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**ORIGINAL ARTICLE**

# Effects of obesity and diabetes on rate of bone density loss

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**Abstract**

*Summary* In this large registry-based study, women with diabetes had marginally greater bone mineral density (BMD) loss at the femoral neck but not at other measurement sites, whereas obesity was not associated with greater BMD loss. Our data do not support the hypothesis that rapid BMD loss explains the increased fracture risk associated with type 2 diabetes and obesity observed in prior studies.

*Introduction* Type 2 diabetes and obesity are associated with higher bone mineral density (BMD) which may be less protective against fracture than previously assumed. Inconsistent data suggest that rapid BMD loss may be a contributing factor.

*Methods* We examined the rate of BMD loss in women with diabetes and/or obesity in a population-based BMD registry for Manitoba, Canada. We identified 4960 women aged ≥ 40 years undergoing baseline and follow-up BMD assessments (mean interval 4.3 years) without confounding medication use or large weight fluctuation. We calculated annualized rate of BMD change for the lumbar spine, total hip, and femoral neck in relation to diagnosed diabetes and body mass index (BMI) category.

*Results* Baseline age-adjusted BMD was greater in women with diabetes and for increasing BMI category (all $P < 0.001$). In women with diabetes, unadjusted BMD loss was less at the lumbar spine ($P = 0.017$), non-significantly greater at the femoral neck ($P = 0.085$), and similar at the total hip ($P = 0.488$). When adjusted for age and BMI, diabetes was associated with slightly greater femoral neck BMD loss ($-0.0018$ g/cm$^2$/year, $P = 0.012$) but not at the lumbar spine or total hip. There was a strong linear effect of increasing BMI on attenuated BMI loss at the lumbar spine with negligible effects on hip BMD.

*Conclusions* Diabetes was associated with slightly greater BMD loss at the femoral neck but not at other measurement sites. BMD loss at the lumbar spine was reduced in overweight and obese women but BMI did not significantly affect hip BMD loss.

**Keywords** Bone densitometry · Diabetes · Obesity · Osteoporosis · Women

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## Introduction

Despite being associated with higher bone mineral density (BMD), type 2 diabetes is a risk factor for osteoporotic fracture independent of FRAX probability [1, 2]. Obesity, also associated with higher BMD, may be less protective against fracture than previously assumed [3, 4] and may be associated with increased fracture hazard when adjusted for higher BMD [5].

Mechanisms responsible for these observations are unclear but are likely to be multifactorial and include impaired muscle strength and quality, falls, greater skeletal impact forces related to a fall, and alterations in bone strength [5–13]. Inconsistent data also suggest that more rapid BMD loss in obese individuals or those with type 2 diabetes may be a contributing factor [14–16]. In support of the latter, there are data suggesting that serum parathyroid hormone is positively

correlated with body fat, with this relationship being independent of vitamin D status [17].

To test the hypothesis that there is more rapid BMD loss in women with diabetes and/or obesity contributing to their higher fracture risk, we examined the rate of BMD loss in a large clinical cohort of women with longitudinal BMD measurements, clinical diagnosis of diabetes, and repeated measures of weight.

## Methods

### Study population

We included all women age 40 years and older registered for health coverage in the province of Manitoba (Canada) who underwent baseline and follow-up bone density measurements of the lumbar spine and proximal femur with a single fan-beam scanner configuration (Prodigy or iDXA, GE Healthcare) between 1996 and 2013. We excluded women with significant exposure to osteoporosis medications, systemic estrogens, glucocorticoids or aromatase inhibitors, or women with measured weight change > 10% due to possible confounding. In Manitoba, health services are provided to virtually all residents and recorded through a single public healthcare system. Bone density testing with DXA has been managed as an integrated program since 1997 and uses targeted case-finding prior to age 65 years, with screening of women after age 65 years [18]. The program maintains a database of all DXA results which can be linked with other population-based computerized health databases through an anonymous personal identifier [19]. The DXA database has been previously described with completeness and accuracy in excess of 99%. The study was approved by the University of Manitoba Health Research Ethics Board.

### Bone density measurements

DXA scans were performed and analyzed in accordance with manufacturer recommendations. Hip T-scores and Z-scores were calculated using NHANES III white female reference values [20]; manufacturer reference data for white females were used to compute lumbar spine T-scores and Z-scores. The DXA instruments used in the province were cross-calibrated using anthropomorphic phantoms and no clinically significant differences were identified (T-score differences < 0.1). Therefore, all analyses are based upon the unadjusted numerical results provided by the instrument. Rate of BMD change ($g/cm^2$/year) for the lumbar spine (L1-L4), total hip, and femoral neck was studied in relation to previously diagnosed diabetes and body mass index (BMI). Densitometers showed stable long-term performance (coefficient of variation

[CV] < 0.5%) and satisfactory in vivo precision (CV 1.1% for total hip to 2.3% for femoral neck).

### Obesity and diabetes

Weight and height were obtained at the time of each DXA examination using a wall-mounted stadiometer and floor scale, respectively. Diabetes diagnosed prior to the baseline DXA was ascertained from the presence of at least two physician billing claims with a diabetes diagnosis within 2 years or at least one hospitalization with a diabetes diagnosis [21, 22]. Hospital discharge abstracts (diagnoses and procedures) were coded using the International Classification of Diseases (ICD), 9th revision, Clinical Modification [i.e., ICD-9-CM] prior to 2004 and the 10th revision of ICD, Canadian version [i.e., ICD-10-CA] thereafter. Physician billing claims were coded using ICD-9-CM as previously described [23, 24]. Medication use was obtained from the provincial pharmacy system [25].

### Statistical analysis

Rate of BMD change ($g/cm^2$/year) approximated a normal distribution (confirmed graphically and with the Kolmogorov-Smirnov test). Independent sample $t$-tests and analysis of variance (ANOVA) were used to compare baseline measures. Generalized additive models were fit to the annual rate of BMD change (cubic splines with four degrees of freedom [df] [26]) with covariates: BMI (coded as WHO category or continuous); age (coded as continuous); and a diagnosis of diabetes (coded as categorical). Statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc., Tulsa, OK).

## Results

The final study population included 4960 women (mean age 62.1, SD 9.8 years). The mean BMD testing interval was 4.3 years. Average rates of BMD loss varied from 0.4% per year for the lumbar spine to 0.7% per year for the femoral neck. Baseline BMD T-scores and age-adjusted BMD Z-scores were greater at all sites for women with versus without diabetes (Table 1, all $P < 0.001$) and for each category of increasing BMI (Table 2, all $P$ trend < 0.001).

In women with diabetes ($N = 346$) versus without diabetes ($N = 4614$), unadjusted BMD loss was less at the lumbar spine ($-0.0026$ vs $-0.0050$ $g/cm^2$/year, $P = 0.017$), not significantly greater at the femoral neck ($-0.0068$ vs $-0.0056$ $g/cm^2$/year, $P = 0.085$), and similar at the total hip ($-0.0082$ vs $-0.0068$ $g/cm^2$/year, $P = 0.488$). Adjusted for age and BMI category, diabetes was associated with slightly greater femoral neck BMD loss ($-0.0018$ $g/cm^2$/year, $P = 0.012$) but no statistically significant effect of diabetes was seen on the lumbar spine or total hip (Table 3). Further adjustment for weight

**Table 1** Study population characteristics according to diabetes status

| Descriptives | All | Diabetes | No diabetes | P value |
|---|---|---|---|---|
| N = | 4960 | 346 | 4614 | |
| Age (years) | 62.1 ± 9.8 | 66.5 ± 8.5 | 61.7 ± 9.8 | < 0.001 |
| Body mass index (kg/m$^2$) | 26.9 ± 5.2 | 30.6 ± 5.9 | 26.6 ± 5 | < 0.001 |
| Lumbar spine T-score | − 0.9 ± 1.3 | − 0.5 ± 1.4 | − 0.9 ± 1.3 | < 0.001 |
| Femoral neck T-score | − 1.3 ± 0.8 | − 1.1 ± 0.9 | − 1.3 ± 0.8 | < 0.001 |
| Total hip T-score | − 0.7 ± 1.3 | − 0.4 ± 1.1 | − 0.8 ± 1.3 | < 0.001 |
| Lumbar spine Z-score | 0.3 ± 1.3 | 0.9 ± 1.4 | 0.2 ± 1.3 | < 0.001 |
| Femoral neck Z-score | 0.1 ± 0.8 | 0.4 ± 0.9 | 0.0 ± 0.8 | < 0.001 |
| Total hip Z-score | 0.3 ± 1.3 | 0.9 ± 1.1 | 0.3 ± 1.3 | < 0.001 |
| Lumbar spine BMD change (g/cm$^2$/year) | − 0.0049 ± 0.0164 | − 0.0026 ± 0.0200 | − 0.0050 ± 0.0162 | 0.017 |
| Femoral neck BMD change (g/cm$^2$/year) | − 0.0057 ± 0.0127 | − 0.0068 ± 0.0169 | − 0.0056 ± 0.0124 | 0.085 |
| Total hip BMD change (g/cm$^2$/year) | − 0.0069 ± 0.0364 | − 0.0082 ± 0.0144 | − 0.0068 ± 0.0375 | 0.488 |
| Lumbar spine BMD change (%/year) | − 0.4 ± 1.5 | − 0.2 ± 1.8 | − 0.5 ± 1.5 | 0.005 |
| Femoral neck BMD change (%/year) | − 0.6 ± 1.5 | − 0.8 ± 1.8 | − 0.6 ± 1.4 | 0.074 |
| Total hip BMD change (%/year) | − 0.7 ± 1.3 | − 0.8 ± 1.5 | − 0.7 ± 1.3 | 0.045 |

Data expressed as mean ± SD or N (percent)

change between the scans did not alter the results (data not shown). There was no evidence of differential age effect on BMD loss in those with diabetes for any of the BMD measurement sites (all ANOVA $P \geq 0.2$).

Unadjusted BMD loss was less with increasing BMI category (Table 2). Compared with normal BMI, overweight and obesity categories were associated with reduced BMD loss at the lumbar spine (adjusted for age and diabetes status) but BMI category did not affect BMD loss at the total hip or femoral neck (Table 3). When modeled as a continuous variable, there was a strong linear effect of greater BMI to attenuate BMD loss at the lumbar spine while there were negligible effects of BMI on hip BMD loss (Fig. 1). There was no evidence of a threshold above which BMI was associated with more rapid BMD loss.

## Discussion

Diabetes was associated with slightly greater unadjusted and covariate-adjusted BMD loss at the femoral neck but not at other measurement sites. The clinical significance of this finding is questionable, however, as baseline BMD was significantly greater in women with diabetes and this higher rate of BMD loss would need to be sustained for over 20 years before femoral neck BMD would even become average for age. Therefore, our data do not support the hypothesis that rapid BMD loss explains the increased fracture risk that has been associated with type 2 diabetes [1, 2]. BMD loss at the lumbar spine was reduced in overweight and obese women, while BMI did not significantly affect hip BMD loss. This would suggest that other factors are more important in explaining

**Table 2** Study population characteristics according to BMI category

| Descriptives | Underweight < 18.5 kg/m$^2$ | Normal 18.5–24.9 kg/m$^2$ | Overweight 25.0–29.9 kg/m$^2$ | Obese 1 30.0–34.9 kg/m$^2$ | Obese 2 ≥ 35.0 kg/m$^2$ | P trend |
|---|---|---|---|---|---|---|
| N = | 77 | 1962 | 1748 | 813 | 360 | |
| Age (years) | 57.1 ± 11.2 | 60.0 ± 10.0 | 63.7 ± 9.6 | 64.1 ± 9.4 | 62.4 ± 8.3 | < 0.001 |
| Body mass index (kg/m$^2$) | 17.7 ± 0.8 | 22.5 ± 1.6 | 27.4 ± 1.4 | 32.0 ± 1.4 | 38.9 ± 3.5 | < 0.001 |
| Lumbar spine T-score | − 1.6 ± 1.3 | − 1.2 ± 1.2 | − 0.8 ± 1.3 | − 0.6 ± 1.3 | − 0.4 ± 1.3 | < 0.001 |
| Femoral neck T-score | − 1.8 ± 0.9 | − 1.5 ± 0.8 | − 1.2 ± 0.8 | − 1.1 ± 0.8 | − 0.8 ± 0.9 | < 0.001 |
| Total hip T-score | − 1.7 ± 1.0 | − 1.1 ± 0.9 | − 0.7 ± 0.9 | − 0.4 ± 2.1 | 0.0 ± 1.1 | < 0.001 |
| Lumbar spine Z-score | − 0.7 ± 1.1 | − 0.2 ± 1.2 | 0.4 ± 1.3 | 0.7 ± 1.4 | 0.8 ± 1.3 | < 0.001 |
| Femoral neck Z-score | − 0.7 ± 0.8 | − 0.2 ± 0.8 | 0.2 ± 0.8 | 0.3 ± 0.8 | 0.5 ± 0.9 | < 0.001 |
| Total hip Z-score | − 0.9 ± 0.9 | − 0.1 ± 0.9 | 0.5 ± 0.9 | 0.8 ± 2.1 | 1.1 ± 1.0 | < 0.001 |
| Lumbar spine BMD change (g/cm$^2$/year) | − 0.0093 ± 0.0154 | − 0.0068 ± 0.0159 | − 0.0033 ± 0.0164 | − 0.0028 ± 0.0175 | 0.0004 ± 0.0186 | 0.000 |
| Femoral neck BMD change (g/cm$^2$/year) | − 0.0094 ± 0.0123 | − 0.0058 ± 0.0117 | − 0.0049 ± 0.0125 | − 0.0050 ± 0.0139 | − 0.0071 ± 0.0180 | 0.001 |
| Total hip BMD change (g/cm$^2$/year) | − 0.0089 ± 0.0121 | − 0.0065 ± 0.0103 | − 0.0058 ± 0.0111 | − 0.0084 ± 0.0845 | − 0.0076 ± 0.0153 | 0.475 |
| Lumbar spine BMD change (%/year) | − 0.9 ± 1.5 | − 0.6 ± 1.5 | − 0.3 ± 1.5 | − 0.2 ± 1.6 | 0.1 ± 1.7 | < 0.001 |
| Femoral neck BMD change (%/year) | − 1.2 ± 1.6 | − 0.7 ± 1.4 | − 0.5 ± 1.4 | − 0.5 ± 1.6 | − 0.8 ± 2.0 | < 0.001 |
| Total hip BMD change (%/year) | − 1.1 ± 1.5 | − 0.7 ± 1.2 | − 0.6 ± 1.2 | − 0.6 ± 1.6 | − 0.7 ± 1.6 | 0.001 |

P value is for linear trend

**Table 3** Effect of BMI (categorical) and diabetes on rate of BMD change

| | N | Lumbar spine BMD change g/cm²/year (95% CI) | P | Total hip BMD change g/cm²/year (95% CI) | P | Femoral neck BMD change g/cm²/year (95% CI) | P |
|---|---|---|---|---|---|---|---|
| BMI category | | | | | | | |
| Underweight (< 18.5 kg/m²) | 77 | − 0.0007 (− 0.0044:0.0030) | 0.704 | − 0.0016 (− 0.0100:0.0067) | 0.699 | − 0.0029 (− 0.0058:0.0000) | 0.052 |
| Normal (18.5–24.9 kg/m²) | 1962 | Referent | N/A | Referent | N/A | Referent | N/A |
| Overweight (25.0–29.9 kg/m²) | 1748 | 0.0019 (0.0008:0.0030)* | < 0.001* | 0.0004 (− 0.002:0.0028) | 0.731 | 0.0006 (− 0.0002:0.0014) | 0.163 |
| Obese 1 (30.0–34.9 kg/m²) | 813 | 0.0024 (0.0010:0.0038)* | < 0.001* | − 0.0023 (− 0.0053:0.0007) | 0.138 | 0.0003 (− 0.0008:0.0013) | 0.611 |
| Obese 2 (≥ 35.0 kg/m²) | 360 | 0.0063 (0.0044:0.0083)* | < 0.001* | − 0.0006 (− 0.0048:0.0035) | 0.775 | − 0.0012 (− 0.0026:0.0003) | 0.107 |
| Diabetes | 346 | − 0.0013 (− 0.0032:0.0007) | 0.203 | − 0.0015 (− 0.0056:0.0026) | 0.470 | − 0.0018 (− 0.0032:− 0.0004)* | 0.012* |

All results are age-adjusted

*P value < 0.05

higher fracture risk in diabetes and obesity and likely include skeletal and non-skeletal mechanisms [5–13].

Previous studies that have examined the effect of diabetes on BMD loss have shown conflicting results. Schwartz et al. [14] examined change in hip BMD over 4 years in 480 participants with diabetes, 439 with impaired glucose metabolism, and 1172 with normal glucose metabolism from the Health ABC study of 70–79 year-old well-functioning white and black men and women. Diabetes was associated with higher baseline hip BMD; among white women with diabetes (but not among men or black women), there was greater loss in femoral neck BMD (− 0.33%/year) while total hip BMD loss was similar. More recently, Schwartz et al. [27] reported annualized BMD change in the Study of Osteoporotic Fractures (SOF) cohort, which included 409 older women with diabetes at baseline. Baseline BMD was higher in women with diabetes but there was greater BMD loss at the femoral neck, total hip, calcaneus, and spine (but not the distal radius). Greater total hip BMD loss has also reported among older men from the MrOS cohort [15]. The Study of Women's Health Across the Nation (SWAN), which included 117 women classified as having diabetes at baseline, also noted more rapid hip BMD loss (but slower spine BMD loss) in women with diabetes during menopausal transition (median follow-up was 3.1 years) [28]. In part, this may have been related to earlier menopause in women with diabetes, and the authors noted a significant interaction between menopause status and diabetes for both the total hip and lumbar spine. Greater total hip BMD loss (with a similar change in lumbar spine BMD) was seen in the placebo arm of the Fracture Intervention Trial (FIT) for diabetic versus non-diabetic women [29]. In contrast, a small cohort with 12-year follow-up found that radial bone loss was slower than expected in patients with type 2 diabetes [30]. This is consistent with the observation that bone turnover is generally reduced in those with type 2 diabetes [31], possibly mediated through increased levels of sclerostin or the accumulation of advanced glycation end products [12, 32].

Lloyd et al. [33] reported that BMD change evaluated up to 10 years according to baseline BMI (excluding underweight) in 2570 men and women of black and white race/ethnicity (age 70–79 years at enrollment). Change in total hip and whole body BMD did not differ according to BMI group, but among obese older adults, there was 0.003 g/cm²/year greater femoral neck BMD loss compared with normal weight

**Fig. 1** Partial residual plot of the estimated association between body mass index (BMI) on and rate of BMD loss (dashed lines = 95% CIs; Y-axis negative = greater BMD loss; positive = attenuated BMD loss; zero = average BMD loss). No threshold was seen above which BMI was associated with more rapid BMD loss. Results are from generalized additive models adjusted for the effects of age and diabetes. Upper panel = lumbar spine; middle panel = total hip; lower panel = femoral neck

**Lumbar spine**



**Total Hip**



**Femoral Neck**
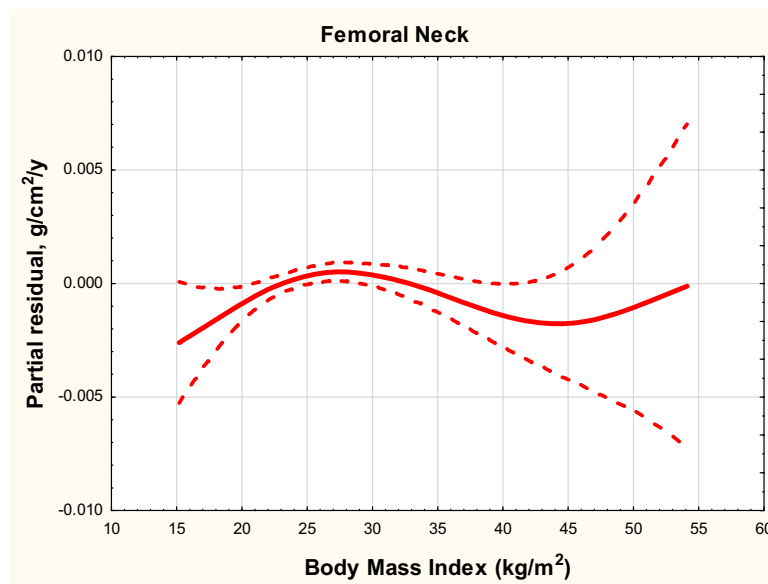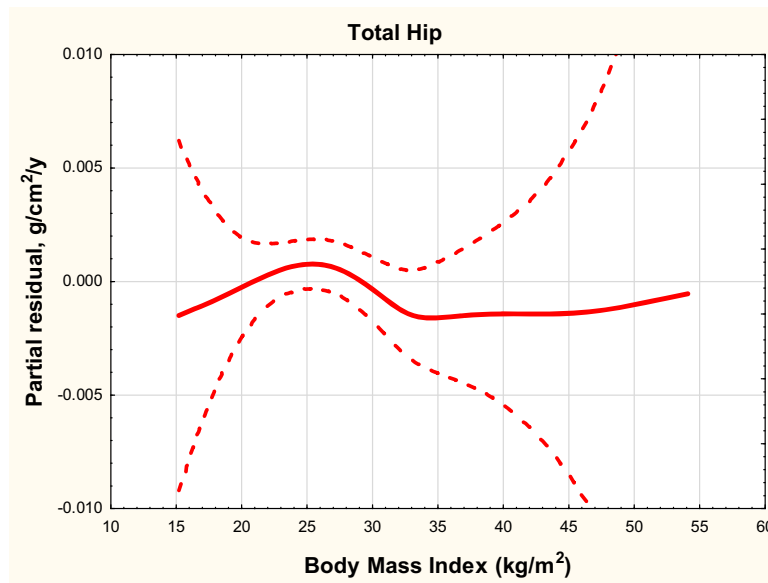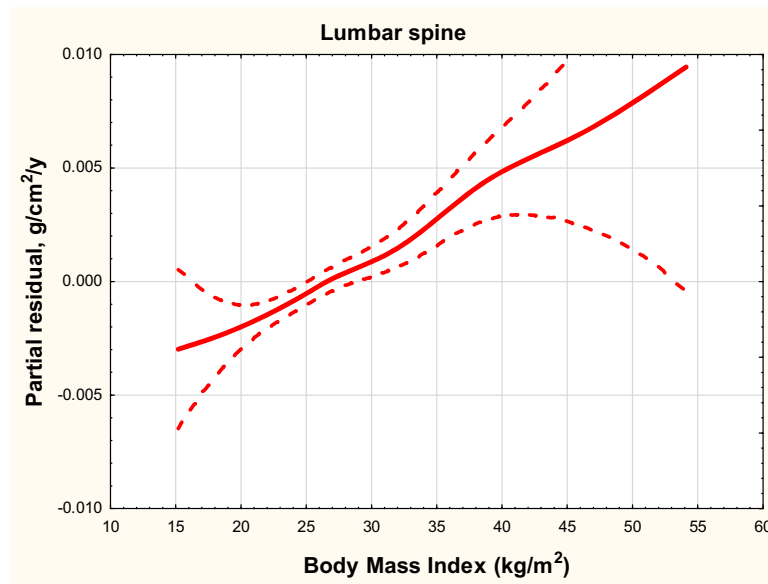
older adults ($P < 0.001$). Mean BMD values were not statistically different from the normal weight group at year 10, however, and the analysis did not account for possible change in BMI over time. In contrast, SWAN reported that greater BMI was related to slower loss rates [34].

It is difficult to reconcile these conflicting findings. Differences in population demographics and characteristics likely contribute to variations in the results. Technical factors in assessing BMD change further complicate interpretation. The well-known problem of age-related degenerative changes in the lumbar spine likely contributes to inconsistent results and the tendency of spine BMD to increase over time, particularly among obese individuals [29, 35]. Hip BMD measurements are also confounded by obesity, overlapping fat panniculus, and weight change [36, 37]. Femur neck BMD is more sensitive to the effects of fat panniculus than the total hip [37], while the latter provides a more reproducible site for detecting BMD change and may be more accurate for assessing changes in those with diabetes. We attempted to minimize these technical problems by excluding individuals with a large degree of weight change.

Strengths of our study include the large number of subjects, including the number with diabetes and broad representation across the spectrum of BMI. Limitations are also recognized, including reliance on a clinical registry with potential for referral bias, particularly in women less than age 65 years (confounding by indication). Linkage to population-based data made it possible to exclude individuals with confounding medication use. It is uncertain whether differential DXA utilization according to diabetes and BMI status would confound results, although we also note that neither diabetes nor obesity is an approved reason that community-based physicians order DXA tests irrespective of other indications. However, observed rates of BMD loss are similar to what would be expected in postmenopausal women not receiving anti-osteoporosis therapy [38]. Although type 1 and type 2 diabetes cannot be definitively distinguished in administrative data, our case definition is dominated by type 2 diabetes (over 97% based upon use of oral anti-diabetes agents and/or non-use of insulin). Menopausal status is an important determinant of BMD loss in women. Unfortunately, we did not have information on menopausal status, though the vast majority of women in this cohort is expected to be postmenopausal. The testing interval was slightly shorter in those with versus without diabetes (3.9 vs 4.3 years), but since BMD change was annualized to account for varying testing intervals, this should not affect the results. Finally, we were unable to assess diabetes complications or other diabetes-specific risk factors as modifiers of BMD loss, and this might be an important direction for future research.

In summary, our findings suggest that diabetes is associated with a slightly greater rate of BMD loss at the femoral neck but this small difference is unlikely to be clinically significant or explain the increased fracture risk that has been associated with type 2 diabetes. No significant effect of diabetes was seen on BMD loss at the total hip or lumbar spine. BMD loss at the lumbar spine was lower in overweight and obese women but BMI did not significantly affect hip BMD loss.

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