Mortality risk in people with type 2 diabetes: a large prospective population-based cohort study (The Ayrshire Diabetes fOllow-up Cohort (ADOC) study)

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Abstract

Background

The aims of this study were to investigate the effects of age, gender, body mass index (BMI), glycaemic control, socio-economic status, dyslipidaemia, hypertension, ischaemic heart disease (IHD) and smoking status in type 2 diabetes in a population-based analysis.

Methods

Data were collected from 46 General Practice databases in 2009 and 2014. Cox regressions were run in the non-diabetes population plus type 2 diabetes patients.

Results

People with type 2 diabetes (n=16,643) had higher mortality rates than non-diabetes subjects. Ranked in order of Hazard Ratio (HR), increasing age (HR 2.31), smoking (HR 1.79), IHD (HR 1.65), deprivation (HR 1.36), hypertension (HR 1.23) and male gender (HR 1.20) all increased mortality risk ($p<0.01$). Statin therapy was associated with better outcome (HR 0.65, $p<0.01$). Abnormal lipid levels whilst not on a statin significantly increased mortality risk for raised total-cholesterol (HR 1.74) and low HDL-cholesterol (HR 1.48) but not for triglycerides (HR 0.67) (all $p<0.01$).

Conclusions

This large study confirmed that the all-cause mortality risk in people with type 2 diabetes remains elevated. In the study we demonstrated that a man with type 2 diabetes of 5-10 years duration who smoked, had hypertension and IHD plus lived in the most deprived area had a HR of 6.2 compared with a non-smoking, normotensive, non-diabetes subject without IHD living in the least deprived area. . Further research is required to understand the gender risk difference in all-cause mortality in type 1 compared with type 2 diabetes and why obesity plus raised triglycerides appear to be protective.

Highlights

- Ranked in order of Hazard Ratio (HR), increasing age (HR 2.31), smoking (HR 1.79), Ischaemic Heart Disease (IHD) (HR 1.65), deprivation (HR 1.36), hypertension (HR 1.23) and male gender (HR 1.20) all increased mortality risk ($p<0.01$).
- This study demonstrated that a man with type 2 diabetes of 5-10 years duration who smoked, had hypertension and IHD plus lived in the most deprived area had a HR of 6.2 compared with a non-smoking, normotensive, non-diabetes subject without IHD living in the least deprived area.
- Smoking prevalence decreased with duration falling from 26.8% for diabetes <5 yrs to 17.7% for diabetes >10 yrs.
- Body Mass Index > 30kg/m^2 appeared to reduce mortality risk (HR 0.77, $p<0.01$).

- Abnormal lipid levels whilst not on a statin significantly increased mortality risk for raised total-cholesterol (HR 1.74) and low HDL-cholesterol (HR 1.48) but not for triglycerides (HR 0.67) (all p<0.01).

Background

The increasing prevalence of type 2 diabetes has been multifactorial, related to the ageing of populations, economic development, and associated changes in culture and lifestyle [1,2]. In Scotland, the incidence of type 2 diabetes is thought to have stopped rising, with increasing prevalence due to reducing mortality and demographic change [3]. The increase in numbers is particularly important because of the demands it makes on health systems [4]. Type 2 diabetes is a chronic complex metabolic disease and is associated with numerous macrovascular and microvascular complications [4]. The management of type 2 diabetes management is expensive, requiring affected people to change lifestyle behaviours, manage multiple risk factors and attend health care professionals on a regular basis [4]. The evidence base for managing type 2 diabetes and preventing complications has improved greatly. Particularly, cardiovascular risk factor management, glycaemic control studies and smoking cessation have resulted in better outcome data and improved care [5-10].

The initial goal of treatment in patients with type 2 diabetes is to reduce the mortality risk to a level comparable to non-diabetes individuals. The aims of this study were to compare all-cause mortalities in type 2 diabetes with a non-diabetes population, and to investigate the effects of age, gender, social deprivation, body mass index (BMI), dyslipidaemia, hypertension, ischaemic heart disease and smoking status in a population-based analysis in the county of Ayrshire and Arran, Scotland over a five-year period.

Methods

Forty six out of fifty-five General Practices in NHS Ayrshire & Arran covering 85% of the total patient population (above 18 yrs) of Ayrshire & Arran contributed data from their practice computer systems. Data were provided in 2009 and then again in 2014. There was no significant difference in the prevalence of diabetes between practices that did and did not provide data (5.5% vs. 5.7% χ^2=3.3 p=0.07).

In a recently published study, we investigated the outcome of patients with type 1 diabetes over the same five-year period where further information on methodology is available. [11]. Survival was measured in days from a ‘start date’ of 1/10/2009 to an 'end date' of 30/09/2014. The number of days between the start and end date (survival time) was calculated for each subject. Duration of duration was calculated as the time between diagnosis and the end date. Data on age, gender, deprivation, smoking status, ischaemic heart disease and hypertension, were collected for all subjects. Ischaemic heart disease was defined as per the Quality Outcome Framework document [12]. Hypertension was defined as BP $\geq$ 140/90 or on anti-hypertensive medication. Data on glycaemic control and lipid levels were only routinely collected for those patients with diabetes. Abnormal lipids were defined as total cholesterol > 5mmo/l (or on statin therapy), low HDL-cholesterol [men < 1mmol/l; women < 1.3mmol/l (or on statin therapy)] or non-fasting triglycerides > 1.7mmol/l (or on statin therapy).

Socioeconomic groups based on the Scottish Index of Multiple Deprivation (SIMD) 2012 were derived using patient postcodes. SIMD quintiles ranged from 1 (least deprived) to 5 (most deprived) [13]. As Ayrshire and Arran is more deprived than the rest of Scotland, deprivation weighted quintiles were used [14]. Ethical opinion was not required for this study. The audit was registered with the Clinical Governance Department, NHS Ayrshire and Arran, UK and Caldicott Guardian approval was obtained from each General Practice.

Statistics

A Cox regression was run on survival time with gender, age (in decades), deprivation (quintile), type 2 diabetes, smoking, hypertension and IHD as covariates. Interactions of diabetes groups with all the other covariates were also included. Reference group were female, quintile 1 (least deprived), non-diabetes, non-smoker, normotensive and no IHD [11].

BMI data was not included in the initial survival model. Instead a matched sample of two non-diabetes subjects for each type 2 diabetes subject was selected using propensity score matched on the latest BMI reading. After matching there was data on 49371 subjects (66.6% non-diabetes subjects and 33.3% with type 2 diabetes) and the two groups had similar BMI (type 2 diabetes 31.21±6.88 [mean $\pm$ SD] vs. non-diabetes 31.17±6.84, $p = 0.52$). The previous Cox regression was run on this subset with BMI $\geq$ 30k/m^2 included as a covariate.

A Cox regression including only patients with type 2 diabetes was also run using the same covariates as previously but including BMI, glycaemic control, lipid levels and complications. Baseline categories were as above; the baseline for diabetes was duration of less than 5 yrs. Statistical analysis was performed using SPSS V21

Results

In total 269,947 subjects were tracked from 2009 to 2014. 93.8% were non-diabetes subjects. 6.2% (16643) had type 2 diabetes. 2.3% (6260) had diabetes for less than 5 years, 2% (5353) had diabetes for between 5 & 10 years and 1.9% (5030) had diabetes for more than 10 years. Between 2009 & 2014, 4.5% of the subjects died and 6.5% moved out with the practices included in the study; the remaining 89.1% remained registered. All-cause mortality was 3.9% for non-diabetes subjects but was significantly higher for type 2 diabetes. Mortality was lowest for duration of diabetes less than 5 yrs and greatest for those with duration 5-10yrs (<5 yrs 10.1%, OR 2.8; 5-10 yrs 14.7%, OR 4.2; >10 yrs 13.9%, OR 4.0) (table 1).

Gender & Age

There were significantly more males among the patients with type 2 diabetes (regardless of duration) than non-diabetes subjects (55% vs. 49%) (χ^2= 254.7, $p < 0.01$). Non-diabetes subjects were significantly younger than type 2 diabetes groups ([mean±sd] 45.2±22.2 vs. 64.3±13.2 (diabetes < 5 yrs) vs. 68.1±12.2 (5-10 yrs) and 71.1±11.1(>10 yrs), all $p < 0.01$). Females were older than males for all groups [mean diff

(95% CI) non-diabetes 3.0yrs (2.8,3.2); diabetes <5 yrs 1.8yrs (1.2,2.5); diabetes 5-10 yrs: 2.0yrs (1.4,2.6); diabetes >10 yrs: 2.0yrs (1.4,2.6), all $p < 0.01$].

Relative mortality of patients with type 2 diabetes compared to non-diabetes subjects was similar for both males and females (table 1). The survival analysis (table 2); showed that mortality risk was higher for males once age was taken into account but there was no gender difference by duration of diabetes (no interaction). Mortality increased by age and was higher for type 2 diabetes across all age groups.

Table 1: Mortality by diabetes duration (not adjusted for covariates).

	Non diabetes	Type 2 diabetes			OR (95% CI) Mortality vs. Non-diabetes		
		< 5 yrs	5-10 yrs	> 10 yrs	< 5 yrs	5-10 yrs	> 10 yrs
	n = 253304	n= 6260	n= 5353	n = 5030			
Total	3.9% (9923)	10.1% (632)	14.7% (785)	13.9% (698)	2.8 (2.5,3.0)	4.2 (3.9,4.6)	4.0 (3.6,4.3)
Gender							
Female	4.1% (5370)	10.2% (289)	14.6% (353)	14.1% (319)	2.6 (2.3,3.0)	4.0 (3.5,4.5)	3.8 (3.4,4.3)
Male	3.7% (4553)	10.0% (343)	14.7% (432)	13.7% (379)	2.9 (2.6,3.2)	4.5 (4.0,5.0)	4.1 (3.7,4.6)
Age *							
<49	0.4% (531)	2.3% (20)	2.0% (8)	3.3% (6)	6.3 (4.0,9.9)	5.4 (2.7,10.9)	9.2 (4.1,20.9)
50-59	1.6% (630)	3.8% (52)	3.8% (34)	3.1% (20)	2.4 (1.8,3.1)	2.3 (1.6,3.3)	1.9 (1.2,3.0)
60-69	4.4% (1436)	7.1% (122)	9.9% (147)	6.5% (82)	1.7 (1.4,2.0)	2.4 (2.0,2.8)	1.5 (1.2,1.9)
70-79	11.1% (2532)	13.6% (203)	18.1% (286)	15.2% (265)	1.3 (1.1,1.5)	1.8 (1.6,2.0)	1.4 (1.3,1.7)
80+	28.4% (4793)	29.6% (235)	31.7% (310)	27.1% (325)	1.1 NS p=.47	1.2 (1.0,1.30	0.9 NS p=.35
Deprivation*							
Quintile 1	3.7% (1727)	10.5% (94)	13.3% (110)	12.9% (99)	3.1 (2.5,3.8)	4.0 (3.3,4.9)	3.9 (3.1,4.8)
Quintile 2	2.8% (1399)	7.8% (88)	10.9% (104)	9.2% (77)	3.0 (2.4,3.7)	4.3 (3.5,5.3)	3.5 (2.8,4.5)
Quintile 3	4.3% (2157)	11.2% (143)	15.2% (168)	14.2% (154)	2.8 (2.3,3.3)	4.0 (3.3,4.70	3.7 (3.1,4.4)
Quintile 4	4.6% (2376)	11.6% (165)	16.4% (191)	15.8% (185)	2.7 (2.3,3.2)	4.1 (3.5,4.8)	3.9 (3.3,4.6)
Quintile 5	4.1% (2123)	9.0% (134)	15.6% (196)	15.2% (173)	2.3 (1.9,2.8)	4.3 (3.7,5.1)	4.2 (3.6,5.0)
Smoking*							
Non smoker	3.7% (7095)	10.1% (461)	14.5% (611)	13.7% (568)	2.9 (2.6,3.2)	4.4 (4.0,4.8)	4.1 (3.7,4.5)
Smoker	5.0%	10.3%	15.3%	14.6%	2.2	3.4(2.9,4.0)	3.2

	(2687)	(169)	(174)	(130)	(1.8,2.5)		(2.7,3.9)
Hypertension							
Normotensive	2.6% (5939)	7.9% (310)	11.9% (280)	12.0% (224)	3.2 (2.8,3.6)	5.0 (4.4,5.6)	5.0 (4.4,5.8)
Throughout	14.0% (3984)	13.7% (322)	16.8% (505)	15.0% (474)	1.0 NS p=.75	1.2 (1.1,1.4)	1.1 NS p=.14
IHD							
No	3.1% (7644)	7.8% (415)	11.5% (481)	10.8% (395)	2.6 (2.4.2.9)	4.0 (3.6,4.4)	3.7 (3.3,4.1)
Throughout	23.0% (2279)	22.5% (217)	26.1% (304)	22.3% (303)	1.0 NS p=.71	1.2 (1.0,1.4)	1.0 NS p=.58

* Missing values: smoking 13496 (5.0%) Deprivation 2234 (0.9%) Age 25 (0.009%)

Table 2: Regression coefficients and effect sizes for factors in the cox regression model comparing type 2 diabetes and non-diabetes subjects (adjusted for covariates).

Factor	Beta±SE	p	HR (95% CI)
Type 2 DM compared to non-diabetics			
Diabetes duration < 5 yrs	0.22±0.06	<0.01	1.24 (1.11,1.39)
Diabetes duration 5-10 yrs	0.36±0.06	<0.01	1.43 (1.27,1.62)
Diabetes duration >10 yrs	0.19±0.07	<0.01	1.21 (1.06,1.39)
Age (decades)	0.84±0.01	<0.01	2.31 (2.28,2.35)
Gender (Male)	0.18±0.02	<0.01	1.20 (1.15,1.25)
Deprivation compared to Q1			
Quintile 2	-0.12±0.03	<0.01	0.89 (0.83,0.95)
Quintile 3	0.20±0.03	<0.01	1.22 (1.15,1.30)
Quintile 4	0.31±0.03	<0.01	1.36 (1.29,1.45)
Quintile 5	0.31±0.03	<0.01	1.36 (1.29,1.45)
Smoker compared to non-smoker	0.58±0.02	<0.01	1.79 (1.71,1.87)
IHD compared to none	0.50±0.02	<0.01	1.65 (1.59,1.75)
Hypertensive compared to normotensive	0.21±0.02	<0.01	1.23 (1.18,1.28)
Diabetes group *Hypertension			
Diabetes duration <5 yrs and hypertension	-0.07±0.08	0.39	0.93 NS
Diabetes duration 5-10 yrs and hypertension	-0.13±0.08	0.10	0.88 NS
Diabetes duration >10 yrs and hypertension	-0.24±0.08	<0.01	0.79 (0.67,0.93)

*Final model Cox & Snell R of 0.10 (p< 0.01). * Missing cases 4.4% A Cox regression that omitted smoking was undertaken with far fewer missing cases (0.9%). This analysis showed no substantial changes for all the other covariates.*

Deprivation & Smoking

As deprivation was Health Board weighted, there were approximately 20% non-diabetes subjects in each deprivation quintile. For type 2 diabetes (regardless of duration) there was a clear pattern, increasing from 15.1% in the least deprived quintile to 23.5% in the most deprived (X^2 = 236.3, p < 0.001) (fig 1). Mortality increased with increasing deprivation and was consistently higher for type 2 diabetes in each quintile (Figure 1). The mortality differential between patients with type 2 diabetes and non-diabetes subjects remained similar and in line with the overall differential found earlier (Table 1). While both deprivation and type 2 diabetes were associated with increased mortality there was no evidence of an interaction effect.

Figure 1. Social deprivation in non-diabetes subjects compared with type 2 diabetes (SIMD quintiles).

Smoking prevalence at baseline was 22% for non-diabetes subjects. For type 2 diabetes prevalence decreased with duration falling from 26.8% for diabetes <5 yrs; 21.3% for diabetes 5-10 yrs to 17.7% for diabetes >10 yrs. Mortality rates were higher for smokers than non-smokers, but the differential was smaller among patients with type 2 diabetes. Among non-smokers mortality was around four times higher for patients with type 2 diabetes (depending on duration) while among smokers' mortality was only around three times higher for patients with type 2 diabetes. However once other factors were considered there was no evidence of an interaction between smoking and type 2 diabetes as confirmed by the survival analysis (table 2).

Hypertension and Ischaemic heart disease (IHD)

The prevalence of hypertension at baseline was 11.2% for non-diabetes. For type 2 diabetes, the prevalence of hypertension increased with duration rising from 37.4% for diabetes duration <5 yrs; 56.0% for diabetes duration 5-10 yrs to 63.0% for diabetes duration >10 yrs ($p<0.01$). Mortality rates were higher for hypertensive patients compared with normotensive patients, but the differential was smaller among type 2 diabetes patients. Among normotensive patients' mortality was around three to five times higher for type 2 diabetes patients (depending on duration). However, among hypertensive patients' mortality was similar for both non-diabetes and patients with type 2 diabetes (Table 1). Once other factors were taken into account there was still evidence of an interaction between hypertension and type 2 diabetes as confirmed by the survival analysis (Table 2). Therefore, the increase in mortality risk from a combination of type 2 diabetes and hypertension was not simply additive.

The prevalence of IHD at baseline was 3.9% for non-diabetes subjects. For type 2 diabetes the prevalence increased with duration rising from 15.4% for diabetes duration < 5 yrs; 21.7% for diabetes duration 5-10 yrs to 27.0% for diabetes duration >10 yrs ($p<0.01$). Mortality rates were higher for IHD than non IHD patients, but the differential was smaller among patients with type 2 diabetes. Among patients with no history of IHD, mortality risk was around three to four times higher for type 2 diabetes (depending on duration). Among IHD patients, however, mortality was similar for both non-diabetes subjects and type 2 diabetes patients (Table 1). Once other factors, particularly age, were considered there was no evidence of an interaction between IHD and type 2 diabetes as confirmed by the survival analysis (Table 2).

Survival analysis

The Cox regression model which compared patients with type 2 diabetes and non-diabetes subjects included 95.6% of cases. 12,003 (4.4%) of the whole cohort were excluded mostly due to lack of smoking data. There were 11,717 (4.3%) deaths among the included cases. Table 2 gives the significance (p) and effect size (HR) for the variables in the model. Only significant interactions are included.

When all other factors were considered, patients with type 2 diabetes had higher mortality risk than non-diabetes subjects. Mortality risk was highest for those with diabetes for between 5-10 years and lowest for those with diabetes >10 yrs. This, in part, probably reflects selection bias as there will have been mortalities in this group that occurred prior to the commencement of the study

Increasing age, deprivation and being male all increased mortality risk. Smoking, hypertension and IHD also increased the mortality risk compared with non-smokers, normotension and no history of IHD.

Apart from hypertension, there were no significant interaction effects with type 2 diabetes. Patients with type 2 diabetes and hypertension had a lower mortality risk than would be expected from the individual risk factors although this was only statistically significant for those with diabetes for over 10 years. This is in line with the evidence from table 1 that the increase in mortality risk from a combination of type 2 DM and hypertension is not additive.

Body Mass Index (matched sample)

In the smaller matched sample, 52.4% of non-diabetes subjects and 52.6% of type 2 diabetes had a BMI at $\geq$ 30kg/m^2 (p=0.70). The prevalence of BMI at $\geq$ 30kg/m^2 decreased with duration of diabetes falling from 56.6% for <5 yrs to 49.3% for >10 yrs (Table 3).

Table 3: Mortality by BMI in non-diabetic subjects and type 2 diabetes according to duration (matched file)

Type of patient	n	% with BMI ($\geq$30kg/m^2)	Mortality			
			Overall	BMI (<30kg/m^2)	Raised BMI ($\geq$30kg/m^2)	OR (95%CI) BMI $\geq$30kg/m^2 v <30kg/m^2
Non-diabetes	32907	52.4% (17238)	3.9% (1274)	4.8% (752)	3.0% (522)	0.62 (0.55,0.69) p<0.001
Diabetes duration < 5yrs	6150	56.6% (3481)	9.6% (593)	14.3% (382)	6.1% (211)	0.39 (0.32,0.46) p<0.001
Diabetes duration 5–10yrs	5324	50.9% (2712)	14.5% (772)	18.9% (494)	10.3% (278)	0.49 (0.42,0.57) p<0.001
Diabetes duration >10yrs	4990	49.3% (2462)	13.7% (685)	17.6% (444)	9.8% (241)	0.51 (0.43,0.60) p<0.001
Total	49371	52.4% (25893)	6.7% (3324)	8.8% (2072)	4.8% (1252)	0.53 (0.49,0.57) p<0.001

Mortality was significantly lower for those with BMI $\geq$ 30kg/m^2 for all groups (Table 3). However, those with BMI $\geq$ 30kg/m^2 were significantly younger than those with lower BMI in all type 2 diabetes groups (<5 yrs: 60.9±12.6 vs. 68.5±12.4; 5-10 yrs 64.5±11.6 vs. 71.8±11.8; >10 yrs: 67.9±10.5 vs. 74.1±10.8; all p <.001) and this will have exaggerated the difference in mortality rates.

A similar survival model was undertaken on the matched file with the addition of BMI as a covariate. The Hazard Ratio (HR) for BMI $\geq$ 30kg/m^2 was 0.77 (95% CI: 0.71,0.83) indicating that those with BMI $\geq$ 30kg/m^2 had a lower mortality risk once other covariates were considered. There was no significant interaction between diabetes and BMI and there were no substantive differences on any of the other covariates included in the previous model.

Glycaemic control and lipid levels (type 2 diabetes patients only)

As HbA_{1c} and lipids were not routinely measured in subjects without diabetes only patients with type 2 diabetes were analysed and the latest reading used. There was no significant difference in mean HbA_{1c} between those who survived and those who died when diabetes duration was less than 5 years. For subjects with a diabetes duration of over 5 years, those who survived had a significantly higher mean HbA_{1c} (Table 4).

7.5% (1249) had no defined lipids abnormality and were not on statin therapy. 73.9% (12293) were on statin therapy and prevalence increased by duration of diabetes (< 5 years 67.2%; 5-10 years 76.3%; >10 years 79.5%; $p < 0.01$). 18.6% (3101) had at least one defined lipid abnormality and were not on statin therapy; prevalence decreased by duration of diabetes (< 5 years 23.9%; 5-10 years 17.1%; >10 years 13.6%; $p < 0.01$).

9.3% (1538) had a total-cholesterol >5mmol/L but were not on statin therapy; 10.5% (1714) had a low HDL-cholesterol but were not on statin therapy and 12.9% (2095) had non-fasting triglycerides >1.7mmol/L but were not statin therapy. In all cases prevalence decreased by duration (total-cholesterol 12.9%; 8.2%; 5.9%: HDL-cholesterol 13.3%; 9.6%; 8.1%: non-fasting triglycerides 17.3%; 11.7%; 8.6%: all $p < 0.01$).

Table 4: Mortality in type 2 diabetes by lipids levels and complications (not adjusted for covariates).

	Duration of diabetes					
	< 5 yrs (n=6260)		5-10 yrs (n=5353)		> 10 yrs (n=5030)	
Mortality	10.1% (632)		14.7% (795)		13.9% (698)	
HbA_{1c} (Mean±SD)		Diff (95%CI)		Diff (95%CI)		Diff (95%CI)
Survived % (mmol/mol)	7.0±1.3 (52.7±14.3)	NS p=0.93	7.3±1.5 (56.2±16.4)	2.64 (1.39,3.89)	7.6±1.6 (60.0±17.5)	3.91 (2.51,5.33)
Deceased % (mmol/mol)	7.0±1.5 (52.6±16.8)		7.1±1.6 (53.6±17.3)		7.3±1.6 (56.1±17.7)	
On statin therapy		OR† (95% CI)		OR† (95% CI)		OR† (95% CI)
No	12.8% (263)	0.66 (0.55,0.76)	20.1% (255)	0.59 (0.50,0.70)	20.9% (215)	0.52 (0.44,0.62)
Yes	8.8% (369)		13.0% (530)		12.1% (483)	
Cholesterol						
<5mmol/l	12.1% (146)	1.11 NS p=0.43	18.1% (149)	1.43 (1.08,1.89)	19.4%% (141)	1.30 NS p=0.12
≥5mmol/l & not on statin therapy	13.3% (106)		24.0% (106)		23.8% (71)	
HDL-cholesterol						
Male ≥1 mmol/l; Female ≥1.3mmol/l	14.2% (127)	0.65 (0.49,0.86)	21.1% (130)	0.84 NS p=0.22	23.2% (130)	0.73 NS (P=0.06)
Male <1 mmol/l; Female <1.3mmol/l & not on statin therapy	9.7% (102)		18.3% (112)		18.1% (77)	
Non-fasting						

triglycerides						
<1.7mmol/l	11.7% (133)	1.02 NS p=0.90	18.9% (135)	1.11 NS p=0.49	16.7% (97)	1.75 (1.28,2.39)
≥1.7mmol/l & not on statin therapy	11.9% (96)		20.4% (103)		26.0% (104)	
Retinopathy						
No	11.4% (457)	0.66 (0.55,0.79)	18.7% (430)	0.57 (0.49,0.67)	17.4% (256)	0.68 (0.57,0.80)
Yes	7.8% (175)		11.6% (355)		12.4% (442)	
Neuropathy/ Foot Ulcer[1]						
No	10.0% (611)	1.92 (1.19,3.10)	13.9% (704)	2.27 (1.74,2.97)	13.3% (603)	1.48 (1.17,1.88)
Yes	17.5% (21)		26.9% (81)		18.6% (95)	

† comparing at risk with OK. *Missing values: triglycerides 361 (2.2%), HDL 387 (2.3%) cholesterol 75 (0.5%).*[1]Theprevalence of both neuropathy and foot ulcer were low (around 5%) and the overlap between the two conditions was small so the two conditions were merged to give more robust estimates.

Those on statin therapy had significantly lower mortality risk regardless of duration of diabetes. Those not on statin therapy and with a raised cholesterol and low HDL-cholesterol had higher mortality than those with normal levels. Probably due to the relatively small numbers, the difference was only significant for those with 5-10 years diabetes duration (total-cholesterol) and over 10 years duration (HDL-cholesterol). For non-fasting triglycerides, mortality was lower for those with levels > 1.7mmol/l but was only significant for those with diabetes duration of less than 5 years (Table 4).

Diabetes complications

The prevalence of retinopathy was 53.2% while the prevalence of neuropathy/foot ulcer was 5.6%. In both cases prevalence increased by duration of diabetes (retinopathy 36.0%; 57.0%; 70.7%: neuropathy/foot ulcer 1.9%; 5.6%; 10.2%: all $p < 0.01$). Mortality was significantly higher for those with neuropathy/foot ulcer regardless of duration of diabetes (table 4). Mortality was significantly lower for those with retinopathy regardless of duration of diabetes. This may be related to the use of statin therapy and hypertensive medication both of which were significantly higher for those with retinopathy [statin therapy: 78% vs. 69% (OR=1.55) and anti-hypertensive medication: 55% vs. 47% (OR 1.40)].

Survival analysis (type 2 diabetes only)

In the Cox regression model including only type 2 diabetes there were 15852 patients with 792 (4.8%) excluded mostly due to missing lipid level data. There were 1856 (11.2%) deaths among the included

cases. Table 5 gives the significance (p) and effect size (HR) for the variables in the final model. Only significant interactions are included.

As with the previous model, increasing age, being male, deprivation, smoking, and IHD all increased mortality risk. Duration of diabetes 5-10 yrs also increased mortality risk but not with the longer duration (>10 yrs). This may be related to selection bias discussed earlier. Hypertension now did significantly affect mortality risk although the effect size was small. This confirms the results in table 1 where there was a small increase in mortality for hypertensive type 2 diabetes patients compared with normotensive type 2 diabetes patients.

Being on statin therapy had a beneficial effect. Abnormal lipid levels whilst not on a statin significantly increased mortality risk for raised cholesterol and low HDL-cholesterol but not for triglycerides. Patients with foot ulcer/neuropathy had increased mortality risk but patients with retinopathy had reduced mortality risk (Table 5).

Table 5: Regression coefficients and effect sizes for factors in the cox regression model of type 2 diabetes (adjusted for covariates).

Factor	Beta±SE	p	HR (95% CI)
Type 2 diabetes compared to diabetes duration <5yrs			
Diabetes duration 5-10 yrs	0.16±0.07	0.03	1.17 (1.02,1.36)
Diabetes duration >10 yrs	-0.03±0.08	0.72	0.97 NS
Age (decades)	0.58±0.02	<.01	1.79 (1.71,1.88)
Gender (Male)	0.18±0.05	<.01	1.19 (1.08,1.31)
BMI $\geq$ 30k/m^2 and diabetes duration <5 yrs	-0.54±0.09	<.01	0.58 (0.48,0.70)
BMI $\geq$ 30k/m^2 and diabetes duration 5-10 yrs	-0.25±0.08	0.02	0.78 (0.66,0.91)
BMI $\geq$ 30k/m^2 and diabetes duration >10 yrs	-0.22±0.09	<.01	0.81 (0.68,0.95)
Deprivation compared to Q1			
Quintile 2	-0.21±0.09	0.02	0.81 (0.68,0.97)
Quintile 3	0.11±0.08	0.15	1.12 NS
Quintile 4	0.26±0.08	<.01	1.30 (1.12,1.51)
Quintile 5	0.21±0.08	<.01	1.23 (1.05,1.43)
Smoker compared to non-smoker	0.32±0.06	<.01	1.38(1.23,1.55)
Hypertensive compared to normotensive	0.16±0.05	<.01	1.17 (1.06,1.29)
IHD compared to none	0.65±0.05	<.01	1.92 (1.74,2.11)
HbA1c	0.02±0.02	0.22	1.02 NS
On statin therapy	-0.43±0.07	<.01	0.65 (0.56,0.76)
Raised cholesterol & not on statin therapy	0.56±0.09	<.01	1.74 (1.47,2.06)
Low HDL-cholesterol & not on statin therapy	0.39±0.09	<.01	1.48 (1.24,1.75)
Raised triglycerides & not on statin therapy	-0.40±0.09	<.01	0.67 (0.56,0.80)
Retinopathy	-0.36±0.05	<.01	0.70 (0.63,0.77)
Ulcer/Neuropathy	0.43±0.08	<.01	1.53 (1.31,1.79)

Final model Cox & Snell R of 0.12 (p< 0.01).

There were no significant interactions with duration of type 2 diabetes except for BMI at risk. Those with diabetes <5yrs and BMI >30kg/m2 had a lower mortality risk than those with diabetes duration of >5 yrs. This is in line with the results in table 3. Age corrected in this model had HR for BMI > 30Kg/m2 at 0.58 for type 2 diabetes <5yrs; at 0.78 for diabetes 5-10 yrs and 0.81 for diabetes >10yrs.

Patient and Public Involvement

There was no patient nor public involvement, but the anonimysed data analysis has been shared with Health Board in the hopes of informing policy.

Discussion

The present “real world” study confirmed that patients with type 2 diabetes still have an increased mortality risk [3,4,15]. This large observational study had an accurate data base and is much larger than previous studies. Although some of the findings are not new, they are consistent with previous work and the size of the study allows us to assess the importance of the different risk factors in terms of their importance in contributing to mortality risk. Increased mortality risk in type 2 diabetes was associated with being male while we previously demonstrated that the increased mortality risk in type 1 diabetes was associated with women [11]. Increased mortality was also associated with social deprivation, smoking, ischaemic heart disease and hypertension but not glycaemic control. Obesity and statin therapy appeared to be associated with reduced mortality risk. The present study showed that a male type 2 diabetes subject of 5-10 years duration who smoked, had hypertension and IHD plus lived in the most deprived area had a HR of 6.2 compared with a non-smoking, normotensive, non-diabetes subject without IHD living in the least deprived area.

The effect of duration on mortality risk in type 2 diabetes is complex. The HRs for type 2 diabetes with duration less than 5 years and for 5-10 years were increased but fell slightly with duration greater than 10 years. This probably reflects selection bias among those with longer diabetes duration. These patients with longer duration will have had diabetes for varying periods prior to the study and so there will have been mortalities in this group that occurred prior to the study. Hence mortality risk among this “healthier” group of patients’ will have underestimated the impact of duration and is an issue in any cross-sectional cohort study.

Social deprivation, measured by SIMD, has previously been shown to be associated with type 2 diabetes and poorer outcome [15,16]. SIMD provides an area-based measure of deprivation. This may not reflect all individuals within a SIMD data zone and may underestimate socioeconomic disparities. SIMD, however, is a relatively robust measure compared with previous indices used to measure social deprivation [13]. Although debate continues as to the explanations, social deprivation-related health inequalities are observed in many societies, populations and disease processes. The morbidity and mortality differences observed in a population with type 2 diabetes include material deprivation, childhood social development, social exclusion, occupational status and security, educational attainment, and housing environment [15,17]. There was no interaction seen between type 2 diabetes and social deprivation. This is consistent with the increased mortality risk being due to increased prevalence of type 2 diabetes in quintile 5 rather than the impact of social deprivation [15].

There are numerous studies demonstrating that good glycaemic control improves microvascular outcomes [4-7]. The relationship between good glycaemic control and improvement in cardiovascular outcome has

been more difficult to demonstrate in type 2 diabetes [4,7]. In our study, in people with type 2 diabetes of less than 5 years duration, there was no difference in mean HbA_{1c} between those who survived and those who died. For type 2 diabetes patients of more than five years duration, those who survived had a very small but significantly higher mean HbA_{1c}. This may reflect a selection bias. In addition, it may be that at this level of mean glycaemic control, differences in outcome will be difficult to demonstrate and that five years is too short a period to demonstrate improvement in outcome. In addition, those patients with diabetes-related or unrelated end stage disease may have had a lower HbA_{1c} which would have skewed the results.

The prevalence of obesity in the type 2 diabetes patients in this study was, as previously demonstrated, considerably greater than in the background population [16]. The presence of obesity appeared to protect against mortality risk in people with type 2 diabetes duration of less than five years. Thereafter the presence of obesity in type 2 diabetes increased the mortality risk but the HR but still appeared protective. Previously, this effect has been described as the “Obesity Paradox” and has been demonstrated in type 1 diabetes [11], patients with coronary heart disease undergoing percutaneous coronary intervention, patients with hypertension, coronary heart disease and chronic heart failure [18-20]. Numerous mechanisms have been suggested including greater medical interventions in obese patients, increased muscle mass, better nutritional status in the obese plus the failings of BMI as a marker of obesity [18-20]. Alternatively, pre-existing illness and smoking [21] may result in weight loss and higher mortality among lower BMI groups, making obesity appear protective. A recent study undertaken on UK primary care data, demonstrated a J-shaped relationship between BMI and all-cause mortality, and between BMI and a comprehensive range of cause-specific mortality outcomes [22].

Both hypertension and IHD were more prevalent in type 2 diabetes and became more prevalent with increased duration of diabetes. The mortality risk for hypertension and IHD was significantly higher for both normal and type diabetes subjects. When age was adjusted for in the survival model there was an interaction between hypertension and type 2 diabetes with little increase in mortality risk. This does not suggest that having hypertension is a positive factor for type 2 diabetes. It demonstrates that in type 2 diabetes, hypertension does not further increase your mortality risk significantly. It is likely that the mechanism(s) underlying hypertension and type 2 diabetes are similar [23,24]. In addition, hypertension may be better managed among type 2 patients with greater use of cardio-protective antihypertensive medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers [25]. Furthermore, it is likely that hypertensive type 2 patients are more likely to be taking statin therapy than their non-diabetes counterparts [24].

This study also confirmed that those type 2 patients on statin therapy had a significantly lower mortality risk [26,27]. Those patients not on statin therapy and with a raised total cholesterol or low HDL-cholesterol had a higher mortality risk than those with normal levels. For non-fasting triglycerides, mortality was lower for those with levels >1.7mmol/l. An inverse association or lack of any association between triglycerides levels and outcome has been reported before [28]. Low triglyceride levels may result from malnourishment

and weight loss related to chronic illness and the explanation may also be tied into the “Obesity Paradox” already discussed.

The high level of statin therapy and treatment of hypertension probably reflects the QOF-driven [29] general improvement in diabetes care in Scotland and the UK. In addition, the management of type 2 diabetes is guideline-driven [30] and as a result management is very similar Scotland and UK-wide. Therefore, we believe that our results are generalisable nationally.

Conclusion

This study confirmed that the all-cause mortality risk in people with type 2 diabetes remains elevated. In excess of 98% of our subjects were Caucasian so this work is required in other ethnic groups. Further work is required to understand the interaction between hypertension and type 2 diabetes, why some patients of longer duration appear to be “protected”, the role of the “Obesity Paradox” and why raised non-fasting triglycerides appears to reduce mortality risk.

Abbreviations

HR Hazard Ratio

IHD Ischaemic Heart Disease

BMI Body Mass Index

HDL-cholesterol High-density lipoprotein

SIMD Scottish Index of Multiple Deprivation

SPSS Statistical Package for the Social Sciences

s.d. Standard Deviation

UK United Kingdom

Declarations

- Ethics approval and consent to participate: Ethical opinion was not required for this study. The audit was registered with the Clinical Governance Department, NHS Ayrshire and Arran, UK and Caldicott Guardian approval was obtained from each General Practice.
- Consent for publication: All data were anonimysed.
- Availability of data and materials: We are willing for all data to be made available.
- Competing interests: There were no competing interests.

- Funding: The data collection and statistical analysis was supported by an Educational Grant from Astra Zeneca.
- Authors' contributions: AC, MH and LC set up the study. AC, SG and NW undertook the literature search. LC collected the data while MH undertook the statistical analysis. All the authors, AC, MH, LC, SG, JB, MW and NW were involved in the writing of the paper.
- Acknowledgements: N/A
- Authors' information: N/A

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Figures

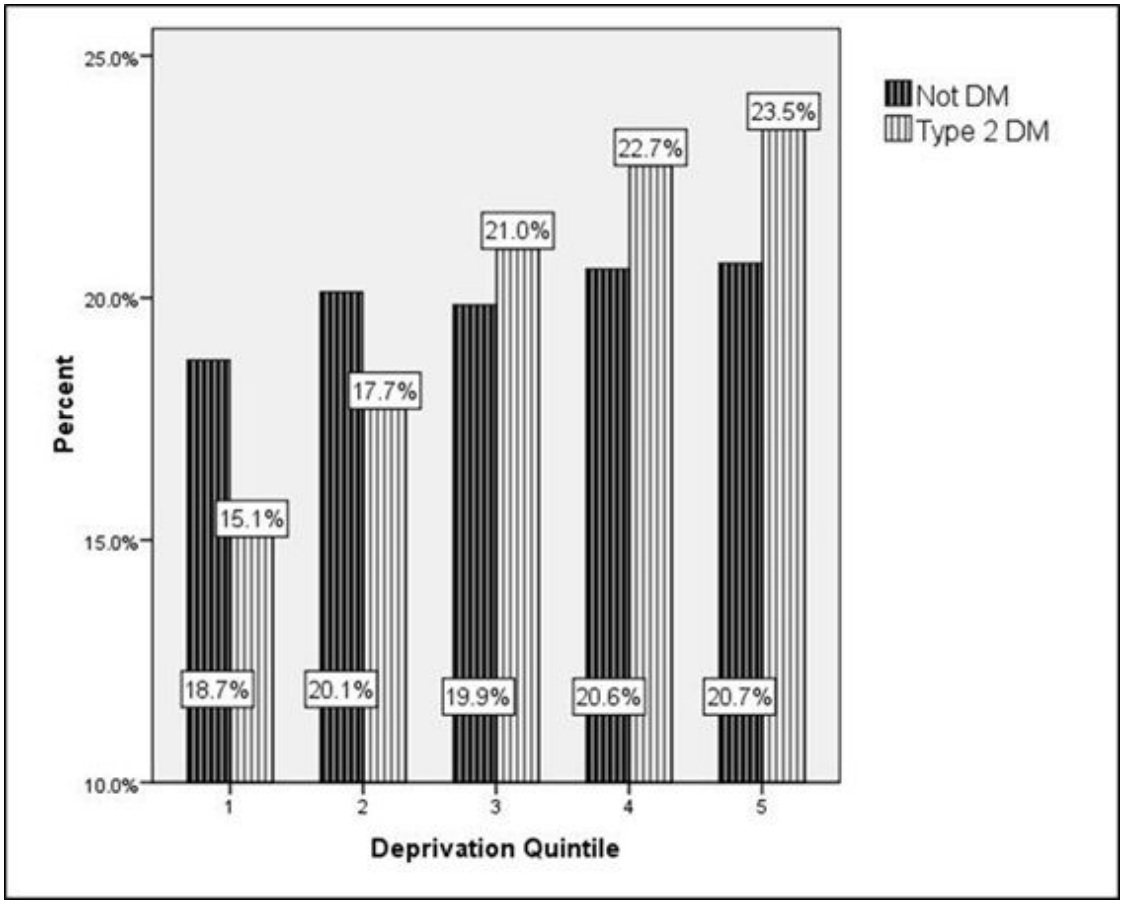

Figure 1

Social deprivation in non-diabetes subjects compared with type 2 diabetes (SIMD quintiles).