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# Bone mineral density and association of osteoarthritis with fracture risk

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SUMMARY

*Objective:* High body mass index (BMI) is associated with increased risk of osteoarthritis (OA) and reduced risk of fragility fracture. However, the relationship between fragility fracture and OA remained unclear. This study sought to investigate the effect of bone mineral density (BMD) in the OA-fracture relationship.

*Methods:* Data from 2412 women and 1452 men aged >45 years in the Dubbo Osteoporosis Epidemiology Study (DOES) were analyzed. Individuals have been followed for up to 22 years (median: 7.5 years; range: 0.1–22 years). Femoral neck BMD (FNBMD) and lumbar spine BMD (LSBMD) was measured by dual energy X-ray absorptiometry (DXA) (GE LUNAR, Madison, WI). The presence of OA was ascertained at baseline by self-reported diagnosis. The incidence of low-trauma fracture was ascertained from X-ray reports.

*Results:* Overall, 29% of women and 26% of men had reported a diagnosis of OA. Fracture risk was significantly higher in women with OA than those without OA (Hazard ratio (HR) = 1.50; 95% confidence interval (CI), 1.28–1.76). However, the association was mainly observed in women with osteopenic BMD (HR = 1.74; 95% CI, 1.38–2.17) and normal-BMD (HR = 1.50; 95% CI, 1.06–2.13) and not in those with osteoporosis. Further analysis revealed that osteopenic women with OA had significant increase in risk of vertebral (HR = 1.85; 95% CI, 1.24–2.75) and limb fracture (HR = 2.49; 95% CI, 1.77–3.48), but not in hip fracture. In men, no comparable relationship was found before and after adjustment for covariates.

*Conclusion:* Women with OA have an increased risk of fragility fracture, and the risk was mainly observed in non-osteoporotic group.



## Introduction

Osteoarthritis (OA) and fragility fracture due to osteoporosis impose significant health burden in the elderly population. Approximately 30% of people aged over 65 have radiographic evidence of OA[1]. Globally, OA is the sixth leading disabling condition which accounts for nearly 3% of total global years of living with disability[2]. Fragility fracture risk also increases with advancing age. The residual lifetime risk of fragility fracture is 44% in women and 30% in men aged 60 and above[3]. Although the prevalence of these two conditions is high, their association has not been well documented.

The etiology of OA is complex, but several risk factors have been identified to be associated with the disease. High body mass index (BMI) is a well-recognized risk factor for both the onset[4–6] and progression of OA[7,8]. High bone mineral density (BMD) is also found to be associated with greater risk of OA at the knee and hip[9–11]. However, it is unclear whether OA, with its link to greater bone density, could be translated into a reduced risk of fragility fracture.

The relationship between OA and fragility fracture was first reported in 1972, based on the observation that OA seldom co-existed

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in patients with hip fracture[12]. Since then, it has been widely assumed that OA is a protective factor against fragility fracture[13–15]. An earlier study has reported that hip fracture risk was 62% lower in the OA cases compared to the controls[13]. However, several recent studies have suggested that the incidence of fracture was higher in those with than without OA[16–18]. For example, in the Women's Health Initiative (WHI) study, the risk of any fracture and spine fracture were increased by 1.1-fold and 1.2-fold, respectively, in subjects with self-reported OA[18]. A study of 6641 men and women also found a significant increase in non-vertebral fracture risk in patients with knee OA[17]. Although it has been suggested that the increased fracture risk in patients with OA was attributed to their higher tendency of falling[17,19,20], there is evidence that greater risk of falls did not fully explain the higher fracture incidence in the OA population[16–18]. BMD is a robust predictor of fracture risk, but it is not known whether BMD is an intermediary in the OA-fracture relationship. Hence, we sought to examine the effect of BMD on the association between OA and fracture risk in both men and women.

## Methods

### *Participants and setting*

This study is part of the on-going Dubbo Osteoporosis Epidemiology Study (DOES), a population-based prospective study commenced in 1989 in the city of Dubbo about 400 km northwest of Sydney, Australia. The Dubbo population, at that time, was ~32,000 and had expanded to ~41,000 by 2009. Full details of the population and study design have been described elsewhere[21]. Initially, the study population of DOES project was comprised of ~1600 men and 2095 women aged $\geq$60 years with 98.6% of Caucasian origin. Recruitment has been extended to include those who were older than 18 year of age since early 1990s. However, the selection criteria for the present study were restricted to those participants who were older than 45 and free of rheumatoid arthritis, malignancy or metabolic bone diseases. As a result, 2412 women and 1452 men recruited between 1989 and 2011, who had been followed for a median of 7.5 years (range 0.1–22 years), were included in the final analysis. This study was approved by the St Vincent's Hospital Ethics committee and written informed consent was obtained from all participants.

### *Bone measurements and risk factors assessment*

BMD was measured at the femoral neck and lumbar spine by dual energy X-ray absorptiometry (DXA), using GE LUNAR DPX-L and later PRODIGY densitometer (GE LUNAR, Madison, WI, USA). The radiation dose used is less than 0.1 μGy and the coefficient of variation of BMD at our laboratory is 1.5% for lumbar spine and 1.3% for femoral neck[22,23].

Body weight (kg) was measured in light clothing and without shoes using an electronic scale. Height (cm) was measured without shoes by a wall-mounted stadiometer. (BMI, kg/m$^2$) was calculated based on the weight and height measured at baseline. Other anthropometric variables, history of falls, smoking, physical activity level, uses of glucocorticoid, hormonal replacement therapy (HRT) were obtained via a structured questionnaire administered by a trained nurse during the interviews at baseline and biennial follow-up visits.

### *OA ascertainment*

The presence of OA was based on self-reporting and recorded in the questionnaires during the baseline interview. Participants were asked if they had ever had arthritic diseases. In the case of an affirmative answer, further questions were asked to clarify the type of arthritic disease and whether they had been medically diagnosed or treated for the conditions. Those who had been diagnosed as OA by their clinicians were referred as “OA cases”.

### *Fracture ascertainment*

Incident fracture occurring during the study period were identified through radiologists' reports from two to three radiology centers within the Dubbo region as previously described[22]. Only those resulting from low-energy trauma such as falls from standing height or less were included in this analysis. Fractures due to malignant diseases or high impact trauma (e.g., motor vehicle accident, sport injury or fall from above standing height) were excluded. Vertebral fractures were clinically diagnosed. No systemic X-ray screening for asymptomatic vertebral fracture was conducted prior to the study.

### *Data analysis*

Descriptive analyses were performed using Student's *t* test for continuous variables and chi-square tests for categorical variables. Cox's proportional hazard regression was used to assess the strength of association between OA and any fracture risk, with time to fracture being the outcome. Hazard ratios (HR) with 95% confidence intervals (CI) were computed in the presence of OA before and after adjustment for potential confounders (i.e., age, falls, prior fracture, glucocorticoid use, smoking, physical activity and HRT). The full model was selected through stepwise backward algorithm with minimum Akaike information criterion (AIC) values and the chosen covariates are all known to be associated with fracture risk. The proportional hazard assumption was tested by regression of the Schoenfeld residuals for each covariate against time to determine the independence between residuals and time[24]. No significant relationship between residuals and time was found in any of the covariates involved. Subgroup analyses were performed on individual BMD (i.e., osteoporotic, osteopenic and normal-BMD) and BMI subgroups (i.e., normal-BMI = BMI < 25 kg/m$^2$; overweight = BMI 25–29 kg/m$^2$; obese = BMI $\geq$ 30 kg/m$^2$). The areas under the receiver operating characteristic (ROC) curve (AUCs) were used to assess the models' performance with and without inclusion of OA, in terms of their discriminatory ability of fracture cases. Both models were adjusted for age, falls, FNBMD, prior fracture, smoking, glucocorticoid use, physical activity level, and HRT (in women). Net reclassification improvements (NRIs) were calculated, using the reclassification method[25], to quantify the level of improvement with the inclusion of OA. Participants were classified into three risk groups (i.e., low risk, medium risk and high risk group) based on their absolute 10-year risk of fracture for the model with OA and the model without OA included. The cut-off values were chosen according to the distribution of fracture risk in the study population (i.e., lower, middle and upper tertiles) so as to have a comparable sample size for each of the three groups. The difference in proportion of those with and those without fracture moving up or down risk category was calculated as follows:

$$\mathrm{NRI} = [\Pr(\mathrm{up}|\mathrm{cases}) - \Pr(\mathrm{down}|\mathrm{cases})] - [\Pr(\mathrm{up}|\mathrm{control}) - \Pr(\mathrm{down}|\mathrm{controls})]$$

where Pr stands for probability. All statistical analyses were performed using the R program, version R 2.15.2, for Windows[26].

## Results

### *Baseline characteristics*

Overall, 33% of women and 18% of men sustained at least one fragility fracture during the follow-up period. As expected, individuals with OA were older and had higher body weight, BMI, FNBMD and LSBMD, compared with those without OA. The incidence of falls in the past 12 months was significantly higher in the OA group than the non-OA group. Women with OA were less likely to receive HRT; whereas, men with OA were more likely to be current or past smokers compared to their non-OA counterparts. However, no significant difference in physical activity level and glucocorticoid use was found between the two groups (Table I).

### *OA and fracture risk*

At baseline, 29% of women and 26% of men reported a diagnosis of OA. As expected, prevalence of OA increased with each higher BMI and BMD category (Fig. 1). In women, the presence of OA had significantly increased the risk of any fracture (HR = 1.50; 95% CI, 1.28–1.76), hip (HR = 1.87; 95% CI, 1.34–2.62), vertebral (HR = 1.68; 95% CI, 1.28–2.21) and limb fracture (HR = 1.88; 95% CI, 1.48–2.38). After adjusting for age, the association between OA and fracture risk in women remained significant for any fracture (HR = 1.28; 95% CI, 1.09–1.50), vertebral (HR = 1.32; 95% CI, 1.01–1.74) and limb fracture (HR = 1.67; 95% CI, 1.33–2.16), but not for hip fracture. Similar results were observed when BMI or BMD was included in the model. Further adjustment for clinical risk factors (age, falls, prior fracture, smoking, physical activity, glucocorticoid use and HRT) did not alter the results significantly. In men, there was no significant association between OA and fracture risk at all skeletal sites examined, before and after adjustment for covariates (Table II).

**Table I**
Characteristics of the study population

| | Non-OA | OA |
|---|---|---|
| *Women* | $n = 1721$ | $n = 691$ |
| Age (years) | 67.46 (8.50) | 69.25 (7.10)*** |
| Weight (kg) | 66.93 (13.47) | 71.70 (14.45)*** |
| Height (cm) | 160.30 (6.41) | 159.93 (6.07) |
| BMI (kg/m$^2$) | 26.02 (4.95) | 28.02 (5.46)*** |
| FNBMD (g/cm$^2$) | 0.82 (0.15) | 0.85 (0.14)** |
| LSBMD (g/cm$^2$) | 1.06 (0.19) | 1.10 (0.21)*** |
| Fracture incidence (%) | 31.61 ($n = 544$) | 37.88 ($n = 261$)** |
| Fall in last 12 months (%) | 32.02 ($n = 551$) | 38.49 ($n = 266$)** |
| Physical activity index (MET) | 30.82 (3.08) | 30.38 (2.67) |
| Glucocorticoid use (%) | 7.67 ($n = 132$) | 7.81 ($n = 54$) |
| HRT (%) | 10.05 ($n = 173$) | 8.68 ($n = 60$)*** |
| History of smoking (%) | 32.01 ($n = 551$) | 30.54 ($n = 211$) |
| Median follow-up time (year) | 7.47 | 7.42 |
| *Men* | $n = 1066$ | $n = 386$ |
| Age (years) | 67.95 (7.54) | 69.32 (6.76)*** |
| Weight (kg) | 80.20 (13.81) | 84.12 (13.64)*** |
| Height (cm) | 173.57 (6.92) | 173.45 (6.59) |
| BMI (kg/m$^2$) | 26.56 (3.93) | 27.92 (4.03)*** |
| FNBMD (g/cm$^2$) | 0.92 (0.15) | 0.95 (0.15)*** |
| LSBMD (g/cm$^2$) | 1.24 (0.21) | 1.32 (0.22)*** |
| Fracture incidence (%) | 18.86 ($n = 201$) | 16.58 ($n = 64$) |
| Fall in last 12 months (%) | 22.80 ($n = 243$) | 26.68 ($n = 103$)** |
| Physical activity index (MET) | 33.27 (5.55) | 32.88 (5.18) |
| Glucocorticoid use (%) | 7.41 ($n = 79$) | 5.67 ($n = 22$) |
| History of smoking (%) | 59.19 ($n = 631$) | 65.28 ($n = 252$)* |
| Median follow-up time (year) | 7.39 | 7.55 |

Values are means (SD) unless specified otherwise; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

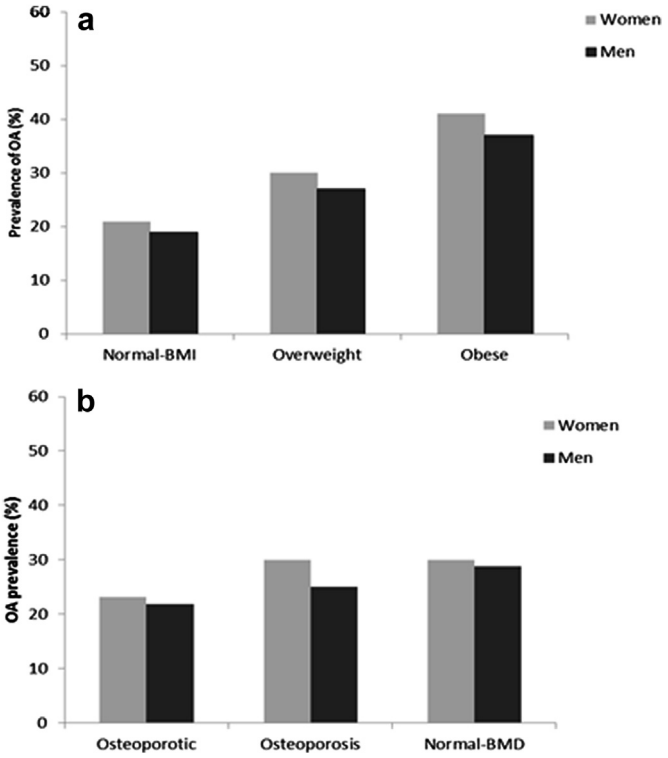


**Fig. 1.** Prevalence of OA for different (a) BMI and (b) BMD groups in women and men.

### *OA and fracture risk by BMD*

The incidence rates of fracture were consistently higher in women with OA rather than without OA across all BMD groups [Fig. 2(a)]. However, the association between OA and fracture risk was only significant in women with osteopenia or normal-BMD, and not in those with osteoporosis. The unadjusted HR of any fracture for OA were 1.02 (95% CI, 0.73–1.43), 1.63 (95% CI, 1.31–2.01) and 1.58 (95% CI, 1.15–2.20) in osteoporotic, osteopenic and normal-BMD women, respectively. Further adjustment for clinical risk factors yielded similar associations (Table III). The risk of hip fracture was not significantly associated with OA after adjusted for confounders, regardless of the BMD status. On the other hand, the adjusted risk of vertebral and limb fracture were significantly increased by 1.9-fold (95% CI, 1.24–2.75) and 2.5-fold (95% CI, 1.77–3.48) respectively, with the presence of OA in osteopenic women; but not in those with osteoporotic and normal-BMD (Table III).

In men, the fracture incidence rates were not much different between OA and non-OA groups for those with osteopenic and normal-BMD [Fig. 2(b)], and no significant association was found between OA and risk of any fracture, hip, vertebral and limb fracture (Table III). Although men with osteoporosis appeared to have lower fracture incidence rate among those with OA (39%) than those without (42%) [Fig. 2(b)], the associations were not significant before and after adjusting for covariates (Table III).

### *OA and fracture risk by BMI categories*

The association between OA and fracture risk was assessed for each BMI subgroup (i.e., normal-BMI, overweight and obese) as shown in Table III. In men, OA was not a significant predictor of fracture risk in any of the BMI category or fracture type. However, a significant increase in risk of any fracture was observed in OA women across all BMI categories. The presence of OA was

**Table II**
Association between OA and fracture risk before and after adjustment for covariates in women and men

| | HR (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Women | | | | Men | | | |
| | Any fracture ($n = 805$) | Hip fracture ($n = 178$) | Vertebral fracture ($n = 274$) | Limb fracture ($n = 353$) | Any fracture ($n = 265$) | Hip fracture ($n = 59$) | Vertebral fracture ($n = 99$) | Limb fracture ($n = 107$) |
| OA (unadjusted) | **1.50 (1.28–1.76)** | **1.87 (1.34–2.62)** | **1.68 (1.28–2.21)** | **1.88 (1.48–2.38)** | 0.81 (0.61–1.07) | 1.00 (0.57–1.77) | 0.82 (0.52–1.29) | 0.71 (0.45–1.12) |
| OA (adjusted for age) | **1.28 (1.09–1.50)** | 1.29 (0.92–1.81) | **1.32 (1.01–1.74)** | **1.67 (1.33–2.16)** | 0.94 (0.69–1.28) | 1.06 (0.57–1.95) | 0.97 (0.59–1.61) | 0.87 (0.52–1.46) |
| OA (adjusted for age, BMI) | **1.29 (1.10–1.51)** | 1.38 (0.98–1.93) | **1.33 (1.01–1.75)** | **1.70 (1.32–2.16)** | 0.96 (0.70–1.29) | 1.09 (0.60–2.01) | 0.98 (0.60–1.62) | 0.88 (0.52–1.46) |
| OA (adjusted for age, FNBMD) | **1.35 (1.15–1.59)** | 1.36 (0.97–1.92) | **1.43 (1.09–1.89)** | **1.81 (1.42–2.31)** | 1.02 (0.75–1.38) | 1.19 (0.65–2.18) | 1.09 (0.66–1.79) | 0.92 (0.55–1.54) |
| OA (adjusted for age, LSBMD) | **1.35 (1.15–1.58)** | **1.45 (1.04–2.03)** | **1.52 (1.15–2.00)** | **1.81 (1.42–2.30)** | 1.06 (0.78–1.44) | 1.23 (0.66–2.27) | 1.17 (0.71–1.94) | 0.96 (0.57–1.61) |
| OA (adjusted for age, BMI and clinical risk factors) | **1.38 (1.17–1.63)** | 1.38 (0.97–1.94) | **1.45 (1.08–1.94)** | **1.87 (1.44–2.42)** | 1.01 (0.73–1.39) | 1.16 (0.62–2.17) | 0.93 (0.56–1.59) | 0.94 (0.55–1.62) |
| OA (adjusted for age, FNBMD and clinical risk factors) | **1.43 (1.21–1.68)** | 1.35 (0.95–1.91) | **1.59 (1.19–2.12)** | **1.96 (1.52–2.53)** | 1.05 (0.77–1.45) | 1.27 (0.67–2.39) | 1.04 (0.61–1.75) | 0.97 (0.56–1.66) |
| OA (adjusted for age, LSBMD and clinical risk factors) | **1.45 (1.23–1.71)** | **1.47 (1.04–2.07)** | **1.68 (1.26–2.24)** | **2.01 (1.56–2.61)** | 1.13 (0.82–1.56) | 1.37 (0.72–2.61) | 1.19 (0.70–2.02) | 1.03 (0.59–1.77) |

Clinical risk factors included falls in the past 12 months, prior fracture after age 50, history of smoking, glucocorticoid use, physical activity level and HRT (in women); bold-faced letters are statistically significant.

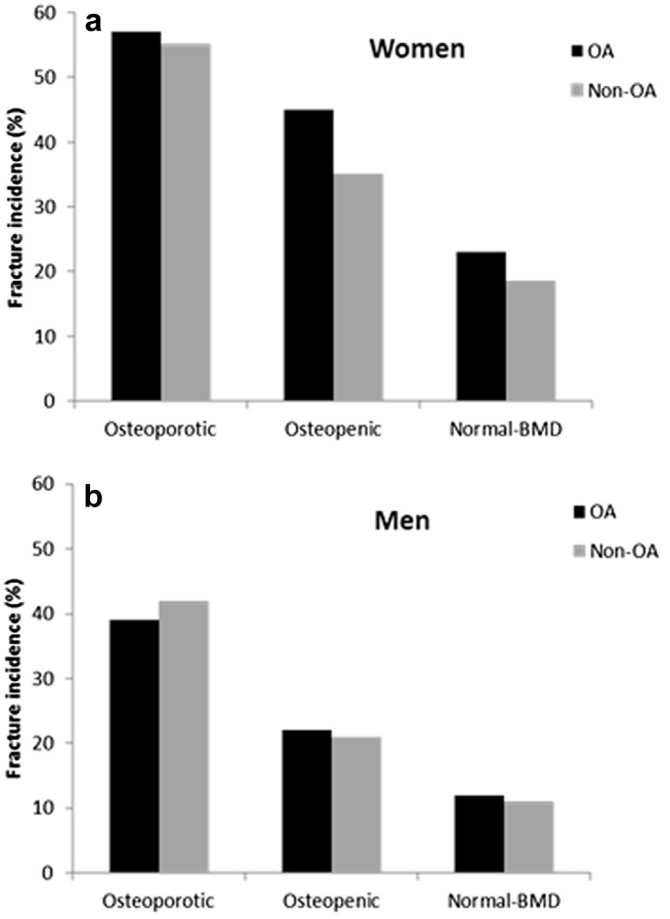


**Fig. 2.** Fracture incidence (%) of OA and non-OA group as stratified by different BMD categories in (a) women and (b) men.

associated with a 1.50-fold (95% CI, 1.15–1.93), 1.49-fold (95% CI, 1.14–1.94) and 1.73-fold (95% CI, 1.22–2.46) increase in any fracture among women with normal-BMI, overweight and obese respectively. After adjusting for clinical risk factors, the associations remained significant in those with normal-BMI (HR = 1.29; 95% CI, 1.01–1.65) and overweight (HR = 1.46; 95% CI, 1.10–1.94). Similarly, limb fracture risk was also higher in women, independent of their BMI status. However, after adjusted for potential confounders, the association was only significant in normal-BMI (HR = 1.80; 95% CI, 1.19–2.72) and overweight (HR = 2.05; 95% CI, 1.35–3.09) women. An increased risk of hip fracture was found in OA women with normal-BMI (HR = 2.29; 95% CI, 1.50–3.53), but the significance was not reached after adjusting for clinical risk factors. Meanwhile, in obese women with OA, vertebral fracture risk was increased by approximately 2-fold (95% CI, 1.04–4.29) after multivariable adjustment (Table III).

### *OA and fracture discrimination*

The fracture discriminatory power was examined in terms of the area under the ROC curve (i.e., AUC) of the models with and without the inclusion of OA. In women, the discriminatory ability of the model with OA was significantly improved (4%, AUC: 0.70 vs 0.74; $P < 0.001$). While there was little difference in the AUCs between models with and without OA in osteoporotic women (AUC: 0.58 vs 0.57; $P > 0.5$), the model performance was improved in women with osteopenic and normal-BMD by 6% (AUC: 0.70 vs 0.64; $P < 0.001$) and 4% (AUC: 0.70 vs 0.66; $P < 0.001$), respectively.

**Table III**
Association between OA and fracture risk as stratified by BMD and BMI groups in women and men

| | HR (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Any fracture | | Hip fracture | | Vertebral fracture | | Limb fracture | |
| | OA unadjusted | OA multivariate adjustment | OA unadjusted | OA multivariate adjustment | OA unadjusted | OA multivariate adjustment | OA unadjusted | OA multivariate adjustment |
| **Women** | | | | | | | | |
| *BMD groups* | | | | | | | | |
| Osteoporotic | 1.02 (0.73–1.43) | 1.06 (0.75–1.50) | 1.53 (0.95–2.48) | 1.38 (0.84–2.29) | 0.81 (0.41–1.58) | 1.06 (0.51–2.17) | 1.05 (0.53–2.08) | 1.28 (0.61–2.69) |
| Osteopenic | **1.63 (1.31–2.01)** | **1.74 (1.38–2.17)** | **1.69 (1.02–2.81)** | 1.47 (0.87–2.48) | **1.94 (1.33–2.83)** | **1.85 (1.24–2.75)** | **2.20 (1.62–2.98)** | **2.49(1.77–3.48)** |
| Normal-BMD | **1.58 (1.15–2.20)** | **1.50 (1.06–2.13)** | 1.68 (0.52–5.41) | 1.41 (0.43–4.63) | **2.07 (1.25–3.44)** | 1.44 (0.82–2.50) | 1.59 (1.00–2.53) | 1.41 (0.86–2.31) |
| *BMI groups* | | | | | | | | |
| Normal-BMI | **1.50 (1.15–1.93)** | **1.29 (1.01–1.65)** | **2.29 (1.50–3.53)** | 1.47 (0.93–2.31) | 1.55 (0.99–2.43) | 1.33 (0.84–2.13) | **1.97 (1.34–2.89)** | **1.80 (1.19–2.72)** |
| Overweight | **1.49 (1.14–1.94)** | **1.46 (1.10–1.94)** | 1.41 (0.69–2.86) | 1.33 (0.64–2.78) | **1.83 (1.17–2.84)** | 1.38 (0.85–2.25) | **1.80 (1.23–2.61)** | **2.05 (1.35–3.09)** |
| Obese | **1.73 (1.22–2.46)** | 1.47 (0.98–2.19) | 2.22 (0.93–5.24) | 1.44 (0.54–3.84) | **1.94 (1.09–3.44)** | **2.11 (1.04–4.29)** | **2.08 (1.24–3.50)** | 1.59 (0.88–2.87) |
| **Men** | | | | | | | | |
| *BMD groups* | | | | | | | | |
| Osteoporotic | 0.45 (0.18–1.14) | 0.39 (0.15–1.03) | 0.78 (0.22–2.71) | 0.76 (0.20–2.95) | 0.23 (0.03–1.76) | 0.20 (0.02–1.62) | 0.28 (0.04–2.15) | 0.19 (0.02–1.56) |
| Osteopenic | 1.26 (0.83–1.92) | 1.23 (0.78–1.95) | 1.59 (0.68–3.72) | 1.36 (0.55–3.35) | 1.36 (0.67–2.76) | 1.26 (0.59–2.69) | 1.28 (0.64–2.56) | 1.29 (0.61–2.75) |
| Normal-BMD | 1.43 (0.86–2.39) | 1.18 (0.69–2.03) | 2.06 (0.58–7.26) | 2.12 (0.58–7.79) | 1.89 (0.86–4.16) | 1.46 (0.62–3.48) | 1.03 (0.45–2.37) | 0.91 (0.38–2.12) |
| *BMI groups* | | | | | | | | |
| Normal-BMI | 0.94 (0.50–1.41) | 0.73 (0.42–1.23) | 1.08 (0.41–2.81) | 0.91 (0.34–2.45) | 1.08 (0.50–2.32) | 0.79 (0.36–1.76) | 0.58 (0.21–1.62) | 0.48 (0.17–1.39) |
| Overweight | 1.13 (0.71–1.80) | 1.06 (0.64–1.72) | 1.71 (0.71–4.12) | 1.44 (0.56–3.72) | 0.97 (0.43–2.22) | 0.93 (0.39–2.25) | 1.13 (0.54–2.35) | 1.15 (0.53–2.51) |
| Obese | 2.51 (0.25–5.03) | 2.41 (0.17–5.41) | 3.62 (0.49–26.6) | 4.99 (0.53–47.1) | 3.04 (0.42–9.06) | 2.45 (0.69–8.62) | 2.26 (0.80–6.38) | 1.89 (0.52–6.86) |

Multivariate adjustment: adjusted for age, falls in the past 12 months, prior fracture after age 50, history of smoking, glucocorticoid use, physical activity level, HRT (in women); bold-faced letters are statistically significant.

Reclassification analysis also found a total of ~6% ($P < 0.001$) net reclassification improvement (NRI) with the inclusion of OA in the predictive model in women (Table IV). In men, no significant improvement in fracture identification was noted after OA was added to the models (AUC: 0.71 vs 0.70; NRI: −0.17%).

## Discussion

The relationship between OA and fracture risk remains controversial with conflicting results reported. So far, few data are available regarding the effect of BMD on the OA-fracture relationship. In this prospective study, we show that the relationship between OA and fracture risk is not only gender-specific, but also BMD-dependent. We found that OA was a significant risk factor for any fracture in women with osteopenia and normal-BMD, but not in men or osteoporotic women. This is partly in line with the Rotterdam Study, in which knee OA patients with high BMD had greater and significant risk of non-vertebral, hip and wrist fracture compared to the low BMD group[16]. We further demonstrated that the adjusted associations between OA and risk of vertebral and limb fracture were significant only in osteopenic women, suggesting that BMD is a potential mediator in the OA-fracture relationship.

Consistent with many previous findings[27–29], we also observed a significantly higher baseline BMD in OA patients. However, the increase in BMD did not translate into a reduction in fracture risk in both sexes, and this finding is consistent with previous data[18,19,30]. Interestingly, after stratified by BMD, it was revealed that 23% of women and 22% of men with osteoporosis had self-reported OA. Such findings are also in line with a recent study on severe knee and hip OA, which showed 23% of the patients to be osteoporotic and 43% to be osteopenic[31]. A study on advanced hip OA also found 25% of OA patients with occult osteoporosis[32], suggesting that there is some overlap between osteoporosis and OA.

Individuals with OA tend to have greater bone loss over time than their non-OA counterparts[33–35]. In a study of 3000 elderly men and women, radiographic hip OA was associated with an annual bone loss of 2% in men and 1.4% in women, despite 3–8% higher BMD values compared with controls[33]. Similar bone loss was also found in metacarpal OA, particularly at the cortical region[34]. Since not all OA cases, as shown by our study, have normal or high initial BMD, further bone loss in these patients will be detrimental to their bone health and would significantly increase their likelihood of subsequent fractures.

Other potential factors contributing to the increased fracture risk in OA patients could be related to bone structure and bone quality of the affected joints. A previous *in vitro* study showed that not only was trabecular bone volume lower in subjects with OA, but also trabecular separation was wider compared with normal

**Table IV**
Comparison of NRI between models with and without OA inclusion across different absolute risk tertile groups in women

| Model without OA | Model with OA | | | NRI |
|---|---|---|---|---|
| | Low risk | Medium risk | High risk | |
| Women | | | | |
| *Fracture group* | | | | |
| Low risk | 107 | 20 | 0 | 1.7% |
| Medium risk | 14 | 226 | 32 | |
| High risk | 0 | 24 | 382 | |
| *Non fracture group* | | | | |
| Low risk | 625 | 19 | 0 | 4.0% |
| Medium risk | 63 | 467 | 24 | |
| High risk | 0 | 44 | 365 | |
| *Total* | | | | 5.7% |
| Men | | | | |
| *Fracture group* | | | | |
| Low risk | 43 | 0 | 0 | |
| Medium risk | 0 | 75 | 0 | 0% |
| High risk | 0 | 0 | 147 | |
| *Non fracture group* | | | | |
| Low risk | 455 | 2 | 0 | |
| Medium risk | 0 | 405 | 2 | −0.17% |
| High risk | 0 | 2 | 321 | |
| *Total* | | | | −0.17% |

All models included age, FNBMD, falls in the past 12 months, prior fracture after age 50, history of smoking, glucocorticoid use, physical activity level and HRT.

controls[36]. Furthermore, in comparison to the osteoporotic bones, those obtained from patients with OA were observed to have significantly higher cortical porosity[37]; and their material properties were inferior to both normal and osteoporotic bones[38].

The association between OA and fracture risk could also be related to the higher tendency of falling in OA patients, possibly due to postural instability, quadriceps weakness, joint pain and stiffness[16,19,20]. In accordance with previous studies[18–20], our data also demonstrated a significantly higher prevalence of falls in women with OA (39%) compared with those without OA (32%). Nevertheless, when history of falls was taken into account in the regression models, the associations between OA and fracture risk were attenuated but remained significant; suggesting that increased risk of falling, may have played some part, but it alone could not fully explain the OA-fracture relation.

In the present study, the association between OA and fracture risk was only significant in women but not in men. Although it is not clear what constituted the gender-related difference, it is possible that the low number of fracture case in men may reduce the statistical power to detect an association. However, we noticed that the BMD measurements of men were, on average, higher than that of women. Also, the percent of OA men in the higher BMD categories were greater than that of OA women, suggesting that the gender-related difference in the OA-fracture relation could be a result of the intrinsic differences in bone biology between the two sexes. This is supported by a recent observation that age-related loss of bone density[39] and bone strength loss[40] were significantly higher in women compared to men.

The findings of this study have important clinical implications. Although low BMD is a major determinant of fragility fracture, more than 50% of the fracture cases did not have osteoporotic BMD[22]. Our finding of higher fracture incidence in OA individuals with normal or osteopenic BMD may provide some insight into the development of non-osteoporotic fragility fracture. At present, the Garvan fracture risk calculator and the fracture risk assessment tool (FRAX) are the most commonly used models for fracture risk assessment, but neither of them has included OA as a risk factor. Our data suggest that inclusion of OA in fracture risk assessment may help to improve the identification of at-risk individuals, particularly women without low BMD. More importantly, patients with OA should not be overlooked for fracture risk assessment and preventive intervention. However, whether current anti-fracture treatments, which were primarily targeted at low BMD, will be appropriate for use in patients with OA has yet to be determined.

The strengths of the present study are the large sample size and its long duration of follow-up period. Our findings are derived from the community-dwelling population and prospective data, and hence, are less likely subjected to the potential biases inherent in the volunteer-based and cross-sectional studies. However, a number of weaknesses should be taken into account in the interpretation of the findings. Since the ascertainment of OA was dependent on self-reported information, we cannot rule out the possibility of underestimation regarding the number of OA cases. However, the reliability of case-assignment, in this study, was supported by the finding that individuals with OA were both older and had higher body weight, the two major determinants of OA. Moreover, nearly all of the OA cases were receiving some form of medical treatment (including non-steriodal anti-inflammatory therapy and surgical intervention), suggesting the presence of OA symptoms. Besides, previous studies have shown high reproducibility using self-reported method[14,41]. Indeed, a concordance rate of more than 80% has been reported between self-reported OA and clinically diagnosed OA[42]. In a separate study, 90% of the self-reported cases were able to be validated by their corresponding medical records or radiographic evidences[43]. Another limitation is that the definition of OA was not site-specific due to insufficient sample size to perform further stratification. Moreover, the majority of the OA cases reported had involved more than one joint, making it difficult to obtain an accurate classification. Finally, the present study is based on a population mainly of Caucasian background and aged above 45 years, and therefore, its findings may not be readily applicable to other populations with different ethnicity and age structures.

In conclusion, OA is a risk factor for fracture in women, and this risk was observed predominantly in non-osteoporotic women. This finding highlights the importance of considering OA as a risk factor in fracture risk assessment in clinical setting.

## Author contributions

Conception and design: MYC and TVN. Data analysis: MYC and TVN. Data interpretation: MYC and TVN. Drafting manuscript: MYC. Revising manuscript content: TVN, JAE and JRC. Approving final version of manuscript: MYC, TVN, JRC and JAE. MYC and TVN take responsibility for the integrity of the data analysis.

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## Conflict of interest

JAE has served as consultant on the Scientific Advisory Board for Amgen, Eli Lilly, Merck Sharp & Dohme, Novartis, sanofi-Aventis, Servier and deCode. He was the editor-in-chief for the Journal of Bone and Mineral Research from 2003 to 2007 and was a committee member of Department of Health and Aging, Australian Government and Royal Australian College of General Practitioners. Dr JRC has given educational talks for Eli Lilly, Merck Sharp & Dohme, and sanofi-Aventis. Professor TVN has received honorarium for consulting and speaking in symposia sponsored by Merck Sharp & Dohme, Roche, Servier, sanofi-Aventis and Novartis. Other author has no conflict of interest.

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