

TITLE: “Differential mortality and the excess rates of hip fracture associated with type 2 diabetes: accounting for competing risks in fracture prediction matters”

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## ABSTRACT

Type 2 diabetes (T2DM) is associated with a reduced life expectancy. Latest published evidence suggests an increased risk of fractures among T2DM patients. We conducted a population-based cohort study to determine the impact of mortality as a competing risk in the study of the association between T2DM and hip fracture rates. Participants were all diagnosed T2DM patients registered in the SIDIAP database aged 65 years and older; up to two non-T2DM were matched by age, sex, and primary care facility. We used Cox regression models to estimate cause-specific Hazard Ratio (HR) of death or hip fracture according to T2DM status. Fine and Gray models were then fitted to estimate the Subhazard Ratio (SHR) of hip fracture while accounting for competing risk with death and to estimate the probability of hip fracture within 5 years. 55,891 T2DM and 103,093 matched non-T2DM patients were observed for a median of 8 years. Mortality was 48.8 per 1000 person years (py) in T2DM, and 33.8 per 1,000 py in non-T2DM; hip fracture rates were 6.0 per 1,000 py and 4.9 per 1,000 py respectively. Cox models confirmed a significant association for death and hip fracture: HR=1.51 [95% CI 1.48 to 1.55], and HR=1.32 [95% CI 1.24 to 1.40] respectively. Accounting for death as a competing event (Fine-Gray models), the association between T2DM and hip fracture risk remained statistically significant (sHR=1.15 [95% CI 1.09 to 1.21]) and the probability of a hip fracture within 5 years was 2.3% for TD2M and 1.9% for non-TD2M patients compared to 2.6% and 2.1% respectively using KM estimates. T2DM patients have a 50% increased mortality and, after adjusting for differential survival at 5 years, a 21% increased incidence of hip fracture when compared to matched non-T2DM. Failing to account for differential mortality leads to an overestimation of fracture risk.

Key words: Fracture Risk Assessment, Type 2 Diabetes Mellitus, Competing Risk, Epidemiology and Osteoporosis.

## INTRODUCTION

Diabetes is a leading underlying or contributing cause of death in high-income countries<sup>1</sup> and is associated with a known reduction in life expectancy<sup>2</sup>. Moreover, diabetes is a long-term increasingly prevalent condition in both developed and developing countries. People with diabetes are at a greater risk of developing cardiovascular diseases, sight loss, foot and leg amputation and renal failure requiring dialysis or transplantation<sup>3,4</sup>. If diabetes is poorly controlled, the risk of developing these diseases and suffering severe consequences is higher<sup>5,6</sup>. A meta-analysis of studies of mortality in type 2 diabetes (T2DM) patients showed an 85% increase risk for all-cause mortality, a 76% excess cardiovascular mortality and over a 2-fold increase risk for stroke<sup>7</sup>. In the US alone, diabetes is reported to account for an average of 3.3 to 18.7 years lifespan loss<sup>8</sup>.

Published evidence suggests an association between diabetes and bone fragility<sup>9</sup>. Despite diabetes being associated with higher bone mineral density (BMD)<sup>10</sup>, a systematic review and meta-analysis concluded that type 2 diabetics have a 40% excess risk of hip fracture compared to non-diabetic peers<sup>11</sup>. Recent evidence, mostly published in the last 10-15 years, reinforces these findings<sup>12-16</sup>. Furthermore, the time from diabetes onset (metabolic control) appears to contribute to this association and T2DM complications such as neuropathy, nephropathy, and visual impairment or cataracts, are associated with an increased number of falls and related fractures<sup>17</sup>.

Hip fractures are the most devastating consequence of osteoporosis and bone fragility, and their incidence increases markedly with age<sup>18-20</sup>. Death and fracture are clearly competing events that cluster in the elderly, and T2DM is reportedly a risk factor for both. Standard methods, such as Kaplan-Meier or Cox regression fail to account for competing events, and alternative analytical approaches are required<sup>21</sup>. However, most

of the literature on the association between type 2 diabetes and hip fractures has failed to account for a competing risk with death. We therefore used a large population-based computerized records database to study the impact of differential mortality on the association between type 2 diabetes and hip fracture risk.

## MATERIALS AND METHODS

We conducted a population-based cohort study using data from the SIDIAP Database ([www.sidiap.org](http://www.sidiap.org)). SIDIAP contains clinical information from primary care records, hospital admissions, and pharmacy invoice data for >5 million patients (80% of the population) in Catalonia, Spain<sup>22</sup>.

Eligible participants were all those diagnosed with T2DM registered in SIDIAP and  $\geq 65$  years old on 1 January 2006 (“the index date”). Up to two non-T2DM were matched to each of the participants in the T2DM cohort by age ( $\pm 2$  years), sex, and primary care practice. Non-T2DM patients that were users of anti-T2DM drugs or with two measures of glycated haemoglobin above 6.5% were excluded. Non-T2DM and T2DM patients with a recorded hip fracture or death on index date were excluded (as they did not contribute to observation time). Patients (either T2DM or non-T2DM) that ended unmatched (i.e. with no matched peer remaining) because of the above exclusion criteria were also excluded.

Both T2DM and matched non-T2DM cohorts were followed from index date until death, fractured a hip, or transferred out of catchment area or end of study on 12/31/2013, whichever came first (treated as censored). The main outcome was incident hip fracture and all-cause mortality was a secondary (competing) event. Previously validated lists of ICD10 codes<sup>22,23</sup> were used to identify both the study exposure (T2DM status) and outcome/s (fracture and death). SIDIAP is a validated source of information for epidemiological research<sup>22</sup>. Potential confounders considered for adjustment in the multivariable models were those with a raw statistical significant association and a Hazard Ratio (HR) above 1.1 or below 0.9 (see directed acyclic graphs for hip fracture and death at appendix 1).

Baseline characteristics of T2DM and non-T2DM patients were described using mean and standard deviation for continuous variables and frequencies for categorical variables. We used Cox regression<sup>24</sup> models stratified by match sets to estimate cause-specific hazards (Hazard Ratio –HR– and 95% Confidence Intervals –95%CI–) in T2DM compared to non-T2DM patients. Two cause-specific hazards were studied: hip fracture and death. Similarly, Cox regression models were then used to estimate (matched) multivariable adjusted cause-specific hazards according to T2DM status. Finally, Fine and Gray modelling<sup>25</sup> was used to estimate risk prediction whilst illustrating the effect of competing risk with death. Cause-specific HR are reported from the Cox model; as are Subhazard ratio (SHR) and cumulative incidence function (CIF) from the Fine and Gray regressions<sup>26</sup>. We tested the PH assumption graphically with the log-log plot of survival and analytically with the test of proportional-hazards assumption. All statistical analyses were conducted using STATA v13.



## RESULTS

In total, 55,891 T2DM patients and 103,093 matched non-T2DM met inclusion criteria (Figure 1). T2DM patients were observed for a median of 6.4 years comprising 358,428 person-years of observation and non-T2DM patients were observed for a median of 8.0 years making up to a total of 695,340 person-years of observation.

Baseline characteristics for study participants stratified by T2DM status are presented in Table 1. T2DM patients had a higher prevalence of cardiovascular disease, neuropathy, and nephropathy. No discernible differences were observed for history of previous osteoporotic fracture, but non-T2DM subjects were more often users of calcium, vitamin D, and anti-osteoporotic treatments in the year before inclusion.

A total of 17,774/55,891 (31.8%) T2DM and 23,794/103,093 (23.1%) non-T2DM patients died during follow-up, equivalent to mortality (95% CI) rate of 48.8 (48.1, 49.5) per 1,000 person years and 33.8 (33.3, 34.2) per 1,000 person years respectively (Figure 2). In an age-sex-practice matched Cox model a higher mortality hazard in T2DM respect non-T2DM was found: HR 1.51 (95% CI 1.48 to 1.55), which remained significant in a multivariable-adjusted model (adjusted HR 1.46; 95%CI 1.42 to 1.49) (Table 2).

Similarly, 2,154/55,891 (3.9%) T2DM and 3,388/103,093 (3.3%) non-T2DM patients sustained a hip fracture in the study period, with estimated incidence rates of 6.0 (5.76 to 6.27) per 1,000 person-years and 4.9 (4.71 to 5.04) per 1,000 person-years respectively. Cox models showed a significant association between T2DM and hip risk fracture in a matched model (HR 1.32; 95%CI 1.24 to 1.40), which remained significant in a multivariable-adjusted model (adjusted HR 1.31; 95%CI 1.23 to 1.40). Accounting for death as a competing event, the association between T2DM and hip hazard fracture

remained statistically significant (matched –unadjusted- sHR 1.17; 95% CI 1.11 to 1.23). Adjustment for significant confounders did not modify substantially these estimates (adjusted sHR 1.15; 95%CI 1.09 to 1.21) (Table 2). In Figure 3, Kaplan-Meier functions of hip fracture probability according to T2DM status (failing to account for differential mortality) are compared to Cumulative Incidence Functions, which do account for the effect of death. The 5-year cumulative incidence of hip fracture using Kaplan–Meier was 2.6% in T2DM patients and 2.1% in non-T2DM patients. Using competing risk methodology, 5-year cumulative incidence of hip fracture differed, with an incidence of 2.3% among T2DM, slightly worse than the estimate of 1.9% for non-T2DM.

## DISCUSSION

T2DM patients have a 50% higher mortality than matched non-T2DM. Using survival analysis methods such as Cox regression, T2DM patients have a 35% higher risk of hip fracture; we have shown, however, that models accounting for the differential mortality as a competing event reduce this estimate of excess risk of hip fracture amongst T2DM to 15% and show a 21% increased incidence of hip fracture at 5 years in T2DM participants when compared to matched non-T2DM. Failure to account for competing risk with death overestimates the effect size of the association between T2DM and hip fracture risk.

T2DM is a well-known risk factor for numerous health problems. Individuals with high blood glucose levels during a long period are at higher risk to develop cardiovascular disease, blindness, kidney failure, and lower limb amputation. Therefore, T2DM is a key predictor, such as smoking or hypertension, in cardiovascular risk functions<sup>27,28</sup>. This does therefore explain the known increased mortality associated with this long-term condition<sup>7</sup>. In addition, previous studies have also shown that T2DM patients have higher hip fracture risk with a 38% increase compared to non-T2DM<sup>11</sup>.

The existence of these two parallel associations is a crucial methodological conundrum, as death precludes the occurrence of a hip fracture. Therefore, the competing risks with death should be taken into account when analysing the association between T2DM and fractures. However, most of the existing literature fails by using classic methods such as Cox PH with data death censored. For illustration, in the eight studies used in the metanalysis by Vestergaard<sup>11</sup> all use Cox PH taking with death censored to estimate the effects of diabetes on the hazard of hip fracture. In a competing event scenario, there is no correspondence between cause-specific hazard and cumulative incidence thus failure to account for death as a competing risk results in an unrealistic estimate of this

association<sup>26,29</sup>. According to our results, failing to account for differential mortality is an overestimation in the excess risk of hip fracture associated with T2DM.

Other studies on T2DM or in fracture risk have described this same issue in other settings. A study focused on assessing the impact of diabetes on relapse-free period and overall mortality in elderly breast cancer patients<sup>30</sup>. They found that when taking competing mortality into account, relapse-free period was better in elderly breast cancer patients with diabetes compared with patients without diabetes. Another study assessed whether assisted peritoneal dialysis was associated with a lower risk for technique failure<sup>31</sup>. In contrast with the results of a traditional cox model, they found using Fine and Gray that assisted peritoneal dialysis was associated with a lower risk for transfer to hemodialysis. A study to determine the association of weight loss with risk of clinical fractures at the hip, spine, and pelvis in older men, found that ignoring the competing mortality risk among men with weight loss substantially overestimates their long-term fracture probability and relative fracture risk<sup>32</sup>. Finally another study focused on analyse the peritonitis-free survival in the peritoneal dialysis. They found that using a competing risk approach the cumulative incidence of at least one peritonitis episode was lower than reported by the Kaplan–Meier method<sup>33</sup>.

However, there are some limitations in our study. First, our data is based on clinical records and we lack validation of each individual fracture. However, coding of fractures in SIDIAP has been compared to classical cohort data and hospital databases and shown to be highly specific (>95% for all fracture sites tested) and moderately sensitive (almost 70% for hip fractures)<sup>19</sup>. Also, ICD-10 does not distinguish between traumatic fractures and fragility fractures. A recent study including a random sample of 300 SIDIAP participants aged > 50 years old who suffered a fracture during 2012 has showed that >90% of hip fractures and >80% of major fractures were fragility (not

related to high impact trauma)<sup>23</sup>. Residual confounding is possible in our study, as some key potential risk factors for fracture such as parental hip fracture history were not available in the dataset. Finally, we are uncertain whether these findings are generalizable to other populations, but previous research by Giangregorio et al<sup>34</sup> have found a similar association in Manitoba cohort, Canada.

In summary, we conclude that estimation of hip fracture risk without accounting for death as a competing event results in an overestimation of fracture risk. All fracture risk estimation/s on T2DM patients should therefore be addressed accounting for death as a competing risk. Our data do however confirm that T2DM patients are at higher risk of hip fracture even after accounting for death as a competing risk. Conventional fracture risk assessment models like FRAX do not include T2DM as a risk factor so a limited predictive accuracy in T2DM patients is expected. Studies on the anti-fracture effectiveness of anti-osteoporosis medications (or non-pharmacological treatments) should account for a competing risk with death. This is particularly relevant if such interventions can affect mortality, similar to the effects observed in our T2DM vs non-T2DM example.

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Cristian Tebe, Daniel Martinez-Laguna, and Daniel Prieto-Alhambra designed the study, performed data management, statistical analysis, and drafted the paper. Cyrus Cooper, Victor Moreno, Adolfo Diez-Perez and Gary S. Collins supervised epidemiological/analytical aspects, participated in the discussion and interpretation of results, and reviewed and critically edited the paper. All authors read the final version and approved submission.

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## FIGURE LEGENDS

## TABLES

**Table 1:** Baseline characteristics of the SIDIAP cohort, according to T2DM status.

	non-T2DM		T2DM patients	
N	103,093		55,891	
	mean	sd	mean	sd
Age (years)	74.68	6.52	74.63	6.46
BMI (kg/m <sup>2</sup> )	28.70	4.51	29.91	4.84
	n	%	n	%
Sex: Men	45094	43.74	24413	43.68
Smoking status: Never Smoker	29442	28.56	20708	37.05
Former Smoker	7822	7.59	5503	9.85
Current Smoker	4914	4.77	2834	5.07
Missing	60915	59.09	26846	48.03
Previous hip fracture	220	0.21	142	0.25
Previous major fracture	282	0.27	160	0.29
Previous osteoarthritis	23483	22.78	13367	23.92
Previous CVA	5466	5.30	4752	8.50
Previous IHD	6681	6.48	7405	13.25

<b>Previous nephropathy</b>	12137	11.77	11084	19.83
<b>Previous neuropathy</b>	14	0.01	931	1.67
<b>Previous Falls</b>	883	0.86	668	1.20
<b>Corticoids prescriptions</b>	6749	6.55	3816	6.83
<b>Calcium + vitamin D</b>	13686	13.28	6108	10.93
<b>Anti-Osteoporosis drugs</b>	12271	11.90	5162	9.24
<b>Insulin prescriptions</b>	0	0.00	11619	20.79
<b>Oral antidiabetic drug prescriptions</b>	0	0.00	37163	66.49

BMI: Body Mass Index; IHD: Ischemic heart disease; CVA: Cerebrovascular accident; SD: Standard Deviation.

Table 2. Hazard and Subhazard ratio of risk fracture between groups.

	<b>Raw*</b>	<b>CI 95%</b>	<b>Adjusted</b>	<b>CI 95%</b>
<b>HR<sub>death</sub></b>	1.51	1.48 to 1.55	1.46**	1.42 to 1.49
<b>HR<sub>hip fracture</sub></b>	1.32	1.24 to 1.40	1.31***	1.23 to 1.40
<b>SHR</b>	1.17	1.11 to 1.23	1.15***	1.09 to 1.21

HR<sub>death</sub>: Death Cause-Specific Hazard Ratio ; HR<sub>hip fracture</sub>: Hip fracture Cause-Specific Hazard Ratio; SHR: SubHazard Ratio; CI95%; 95% confidence interval.

\*Match by age and sex; \*\*Adjusted by age, previous cerebrovascular accident, previous Ischemic heart disease, previous osteoarthritis, previous nephropathy, previous falls, corticoids prescriptions and anti-osteoporosis prescriptions. \*\*\*Adjusted by previous major osteoporotic fracture, previous cerebrovascular accident, previous Ischemic heart disease, previous osteoarthritis, previous nephropathy, previous falls, corticoids prescriptions and anti-osteoporosis prescriptions.

**FIGURES**

Figure 1. Population Flow-chart

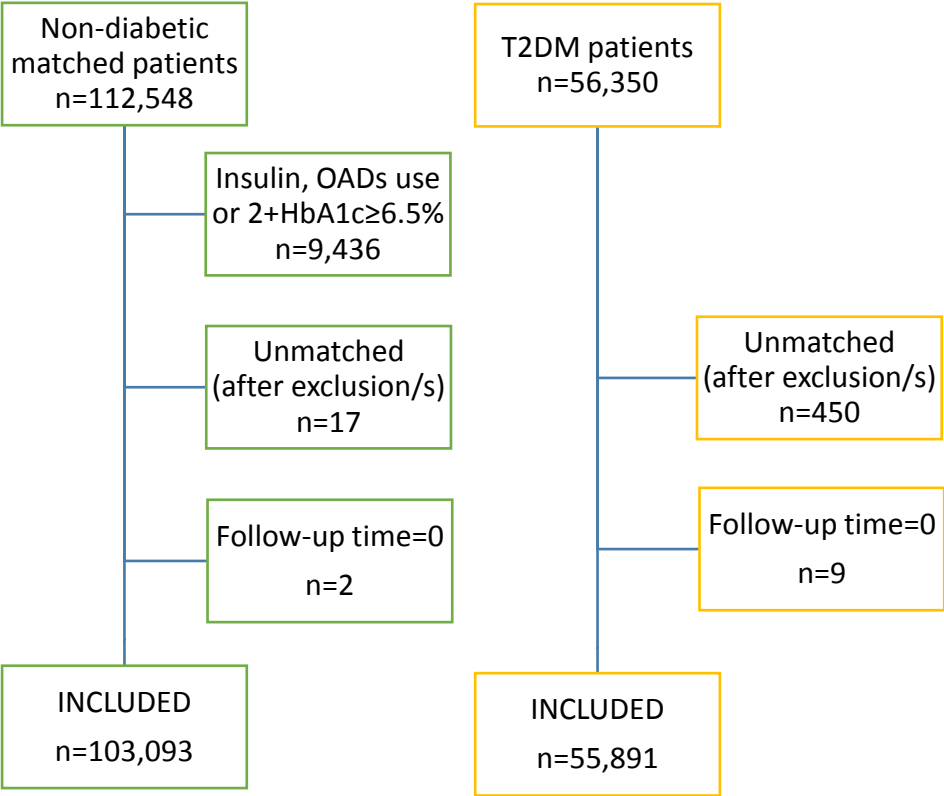


Figure 2. Kaplan-Meier mortality risk function in T2DM and matched non-T2DM patients

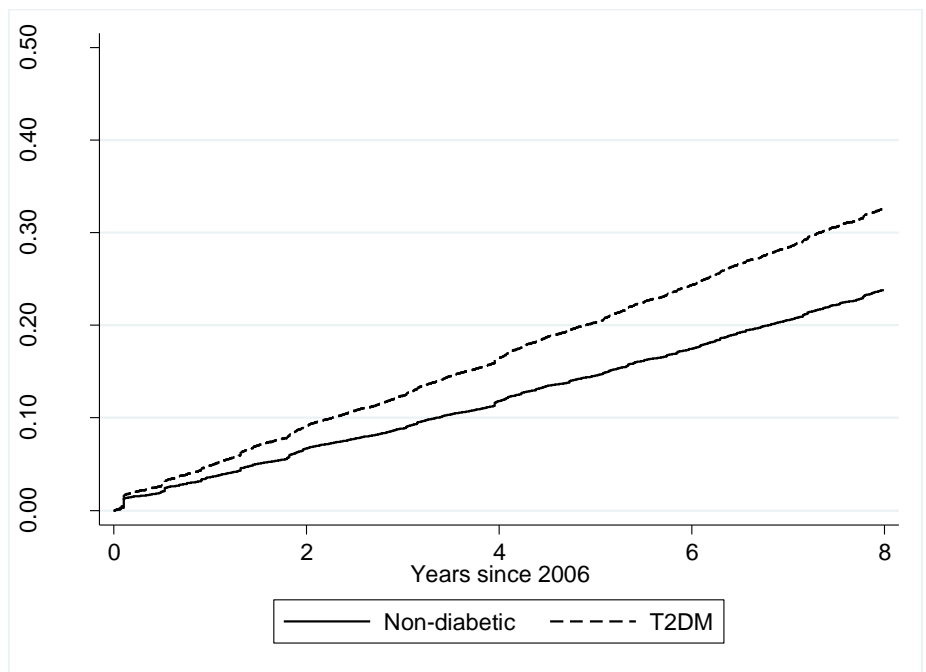


Figure 3. Estimates probabilities of hip fracture in non-T2DM and T2DM using Kaplan-Meier and Cumulative Incidence Function.

