Title Page

Full title: Incident type 2 diabetes and risk of fracture: a comparative cohort analysis using UK primary care records

Short title: Incident type 2 diabetes and risk of fracture

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Abstract

Objective To estimate risk of fracture in men and women with recent diagnosis of type 2 diabetes compared to individuals without diabetes.

Research Design and Methods In this cohort study we used routinely-collected UK primary care data from The Health Improvement Network. In adults (>35 years) diagnosed with type 2 diabetes between 2004-2013 fractures sustained until 2019 were identified and compared to fractures sustained in individuals without diabetes. Multivariable models estimated time to first fracture following diagnosis of diabetes. Annual prevalence rates included at least one fracture in a given year.

Results Among 174,244 individuals with incident type 2 diabetes and 747,290 without diabetes, there was no increased risk of fracture among males with diabetes (adjusted hazards ratio (aHR) 0.97 (95%CI 0.94, 1.00)) and a small reduced risk among females (aHR 0.94, (95%CI 0.92, 0.96)). In those aged 85 years and over those in the diabetes cohort were at significantly lower risk of incident fracture (Males: aHR 0.85, 95%CI 0.71, 1.00; Females: aHR 0.85, 95%CI 0.78, 0.94). For those in the most deprived areas, aHRs were 0.90 (95%CI 0.83, 0.98) for males and 0.91 (95%CI 0.85, 0.97) for females. Annual fracture prevalence rates, by sex, were similar for those with and without type 2 diabetes.

Conclusion We found no evidence to suggest a higher risk of fracture following diagnosis of type 2 diabetes. After a diagnosis of type 2 diabetes individuals should be encouraged to make positive lifestyle changes, including undertaking weight-bearing physical activities that improve bone health.

Introduction

Diabetes has been described as, by far, one of the world's largest health challenges of this time.[1] The International Diabetes Federation has predicted that the number of people with diabetes will increase from 464 million in 2019 to 700 million by 2045.[2] According to primary care registers in England, diabetes is the fourth most common long-term condition after hypertension, depression and obesity, and it affects around seven percent of the population.[3] Around 95 percent of those with diabetes in the UK are over 40 years of age and 90 percent of individuals living with diabetes in the UK have type 2 diabetes.[4]

Diabetes is associated with increased morbidity and mortality. [2, 5] In those with traumatic injuries diabetes has been reported as both a risk factor and predictor of worse outcomes.[6] A number of studies conclude that those with type 2 diabetes have a higher risk of fracture than those without diabetes although risk estimates vary considerably from 20% higher to three-fold depending on the inclusion criteria (e.g. type of diabetes, age of patients), skeletal site, diabetes duration and study design.[7-9] Possible reasons stated for the observed increased fracture risk include poor mobility, impaired vision, type of treatment (in particular thiazolidinediones and SGLT2-inhibitors), change in bone properties and hypoglycaemia.[1, 10-14] It has been suggested that by restricting to those with incident type 2 diabetes, fracture risk can be estimated over a period when anti-diabetic medications and related complications are relatively low.[15] There are few databases worldwide from which those with incident type 2 diabetes can be identified and their fracture incidence assessed. Through using a large primary care database in Spain, a 20% excess risk of hip fracture was estimated in the first years following disease onset compared to matched patients without diabetes.[15]

This research sought to estimate the risk of medically-attended fractures in men and women over the age of 35 years after diagnosis with type 2 diabetes compared to those without

diabetes by using data available from a large primary care database in the UK. The secondary aim was to investigate patterns of fracture risk by age, social deprivation, body mass index (BMI) and duration of diabetes as existing evidence of these relationships is either scarce or non-existent.

Methods

This retrospectively-designed prospective cohort study used The Health Improvement Network (THIN) primary care database to identify individuals with incident type 2 diabetes and compared their fracture risk over 15 years to age-sex-practice matched individuals without diabetes. The study protocol was reviewed and approved by the THIN Scientific Review Committee (Protocol reference number: 19THIN038). As at 31 January 2019, THIN contained pseudonymised patient data from over 700 general practices across the United Kingdom, comprising approximately 6% of the UK population.[16] A wide range of data relevant to general practice encounters is recorded electronically by healthcare professionals using specific software systems that enable THIN to collect fully-coded patient electronic health records. For this study, individuals were eligible for inclusion if they were permanently registered with a THIN general practice that, between January 2004 and December 2018, had adequate acceptable computer usage (ACU) and acceptable mortality rate (AMR).[17] [18]

Individuals with a diagnosis of type 2 diabetes were identified using the methods of previous studies by a combination of Read codes, drug codes and additional health records.[19] [20] Read codes are a medical coding system, used throughout UK primary care, with a similar structure to the International Classification of Diseases (ICD). Clinicians in the UK follow the National Institute of Health and Care Excellence guidance in which a diagnosis of type 2

diabetes is made based on HbA1c or Oral Glucose Tolerance Test results consistent with WHO definitions of diagnostic criteria for type 2 diabetes.[21] Those with incident type 2 diabetes were identified as those with a first recording of type 2 diabetes within the ten-year period from 1 January 2004 to 31 December 2013 with a date of type 2 diabetes diagnosis derived from this. The comparison cohort was obtained via age-sex-practice frequency matching using eligible individuals in THIN that did not have a diagnosis of diabetes (either type 1 or type 2) within 1 January 2004 to 31 December 2013 (the same ten-year period in which incident cases were diagnosed). For each incident case, up to five individuals of the same sex and 5-year age band and from within the same practice were included. To enable analysis using follow-up time, each individual in the comparison cohort was randomly assigned an index date within the same ten-year period and followed up from this date. From here on, 'date of type 2 diabetes diagnosis' will refer to the actual diagnosis date for incident cases and the index date for those in the comparison cohort.

For both cohorts, individuals were restricted to those 35 to 99 years of age at the date of diagnosis with type 2 diabetes and to those for which their practice-level AMR and ACU dates were before their diagnosis date. In addition, those with a diagnosis of type 2 diabetes within nine months of registration at their general practice were excluded as they were assumed to be prevalent cases of diabetes. [22] All individuals entered the cohort on their date of diagnosis and were followed up for at most 15 years, i.e. where possible from 1 January 2004 to 31 December 2018.

As multiple Body Mass Index (BMI) measurements may be recorded per person, the BMI with a date of recording closest to the date of type 2 diabetes diagnosis was used. Only BMI measurements within two years of the baseline date with a value within 15-60 were included. Social deprivation, as measured by quintiles of Townsend scores, was also extracted. The

Townsend Index is an area-based measure of material deprivation derived from four census variables.[23] Due to substantive missing data in the variables BMI and Townsend score, multivariate multiple imputation using chained equations was undertaken to obtain 20 imputations separately for each cohort (type 2 diabetes and comparison) by sex. [24] BMI was imputed as a continuous variable whereas Townsend score was imputed using ordinal logistic regression. Individuals with a BMI less than 18.5 were then classified as Underweight, 18.5 to <25 as Normal, 25.0 to <30 as Overweight, 30.0 to <35 as Class I Obese, 35.0 to <40 as Class II Obese and 40 or higher as Class III Obese. Variability between imputations was accounted for using Rubin's rules. [25]

Medically-attended fractures, the outcome, were identified from the medical records based on relevant Read codes. The fracture Read code list used was adapted from one used in previous studies, to include newer fracture Read codes.[26] [27] The full fracture code list used in this study contains 1,792 Read codes. (Supplemental Table S1) Fracture Read codes entered within 9 months of patient's registration date with a practice were excluded as these may refer to fractures in the past; those with missing fracture event dates were also excluded.

For incidence calculations, all individuals were followed-up until the earliest of: 31 December 2018, date of transfer out of practice, date of death or date of first fracture following date of diagnosis (actual or index) of type 2 diabetes. To understand patterns in fracture risk over time following diagnosis with type 2 diabetes Kaplan-Meier functions of time to incident fracture were produced by age group for males and females separately. Parametric survival models using the exponential survival distribution were used to estimate hazards ratios for incident fracture for those with type 2 diabetes relative to those without. Crude and adjusted hazard ratios (aHRs), with 95% confidence intervals (CIs), were estimated using the multiply imputed dataset. Patterns in hazard ratios for males and females

by age, social deprivation, BMI, and year of type 2 diabetes diagnosis (actual or index) were examined using stratified models.

The calculation of annual fracture prevalence rates enabled consideration of multiple fractures over time. Crude annual prevalence estimates for those with type 2 diabetes and those without were calculated by determining who had a record of at least one fracture in a given year of those at risk for the full year. Date of death and date of transfer out of practice, where relevant, were used to determine annual periods of risk. Annual fracture prevalence rates and 95% CIs were estimated for males and females separately.

Intercooled Stata version 15.1 was used for data management and analysis. [28]

Ethical approval was received from the Scientific Review Committee on the 10th July 2019. (SRC Reference Number: 19THIN038).

Results

This study included 174,244 individuals with an initial diagnosis of type 2 diabetes between 2004 and 2013; and a sample of 747,290 without diabetes. (Table 1) Males represented 53% of both groups, with those aged 35-64 years of age accounting for around 60%. Those with type 2 diabetes were more likely to have had BMI recorded; only 7% of those with type 2 diabetes didn't have a BMI value recorded within two years of their diabetes diagnosis compared to 41% of those without Type 2 diabetes. Of those with BMI recorded, 54% of those with type 2 diabetes were considered obese compared to 26% of those without diabetes. Similar percentages were missing Townsend scores in both groups although 34% of those with type 2 diabetes lived in the two most deprived quintiles compared to 30% of the comparison cohort. Of those without diabetes, 31% had less than 2.5 years of follow-up

compared with only 17% of those with type 2 diabetes. The median length of follow-up was 5.8 years for those with type 2 diabetes compared to 4.4 for those without diabetes. Around 12% of individuals from both groups died during the follow-up period.

<Insert Table 1 here>

A total of 22,569 males and 40,917 females had at least one fracture recorded in THIN during median follow-up periods of 4.8 and 4.7 years respectively. The incidence rate for having at least one fracture during the follow-up period was 8.6 per 1,000 person-years at risk (PYAR; 95%CI 8.4, 8.8) for the 93,270 males in the type 2 diabetes cohort compared to 8.9 per 1,000 PYAR (95%CI 8.8, 9.1) for the 398,935 males without diabetes (Table 2). For the 80,974 females in the type 2 diabetes cohort, the fracture incidence rate was 17.2 per 1,000 PYAR (95%CI 16.9, 17.6); lower than the rate for the 348,355 females without diabetes (18.9 per 1,000 PYAR; 95%CI 18.7, 19.1). For those with type 2 diabetes steady increases in the fracture incidence rates by age were apparent over the follow-up period for males and females with older age groups having higher rates (Figure 1).

<Insert Figure 1 here>

Based on these findings, a sex by age interaction term was included in the multivariable regression. As it was statistically significant, hazard ratios were estimated stratified by sex (Table 2). Males in the type 2 diabetes cohort were estimated to have a slightly lower risk of

incident fracture (crude HR 0.96, 95%CI 0.93, 0.99) than males without diabetes. This small difference in risk decreased (aHR 0.97, 95%CI 0.94, 1.00) once adjustment had been made for age, BMI, Townsend score and year of type 2 diabetes diagnosis using the multiply imputed dataset. Females in the type 2 diabetes cohort were estimated to have a lower risk of incident fracture (crude HR 0.91, 95%CI 0.89, 0.93) than females without diabetes. The adjusted HR for females was 0.94, 95%CI 0.92, 0.96). Comparison of hazards ratios obtained from complete case analyses with those obtained following multiple imputation indicate that for these models, excluding those with missing data inflates differences in risk. (Supplemental Table S2)

<Insert Table 2 here>

Whereas the incidence rates for fracture in females aged 35-64 years were comparable, females aged 85 years and over had an incidence rate of 55.2 (95%CI 52.8, 57.7) per 1000 PYAR in those without diabetes compared to 45.5 (95%CI 41.9, 49.3) per 1000 PYAR for the type 2 diabetes cohort. (Table 2) A similar pattern was observed for males although incidence rates were noticeably lower in the oldest age group; 31.1 (95%CI 28.7, 33.8) per 1000 PYAR in those without diabetes compared to 24.7 (21.3, 28.6) per 1000 PYAR for the type 2 diabetes cohort. The difference in fracture risk increased between those in the type 2 diabetes cohort and those without diabetes, as age increased, for both males and females. Similar risks were observed for those in the youngest age group (Males: aHR 1.02, 95%CI 0.91, 1.13; Females: aHR 0.99, 95%CI 0.88, 1.12) whereas in those aged 85 years and over those in the diabetes cohort were at significantly lower risk of incident fracture (Males: aHR 0.85, 95%CI 0.71, 1.00; Females: aHR 0.85, 95%CI 0.78, 0.94).

With BMI, fracture risk for those in the type 2 diabetes cohort generally decreased relative to those without diabetes as BMI increased, although precision of the point estimates was limited. In males classified as overweight, those with type 2 diabetes were at lower risk of fracture than those without (aHR 0.91, 95%CI 0.86, 0.96). For females classified as being Class 1 or II obese, those with type 2 diabetes were also at lower risk of fracture than those without (aHR 0.91, 95%CI 0.87, 0.95).

For males in the two most deprived Townsend score quintiles, those in the type 2 diabetes cohort were at lower risk of fracture than those without diabetes (Quintile 4: aHR 0.91, 95%CI 0.84, 0.98; Quintile 5: aHR 0.90, 95%CI 0.83, 0.98). For females, those in the most deprived quintile had the largest difference; those with type 2 diabetes had an adjusted HR of 0.91 (95%CI 0.85, 0.97) compared to those without diabetes.

Males and females diagnosed with type 2 diabetes in 2004-2005 were estimated to have lower risk of an incident fracture than those without diabetes (Males: aHR 0.92, 95%CI 0.79, 0.98; Females: aHR 0.90, 95%CI 0.86, 0.95). For males diagnosed in 2012-2013, there was no evidence of a difference (adjusted HR 1.00, 95%CI 0.92, 1.09) whereas a slight protective effect for those with type 2 diabetes remained for females diagnosed in 2012-2013 (aHR 0.94, 95%CI 0.88, 1.01).

Similar distributions in terms of the total number of fractures recorded over the follow-up period were observed between those with type 2 diabetes and those without (Supplemental Table S3). Of males with type 2 diabetes that had at least one fracture during the follow-up period, 72.3% had only one, 19.7% had two and 8.0% had three or more; of males without diabetes the corresponding figures were 72.5%, 19.1% and 8.4%. For females with type 2 diabetes, 66.6% of those that had at least one fracture during the follow-up period had only

one, 22.4% had two and 11.1% had three or more; of females without diabetes the corresponding figures were 66.6%, 22.7% and 10.8%.

<Insert Figure 2 here>

The annual prevalence of at least one fracture was markedly higher for females compared to males; in 2018 females with type 2 diabetes and those without diabetes had fracture prevalence rates of 80.8 (95%CI 73.9, 88.2) and 83.9 (95%CI 80.0, 87.9) per 1,000 PYAR respectively compared to rates of 37.5 (95%CI 33.3, 42.2) and 35.9 (95%CI 33.5, 38.4) per 1,000 PYAR respectively for males (Figure 2, Supplemental Table S4). For females, the annual fracture prevalence rate was, on average, 8% higher for those without diabetes than those in the type 2 diabetes cohort with higher annual rates observed in all years except 2011 and 2016. For males, annual fracture prevalence rates from 2006-2010 were lower for those in the type 2 diabetes cohort compared with those without diabetes; higher rates for males with type 2 diabetes were observed from 2013 to 2018.

Discussion

No evidence was found to suggest a higher risk of fracture following diagnosis of type 2 diabetes. From our cohort of close to one million individuals over 35 years of age followed up for a median of 4.8 years, risk of having at least one fracture was estimated to be 6% lower for females and 3% lower for males in the type 2 diabetes cohort than for females and males without diabetes. Patterns of fracture risk by age, BMI, social deprivation and duration of diabetes were also apparent. Significantly lower fracture risk was observed in the type 2

diabetes cohort compared to those without for males and females aged 85 years and over. We also found that, for both males and females, overweight adults in the diabetes cohort were at significantly lower risk of incident fracture as were those from the most deprived areas. Males and females diagnosed with type 2 diabetes in 2004-2005 had a lower risk of incident fracture than those without diabetes; this pattern was less evident for those diagnosed in later years, particular for males. This study was limited in its ability to provide further insight into the findings by year of diabetes diagnosis; future studies may be better placed to explore age-period-cohort effects and the relationships between length of time on antidiabetic medications and risk of fracture.

The main finding from a similar population-based matched cohort study that used a Spanish primary care database was that newly diagnosed individuals with type 2 diabetes were at 20% increased risk of hip fracture with a median follow-up of 2.6 years after adjusting for BMI, previous fracture and use of oral corticosteroids.[15] However the Spanish study also reported that it found no evidence of increased risk for major osteoporotic or any osteoporotic fractures and did not include any fracture as an outcome. In another study from Germany that followed individuals for up to 10 years, those with newly diagnosed type 2 diabetes were estimated to be at significantly increased risk of fracture (adjusted HR 1.36) compared to matched controls without diabetes. [29] One possible reason for the marked difference in findings from ours could be that the study by Rathmann et al. contained a number of exclusion criteria (e.g. individuals with osteoporosis, bone metastases, cerebrovascular disease, dementia). Those with first diagnosis of any fracture prior to the first diabetes diagnosis were also excluded. In comparison, our study, with a different definition of incident fracture, had wider inclusion criteria thus making it more generalisable with greater real world applicability.

It has been proposed that the pattern of fracture risk could be biphasic; those with newly diagnosed with diabetes having reduced fracture risk and those with long-term diabetes having increased fracture risk.[30] A historical cohort study from the U.S. reported hip fracture risk increased only after ten years following diagnosis with type 2 diabetes.[31] There is evidence to suggest that type 2 diabetes actually leads to an increase in bone mineral density, although there is a negative impact on bone structure and microarchitecture.[9] This may, to some degree, explain why some studies, including ours, find that those with a recent diagnosis of type 2 diabetes have a lower risk than those without diabetes. Antidiabetic medication may also play a role in a biphasic pattern; with increased risk of fracture with rosiglitazone apparent after approximately 12 months of treatment and pioglitazone after two years. [11, 13]

A stepwise reduction in relative rates of osteoporotic fractures as age group increased was observed in a Canadian study among those with new diagnoses of type 2 diabetes.[30] In a cohort of adults with diabetes (91% with type 2) identified from a Taiwanese insurance database, the risk of fracture was estimated to be higher for those with diabetes, although the difference in risk was lower for those 70 years and older than for younger individuals. [32] This is likely to be due to the risk of fracture increasing more in the general population with age compared to those with diabetes.

Significantly lower fracture risk was observed for both overweight (BMI 25-30) males and females in our type 2 diabetes cohort compared to males and females without diabetes. There was also a tendency for the difference in fracture risk between those in the type 2 diabetes cohort and the comparison cohort to increase as BMI increased. A similar finding has previously been reported; in that study those with incident type 2 diabetes that had a baseline BMI between 30 and 35 had lower fracture risk than other categories of BMI. [15] Reasons behind this pattern are unknown but bone density, exercise and injury risk may play a part.

To our knowledge, previous studies have not examined fracture risk by deprivation among those with type 2 diabetes. It is a considerable strength of this study that we could explore this using data from THIN; interestingly distinct fracture risk patterns by deprivation were observed. For males, the difference in fracture risk between those in the type 2 diabetes cohort and those without diabetes was nearly 10% lower for those in the most deprived quintile compared to those in the least deprived quintile. For females, the comparable estimate was 4%. Fracture incidence rates for the type 2 diabetes cohort and those without diabetes provide some explanation as to why the comparative risk of fracture shows a greater reduction in the more deprived areas than the less deprived ones. As was observed with increasing age, fracture incidence rates increased more as deprivation increased in those without diabetes than in the type 2 diabetes cohort. Possible explanations for this could include different patterns of comorbidity and/or behaviours such as exercise.

Another major strength of this study is that it utilised a large primary care database that enabled the follow-up of nearly 175,000 individuals with incident type 2 diabetes and almost 750,000 without diabetes. This was possible through its retrospective design, which may on the other hand be seen as a limitation. Data obtained from individuals in the UK primary care database, THIN, has been shown to be generalizable to the wider UK population.[33, 34] The use of Read code lists to categorise those with diabetes and fractures is valid, effective and efficient. As the majority of diabetes is usually treated and managed in primary care in the UK, diagnoses, monitoring and treatments will be captured by THIN. THIN has also previously been used successfully to identify injury rates (including fracture) and to compare risk between groups of interest.[26] [35]

Incomplete capture of data is often a limitation in research using secondary data. As THIN data are taken from clinical records and not data collection forms for medical research, only data perceived by health professionals to be relevant to the consultation is recorded. For this

reason, data on potential confounders such as smoking status and alcohol consumption is poorly collected in primary care databases.[36] Electronic records may not always classify or code the type of diabetes accurately.[37] Undercounting of injuries is also possible due to them not being medically-attended, or incomplete coding of hospital admissions or emergency department attendances for fracture in the primary care record. However, it has been stated that in THIN, "for some injuries such as fractures, ascertainment is likely to be virtually complete as the vast majority will be medically attended".[38]

Over 40% of individuals without diabetes were missing BMI compared to only 7% of those with type 2 diabetes. The Quality and Outcomes Framework, an incentive programme for GP practices that rewards collection of public health indicators such as diabetes and obesity is likely to explain this differential missingness.[3] Multiple imputation was thus undertaken separately for the two cohorts (type 2 diabetes and comparison) by sex to account for missing data in both BMI and Townsend scores. Previous research exploring missing data in THIN reported height and weight (from which BMI are calculated) were 'missing at random', a requisite for valid results from multiple imputation.[39] In a more recent paper, BMI in THIN was reported to be MAR dependent on sex, age, social deprivation and disease status.[36] Since less than four percent of individuals in both cohorts were missing Townsend scores incorrect assumptions around missing data mechanisms for this variable are likely to be minimal.

For studies using routinely collected data, often data on all potential risk factors for a given outcome are not available. Potential risk factors for fracture such as steroid use and rheumatoid arthritis, in addition to behavioural factors such as smoking and alcohol use, were not included in this study due to data unavailability, data quality and complexity of inclusion.

This study focuses on the first few years after diagnosis. Interestingly there is some evidence however from studies not focused on newly diagnosed diabetes where there does seem to be a

small increase in hip fractures in particular so people with diabetes should take measures to protect their long-term bone health. [40] This would include physical activity, vitamin D supplementation and adequate dietary calcium intake.

Conclusion

This population-based comparative cohort study, that included nearly one million individuals, found no evidence to suggest that those newly diagnosed with type 2 diabetes are at higher risk of fracture than those without diabetes; females, in fact, had a small but statistically significant lower fracture risk. For those with a recent diagnosis of type 2 diabetes, a number of other groups including the elderly, those with an 'overweight' BMI and those that live in more deprived areas were also estimated to have lower fracture risk than their counterparts without type 2 diabetes. This suggests that following a diagnosis of type 2 diabetes, individuals should be encouraged to make positive lifestyle changes, including where possible, undertaking weight-bearing physical activities that improve bone health.

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Gabrielle Davie is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions: GD - Conceptualisation, Funding Acquisition, Data Curation, Formal Analysis, Writing – original draft preparation, Guarantor; KP - Conceptualisation; Data Curation, Interpretation; IP - Conceptualisation, Formal Analysis; Interpretation; EO & ET - Conceptualisation, Interpretation; All - Writing – Review and Editing.

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Table 1. Baseline and follow-up characteristics of those newly diagnosed with type 2 diabetes (n=174,244) and the comparison cohort without diabetes (n=747,290)

					Incident type 2 diabetes:					
					Yes			No		
					n	col %		n	col %	
Baseline Characteristics										
	Sex									
		Male			93,270	53.5		398,935	53.4	
		Female			80,974	46.5		348,355	46.6	
	Age (years)									
		35-44			17,441	10.0		79,421	10.6	
		45-54			34,426	19.8		153,487	20.5	
		55-64			46,836	26.9		209,654	28.1	
		65-74			43,979	25.2		183,864	24.6	
		75-84			25,367	14.6		99,040	13.3	
		85-99			6,195	3.6		21,824	2.9	
	BMI									
		Underweight			1,070	0.6		9,533	1.3	
		Normal			20,985	12.0		145,105	19.4	
		Overweight			51,953	29.8		173,097	23.2	
		Class I & II Obesity			71,767	41.2		104,194	13.9	
		Class III Obesity			16,242	9.3		10,154	1.4	
		Missing			12,227	7.0		305,207	40.8	
	Townsend Quintile									
		1 (least deprived)			38,895	22.3		188,718	25.3	
		2			36,277	20.8		167,084	22.4	
		3			36,222	20.8		151,973	20.3	
		4			33,079	19.0		126,352	16.9	
		5 (most deprived)			23,846	13.7		86,974	11.6	
		Missing			5,925	3.4		26,219	3.5	
	Year of type 2									

	diabetes diagnosis*									
		2004-2005			31,989	18.4		151,074	20.2	
		2006-2007			33,285	19.1		145,613	19.5	
		2008-2009			35,783	20.5		147,786	19.8	
		2010-2011			34,976	20.1		146,876	19.7	
		2012-2013			38,211	21.9		155,941	20.9	
Follow-up Characteristics										
	Duration of follow-up (years)									
		<2.5			28,723	16.5		228,511	30.6	
		2.5 - 5			35,490	20.4		156,948	21.0	
		5 - 7.5			45,866	26.3		162,001	21.7	
		7.5 - 10			33,385	19.2		106,568	14.3	
		10 - 12.5			21,015	12.1		63,336	8.5	
		12.5 - 15			9,765	5.6		29,926	4.0	
		Median (IQR)			5.8	3.2 - 8.6		4.4	1.8 - 7.4	
	Died during follow-up									
		No			152,203	87.4		657,642	88.0	
		Yes			22,041	12.6		89,648	12.0	

*An index date was randomly assigned for those without diabetes

Table 2. Incidence rates and hazards ratios for at least one fracture by demographic factors and year of type 2 diabetes diagnosis for those newly diagnosed and a comparison cohort

				Type 2 diabetes:											Stratified results from analysis using multiple imputation						
				Yes						No											
						PYAR per 1000 for ≥1 fracture						PYAR per 1000 for ≥1 fracture				Crude Hazards Ratio				Adj. Hazards Ratio*		
				N						N						Est.	95% CI			Est.	95% CI	
						(95% CI)						(95% CI)										
Males																					
	Overall			93,270		8.6	(8.4,	8.8)		398,935		8.9	(8.8,	9.1)		0.961	(0.931,	0.992)		0.972	(0.940,	1.005)
	Age (years)																				
		35-44		9,084		8.4	(7.7,	9.2)		41,957		8.6	(8.2,	9.0)		0.982	(0.888,	1.087)		1.015	(0.908,	1.134)
		45-54		19,911		7.4	(7.0,	7.9)		89,711		7.7	(7.5,	8.0)		0.959	(0.893,	1.029)		0.983	(0.911,	1.061)

		55-64		27,195		7.1	(6.7,	7.5)		119,992		7.4	(7.2,	7.6)		0.955	(0.898,	1.016)		0.989	(0.926,	1.056)
		65-74		23,455		8.5	(8.0,	9.0)		95,998		9.1	(8.8,	9.4)		0.934	(0.876,	0.995)		0.964	(0.902,	1.030)
		75-84		11,413		14.5	(13.5,	15.5)		43,842		15.6	(15.0,	16.2)		0.928	(0.859,	1.003)		0.985	(0.909,	1.067)
		85-99		2,212		24.7	(21.3,	28.6)		7,435		31.1	(28.7,	33.8)		0.792	(0.669,	0.938)		0.845	(0.710,	1.004)
	BMI																					
		Underweight		275		20.8	(13.7,	31.6)		3,032		25.8	(22.8,	29.2)		1.206	(0.779,	1.865)		1.032	(0.665,	1.603)
		Normal		10,157		11.7	(10.8,	12.6)		65,460		11.9	(11.5,	12.3)		1.097	(1.010,	1.190)		0.972	(0.895,	1.055)
		Overweight		31,241		8.3	(7.9,	8.8)		99,550		9.2	(8.9,	9.5)		0.981	(0.929,	1.036)		0.912	(0.864,	0.964)
		Class I & II Obesity		39,722		8.1	(7.8,	8.5)		52,672		8.3	(8.0,	8.7)		1.080	(1.018,	1.145)		1.044	(0.985,	1.107)
		Class III Obesity		6,306		7.7	(6.9,	8.6)		3,307		9.6	(8.1,	11.2)		0.874	(0.721,	1.060)		0.868	(0.716,	1.052)
		Missing		5,569						174,914												
	Townsend Quintile																					
		1 (least deprived)		21,827		7.7	(7.2,	8.1)		102,191		7.9	(7.6,	8.1)		0.971	(0.907,	1.039)		0.984	(0.918,	1.054)
		2		19,750		8.3	(7.8,	8.8)		89,286		8.1	(7.9,	8.4)		1.015	(0.948,	1.088)		1.031	(0.962,	1.106)
		3		19,339		8.8	(8.3,	9.3)		80,477		8.9	(8.6,	9.2)		0.988	(0.922,	1.058)		1.011	(0.944,	1.084)
		4		17,088		8.8	(8.3,	9.4)		66,829		10.0	(9.7,	10.4)		0.883	(0.821,	0.950)		0.909	(0.844,	0.979)
		5 (most deprived)		12,118		10.1	(9.4,	10.9)		46,603		11.7	(11.3,	12.2)		0.868	(0.716,	1.052)		0.904	(0.832,	0.982)

		Missing		3,148						13,549												
	Year of type 2 diabetes diagnosis **																					
		2004-2005		17,039		8.1	(7.6,	8.6)		80,254		8.9	(8.6,	9.2)		0.911	(0.854,	0.971)		0.919	(0.859,	0.984)
		2006-2007		17,956		8.8	(8.3,	9.3)		77,637		8.8	(8.6,	9.1)		0.998	(0.935,	1.064)		1.011	(0.944,	1.083)
		2008-2009		19,196		8.5	(8.0,	9.0)		79,129		8.9	(8.6,	9.2)		0.957	(0.893,	1.026)		0.969	(0.901,	1.042)
		2010-2011		18,771		8.7	(8.1,	9.3)		78,681		9.2	(8.9,	9.5)		0.947	(0.877,	1.022)		0.971	(0.896,	1.052)
		2012-2013		20,308		9.1	(8.5,	9.8)		83,234		9.0	(8.6,	9.3)		1.018	(0.937,	1.106)		1.001	(0.917,	1.093)
Females																						
	Overall			80,974		17.2	(16.9,	17.6)		348,355		18.9	(18.7,	19.1)		0.910	(0.889,	0.932)		0.938	(0.915,	0.962)
	Age (years)																					
		35-44		8,357		7.6	(6.9,	8.4)		37,464		7.6	(7.2,	8.0)		1.003	(0.899,	1.118)		0.991	(0.876,	1.122)
		45-54		14,515		11.1	(10.4,	11.8)		63,776		11.6	(11.2,	11.9)		0.959	(0.896,	1.027)		1.019	(0.944,	1.099)
		55-64		19,641		14.3	(13.7,	15.0)		89,662		15.6	(15.3,	16.0)		0.916	(0.870,	0.964)		0.978	(0.926,	1.033)
		65-74		20,524		18.9	(18.2,	19.7)		87,866		21.4	(21.0,	21.9)		0.885	(0.846,	0.925)		0.950	(0.907,	0.996)
		75-84		13,954		30.1	(28.8,	31.4)		55,198		36.7	(35.9,	37.5)		0.820	(0.781,	0.860)		0.889	(0.846,	0.934)

		85-99		3,983		45.5	(41.9,	49.3)		14,389		55.2	(52.8,	57.7)		0.824	(0.751,	0.903)		0.854	(0.778,	0.938)
	BMI																					
		Underweight		795		36.8	(30.8,	44.0)		6,501		39.5	(37.0,	42.2)		1.283	(1.067,	1.541)		1.054	(0.878,	1.264)
		Normal		10,828		25.1	(23.9,	26.5)		79,645		22.6	(22.1,	23.0)		1.173	(1.110,	1.239)		0.957	(0.906,	1.011)
		Overweight		20,712		19.9	(19.2,	20.7)		73,547		19.3	(18.8,	19.7)		1.084	(1.037,	1.134)		0.940	(0.899,	0.983)
		Class I & II Obesity		32,045		14.9	(14.3,	15.4)		51,522		16.6	(16.1,	17.1)		0.949	(0.909,	0.992)		0.913	(0.875,	0.954)
		Class III Obesity		9,936		11.1	(10.3,	12.0)		6,847		12.4	(11.3,	13.7)		0.895	(0.796,	1.008)		0.974	(0.865,	1.096)
		Missing		6,658						130,293												
	Townsend Quintile																					
		1 (least deprived)		17,068		16.6	(15.8,	17.4)		86,527		17.9	(17.5,	18.3)		0.931	(0.884,	0.981)		0.950	(0.902,	1.001)
		2		16,527		17.5	(16.7,	18.3)		77,798		18.6	(18.2,	19.0)		0.940	(0.892,	0.990)		0.954	(0.905,	1.006)
		3		16,883		17.1	(16.3,	17.9)		71,466		18.9	(18.4,	19.3)		0.908	(0.862,	0.957)		0.947	(0.898,	0.999)
		4		15,991		17.3	(16.5,	18.2)		59,523		20.0	(19.5,	20.5)		0.874	(0.828,	0.923)		0.919	(0.870,	0.971)
		5 (most deprived)		11,728		17.7	(16.8,	18.7)		40,371		20.9	(20.3,	21.6)		0.849	(0.797,	0.905)		0.910	(0.853,	0.970)
		Missing		2,777						12,670												
	Year of type 2 diabetes																					

	diagnosis **																				
		2004-2005		14,950		17.2	(16.5,	18.0)		70,820		19.9	(19.5,	20.3)		0.866	(0.826,	0.908)		0.903	(0.858,	0.950)
		2006-2007		15,329		17.0	(16.3,	17.8)		67,976		19.0	(18.5,	19.4)		0.897	(0.853,	0.943)		0.931	(0.883,	0.982)
		2008-2009		16,587		17.6	(16.8,	18.4)		68,657		18.8	(18.3,	19.2)		0.935	(0.887,	0.985)		0.976	(0.924,	1.031)
		2010-2011		16,205		16.7	(15.9,	17.7)		68,195		17.8	(17.4,	18.3)		0.938	(0.884,	0.996)		0.952	(0.895,	1.014)
		2012-2013		17,903		17.6	(16.7,	18.7)		72,707		18.7	(18.1,	19.2)		0.945	(0.887,	1.007)		0.941	(0.880,	1.006)

*Adjusted for other variables considered: age band, baseline BMI, baseline Townsend Quintile and diagnosis year

**An index date was randomly assigned for those without diabetes

Figure 1. Kaplan-Meier Failure time graphs of incident fracture for those newly diagnosed with type 2 diabetes by age group and sex

Figure 2. Annual prevalence rate of at least one fracture for those with type 2 diabetes and those without diabetes by sex