Diabetes –What has changed and what is the impact on risk?

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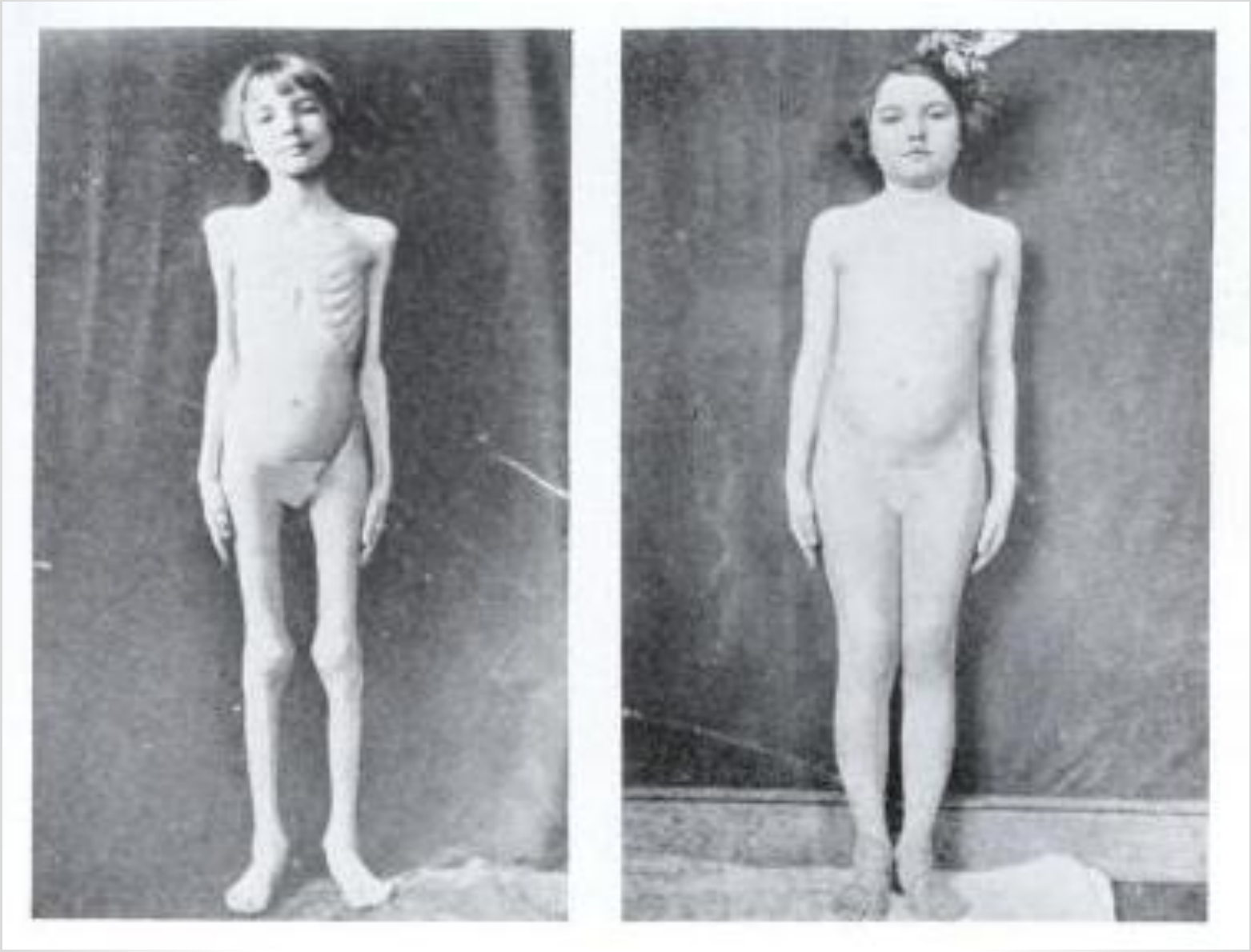
Banting and Best



What is Diabetes?

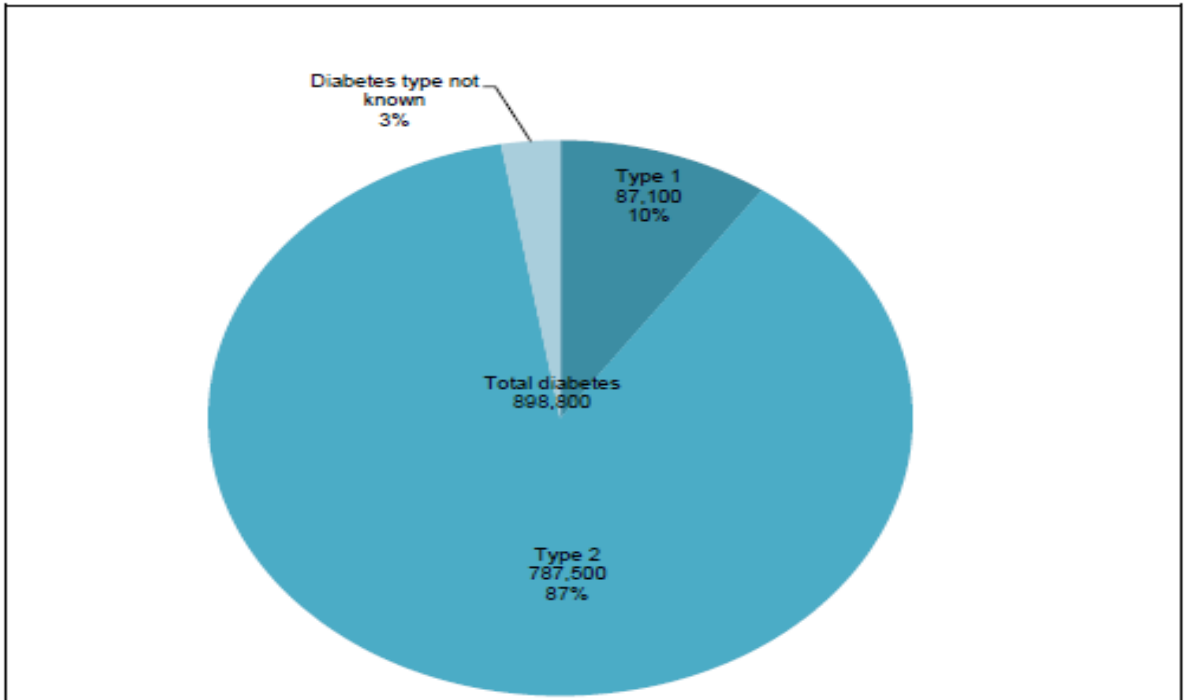
Quick summary of the anatomy and physiology

- Is the inadequate control of carbohydrate metabolism leading to higher than “normal” blood sugars
- Glucose is the basic molecule needed for metabolism of the body’s cells
- The body seeks to maintain a near constant blood sugar level to respond to needs of body for sugar at any 1 point in time
- What “goes in” must “go out” or one seeks to balance the scale to maintain an equilibrium – this is “biostatsis”
- Hormones are used to help control this biostasis
- Insulin and glucagon are the prime ones

Quick summary of the anatomy and physiology

- Food (carbs, fat and protein) ingested → broken down in GIT to many components including glucose
- Glucose absorbed into blood → rising blood sugar →stimulates the islet cells → releases insulin →facilitates entry of glucose into muscle/ liver cells in particular - all cells that require sugar for metabolic function
- Glucose is stored in the muscle/liver as glycogen for future use
- Once level of absorbed blood sugar comes down to a certain level, the amount of released insulin decreases to keep the blood sugar from going too low.

The prevalence of diabetes in Australia

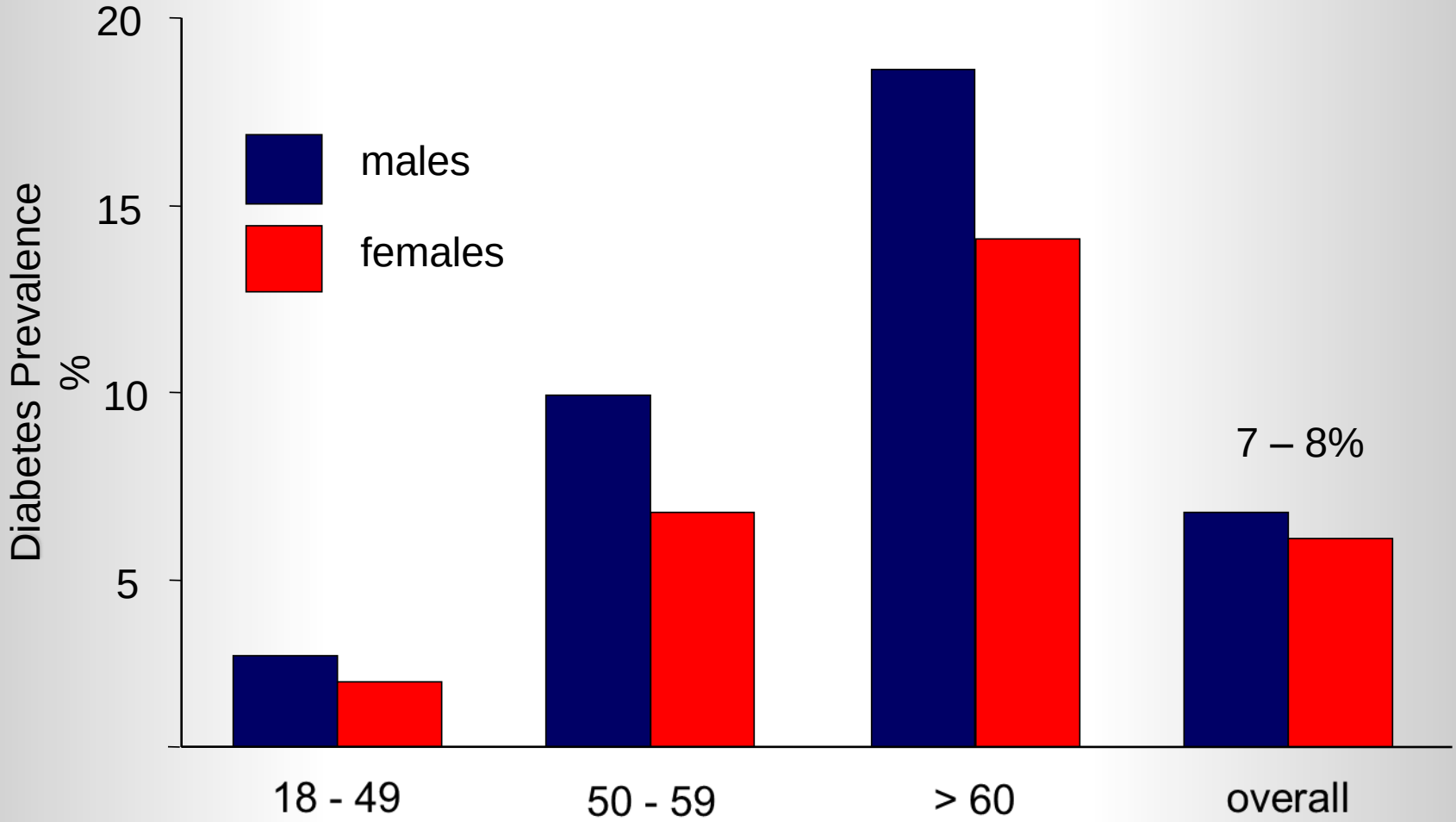


Note: Gestational diabetes is not included in 'Total diabetes'.

Source: AIHW analysis of the ABS 2007–08 NHS Confidentialised Unit Record File.

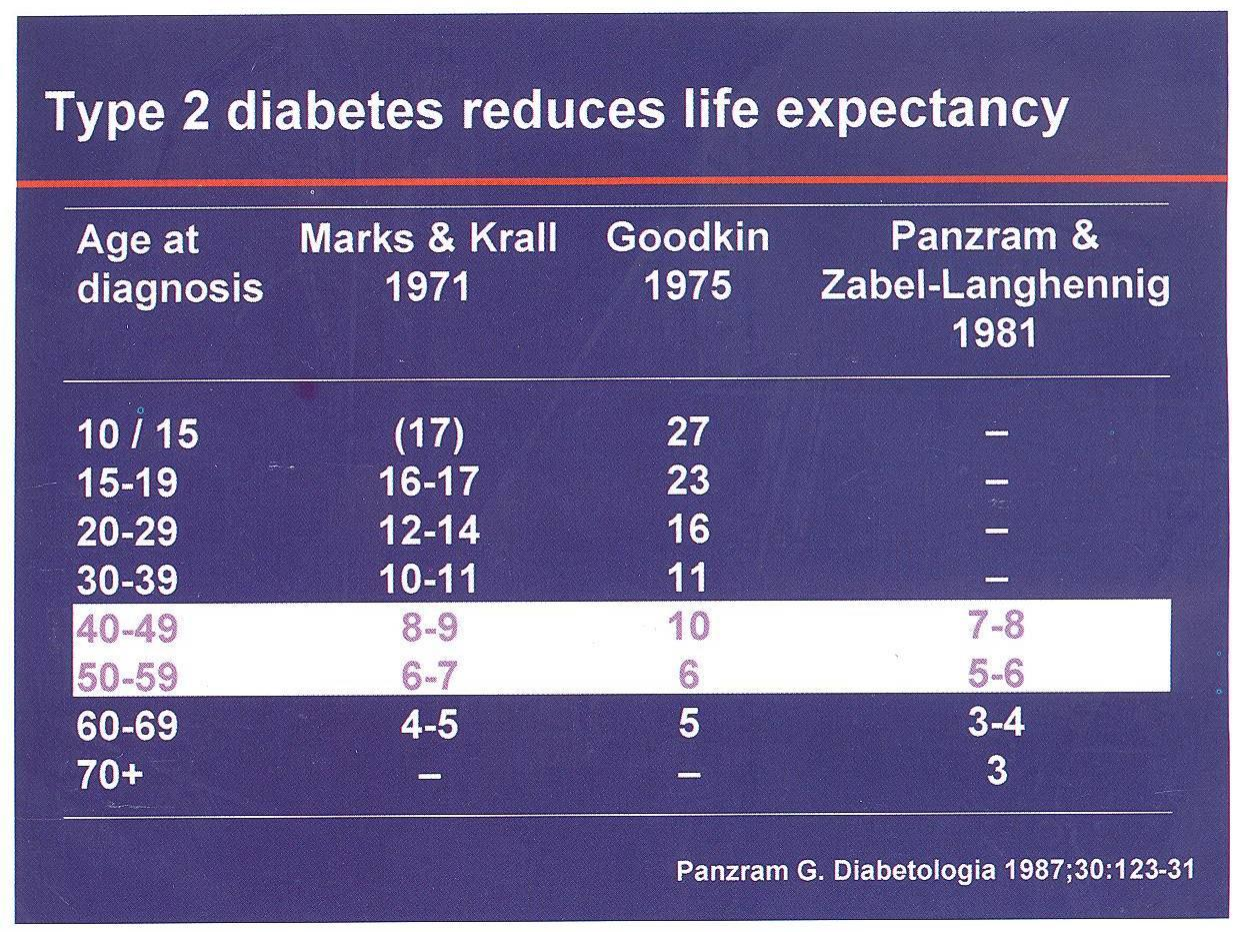
Figure 1: Number of people with diagnosed diabetes by type of diabetes, Australia 2007–08

What is the prevalence of diabetes in Australian and New Zealand adults?



What was life expectancy for diabetics in the past?

Reduction in Life Expectancy (Mean Years) in Diabetic Versus Non-diabetic Subjects



Type 2 diabetes reduces life expectancy

Age at diagnosis	Marks & Krall 1971	Goodkin 1975	Panzram & Zabel-Langhennig 1981
10 / 15	(17)	27	–
15-19	16-17	23	–
20-29	12-14	16	–
30-39	10-11	11	–
40-49	8-9	10	7-8
50-59	6-7	6	5-6
60-69	4-5	5	3-4
70+	–	–	3

Panzram G. Diabetologia 1987;30:123-31

What has changed since the PANZRAM Study?

- before HbA1c available
- before Blood Sugar monitors
- before disposable syringes and needles
- before structured diabetes education

Type 1 diabetes mortality experience

Table 6: Mortality in Canterbury's insulin-treated diabetic population compared with the general population (I January 1984 – 1 January 1993).

Source: Brown *et al. Diabetes Care* 2001;24:56 – 63.

Age-group (years)	Follow-up (person-years)	Observed number of deaths	Death rate (per 1,000 person-years) (95% CI)	Death rate in the Canterbury population (per 1,000 person-years)	Expected number of deaths	SMR (95% CI)
0–29						
Female	674.5	2	3.0 (0.4–10.8)	0.67	0.5	4.43 (0.48–14.44)
Male	800.5	2	2.5 (0.3–9.0)	1.24	1.0	2.01 (0.24–7.22)
Total	1,475.0	4	2.7 (0.7–6.9)	0.98	1.5	2.67 (0.73–6.84)
30–39						
Female	557.4	5	9.0 (2.9–20.9)	0.96	0.5	10.00 (3.24–23.30)
Male	462.0	7	15.2 (6.1–31.2)	1.66	0.8	8.75 (3.51–18.03)
Total	1,019.4	12	11.7 (6.1–20.5)	1.31	1.3	9.23 (4.77–16.15)
40–49						
Female	478.0	4	8.4 (2.3–21.4)	1.76	0.8	5.00 (1.36–12.80)
Male	533.7	8	15.0 (6.5–29.5)	2.73	1.5	5.33 (2.30–10.50)
Total	1,011.7	12	11.9 (6.1–20.8)	2.24	2.3	5.22 (2.70–9.14)
50–59						
Female	487.4	13	26.7 (14.2–45.6)	4.73	2.3	5.65 (3.01–9.66)
Male	644.4	20	31.0 (19.0–47.8)	8.45	5.4	3.70 (2.26–5.70)
Total	1,131.8	33	29.2 (20.1–41.0)	6.59	7.7	4.29 (2.95–6.03)
60–69						
Female	818.1	37	45.2 (31.8–62.4)	12.31	10.1	3.66 (2.58–5.04)
Male	621.2	39	62.8 (44.6–85.7)	22.48	14.0	2.79 (1.98–3.81)
Total	1,439.2	76	52.8 (41.1–67.5)	16.86	24.0	3.17 (2.51–3.99)
70–79						
Female	598.7	45	75.2 (54.8–100.7)	33.96	20.3	2.22 (1.62–2.97)
Male	439.5	53	120.6 (90.4–158.5)	57.83	25.4	2.09 (1.57–2.75)
Total	1,038.2	98	94.4 (71.1–115.5)	43.78	45.8	2.14 (1.75–2.62)
≥80						
Female	165.9	41	247.1 (177.2–335.1)	113.33	18.8	2.18 (1.56–2.96)
Male	90.7	27	297.7 (196.2–434.6)	145.39	13.2	2.05 (1.35–2.99)
Total	256.6	68	265.0 (207.2–338.1)	123.15	32.0	2.13 (1.67–2.72)
Total						
Female	3,780	147	38.9 (33.0–45.9)	8.09	53.2	2.76 (2.34–3.26)
Male	3,592	156	43.4 (37.0–51.0)	8.88	61.4	2.54 (2.16–2.98)
Total	7,372	303	41.1 (36.7–46.1)	8.48	114.6	2.64 (2.36–2.96)

Type 1 diabetes mortality experience

Table 7: Rates of mortality by diabetes classification.
Source: Brown *et al. Diabetes Care* 2001;24:56 – 63.

Age-group (years)	Follow-up (person-years)	Observed number of deaths	Death rate (per 1,000 person-years) (95% CI)	SMR (95% CI)
Group A				
0–29	1,473.4	4	2.7 (0.7–6.9)	2.67 (0.73–6.84)
30–39	911.1	12	13.2 (6.8–23.1)	10.00 (5.17–17.50)
40–49	604.7	8	13.2 (5.7–26.0)	5.71 (2.46–11.25)
50–59	356.9	11	30.8 (15.4–55.1)	4.58 (2.29–8.20)
60–69	141.5	6	42.4 (15.6–92.4)	2.50 (0.68–6.40)
70–79	61.2	3	49.0 (10.1–143.1)	1.03 (0.21–3.10)
≥80	1.9	1	526.3 (13.3–2,931.5)	3.33 (0.08–18.50)
Total	3,550.7	45	12.7 (9.3–17.0)	3.72 (2.71–4.98)
Group B				
0–29	—	—	—	—
30–39	91.8	0	0.0	—
40–49	338.1	2	5.9 (0.7–21.3)	2.86 (0.35–10.32)
50–59	515.1	13	23.8 (12.7–40.7)	3.33 (1.77–5.69)
60–69	801.8	37	46.1 (32.5–63.6)	2.70 (1.9–3.72)
70–79	641.3	54	84.2 (63.4–110.3)	1.91 (1.44–2.50)
≥80	145.5	34	233.7 (162.0–327.0)	1.87 (1.3–2.54)
Total	2,563.9	140	54.6 (46.1–64.6)	2.16 (1.82–2.56)
Group C				
0–29	1.6	0	0.0	—
30–39	16.5	0	0.0	—
40–49	67.2	1	14.9 (0.4–83.0)	5.00 (0.13–27.85)
50–59	229.0	9	39.3 (18.0–74.7)	6.00 (2.75–11.40)
60–69	496.0	33	66.5 (45.8–93.8)	4.13 (2.84–5.81)
70–79	335.7	41	122.1 (89.4–166.1)	2.79 (2.00–3.78)
≥80	101.9	30	294.4 (198.7–421.0)	2.34 (1.58–3.35)
Total	1,247.9	114	91.4 (75.8–110.8)	3.06 (2.53–3.69)

SMR was standardized against Canterbury's general population. †Group A includes subjects who were diagnosed at age <30 years and who commenced insulin therapy within 12 months of diagnosis. Group B comprises cases defined by age at onset of diabetes of ≥30 years and commencement of insulin treatment within 12 months of diagnosis. Group C subjects are those in whom insulin therapy commenced >12 months after diagnosis.

Type 1 diabetes mortality experience

Table 8: All-cause death rates and standardised mortality ratios (SMR) by diabetes groups and gender.

Source: Florkowski *et al. Diab Med* 2003;20:191 – 197.

Group	Sex	Person-years follow-up	Mortality per 1000	Expected mortality per 1000 person years	SMR	95% CI	
A	F	2870.4	10.8	4.0	2.7	1.9	3.9
	M	2964.1	15.5	5.2	3.0	2.2	4.0
B	F	1903.5	50.4	29.6	1.7	1.4	2.0
	M	1839.6	55.4	34.6	1.6	1.3	1.9
C	F	950.2	85.2	32.8	2.6	2.1	3.3
	M	698.5	90.2	47.5	1.9	1.5	2.4

Group A, Diagnosis age < 30 years and commenced insulin within 12 months; group B, diagnosis of diabetes ≥ 30 years and started insulin within 12 months; group C, insulin therapy commenced > 12 months after diagnosis.

Type 1 diabetes mortality experience

Table 9: All cause standardised mortality ratio (SMR, O/E) and standardised mortality difference (SMD ((O/E)/person years)) x1000) by duration and age at onset.
Source: Florkowski *et al. Diab Med* 2003;20:191 – 197.

		Duration (years)							
		0–9		10–19		20+		Total (95% CI)	
Age at onset	Gender	SMR	SMD	SMR	SMD	SMR	SMD	SMR	SMD
0–29	F	5.68	3.95	4.88	5.56	2.82	15.9	3.3 (2.4–4.6)	8.4 (4.3–12.4)
	M	1.48	0.83	3.79	9.65	2.87	29.9	2.8 (2.1–3.7)	9.9 (5.5–14.3)
30–39	F	2.22	3.92	3.15	20.77	2.30	51.3	2.8 (1.9–4.0)	20.8 (9.2–32.5)
	M	2.93	10.36	1.67	9.78	2.16	45.1	2.2 (1.5–3.2)	18.7 (5.6–31.8)
40–49	F	3.05	18.34	2.69	32.97	1.30	17.0	1.9 (1.4–2.6)	24.8 (8.6–40.9)
	M	1.76	11.29	2.51	45.60	1.79	60.2	2.1 (1.6–2.7)	33.5 (16.1–51.0)
50–59	F	1.96	21.60	1.91	37.84	3.29	128.1	2.0 (1.5–2.7)	31.5 (13.8–49.1)
	M	1.20	6.56	1.59	41.58	1.99	124.4	1.5 (1.1–2.0)	25.4 (2.7–48.0)
60–69	F	1.67	31.84	1.63	58.48	—	—	1.7 (1.2–2.3)	40.6 (4.3–76.9)
	M	1.81	57.43	0.89	–14.41	4.10	1316.67	1.4 (1.0–2.1)	37.0 (–12.9–87.0)
70–79	F	1.49	51.94	2.68	309.71	—	—	1.6 (1.0–2.5)	65.6 (–11.2–142.49
	M	2.11	122.51	0.69	–68.12	—	—	1.4 (0.8–2.5)	58.2 (–58.3–174.7)
80+	F	2.02	203.83	—	—	—	—	2.0 (0.8–5.4)	203.8 (–191.7–599.4
	M	0.98	–5.13	—	—	—	—	1.0 (0.2–3.9)	–5.1 (–289.7–279.4
Total (95% CI)	F	1.9 (1.5–2.4)	13.6 (6.8–20.4)	2.2 (1.8–2.8)	21.7 (12.7–30.7)	2.2 (1.7–2.7)	24.0 (13.0–35.0)	2.1 (1.8–2.4)	18.9 (13.9–23.8)
	M	1.6 (1.3–2.1)	8.4 (3.0–13.8)	1.7 (1.4–2.1)	19.6 (9.0–30.2)	2.3 (1.8–2.9)	39.5 (23.7–55.4)	1.9 (1.3–2.1)	17.7 (12.6–22.9)

SMR is the ratio of observed to expected deaths; SMD is 1000 times the difference in observed and expected mortality rates.

Diabetes Mortality in Insured Population

- Total mortality experience of 41,972 insurance policies issued 1989 – 2002 with MIB code for diabetes
- Mortality compared to 2001 Valuation Basic Table
- 495 deaths
- Mortality Ratio (MR) 187%
  - If issued “standard” MR was 132%

Milano AF et al, J Insur Med. 2005;37(2):140-2

Mortality in Diabetics Update

- RM Males
  - 1.38 to 1.27
- RM Females
  - 1.62 to 1.44

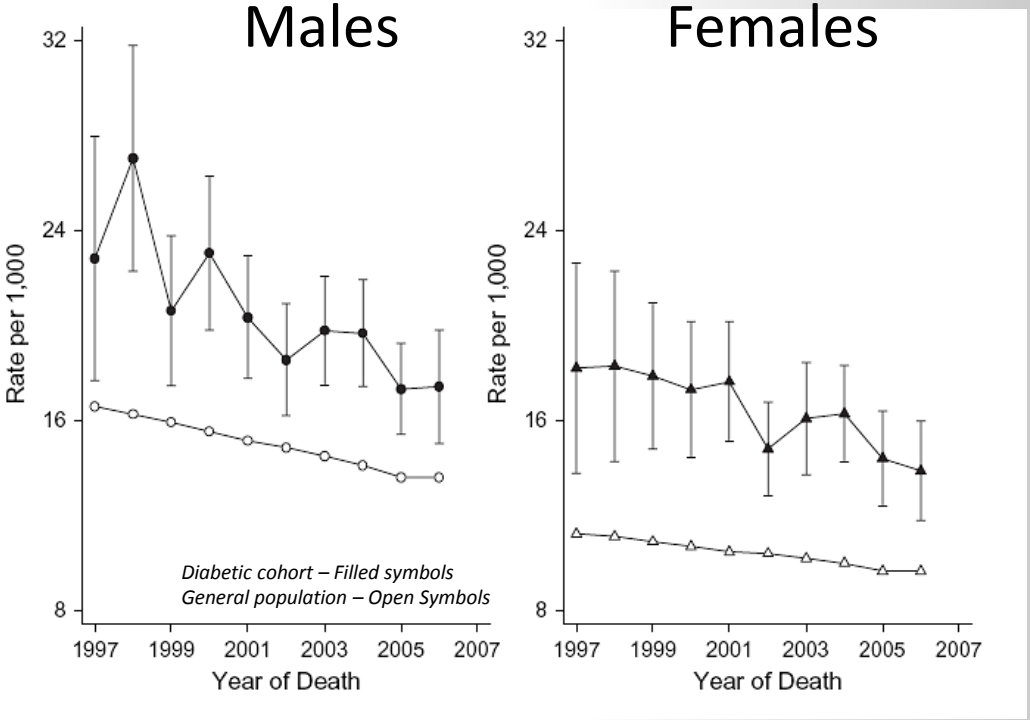


Figure from Gulliford & Charlton *Am J Epidemiol* 2009;169:455–461

What are the major causes of death

Table 11: Cause of death by diabetes group.

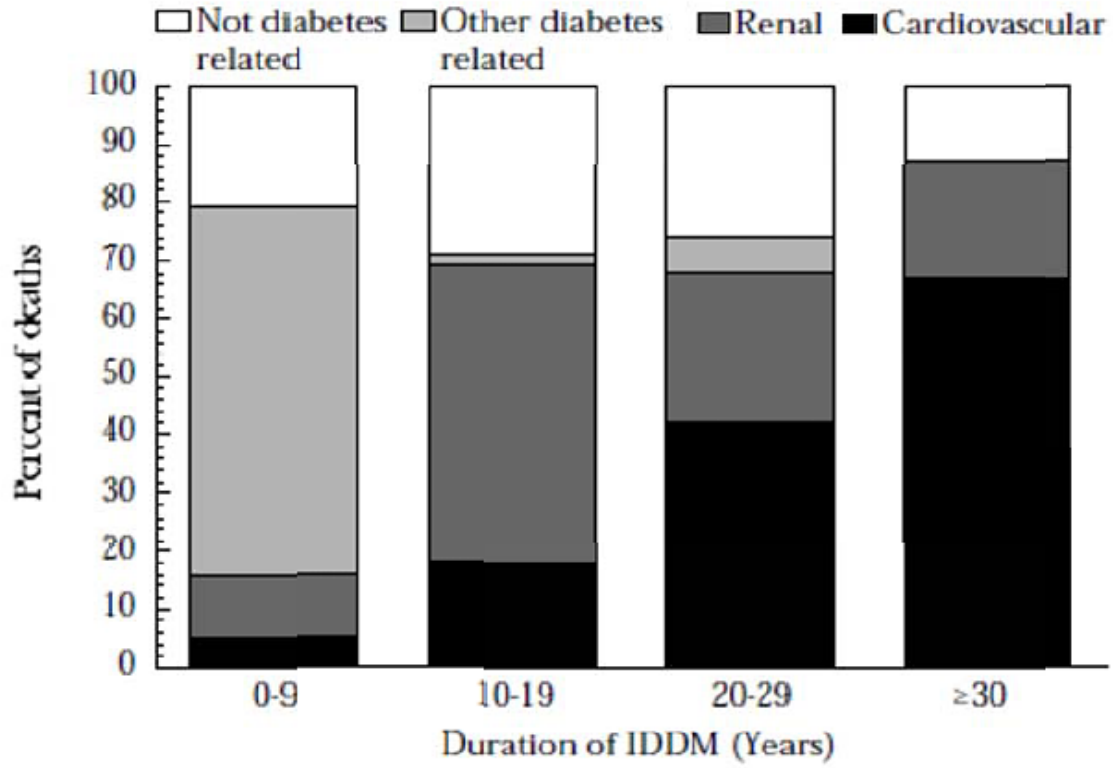
Source: Florkowski *et al. Diab Med* 2003;20:191 – 197.

Cause of death	Diabetes group	Number of deaths	Mortality rate per 1000 person years	SMR	95% CI	
Diabetes and hypoglycaemia	A	4	0.7	7.52	2.82	20.04
	B	2	0.5	0.89	0.22	3.55
	C	3	1.8	2.69	0.87	8.35
Cardiovascular disease	A	43	7.4	4.48	3.32	6.04
	B	122	32.5	2.05	1.72	2.45
	C	100	60.7	3.22	2.65	3.92
	A	8	1.4	35.74	17.88	71.48
	B	7	1.9	4.71	2.25	9.88
Renal failure	C	6	3.6	7.48	3.36	16.66
Respiratory disease	A	3	0.5	1.51	0.49	4.69
	B	28	7.5	1.95	1.35	2.82
	C	13	7.9	1.65	0.96	2.83
Malignancy	A	6	1.0	0.72	0.32	1.59
	B	22	5.9	0.70	0.46	1.06
	C	14	8.5	0.87	0.52	1.48

What are the major causes of death – US Study

Figure 28: Causes of death by duration of IDDM, Pittsburgh PA Epidemiology of Diabetes Complications Study.

Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter10.pdf

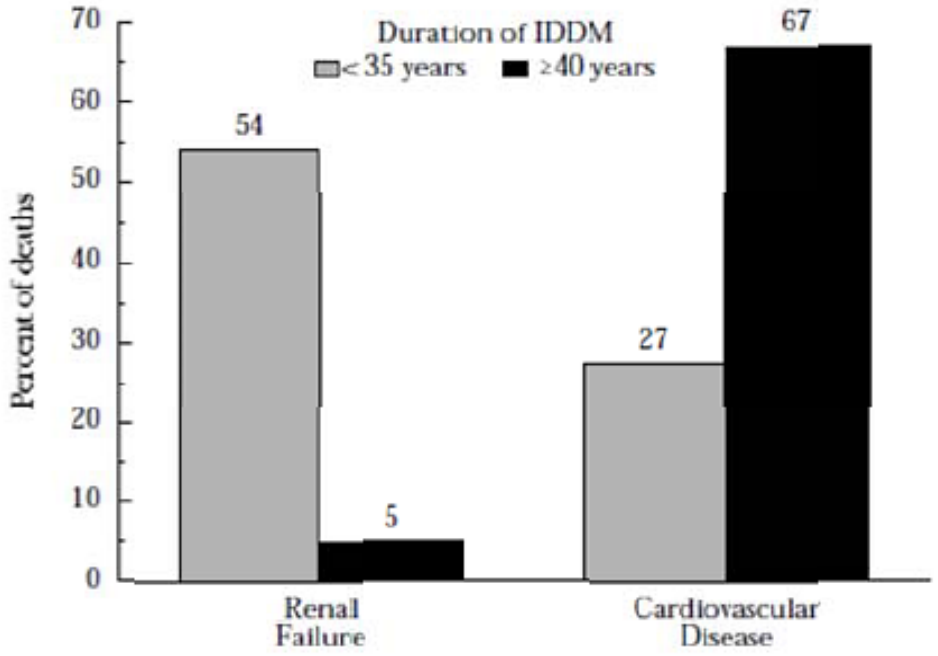


Other diabetes-related causes are primarily acute diabetic coma.

What are the major causes of death – Danish Study

Figure 29: Causes of death by duration of IDDM, Steno Memorial Hospital, Denmark.

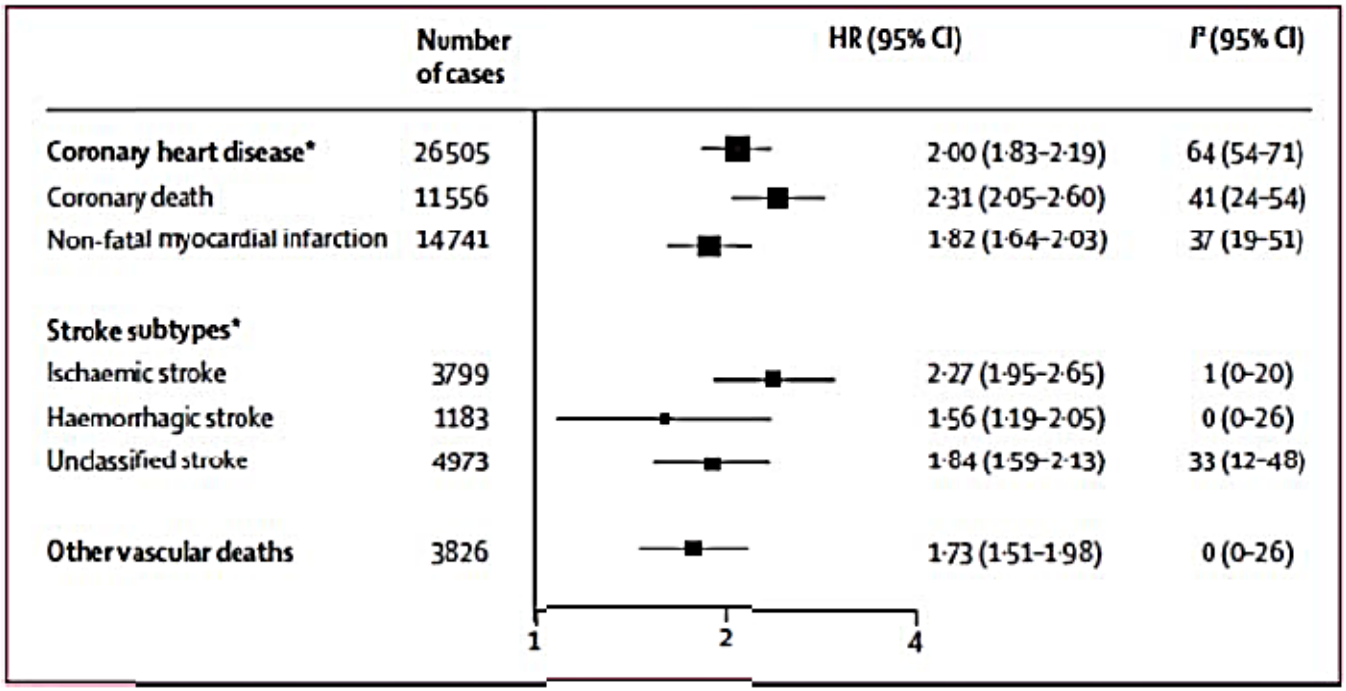
Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter10.pdf



Data are based on patients with IDDM diagnosed at age ≤30 years prior to 1943 and followed to death or January 1, 1984. Renal failure deaths were due to diabetic nephropathy.

Diabetes and the risk of macrovascular disease

Figure 22: Hazard ratios for vascular outcomes in people with vs. those without diabetes at baseline.
Source: Emerging Risk Factors Collaboration. *Lancet* 2010;375:2215 – 2222.

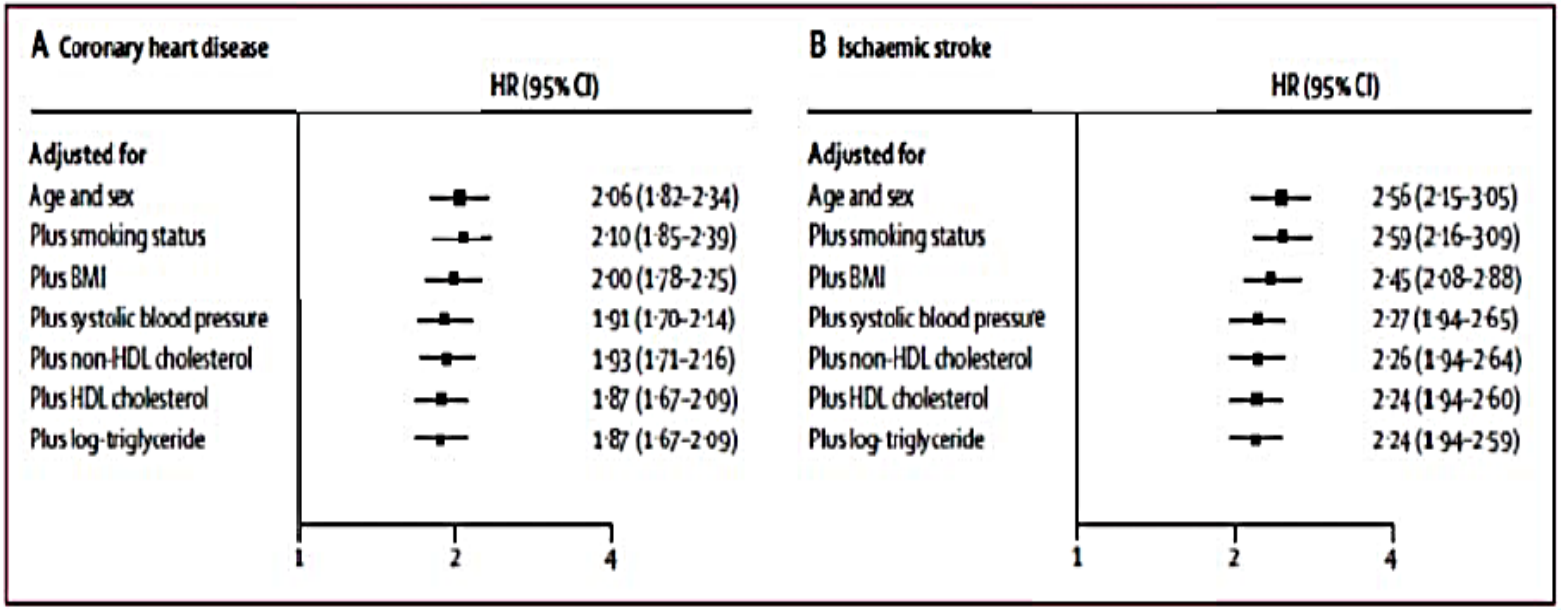


*Analyses were based on 530 083 participants. HRs were adjusted for age, smoking status, body-mass index, and systolic blood pressure, and, where appropriate, stratified by sex and trial arm. 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal myocardial infarction because there were fewer than 11 cases of these coronary disease subtypes in some studies. *Includes both fatal and non-fatal events.*

Diabetes and the risk of macrovascular disease

Figure 24: Hazard ratios for coronary heart disease and ischaemic stroke in people with vs. those without diabetes, progressively adjusted baseline levels of conventional risk factors.

Source: Emerging Risk Factors Collaboration. *Lancet* 2010;375:2215 – 2222.



Analyses were based on 264 353 participants (11 848 cases) for coronary heart disease and 157 315 participants (2858 cases) for ischaemic stroke with complete information on all covariates listed. BMI=body-mass index.

Complications of Diabetes and why we care

- People don’t usually die directly due to the diabetes except in coma states
- Coma - too high blood sugar (hyper) and too low blood sugar (hypo)
- It is the damage the diabetes wroughts over time
- Widespread systemic complications - Atherosclerosis
  - Cardiovascular
  - Cerebrovascular
  - Peripheral vascular
  - Renal (nephropathy)
  - Neuropathy (peripheral and sympathetic systems)
  - Retinopathy/cataracts
- If an individual with diabetes survives more than 20 years after the onset of disease without developing significant complications then they have a reasonable chance of good health

Complications of Diabetes and why we care

- Type 1 diabetics tend to get more “Small” vessel involvement - microvascular
  - The angiopathy - the fine coronary, renal and peripheral vessels in the limbs
- Type 2 diabetes affects the “larger” vessels - macrovascular
  - The coronaries, aorta, carotids and the renal arteries
- There is however a crossover between the 2

What is the relative risk of complications vs population

	Age Standardized Relative Risk Ratio (DM over General Population)	
	Male	**Female**
death & disability	201%	185%
blindness	359%	297%
stroke	339%	275%
ESRF	557%	518%
CABG	149%	179%
cancer & CIS	125%	130%

Albuminuria and its importance as a predictor

Table 48: Progression of eGFR as a function of the category of AER in the DCCT/EDIC study (n = 1439) based on current AER value or the history of AER values.

Source: Molitch *et al. Diabetes Care* 2010;33:1536 – 1543.

Models	Effect	Number with event (n = 89)†	Patient-years‡	Rate per 1,000 patient-years	Cox proportional hazard model* Hazard ratio (95% CI)	Pair-wise P value	GLMM§ % Decrease per year (95% CI)‖	Pair-wise P value
Current albuminuria model	Normal (N)	30	28,123	1.1	1	M vs. N <0.0001	1.2% (1.2–1.3)	M vs. N <0.0001
Albuminuria category defined from the AER value at the time of estimated GFR assessment	Microalbuminuria (M)	18	4,041	4.4	3.3 (1.8–6.1)	A vs. M <0.0001	1.8% (1.6–1.9)	A vs. M <0.0001
	Macroalbuminuria (A)	41	837	46.7	15.3 (8.9–26.3)	A vs. N <0.0001	5.7% (4.5–6.8)	A vs. N <0.0001
History of albuminuria model	Normal (N)	21	21,069	1.0	1	M vs. N 0.281	1.2% (1.2–1.3)	M vs. N 0.0007
Albuminuria category defined from the highest AER value observed before or at the time of estimated GFR assessment	Microalbuminuria (M)	14	10,492	1.3	0.7 (0.4–1.4)	A vs. M <0.0001	1.4% (1.3–1.4)	A vs. M <0.0001
	Macroalbuminuria (A)	54	1,440	36.1	8.6 (5.0–14.7)	A vs. N <0.0001	5.1% (4.0–6.2)	A vs. N <0.0001

Crude risk of developing sustained estimated GFR <60 ml/min/1.73 m^2 (or ESRD) and the relative risk (hazard ratio) estimated from the Cox proportional hazards model are shown. Mean of the rate of decline (% decrease per year) in estimated GFR was obtained from the general linear mixed model. *Cox proportional hazard model of the time from DCCT randomization to the initial sustained eGFR <60 ml/min/1.73 m^2 through EDIC year 14, after adjustment for mean arterial pressure and ACE inhibitor use versus not at each visit as time dependent covariates. For those with a missing covariate value at a visit, the prior observed value was carried forward. Mean arterial pressure was computed as (2/3 diastolic blood pressure + 1/3 systolic blood pressure). ACE inhibitor use was prescribed during DCCT (1983–1993). †The 89 patients with events are subjects with sustained eGFR <60 ml/min/1.73 m^2. ‡For each patient, patient-years is calculated as the elapsed whole years from randomization into the DCCT to either the visit at which a sustained eGFR <60 ml/min/1.73 m^2 was first observed or the last visit at which the eGFR was measured if a patient had no event during the time. §Percent decrease in eGFR per year while in each category of albuminuria obtained from the generalized linear mixed model of log-transformed levels of eGFR as a function of time, with heterogeneous random intercept, random slope over time, and residual errors among the time-dependent AER categories, after adjustment for time dependent use of ACE inhibitor and time-dependent mean blood pressure at each DCCT-EDIC visit. For subjects with a missing covariate (AER, ACE inhibitor use, or mean blood pressure) at a visit, the prior observed value was carried forward. For subjects reaching ESRD, an eGFR value of 10 ml/min/1.73 m^2 was assigned thereafter for annual visits.

Standards of Medical Care

Table 15 – Stages of CKD

Stage	Description	GFR (ml/min per 1.73m^2 body surface area)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 or dialysis

* Kidney damage defined as abnormalities on pathologic, urine, blood or imaging tests. Adapted from ref 283.

Albuminuria and its importance as a predictor

Is it associated with progressive renal disease and development of cardiovascular disease?

- It is believed an increasing Albumin Excretion Rate (AER) is a predictor of falling Glomerular Filtration Rate (GFR) and therefore development of diabetic renal disease.
- However some studies have shown that those with a reduced GFR do not necessarily have an increased AER.
- Transient elevations in AER are not as strongly associated with a reduction in renal function as sustained levels, even if only to microalbuminuria.
- Renal function is considerably worse when macroalbumnuria is present.
- A higher proportion of those with Type 2 diabetes are found to have microalbuminuria or overt nephropathy at or shortly after diagnosis – disease often present before diabetes is diagnosed

Retinopathy

- Diabetes is the most common cause of blindness in those aged 30 – 69
- Diabetic retinopathy affects nearly all individuals with a duration of at least 15 year
- Increased risk of ischaemic heart disease in those with proliferative versus those with non-proliferative retinopathy

Retinopathy – what are the differences?

- Non proliferative
  - Narrowing of the vessels, increased capillary permeability →serous central retinopathy
  - Hemorrhages→ exudates
  - microaneurysms
- Proliferative
  - new vessel formation → scarring of retina (retinitis proliferans); vitreal hemorrhage, retinal detachment
  - loss of vision

Retinopathy – mortality rates of Type 1 diabetics with types

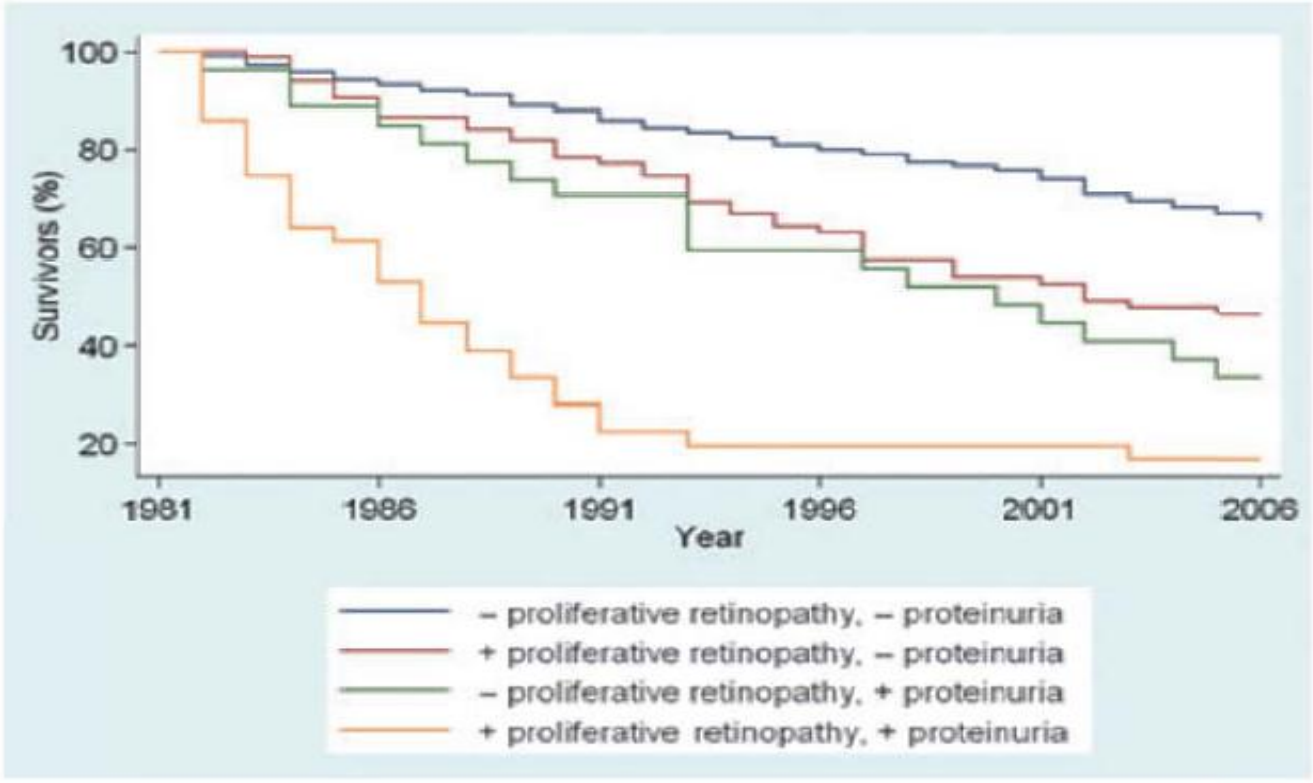
Table 59: Age- and sex-adjusted hazard ratios (HRs) for all cause mortality according to level of retinopathy compared with patients with no retinopathy in type 1 diabetes from Fyn County, Denmark.
Source: Grauslund J. *Acta Ophthalmologica* 2011;89 thesis 1:1 – 89.

	All-cause mortality rate			
	Non-proliferative retinopathy		Proliferative retinopathy	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Model 1: age, sex	1.01 (0.72–1.42)	0.97	2.04 (1.43–2.91)	<0.001
One-by-one adjustment				
Model 1 and diabetes duration	1.01 (0.72–1.42)	0.97	1.96 (1.36–2.80)	0.001
Model 1 and smoking	1.01 (0.73–1.43)	0.92	2.01 (1.41–2.87)	<0.001
Model 1 and HbA_{1c}	1.07 (0.76–1.51)	0.71	2.16 (1.51–3.09)	<0.001
Model 1 and SBP	1.00 (0.71–1.41)	0.99	2.02 (1.42–2.89)	<0.001
Model 1 and DBP	1.01 (0.71–1.41)	0.98	2.03 (1.42–2.90)	<0.001
Model 1 and BMI	1.04 (0.73–1.47)	0.85	2.06 (1.42–2.97)	<0.001
Model 1 and proteinuria	0.98 (0.68–1.41)	0.90	1.49 (0.99–2.24)	0.054
Multivariate model				
Model 1 plus [a]	0.98 (0.68–1.42)	0.91	1.48 (0.98–2.23)	0.060

HR (95% CI) for all-cause mortality rate analysed by Cox's proportional hazards analyses
DBP, diastolic blood pressure; SBP, systolic blood pressure
[a]Model 1 plus diabetes duration, smoking, HbA_{1c}, SBP, DBP, BMI and proteinuria

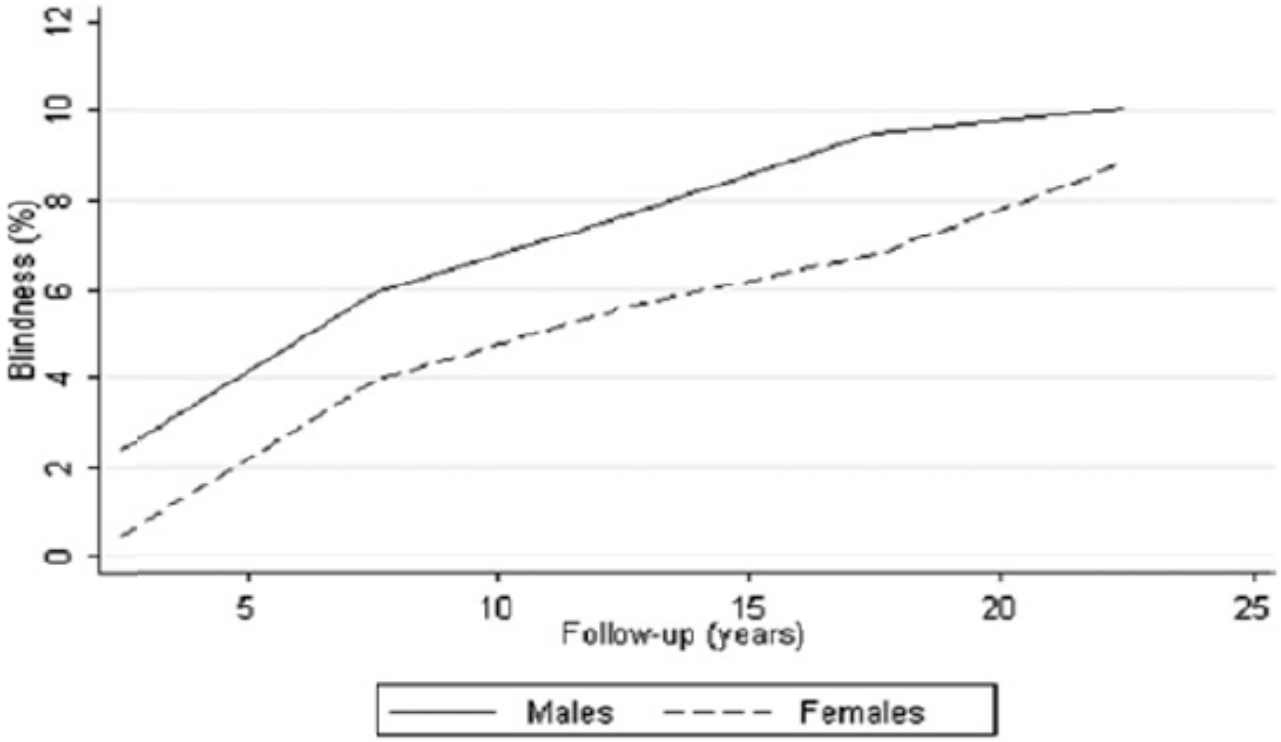
All cause mortality with proliferative retinopathy and/or proteinuria

Figure 42: All-cause mortality rate according to the level of baseline retinopathy and proteinuria.
Source: Grauslund J. *Acta Ophthalmologica* 2011;89 thesis 1:1 – 89.



Incidence of blindness

Figure 43: Mortality-adjusted cumulative incidence of blindness during follow-up.
Source: Grauslund J. *Acta Ophthalmologica* 2011;89 thesis 1:1 – 89.



Retinopathy

- Background – risk to vision, not to life
- Proliferative – risk to both

- Treatment available
  - Good diabetic care
  - Laser photocoagulation
  - Anti VEGF injections (Vascular Endothelial Growth Factor, which is responsible for growth of blood vessels)

Diabetes – morbidity from micro and macrovascular complications

Table 26: Morbidity ratios (MbR) of macrovascular complications by age group: Diabetics vs. non-diabetics.

Source: Naslafkih A, Sestier F. *J Insur Med* 2003;35:102 – 113.

Macrovascular Complications	Age (Years)	Morbidity Ratios MbR (%)
Ischemic heart disease[17]	18–44	1,350
	45–64	304
	≥65	172
Heart disease or stroke[23]	35–64	533
	≥65	162
Stroke[45]	45–64	356
Chronic heart failure[19]	45–64	500
	65–74	247
	≥75	228
Peripheral vascular disease[24]	All ages	560
Lower limb amputation	All ages[37]	890
	Adjusted[38]	1,258
Carotid artery disease[40]	45–64	240

Diabetes and hypertension – stroke risk and mortality

Table 55: HRs for stroke incidence and stroke mortality according to the history of hypertension and diabetes at baseline.

Source: Hu G *et al. Stroke* 2005;36:2538 – 2543.

	HRs (95% CI)					
Variable	No Hypertension and No Diabetes	Hypertension I and No Diabetes	Hypertension II and No Diabetes	Diabetes and No Hypertension	Both Hypertension I and Diabetes	Both Hypertension II and Diabetes
Stroke incidence						
Cases, n	569	730	1538	19	28	94
Person-years	391 630	249 939	276 208	3456	2651	6520
Age, sex, and study year adjustment	1.00	1.35 (1.21 to 1.51)	1.98 (1.79 to 2.19)	2.54 (1.61 to 4.01)	3.51 (2.40 to 5.14)	4.50 (3.60 to 5.61)
Multivariate adjustment*	1.00	1.33 (1.19 to 1.49)	1.90 (1.71 to 2.11)	2.50 (1.58 to 3.95)	3.30 (2.26 to 4.84)	4.09 (3.27 to 5.13)
Stroke mortality						
Cases, n	121	199	540	5	12	47
Person-years	394 995	254 155	284 346	3551	2766	6818
Age, sex, and study year adjustment	1.00	1.47 (1.17 to 1.84)	2.62 (2.14 to 3.21)	3.06 (1.25 to 7.49)	5.59 (3.08 to 10.1)	9.27 (6.58 to 13.1)
Multivariate adjustment*	1.00	1.47 (1.17 to 1.84)	2.51 (2.03 to 3.09)	2.94 (1.20 to 7.21)	5.22 (2.87 to 9.49)	8.01 (5.63 to 11.4)

*Multivariate models included age, sex, study year, BMI, cholesterol, education, smoking, alcohol drinking, and physical activity.

Diabetes and smoking – Relative risk of CHD

Table 58: Age and multivariate adjusted relative risks (95% CI) for total coronary heart disease(CHD), fatal CHD and non-fatal myocardial infarction according to smoking status among diabetic women.
Source: Al-Delaimy WK *et al. Arch Intern Med* 2002;162:273 – 279.

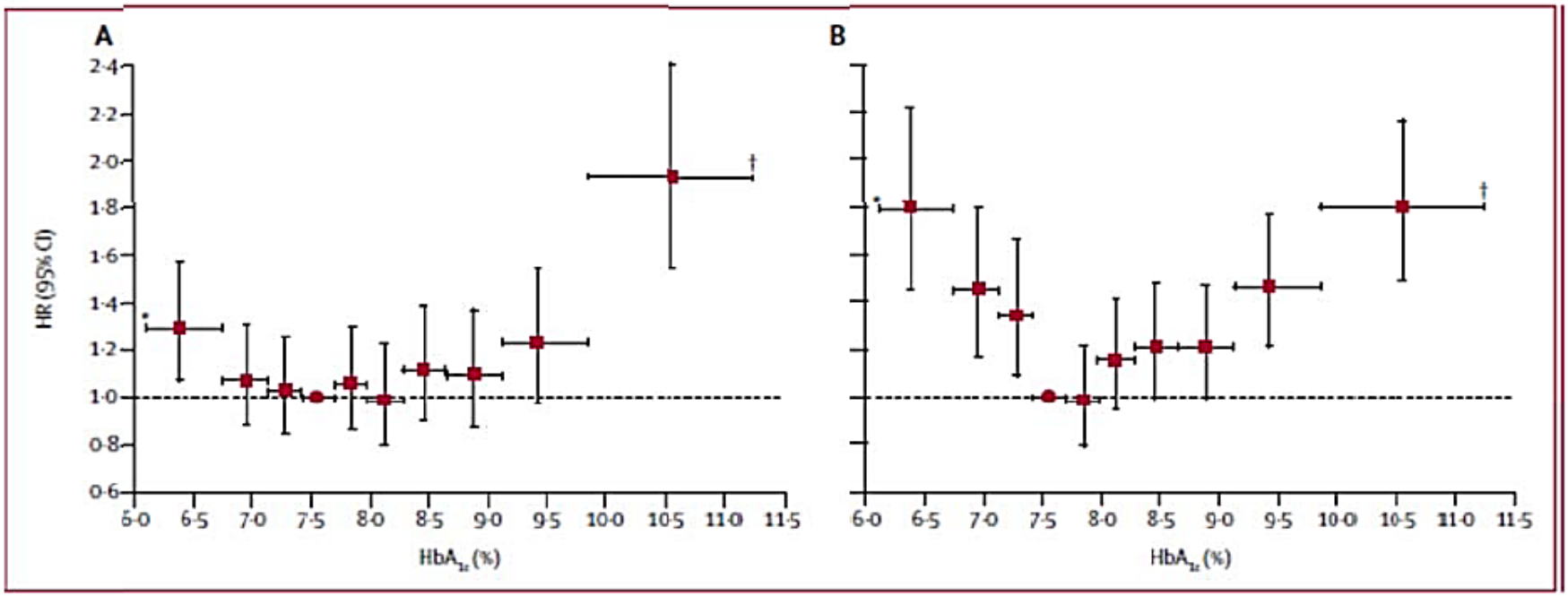
	Smoking Status				
			Current Smokers, Cigarettes per Day		
Variable	Never Smokers†	Past Smokers	1-14	≥15	*P* Value for Trend
Person-years	30 752	23 853	3893	9729	...
Total CHD					
No. of cases	168	160	27	103	...
Age-adjusted RR	1.0	1.17 (0.94-1.46)	1.43 (0.95-2.16)	2.35 (1.83-3.02)	<.001
Multivariate-adjusted RR	1.0	1.21 (0.97-1.51)	1.66 (1.10-2.52)	2.68 (2.07-3.48)	<.001
Fatal CHD					
No. of cases	77	74	13	36	...
Age-adjusted RR	1.0	1.17 (0.85-1.62)	1.55 (0.86-2.80)	1.87 (1.25-2.80)	.002
Multivariate-adjusted RR	1.0	1.24 (0.90-1.72)	1.73 (0.95-3.15)	2.11 (1.39-3.19)	.005
Nonfatal MI					
No. of cases	91	86	14	67	...
Age-adjusted RR	1.0	1.17 (0.87-1.57)	1.34 (0.76-2.35)	2.69 (1.95-3.71)	<.001
Multivariate-adjusted RR	1.0	1.19 (0.88-1.61)	1.56 (0.88-2.77)	3.05 (2.19-4.26)	<.001

*The covariates for the multivariate adjustment are age, period, alcohol consumption, duration of diabetes, postmenopausal hormone use, diabetes medication use, body mass index, family history of MI, physical activity, high cholesterol, and high blood pressure. RR indicates relative risk; CI, confidence interval; CHD, coronary heart disease; MI, myocardial infarction; and ellipses, data not applicable.
†Reference group.

HbA1c control – how tight should control be?

Figure 37: Adjusted hazard ratios for all cause mortality by HbA1c deciles in people given oral combination and insulin-based therapies.

Source: Currie CJ *et al*. *Lancet* 2010;375:481 – 489.



*Cox proportional hazards models were used, with the HbA1c base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA1c range. Red circle – reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).*

ACCORD

- 10,251 patients with Type II Diabetes
- Poor control (average HbA1c of 8.1%)
- Previous CV event or other risk factors

Target

- Intensive control – HbA1c 6.0% or less (actual - 6.4%)
- Standard control – HbA1c 7-7.9% (actual – 7.4%)

Result

- **22% increase in mortality in intensive group**
- TRIAL STOPPED

HbA1c control – how tight should control be?

- There was a U shaped pattern of risk association with HbA1c
- It was similar between insulin and non insulin controlled cohorts
- The findings from this study aligned with the ACCORD trial
- Studies showed a HbA1c of approximately 7.5% associated with lowest all cause mortality + lowest progression rate to large-vessel disease events
- Hypoglycaemia is associated with various sequelae that could increase mortality

HbA1c control – how it affects all cause and CV mortality?

Table 54: Sex-specific analysis of the association between baseline glycosylated haemoglobin quartile and all-cause and cardiovascular mortality, Wisconsin, 1980 – 1982 to 2001.

Source: Shankar A *et al. Am J Epidemiol* 2007;166:393 – 402.

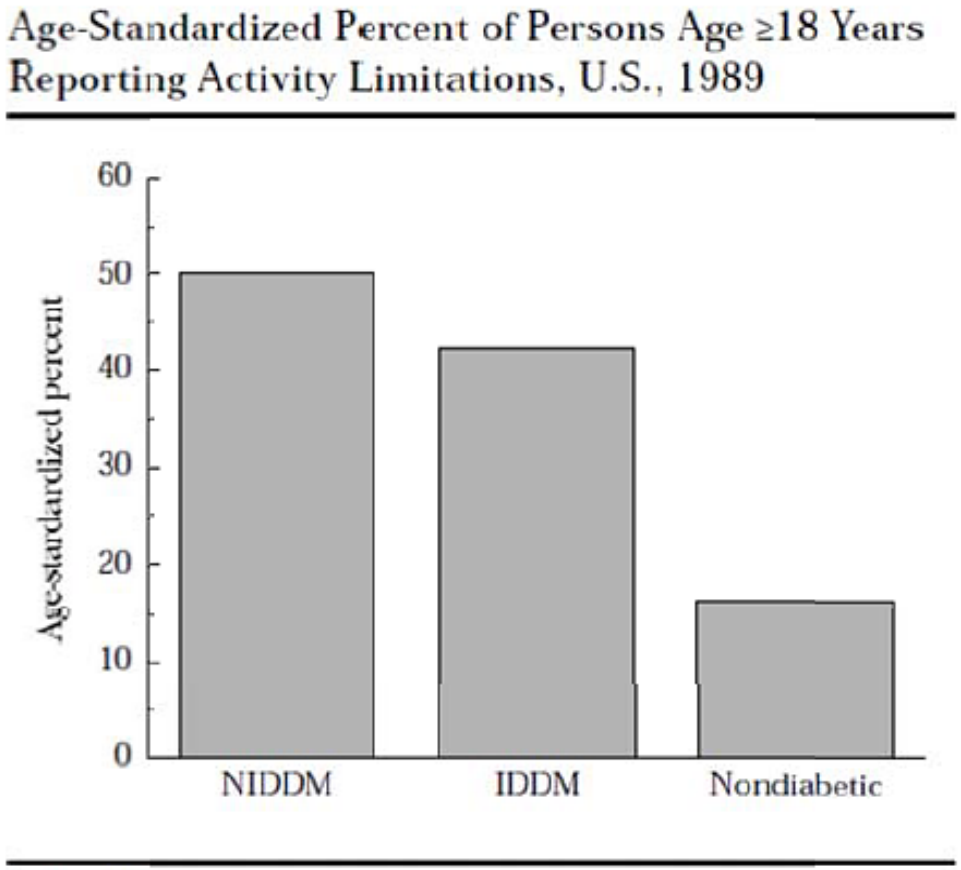
Glycosylated hemoglobin level (range in %)	No. at risk	All-cause mortality					Cardiovascular mortality				
		All-cause deaths (n = 201)	Age- and duration-adjusted model*		Multivariable model*,†		Cardiovascular deaths	Age- and duration-adjusted model*		Multivariable model*,†	
			RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Men (n = 448)											
Quartile 1 (5.6–9.4)	110	17	1	Referent	1	Referent	7	1	Referent	1	Referent
Quartile 2 (9.5–10.5)	118	32	1.30	0.71, 2.36	1.71	0.93, 3.16	21	1.92	0.81, 4.57	1.96	0.82, 4.68
Quartile 3 (10.6–12.0)	110	32	1.69	0.93, 3.05	2.00	1.09, 3.69	26	3.39	1.47, 7.82	3.17	1.36, 7.38
Quartile 4 (12.1–19.5)	110	34	2.73	1.52, 4.92	2.46	1.33, 4.57	23	4.19	1.79, 9.80	4.59	1.95, 10.82
p trend				0.0004		0.004			0.0001		<0.0001
Women (n = 431)											
Quartile 1 (5.6–9.4)	115	13	1	Referent	1	Referent	7	1	Referent	1	Referent
Quartile 2 (9.5–10.5)	91	25	1.82	0.93, 3.59	1.92	0.96, 3.86	16	2.11	0.86, 5.18	2.02	0.82, 4.95
Quartile 3 (10.6–12.0)	112	20	1.30	0.64, 2.63	1.22	0.59, 2.56	16	1.78	0.73, 4.38	1.80	0.73, 4.43
Quartile 4 (12.1–19.5)	113	28	2.34	1.20, 4.56	2.48	1.24, 4.99	16	2.62	1.07, 6.39	2.37	0.95, 5.90
p trend				0.04		0.05			0.06		0.10

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (years) and duration of diabetes (years).

† Additionally adjusted for education (years of schooling), body mass index (kg/m^2), smoking (never, former, current), hypertension (absent, present), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), proteinuria (absent, present), retinopathy (none, nonproliferative, proliferative), history of neuropathy (absent, present), and history of daily aspirin intake (no, yes).

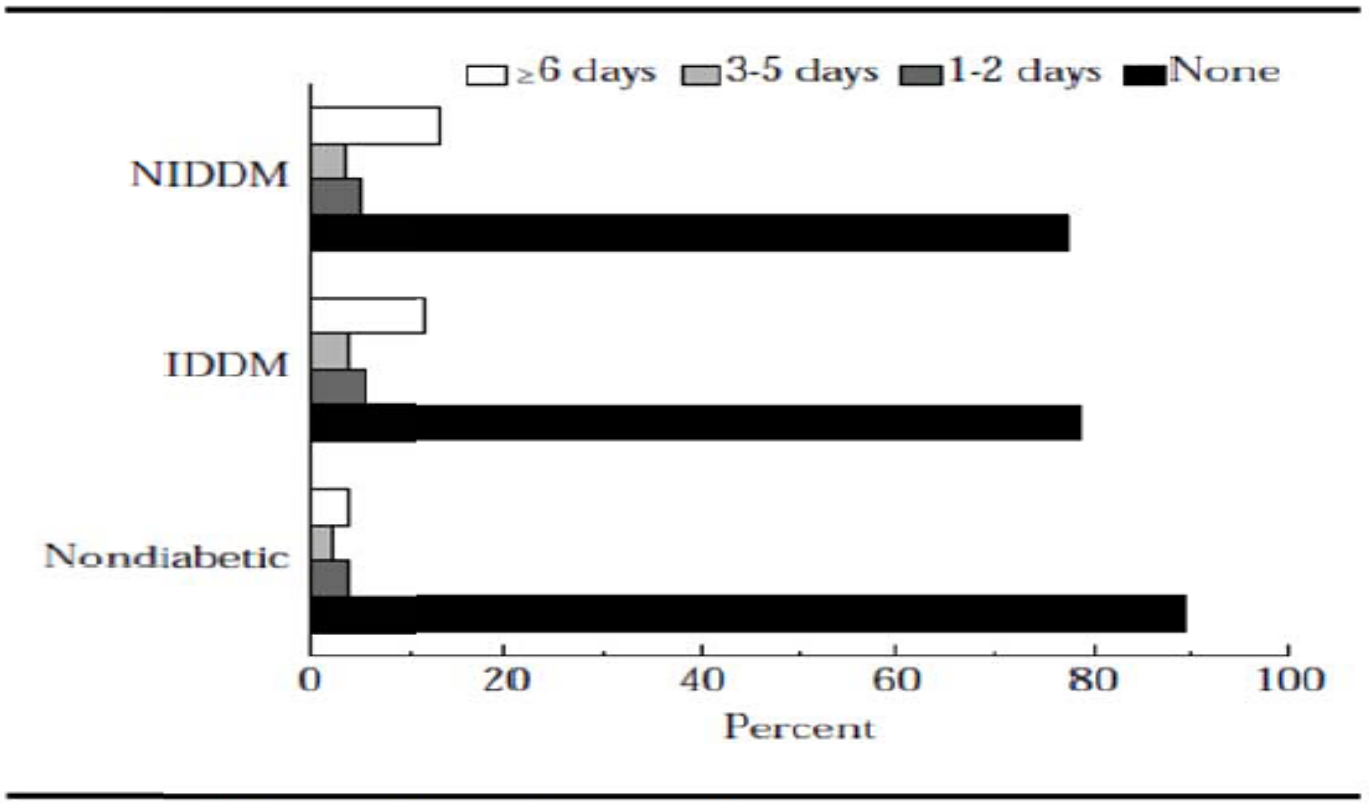
Diabetes and morbidity

Figure 33: Age-standardised percent of persons aged ≥18 years reporting activity limitations, US 1989.
Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter12.pdf



Diabetes and morbidity – how is working restricted

Figure 35: Percent distribution of restricted activity days, by diabetes status, US 1989.
Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter12.pdf

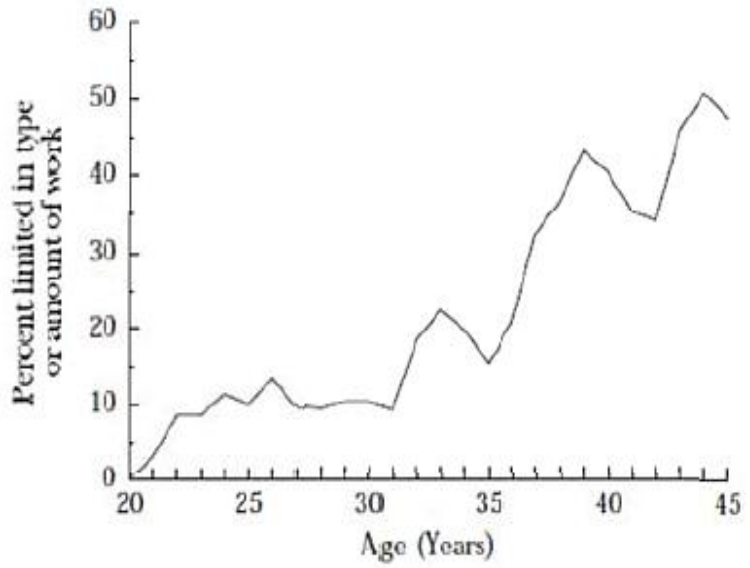


Source: 1989 National Health Interview Survey

Diabetes and morbidity – how is it affected by age

Figure 38: Percent of type 1 patients reporting being limited in type or amount of work activity, by age, Pittsburgh EDC Study 1990 – 1992.

Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter12.pdf



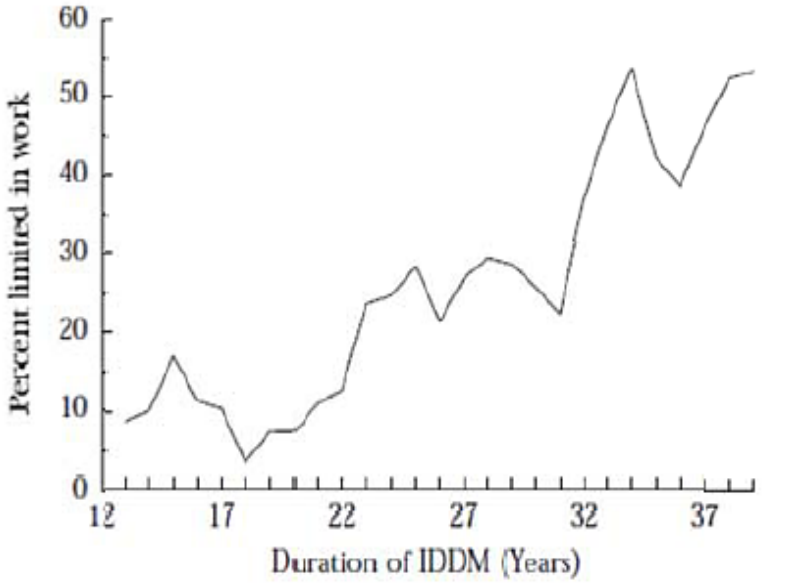
EDC, Epidemiology of Diabetes Complications; Data are 3-year moving average

Source: Pittsburgh Epidemiology of Diabetes Complications Study

Diabetes and morbidity – how is it affected by duration

Figure 39: Percent of type 1 individuals reporting work limitations, by duration of diabetes, Pittsburgh EDC Study, 1990 – 1992.

Source: http://diabetes.niddk.nih.gov/dm/pubs/america/pdf/chapter12.pdf



EDC, Epidemiology of Diabetes Complications. Data are 3-year moving averages. Limitations include those in the type or amount of work that can be performed.

Source: Pittsburgh Epidemiology of Diabetes Complications Study

What conclusions can we draw?

- Mortality has been improving
  - Relative risk reduces with age at onset in 10 year increments
- Morbidity has shown some improvement but only for good risks
- Complications and co-morbid factors remain important
  - Albuminuria
  - Proliferative retinopathy
  - Coronary artery disease
  - Hyperlipidaemia
  - Hypertension
  - Smoking
- Views have changed on intensity of control

Thank you for your attention.