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A History of Foot ulcer increases Mortality among Persons with Diabetes. 10-year Follow-up of the Nord-Trøndelag Health Study, Norway

Running Title: Diabetic foot ulcers and mortality

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Objective — To compare mortality rates for persons with diabetes with and without a history of foot ulcer (HFU) and with the non-diabetic population.

Research design and methods— This population-based study included 155 diabetic persons with a HFU, 1,339 diabetic persons without a HFU, and 63,632 non-diabetic persons who were all followed for 10 years with mortality as the end point.

Results — During the follow-up period, a total of 49.0% of diabetic persons with a HFU died, compared to 35.2% of diabetic persons without a HFU and 10.5% of those without diabetes. In Cox regression analyses adjusted for age, sex, education, current smoking, and waist circumference, having a HFU was associated with more than a twofold (2.29 [95% CI 1.82–2.88]) hazard risk for mortality compared to the non-diabetic group. In corresponding analyses comparing diabetic persons with and without a HFU, a HFU was associated with 47% increased mortality (1.47 [1.14–1.89]). Significant covariates were older age, being male and current smoking. After also including HbA_{1c}, insulin use, microalbuminuria, cardiovascular disease and depression scores in the model, each was significantly related to life expectancy.

Conclusions — A HFU increased mortality risk among community-dwelling adults and elderly people with diabetes. The excess risk persisted after adjusting for comorbidity and depression scores, indicating that close clinical monitoring might be warranted among persons with a HFU, who may be particularly vulnerable to adverse outcomes.

Hospital-based studies have shown that mortality rates in people with diabetic foot ulcers are about twice those observed in people with diabetes without foot ulcers (1, 2). A diabetic foot ulcer reflects the presence of underlying pathologic conditions, and the risk of recurrent ulcers is high (3, 4). It has been suggested that the elevated mortality rate among people with diabetic foot ulcers is related to comorbid disease such as cardiovascular disease and nephropathy (5) or to psychological factors including depression (6). Although the mortality rate in persons with diabetes is high, no large population-based studies have examined the impact on mortality of a history of foot ulcers (HFU) among people with diabetes.

The purpose of this study was to compare mortality rates for persons with diabetes reporting a HFU to those without a HFU and to the non-diabetic population. These issues were investigated in the Nord-Trøndelag Health Study (HUNT 2) which includes a very large population-based sample of men and women from a well-defined geographic area. Participants with self-reported diabetes were well characterized with regard to their diabetes, and information on demographics, lifestyle, and prevalent disease including depression was available.

RESEARCH DESIGN AND METHODS

The HUNT 2 study was conducted during 1995-97 and approved by the Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics. Participation was voluntary, and each participant signed a consent form.

The HUNT 2 study has been described previously (7, 8). Briefly, all inhabitants of Nord-Trøndelag county aged 20 years and older were invited to participate (n = 92,434). A questionnaire was mailed to each person along with an invitation to attend a clinical examination. Of those invited, 65,604 individuals (71%) attended. Participants who responded positively to the question, "Do you have or have you had diabetes?" were classified as having diabetes (n = 1,972) and were invited to take part in the diabetes substudy. Those who in an additional questionnaire answered positively to the question, "Have you had a foot ulcer that required more than three weeks to heal?" were classified as having a HFU (n = 155), and those who responded negatively were classified as having diabetes without a HFU (n = 1,339). Those classified as having diabetes, but who did not take part in the diabetes substudy or did not answer the foot ulcer question were excluded from the analyses (n = 478) (7). Some 63,632 participants reported not having diabetes. Thus, the current study includes a total of 65,126 participants.

In HUNT 2, a non-fasting venous serum sample was analyzed for glucose; for those who reported diabetes, an EDTA whole-blood sample was also analyzed for HbA_{1c}. Those who reported diabetes were given a follow-up appointment (74.8% participated) where a fasting blood sample was drawn and analyzed for glucose, C-peptide, and GAD antibodies. Participants who reported diabetes received tubes for collecting three consecutive first morning urine samples. Among the 1,494 participants with or without a HFU, 94.1% returned the samples, which were analyzed for albumin and creatinine (8). An albumin/creatinine ratio >2.5 mg/mmol in at least two of the three urine samples was used to define microalbuminuria, as recommended by Hallan et al (9).

Other variables included age, sex, body mass index (BMI, weight (kg)/height (m^2), and waist circumference. Education was categorized as fewer than 10 years or 10 years

or more. Smoking was classified as current smoking or not. The baseline questionnaire included information about angina pectoris, myocardial infarction, and stroke; those who responded positively to one or more of these items were defined as having cardiovascular disease. Hypertension was defined as blood pressure of 140/90 mm Hg or more or as current use of antihypertensive drugs. Exercise was dichotomized as less than one hour of physical activity per week or one hour or more. Other diabetes-related questions from the diabetes substudy included treatment, diabetes duration, eye problems due to diabetes, and amputation. Those reporting amputation of a toe, calf/knee, or femur were categorized as having any lower limb amputation.

Depression was assessed by the Hospital Anxiety and Depression Scale (HADS) (10, 11). This instrument includes seven items measuring depression (HADS-D subscale). Each item is scored from 0 to 3; thus the maximum score is 21 on each of the subscales. Higher scores indicate higher levels of symptom load. Missing substitution was performed for individuals who responded to five or six of the seven HADS-D questions. This was done by multiplying the obtained score by 7/5 if five of the seven questions were answered and by 7/6 if six questions were answered. Such missing substitution was needed for 5.8% of the HADS-D scale; 4.6% of the respondents answered fewer than five questions on the HADS-D and were excluded. Caseness was defined by a score of 8 or above on the HADS-D. This cutoff level has been shown to optimally balance sensitivity and specificity on receiver-operating characteristic curves (11) and was applied also in our study. Factor analysis of HADS in HUNT was reported to result in a two-factor solution consistent with the two subscales, anxiety and depression. Cronbach's alphas for internal consistency for the anxiety and depression subscales in HUNT were reported as 0.80 and 0.76, respectively (12).

Follow-up. Participants were followed for up to 10 years with mortality as the end point. Information on mortality was obtained from the Norwegian Causes of Death Registry using the Norwegian 11-digit personal identity number unique for each resident. Information on persons who emigrated from Nord-Trøndelag county during the follow-up period was estimated to be negligible (< 0.5%, *http://www.ssb.no/english/subjects/02/02/20/innvutv_en/tab-2009-05-07-02-en.html*).

Mortality diagnoses were coded according to the International Classification of Diseases (10^{th} revision). The main mortality diagnoses were categorized into diseases as follows: diabetes mellitus (E10–14), ischemic heart disease (I20–25), cerebrovascular disease (I60–69), other circulatory diseases (I00–15, I26–28, I30–52, I70–79, I80–99), renal disease (N00–39), cancer (C), and other diseases (A, B, D, E00–07, E15–90, F–H, J–M, N40–99, O–Y).

Statistical analyses. Power calculations were performed before the study and showed a statistical power of 78% to detect an increased risk of 33% among the foot ulcer group compared with the population with diabetes without a HFU, assuming a mortality of 30% during the follow-up in the latter group. We used t tests and χ^2 tests to compare characteristics of the three subgroups at baseline.

Cox proportional hazards regression analyses were used to estimate mortality rate ratios (hazard ratios, HR) and 95% CI from the date of inclusion in the study (1995–97) to December 31, 2005. We created dummy variables for the diabetic patients without a HFU and the diabetic patients with a HFU such that the HR for each category represents the comparison of that category to the non-diabetic population. Preliminary, simple Cox

regression analyses were performed for all baseline covariates and all-cause mortality. For covariates with more than 2% missing data in the foot ulcer group, separate "unknown" categories were used. This involved education (n = 16), waist circumference (n = 5), microalbuminuria (n = 10), and depression (n = 11).

Multiple Cox proportional hazards regression analyses were then performed with adjustment for other known risk factors for mortality. Covariates were organized thematically in blocks, and increasingly complex models were developed by adding one set of variables at a time using forced entry. We chose this model because diabetes increases the risk of cardiovascular disease and therefore the development of cardiovascular disease is in the causal pathway leading from diabetes to a higher risk of death (13).

Variable selection in multivariable modeling was made a priori based on previous knowledge, and assessment of the variable in relation to time, cause, and effect. For example, a history of amputation was not taken into the model because this most probably occurred after a diabetic foot ulcer. Severity of illness (judged by insulin use and HbA_{1c}), microalbuminuria, a history of cardiovascular disease, and depression (HADS-D ≥ 8) were entered into the model.

The two diabetes groups were first compared to the non-diabetic population after adjusting for demographic factors, lifestyle variables, cardiovascular disease, and depression. Covariates in model 1 included age (continuous); being male (no/yes); level of education (high, low, unknown); current smoking (no/yes); and high waist circumference of ≥102 cm in men or ≥88 cm in women (no/yes/unknown). Covariates in model 2 included cardiovascular disease status (no/yes) and depression (HADS-D ≥8) (no/yes).

Analyses involving only the diabetic groups were adjusted similarly for age, being male, level of education, current smoking, and waist circumference (model 3). The following additional factors were also included: cardiovascular status (no/yes) and depression (HADS-D <8 versus ≥8) (model 4); microalbuminuria (no/yes/unknown), HbA_{1c} (continuous) and insulin use (no/yes) (model 5).

Cox regression analyses were also performed to test for possible interactions between the main exposure (non-diabetic subjects and diabetic subjects with and without a HFU) and the other covariates in the model among persons with diabetes. Kaplan–Meier survival curves were estimated to describe all-cause mortality in the subgroups. Statistical significance was assigned as $P < 0.05$. Statistical analyses were conducted using SPSS version 16.0.

RESULTS

Baseline characteristics. Compared to the non-diabetic sample, those with a HFU were older; had higher BMI, waist circumference and depression scores, a higher proportion was male, physically inactive, had low education, angina pectoris, myocardial infarction, stroke and hypertension and a lower proportion were smokers. Comparing the two diabetes groups, those with a history of diabetic foot ulcer had higher mean waist circumference and HbA_{1c}, and a larger proportion were physically inactive, used insulin, had a long diabetes duration, microalbuminuria, and had a history of stroke, peripheral vascular surgery, eye problems due to diabetes, and lower limb amputations (Table 1).

Mortality. During the follow-up period, 49% of the 155 diabetic persons with a HFU died compared with 35.2% of the 1,339 diabetic persons without a HFU and 10.5% of the 63,632 non-diabetic persons.

Among persons with a HFU, the main causes of death were cardiovascular events (48.7%), diabetes mellitus (23.7%), and cancer (14.5%). Corresponding figures among those with diabetes without a HFU were 50.1%, 11.7%, and 18.6%, and among the non-diabetic group 44.9%, 0.5%, and 27.5%, respectively. The mortality rates from cardiovascular causes were not statistically different between the diabetes groups, although patients with a history of foot ulcers had more prevalent cardiovascular disease and more CVD risk factors at baseline than those without a HFU. After adjusting for age, sex, education, smoking, and waist circumference, compared to the non-diabetic group, diabetic persons with and without a HFU had a significantly higher mortality rate (HR, 2.29; 95% CI, 1.82–2.88 and HR, 1.70; 95% CI, 1.54–1.86, respectively) (Table 2, model 1). Covariates significantly associated with increased mortality risk were older age, male sex, low education, smoking, and larger waist circumference. The risk of mortality associated with having a HFU did not change markedly when cardiovascular disease and depression (HADS ≥8) also were included in the model (Table 2, model 2).

Among persons with diabetes, after adjusting for age, sex, education, smoking, waist circumference, a HFU was associated with a 47% increased risk of mortality. Covariates significantly associated with mortality were older age, male sex, and smoking (Table 2, model 3). The association between a HFU and mortality did not change markedly when cardiovascular disease and depression (HADS ≥8) were included in the model. When HbA_{1c}, insulin use, and microalbuminuria entered the model, the hazard ratios for a HFU were slightly reduced to 1.41; 95% CI, 1.09–1.82 (Table 2, model 5). Significant predictors for reduced life expectancy in the final model were older age, male sex, smoking, the presence of cardiovascular disease and depression (HADS ≥8), microalbuminuria, HbA_{1c} and insulin use. To study the effect of HbA_{1c} among diabetic persons with a HFU only, we repeated the analyses restricted to this subgroup and found an effect of HbA_{1c} that was slightly stronger than among all people with diabetes, although not significant (HR, 1.11; 95% CI, 0.97–1.28).

We included missing cases for education, waist circumference, microalbuminuria, and depression as separate subgroups in the Cox regression analyses. In general, the categories for missing values tended to have higher hazard ratio estimates (not shown in the table), although these were not significant, which probably reflects the small numbers. We also performed additional analyses that excluded people with diabetes who reported a history of amputation, but this did not alter the results markedly. Diabetes classification and diabetes duration were also included in the Cox regression analyses. The estimated effects of a HFU changed only marginally, and these covariates were not significantly associated to mortality.

A total of 478 individuals with diabetes did not participate in the substudy on diabetes or did not answer the question on foot ulcers. In order to assess the validity of the findings among those with diabetes, we compared those who completed the foot ulcer question with those who did not, with regard to demographics, prevalent disease and health behaviours and found that those who did not complete this question had more advanced disease.

To illustrate the excess mortality attributable to diabetes with and without a HFU, Kaplan–Meyer curves were drawn for data stratified into age groups 65–74 and 75 years or older. As seen in Figure 1, participants with diabetes and a HFU consistently had the highest mortality rates.

Tests for interactions revealed interaction in model 5, which showed that the effect of age was less important for those with a HFU ($P = 0.040$).

CONCLUSIONS

In this 10-year follow-up study, a HFU was associated with more than a twofold elevated risk of mortality compared to the non-diabetic group and an approximately 40% higher mortality compared to participants with diabetes but without a HFU. Compared to diabetes without a HFU, the excess risk was explained only partly by older age, being male, higher HbA_{1c}, current smoking, insulin use, microalbuminuria, cardiovascular disease and depression.

This large community-based study showed that foot ulceration increases mortality risk among persons with diabetes. As far as we are aware, this is the first such study to identify a higher mortality rate in persons with diabetes and a HFU among community-dwelling adults and elderly. Previous studies have to our knowledge included samples from hospitals, foot clinics, or outpatient settings (2, 14, 15). A substantial proportion of patients with foot ulcers are treated in primary care, and with the increasing prevalence of diabetes worldwide (16), the number of patients with diabetes and a HFU will increase over the next decade. Most of these patients are expected to have limited or infrequent access to multidisciplinary treatment teams (17). The present study underlines the importance of organizing future health care services with follow-up routines that allow for close clinical monitoring of persons with a HFU in primary care.

In a five-year observational study in Sweden, patients with diabetic foot ulcers attending a foot clinic had a twofold increase in mortality rates compared to non-diabetic persons, after adjusting for age and sex (1). We found a similar increased risk after adjusting for additional potential confounders and after a longer follow-up period. In a study of ambulatory male patients with diabetes (2), the relative risk of death during four-years follow-up was 2.39 in those who developed a new foot ulcer compared with those who did not. The excess mortality rate was substantially higher than in our study. This difference might reflect the more advanced illness in hospital-based patients, on the other hand the study by Boyko and colleagues was conducted between 1990 and 1994 and diabetes treatment has improved in recent years (18). Although the survival rate among persons with a HFU might have improved in recent years, our data indicate a continued excess mortality for those with a HFU. In addition, those with a HFU had a larger extent of severe diabetes complications compared to those with diabetes without a HFU. Further, among those with a HFU, a higher proportion of deaths was caused by diabetes and its complications, whereas the effect of age was less important among those with a HFU.

To our knowledge, our results relating poor glycemic control to higher mortality in persons with diabetes and a HFU are novel and in contrast to the results presented by Winkley et al. (4) where better glycemic control was significantly associated with higher mortality in persons with a diabetic foot ulcer after 18 months of follow-up. Our findings underline the importance of early identification of foot ulcers and intensified treatment at an early stage

Depression has previously been associated with increased mortality in people with diabetes (19, 20). Ismail (6) found that one-third of people with their first foot ulcer suffered from depression and that this condition was associated with increased mortality. Results from the present study support an increased risk of mortality among those depressed, over and beyond the

increased risk associated with a HFU. Systematic monitoring and treatment of depression among those with a HFU should be considered (4).

Previous longitudinal studies of individuals with diabetes and a HFU have included mainly hospital or foot clinic patients (1, 2, 14). The present long-term study of more than 60,000 men and women including 1,494 individuals with validated diabetes (21) support these previous findings.

As with all large-scale epidemiologic studies, ours also has inherent shortcomings. During the 10-year follow-up period, new diabetes cases probably developed, but the only information we have among non-diabetic subjects is that 0.5% of deaths were diabetes-related. The inclusion of an unknown number of subjects with diabetes in the non-diabetic group at baseline may influence the findings. Among those without known diabetes, a total of 62,757 delivered a non-fasting blood glucose (venous serum). The 217 persons with a non-fasting glucose above 11 mmol/l were contacted and recommended to take contact with their GP. In the analysis of the present study these ~0.003% (217/62,757) were not defined as having diabetes due to uncertainty. Due to this very low number it is unlikely that any of the risk estimates have been influenced by these cases. It is likely that these procedures underestimated the number of subjects with diabetes. Further, among persons who reported a HFU at baseline we have no information about the development of HFU after baseline. A closer follow-up of these persons would have enabled more detailed analyses to determine the real causes of the increased mortality in this group. We found that the diabetic persons who did not respond to the questionnaire on foot ulcers reported otherwise more advanced disease (7) corresponding to results from other studies of nonresponders (22). The mortality risk associated with a HFU in the present study might therefore have been underestimated.

In previous studies the threshold of microalbuminuria varied from 2.5-3.5 mg/mmol for men and women (9). In the present study we used a cut-off of 2.5 mg/mmol for both sexes. Thus the results of the present study might overestimate the proportion of females with MA. Finally, compared to other studies (1, 23) a relatively low proportion of participants reported a history of amputation, which may be explained by recruitment procedures that made it difficult for housebound or institutionalized people to participate. On the other hand these two studies are from specialized foot care clinics and probably included people with more advanced disease and complications.

In conclusion, a HFU among persons with diabetes among community-dwelling adults and elderly was significantly related to increased mortality. This excess risk persisted after adjustment for relevant covariates of comorbidity and depression scores thus indicating that close clinical monitoring is warranted among persons with a HFU, who may be particularly vulnerable for adverse outcomes.

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Table 1— Description of the study population; the HUNT 2 study

Characteristics	**Non-diabetic subjects** n = 63,632*	**Diabetic subjects without a history of foot ulcer** n = 1,339*	**Diabetic subjects with a history of foot ulcer** n = 155*	***P* value**†	***P* value**‡
Demographic characteristics					
Age (years)	49.7 (SD 17.3)	65.6 (SD 13.6)	67.2 (SD 14.0)	<0.001	0.157
Male sex (%)	46.7	49.7	56.8	0.012	0.097
Single (%)	40.1	38.1	45.8	0.150	0.064
Education (≥10 years) (%)	64.0	37.7	33.8	<0.001	0.367
Lifestyle characteristics					
BMI (kg/m^2)	26.3 (SD 4.1)	28.9 (SD 4.8)	29.3 (SD 5.3)	<0.001	0.396
Waist circumference (cm)	86.2 (SD 11.6)	95.0 (SD 12.0)	98.2 (SD 12.3)	<0.001	0.002
Physical activity <1 h/week (%)	19.8	27.5	37.2	<0.001	0.026
Current smokers (%)	29.0	16.8	11.1	<0.001	0.070
Cardiovascular disease status					
Self-reported stroke (%)	1.8	5.0	12.2	<0.001	<0.001
Self-reported myocardial infarction (%)	3.0	12.6	15.3	<0.001	0.345
Self-reported angina pectoris (%)	4.6	18.5	22.0	<0.001	0.307
Hypertension	23.9	56.4	57.4	<0.001	0.81
Subgroups of diabetes					
Type 1 (%)	–	16.9	26.0		
Type 2 (%)	–	83.1	74.0		
Diabetes-specific variables					
HbA_{1c} (% units)	–	8.1 (SD 1.7)	8.4 (SD 2.0)	–	0.015
Insulin use (%)	–	31.8	43.5	–	0.004
Microalbuminuria §	–	27.3	40.0	–	0.001
Duration of diabetes (years) (median)	–	6.0	10.0	–	0.001
Peripheral vascular surgery (%)	–	2.7	10.7	–	<0.001
Eye problems due to diabetes (%)	–	11.9	24.8	–	<0.001
Any lower limb amputations (%)	–	0.7	5.2	–	<0.001
Psychological assessment					
HADS-depression score (0–21)	3.5 (SD 3.1)	4.3 (SD 3.4)	4.7 (SD 3.6)	<0.001	0.180
HADS-depression (score ≥8) (%)	10.8	17.1	18.8	0.002	0.614
HADS-depression (score ≥11) (%)	3.2	6.0	7.6	0.002	0.439

Data are means (SD) or %. * Sample sizes vary somewhat depending on the actual completion of the different tests and questionnaires. † Significance of *t* test or χ^2 test for difference between participants with a history of diabetic foot ulcers and those without diabetes. ‡Significance of *t* test or χ^2 test for difference between participants with and without a history of diabetic foot ulcer. § Microalbuminuria was defined as albumin/creatinine ratio >2.5 mg/mmol in at least two of three urine samples.

Table 2— Results of unadjusted and adjusted Cox proportional hazards models for all-cause mortality in diabetic participants with and without a history of foot ulcer (HFU) compared with the non-diabetic participants and diabetic participants with a history of HFU compared to the non-diabetic population (models 1–2); and in diabetic participants with a HFU compared with those without a HFU (models 3–5)

	Unadj HR (CI)	Model 1 HR (CI)	Model 2 HR (CI)	Unadj HR (CI)	Model 3 HR (CI)	Model 4 HR (CI)	Model 5 HR (CI)
	n = 64,109*	n = 64,109	n = 64,109	n = 1,435†	n = 1,435	n = 1,435	n = 1,435
Non-diabetic subjects	Ref. ‡	Ref. ‡	Ref. ‡	–	–	–	–
Diabetes without a HFU	4.21 (3.83–4.62)	1.70 (1.54–1.86)	1.62 (1.48–1.78)	Ref. ‡	Ref. ‡	Ref. ‡	Ref. ‡
Diabetes with a HFU	6.80 (5.40–8.55)	2.29 (1.82–2.88)	2.20 (1.75–2.77)	1.68 (1.31–2.16)	1.47 (1.14–1.89)	1.46 (1.14–1.89)	1.41 (1.09–1.82)
Age (years)	1.12 (1.11–1.12)	1.12 (1.12–1.12)	1.11 (1.11–1.12)	1.10 (1.09–1.11)	1.11 (1.09–1.12)	1.10 (1.09–1.11)	1.10 (1.09–1.11)
Male sex	1.41 (1.35–1.48)	1.74 (1.66–1.83)	1.67 (1.58–1.75)	1.05 (0.88–1.25)	1.49 (1.23–1.79)	1.46 (1.20–1.76)	1.44 (1.18–1.74)
Education (<10 years)§	4.08 (3.86–4.32)	1.10 (1.04–1.17)	1.08 (1.02–1.14)	1.93 (1.55–2.39)	0.98 (0.78–1.22)	0.94 (0.75–1.19)	0.98 (0.78–1.24)
Current smoking	0.85 (0.80–090)	1.64 (1.54–1.73)	1.64 (1.55–1.74)	1.09 (0.87–1.37)	1.80 (1.42–2.27)	1.76 (1.39–2.23)	1.75 (1.38–2.22)
Waist circumference >102 or 88 cm§	1.97 (1.87–2.01)	1.14 (1.08–1.20)	1.12 (1.06–1.18)	1.17 (0.98–1.39)	1.16 (0.96–1.39)	1.11 (0.92–1.33)	1.13 (0.94–1.35)
Cardiovascular disease‖	6.38 (6.06–6.73)		1.56 (1.48–1.65)	2.56 (2.15–3.04)		1.53 (1.28–1.83)	1.50 (1.25–1.80)
Depression (score ≥8)§	2.32 (2.18–2.47)		1.35 (1.27–1.44)	1.49 (1.20–1.86)		1.37 (1.10–1.72)	1.35 (1.08–1.69)
Microalbuminuria¶§	–		–	2.34 (1.96–2.81)			1.55 (1.25–1.82)
HbA_{1c}	–		–	1.11 (1.06–1.16)			1.07 (1.02–1.13)
Insulin use	–		–	1.02 (0.85–1.23)			1.37 (1.13–1.66)

Data are hazard ratios (HR) with 95% CI. * n = 64,109 (62,623 = non-diabetic participants; 1,333 = participants with diabetes without a HFU; and 153 = participants with diabetes with a HFU); †n = 1,435 distributed as n = 1,290 (diabetes without a HFU) and n = 145 (diabetes with a HFU); ‡ reference category; § unknown cases entered as separate category; ‖ known angina, stroke, or myocardial infarction, as reported at baseline; ¶ albumin/creatinine ratio >2.5 mg/mmol in at least two of the three urine samples was used to define microalbuminuria.

Figure legend
Fig. 1— Kaplan–Meyer survival curves (all-cause mortality) comparing non-diabetes, diabetes, and diabetes with a HFU subgroups by sex and age. Dotted line = non-diabetes; thin line= diabetes without a HFU; thick line = diabetes with a HFU.

Fig. 1a

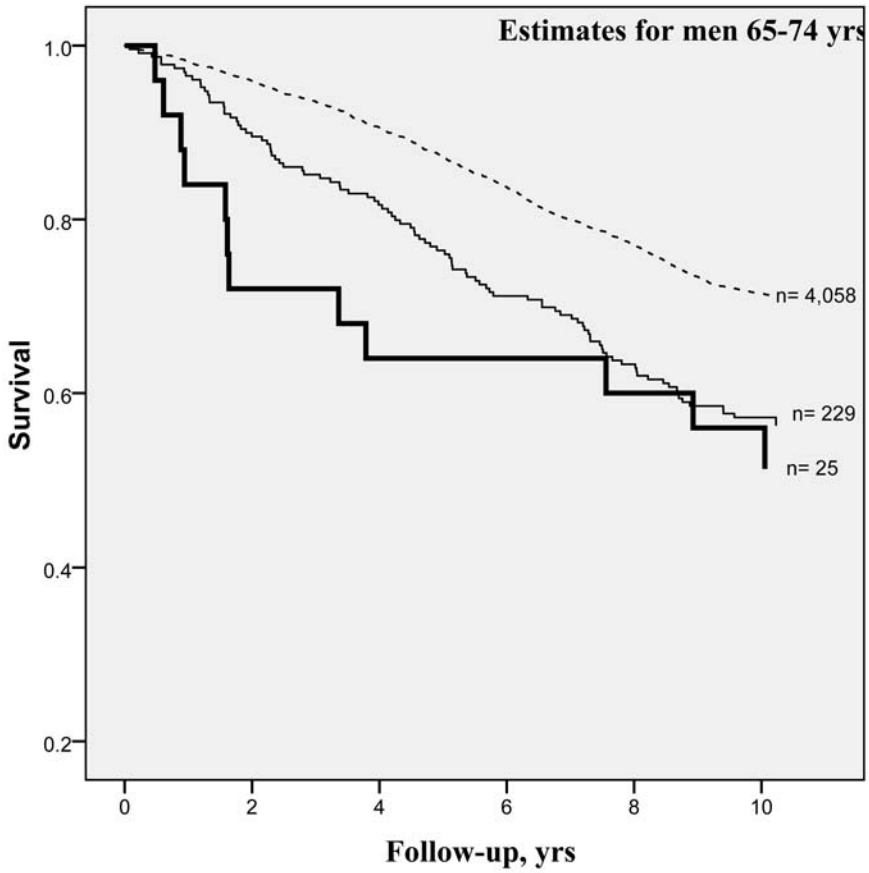


Fig 1b

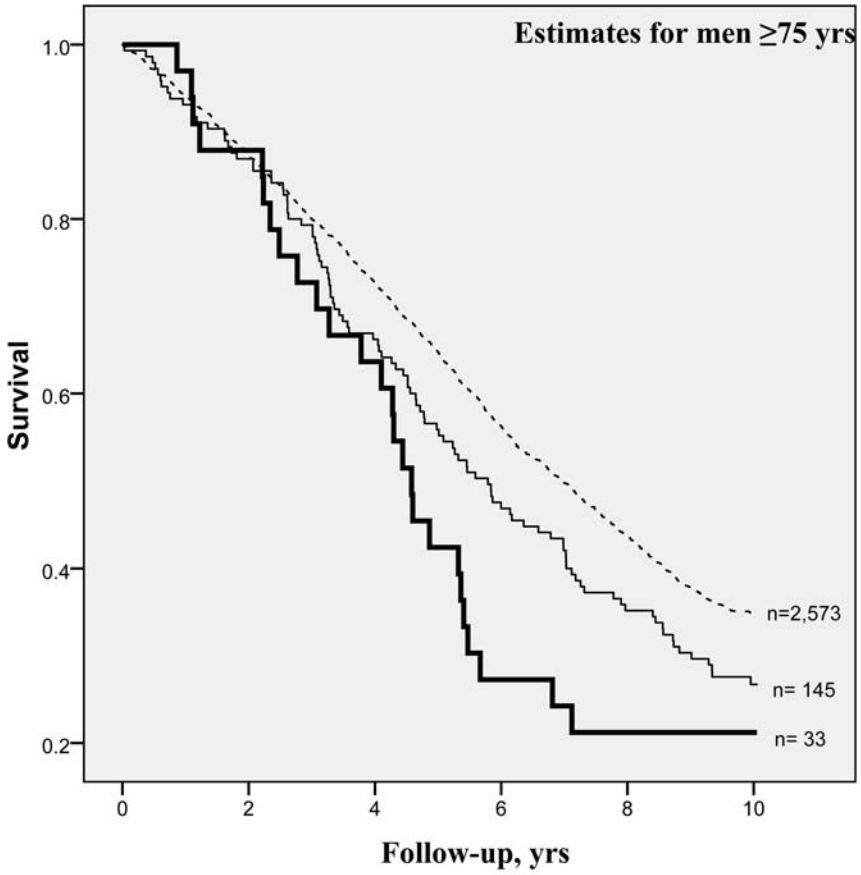

Estimates for men ≥75 yrs
Survival
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
Follow-up, yrs
n=2,573
n= 145
n= 33

Fig 1c

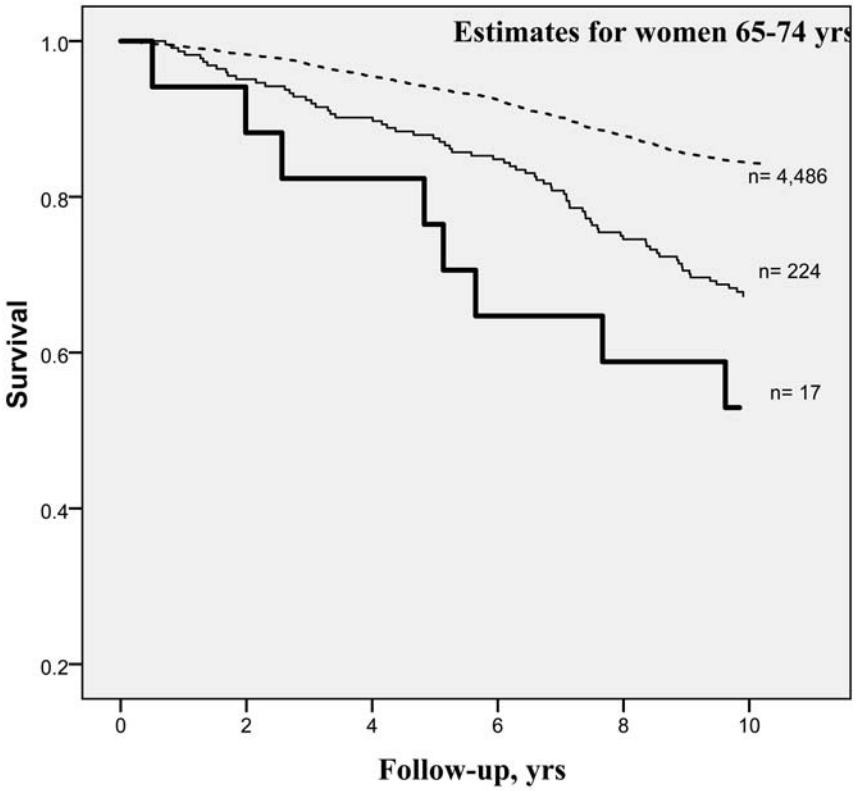
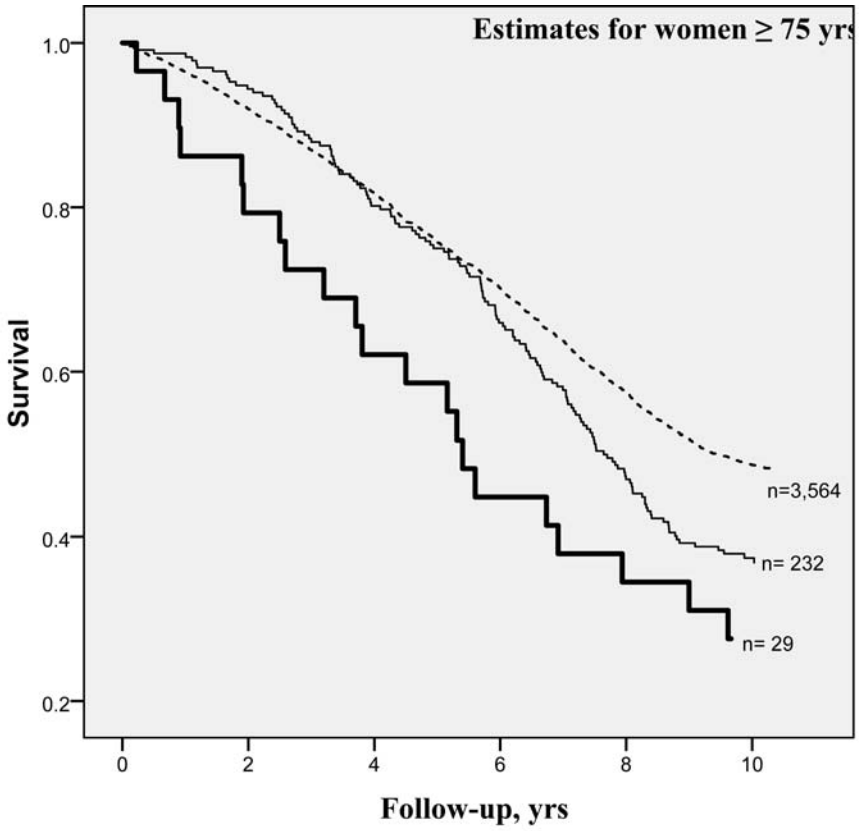

Estimates for women 65-74 yrs
n= 4,486
n= 224
n= 17
Survival
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
Follow-up, yrs

Fig 1d


Estimates for women ≥ 75 yrs
Survival
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
Follow-up, yrs
n=3,564
n= 232
n= 29