

THE PRESENCE AND SEVERITY OF CHRONIC KIDNEY DISEASE PREDICTS ALL-CAUSE MORTALITY IN TYPE 1 DIABETES

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Objectives: This study aims to identify clinical features associated with premature mortality in a large contemporary cohort of adults with type 1 diabetes.

Research Design and Methods: The Finn Diane study is a national multi-centre, prospective, follow-up study of 4,201 adults with type 1 diabetes, from 21 university and central hospitals, 33 district hospitals, and 26 primary health care centres across Finland.

Results – During a median 7 years of follow-up, there were 291 deaths (7%), 3.6-fold (95% CI, 3.2 - 4.0) more than observed in the age-gender matched general population. Excess mortality was only observed in individuals with chronic kidney disease. Individuals with normoalbuminuria showed no excess mortality beyond the general population (SMR 0.8, 95% CI 0.5 -1.1), independent to the duration of diabetes. The presence of microalbuminuria, macroalbuminuria and end-stage kidney disease was associated with an increased standardised mortality ratio (SMR) of 2.8, 9.2 and 18.3 times respectively. The increase in mortality across each stage of albuminuria was equivalent to the risk conferred by pre-existing macrovascular disease. In addition, the glomerular filtration rate was independently associated with mortality, such that individuals with impaired kidney function, as well as those demonstrating hyperfiltration, had an increased risk of death.

Conclusions: An independent, graded association was observed between the presence and severity of kidney disease and mortality in a large, contemporary cohort of individuals with type 1 diabetes. These findings highlight the clinical and public health importance of CKD and its prevention in the management of type 1 diabetes.

Despite modern therapeutics, type 1 diabetes continues to be associated with premature death. For example, mortality in individuals with type 1 diabetes from Finland is 3-4 times higher than in the general population(1). However, not all individuals with type 1 diabetes share this risk. In order to determine the current prognosis of any individual with type 1 diabetes and direct preventive interventions, it is important to identify those individuals at increased risk of death.

Chronic kidney disease (CKD) is a common complication of type 1 diabetes, affecting up to 30% of patients(2). Previous studies have identified CKD as a risk factor for mortality in type 1 diabetes(3-6). However, many of these observations were made when current management paradigms, including intensified metabolic control and blockade of the renin angiotensin system, were not widely applied. In this paper, we examine the incidence and predictors of all-cause mortality in a nationally representative cohort of adults with type 1 diabetes, showing that the presence and severity of CKD remains the major determinant of excess mortality associated with type 1 diabetes.

METHODS

Study sample: The Finnish Diabetic Nephropathy (FinnDiane) study is an ongoing nationwide prospective multi-center study, established to identify risk factors for type 1 diabetes and its complications. The FinnDiane registry has been described in detail in previous publications(7; 8). In brief, between January 1997 and April 2006, 4201 adults with type 1 diabetes were recruited from 21 university and central hospitals, 33 district hospitals, and 26 primary health care centres across Finland. The mean response rate was 78%. Type 1 diabetes was defined by insulin dependence within 1-year of diagnosis, the absence of circulating C-peptide (<0.3

nmol/L) and an age of onset <35 years. Every participant gave written informed consent. The study was approved by ethics committees of participating centres and conducted in accordance with the Declaration of Helsinki.

Characteristics of the subjects: Data on smoking habits, alcohol intake, educational level and social class were obtained using a patient questionnaire. Details on clinical status, including age at diagnosis, insulin therapy and other regular medications, together with presence, severity and management of diabetic complications including retinopathy and macrovascular disease, were obtained from medical records by the attending physician using a standardised questionnaire. The presence of proliferative retinopathy was arbitrarily defined by the previous use of laser treatment. The presence of pre-existing macrovascular disease was defined in individuals with a clinical history of myocardial infarction, unstable angina requiring hospitalisation, coronary revascularisation, stroke, carotid surgery, peripheral revascularisation and amputation for critical limb ischaemia.

Fasting blood samples were obtained for the measurement of HbA_{1c}, lipids and creatinine. The glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation(9). Baseline urinary albumin excretion (UAE) was stratified according to IDF guidelines(10), such that microalbuminuria was defined by a UAE of 20–200 µg/min, macroalbuminuria by a UAE >200 µg/min, and normoalbuminuria by a UAE <20 µg/min in two out of three consecutive urine collections. The presence of CKD was defined, according to Dialysis Outcomes Quality Initiative (DOQI) guidelines, by the presence of either microalbuminuria, macroalbuminuria, an

estimated GFR < 60 ml/min/1.73m² or ESKD(9).

Blood pressure measurements were performed twice in the sitting position, with a five-minute interval between testing. Hypertension was defined by antihypertensive medication use or a blood pressure greater than target levels of 130/85 mmHg over two readings in an untreated individual.

Ascertainment of outcomes: The primary outcome was death from any cause through to the 1st of April, 2007. Deaths were identified via a search of the Finnish National Death Registry, and centre databases. All deaths were confirmed with death certificate data. Expected mortality was estimated from general population life tables (Tilastokeskus, Helsinki, Finland) using person-year methods. Age and gender-adjusted standardised mortality ratios (SMRs) were estimated by dividing the observed number of deaths by the expected number of deaths, in each age and gender category.

Statistical analysis: To evaluate the independent predictors of mortality in individuals with type 1 diabetes, we used Cox proportional-hazards models in both the total cohort and selected subgroups. All variables known to be associated with mortality were included in the final models, along with any variables associated with mortality in univariate analyses with a P value of less than 0.01. In each case, model selection from candidate variables was accomplished by minimization of the Akaike and Bayesian information criteria(11). Baseline urinary albumin excretion was entered as a categorical variable (normoalbuminuria, microalbuminuria, macroalbuminuria). The potential for multiple colinearity was tested using the variance inflation factor and condition number, where VIF <10 and CN <30 are desirable (12). Covariate functional form (including assessment of non-linear effect) was adjudged by residual-by-time analysis; fractional polynomials(13) and

(cubic) regression splines(14). Overall, Cox model fit was assessed by (i) approximation of cumulative Cox–Snell residuals to (-log) Kaplan–Meier estimates, residual plots and specific testing of the proportional hazards assumption(15) and (ii) Harrell’s C statistic(16) and “added-variable” goodness-of-fit tests(17). Cox model performance was adjudged by the explained variation using 5000 bootstrap repetitions of the whole data set, adjusting for covariates(18). Analyses were conducted with the use of Stata™ statistical software (version 10.0, 2007; StataCorp, College Station, TX) and SPSS software (version 13.0, SPSS, Chicago, IL).

RESULTS

Cohort characteristics: FinnDiane recruited 4201 adults with type 1 diabetes, equivalent to 16% of patients with type 1 diabetes in Finland (**table 1**). At baseline, 504 individuals (12%) had UAE in the microalbuminuric range, 578 individuals (14%) had a UAE in the macroalbuminuric range and 293 individuals (7%) were receiving renal replacement therapy (RRT), including 72 individuals on dialysis and 221 individuals with a functioning kidney transplant. 2296 individuals (55%) had a UAE in the normoalbuminuric range. A further 13% of study participants were unclassified (n=530) because of an inadequate number of urine collections (<3). The clinical characteristics of these individuals were intermediate between those with normoalbuminuria and microalbuminuria (*data not shown*). In individuals not receiving RRT, 14% (N=462) had an estimated GFR < 60 ml/min/1.73m². The characteristics of these patients are shown in **table 2**. When the number of individuals with an estimated GFR < 60 ml/min/1.73m² were added to micro- or macroalbuminuria and those receiving RRT, 33% of study participants had CKD. In addition, over half (57%) had established retinopathy, 63% of whom had received laser

therapy for proliferative changes. Ten percent of the cohort had established macrovascular disease.

Overall mortality in individuals with type 1 diabetes: Median follow-up was 7 years, totalling 26,863 patient-years of surveillance, during which time there were 291 deaths (7%, 1.1 per hundred person-years). This mortality rate was 3.6 times higher (95% CI 3.2 to 4.0) than in the age-gender-matched general population. Excess mortality associated with type 1 diabetes was more pronounced among women (adjusted SMR 4.8 (95% CI 4.0-5.8) than among men (adjusted SMR 3.0 (95% CI 2.6-3.5), gender difference $p < 0.001$), eliminating the gender difference in mortality as previously described (19). The distribution of the listed primary cause of death is shown in **table 3**.

Chronic kidney disease and mortality in type 1 diabetes: The presence and severity of CKD was the major predictor of all-cause mortality in the FinnDiane cohort (figure 1a, 1b & 2, and the supplemental table available in the online appendix at <http://diabetes.diabetesjournals.org>).

Indeed, excess mortality, beyond that observed in the age-gender-matched general population, was only demonstrated in individuals with CKD (**figure 2**). Mortality in the FinnDiane participants without CKD (66% of the total cohort) was not significantly different to that observed in the general population (adjusted SMR 0.8, 95% CI 0.5 to 1.1), regardless of the duration of their diabetes.

The impact of each stage of diabetic kidney disease on mortality across the total cohort was equivalent to the presence of pre-existing macrovascular disease (adjusted hazard ratio 2.5, 95% CI 1.7 to 3.7). In addition, the survival in individuals with both macrovascular disease and CKD was significantly reduced compared to individuals with either condition alone, and not significantly different from that observed in

individuals receiving renal replacement therapy. While dyslipidemia, insulin sensitivity and hypertension were strongly linked to CKD in this cohort (**table 1**), the association between CKD and mortality was independent with respect to the achieved control, the use and intensity of therapies, including statins and blockade of the RAS, although such associations may be confounded by indication.

The estimated GFR was also associated with all-cause mortality ($p < 0.001$), independent of the level of UAE, macrovascular disease and other baseline factors. The relationship between estimated GFR and mortality exhibited non-linearity and was characterised using a regression spline (**figure 3a**). Mortality was increased in individuals with an estimated GFR < 60 ml/min/1.73m² (adjusted hazard ratio 1.7, 95% CI 1.1 to 2.6, **figure 1b**). In addition, individuals with an estimated GFR > 120 mL/min/1.73m² also displayed increased mortality, independent of the presence or severity of albuminuria (**figure 1b**).

A history of proliferative retinal disease (defined by the previous requirement for laser therapy) was also associated with increased mortality in the FinnDiane cohort (**figure 1c**). However, this association was eliminated after adjusting for baseline albuminuria. Since proliferative retinopathy and markers of diabetic kidney disease are strongly associated in this cohort (**table 1**), and indeed may be considered manifestations of the same microangiopathy, it may not be appropriate both from either physiological or a statistical point of view to include retinopathy and CKD in the same multiple regression analyses. In the absence of proliferative changes, background retinopathy was not associated with mortality in this cohort (**figure 1c**).

Mortality individuals with ESKD and in type 1 diabetes: Forty-six percent of all individuals with ESKD died during the

follow-up period (n=135/293). This mortality was 18.3 times that observed in the general population (95% CI 15.8 to 22.1). Mortality was highest in individuals on dialysis (68%) compared to those with a functioning kidney transplant (39%, $p < 0.001$). The independent predictors of mortality in individuals on dialysis (n=49/72) were the years on dialysis (adjusted hazard ratio, per year, 1.4, 95% CI 1.2 to 1.7) and the pulse pressure (per 10 mmHg, adjusted hazard ratio 1.3, 95% CI 1.0 to 1.5). Glycaemic control in individuals on dialysis was not associated with all-cause mortality. In individuals with a functioning renal transplant (n=86/221), the duration of diabetes (decades, adjusted hazard ratio 2.6, 95% CI 1.8 to 3.7) and the HbA_{1c} (adjusted hazard ratio 1.3, 95% CI 1.1 to 1.5) were predictors of all-cause mortality. In addition, individuals with impaired graft function characterised by an estimated GFR < 60 ml/min/1.73m² were over twice as likely to have died during follow-up than those with preserved graft function (adjusted hazard ratio 2.4, 95% CI 1.3 to 4.1).

Mortality in individuals with macroalbuminuria: In individuals with macroalbuminuria, 15% (n=89/578) died during the follow-up period. This mortality rate was over nine times that observed in the age-gender matched general population (adjusted SMR 9.2, 95% CI 8.1 to 10.5). The major independent predictors of all-cause mortality in individuals with macroalbuminuria were duration of diabetes (decades; adjusted HR 1.6; 95% CI, 1.2 to 2.1) and the presence of pre-existing macrovascular disease (adjusted HR 2.1, 95% CI, 1.2 to 3.4) and HbA_{1c} (adjusted HR 1.3; 95% CI, 1.2 to 1.5). In addition, individuals with macroalbuminuria and an estimated GFR < 60 ml/min/1.73m², were twice as likely to have died during follow-up as those with preserved kidney function (adjusted HR 2.0; 95% CI, 1.1 to 3.4), independent of other baseline risk factors and the use of preventive

therapies (**figure 3b**). The presence of a reduced estimated GFR was equivalent (in terms of mortality risk) to that of pre-existing macrovascular disease.

Mortality in individuals with microalbuminuria: In individuals with microalbuminuria, 5.2% (n=26/504) died during follow-up. This mortality rate was over twice that observed in the general population (adjusted SMR 2.8, 95% CI 2.0 to 4.2). The major independent predictors of all-cause mortality in microalbuminuria were the duration of diabetes (decades; adjusted HR 2.0; 95% CI, 1.3 to 3.0) and the presence of pre-existing macrovascular disease (adjusted HR 6.0, 95% CI, 2.4 to 14.5). All-cause mortality was not significantly associated with treatments, the achieved level of BP or lipid levels. The estimated GFR was also independently associated with mortality risk ($p < 0.01$). This relationship was non-linear and was characterised using a regression spline (**figure 3c**). Individuals with microalbuminuria and estimated GFR < 60 ml/min/1.73m² (8%) were more likely to have died during follow-up than those with preserved kidney function (unadjusted mortality 18% vs. 4%, $p < 0.01$). Equally, individuals with microalbuminuria and an estimated GFR >120ml/min/1.73m² had increased mortality compared to those with normal renal function (unadjusted mortality 7% vs. 3%, $p < 0.01$).

Mortality in individuals with normoalbuminuria: In individuals with normoalbuminuria, only 1.3% (n=30/2296) died during follow-up. This rate was not significantly different from the general population (adjusted SMR 0.8, 95% CI 0.5 to 1.1) and was independent to the duration of diabetes. The major independent predictors of mortality in individuals with normoalbuminuria were age (decades; adjusted HR 1.7; 95% CI, 1.2 to 2.4) and the presence of pre-existing macrovascular disease (adjusted HR 6.7, 95% CI, 2.5 to

17.6). Again, mortality in these individuals was not associated with the lipid levels or BP control. However, the estimated GFR was independently associated with mortality ($p < 0.001$). The relationship between estimated GFR and the hazard ratio for mortality in individuals with normoalbuminuria again exhibited non-linearity (**figure 3d**). Although less than 3% of individuals with normoalbuminuria had an estimated GFR $< 60 \text{ ml/min/1.73m}^2$, significantly more of these individuals died during follow-up than those with normal kidney function (unadjusted mortality 5% vs. 1%, $p < 0.01$). In addition, individuals with an estimated GFR $> 120 \text{ mL/min/1.73m}^2$ also displayed increased mortality compared to those with normal renal function (unadjusted mortality 3% vs. 1%, $p < 0.01$).

Mortality and glycaemic control in type 1 diabetes: Glycaemic control is an important target for the management of individuals with type diabetes. In FinnDiane participants not receiving RRT, glycaemic control, as estimated by the HbA_{1c}, was independently and continuously associated with all-cause mortality (adjusted HR 1.3, 95% CI, 1.2 to 1.4). However, the relationship between HbA_{1c} and the hazard for mortality exhibited some non-linearity and was modelled as a multivariate cubic spline (**figure 4**). Notably, there was no difference in the relationship between HbA_{1c} and mortality risk across different subgroups of albuminuria (interaction $p > 0.34$).

Insulin resistance has also been associated with CVD in individuals with type 1 diabetes(20), although this relationship is confounded by the strong association between the insulin sensitivity and CKD in type 1 diabetes(7). In the FinnDiane cohort, insulin sensitivity, as measured by the estimated glucose disposal rate(20) was inversely associated with all cause mortality ($p < 0.001$), independent of age, duration of diabetes and glycaemic control. However, this association

was eliminated after adjusting for the presence and severity of CKD ($p = 0.9$).

DISCUSSION

In a large sample of adults with type 1 diabetes from Finland, an independent, graded association was observed between the presence and severity of CKD and all-cause mortality. In this population, excess mortality associated with type 1 diabetes was only observed in individuals with CKD (**figure 2**), while mortality in participants without CKD (66% of the total cohort) was identical to the general population. These results from a stable, nationally-representative cohort of adults with type 1 diabetes complement and extend evidence from the last two decades showing the link between mortality and CKD(3-6). These findings highlight the continuing clinical and public health importance of CKD and its prevention in the management of type 1 diabetes.

Our findings in individuals with type 1 diabetes are analogous to the relation between CKD and mortality previously described in persons with type 2 diabetes(21), and in non-diabetic individuals(22). The observed association between CKD and mortality can be explained by several plausible mechanisms. It has been suggested that kidney damage in individuals with type 1 diabetes reflects more generalised damage to the cardiovascular system leading to cardiovascular disease and subsequently mortality(23). The association of mortality with proliferative retinopathy (**figure 1c**) may be explained in the same way. However, impaired kidney function may also directly contribute to hypertension(24), oxidative stress, insulin resistance(7), inflammation(8), dyslipidemia(25), elevated plasma homocysteine(26), the accumulation of advanced glycation end products (AGEs)(27), anemia(28), left ventricular hypertrophy(29), arterial calcification(30) and endothelial dysfunction(31). CKD is also associated with

impaired immune function, which alongside vascular compromise probably contributed to increased frequency of death from infection observed in those with CKD.

The observed hazards associated with each stage of kidney disease are similar to those reported in cohort studies over twenty years ago(3-6), although the absolute mortality in the FinnDiane cohort is significantly lower. While it is possible to argue that improvements in diabetic management have not led to changes in the relative risk of mortality in individuals with CKD, there is little doubt that the absolute risk reduction has been considerable over this time period, *via* the prevention of CKD(2), and the management of individuals with proteinuria(32) and/or macrovascular disease, who carry the majority of the risk burden. However, the contemporary hazard associated with CKD demonstrated in this study emphasises that more remains to be done to address this enhanced risk beyond currently available regimens.

This study also demonstrates that estimated GFR is an independent risk factor for mortality in type 1 diabetes. Regardless of the level of albuminuria, those with an estimated GFR < 60mL/min/1.73m² were twice as likely to have died during follow-up. In addition, an elevated estimated GFR was also associated with increased mortality (**figure 1b**) that was identified by non-linear analysis (**figure 3**). While it should be noted that the MDRD equation overestimates renal function in this range and the ability of this formula to discriminate hyperfiltration from normal function is suboptimal(33), particularly as a single measurement, it was nonetheless able to stratify mortality risk. In so far as hyperfiltration precedes progressive kidney disease(34; 35), this association is not surprising, and probably reflects early pathological changes both in the kidney and in other parts of the vasculature.

While hyperglycemia has been implicated in the development of microvascular complications in type 1 diabetes, an association between glycaemic control and mortality has only been observed in some(36), but not all studies(20; 37). In the FinnDiane cohort, glycaemic control was also independently associated with all-cause mortality (**figure 4**). A significant association between HbA_{1c} and mortality was also present in individuals with a kidney transplant, consistent with previous reports(38). However, when modelled as a linear variable, no clear association was observed between HbA_{1c} and mortality in individuals with normo- or microalbuminuria ($p \geq 0.38$). It is possible that this reflects a type II error due to the lower number of deaths in these subgroups. However, when modelled as a multivariate cubic spline (**figure 4**), there was no interaction between HbA_{1c} and albuminuria ($p > 0.34$) in determining mortality, suggesting the impact of poor glycaemic control is homogeneous across all levels of albuminuria.

Strengths of our study include its large cohort of individuals with type 1 diabetes, high participation rate, access to subsidised care (75-100% of costs) and contemporary treatment regimens, including a range of insulin regimens, statins, blockers of the RAS, and self-monitoring technologies. Our methods of measuring urinary albumin excretion and serum creatinine were reliable, validated centrally using standardised methodologies. We used validated methods to identify deaths and all deaths in our cohort were confirmed through death records. Surveillance bias is unlikely given the uniform vital status follow-up procedures used by our staff masked to participants' CKD status levels. In our questionnaire, we had broad data on tobacco or alcohol use, diet, education, socioeconomic status, other possible confounders (e.g. insulin resistance), or the severity of disease (e.g. level of blood

pressure). Finally, few changes in diabetes treatment and health care over the short study period will have affected mortality results.

Several study limitations need to be considered. First, our study results may not be generalizable because of selection bias in enrolment and subsequently in ascertainment. Our study was conducted among adults with longstanding diabetes. Consequently our results may reflect past management practices that are less generalizable to adults with newly diagnosed diabetes. These studies were also limited by the use of broad definitions of diminished kidney function and the inclusion of relatively small numbers of persons with renal impairment, thus reducing the statistical power to examine different levels of reduced estimated GFR. It is also likely that our clinical history was not sufficiently sensitive to accurately discriminate between the presence or absence of macrovascular disease in this population, given that diabetes is often associated with silent ischaemia and subjects with type 1 diabetes can often have a normal resting electrocardiogram and still have suffered a previous myocardial infarction or have significant coronary lesions(39). Such standardised exercise testing and/or coronary imaging was not feasible in a large study such as FinnDiane. Consequently, the true contribution of underlying macrovascular disease to the observed changes in mortality cannot be ascertained in this study. Nonetheless, a reliance on clinical history is potentially more representative of the true clinical setting. Changes in medications and risk factor control during follow up cannot be controlled for. Finally, it is possible that our results were biased by residual confounding by factors not measured in the study but potentially related to cardiovascular disease/mortality in type 1 diabetes, including silent CVD, lipoprotein subclasses(40), oxidative stress(41), endothelial(31) and autonomic dysfunction(42).

In conclusion, results from our study clearly demonstrate that CKD is the dominant contributor to excess mortality in type 1 diabetes. Consequently, if you have type 1 diabetes, prevention of CKD is currently the best way to reduce your risk of a premature death. Modern multifactorial therapeutic approaches, such as those detailed in ADA guidelines, are effective in preventing the development of kidney disease. For those with established CKD, more intensive multifactorial interventions are also valuable in reducing the progression of CKD, and with it, mortality.

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FIGURE LEGENDS

Figure 1. Survival plots showing Cox-adjusted survival of individuals with type 1 diabetes from the FinnDiane study, stratified for the presence and severity of albuminuria (A), eGFR (B), and the presence and severity of retinopathy (C) at baseline. All figures are adjusted for age, gender, duration of diabetes, body habitus, the presence and extent of macro- and microvascular complications, glycemic, lipid and BP control, and drug management. The latter figure (C) is not adjusted for the presence and severity of nephropathy, as discussed in the text.

Figure 2. Risk of mortality in individuals with type 1 diabetes from the FinnDiane study associated each level of albuminuria and ESKD. Adjusted hazard ratios (shaded bars) with 95% confidence intervals are standardised against individuals with urinary albumin excretion in the normoalbuminuric range (arbitrary value of 1.0). Adjusted SMRs (white bars) with 95% confidence intervals are provided standardised against the age-gender matched Finnish general population (arbitrary value of 1.0).

Figure 3. Relationship of estimated GFR to the hazard ratio for mortality in individuals with type 1 diabetes without ESKD from the total FinnDiane cohort (A), and in individuals with macroalbuminuria (B), microalbuminuria (C) and normoalbuminuria (D). Dotted line shows point estimate for cubic regression spline adjusted for other predictive variables. Grey area denotes 95% confidence interval.

Figure 4. Relationship of HbA_{1c} to the hazard ratio for mortality in individuals with type 1 diabetes without ESKD. Dotted line shows point estimate for the cubic regression spline adjusted for other predictive variables. Grey area denotes its 95% confidence interval.

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Table 1. Baseline characteristics of FinnDiane study participants, stratified according to UAE*

Characteristic^a	Normoalbuminuria (N=2296)	Microalbuminuria (N=504)	Macroalbuminuria (N=578)	ESKD (N=293)
Age – yr	36 ± 12	38 ± 12*	41 ± 10*	44 ± 8*
Male Gender – no. (%)	1088 (47)	296 (59) [#]	338 (58) [#]	178 (61) [#]
Duration of diabetes – yr	20 ± 12	26 ± 11*	29 ± 8*	32 ± 8*
Insulin dose - IU/kg	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.2	0.8 ± 0.4
Insulin injections/day	4.8 ± 1.0	4.8 ± 1.0	4.5 ± 1.0*	4.2 ± 1.0*
HbA _{1c} - %	8.2 ± 1.4	8.8 ± 1.5*	9.0 ± 1.5*	8.6 ± 1.6
Estimated glucose disposal rate - mg/kg/min ^b	7.3 ± 2.2	5.1 ± 2.0*	4.0 ± 1.6*	4.0 ± 1.6*
Hypertension – no. (%)	1344 (59)	444 (88)	557(96)	288 (97)
Systolic Blood pressure – mmHg	129 ± 15	136 ± 16*	145 ± 20*	153 ± 25*
Diastolic Blood pressure – mmHg	78 ± 9	80 ± 10*	83 ± 10*	86 ± 13*
Medication use – no (%)				
ACE inhibition	204 (9)	271 (54) [#]	425 (75) [#]	61 (21)
Angiotensin receptor blocker	44 (2)	42 (8) [#]	75 (13) [#]	31 (5) [#]
Calcium channel blocker	60 (3)	40 (8) [#]	208(36) [#]	163 (56) [#]
Beta-blocker	90 (4)	46 (9) [#]	190 (33) [#]	188 (64) [#]
Other antihypertensive agents	64 (3)	48 (10) [#]	282 (49) [#]	170 (58) [#]
Lipid lowering therapy	135 (6)	49 (10) [#]	137(23) [#]	76 (26) [#]
Total cholesterol - mmol/L	4.8 ± 0.9	5.0 ± 0.9	5.4 ± 1.1	5.5 ± 1.2
Low density lipoprotein cholesterol - mmol/L	3.0 ± 0.8	3.1 ± 0.8	3.5 ± 0.9	3.5 ± 1.1*
High density lipoprotein cholesterol - mmol/L	1.1 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4
Triglycerides - mmol/L	1.1 ± 0.7	1.3 ± 0.9	1.7 ± 1.2	1.7 ± 0.9*
Any retinopathy – no. (%)	889 (39)	382 (76) [#]	547 (95) [#]	290 (99) [#]
Retinopathy requiring laser therapy – no. (%)	340 (15)	241 (48) [#]	460 (80) [#]	288 (97) [#]
Current smoker – no. (%)	491(21)	153 (30)	164 (29)	49 (16)
Established macrovascular disease – no. (%)	88 (4)	37 (7) [#]	105 (18) [#]	138 (47) [#]
eGFR < 60ml/min/1.73m ² – no. (%)	73 (3)	45 (9) [#]	354 (61) [#]	N/A

^a plus minus values are means ± SD, unless otherwise stated. To convert values for cholesterol to milligrams per decilitre, divide by 0.2586.

^b a measure of insulin sensitivity using the formula proposed by Williams *et al* (43).

* p value versus patients with normoalbuminuria < 0.05, calculated by t-test

[#] p value versus patients with normoalbuminuria < 0.05, calculated by Chi squared

Table 2. Baseline characteristics of FinnDiane study participants stratified according to eGFR.*

Characteristic ^a	>120 (n=272)	60-120 (n=2699)	<60 (n=462)	ESKD (N=293)
Age – yr	28 ± 10*	37 ± 12	44 ± 10*	44 ± 8*
Male Gender – no. (%)	194 (71) [#]	1320 (49)	214 (46)	178 (61) [#]
Duration of diabetes – yr	17 ± 11	20 ± 12	30 ± 9*	32 ± 8*
Insulin dose - IU/kg	0.8 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.8 ± 0.4
Insulin injections/day	4.9 ± 1.0	4.8 ± 1.0	4.5 ± 1.0*	4.2 ± 1.0*
HbA _{1c} - %	8.6 ± 1.6	8.4 ± 1.5	8.8 ± 1.5*	8.6 ± 1.6
Estimated glucose disposal rate - mg/kg/min ^b	7.9 ± 2.0	7.3 ± 2.2	4.6 ± 2.0*	4.0 ± 1.6*
Hypertension – no. (%)	176 (65)	1888 (70)	444 (96) [#]	288 (97) [#]
Systolic Blood pressure – mmHg	128 ± 14	132 ± 16	145 ± 20*	153 ± 25*
Diastolic Blood pressure – mmHg	78 ± 9	79 ± 9	81 ± 10*	86 ± 13*
Medication use – no (%)				
ACE inhibition	30 (11) [#]	611 (23)	294 (64) [#]	61 (21)
Angiotensin receptor blocker	3(1) [#]	118 (4)	55 (12) [#]	31 (5) [#]
Calcium channel blocker	2(1) [#]	134 (5)	177 (39) [#]	163 (56) [#]
Beta-blocker	1(0) [#]	150 (6)	185 (40) [#]	188 (64) [#]
Other antihypertensive agents	1(0) [#]	154 (6)	219 (47) [#]	170 (58) [#]
Lipid lowering therapy	11(4) [#]	206 (8)	123 (27) [#]	76 (26) [#]
Total cholesterol - mmol/L	4.9 ± 0.9	4.9 ± 0.9	5.3 ± 1.0*	5.5 ± 1.2*
Low density lipoprotein cholesterol - mmol/L	3.0 ± 0.8	3.0 ± 0.8	3.5 ± 1.0*	3.5 ± 1.1*
High density lipoprotein cholesterol - mmol/L	1.4 ± 0.4*	1.1 ± 0.4	1.3 ± 0.4*	1.3 ± 0.4*
Triglycerides - mmol/L	1.2 ± 0.7	1.2 ± 0.8	1.7 ± 1.2*	1.7 ± 0.9*
Any retinopathy – no. (%)	76 (29) [#]	1313 (50)	420 (93) [#]	290 (99) [#]
Retinopathy requiring laser therapy – no. (%)	27(10) [#]	683 (25)	360 (78) [#]	288 (97) [#]
Current smoker – no. (%)	98 (37) [#]	614 (24)	95 (22)	49 (16) [#]
Established macrovascular disease – no. (%)	31(11) [#]	123 (5)	116 (25) [#]	138 (47) [#]
Macroalbuminuria – no. (%)	2(3) [#]	210 (8)	338 (73) [#]	N/A
Microalbuminuria -	2 (5) [#]	405 (15)	37 (8) [#]	N/A

^a plus minus values are means ± SD, unless otherwise stated. To convert values for cholesterol to milligrams per decilitre, divide by 0.02586.

^b a measure of insulin sensitivity using the formula proposed by Williams *et al* (43).

* P <0.05 versus patients with an eGFR 60-120, calculated by t-test

[#] P <0.05 versus patients with an eGFR 60-120, calculated by Chi squared

Table 3. Primary cause of death of FinnDiane study participants stratified according to urinary albumin excretion (A) and estimated glomerular filtration rate (B).

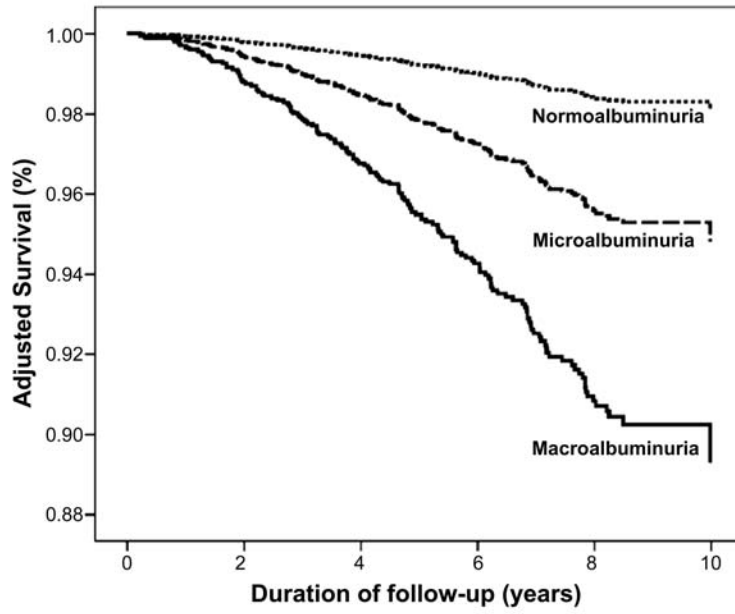
	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	ESKD
A. Primary cause of death	n=2296	n=504	n=578	n=293
Cardiovascular – no. (% deaths)	14(47)	15(56)*	40(45)*	78(58)*
Cancer – no. (% deaths)	2(7)	1(4)	3(3)*	7(5)*
Infection – no. (% deaths)	2(7)	3(11)*	18(20)*	24(18)*
Other causes – no. (% deaths)	12(40)	7(30)*	28(31)*	26(19)*
All cause – no. (% cohort)	30(1.3)	26(5.2)*	89(15.4)*	135(46.1)*
	>120	60-120	<60	ESKD
B. Primary cause of death	(n=272)	(n=2699)	(n=462)	(N=293)
Cardiovascular – no. (% deaths)	5 (42)	28(46)	42 (51) †	78(58) †
Cancer – no. (% deaths)	1(8)	3(5)	3(4) †	7(5) †
Infection – no. (% deaths)	1(8)	8(13)	15(18) †	24(18) †
Other causes – no. (% deaths)	5(42)	22(36)	22(27) †	26(19) †
All cause – no. (% cohort)	12 (4.4) †	61(2.3)	82(17.7) †	135(46.1) †

* p value < 0.05 versus patients with normoalbuminuria < 0.05, calculated by Chi squared

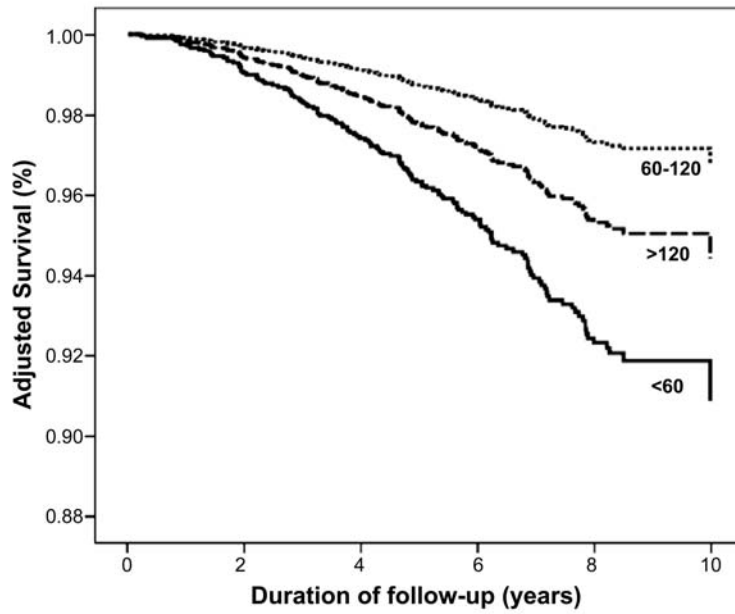
† p value < 0.05 versus patients with an eGFR 60-120 ml/min/1.73m², as calculated by Chi squared

Figure 1.

A.



B.



C.

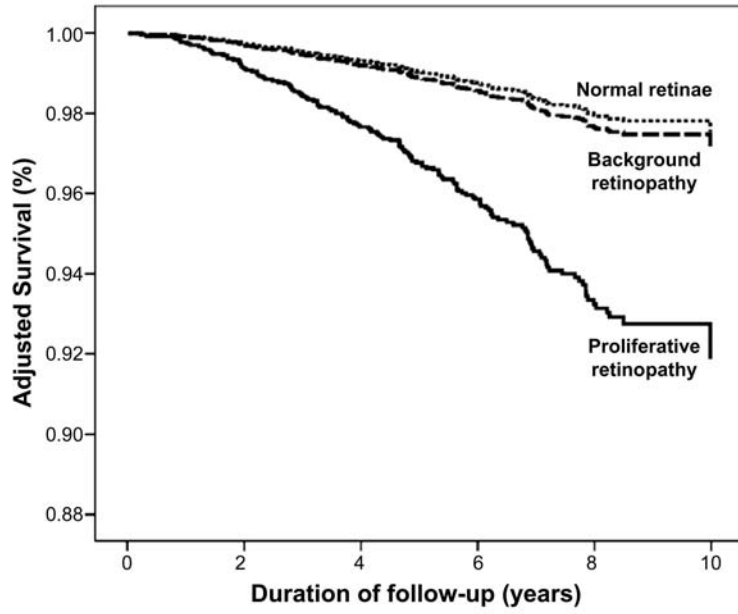


Figure 2

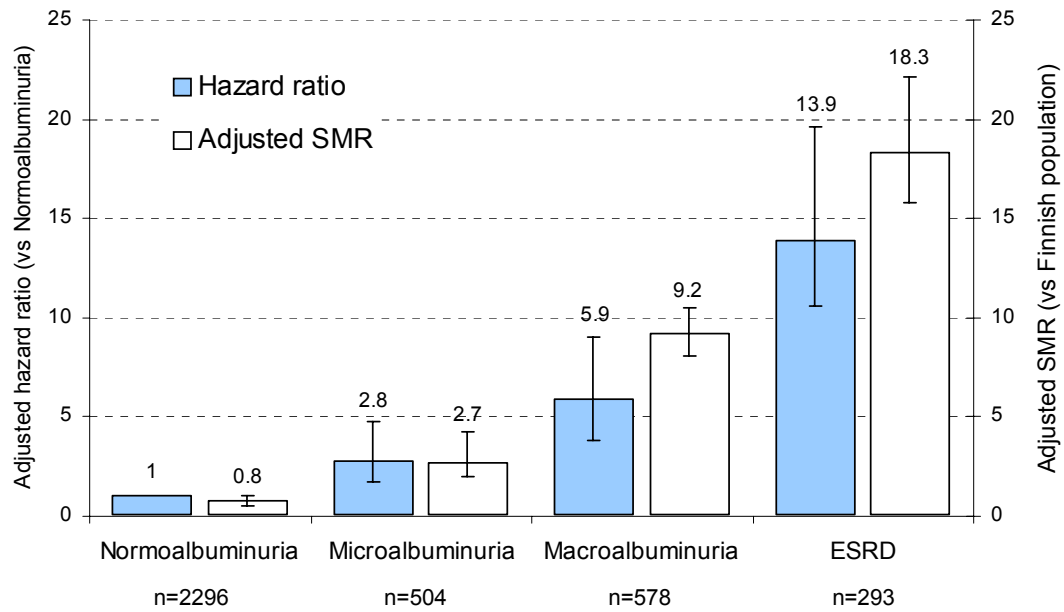


Figure 3

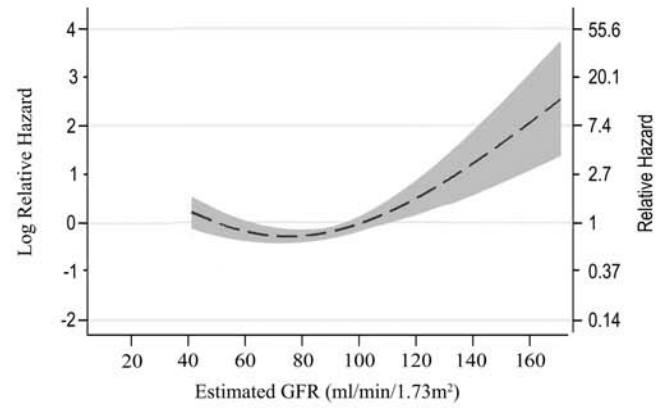
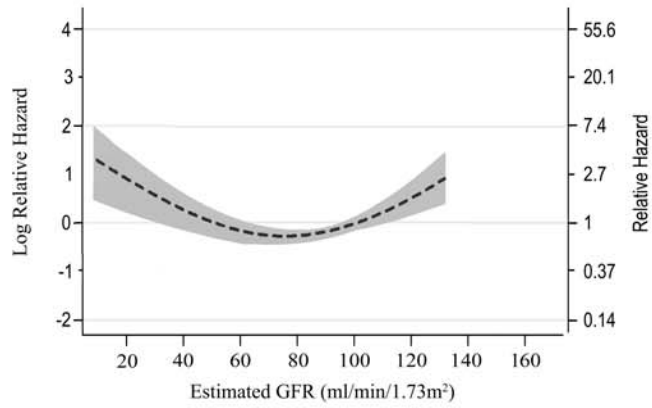
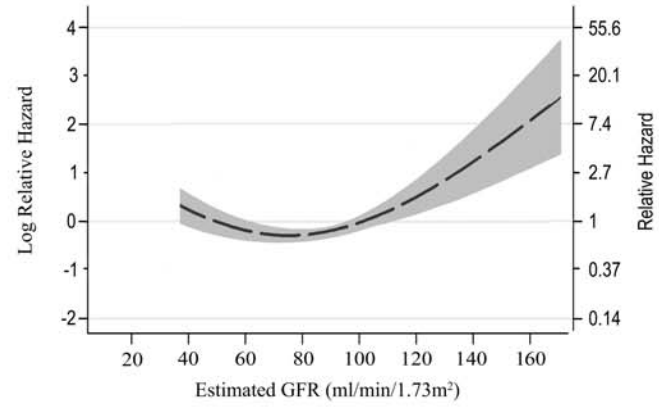
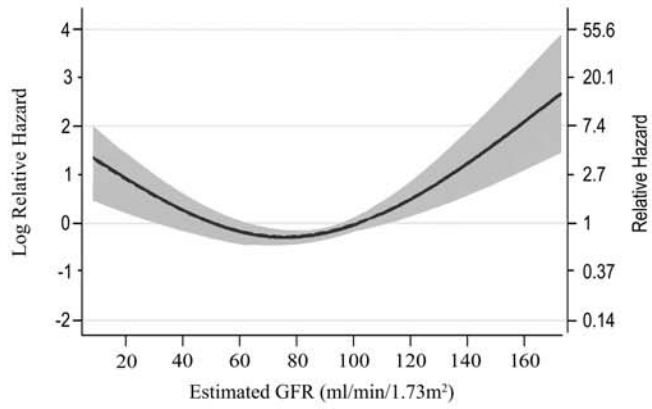


Figure 4

