

# Natural history and risk factors for bone loss in postmenopausal Caucasian women: a 15-year follow-up population-based study

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## Abstract

**Summary** In this 15-year follow-up study, we found that the estimated rate of bone loss at the femoral neck (FN) for women aged 45–68 was linear at a rate of 1.67% per year, but quadratic for lumbar spine (LS) at a rate of 3.12% initially, and slowing down with age. We also confirmed the protective role of HRT, increasing weight, and lean mass in long-term bone loss.

**Introduction** The objective was to describe the natural history of bone loss and explore the role of environmental factors in postmenopausal women over a 15-year period.

**Methods** Bone mineral density (BMD) at the FN and the LS were measured in postmenopausal women from the Chingford Study. Height, weight, HRT status, and calcium/vitamin D supplement were assessed at each visit. Osteoarthritis of hip and spine was assessed by X-ray at baseline and at year 8.

**Results** A total of 955 postmenopausal women with an average age of 54.7 at baseline were included. Both FN and LS BMD decreased significantly with age ( $p < 0.0001$ ). The decline was larger in the LS (–3.12% per year), which showed a quadratic relationship, than in the FN (–1.67% per year) with a linear relationship. The rate of bone loss was reduced by one third annually for the FN and LS

respectively in current HRT users. Change in weight was positively associated with both  $\Delta$ FN and  $\Delta$ LS BMD ( $\beta = 0.16\%$  and  $0.09\%$  change in  $\Delta$ FN and  $\Delta$ LS BMD per kilogramme change in weight respectively,  $p < 0.0001$  for both sites). Spine OA and progression were positively associated with  $\Delta$ LS BMD ( $\beta = 1.22\%$  change in  $\Delta$ LS BMD per grade in spine OA and  $0.45\%$  change in  $\Delta$ LS BMD for patients who progressed,  $p < 0.0001$  for spine OA and  $p = 0.002$  for spine OA progression). Spine OA ( $\beta = 0.54\%$  change in  $\Delta$ FN BMD per grade,  $p < 0.0001$ ), but not progression, and hip OA were positively associated with  $\Delta$ FN BMD. Furthermore, both age and body weight at baseline were positively associated with both  $\Delta$ FN and  $\Delta$ LS BMD ( $\beta = 0.02$ – $0.04\%$  change in  $\Delta$ FN and  $\Delta$ LS BMD per year increase in age at baseline and  $0.004$ – $0.007\%$  change in  $\Delta$ FN and  $\Delta$ LS BMD per kilogramme increase in weight at baseline, all  $p < 0.0001$ ).

**Conclusion** This large population-based longitudinal study demonstrated that the decline of BMD over 15 years is linear with age for the FN, but quadratic for the LS. The study confirmed the protective role of HRT, increased weight and lean mass in long-term bone loss.

**Keywords** Age · Bone loss · HRT · Weight

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## Introduction

Osteoporosis is a systemic skeletal disease characterized by a low bone mass and a microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1]. These fragility fractures have devastating health consequences through their association with increased mortality and morbidity and are consequently a considerable burden to the health care system [2].

Bone mineral density (BMD)-based diagnostic criteria for osteoporosis have been widely used in identifying risk factors for osteoporosis. However, low BMD can result from reduced peak bone mass achieved during growth and/or excessive bone loss in later life. Risk factors for peak bone mass may be different from those for bone loss. A 6-year follow-up study [3] found that women who reported modest alcohol consumption had a greater BMD T-score at the femoral neck (FN), but no significantly different rate of BMD change than women who reported abstinence. Similar results were seen for women who reported high-school sports participation. Identifying specific risk factors for bone loss could be crucial in the prevention and intervention of osteoporosis.

Further, although it has been often stated that postmenopausal women suffer a rapid bone loss soon after menopause and then follow a gradually age-related bone loss [4], there are few data on the natural history of bone loss over long periods of time. The follow-up period in most longitudinal studies [5] was too short to assess the natural history of bone loss. Some studies [3, 6] with longer periods of follow-up had only two time-point measurements and could only give an approximate average bone loss. We therefore undertook a large population-based prospective cohort study to evaluate natural history and risk factors of bone loss over 15 years follow-up with multiple time-point BMD measurements at the lumbar spine (LS) and the FN in postmenopausal Caucasian women.

## Participants and methods

The study participants were from the Chingford Study, a well-described prospective population-based longitudinal study of osteoarthritis and osteoporosis, comprising 1,003 women aged 43 or above at entry, derived from the age/sex register of a large general practice in Chingford, North London, who are seen annually and have been described in detail previously [7, 8]. Women from this practice are similar to women in the UK general population in terms of weight, height and smoking characteristics [7]. The study was established in 1989 and the original response rate of the sample was 78%. After 15-year follow-up, 654 women remained for examination. One hundred and eleven women had died, 21 were incapacitated, and 217 lost to follow-up. The study was approved by the local ethics committee and written consent was obtained from each woman.

Bone mineral density was measured at the LS and FN by dual energy X-ray absorptiometry (DXA; Hologic QDR 1000 for year 1 to year 3; Hologic QDR 2000 for year 4 to year 6; Hologic Delphi W for year 8 to year 10, and Hologic Discovery for year 15; Hologic, Waltham, MA, USA). A cross-calibration was performed each time the

machine was upgraded. The cross calibration involved scanning 30 patients on the old scanner and then again on the new one on the same day. The coefficient of variation for inter-scanner variation was 0.05% and 0.2% for BMD and BMC respectively. Intra-scanner reproducibility, expressed as a coefficient of variation from duplicate measurements in healthy volunteers 1 week apart, was 0.8% at the LS and 1.6% at the FN. Quality control was performed regularly by using a phantom to ensure the reliability of the densitometer. All BMD measurements were performed by the same operator by a standardized protocol of measurement. In addition, the whole body DXA scan was performed at year 8 and both lean and fat mass were measured.

At each annual visit, height and weight were measured. All women completed a standardized, nurse-administered questionnaire on medical history for a number of known risk factors for osteoporosis. Medication information was detailed, particularly for those drugs that influence bone loss such as bisphosphonates and steroids. Details and duration of smoking and average number of cigarettes smoked per day were recorded at baseline. Use of hormone replacement therapy (HRT) was assessed and women were classified as “current” and “no HRT” use for each visit year. Information on the use of calcium and/or vitamin D supplementation, including duration and dosage, was also collected.

X-rays of hip and LS were performed at both baseline and year 8 visit. The Kellgren-Lawrence (KL) scoring system with a 4-point scale was utilized in the assessment of the presence of OA. Summation of KL scores was then calculated. The difference in the total score between baseline and year 8 was also calculated and OA progression was then defined as the difference  $\geq 1$ .

Since a series of BMD measurements during the 15-year follow-up period were available and the number of measurements and their time interval differed across individuals, a multilevel regression model for longitudinal data was chosen for the analysis. Multilevel models are extensions of regression models in which data are structured in groups. In particular, the data we have at hand involve repeated BMD measurements on persons—thus, BMD measurements are clustered within persons; hence, we have a two-level data structure with measurement and person levels. Note that predictors/covariates can be available at the measurement or person level.

The advantage of the multilevel model is that it uses all available data for each participant, regardless of whether the participants represent complete cases (in this case having all nine BMD measurements) or not. Effectively all participants with at least one BMD measurement make a contribution to the estimates of association. In addition, this model accounts for the between- and within-individual correlation among the

repeated measurements for a given participant. The general multilevel linear regression model for longitudinal data takes the form:

$$Y_{ti} = \beta_{00} + \beta_{10} * X_{ti} + \beta_{01} * Z_i + \beta_{11} * X_{ti}Z_i + r_{1i}X_{ti} + r_{0i} + e_{ti},$$

where  $Y_{ti}$  represents the response variable (BMD measurement) for participant  $i$  at time  $t$ ;  $X_{ti}$  represents a measurement level variable (time-varying covariate) for person  $i$  at time  $t$ , which included time elapsed at each visit from the baseline, change in body weight at each visit, and HRT status at each visit. On the other hand  $Z_i$  represents a person level variable (time-invariant covariate) for person  $i$ , which included age at baseline, body weight at baseline, and any other variables measured at person level, including age at menopause, hysterectomy, smoking status, calcium supplementation, spine and hip OA and progression, and lean mass and fat mass, which we measured only once. Furthermore  $r_{1i}$  and  $r_{0i}$  represent between-participant variations, while  $e_{ti}$  is within-participant residual error term. The estimates of the variance of these residual error terms were then used to approximate the amount of variance in bone loss that can be explained by the first and second level variables. The difference in estimated variance of the within-participant residual error term for the model that contained only the intercept and the model that contained the first-level variables was the amount of variance in bone loss that was explained by the first-level variables. The difference in estimated variance of the random intercept for the model that contained only first-level variables and the model that contained both first-level and second-level variables was the amount of the variance in bone loss that was explained by the second-level variables. More details for the method can be found in Hox [9].

The analysis was done in three stages. First, the relationship between change in BMD and time variable (e.g. increasing age) was examined. The time variable and its exponentials were entered into the model; the term was removed from the model if its estimated coefficient was not statistically significant. Second, potential risk factors were entered into the model and a factor was removed from the model if its coefficient estimate was not statistically significant. Third, interaction between the time variable and other study factors was examined by entering the products of the time variable and each of the study factors in the model. Subsequently all significant interaction term(s) remained in the final model.

A coefficient estimate was considered statistically significant if its  $p$  value (two-sided) was less than 0.05. All statistical analyses were performed using STATA/SE

version 9 for Windows (StatCorp LP, College Station, TX, USA). The STATA command used in the analysis was “*xtmixed depvar indepvar || levelvar: timevar, covariance (unstructured) variance*”, where *depvar* was BMD measurement, *indepvar* stood for factors we studied including first- and second-level variables, *levelvar* was individual indicator, and *timevar* was the time indicator. For more details, please see the STATA reference manual for longitudinal/panel data.

## Results

A total of 1,003 postmenopausal women with an average age of 54.7 (range 45–68) at baseline participated in the study and 955 had at least two DXA measures. The mean age at menopause was 49 and 26% of women had undergone hysterectomy. There were 33 women lost completely to follow-up (1 died, 14 moved, 5 withdrew, and 13 unknown) from the year 2 visit, and another 15 women who had only one DXA scan, who were not included in the analysis. However, apart from older age, there were no differences in demographic characteristics including height, weight, BMI, smoking status, and HRT use (all  $p > 0.14$ ) between the study sample and those who were not included in the analysis. By the year 15 visit, 111 women had died, 21 were incapacitated, and 217 lost to follow-up in total, but the majority of them (301 women) were still included in the analysis as they had multiple DXA measures before they dropped out. The characteristics of the sample at baseline are presented in Table 1. Only 4 women were on calcium and/or vitamin D supplementation at baseline, but 178 women were at year 15. At years 10 and 15, there were 52 and 145 women reported to be on either bisphosphonates or steroids respectively and they were excluded from the analysis after this point.

The average duration of HRT use was 27 months for the current HRT users. There was no significant difference in age, BMI, lean mass between current HRT users and the non-HRT users ( $p = 0.52$  for age,  $p = 0.75$  for BMI,  $p = 0.12$  for lean mass). But there was a significant difference in fat mass between the current HRT users and non-HRT users (non-HRT users had slightly higher fat mass than HRT users,  $p < 0.0001$ ).

Women were invited to come back for examination every year and DXA scan was performed at baseline, years 2, 3, 4, 5, 6, 8, 10, and 15. Table 2 presents the number of participants with number of BMD measurements. On average, women had their BMD measured at the FN and spine 6 times and over 955 participants had at least two BMD measurements. The mean BMD was 0.79 g/cm<sup>2</sup> and 0.98 g/cm<sup>2</sup> at the FN and spine at baseline respectively.

**Table 1** Characteristics of the study sample at baseline

|  | Mean (SD)/<br>prevalence |
|--|--------------------------|
| Age (years) at baseline                                | 54.68 (6.02)             |
| Age (years) at menopause                               | 49.49 (3.68)             |
| Age (years) at hysterectomy                            | 45.34 (7.76)             |
| Hysterectomy (%)                                       | 26 <sup>a</sup>          |
| Height (cm) at baseline                                | 161.62 (5.91)            |
| Weight (kg) at baseline                                | 66.89 (11.89)            |
| BMI (kg/m <sup>2</sup> ) at baseline                   | 25.60 (4.30)             |
| Average change in weight over 15 years (%)             | 4.65                     |
| Average change in BMI over 15 years (%)                | 7.65                     |
| Smoking status at baseline                             |                          |
| Current smoker (%)                                     | 23                       |
| Ex-smoker (%)  | 23                       |
| Current HRT user (%) at baseline                       | 24                       |
| Total lean mass (kg) at year 8                         | 38.36 (4.56)             |
| Total fat mass (kg) at year 8                          | 29.77 (10.03)            |
| Hip Kellgren-Lawrence score (range 0–4) at baseline    | 0.28 (0.67)              |
| Spine Kellgren-Lawrence score (range 0–16) at baseline | 4.17 (3.09)              |
| Femoral neck BMD (g/cm <sup>2</sup> ) at baseline      | 0.79 (0.13)              |
| Spine total BMD (g/cm <sup>2</sup> ) at baseline       | 0.98 (0.16)              |

<sup>a</sup>40% of those who had hysterectomy also had oophorectomy

The results of multilevel linear regression modelling of the change in BMD at the FN and LS with regard to the studied factors are shown in Tables 3 and 4 respectively.

For the bone loss at the FN, the variance of the within-participant residual error was 0.0012404 in the model that only contained the intercept and reduced to 0.0006895 in the model that contained first-level variables, indicating that 44.4% intra-participant variance of the bone loss at the FN was explained by the first-level variables including increasing age, change in weight at each visit and HRT use. The variance of the intercept was 0.0151581 in the model that contained the first-level variables and reduced to 0.0115405 in the model that contained both the first- and second-level variables listed in Table 3, suggesting that 23.9% inter-participant variance of the bone loss at the FN was explained by the second-level variables.

For the bone loss at the LS, the variance of the within-participant residual error was 0.0022875 in the model that only contained the intercept and reduced to 0.0013488 in the model that contained first-level variables, indicating that 41.0% intra-participant variance of the bone loss at the LS

was explained by the first-level variables including increasing age, change in weight at each visit and HRT use. The variance of the intercept was 0.0241537 in the model that contained the first-level variables and reduced to 0.0189383 in the model that contained both the first- and second-level variables listed in the Table 4, suggesting that 21.5% inter-participant variance of the bone loss at the LS was explained by the second-level variables.

The bone loss at the FN was linear with a rate of 1.67% per year whereas the bone loss at the LS was quadratic with a rate of 3.12% per year initially and slowed down with increasing age. The bone loss at both FN and LS was decreased by 0.33% per year in the current HRT users. People who were heavier and older at baseline had a reduction in bone loss. Change in weight and BMI were significantly and positively associated with change in BMD at the FN and spine (Tables 3 and 4). Both lean mass and fat mass measured by DXA at year 8 were also significantly associated with change in BMD at both the FN and spine. The magnitude of the association was larger with lean mass than with fat mass (Tables 3 and 4). Spine OA at baseline and progression at year 8 were both significantly and positively associated with change in LS BMD, but not with hip OA. Only spine OA at baseline was associated with change in FN BMD (Tables 3 and 4). Smoking was not associated with change in BMD at either LS or FN in this longitudinal sample. Calcium supplementation was not significantly associated with change in BMD at either LS or FN. The results remained the same when only analysing the data of participants who were on calcium supplementation for more than 12 months or a daily calcium dose higher than 500 mg. Age at menopause and hysterectomy were not statistically significantly associated with bone loss at either the FN or the LS.

## Discussion

To our knowledge, this study is the first large population-based longitudinal study reporting 15-year bone loss. A particular strength of this study is that participants had BMD measured at multiple time-points, which has allowed us to assess the true relationship between bone loss and age. In addition, we used the same acquisition protocol throughout the 15-year period, thus reducing any potential confounding related to acquisition.

**Table 2** Number of participants with different times of measurements of BMD

|                  | ≥2 times | ≥3  | ≥4  | ≥5  | ≥6  | ≥7  | ≥8  | ≥9  |
|------------------|----------|-----|-----|-----|-----|-----|-----|-----|
| Femoral neck BMD | 958      | 934 | 895 | 797 | 609 | 481 | 360 | 153 |
| Spine BMD        | 955      | 922 | 895 | 830 | 667 | 502 | 410 | 259 |

**Table 3** Multilevel linear regression of BMD at the femoral neck with regard to the studied risk factors

|  | Change in the femoral neck BMD (%) |                |
|--|------------------------------------|----------------|
|  | $\beta$ (SE)                       | <i>p</i> value |
| Age (years) at baseline                    | -0.85(0.07)                        | <0.0001        |
| Time (years) <sup>a</sup>                  | -1.67(0.20)                        | <0.0001        |
| Time*age at baseline (years <sup>2</sup> ) | 0.02(0.003)                        | <0.0001        |
| Weight at baseline(kg)                     | 0.34(0.04)                         | <0.0001        |
| Time*weight at baseline (per year kg)      | 0.004(0.002)                       | 0.014          |
| Change in weight (kg)                      | 0.16 (0.01)                        | <0.0001        |
| Change in BMI (kg/m <sup>2</sup> )         | 0.35 (0.03) <sup>b</sup>           | <0.0001        |
| Lean mass (kg) at year 8                   | 0.53 (0.10) <sup>b</sup>           | <0.0001        |
| Fat mass (kg) at year 8                    | 0.32 (0.05) <sup>b</sup>           | <0.0001        |
| Current HRT use (yes/no)                   | -1.20(0.23)                        | <0.0001        |
| Time*HRT use (per year for users)          | 0.32(0.03)                         | <0.0001        |
| Spine OA score at baseline                 | 0.54 (0.13)                        | <0.0001        |

All the variables listed in the table were included in the model except as indicated

<sup>a</sup> Time is the time elapsed at each visit from the baseline

<sup>b</sup> Model excluded weight-related variables

Age at menopause, hysterectomy, smoking status, calcium supplementation, spine OA progression, and hip OA and progression were not statistically significant and not included in the final model

The  $\beta$ s are interpreted as percentage change in BMD at the femoral neck per unit increase in the studied factors listed in the table. For example: -1.67 for the time variable represents a 1.67% decrease in BMD at the femoral neck per year during the follow-up period

Consistent with other studies [3, 5], we found significant bone loss at both the spine and the FN with increasing age in postmenopausal women. Furthermore, we demonstrated that the relationship between bone loss at spine and age was not linear, but quadratic, with loss rates tailing off in older age. Postmenopausal women (non-HRT users) experience a fast bone loss at the spine initially, with an estimated rate of bone loss of 3.12% per year, which slows down by 0.02% per squared age increase. This is consistent with Guthrie et al.'s report [5] in which they documented that the rate of bone loss increased for the first 3 years post-menopause and then slowed with increasing years since menopause. In contrast, in a 6-year follow-up study of 614 younger premenopausal women aged 24 to 44 at baseline, Bainbridge et al. [3] reported a linear bone loss of 0.09 g/cm<sup>2</sup> for the spine. In a smaller study of 75 Caucasian women aged 40 at baseline with 12-year follow-up, Liu-Ambrose et al. [6] reported 0.04 g/cm<sup>2</sup> bone loss at the spine over 12 years, but did not examine the relationship between bone loss and age. The discrepancy between these latter three studies and our results is likely to be due to smaller sample sizes and younger populations.

The reason for the site specificity of rate of loss with age is unclear, but the magnitude of bone loss was higher at the spine (-3.12% per year) than that at the FN (-1.67% per

year), suggesting that the effect of the hypothesized estrogen deficiency responsible for bone loss could act differently at different bone sites. Alternatively, they may also represent differing influences of weight gain with age, which may preferentially prevent some bone loss at the hip. The results are in contrast to a previous study of 224 women aged 46–59 with an average of 25 months' follow-up in which the rate of bone loss at the FN increased for the first 3 years post-menopause and then slowed down [5]. The shorter follow-up time may be an explanation for the discrepancies.

We confirmed in our cohort that women who were heavier at baseline had a slower rate of bone loss, and that change in BMI and weight were positively associated with change in BMD at both sites. This is consistent with previous studies [3, 10–14]. The protective effect of excess weight may be explained by a combination of hormonal and mechanical factors [15, 16]. We also demonstrated that lean mass had larger protective effects against bone loss than fat mass. A decline in lean body mass and an accompanying increase in fat mass occur with aging and constitute one of the major causes of disability in older persons [17]. The mechanisms behind these age-related events may include changes in the hormonal and cytokine mediators that regulate body composition [18]. Our

**Table 4** Multilevel linear regression of BMD at the lumbar spine with regard to the studied risk factors

|  | Change in spine BMD (%)  |                |
|--|--------------------------|----------------|
|  | $\beta$ (SE)             | <i>p</i> value |
| Age (years) at baseline                    | -0.92 (0.06)             | <0.0001        |
| Time (years) <sup>a</sup>                  | -3.12 (0.18)             | <0.0001        |
| Time squared (years <sup>2</sup> )         | 0.02 (0.002)             | <0.0001        |
| Time*age at baseline (years <sup>2</sup> ) | 0.04 (0.003)             | <0.0001        |
| Weight at baseline (kg)                    | 0.21 (0.03)              | <0.0001        |
| Time*weight at baseline (per year kg)      | 0.007 (0.002)            | <0.0001        |
| Change in weight (kg)                      | 0.09 (0.01)              | <0.0001        |
| Change in BMI (kg/m <sup>2</sup> )         | 0.23 (0.03) <sup>b</sup> | <0.0001        |
| Lean mass (kg) at year 8                   | 0.52 (0.09) <sup>b</sup> | <0.0001        |
| Fat mass (kg) at year 8                    | 0.16 (0.04) <sup>b</sup> | <0.0001        |
| Current HRT use (yes/no)                   | -0.31 (0.21)             | 0.134          |
| Time*HRT use (per year for users)          | 0.33 (0.03)              | <0.0001        |
| Spine OA score at baseline                 | 1.22 (0.11)              | <0.0001        |
| Spine OA progression at year 8             | 0.45 (0.15)              | 0.002          |

All the variables listed in the table were included in the model except as indicated

<sup>a</sup> Time was the time elapsed at each visit from the baseline

<sup>b</sup> Model excluded weight-related variables

Age at menopause, hysterectomy, smoking status, calcium supplementation, and hip OA and progression were not statistically significant and were not included in the final model

The  $\beta$ s are interpreted as percentage change in BMD at the lumbar spine per unit increase in the studied factors listed in the table. For example: -3.12 for time variable represents a 3.12% decrease in BMD at the lumbar spine per year during the follow-up period

observational data suggest that increasing lean mass could constitute a preventive measure against bone loss and possibly musculoskeletal aging.

In addition, we confirmed the protective effect of HRT on bone loss. The effect of HRT in slowing down bone loss is similar on the FN and LS. Also, we demonstrated that the presence of spine OA and subsequent OA progression are both positively associated with change in LS BMD, but not FN BMD. Only spine OA at baseline was associated with FN BMD change. OA of the spine is known to artefactually increase LS BMD levels [19] and this could be a possible explanation why the bone loss at LS is slowed down with increasing age but not at FN. However, the quadratic relationship between the bone loss at LS and age still remained even after adjustment for spine OA, suggesting the quadratic relationship observed is not due to the association of spine OA and age.

Contrary to expectations, we did not find any association between smoking and bone loss. However, a recent meta-analysis of the effect of smoking on BMD showed little effect [20]. This is in contrast to a previous meta-analysis [21] in which smoking was found to be associated with a greater rate of bone loss. Most studies included in this meta-analysis were cross-sectional and therefore a poor guide to real bone loss, possibly explaining the discrepancy. We also did not find any significant association between calcium supplementation and bone loss. Although several cross-sectional studies justify the recommendation of calcium supplementation to avoid calcium deficiency and to maintain bone health in postmenopausal women [22], the anti-bone loss and fracture effect of calcium alone is still questionable [23]. A recent animal study reported that calcium supplementation does not reproduce the pharmacological efficacy of alfacalcidol for the treatment of osteoporosis in rats [24]. Our results suggest that the effect of calcium supplementation in reducing bone loss might be minimal. Insufficient numbers of participants were taking vitamin D alone or in combination with calcium to estimate the effectiveness of vitamin D in this sample.

There are some limitations in the study. First, with such a long-term follow-up, there was bound to have been some participants lost to follow-up, which may bias the observations in the study. Thirty-three women were lost completely to follow-up after the year 2 visit and were not included in the analysis. However, there were no difference in terms of weight, height, BMI, smoking and HRT use between those women who were not included in the analysis and those who were, except for age, as expected. At the year 15 visit, there were 349 women who did not attend the clinic, but 301 were still included in our analysis and made a contribution to our observations. Therefore, responder bias is not a major issue in the study. Second, we upgraded our DXA scanner several times during the follow-up period. This may have led to a larger measurement error and thus

potentially reduce our power to find a significant association. However, the inter-scanner variation was minimal and we had high intra-scanner reproducibility, together with the fact that all women were scanned on the same machine at the same year visit; therefore, any misclassification due to different scanners is minimal. Other limitations include our inability to extrapolate to older women or to men.

In summary, this population-based longitudinal study reporting 15 years of bone loss documented that the decline in BMD is linear with age at the hip with a rate of 1.67%, but quadratic at the spine with an average initial loss of 3.12% occurring in middle age. The study confirmed the protective role of HRT, increased weight and particularly lean mass in long-term bone loss, which could assist prevention strategies for osteoporosis.

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**Conflicts of interest** None.

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