

**ARE BONE MINERAL DENSITY AND FRACTURES RELATED TO THE INCIDENCE AND
PROGRESSION OF RADIOGRAPHIC OSTEOARTHRITIS OF THE KNEE, HIP AND HAND IN
ELDERLY MEN AND WOMEN?
THE ROTTERDAM STUDY**

Running title: bone mineral density, fractures and osteoarthritis

ARJAN P. BERGINK^{1,5}, MD, FERNANDO RIVADENEIRA^{1,2}, MD, PhD, SITA M. BIERMA-
ZEINSTR^{3,4}, PhD, M. CAROLA ZILLIKENS¹, MD, PhD, M. ARFAN IKRAM², MD, PhD, ANDRÉ G.
UITTERLINDEN^{1,2}, PhD and JOYCE B. VAN MEURS¹, PhD

Departments of ¹Internal Medicine, ²Epidemiology, ³General Practice and ⁴Orthopaedics, Erasmus
Medical Center, Rotterdam, the Netherlands, ⁵Center for Orthopedic Surgery OCON, Hengelo, the
Netherlands

Supported by:

The Netherlands Organization for Scientific Research (NWO),

grant numbers: 925-01-010, 014-90-001 & 903-46-178

This article has been accepted for publication and undergone full peer review but has not
been through the copyediting, typesetting, pagination and proofreading process, which may
lead to differences between this version and the Version of Record. Please cite this article as
doi: 10.1002/art.40735

This article is protected by copyright. All rights reserved.

Key words: bone mineral density, BMD, osteoarthritis, OA

Address all correspondence and requests for reprints to:

Dr Joyce B.J. van Meurs, Genetic Laboratory, Department of Internal Medicine,
Erasmus Medical Center, Room Ee579b, PO Box 1738, Rotterdam 3000 DR, The Netherlands;
j.vanmeurs@erasmusmc.nl

ABSTRACT

Objective. To examine the longitudinal relationship between bone mineral density (BMD) and the incidence and progression of knee, hip and hand osteoarthritis, and the relationship between prevalent vertebral and non-vertebral fractures and the incidence and progression of osteoarthritis in elderly men and women in the Rotterdam Study.

Methods. Age- and sex-specific quartiles of baseline femoral neck BMD (FN-BMD) were constructed for a total number of 4,154 subjects. Radiographs were scored for incidence and progression of knee and hip osteoarthritis, and for incidence of hand osteoarthritis. Prevalent vertebral fractures were scored using the McCloskey/Kanis method, and prevalent non-vertebral fractures were reported by baseline interview.

Results. Subjects in the highest quartile of FN-BMD had an increased risk of incident knee radiographic osteoarthritis (ROA) (OR 1.58; 95%CI: 1.14 to 2.18), and an increased risk of incident hip ROA (OR 1.57; 95%CI: 1.06 to 2.32) compared to the lowest quartile. No

significant relationship was found between high FN-BMD and progression of knee or hip ROA, or the incidence of hand ROA. Prevalent vertebral and non-vertebral fractures were not related to the incidence or progression of knee or hip ROA. Vertebral fractures were however associated with incident hand ROA (OR 1.74; 95%CI: 1.02 to 2.98).

Conclusion. Results from the present study confirm earlier studies and thus provide strong evidence that high FN-BMD is a prognostic risk factor for the development of knee and hip ROA. Vertebral fractures were found to be a risk factor for incident hand ROA.

INTRODUCTION

The inverse relation between osteoporosis (OP) and osteoarthritis (OA) has been described extensively in the past decades^(1, 2). However, whether high bone mineral density (BMD) is the cause or consequence of OA is unclear. A number of prospective studies⁽³⁻⁷⁾ indicated that high BMD at baseline is associated with increased risk of incident knee OA. Two of these studies found a protective effect of high BMD on progression of knee OA^(4, 5), while Nevitt and al. found that progression was not significantly related to BMD⁽⁷⁾.

However, almost no data is available on the relationship between BMD and incidence or progression of hip and hand OA. A previous review concluded that the relationship between OA and OP is elusive and that especially longitudinal studies show no clear relation between OA and OP⁽⁸⁾.

We have previously studied the association between baseline BMD, incident and progressive radiographic OA of the knee and prevalent vertebral and non-vertebral fractures in 1,403 men and women⁽⁹⁾. We found that high baseline BMD was associated with increased incidence of knee OA, and that subjects with a prevalent vertebral fracture had less risk of incident or progressive knee OA. Since our publication, few longitudinal studies have been performed to further examine the influence of BMD on the development of OA. A recent review summarized all available published data on the relationship between BMD and longitudinal OA, adding up to a total of 4,942 individuals (including 1,403 subjects of our own Rotterdam Study), showing increased risk for the development of knee OA in subjects with high baseline BMD⁽¹⁰⁾.

Regarding the development of hip OA, even less longitudinal studies are available. Hochberg mentioned a dose–response relationship between the quartile of baseline BMD and the incidence of radiographic hip OA in the SOF study⁽¹¹⁾, while Barbour et al. recently found no association between high BMD and radiographic hip OA in the Johnston County Osteoarthritis Project⁽¹²⁾.

To our knowledge, only one longitudinal study on baseline BMD and incident hand OA was performed, showing no association⁽³⁾. Hand OA is especially interesting in this respect, since development of OA in the hands, especially of DIP and DIP-joints, is thought to be due to more systemic influences, like adiposity⁽¹³⁾, sex hormone levels⁽¹⁴⁾ and genetic influences⁽¹⁵⁾ rather than local (mechanical) loading.

In the current study, we aimed to study the association between baseline BMD and the development of hip and hand OA, and between prevalent vertebral and non-vertebral fractures and the risk of OA. In addition, we wanted to verify the positive association between high BMD and the development of knee radiographic OA (ROA) we found previously in the Rotterdam Study in an expanded study population (total sample size is 4,154) drawn from the Rotterdam Study-I and II, with extended (now 8.4 years) follow up time.

MATERIALS AND METHODS

Subjects. The study population consisted of subjects of the Rotterdam Study-I (RS-I) and Rotterdam Study-II (RS-II). The rationale and study design have been described previously^(16, 17). The study population consisted of 3,005 subjects (55.8% women), drawn from RS-I, and 1,149 subjects (54.4% women) drawn from RS-II (**Figure 1**: cohorts in the total Rotterdam Study). The selection was based on the availability of radiographs of the knees, hips and hands at baseline and follow-up examinations, and data on BMD, prevalent vertebral and non-vertebral fractures and potentially confounding factors at baseline.

Radiographic osteoarthritis. Radiographs of knees, hips and hands were taken at three visits for RS-I: RS-I-1 (baseline measurement, between 1998 and 1993), RS-I-3 (between 1997 and 1999, mean follow up time 6.5 years) and RS-I-4 (between 2002 and 2004, mean follow up time 11.9 years, **Figure 1**). For RS-II, radiographs were taken at two visits: RS-II-1 (baseline, between 2000 and 2001) and at RS-II-2 (between 2004 and 2005, mean follow-up time 4.1). The overall mean follow-up time was 8.4 years (standard

deviation (SD) 2.2, range 3.7 to 13.6) for subjects in RS-I and for RS-II 4.1 years (SD 0.6, range 1.1 to 5.8). Prevalence, incidence and progression of ROA were scored by the Kellgren/Lawrence (K/L) grading system⁽¹⁸⁾ as described previously^(9, 19, 20). In short, prevalence of ROA of the knee or hip was defined as a K/L score of ≥ 2 at baseline at one or both knees/hips. Prevalence of hand ROA was defined as presence of a K/L score ≥ 2 in 2 out of 3 hand joint groups for one or both hands. Incident ROA was defined when a subject had no prevalent ROA (a K/L score < 2) of both knees, both hips or both hands at baseline, and a K/L score of ≥ 2 at follow-up (RS-I-3, RS-I-4 or RS-II-2) of one or both knees, one or both hips or one or both hands, respectively. Progressive ROA was defined as an increase of K/L score in subjects with prevalent ROA of that same joint. Thus, the analysis is person-based: incident OA can only occur in subjects without prevalent ROA at both the left and right joint, progression of ROA can only occur in subjects with prevalent ROA at the left, right or both joints. A third measure was calculated: incidence or progression of OA. This was defined by having either incident ROA or showing progression of ROA. This measure was constructed for comparison with our previous study⁽⁹⁾, and for reasons of power when stratifying for study population. Subjects that received total joint replacement during follow up were excluded from the analysis of that joint group. The radiographs in RS-I and RS-II were obtained using the same protocol, and were scored by PhD-students trained by a radiologist. The interobserver agreement was 0.71 for RS-I and 0.68 for RS-II⁽²⁰⁾. Data on incidence of hand OA was available for 2,118 subjects.

Fracture assessment. Prevalent non-vertebral fractures: Between 1989 and 1993, an extensive baseline home interview on medical history and of risk factors for chronic diseases was performed by trained interviewers. Data on non-vertebral fracture history at or after age of 50 was obtained as described previously^(9, 16). Vertebral fractures: Both at baseline (between 1989 and 1993) and at the second follow-up visit (between 1997 and 1999), radiographs of the thoracolumbar spine were available for 2,920 individuals from RS-I. The thoracolumbar spine radiographs of the follow-up visit were scored for the presence of vertebral fracture using the McCloskey/Kanis method, as described previously⁽²¹⁾. If vertebral fractures were detected, the baseline radiograph was also evaluated. If the vertebral fracture was already present at baseline, it was considered to be a prevalent fracture. If it was not present at baseline, the fracture was defined as incident.

Bone mineral density. BMD measurements of the femoral neck were performed at baseline using dual energy X-ray absorptiometry (DXA, Lunar DPX-L densitometer). Standard positioning was used with anterior-posterior scans of the right proximal femur unless there was a history of hip fracture or prosthesis implantation. In the latter case, the left side was scanned^(9, 22).

Other variables. Data on age, sex, height, weight, body mass index (BMI) and other potentially confounding (use of a walking aid, lower limb disability and smoking) variables were obtained as described previously^(9, 16).

Statistical analysis. Age- and sex-specific quartiles of femoral neck BMD (FN-BMD)

for RS-I and RS-II were created by forming quartiles of FN-BMD by age groups per 5 years for men and women separately. The significance of the differences in height, weight and BMI by these quartiles was calculated by means of a linear regression model. Odds ratios (ORs) with 95% confidence intervals (95%CI) for the association between FN-BMD quartiles and ROA were calculated by means of logistic regression modeling, and were adjusted for baseline age, sex, BMI, study population, follow up time and corresponding K/L sum score at baseline. This sum score was calculated by adding up the K/L scores (0-4) of both knees, both hips or both hand joints, thus creating sum scores for each separate joint group. This was done in order to adjust for the potential confounding effect of mild OA at baseline (a K/L score 1 of one or both joints) on the incidence of ROA, and of the severity of OA at baseline for progression of ROA. FN-BMD per SD was calculated stratified by sex and study population, and ORs for the association between SD increase in FN-BMD and ROA were calculated by means of logistic regression modeling as well, and adjusted for baseline age, sex, BMI, study population, follow up time and corresponding K/L sum score at baseline. ORs for the association between the incidence or progression of knee, hip and hand ROA and prevalent vertebral and non-vertebral fractures in RS-I were calculated by means of logistic regression modeling, and were adjusted for baseline age, sex, body mass index, femoral neck bone mineral density, use of walking aid, lower limb disability, fall tendency and corresponding K/L sum score at baseline. We used IBM® SPSS version 22 for all our analyses.

RESULTS

In **Table 1** the baseline characteristics of the RS-I and RS-II study populations by age- and sex-specific quartiles of FN-BMD are shown. The mean height, weight and BMI were significantly higher with increasing FN-BMD. Subjects in RS-II were on average 2 years younger compared to those in RS-I, and had significantly increased weight and BMI. RS-I included 389 incident and 236 progressive knee ROA cases, 221 incident and 116 progressive hip ROA cases, and 320 incident hand ROA cases. In RS-II, 65 incident and 51 progressive knee ROA cases were present, 32 incident and 21 progressive hip ROA cases, and 96 incident hand ROA cases.

Bone mineral density

Table 2 shows the association between age- and sex-adjusted quartiles of FN-BMD and the incidence of knee and hip ROA, the progression of knee and hip ROA, and the combined measure for incidence or progression. An increase of incidence in knee ROA was seen with high FN-BMD: subjects in the highest FN-BMD quartile had a 58% increased risk of incident knee ROA compared to subjects in the lowest quartile (OR 1.58; 95%CI: 1.14 to 2.18). The effect for progression of knee OA was non-significant (OR 1.07; 95%CI: 0.64 to 1.78), the risk for incident knee ROA or progression of knee ROA was 42% increased (OR 1.42; 95%CI: 1.09 to 1.86). The risk for incident knee ROA increased 15% with each SD increase in FN-BMD (OR 1.15; 95%CI: 1.04 to 1.28). No significant progression of ROA was seen per SD increase in FN-BMD (OR 0.89; 95%CI: 0.77 to 1.03).

Subjects in the highest FN-BMD quartile had a 57% higher risk for incident hip ROA compared to the lowest quartile (OR 1.57; 95%CI: 1.06 to 2.32). The higher risk for progression of radiographic hip OA was not significant (OR 2.17; 95%CI: 0.99 to 4.79), while an 82% increased risk of incidence or progression of hip ROA (OR 1.82; 95%CI: 1.28 to 2.59) was observed. The increased risk for incidence or progression of hip ROA per SD FN-BMD was 16% (OR 1.16; 95%CI: 1.05 to 1.29). In contrast to radiographic knee OA, the latter association was driven by the progression of radiographic hip OA: the increased risk of progression per SD FN-BMD increase was 32% (OR 1.32; 95%CI: 1.04 to 1.66). The increased risk of incident hip ROA per SD FN-BMD was not significant (OR 1.07; 95%CI: 0.95 to 1.22).

No significant association between high FN-BMD and the incidence of radiographic hand OA was found, as is shown in **Table 3**. Additional adjustment for other potentially confounding variables (use of a walking aid, lower limb disability and smoking) available for subjects in RS-I, did not change the risk estimates for knee, hip or hand ROA (data not shown).

In **Supplementary Table 1** the incidence and progression of ROA by quartiles of FN-BMD for RS-I and RS-II separately are shown. The incidence or progression of knee and hip ROA for subjects in RS-II was approximately half compared to the incidence or progression for subjects in RS-I in each quartile. The incidence or progression of knee and hip ROA increased per quartile in both RS-I and RS-II. This resulted in a 36% increased risk for incident or progressive knee ROA for subjects in the highest quartile compared those in the

lowest quartiles in RS-I (OR 1.36; 95%CI: 1.01 to 1.84), and a 84% increased risk for hip ROA (OR 1.84; 95%CI: 1.26 to 2.70). In RS-II, the increased risks in the highest quartiles failed to reach significance. However, for the incidence or progression of knee ROA a 30% increased risk per SD FN-BMD was observed in RS-II.

In RS-I, the percentage of subjects with incident hand OA tended to increase in the higher BMD quartiles (**Supplementary Table 2**), with a significantly increased risk of 52% for subject in the third quartile (OR 1.52; 95%CI: 1.03 to 2.23), but no significant association was seen for the highest quartile (OR 1.18; 95%CI: 0.79 to 1.76). In RS-II, no significant association between FN-BMD and incident hand ROA was found.

Prevalent fractures

Table 4 shows the association between prevalent vertebral and non-vertebral fractures and the combined measure of incidence or progression of radiographic knee and hip OA, and the incidence of radiographic hand OA. No significant associations were found between fractures and radiographic knee and hip OA, and with non-vertebral fractures and the incidence of hand ROA. Subjects with a vertebral fracture at baseline, however, had a 74% increased risk of incident hand ROA (OR 1.74; 95%CI: 1.02 to 2.98) after adjustments for possible confounding factors.

DISCUSSION

Results of this study present strong evidence that high BMD is a significant risk factor for the development of subsequent knee and hip OA. High baseline FN-BMD is significantly related to the incidence of radiographic knee and hip OA, but not to the incidence of radiographic hand OA. Furthermore, high baseline FN-BMD is not associated with the progression of radiographic knee OA. The association between high FN-BMD and the progression of radiographic hip OA is not significant, but there is a significant increase in risk of progressive hip OA per SD increase of FN-BMD. Prevalent vertebral fractures are associated with the incidence of radiographic hand osteoarthritis, but not with any of the measures in knee and hip ROA. Non-vertebral fractures are not associated with incidence or progression of knee, hip or hand OA.

Bone mineral density

Results on the relationship between BMD and the incidence on knee ROA confirm earlier studies⁽³⁻⁷⁾, and strengthens the evidence that high FN-BMD is an important risk factor for developing subsequent knee ROA. In contrast to knee OA, almost no previous data was available on the association between high BMD and incident hip OA. The current study provides evidence that high BMD is also a significant risk factor for incident radiographic hip ROA. This finding confirms the results mentioned by Hochberg et al.⁽¹¹⁾ They concluded that a greater BMD increases the risk that an elderly white woman will develop radiographic hip OA when the diagnosis of OA is based upon osteophytosis, but not when the diagnosis is based upon the development of JSN alone. However, no numbers, percentages or ORs were

presented in this paper. The conflicting results reported by Barbour et al.⁽¹²⁾ on the other hand, might be explained by the limited number of subjects in their study. In our study, we observed that in the smaller sub group, RS-II, the association between the highest quartile of FN-BMD and incidence or progression of knee and hip ROA failed to reach significance, probably due to lack of power (**Supplementary Table 1**). The increase in risk of incident or progressive knee ROA per SD increase of FN-BMD however was significant in RS-II. This could be due to the increased power by analyzing per SD increase in BMD, instead of per quartile.

No association of high FN-BMD and progression of knee ROA was observed in this study. This is consistent with previous findings⁽⁷⁾ and might be due to collider bias⁽²³⁾ or lack of power, since the number of cases with progressive knee OA is low.

Comparing the results on knee ROA of the present study with results reported by Bergink et al. in 2005 (**Table 5**), it can be concluded that both studies found that high BMD at baseline is associated with increased risk of incident knee OA during follow-up. The present study, thus, confirms previous results and provides stronger evidence. Nevertheless, the increased risk of incident knee ROA per SD increase of FN-BMD in 2005 was 50% (OR 1.5; 95%CI: 1.1 to 1.9), while in the present study the increased risk is lower, 15% (OR 1.15; 95%CI: 1.04 to 1.28). Looking at the results from RS-I and RS-II separately, it can be concluded that the increased risk per SD increase of FN-BMD is higher in RS-II than in RS-I (OR 1.30; 95%CI: 1.08 to 1.58 and OR 1.00; 95%CI: 0.90 to 1.10, respectively, **Supplementary Table 1**). A possible explanation for the higher OR in RS-II, which is more similar to the OR in 2005, is that the mean age of the RS-II study population in the present study, like the mean age of the subjects in RS-I in 2005, is relatively low, and that the risk attenuates with

extended follow-up time and aging of participants. In younger patients the development of subsequent ROA might be more likely to be caused by systemic effects associated with high BMD, and to a lesser extent by environmental influences.

The present study is the first prospective study to provide consistent evidence for the relationship between high baseline BMD and incident hip OA. The risk for incident hip ROA and knee ROA is similar. But other than for knee ROA, a significant increased risk was found for progression of hip ROA per SD FN-BMD. This is also translated into the higher increased risk for incidence or progression in hip ROA, compared to knee ROA. However, the risk for progression of hip ROA alone was not significantly increased for subject in the highest FN-BMD quartile.

Following the fact that contrary to knee and hip ROA, no associations were found between BMD and the incidence of hand ROA, it seems that the positive association between BMD and ROA is strongest in weight-bearing joints. This might be due to local mechanical influences. Repetitive forces on subchondral bone with altered bone characteristics, like increased stiffness of cortical bone, might lead to increased deterioration of overlying cartilage. Consequently this is more pronounced in weight-bearing joints.

Osteophytes around the femoral head may influence femoral neck BMD and will result in higher BMD measured at the femoral neck. They can, thus confound the association between BMD and hip OA. However, previous studies with data from the Rotterdam Study showed that hypertrophic hip OA was associated with elevated BMD also measured at remote sites, like the skull⁽²⁴⁾. Discrimination between atrophic and hypertrophic ROA seems important since atrophic OA is associated with decreased BMD, and

hypertrophic OA with increased BMD⁽²⁴⁾. In the present study radiographic OA was classified using the K/L score, in which the formation of osteophytes, besides joint space narrowing, determines the severity of OA. Consequently, this study focused on the incidence and progression of hypertrophic, rather than atrophic AO. Since atrophic AO is considered to be a different disease type than hypertrophic OA^(25, 26), and associated with different risk factors^(24, 27), the present results can't be generalized to all types of OA, especially atrophic OA.

Prevalent fractures

In our previous research a significant protective effect of prevalent vertebral fractures on the risk of incidence and progression of knee ROA was reported. These results were not confirmed by the present study. Although a decreased risk of incident and progressive knee OA was observed, the association was not significant (OR 0.72; 95%CI: 0.48 to 1.09). The present study, however, provides evidence for an increased risk of hand ROA in subjects with prevalent vertebral fractures (OR 1.74; 95%CI: 1.02 to 2.98). It is likely that a common risk factor influences both the incidence of OA in non-weight bearing joints and vertebral fracture risk. Stronger correlations between genetic factors and OA are seen in hand OA compared to knee or hip OA^(15, 28). Likewise recent studies show that vertebral fracture risk is influenced by genetic factors^(29, 30). It is plausible that a common (heritable) bone characteristic affects both vertebral fracture risk and the incidence of hand OA. Another possible explanation for this observation might be that subjects with a prevalent vertebral fracture are more dependent on the use of a walking aid, leading to an increased risk of hand OA⁽³¹⁾.

Methodological considerations

In the present study, the incidence and progression of ROA were combined in a composite measure 'incidence or progression' to be able to compare our results to our past study⁽⁹⁾ and to decrease multiple testing when analyzing RS-I and RS-II separately, and when analyzing the association between prevalent fractures and ROA. In addition, we feel this is a valid approach considering that the development and worsening of OA is a continuous process and the distinction between incident and progressive OA remains artificial. We constructed quartiles of FN-BMD to compare subjects with low BMD to those with high BMD, and analyzed per increase SD FN-BMD to evaluate the effect of BMD change on incidence or progression of OA in the total study population, thus increasing power. To avoid multiple testing and to avoid the known profound confounding effect of lumbar spine osteophytes on BMD measurements, analyses were done with FN-BMD, and not with lumbar spine BMD.

Participants were selected based on the availability of follow-up radiographs. This selection introduces a possible selection bias, since these subjects survived the follow-up period, and were healthy enough to visit the research center. Furthermore, since selection of the study population was based on both the availability of data on exposure (BMD) and outcome (incidence or progression of OA), collider bias may be introduced⁽²³⁾. A possible association between baseline BMD and especially progressive knee or hip OA could be obscured by this type of bias, since subjects with progressive OA are less likely to return to the research center for follow examinations.

In order to adjust for the potential confounding effect of mild OA at baseline (K/L score 1 at one or both joints) on the incidence of ROA, and of the severity of OA at baseline for progression of ROA, we adjusted for site-specific K/L sum score. However, if mild OA at baseline does not confound the possible association between baseline BMD and incidence or progressive OA, but is independently associated with exposure (BMD) and outcome (incidence or progressive OA), adjusting for it could lead to collider bias^(23, 32). Therefore we performed additional analyses without adjustment for baseline site-specific K/L sumscore. The odds ratio's without adjustment for the baseline sumscore were marginally higher than with adjustment for the baseline K/L sumscore, which argues against collider bias.

Finally, we excluded subjects with joint replacements in our analyses as they are not merely an expression of worsening of OA, but also –and perhaps mainly- of pain experience and burden to daily living. This could weaken an association between baseline BMD and radiographic OA. In our study population RS1, 21 subjects received a total knee replacement (TKR) and 46 subjects received a total hip replacement (THR) during a mean follow up time of 8.4 years. Including subjects with TKRs and THPs in the analyses resulted in slightly increased ORs for incident knee and hip OA of subjects in the highest quartiles of baseline BMD compared to those in the lowest BMD quartiles (data not shown).

In conclusion, the present large longitudinal study confirms earlier studies and thus provides strong evidence that high FN-BMD is a prognostic risk factor for the development of subsequent radiographic knee and hip OA. No evidence was provided for high FN-BMD as a prognostic risk factor for progression of radiographic knee or hip, or for the incidence of radiographic hand OA. However, a significant higher risk of progression of hip ROA was

found for each SD increase in FN-BMD. The protective effect of vertebral fractures for the incidence or progression of radiographic knee OA could not be confirmed by the present study, but vertebral fractures were found to be a risk factor for the incidence of hand OA.

ACKNOWLEDGMENTS

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

REFERENCES

1. Stewart A, and Black AJ. Bone mineral density in osteoarthritis, *Current opinion in rheumatology* 2000;12:464-467.
2. Dequeker J, Aerssens J, and Luyten FP. Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship, *Aging clinical and experimental research* 2003;15:426-439.

- Accepted Article
3. Sowers M, Lachance L, Jamadar D, et al. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women, *Arthritis and rheumatism* 1999;42:483-489.
 4. Zhang Y, Hannan MT, Chaisson CE, et al. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study, *The Journal of rheumatology* 2000;27:1032-1037.
 5. Hart DJ, Cronin C, Daniels M, et al. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study, *Arthritis and rheumatism* 2002;46:92-99.
 6. Hochberg MC, Lethbridge-Cejku M, and Tobin JD. Bone mineral density and osteoarthritis: data from the Baltimore Longitudinal Study of Aging, *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2004;12 Suppl A:S45-48.
 7. Nevitt MC, Zhang Y, Javaid MK, et al. High systemic bone mineral density increases the risk of incident knee OA and joint space narrowing, but not radiographic progression of existing knee OA: the MOST study, *Annals of the rheumatic diseases* 2010;69:163-168.
 8. Im GI, and Kim MK. The relationship between osteoarthritis and osteoporosis, *Journal of bone and mineral metabolism* 2014;32:101-109.
 9. Bergink AP, Uitterlinden AG, Van Leeuwen JP, et al. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study, *Bone* 2005;37:446-456.

- Accepted Article
10. Hardcastle SA, Dieppe P, Gregson CL, et al. Osteoarthritis and bone mineral density: are strong bones bad for joints?, *BoneKEy reports* 2015;4:624.
 11. Hochberg MC. Do risk factors for incident hip osteoarthritis (OA) differ from those for progression of hip OA?, *The Journal of rheumatology. Supplement* 2004;70:6-9.
 12. Barbour KE, Murphy LB, Helmick CG, et al. Bone Mineral Density and the Risk of Hip and Knee Osteoarthritis: The Johnston County Osteoarthritis Project, *Arthritis care & research* 2017.
 13. Visser AW, Ioan-Facsinay A, de Mutsert R, et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study, *Arthritis research & therapy* 2014;16:R19.
 14. Sowers MF, Hochberg M, Crabbe JP, et al. Association of bone mineral density and sex hormone levels with osteoarthritis of the hand and knee in premenopausal women, *American journal of epidemiology* 1996;143:38-47.
 15. Doherty M. Genetics of hand osteoarthritis, *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2000;8:S8-10.
 16. Hofman A, Grobbee DE, de Jong PT, et al. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study, *European journal of epidemiology* 1991;7:403-422.
 17. Hofman A, Darwish Murad S, van Duijn CM, et al. The Rotterdam Study: 2014 objectives and design update, *European journal of epidemiology* 2013;28:889-926.

- Accepted Article
18. Kellgren JH, Jeffrey MR, and Ball J (1963) *Atlas of Standard Radiographs of Arthritis: The epidemiology of Chronic Rheumatism*, Vol. 2, Blackwell Scientific Publications, Oxford.
 19. Odding E, Valkenburg HA, Algra D, et al. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study, *Annals of the rheumatic diseases* 1998;57:203-208.
 20. Kerkhof HJ, Bierma-Zeinstra SM, Arden NK, et al. Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors, *Annals of the rheumatic diseases* 2014;73:2116-2121.
 21. McCloskey EV, Spector TD, Eyres KS, et al. The assessment of vertebral deformity: a method for use in population studies and clinical trials, *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1993;3:138-147.
 22. Burger H, van Daele PL, Odding E, et al. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age. The Rotterdam Study, *Arthritis and rheumatism* 1996;39:81-86.
 23. Munafo MR, Tilling K, Taylor AE, et al. Collider scope: when selection bias can substantially influence observed associations, *International journal of epidemiology* 2018;47:226-235.
 24. Castano-Betancourt MC, Rivadeneira F, Bierma-Zeinstra S, et al. Bone parameters across different types of hip osteoarthritis and their relationship to osteoporotic fracture risk, *Arthritis and rheumatism* 2013;65:693-700.

- Accepted Article
25. Panoutsopoulou K, Thiagarajah S, Zengini E, et al. Radiographic endophenotyping in hip osteoarthritis improves the precision of genetic association analysis, *Annals of the rheumatic diseases* 2017;76:1199-1206.
 26. Conrozier T, Ferrand F, Poole AR, et al. Differences in biomarkers of type II collagen in atrophic and hypertrophic osteoarthritis of the hip: implications for the differing pathobiologies, *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2007;15:462-467.
 27. Conrozier T, Merle-Vincent F, Mathieu P, et al. Epidemiological, clinical, biological and radiological differences between atrophic and hypertrophic patterns of hip osteoarthritis: a case-control study, *Clinical and experimental rheumatology* 2004;22:403-408.
 28. MacGregor AJ, Li Q, Spector TD, et al. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee, *Rheumatology* 2009;48:277-280.
 29. Nielson CM, Liu CT, Smith AV, et al. Novel Genetic Variants Associated With Increased Vertebral Volumetric BMD, Reduced Vertebral Fracture Risk, and Increased Expression of SLC1A3 and EPHB2, *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2016;31:2085-2097.
 30. Liu CT, Karasik D, Zhou Y, et al. Heritability of prevalent vertebral fracture and volumetric bone mineral density and geometry at the lumbar spine in three generations of the Framingham study, *Journal of bone and mineral research : the*

official journal of the American Society for Bone and Mineral Research 2012;27:954-958.

31. Werner RA, Waring W, and Maynard F. Osteoarthritis of the hand and wrist in the post poliomyelitis population, *Archives of physical medicine and rehabilitation* 1992;73:1069-1072.
32. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider, *International journal of epidemiology* 2010;39:417-420.

FIGURE LEGEND

Figure 1. Cohorts in the Rotterdam Study

Table 1. Baseline characteristics study populations by age- and sex-specific quartiles of FN-BMD: RS-I & RS-II

	RS-I					p-trend*
	All	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
FN-BMD (gm/cm ² , range)	0.89 (0.49-1.49)	0.74 (0.49-0.88)	0.84 (0.70-0.96)	0.92 (0.76-1.05)	1.05 (0.83-1.49)	
number	3005	755	757	752	741	
women (%)	55.8	55.6	55.9	55.6	56.3	
age (yrs ± sd)	65.3 ± 6.5	65.4 ± 6.6	65.3 ± 6.4	65.3 ± 6.6	65.2 ± 6.5	
height (cm ± sd)	168.4 ± 9.1	167.4 ± 9.5	167.9 ± 9.3	168.7 ± 8.8	169.6 ± 8.9	1.0 × 10 ⁻⁶
weight (kg ± sd)	74.5 ± 11.5	69.4 ± 11.0	73.5 ± 10.8	76.5 ± 10.7	78.8 ± 11.5	1.2 × 10 ⁻⁶⁴
BMI (kg/m ² ± sd)	26.3 ± 3.5	24.7 ± 3.1	26.1 ± 3.4	26.9 ± 3.3	27.4 ± 3.6	3.0 × 10 ⁻⁵⁷
	RS-II					p-trend*
	All	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
FN-BMD (gm/cm ² , range)	0.93 (0.48-1.46)	0.78 (0.48-0.93)	0.89 (0.67-1.00)	0.97 (0.77-1.09)	1.10 (0.85-1.46)	
number	1149	287	290	290	282	
women (%)	54.4	54.4	54.5	54.5	54.3	
age (yrs ± sd)	63.1 ± 6.4	63.3 ± 6.6	63.1 ± 6.4	62.8 ± 6.4	62.8 ± 6.4	
height (cm ± sd)	168.8 ± 8.9	167.8 ± 9.2	168.9 ± 8.7	169.0 ± 9.1	169.8 ± 8.6	0.9 × 10 ⁻²
weight (kg ± sd)	77.1 ± 13.1	71.4 ± 12.4	76.0 ± 12.4	78.9 ± 12.5	82.2 ± 12.8	4.3 × 10 ⁻²⁵
BMI (kg/m ² ± sd)	27.0 ± 3.9	25.3 ± 3.3	26.6 ± 3.5	27.6 ± 3.9	28.5 ± 4.0	2.7 × 10 ⁻²⁶

values are means with standard deviations (sd) or percentages, *unadjusted p-values

FN-BMD: femoral neck bone mineral density, BMI: body mass index, RS: Rotterdam Study

Table 2. Association between age- and sex-adjusted quartiles of FN-BMD and incident and progressive knee and hip ROA

quartiles FN-BMD	Knee ROA, RS-I & -II					
	Incidence cases/total (%)	OR [*]	Progression cases/total (%)	OR [*]	Incidence or progression cases/total (%)	OR [*]
Quartile 1	90/933 (9.6 %)	1 (reference)	42/109 (38.5 %)	1 (reference)	132/1042 (12.7 %)	1 (reference)
Quartile 2	112/902 (12.4 %)	1.29 (0.93 - 1.78)	70/145 (48.3 %)	1.39 (0.82 - 2.38)	182/1047 (17.4 %)	1.34 (1.02 - 1.75)
Quartile 3	116/868 (13.4 %)	1.28 (0.92 - 1.78)	78/174 (44.8 %)	1.09 (0.65 - 1.84)	194/1042 (18.6 %)	1.23 (0.94 - 1.61)
Quartile 4	136/811 (16.8 %)	1.58 (1.14 - 2.18)	97/212 (45.8 %)	1.07 (0.64 - 1.78)	233/1023 (22.8 %)	1.42 (1.09 - 1.86)
	per increase sd FN-BMD	1.15 (1.04 - 1.28)	per increase sd FN-BMD	0.89 (0.77 - 1.03)	per increase sd FN-BMD	1.06 (0.97 - 1.15)
quartiles FN-BMD	Hip ROA, RS-I & -II					
	Incidence cases/total (%)	OR [†]	Progression cases/total (%)	OR [†]	Incidence or progression cases/total (%)	OR [†]
Quartile 1	49/992 (4.9 %)	1 (reference)	21/50 (42.0 %)	1 (reference)	70/1042 (6.7 %)	1 (reference)
Quartile 2	59/991 (6.0 %)	1.01 (0.68 - 1.52)	30/56 (53.6 %)	1.71 (0.74 - 3.96)	89/1047 (8.5 %)	1.17 (0.81 - 1.68)

Quartile 3	59/986 (6.0 %)	1.04 (0.69 - 1.56)	30/56 (53.6 %)	1.61 (0.70 - 3.75)	89/1042 (8.5 %)	1.17 (0.81 - 1.70)
Quartile 4	86/930 (9.2 %)	1.57 (1.06 - 2.32)	56/93 (60.2 %)	2.17 (0.99 - 4.79)	142/1023 (13.9 %)	1.82 (1.28 - 2.59)
	per increase sd FN-BMD	1.07 (0.95 - 1.22)	per increase sd FN-BMD	1.32 (1.04 - 1.66)	per increase sd FN-BMD	1.16 (1.05 - 1.29)

* Adjusted odds ratio's (OR), with 95% confidence intervals between parentheses, are adjusted for age, sex, body mass index, study population, follow up time and knee ROA sum score at baseline

† Adjusted odds ratio's (OR), with 95% confidence intervals between parentheses, are adjusted for age, sex, body mass index, study population, follow up time and hip ROA sum score at baseline

FN-BMD: femoral neck bone mineral density, ROA: radiographic osteoarthritis, RS: Rotterdam Study, sd: standard deviation

Table 3. Association between age- and sex-adjusted quartiles of FN-BMD and incident hand ROA

quartiles FN-BMD	Hand ROA, RS-I & -II	
	Incidence cases/total (%)	OR*
Quartile 1	103/565 (18.2 %)	1 (reference)
Quartile 2	98/532 (18.4 %)	1.01 (0.73 - 1.40)
Quartile 3	112/520 (21.5 %)	1.22 (0.88 - 1.69)
Quartile 4	103/501 (20.6 %)	1.03 (0.74 - 1.44)
	per increase sd FN-BMD	1.01 (0.90 - 1.13)

*Adjusted odds ratio's (OR), with 95% confidence intervals between parentheses, are adjusted for age, sex, body mass index, study population, follow up time and hand ROA sum score at baseline

FN-BMD: femoral neck bone mineral density, ROA: radiographic osteoarthritis, RS: Rotterdam Study, sd: standard deviation

Table 4. Knee, hip and hand ROA by prevalent vertebral and non-vertebral fractures, RS-I

prevalent fracture type	Knee ROA		Hip ROA		Hand ROA	
	Incidence or progression cases/total (%)	OR*	Incidence or progression cases/total (%)	OR*	Incidence cases/total (%)	OR*
vertebral fracture						
absent	541/2597 (20.8 %)	1 (reference)	306/2710 (11.3 %)	1 (reference)	304/1229 (24.7 %)	1 (reference)
present	38/211 (18.0 %)	0.72 (0.48 - 1.09)	25/210 (11.9 %)	0.96 (0.57 - 1.61)	24/74 (32.4 %)	1.74 (1.02 - 2.98)
non-vertebral fracture						
absent	516/2596 (19.9 %)	1 (reference)	290/2686 (10.8 %)	1 (reference)	310/1228 (25.2 %)	1 (reference)
present	148/579 (25.1 %)	1.21 (0.96 - 1.53)	84/596 (14.1 %)	1.25 (0.92 - 1.68)	55/250 (22.0 %)	0.77 (0.54 - 1.10)

OR*: Odds ratio, with 95% confidence intervals between parentheses, adjusted for age, sex, body mass index, femoral neck bone mineral density, use of walking aid, lower limb disability, fall tendency and corresponding ROA sum score at baseline

ROA: radiographic osteoarthritis, RS: Rotterdam Study

Table 5. Characteristics past study versus present study

	Past study*	Present study	
	RS-I	RS-I	RS-II
Number of patients	1,403	3,005	1,149
Follow-up time (yrs)	6.5	8.4	4.1
Incident knee ROA	74	389	65
Progressive knee ROA	25	236	51

ROA: radiographic osteoarthritis

RS: Rotterdam Study

* Bergink AP, Uitterlinden AG, Van Leeuwen JP, Hofman A, Verhaar JA, and Pols HA. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study. Bone 2005;37:446-56.

