Malalignment: a possible target for prevention of incident knee osteoarthritis in overweight and obese women

Jos Runhaar¹, Marienke van Middelkoop¹, Max Reijman², Dammis Vroegindeweij³, Edwin H. G. Oei⁴ and Sita M. A. Bierma-Zeinstra¹,²

Abstract

Objectives. The present study aims to investigate the associations between malalignment and incident knee OA after 2.5 years in a high-risk group of 333 middle-aged overweight women (BMI ≥ 27 kg/m²) free of clinical and radiological knee OA at baseline.

Methods. The primary outcome measure was the incidence of knee OA, defined as the incidence of radiographic knee OA (Kellgren and Lawrence grade ≥ 2), clinical knee OA (ACR criteria) or medial or lateral joint space narrowing (≥ 1.0 mm). Using generalized estimating equations, associations between valgus and varus alignment (compared with neutrally aligned knees) and the primary outcome measure and all its items separately were studied.

Results. Neither varus- nor valgus-aligned knees had a significantly increased risk for incident knee OA according to the primary outcome measure. A significantly increased risk for the development of radiographic knee OA was found for varus-aligned knees [odds ratio (OR) 3.3, 95% CI 1.5, 7.3]. Valgus-aligned knees showed a borderline increased OR (2.8, 95% CI 1.0, 8.0) for the development of radiographic knee OA. No statistically significant effects were found for varus and valgus alignment on the incidence of clinical knee OA or medial or lateral joint space narrowing.

Conclusion. Since this study was performed in a true target population, current data suggest that malalignment might be a target for the prevention of radiographic knee OA in overweight and obese women.

Key words: varus, valgus, knee osteoarthritis, obesity, incidence.
or progression of knee OA features. For instance, malalignment was associated with incident bone marrow lesions [12] and cartilage defects [13], but does not lead to greater cartilage volume reduction [14] and was not associated with chondral defect scores [14]. However, all these studies were among healthy people with mainly normal body weight. Brouwer et al. [15] showed that in overweight and especially obese individuals, malalignment significantly increased the risk of development of knee OA (odds ratio (OR) 2.0 for varus alignment in subjects with a BMI $\geq 25$ and $<30\text{kg/m}^2$ and 3.3 and 5.1 for valgus and varus alignment in subjects with a BMI $\geq 30\text{kg/m}^2$). In subjects with normal body weight, no association between malalignment and incident knee OA was found. It is therefore suggested that malalignment could be a risk factor for initiation of knee OA in combination with a high BMI.

Brouwer et al. [15] based their results on a large cohort study. However, in order to confirm that malalignment can be a target for the prevention of knee OA, the effect of malalignment should be confirmed in a target population of subjects at high risk of developing knee OA. The PRevention of knee Osteoarthritis in Overweight Females (PROOF) study [2] offers such a high-risk group. Hence the objective of the current study was to evaluate the effect of varus and valgus alignment on the onset of knee OA over a 2.5-year follow-up period in a high-risk group of middle-aged overweight or obese women.

Materials and methods
For this study we used data from the PROOF study (ISRCTN 42823086). A description of the study protocol can be found elsewhere [2, 16]. In short, this 2.5-year follow-up study aimed to evaluate the preventive effect of a diet and exercise programme and oral glucosamine sulphate (double blind, placebo controlled) on the initiation of knee OA in a $2 \times 2$ factorial design. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center.

Participants
The PROOF study was conducted among a group of subjects without clinical and radiological knee OA but with a high risk of developing knee OA, i.e. women with a BMI $\geq 27.0\text{kg/m}^2$ and between 50 and 60 years of age. In the region of Rotterdam, The Netherlands, 50 general practitioners sent an information letter about the study, with a reply card, to all women between 50 and 60 years of age, without major co-morbidities, registered at their practice. A total of 6691 women were contacted. Additional information about the study was sent to all women who returned the reply card, indicated they were interested in participating and had a BMI $\geq 27\text{kg/m}^2$ (as calculated by the body weight and body length as stated on the reply card). After several days, all women were contacted by phone to check on all inclusion criteria. Besides criteria on age and BMI, subjects had to be free of knee OA according to the ACR criteria [17], free of contraindications to MRI, free of rheumatic diseases, not using a walking aid, not under treatment for knee complaints, fluent in the Dutch language and not using oral glucosamine during the past 6 months. All women eligible and willing to participate were invited to visit the research institute, where they signed the informed consent according to the Declaration of Helsinki and underwent physical examination and radiographs of both knees.

Measurements
At baseline, body weight and height were measured and a standardized semi-flexed posteroanterior (PA) radiograph of both knees was taken according to the MTP protocol [18]. The width of a horizontal beam, centred at the tibiofemoral joint space, was adjusted to fit both knees on a single image. All subjects filled out a questionnaire that included questions on knee complaints, number of days with knee pain, history of knee injury (Did you ever injure your knee badly enough to visit a doctor or other health care professional?) and Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire [19]. All measurements were repeated after 2.5 years of follow-up.

Data
Measured body height and weight were used for calculation of BMI and date of birth to calculate age. Mild symptoms were defined as any knee pain in the past 12 months. WOMAC pain and function scores were calculated from the KOOS questionnaire. A researcher blinded to clinical outcomes scored all radiographs (baseline and follow-up images at once) using the Kellgren and Lawrence (KL) criteria [20]. Minimal joint space width was measured digitally in each tibiobimalen compartment of both knees by two blinded researchers individually according to the method of Lequesne [21]. The minimal joint space width of each compartment was defined as the mean score of both assessors. Scores with a difference between readers $\geq 2.0\text{mm}$ were re-evaluated by both readers at a consensus meeting. Medial anatomical knee alignment angle was assessed by digitally determining the angle between the line from the centre of the tibial spines through the centre of the femoral shaft at approximately 10 cm from the joint margin and the line from the centre of the tibial spine through the centre of the tibial shaft at $\sim 10\text{cm}$ from the joint margin, since it highly correlates with the mechanical axis of the knee and is assessable on knee radiographs [22]. In healthy adults with neutral alignment, the mechanical axis is between 1° and 1.5° varus [23]. For women, the reported offset between the mechanical and anatomical axis is between 3.5° [22] and 4.6° [23]. Since anatomical knee angles were measured in whole degrees, we defined a mechanical axis of 179° ± 1° as neutral and corrected for an offset of 4°. Hence anatomical knee alignment angles between 182° and 184° were defined as normal, $>184°$ as valgus alignment and $<182°$ as varus alignment [15]. The reproducibility of KL grading and anatomical knee alignment assessment was checked after scoring a random
sample of 20% of all radiographs twice by a second blinded reader.

**Statistical analyses**

All knees with complete data for baseline knee alignment and the primary outcome measure, excluding knees with a KL grade ≥2 or fulfilling the ACR criteria at baseline, were selected for the analyses. The primary outcome measure of the PROOF study was the incidence of knee OA, defined as the incidence of radiographic knee OA (KL grade ≥2), clinical knee OA (clinical and radiographic ACR criteria [17]) or medial or lateral joint space narrowing (>1.0 mm) [2]. Using generalized estimating equations, which takes into account the correlation between two knees within subjects, the relation between varus/valgus alignment and the onset of knee OA according to the primary outcome measure and for all four items separately was determined. Neutrally aligned knees constituted a reference group in all analyses. All analyses were adjusted for KL grade at baseline (as in the original trial [2]) and the randomized groups of both interventions of the PROOF study. A P-value < 0.05 was considered statistically significant. For explorative reasons, the analyses were additionally stratified for baseline BMI and were rerun for overweight (BMI < 30 kg/m²) and obese individuals (BMI ≥ 30 kg/m²) separately. All statistical tests were performed using SPSS 20.0 (IBM, Armonk, NY, USA) and were presented as ORs with corresponding 95% CIs.

**Results**

In total, 635 knees from 333 women were selected for the analyses. Baseline medial joint space width was significantly higher [4.8 mm (s.d. 0.7) vs 4.7 mm (s.d. 0.7), P = 0.01] in the subjects with complete follow-up data compared with those with incomplete data.

Valgus alignment was found in 13% and varus alignment in 39% of all knees. The baseline characteristics are given in Table 1. At baseline, only the mean lateral minimal joint space width was significantly higher in the varus-aligned knees. Tests for reproducibility showed moderate agreement for KL grade (κ = 0.6) and good agreement for alignment (κ = 0.7) and minimal joint space width (κ = 0.7).

For the primary outcome measure, despite higher incidence numbers, no significant effects of varus (18% incidence) and valgus alignment (20% incidence) were found, compared with neutral aligned knees (15% incidence; see Table 2). The incidence of radiographic knee OA (KL grade ≥2) was found in 9% of all varus knees and 6% of all valgus knees at follow-up, compared with only 2% incidence in neutrally aligned knees. Varus-aligned knees had a statistically significant OR (3.3, 95% CI 1.5, 7.3) for the incidence of radiographic knee OA at follow-up, while the OR for valgus-aligned knees reached borderline significance (2.8, 95% CI 1.0, 8.0). The incidence of clinical knee OA was 5% in varus-aligned knees, 4% in valgus-aligned knees and 6% in neutrally aligned knees. These differences did not reach statistical significance. Malalignment also had no significant effects on the incidence of medial and lateral joint space narrowing. See Table 2 for full details.

Table 3 shows the explorative stratified analyses for overweight and obese individuals separately. The presented ORs for varus- and valgus-aligned knees on the incidence of KL grade ≥2 reached borderline significance within the obese group (both P = 0.06). Due to the absence of incidence of KL grade ≥2 in neutrally aligned knees among overweight subjects, no ORs could be calculated for the risk of varus and valgus alignment within this subgroup.

**Discussion**

Since knee malalignment is a modifiable factor and related to knee loading, its role in the onset of knee OA is important in the search for modifiable risk factors for the disease. Among middle-aged women free of clinical and

**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 635)</th>
<th>Neutrally aligned knees (n = 308)</th>
<th>Varus aligned knees (n = 246)</th>
<th>Valgus aligned knees (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>55.7 (3.2)</td>
<td>55.9 (3.1)</td>
<td>55.4 (3.3)</td>
<td>55.6 (3.2)</td>
</tr>
<tr>
<td>BMI, mean (s.d.), kg/m²</td>
<td>32.0 (3.9)</td>
<td>32.1 (3.8)</td>
<td>31.8 (4.0)</td>
<td>32.0 (4.3)</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30 kg/m²), %</td>
<td>45</td>
<td>42</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>KL grade = 1, %</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Mild symptoms (yes), %</td>
<td>5.7 (9.4)</td>
<td>5.9 (9.5)</td>
<td>5.1 (8.7)</td>
<td>7.0 (10.8)</td>
</tr>
<tr>
<td>WOMAC function (0–100)², mean (s.d.)</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>History of knee injury (yes), %</td>
<td>5.7 (9.2)</td>
<td>5.7 (9.0)</td>
<td>4.8 (8.4)</td>
<td>7.4 (111.3)</td>
</tr>
<tr>
<td>Minimal medial JSW, mean (s.d.), mm</td>
<td>6.2 (1.0)</td>
<td>6.1 (1.0)</td>
<td>6.4 (1.1)</td>
<td>5.8 (0.9)</td>
</tr>
</tbody>
</table>

²Higher scores mean worse pain/function. All values are calculated on knee level. KL: Kellgren and Lawrence; JSW: joint space width; neutral: medial anatomical knee angles 182°–184°; varus: medial anatomical knee angles <182°; valgus: medial anatomical knee angles >184°.
radiographic knee OA at baseline, both varus and valgus alignment are associated with an increase in the incidence of radiographic knee OA compared with neutrally aligned knees, despite the fact that the OR for valgus alignment did not reach statistical significance, with a \(P\) value of 0.05. Contrary to previous studies, our population was recruited for a preventive trial in a clinical setting. This makes results highly representative for a possible target population selected for a preventive intervention, for instance, by counteracting the malalignment.

As in many other studies, a discordance between radiographic signs of knee OA and clinical knee OA was found [24]. This phenomenon is probably caused by the variability in pain response between individuals. In an intelligently designed study, Neogi et al. [24] showed that when appropriately accounted for, a strong correlation between structural and clinical signs of knee OA exists, especially among the higher KL grades. Moreover, when this phenomenon is accounted for, radiographic knee OA is strongly associated with an increased risk for the incidence of knee pain [25]. So the higher incidence of KL grade \(\geq 2\), as seen in knees with varus or valgus alignment in the present study, increases the risk for the development of clinical signs over time within these knees.

In the present study, knee alignment was measured on short-limb radiographs. Although full-length radiographs are preferable, alignment measured on short-limb radiographs is a validated measurement of static knee alignment [22], especially in large studies with a wide variety of alignment angles [23]. Nevertheless, alignment measured on radiographs is a static representation of knee alignment and does not fully represent dynamic loads on the tibiofemoral joint [26, 27]. Probably due to a higher baseline BMI in our study, knee alignment was shifted towards varus alignment (Fig. 1). Data from Niu et al. [27] confirm that a shift towards varus alignment is seen in obese non-OA subjects.

It is suggested that altered loading of the knee joint, e.g. by obesity or malalignment, leads to alterations in the composition, structure, metabolism and mechanical properties of articular cartilage [28]. This is probably caused by a shift of the load-bearing contact towards regions in the cartilage that have not adapted to these loads [29, 30]. The association between malalignment and the incidence of radiographic knee OA as found in the present study and the association between obesity and the incidence of knee OA might be partly mediated by meniscal extrusion, since this also affects the load-bearing contact area. Both malalignment and obesity are associated with a higher prevalence of meniscal extrusion [31, 32]. In subjects with KL grades \(<2\) at baseline, Madan-Sharma et al. [33] showed that subjects with meniscal extrusion had higher rates of joint space narrowing over the subsequent 2 years. Other studies have also shown associations between meniscal extrusion and knee OA features [31, 32].

In a recent study, Sharma et al. [13] found that varus alignment is a risk factor for incident cartilage defects, independent of meniscal extrusion, and corroborate that varus alignment might be a target for the prevention of knee OA. However, whether interventions like braces or wedged insoles can counteract the initiated processes of the existing meniscal extrusion and, over time, delay or prevent knee OA has never been studied.

The combined knee OA outcome measure was adopted from the original PROOF study. In order to make a preventive randomized trial feasible over a relatively short follow-up time, the incidence of radiographic knee OA, clinical knee OA and joint space narrowing were combined into one measure. Hence the present results are based on secondary analyses. More sensitive measures, such as MRI, are needed to provide more detailed information about the association between malalignment and the incidence of knee OA. Sharma et al. [13] showed that varus alignment was associated with the onset of new cartilage damage seen on MRI. However, in preclinical subjects at high risk of developing knee OA, as included in the present study, cartilage defects on MRI are probably already common [34]. Moreover, the clinical relevance of these features remains to be demonstrated [35] and defining a target population for the primary prevention of knee OA would preferably be done on clinical or radiographic features rather than on MRI features, given the costs and availability of MRI [36].

The explorative stratified analyses for baseline body weight groups showed identical results as the unstratified analyses: an increased risk for the incidence of KL grade

### Table 2: Associations between varus- and valgus-aligned knees and incident knee OA (n = 635 knees)

<table>
<thead>
<tr>
<th>Knee OA*</th>
<th>Radiographic knee OA</th>
<th>Clinical knee OA</th>
<th>Medial JSN</th>
<th>Lateral JSN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>Incidence, %</td>
<td>(95% CI)</td>
<td>OR</td>
</tr>
<tr>
<td>Valgus</td>
<td>1.4 (0.8, 2.5)</td>
<td>6</td>
<td>2.8 (1.0, 8.0)</td>
<td>4</td>
</tr>
<tr>
<td>Varus</td>
<td>1.1 (0.7, 1.1)</td>
<td>9</td>
<td>3.3 (1.5, 7.3)</td>
<td>5</td>
</tr>
<tr>
<td>Neutral</td>
<td>1 (reference)</td>
<td>2</td>
<td>1 (reference)</td>
<td>6</td>
</tr>
</tbody>
</table>

JSN: joint space narrowing; OR: odds ratio; KL: Kellgren and Lawrence. *Defined as the incidence of radiographic knee OA (KL grade \(\geq 2\)), clinical knee OA (ACR criteria) or medial or lateral joint space narrowing (\(\geq 1.0\) mm) at follow-up. **Statistically significant (\(P < 0.05\)). All analyses were adjusted for KL grade at baseline (0 vs 1) and randomized groups for both interventions of the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study.

---

**www.rheumatology.oxfordjournals.org**
varus- and valgus-aligned knees and no effect of malalignment on the development of clinical OA in both overweight and obese subjects (Table 3). This does not seem to match the results from Brouwer et al. [15], who showed higher ORs for the incidence of radiographic knee OA among malaligned knees within obese rather than overweight individuals. However, the BMI range of their overweight individuals was 25-30 kg/m², while in the present study it ranged from 27 to 30 kg/m². This limits the contrast between the overweight and obese groups in our study. Nevertheless, it can be appreciated that virtually all ORs were higher within the obese subjects in the present study, which suggests a higher risk for incident knee OA for malaligned knees among obese individuals compared with those in overweight individuals.

Malalignment can be partly opposed by non-surgical interventions. Although mainly studied in subjects with knee OA [37, 38], bracing has been shown to be effective in reducing peak knee adduction moment and angular impulse during walking in healthy subjects with varus-aligned knees [9]. Also, full-length wedged insoles have been shown to alter knee joint load in healthy subjects [7, 39]. However, most of these studies did not include overweight or obese individuals. One of the few studies including asymptomatic overweight individuals did show a significant reduction in joint load during gait using a modified shoe with a wedged insole [40], but these subjects did not seem to have malaligned knees. To our knowledge, no trial on the effects of non-surgical interventions on joint biomechanics of malaligned knees in otherwise healthy overweight or obese subjects has been performed. Neither has the preventive effect of such interventions on the development of clinical OA in both overweight and obese subjects (Table 3). This does not seem to match the results from Brouwer et al. [15], who showed higher ORs for the incidence of radiographic knee OA among malaligned knees among obese individuals rather than overweight individuals. However, the BMI range of their obese group (over 30 kg/m²) was higher than in our study, which limits the direct comparison between the two studies.

**Table 3** Stratified associations between varus and valgus alignment and incident knee OA for overweight and obese individuals

<table>
<thead>
<tr>
<th></th>
<th>Knee OAa</th>
<th>Radiographic knee OA</th>
<th>Clinical knee OA</th>
<th>Medial JSN</th>
<th>Lateral JSN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, %</td>
<td>OR (95% CI)</td>
<td>Incidence, %</td>
<td>OR (95% CI)</td>
<td>Incidence, %</td>
</tr>
<tr>
<td>Incidence among</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subjects (BMI &lt;30 kg/m²)</td>
<td>Varus (n=101)</td>
<td>14</td>
<td>0.7 (0.4, 1.5)</td>
<td>8</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Valgus (n=36)</td>
<td>22</td>
<td>1.1 (0.5, 2.9)</td>
<td>3</td>
<td>0.3 (0.0, 3.1)</td>
</tr>
<tr>
<td></td>
<td>Neutral (n=109)</td>
<td>17</td>
<td>Reference</td>
<td>6</td>
<td>Reference</td>
</tr>
<tr>
<td>Incidence among</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>obese subjects (BMI ≥30 kg/m²)</td>
<td>Varus (n=145)</td>
<td>21</td>
<td>1.4 (0.8, 2.6)</td>
<td>9</td>
<td>2.3 (1.0, 5.3)</td>
</tr>
<tr>
<td></td>
<td>Valgus (n=45)</td>
<td>18</td>
<td>1.5 (0.7 - 3.1)</td>
<td>9</td>
<td>3.1 (1.0, 10.1)</td>
</tr>
<tr>
<td></td>
<td>Neutral (n=199)</td>
<td>14</td>
<td>Reference</td>
<td>6</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Defined as the incidence of radiographic knee OA (KL grade ≥2), clinical knee OA (ACR criteria) or medial or lateral joint space narrowing (≥1.0 mm) at follow-up. All analyses were adjusted for KL grade at baseline (0 vs 1) and randomized groups for both interventions of the Prevention of Knee Osteoarthritis in Overweight Females (PROOF) study. n/a: not applicable since reference category is 0%; JSN: joint space narrowing; OR: odds ratio; KL: Kellgren and Lawrence.*

**Fig. 1** Histogram of medial anatomical knee angles
interventions on the development of knee OA been studied. In a direct comparison of the biomechanical effects of varus knee braces and lateral wedged insoles in a study among subjects with knee OA, Jones et al. [8] showed that both interventions reduced medial knee joint load. However, the effects of the wedged insoles were significantly greater than those of the knee braces. Moreover, and very important when administering a preventive intervention, all participants preferred the wedged insole intervention over the knee brace at the end of the trial. Since adherence to the intervention is an important issue when prescribing an active measure to healthy subjects in order to prevent future disease, subjects’ preferences are very important.

In conclusion, both varus and valgus alignment increased the risk for incident radiographic knee OA after 2.5 years in middle-aged overweight or obese women. Contrary to previous studies on the association between malalignment and the incidence of knee OA that focused mainly on large cohorts, this study shows that within a relatively easily obtainable population, malalignment is a risk factor for incident radiographic knee OA. Since malalignment is a modifiable factor, results from the present study suggest that malalignment might be a target for the prevention of radiographic knee OA in middle-aged overweight and obese women. From a health perspective, weight loss would probably be more preferable as a preventive measure. However, given the challenge of adhering to a weight loss intervention and achieving weight loss in this population [16], counteracting malalignment might be an additional option in preventing the development of radiographic knee OA.

Rheumatology key messages

- Varus and valgus alignment are risk factors for incident radiographic knee OA in overweight and obese women.
- Malalignment might be a target for knee OA prevention in overweight and obese women.

Acknowledgements

The original PROOF study was supported by the Netherlands Organization for Health Research and Development, ZonMw (grant number 120520001).

Funding: This study was partly funded by a programme grant from the Dutch Arthritis Foundation for their Centre of Excellence, ‘Osteoarthritis in primary care’.

Disclosure statement: The authors have declared no conflicts of interest.

References

12 Hayashi D, Englund M, Roemer FW et al. Knee malalignment is associated with an increased risk for incident and enlarging bone marrow lesions in the more loaded compartments: the MOST study. Osteoarthritis Cartilage 2012;20:1227–33.


