

Original article

# Risk factors for clinical fractures among postmenopausal women: a 10-year prospective study

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## Abstract

**Objective.** Only scarce data are available on the long-term absolute risk (AR) of all clinical fractures, taking into account the time when they occurred. Therefore, we assessed during a 10-year follow-up the risk factors associated with the occurrence of any first or second clinical fracture.

**Study design.** This was a population-based study in 10 general practice centres. The sample comprised 2372 postmenopausal women, aged between 50 and 80 years at baseline, who completed a questionnaire about the incidence of radiographically confirmed fractures and fracture risks, analysed by multiple Cox regression.

**Main outcome measure.** AR for any clinical fracture.

**Results.** During the 10-year follow-up, 380 women (16%) had a fracture. A first fracture occurred in 267 women (11%). Osteoporosis at the lumbar spine (T-score < -2.5; hazard ratio (HR) 1.8, 95% confidence interval (CI) 1.4–2.3) and age over 60 years (HR 1.4, 95% CI 1.1–1.8) were the only risk factors retained in the Cox analysis. The AR in the lowest-risk group was 10%, and it was 23% in the highest-risk group. A second fracture occurred in 113 women during follow-up (5%). The time when a fracture occurred was the only risk factor retained in the Cox analysis. The AR for a second fracture was 41% in the five years after any first fracture before baseline and 25% if the first fracture had occurred earlier (HR 1.8, 95% CI 1.3–2.7).

**Conclusion.** In postmenopausal women, over a 10-year follow-up, the AR of a second clinical fracture is highest in the five years after any first clinical fracture. The AR for a first clinical fracture is lower and depends on osteoporosis and age.

**Keywords:** Algorithms, fracture, osteoporosis, postmenopausal women, prognosis

## Introduction

The incidence of fractures is rising because of the ageing population.<sup>1–3</sup> In Europe alone, the number of osteoporotic fractures in 2000 was estimated at 3.79 million, 0.89 million of which were hip fractures. The direct costs were estimated at €31.7 billion, and in 2050 the costs are expected to increase to €76.7 billion, based on the expected demographic changes in Europe.<sup>4</sup> Therefore, guidelines on osteoporosis all advocate clinical case finding to identify those groups of patients at high risk in whom interventions to prevent fractures are most effective, in view of the high morbidity, mortality and economic burden.<sup>4,5</sup>

Although prospective population-based studies<sup>6–12</sup> show the incidence of fractures over a certain follow-

up period, only some studies have taken into account the exact timing of the incidence of fractures. This is especially true for morphometric vertebral fractures, which are not accompanied by the clinical signs and symptoms of an acute fracture<sup>13</sup> and the incidence of which is thus detectable only when radiography is performed at short intervals, such as annually. There are only a few reports available about the time course of clinical fractures.<sup>13–17</sup> Several studies suggest that fracture incidence varies over time and that a further fracture is more likely immediately after a fracture than after a longer interval.<sup>13–17</sup> Most of the studies discussed here, though, were short-term investigations,<sup>13,14,16,17</sup> only one study reported a long-term prospective follow-up investigation,<sup>15</sup> but no algorithm was constructed. Up to now, there have been no clinical algorithms

available which can be used by the clinician to predict the 10-year absolute fracture risk, from one consultation, taking into account the time course of clinical fractures.

Therefore, the goal of our study was to assess the 10-year absolute risk of incident clinical fractures, taking into account the time when fractures occurred during the follow-up.

## Methods

### Participants

In 1992–94, a cross-sectional population-based study assessed 4203 postmenopausal women aged 50–80 years (at baseline).<sup>18,19</sup> The study region can best be described as consisting of two cities in the southern part of the Netherlands, surrounded by suburban villages.<sup>18</sup>

By 2002, the study population had been reduced to 3633 postmenopausal women, as two general practices no longer participated.

### Measurements

The assessments in 1992–94 included weight (in kg), height (in cm) and bone mineral density (BMD), measured using a computer-guided dual-energy X-ray absorptiometry (DXA) instrument. The measurements were done by four experienced and specially trained research nurses. The participants then completed a questionnaire, which concentrated on variables possibly related to osteoporosis or low BMD.<sup>18,19</sup> All women were questioned about their medical history (including fracture history), family history and diet.<sup>18</sup>

Between 2003 and 2004, all women in the population received a letter informing them about the present follow-up study, as well as a questionnaire and a return envelope. The questionnaire enquired after their history of fractures in the 10 years since baseline measurements.

The risk of recall bias was kept to a minimum by asking a small number of uncomplicated questions. Since self-reports are more likely to result in over-reporting,<sup>20</sup> the research assistants checked all fractures reported by the patients in the medical files kept at the participating general practitioner (GP) centres. In the Netherlands, clinical fractures are treated at a hospital and then reported to the patient's GP, who always includes this information in the patient's medical file. In our study, every fracture reported by a patient could be confirmed in her medical file. It was assumed that all women remembered the fractures they had sustained.

### Statistics

SPSS software (version 12.0; SPSS Inc. Chicago, IL, USA) was used for the analysis. The dependent variable was the first fracture after menopause suffered by a person after the baseline measurement. The hazard ratio (HR) of the first fracture was used to compute the 10-year probability of fractures. Simple Cox regression was used to analyse possible determinants of a fracture. These analyses revealed significant determinants for a new clinical fracture over a 10-year period. The data of the women who did not sustain a fracture after baseline were censored, meaning that the follow-up time was

calculated from baseline measurement to the end of the study. Before being entered into the regression, all continuous variables were dichotomized at the mean. The 10-year probability of fractures was calculated, controlling for interactions, by entering these significant determinants into a multiple Cox regression. The statistically significant determinants were used to construct an algorithm that included the relative risk (RR) and absolute risk (AR) of a new incident clinical fracture, as well as the 95% confidence intervals (CIs).

Previous studies revealed that a recent fracture is more important than an older one.<sup>13–17</sup> Therefore, subgroup analyses, simple and multiple Cox regressions, were performed in case significant interaction was found with the determinant 'previous fracture'. The subgroup analyses were used to investigate both risk factors for a first fracture, and the influence of the time that had elapsed between a first and second fracture. For that purpose, women with a fracture history were divided into two subgroups: women with a recent fracture history (past five years before baseline) and women with an earlier fracture history (longer than five years previously, but still after menopause). The five-year cut-off point to analyse the time that had elapsed between a previous fracture and a fracture after baseline was the optimum compromise between finding a sufficient number of fractures to allow statistical evaluation and minimizing the loss to recall.<sup>18</sup>

As a cut-off point for the T-score, we used  $-2.5$  (osteoporosis) for the baseline lumbar spine BMD, as it is a threshold for therapy in many guidelines on osteoporosis.<sup>21</sup> This corresponded to 2.5 standard deviations (SD) below the mean L2–L4 BMD measured in a healthy female population aged 30 years.<sup>18</sup>

### Ethics approval

The Ethical Review Committee of Maastricht University and the Maastricht University Hospital approved the study (reference number MEC 94–196.1).

## Results

Of the 3633 women, 2847 were traceable and alive, and 2372 of them agreed to participate. The response rate was thus 83.3% (Figure 1) of the traceable and surviving women. A comparison between non-responders and responders found significant differences for the following variables: age, mean (SD) 64.3 (7.7) versus 61.6 (6.8) years ( $P < 0.01$ ); height, mean (SD) 160.8 (6.4) versus 161.6 (6.1) cm ( $P < 0.01$ ); and BMD of the lumbar spine, mean (SD) 0.92 (0.2) versus 0.93 (0.2) g/cm<sup>2</sup> ( $P = 0.01$ ).

The characteristics of the study population at baseline (1992–94) are shown in Table 1 (continuous variables) and Table 2 (discrete variables). During the 10-year follow-up period, 380 (16.0%) women had an incident clinical fracture (Table 3), 86.1% (327/380) of which were due to a fall from standing height or less. Five women did not answer the question about their fracture history and were therefore not included in further analyses. After baseline, 267 women (11.3% of the total) without a fracture history ( $n = 2029$ ) had a first fracture (13.2%) and 113 women (4.8% of the total) with a fracture history ( $n = 338$ ) had a second fracture (33.4%).

The results of the simple Cox regression are shown in Table 4. Some variables, for example calcium intake and body mass index (BMI), have various accepted cut-off points. The simple Cox regression analyses were therefore extended and used alternative cut-off points for these, for example 1100 mg/day for women aged 50–70 years and 1200 mg/day for women aged over 70 years for calcium intake<sup>22</sup> and underweight, normal, overweight and obese for BMI. However, these variables still failed to be significant predictors of clinical fractures, independent of the chosen cut-off points (data not shown).

**Table 1** Description of the study population at baseline: continuous variables ( $n=2372$ )

Variable	Mean	SD	Range
BMD (g/cm <sup>2</sup> )	0.93	0.16	0.48–2.1
Age (years)	61.6	6.8	50.0–80.0
Weight (kg)	71.3	11.7	40.0–140
Height (cm)	162	6.1	141–183
BMI (kg/m <sup>2</sup> )	27.3	4.4	15.0–53.0
Coffee intake (cups/day)	5.0	3.3	0.0–35.0
Alcohol intake (glasses/week)	1.9	5.1	0.0–42.0
Calcium intake (mg/day)	877	399	85–2837

SD, standard deviation; BMD, bone mineral density; BMI, body mass index.

**Table 2** Description of the study population at baseline: discrete variables ( $n=2372$ )

Variable	Risk factor present (n)	Percentage of sample
Osteoporosis <sup>a</sup>	503	21.2
Previous fracture	338	14.2
Use of systemic corticosteroids	8	0.3
Family history of osteoporosis	239	10.1
Rheumatoid arthritis	46	1.9
Current smoker	589	24.8
Sports at present <sup>b</sup>	911	38.4
Occupational exercise in the past <sup>c</sup>		
mild	332	14.0
moderate	1930	81.4
high	95	4.0

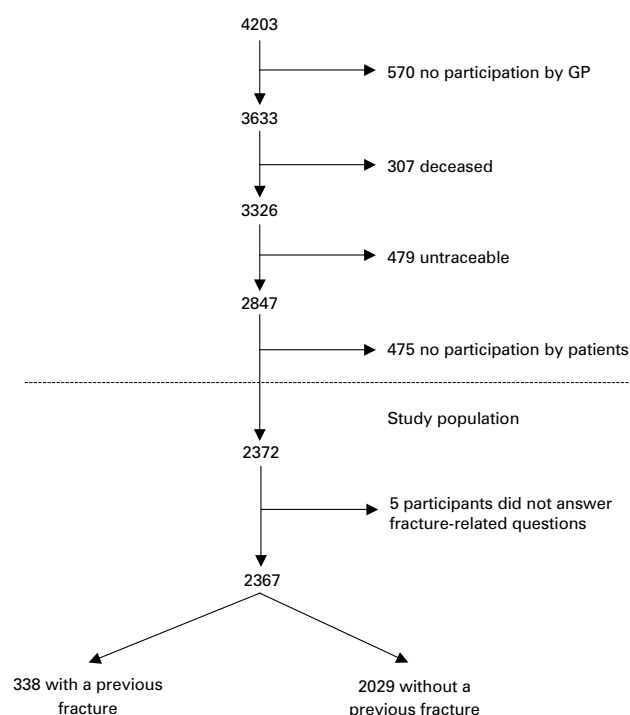
<sup>a</sup> Osteoporosis: T-score of the lumbar spine <−2.5.

<sup>b</sup> Sports at present: all sport-related physical activities (cycling, walking, playing tennis, etc.), with no distinction between duration, level of activity, and frequency.

<sup>c</sup> Participants' assessment of physical nature of employment.

**Table 3** Location and number of new clinical fractures

Location	Number
Vertebra	20
Rib	10
Upper extremities	
humerus	27
wrist	132
other	44
Lower extremities	
hip	47
femur	9
other	91
Total	380



**Figure 1** Flow chart of patient inclusion.

**Table 4** Simple Cox regression, hazard ratio and 95% confidence interval ( $n=2367$ )

Variable	Hazard ratio	95% CI
Osteoporosis <sup>a</sup>	1.7	1.3–2.1
Age > 60 years	1.5	1.2–1.9
Weight ≤ 70 kg	1.0	0.9–1.3
Height > 160 cm	1.2	1.0–1.4
Body mass index ≤ 27 kg/m <sup>2</sup>	1.0	0.8–1.3
Coffee intake > 5 cups daily	1.0	0.8–1.3
Alcohol intake > 2 glasses/week	1.3	1.0–1.7
Calcium intake ≤ 900 mg/day	1.0	0.8–1.2
Previous fracture	2.9	2.3–3.6
Use of systemic corticosteroids	2.4	0.8–7.3
Family history of osteoporosis	1.3	0.9–2.0
Rheumatoid arthritis	1.2	0.6–2.4
Current smoker	1.3	1.0–1.6
Sports at present <sup>b</sup>	1.0	0.8–1.3
Occupational exercise in the past <sup>c</sup>		
mild	1.6	0.8–3.0
moderate	1.4	0.8–2.6
high	Reference	Reference

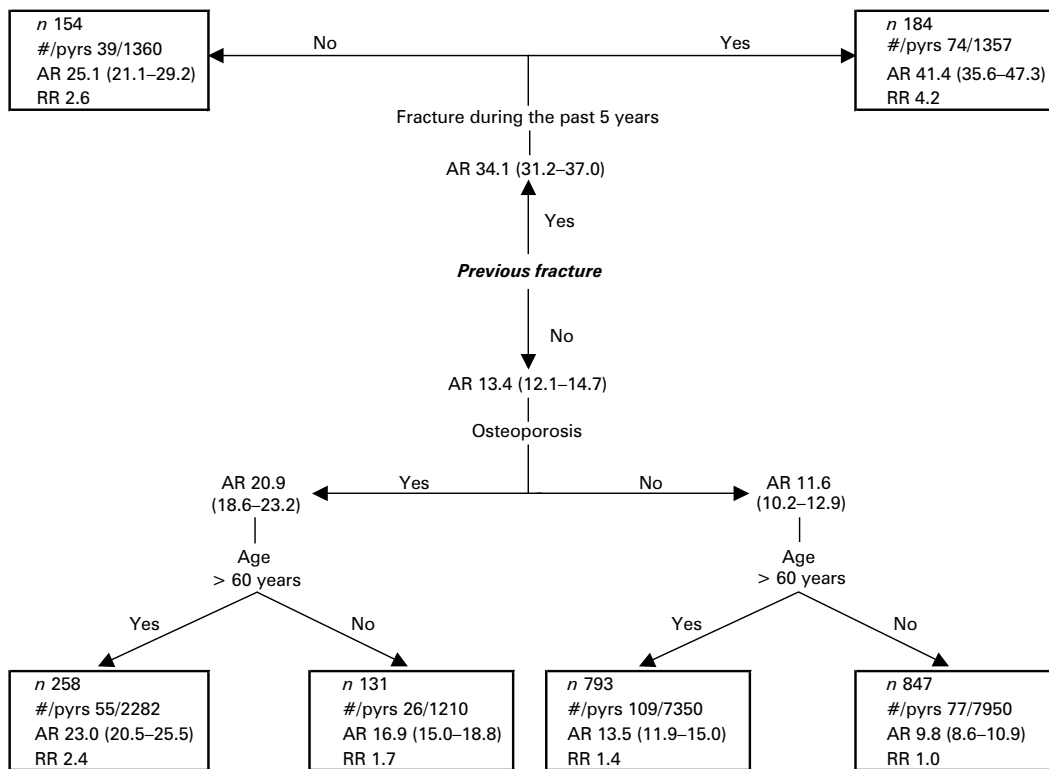
<sup>a</sup> Osteoporosis: T-score of the lumbar spine <−2.5.

<sup>b</sup> Sports at present: all sport-related physical activities, with no distinction between duration, level of activity, and frequency.

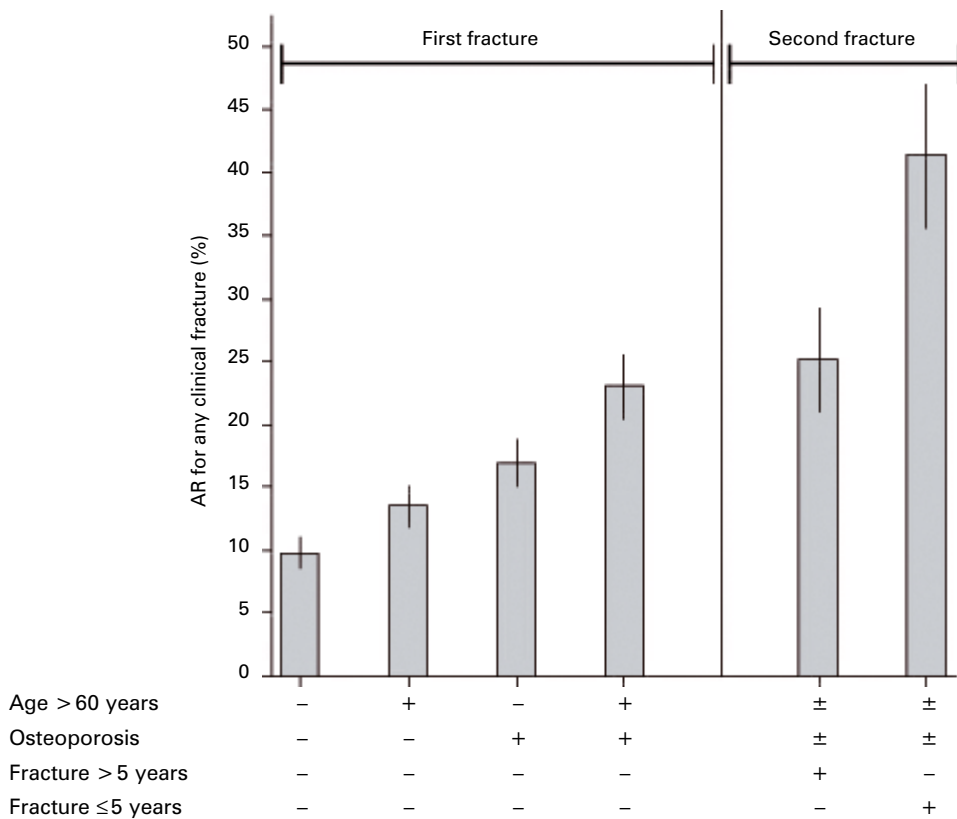
<sup>c</sup> Participants' assessment of physical nature of employment.

All determinants with a  $P$ -value < 0.10 in the simple Cox regression were included in the multiple Cox regression: osteoporosis, age < 60 years, a previous fracture, alcohol intake > 2 glasses/week, and current smoking. The multiple Cox regression for the total group found that a previous fracture (HR 2.6, 95% CI 2.1–3.3), osteoporosis (T-score <−2.5) (HR 1.4, 95% CI 1.1–1.8) and age > 60 years (HR 1.3, 95% CI 1.0–1.6) were significant independent predictors ( $P < 0.05$ ) of an incident clinical fracture. Significant interaction was found between a previous fracture and osteoporosis, indicating that

What of Height (see Table 4 - 95% CI comparable to that of Alcohol?)



**Figure 2** Algorithm of risk factors for a new clinical fracture, with number of patients (n), number of fractures per person-years (#/pyrs), absolute risk (AR) with the 95% confidence interval in parentheses, and relative risk (RR). The lowest risk category is presented at the bottom right of the algorithm. The ‘clinical order’ starts at the centre, with the question concerning a previous fracture. If the answer is ‘no’, the next step is downward; the second and third questions relate to osteoporosis and age over 60. If the answer to the central question (previous fracture) is ‘yes’, the next step is upward, and the next question asks about a recent fracture history.



**Figure 3** Absolute risk for any clinical fractures per fracture risk category. First four categories based on women without a fracture history (n=2029); last two categories based on women with a fracture history (n=338). -, risk factor not present; +, risk factor present; ±, risk factor not necessarily present (or absent).

osteoporosis contributed only as a predictor for the first and not the second fracture.

The only retained risk factors for a first fracture were osteoporosis (HR 1.9, 95% CI 1.4–2.4), followed by age >60 years (HR 1.4, 95% CI 1.1–1.8). These determinants were used to construct an algorithm (Figures 2 and 3).

The only retained risk factor for a second fracture was the time that had elapsed since the first fracture. As Figures 2 and 3 show, more than 40% of the women with a fracture during the past five years ( $n=184$ ) had a new clinical fracture during the follow-up period, compared with 25.1% in women in whom the fracture had occurred earlier ( $n=154$ ; HR 1.8, 95% CI 1.3–2.7).

## Discussion

In postmenopausal women, over a 10-year period, the AR of any clinical fracture is highest within the five years after any clinical fracture. Other risk factors made no further contributions when the time factor was considered in women with a history of fracture after menopause. The AR for a first clinical fracture was much lower and depended on osteoporosis and being over 60 years of age.

This is one of the few studies to investigate the 10-year AR of all clinical fractures while taking account of the time that elapses between a first and second fracture. It confirmed the main outcome of our five-year follow-up study,<sup>14</sup> although the present study includes four times as many fractures, three times as many participants, and a follow-up period which is twice as long.

The significant determinants for a new clinical fracture in our study have been investigated before, leading to partly comparable results.<sup>6–17,23,24</sup> A large meta-analysis reported an HR of 2.0 for fracture history.<sup>23</sup> However, limited data are available about the absolute fracture risk in relation to time that elapses between a fracture after baseline and a previous fracture.<sup>13–17</sup> As shown above, our study confirmed the role of fracture history in predicting incident clinical fractures. The significance of the time that elapsed between a first and second fracture has also been observed after morphometric vertebral fractures, as, within one year of such a fracture, 19% of postmenopausal women with osteoporosis developed an identical one.<sup>13</sup> Other studies showed that fracture risk is highest immediately after a fracture: 34%<sup>16</sup> during the first year, and 12%<sup>17</sup> and approximately 41%<sup>15</sup> during the first two years.

Age has been documented as a risk factor for fractures in several studies, independent of BMD.<sup>24</sup> Our study found comparable results, even though we studied a relatively young population with only 12.5% over the age of 70 years, whereas women included in other studies were aged 65 years and over.<sup>6,9,11</sup> Many factors that change with age have been proposed to be involved, such as skeletal factors (bone turnover, mineralization, matrix collagen quality, repair) and non-skeletal factors (risk of falling).

Apart from age, osteoporosis was the strongest determinant of a new clinical fracture in women without a previous fracture. Measuring BMD in all postmenopausal women without a previous fracture is inefficient, because this subgroup accounts for 85.5% of our total population. However, there are screening tools available

which can be used to increase the efficiency of selection for BMD screening.<sup>18,25</sup>

Our study was subject to several limitations. At baseline (1992–94), no BMD measurements at the hip were performed, owing to a lack of funding. Instead, the BMD measurements at baseline were performed at the lumbar spine. In elderly women, these measurements could have been influenced by the presence of osteoarthritis. Furthermore, 134 women (5.6%) might have improved their lifestyle, since they were given information about calcium intake and exercise after baseline measurements had been completed. However, media publicity, which women often act on, offers the same advice. These 134 women were also treated for osteoporosis. Excluding these participants did not change the results. A further limitation was that only clinical vertebral fractures were used. Morphometric vertebral fractures significantly increase the risk of a new clinical fracture<sup>13</sup> and therefore our results might have been different if the morphometric fractures had also been taken into account. Finally, there was no validation of negative reports. Hence, the number of new clinical fractures could be an underestimation. The assumption was made that women would remember a traumatic experience such as a fracture.

A fracture during the past five years is relevant for identifying postmenopausal women at high risk, since more than 40% of the women with a recent previous fracture had a new clinical fracture. These conclusions are important to a variety of professionals. Policy-makers can use the algorithm presented here for fracture prevention strategies, and GPs and hospital specialists can detect quickly and accurately which postmenopausal women are at high risk. When postmenopausal women are at high risk, appropriate fracture prevention strategies, which have been shown to decrease the risk of fractures in the short term, must be initiated.

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