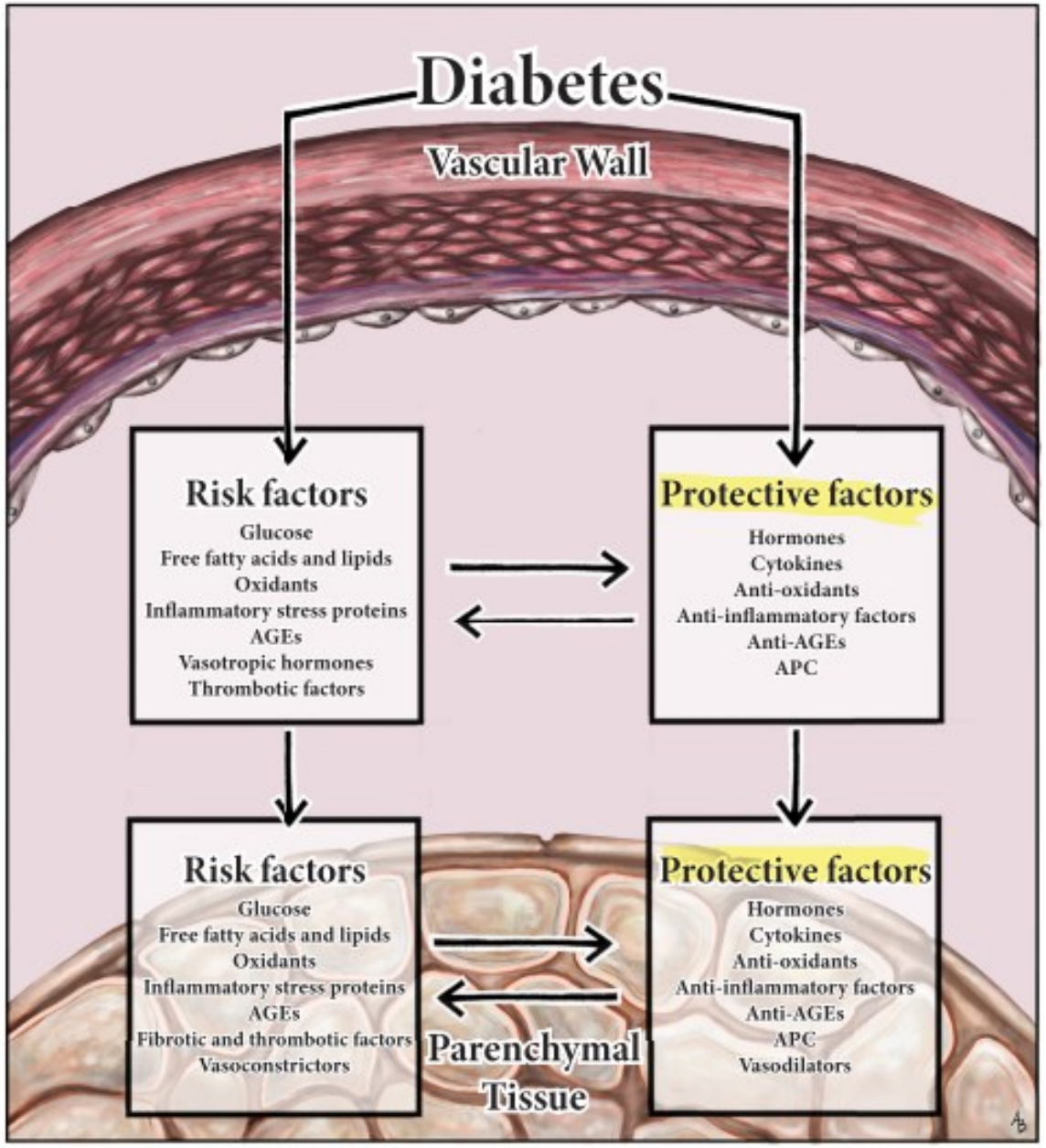


Table 1. Protective factors against chronic complications of diabetes

Systemic protective factors	Reference
Growth factors: Insulin, IGF-1/2, FGF, PDGF, VEGF, TGF-β	(13, 61-67)
High-density lipoprotein	(53)
Vitamins: vitamin C, D, E	(68)
Circulating antioxidant enzymes: catalase, SOD, glutathione peroxidase	(69-72)
Anti-inflammatory mediators: flavonoids, adiponectin	(73-75)
Proresolving mediators: omega-3 polyunsaturated substances, resolvins, maresin-2	(76-79)
Anti-inflammatory cytokines: IL-4, IL-10, IL-13	(80, 81)
Anti-AGEs	(82-84)
APC	(85, 86)
Tissue-Specific Protective Factors	
IGF-1/2	(87, 88)
Retinol-binding protein 3	(89-91)
PDGF	(92-96)
Nitric oxide, 12, 13-diHOME	(97, 98)
VEGF	(97-105)
Glycolytic enzymes: glyoxalase 1, PKM2	(101, 106)
KEAP/NRF2	(68, 107-110)
Antioxidants: SOD, glutathione, vitamins, α-lipoic acid, carotenoids, coenzyme Q_{10}	(72, 111-113)

Endocr Rev. 2024 Mar 4;45(2):227-252

Sammanfattning

- Typ 1-diabetes med lång duration men utan större komplikationer erbjuder en klinisk modell för undersökning av förmodade skyddsmekanismer

- Det finns flera kohorter för att utforska dessa mekanismer, inklusive Joslin-medaljörerna, PROLONG, FinnDiane, ESCAPER, etc. om de också har biobankresurser (dock ej tillgängligt i Golden Year's Cohort, Storbritannien)

- Kvarvarande betacellsfunktion eller bättre lipidsammansättning kan vara en del av förklaringen. Hypotes: Kronisk inflammation är nedreglerad i T1D-escapers på grund av genetisk påverkan av leverfunktionen, eller inverkan av GI mikrobiota

Peter.nilsson@med.lu.se

Thank you!