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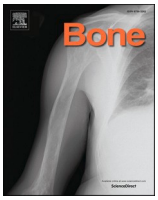

Full Length Article

Risk of hip and forearm fracture in subjects with type 2 diabetes mellitus and latent autoimmune diabetes of adults. The HUNT Study, Norway

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ABSTRACT

Type 1 and type 2 diabetes mellitus incur an increased risk of fracture, with a generally higher risk among individuals with type 1 diabetes. The fracture risk among individuals with latent autoimmune diabetes of adulthood (LADA) is not known. The present cohort study aimed to estimate the risk of hip and forearm fracture among individuals with LADA, alongside type 1 and type 2 diabetes, using data from the second survey of the Trøndelag Health Study (HUNT2) in 1995–97.

All inhabitants aged 20 years or older ($N = 92{,}936$) were invited to attend, of whom 65,234 (70%) participated. A total of 1972 (3%) reported to have diabetes; 1399 were found to have type 2 diabetes, 144 to have LADA, and 138 to have type 1 diabetes. All participants were followed prospectively with respect to hip- and forearm fractures by linkage to the local fracture registry.

During a median follow-up of 16.2 years, 2695 persons with hip fractures and 3533 persons with forearm fractures were identified. There was an increased risk of hip fracture in women with type 2 diabetes (HR = 1.51, 95% CI 1.24–1.85) and LADA (HR = 2.15, 95% CI 1.25–3.72), whereas women with type 1 diabetes did not have a significantly increased risk (HR = 2.13, 95% CI 0.89–5.14). Among men, only LADA was associated with an increased risk of hip fracture (HR = 2.69, 95% CI 1.34–5.41). There was no statistically significant association between any of the diabetes types and forearm fracture. In women with type 2 diabetes, the highest risks of hip fracture were observed among those with highest HbA_{1c} level at baseline, longest time since diagnosis, and most visual and movement impairment.

We found that individuals with LADA had an increased risk of hip fracture similar to that previously reported for individuals with type 1 diabetes, and no increased risk of forearm fracture.

1. Introduction

The prevalence of both type 2 diabetes mellitus and osteoporosis increases with age [1,2]. As the general population ages, the prevalence of both these chronic conditions will likely go up, with an estimated 592 million cases of diabetes mellitus worldwide by 2035 [3]. Both type 1 and type 2 diabetes incur an increased risk of fracture [4,5], with a generally higher risk observed among individuals with type 1. There are to our knowledge no published data on the risk of fracture for individuals with latent autoimmune diabetes of adults (LADA) as compared to type 1 and type 2 diabetes.

Although both type 1 and 2 diabetes incur an increased risk of fracture, the underlying mechanisms seem to differ. Insulin appears to be an anabolic agent in bone, with the insulinopenia during type 1

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diabetes restricting osteoblast activity and potentially increasing osteoclast activity [6]. Accordingly, there is a clear tendency towards lower bone mineral density (BMD) among individuals with type 1 diabetes, and a tendency towards elevated BMD among individuals with type 2 diabetes [5], even after adjustment for body mass index (BMI) [7–10]. It is still unclear whether the increased fracture risk in type 2 diabetes is due to a bone defect, potentially a qualitative rather than quantitative one, or the comorbidities, such as peripheral neuropathy, diabetic retinopathy and stroke. Not surprisingly, there seems to be an increased risk of fracture among those with a long-lasting disease with complications [7]. High BMI further complicates the picture, as it is both an important risk factor for type 2 diabetes [11], while also being protective against osteoporosis and hip fracture [12].

LADA shares pathophysiological traits with both type 1 and type 2 diabetes, although it more closely resembles type 1 diabetes due to the insulinopenia [13]. This presence of insulinopenia could incur an increased risk of fracture, similarly to that among individuals with type 1 diabetes. No cohort study has so far assessed fracture risk among individuals with LADA separately, as information on both circulating autoantibodies and insulin independence at diagnosis, in addition to age at diagnosis, is needed to separate them from individuals with type 1 or type 2 diabetes. The present study includes measurements of serum C-peptide and anti-GAD, which reduces this risk of misclassification. The aim of our study was therefore to examine the risk of hip and forearm fracture associated with having either type 1 diabetes, type 2 diabetes or LADA, separately.

2. Materials and methods

2.1. Study population

The Trøndelag Health Study (HUNT) is a repetitive multipurpose health study of the general population of the Nord-Trøndelag region in Mid-Norway. The current study includes data from the HUNT2 survey, which was conducted between 1995 and 1997 [14]. All inhabitants aged 20 years or older (N = 93,898) were invited to attend [15], of which 65,234 (69.5%) participated.

All participants attended a clinical examination and were asked to fill out a self-administered questionnaire on health- and lifestyle-related items, such as smoking, level of physical activity and history of cardiovascular disease. The questionnaire also included the question “do you have or have you had diabetes” (yes/no). Of the 65,234 included individuals, there were 1972 individuals (3%) who answered “yes” to this question. Of these, 1449 (73%) participated in a phase 2 examination that focused on diabetes and included measurements of HbA_{1c}, C-peptide and anti-GAD in fasting blood samples.

The initial clinical examination for all participants included measurements of blood pressure, heart rate, height, weight and waist circumference, as well as a non-fasting blood sample. Non-fasting glucose was thus measured in 99% of participants.

2.2. Definition of diabetes status

Individuals who started insulin treatment within 1 year of diagnosis and were anti-GAD positive (≥0.08) or had fasting C-peptide levels <150 pmol/l were classified as having type 1 diabetes.

Individuals who had not received insulin treatment within 1 year of diagnosis and were anti-GAD negative (<0.08) were classified as having type 2 diabetes.

Individuals who had not received insulin treatment within 1 year of diagnosis and were anti-GAD positive (≥0.08) were classified as having LADA.

There were 523 individuals who reported to have diabetes on the initial questionnaire but did not participate in the phase 2 examination. Of these, 432 (83%) had their non-fasting blood sample reexamined for anti-GAD, using the non-fasting blood sample that was collected for >99% of participants in HUNT2 during the initial clinical examination. Further details on this reexamination has been described by Sørgjerd [16]. These 432 individuals were categorized according to the same criteria for diabetes as the rest of the study population, except that fasting C-peptide levels could not be considered.

In a sensitivity analysis, age >30 years at the time of diagnosis was included as an additional criterion for LADA.

2.3. Laboratory analysis

Anti-GAD and C-peptide were analysed at the Aker Hormone Laboratory, Oslo University Hospital. Anti-GAD antibody levels were expressed as an antibody index relative to a standard serum, with an index of ≥0.08 being considered positive. C-peptide was measured with a radioimmunoassay method (Diagnostic System Laboratories, Webster, TX). Further details are given in previous publications [16–18].

2.4. Outcome

Fractures were recorded between attendance in HUNT2 (1995–1997) and until end of follow-up (December 31, 2012). Data on fractures were retrieved from a local fracture registry which included all hip and forearm fractures that were treated and/or followed-up during 1995–2012 at the only two hospitals in Nord-Trøndelag; Levanger and Namsos hospital. This registry did not include other types of fracture. The included fractures were identified through the electronic patient administration system at these hospitals, by searching for forearm fracture and hip fracture diagnosis codes and fracture related procedure codes. ICD-9 and the third version of the national classification of surgical procedures (SIFF-95) were in use until January 1, 1999, when both hospitals switched to ICD-10 and the Nomesco Classification of Surgical Procedures (NCSP). The included forearm fracture diagnosis codes were 813 (ICD-9) and S52.0-S52.9 (ICD-10), while the included hip fracture diagnosis codes were 824 (ICD-9), S72.0-S72.2 and S72.9 (ICD-10). Fractures were also identified from the local x-ray registries until December 31, 2007, with no additional fractures being identified between 2003 and 2008 compared to the patient administrative system.

A fracture was defined when: 1) The included ICD codes were accompanied by a procedure code of reduction, surgical intervention, or intervention with a rigid device or 2) A fracture was diagnosed by x-ray. Fractures due to metastatic disease were not included. Fracture diagnoses were retrospectively validated by specially trained health personnel. If there was doubt whether a fracture was new or rather a control of a previous fracture, or if the procedure code was missing, the medical record was reviewed by a medical doctor. Further details, including procedure codes, are described in previous publications [19–22]. Only the first hip fracture and first forearm fracture during follow-up were included in the present study.

Individuals with a self-reported hip or forearm fracture prior to attendance in HUNT2 were included in the main analyses but excluded in separate sensitivity analyses.

2.5. Statistics

Data were analysed using Stata for Windows (Version 15.0, Stata Corporation,

College Station, TX, USA). Risk estimate hazard ratios (HR) with 95% confidence intervals (CI) of hip and forearm fracture according to type of diabetes mellitus (DM) were obtained using multivariable Cox proportional hazard models with observation time from baseline examination until fracture, death, emigration or end of follow-up (31.12.2012), whichever occurred first. The Cox models included the following covariates: Age at baseline (years), BMI (categorical, <18.5–<25–<30–≥30 kg/m^2) and daily cigarette smoking (yes/no).

2.6. Ethics

Participation in HUNT2 was voluntary, and each participant provided an informed written consent. The study was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Data Protection Authority.

3. Results

The total study population consisted of 33,635 (53%) women and 29,626 (47%) men. Of these, 1133 were identified as having type 2 diabetes, 128 as having LADA and 123 as having type 1 diabetes during the phase 2 examination. A further 266 individuals with type 2 diabetes, 16 with LADA and 15 with type 1 diabetes were identified during the reexamination of non-fasting samples, totaling 1399 individuals with type 2 diabetes, 144 with LADA and 138 with type 1 diabetes. Of the 144 individuals with LADA, 47 (33%) were using insulin. Selection of the study population is presented in Fig. 1, and baseline characteristics in Table 1.

Median follow-up time was 16.2 years. There were 1876 women and 819 men who experienced a hip fracture during follow-up, and 2794 women and 739 men who experienced a forearm fracture during follow-up. Among individuals with diabetes, there were 140, 22 and 6 hip fractures among individuals with type 2 diabetes, LADA and type 1 diabetes, respectively, and 70, 4 and 8 forearm fractures (Table 1). Using Cox models adjusting for age, BMI and daily smoking (Table 2), we found an increased risk of hip fracture in women with type 2 diabetes (HR = 1.51, 95% CI 1.24–1.85) and LADA (HR = 2.15, 95% CI 1.25–3.72), while there was no statistically significant association in women with type 1 diabetes (HR = 2.13, 95% CI 0.89–5.14). In comparison, the risk of hip fracture among men was only increased in those with LADA (HR = 2.69, 95% CI 1.34–5.41), while there was no clear difference for type 2 diabetes (HR = 1.04, 95% CI 0.72–1.49) or type 1 diabetes (HR = 0.85, 95% CI 0.12–6.02). In a combined analysis of men

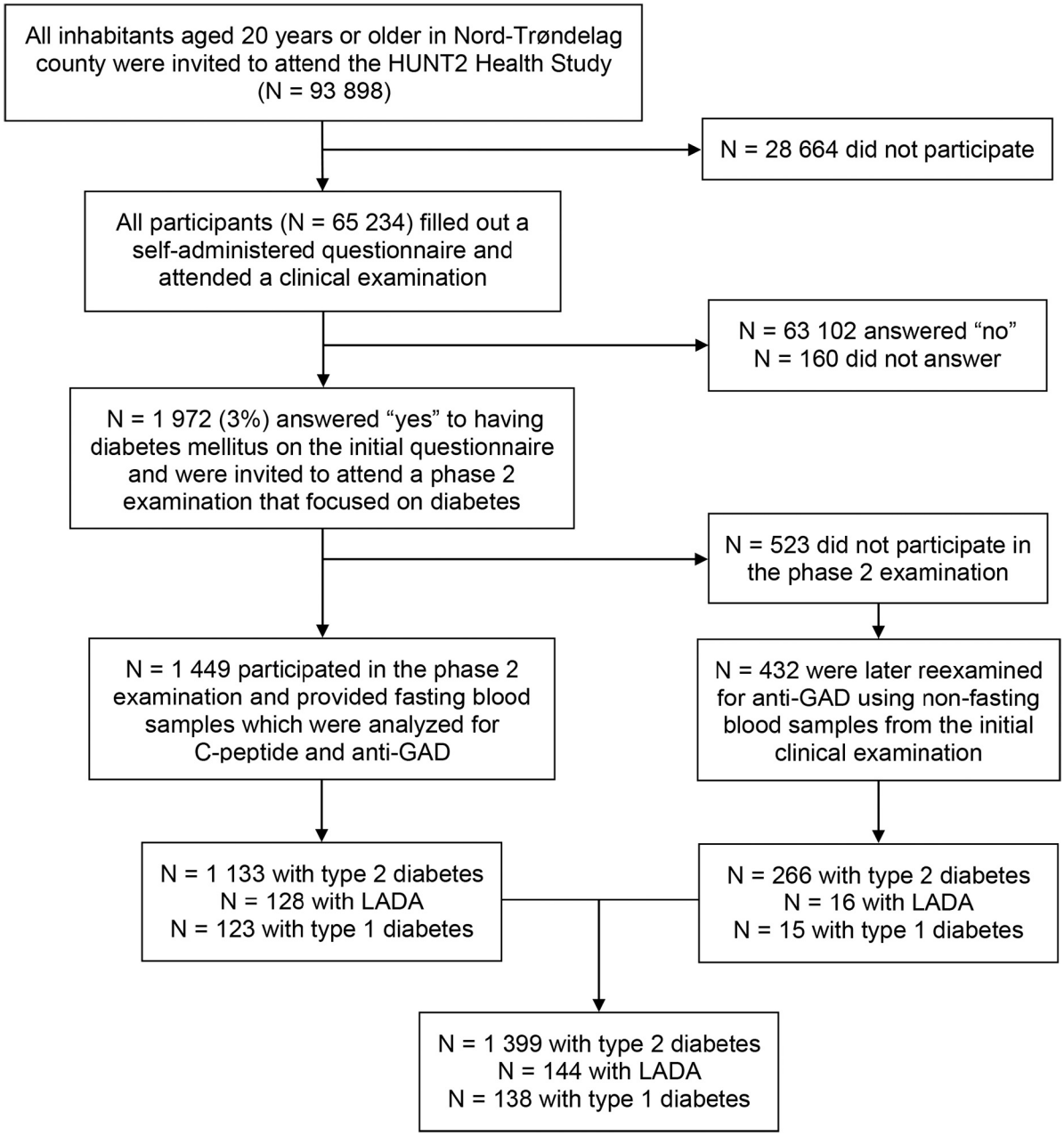

Fig. 1. Study population.

Table 1
Baseline characteristics.

	No diabetes	Diabetes type 2	Latent autoimmune diabetes in adults	Diabetes type 1
Women, N	33,635	733	68	54
Age at baseline, mean years (SD)	49.7 (17.4)	69.1 (12.2)	68.1 (13.4)	52.6 (16.5)
Body mass index (BMI), mean (SD)*	26.2 (4.5)	30.4 (5.4)	29.3 (5.7)	26.4 (4.4)
Daily smokers at baseline, N (%)**	9747 (29.3)	84 (11.7)	3 (4.6)	12 (22.2)
Hip fractures, N (%)	1749 (5.2)	108 (14.7)	14 (20.6)	5 (9.3)
Forearm fractures, N (%)	2727 (8.1)	56 (7.6)	4 (5.9)	7 (13.0)
Men, N	29,626	666	76	84
Age at baseline, mean years (SD)	49.5 (16.7)	67.1 (11.1)	67.6 (12.1)	45.5 (15.7)
Body mass index (BMI), mean (SD)*	26.4 (3.5)	28.4 (3.8)	27.4 (3.7)	25.9 (3.2)
Daily smokers at baseline, N (%)**	8379 (28.6)	139 (21.1)	11 (14.7)	21 (25.0)
Hip fractures, N (%)	778 (2.6)	32 (4.8)	8 (10.5)	1 (1.2)
Forearm fractures, N (%)	724 (2.4)	14 (2.1)	0 (0)	1 (1.2)

* 464 missing for women, 278 missing for men.
** 422 missing for women, 299 missing for men.

and women, we found that there was an increased risk of hip fracture in those with LADA (HR = 2.25, 95% CI 1.46–3.45) and type 2 diabetes (HR = 1.34, 95% CI 1.13–1.60), while there was no statistically significant association in those with type 1 diabetes (HR = 1.68, 95% CI 0.76–3.75).

There were 1037 individuals who self-reported a hip fracture prior to attendance in HUNT2. Excluding these from the analysis did not result in any large change to the reported HRs for hip fracture in either men or women (Supplemental Table 1).

Five individuals who were classified as having LADA were aged ≤30 years at the time of diagnosis. Excluding these from the analyses resulted in almost no change to the reported HRs for hip fracture among women (HR 2.15, 95% CI 1.25–3.72), men (HR 2.70, 95% CI 1.34–5.44) and in the combined analysis (HR 2.25, 95% CI 1.46–3.46).

There was no statistically significant association between any of the categories of diabetes mellitus and forearm fracture in the sex-specific analysis (Table 3), or in the combined analysis for either type 2 diabetes (HR 0.79, 95% CI 0.62–1.00), LADA (HR 0.44, 95% CI 0.16–1.17) or type 1 diabetes (HR 1.21, 95% CI 0.60–2.41). Again, there was virtually no change to the reported HRs if we excluded individuals who self-reported a forearm fracture prior to attendance in HUNT2 (Supplemental Table 2) or individuals with LADA who were aged ≤30 years at the time of diagnosis (data not shown).

Risks of hip fracture for individuals with type 2 diabetes stratified by HbA_{1c} level at baseline, time since diagnosis, and level of visual and movement impairment are presented in Table 4 and Fig. 2. In women with type 2 diabetes, the highest risks were observed among those with highest HbA_{1c} level at baseline, longest time since diagnosis, and most visual and movement impairment. There was little evidence of increased risk of hip fracture for any of the stratified groups among men. We did not have sufficient statistical power to make similar stratifications for individuals with LADA or type 1 diabetes.

4. Discussion

We found an increased risk of hip fracture among women with type 2 diabetes and LADA, and in men with LADA, compared to individuals without diabetes. The difference in risk was highest among individuals with LADA. There was no significantly increased risk of forearm fracture among any group of diabetes. The relatively few events of fracture among individuals with type 1 diabetes precluded precise risk estimates for that group.

To our knowledge, this is the first time non-vertebral fracture risk for

Table 2
Hazard ratios for hip fracture by categories of diabetes mellitus.

Diabetes category	Women					Men				
	Total N	Hip fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI	Total N	Hip fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI
None	32,819	1671	1.00	1.00	Ref.	29,089	753	1.00	1.00	Ref.
Type 2	691	103	1.37	1.51	1.24–1.85	653	31	0.92	1.04	0.72–1.49
LADA	65	13	1.95	2.15	1.25–3.72	72	8	2.41	2.69	1.34–5.41
Type 1	54	5	2.05	2.13	0.89–5.14	83	1	0.75	0.85	0.12–6.02

* Estimated using a Cox proportional hazard model including only age at baseline (years) as a covariate.
** Estimated using a Cox proportional hazard model including the following covariates measured at baseline: Age (years), BMI (categorical, <18.5–<25–<30–≥30) and daily smoking (yes/no).

Table 3
Hazard ratios for forearm fracture by categories of diabetes mellitus.

Diabetes category	Women					Men				
	Total N	Forearm fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI	Total N	Forearm fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI
None	32,818	2662	1.00	1.00	Ref.	29,089	716	1.00	1.00	Ref.
Type 2	691	55	0.71	0.78	0.60–1.02	653	14	1.00	1.02	0.60–1.74
LADA	65	4	0.54	0.58	0.22–1.53	72	0	–	–	–
Type 1	54	7	1.70	1.72	0.82–3.62	83	1	0.51	0.51	0.07–3.59

* Estimated using a Cox proportional hazard model including only age at baseline (years) as a covariate.
** Estimated using a Cox proportional hazard model including the following covariates measured at baseline: Age (years), BMI (categorical, <18.5–<25–<30–≥30) and daily smoking (yes/no).

Table 4
Stratified hazard ratios for hip fracture among individuals with type 2 diabetes mellitus.

	Women					Men				
	Total N	Hip fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI	Total N	Hip fractures N	Age-adjusted HR*	Fully-adjusted HR**	95% CI
No diabetes mellitus (DM)	32,819	1671	1.00	1.00	Ref.	29,089	753	1.00	1.00	Ref.
Type 2 DM										
HbA_{1c} at baseline <64 mmol/mol	386	56	1.35	1.43	1.10–1.87	343	17	0.87	1.02	0.63–1.65
HbA_{1c} at baseline ≥64 mmol/mol	283	45	1.44	1.65	1.22–2.22	290	14	1.05	1.13	0.67–1.93
Time since diagnosis <10 years	428	57	1.20	1.33	1.02–1.74	422	15	0.72	0.83	0.49–1.38
Time since diagnosis ≥10 years	263	46	1.67	1.81	1.35–2.43	231	16	1.25	1.36	0.83–2.24
No or slight vision impairment	353	47	1.25	1.37	1.03–1.84	390	15	0.73	0.84	0.50–1.40
Moderate or severe vision impairment	141	29	1.75	1.90	1.31–2.74	82	7	1.45	1.68	0.80–3.55
No or slight movement impairment	340	48	1.33	1.51	1.13–2.02	347	14	0.75	0.86	0.51–1.47
Moderate or severe movement impairment	111	19	1.70	1.81	1.15–2.86	124	6	0.91	1.07	0.48–2.40

* Estimated using a Cox proportional hazard model including only age at baseline (years) as a covariate.
** Estimated using a Cox proportional hazard model including the following covariates measured at baseline: Age (years), BMI (categorical, <18.5–<25–<30–≥30) and daily smoking (yes/no).

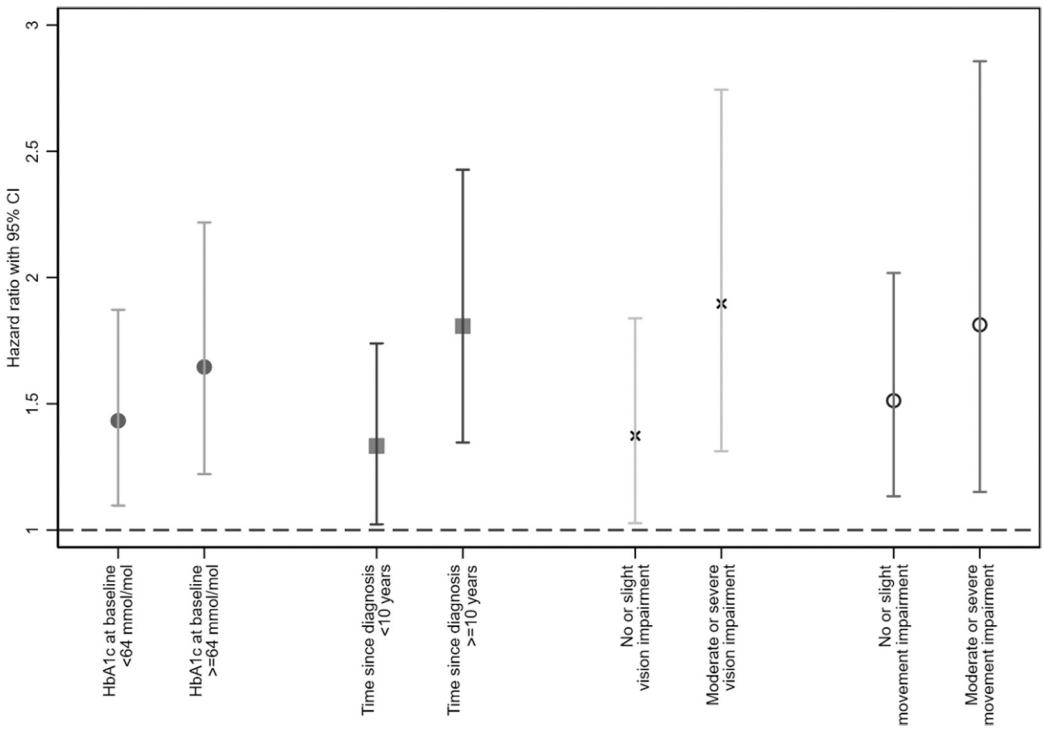

Fig. 2. Hazard ratios of hip fracture among women with type 2 diabetes compared to women without diabetes by level of HbA1c at baseline, time since diagnosis, visual impairment and movement impairment*. *Estimated using a Cox proportional hazards model with non-diabetics as the reference population (hazard ratio = 1) and the following covariates: Age at baseline (years), BMI (<18.5, <25, <30 and ≥30 kg/m^2) and daily smoking (yes/no).

individuals with LADA has been described for a large cohort. This is not surprising, given the common requirements for a precise LADA diagnosis, which include adult age at onset, the presence of circulating autoantibodies and insulin independence at diagnosis [13]. We could account for all of these requirements, with only five individuals in the LADA group reporting an age of <30 years at the time of diagnosis (see sensitivity analysis). Still, it is becoming increasingly clear that individuals with LADA present a broad range of clinical features, with varying degrees of autoimmunity, insulin resistance and association with environmental factors [23]. Previously published data from HUNT have also revealed seroconversion of antibody-positive individuals to antibody-negative during longer follow-up [18], which further complicates precise classification. It is also important to note that the categorization of diabetes was only done at the study baseline, and individuals

with LADA will likely have progressed to an increased insulin deficiency during follow-up, which would further resemble type 1 diabetes. The effect of LADA on fracture risk will thus likely change over time.

We did not have statistical power to evaluate differences in risk between the different diabetes groups. There were particularly few events among individuals with type 1 diabetes and LADA, which is not surprising given their relatively young age at the time of diagnosis, and the low incidence of hip fracture prior to 50 years of age [24]. An increased risk of hip fracture among individuals with LADA is in line with the general notion that the pathophysiology of LADA involves aspects of both type 1 and type 2 diabetes. Individuals with LADA commonly suffer from both insulinopenia and insulin resistance, as well as metabolic syndrome [13]. Although these factors are generally not as pronounced as among individuals with classical type 1 or type 2 diabetes, the combination of these risk factors may attenuate the effect on bone metabolism. Still, as previously mentioned, the relative insulin dependence among individuals with LADA will change over time, which also means that the effect on bone metabolism may change. We could not account for this temporal factor in our study design.

There was no significantly increased risk of forearm fracture among any of the diabetes groups compared to the background population. This is in line with recent meta-analyses that also did not find an increased risk of forearm fracture among individuals with type 1 or type 2 diabetes [4], and even perhaps a decreased one [25]. Forearm fractures do not appear to be tied to frailty in the same manner that hip fractures are. They commonly occur in younger individuals than those suffering a hip fracture [24,26], and are associated with an increased level of activity and level of self-rated health [27]. This link with activity is also reflected by osteoporosis being responsible for a smaller proportion of forearm fractures than hip fractures [28]. Differentiating between high- and low-energy fractures would have been beneficial to our analysis, however we did not have the data available to make this distinction.

Although we have presented data for a large cohort, there were still few events of fracture for each sub-group of diabetes, particularly for individuals with type 1 diabetes and LADA. This was especially the case for men, who as expected had a substantial lower fracture incidence than women. An increased number of participants would certainly help with this problem, but it is perhaps as important that future studies include longer follow-up periods. Individuals with type 1 diabetes and LADA are in most cases identified at a relatively young age, but we nonetheless do not expect most of them to develop fragility fractures until late adulthood. The suspected mechanisms that drive the increased fracture risks are not singular events, but rather long-lasting exposures.

In summary, we have demonstrated an increased risk of hip fracture among women with type 2 diabetes and LADA, and in men with LADA. There were too few events among individuals with type 1 diabetes to draw a conclusion for this group. There was no significantly increased risk of forearm fracture among any of the diabetes groups. Diabetes classification was performed at baseline according to established and detailed criteria but did not account for any pathophysiological development during follow-up, such as increased insulin dependency. Our results indicate that individuals with LADA should at least receive the same attention concerning fracture prevention that individuals with type 1 and 2 diabetes receive, but future studies are needed to precisely determine the relative difference in risk between diabetes groups.

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CRediT authorship contribution statement

Jesper Dahl: Conceptualization, formal analysis, methodology, validation, visualization, writing – original draft.

Hanne Løvdal Gulseth: Conceptualization, methodology, supervision, writing – review & editing.

Lisa Forsén: Conceptualization, methodology, writing – review & editing.

Mari Hoff: Validation of the fracture registry. Conceptualization, methodology, writing – review & editing.

Siri Forsmo: Conceptualization, methodology, writing – review & editing.

Bjørn Olav Åsvold: Conceptualization, methodology, writing – review & editing.

Berit Schei: Conceptualization, methodology, writing – review & editing.

Kristian Midthjell: Conceptualization, methodology, writing – review & editing.

Haakon E. Meyer: Conceptualization, funding acquisition, methodology, supervision, writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.116110.

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