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Can patient and radiological factors predict metal-on-metal hip resurfacings with evidence of a pseudotumour?

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Question	**Response**
Is this a clinical trial? This is defined as any clinical research where patients are being randomized into two treatment groups OR where patients are being followed prospectively comparing two different treatments.	No
Was this study NIH funded?	No
Have any of the illustrations or tables used in this article been published previously (i.e. does another party now own the copyright to any illustration or table)?	No
How will this work influence the practice of Orthopaedics?	We have demonstrated that a combination of patient and radiological factors provided useful information for distinguishing between MoMHRs with and without evidence of pseudotumours. Surgeons may wish to consider these specific patient and radiological factors before proceeding with cross-sectional imaging. Radiographs are important

	when assessing MoMHR patients and should be included in all follow-up protocols.
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Abstract:	Background The role of radiographs in the follow-up of metal-on-metal hip resurfacing (MoMHR) patients is unclear. We investigated whether a combination of patient and radiological factors predicted MoMHRs with evidence of a pseudotumour. Methods We performed a retrospective single-centre case-control study (384 MoMHRs). The pseudotumour group (n=130) all had symptomatic pseudotumours on cross-sectional imaging with the diagnosis confirmed at revision. The non-pseudotumour group (n=254; subgroup previously reported on) had normal cross-sectional imaging. Radiographs immediately prior to revision were assessed in the pseudotumour group and compared with radiographs performed at the time of normal cross-sectional imaging in the non-pseudotumour group. Two blinded independent observers analysed radiographs for signs of failure (excellent inter-observer agreement). Logistic regression modeling identified patient and radiological predictors of pseudotumour revision. Results Pseudotumour hips more commonly had abnormal radiographs (80.0% vs. 63.4%; p=0.001). Patient and radiological factors predicting pseudotumour revision in the multivariable model were: female gender (odds ratio (OR) 3.14 (95% CI 1.85-5.35); p<0.001), high inclination (OR 1.04 per degree (95% CI 1.01-1.07); p=0.006), acetabular osteolysis (OR 5.06 (95% CI 2.14-12.0); p<0.001), femoral osteolysis (OR 17.8 (95% CI 5.09-62.2); p<0.001), and acetabular loosening (OR 3.35 (95% CI 1.34-8.35); p=0.009). Factors predicting being in the non-pseudotumour group were: anteversion >5o (5o to <10o: OR 0.31 (95% CI 0.12-0.77), p=0.012; >10o: OR=0.32 (95% CI 0.15-0.70), p=0.004) and heterotopic ossification (OR 0.19 (95% CI 0.05-0.72); p=0.015). The model was well calibrated (p=0.589) with good discriminatory ability (area under the curve (AUC)=0.801; sensitivity=74.4%, specificity=71.7%). Conclusions A combination of patient and radiological factors provided useful information for distinguishing between MoMHRs with and without evidence of pseudotumours. Surgeons may wish to consider these specific patient and radiological factors before proceeding with cross-sectional imaging. Radiographs are important when assessing MoMHR patients and should be included in all follow-up protocols. Level of Evidence Diagnostic Study (Level III)

Response to reviewer comments for JBJS-D-16-00212R2 "Can patient and radiological factors predict metal-on-metal hip resurfacings with evidence of a pseudotumour?"

We would like to thank the editor and the reviewers for their comments, which we feel have helped us to improve our paper.

Please note all changes to the main manuscript text have been highlighted in **bold text**.

Responses to editor and reviewers' comments are also in **bold text** below.

Deputy Editor Comments

Dear Dr. Matharu:

I have included a comment from one of the reviewers which I think is valid. It is the nature of Editors to be "picky" but also our role to ensure that the nomenclature is correctly used and to avoid confusion between different pathological conditions that might be similar but have slightly different presentations. This is the case in your manuscript where a number of cases without a "tumour" are included in your analysis. As the reviewer points out pseudotumour should in fact refer to those cases with a mass that is non-neoplastic thus the name "pseudotumour". I believe this term may in fact have been coined at your institution. It is therefore inappropriate to include cases that have histologic evidence of reaction to wear debris but without a mass in the pseudotumour category.

I think you could address this by either excluding them from the analysis altogether (the simplest approach) or include them as a subcategory in your analysis if you felt strongly that they should be included. One way or the other I am requesting that you differentiate between those patients with a mass and those patients without.

I hope that you are able to address these concerns in a revised manuscript accompanied by a response letter. In your response letter, each reviewer concern should be reiterated followed by a specific response. Additionally, all corresponding changes to the text should be in bold. The due date for revision will be Jun 30 2016 11:59PM.

I look forward to seeing your re-revised manuscript.

Thank you.

Yours truly,
James P. Waddell, MD, FRCSC
Deputy Editor
The Journal of Bone & Joint Surgery

We have now removed the cases where revisions were performed for non-mass lesions (n=5) from the "pseudotumour" group in our paper. We have subsequently repeated all our analyses and modified the text, tables and figures accordingly.

Reviewer #1:

The authors have appropriately addressed my concerns. I have no further specific comments. I defer to the editor regarding the overall impact of the article and suitability for publication.
No specific comments to address.

Reviewer #2:

It is, I suppose, a minor point of interest to only a small proportion of JBJS readers, but I am still bothered by the "inclusive" definition of pseudotumor used by the authors: "Given the heterogeneous nature of pathological reactions associated with MoMHRs, an inclusive definition for pseudotumour was used: (1) cystic, solid, or mixed masses communicating with the hip joint (n=130), or (2) significant metallosis, synovitis, tissue damage and/or necrosis in the absence of mass lesions (n=5).4,5,17,21,22 The diagnosis of a pseudotumour was confirmed if there was also histological evidence of lymphocytic infiltrates (including aseptic lymphocytic vasculitis and associated lesions) and a phagocytic macrophage response to metal wear debris, with or without tissue necrosis.23-25"

After all, "tumor" indicates a mass. The "pseudo" prefix indicates that the mass is not a neoplasm (it does not indicate that the mass is not a mass). So I continue to be bothered by the inclusion of 5 cases that had no mass lesions, but instead had "significant metallosis, synovitis, tissue damage and/or necrosis", since those findings are common in failed arthroplasty cases without a mass (i.e., without a pseudotumor). The authors go on to indicate that the diagnosis of a pseudotumor was confirmed by lymphocyte infiltrates and a phagocytic macrophage response to debris. So this to me indicates they are including ALVAL cases without mass lesions (they cite the Willert article to support their definition, although as I recall, the term "pseudotumor" was never used in the Willert publication). Incidentally, just because the authors may be able to cite prior work that may have also included "non-mass pseudotumors" doesn't mean they should perpetuate sloppy nomenclature. I suppose I could accept this "inclusive" definition of pseudotumor, as long as the cases in the non-pseudotumor group were reviewed, and those with "histological evidence of lymphocytic infiltrates (including aseptic lymphocytic vasculitis and associated lesions) and a phagocytic macrophage response to metal wear debris" were excluded (in other words, according to the authors' definition any case with ALVAL histology would have to be considered pseudotumor cases). Buy why not just limit the pseudotumor group to those 130 hips with mass lesions? It simplifies everything.

We have now removed the cases where revisions were performed for non-mass lesions (n=5) from the "pseudotumour" group in our paper. Therefore the pseudotumour group now consists of 130 hips all with mass lesions, as requested by the Deputy Editor and Reviewer 2. We have subsequently repeated all our analyses and modified the text (including our definition for pseudotumour), tables and figures accordingly.

Reviewer #3:

The authors have responded to all issues raised in the previous review.

No specific comments to address.

Can patient and radiological factors predict metal-on-metal hip resurfacings with evidence of a pseudotumour?

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Please note that the following author references are blinded in the Revised Manuscript:

19. Authors' names blinded for peer-review purposes.* Prevalence of and risk factors for hip resurfacing revision. A cohort study into the second decade after the operation. *J Bone Joint Surg [Am]* (In Press – accepted 11th April 2016).

**Authors are: Gulraj S Matharu, BSc (hons), MBChB, MRCS, MRes, Andrew Judg,e David W Murray, and Hemant G Pandit.*

27. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW. "Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty* 2011; **26**: 511–518.

Can patient and radiological factors predict metal-on-metal hip resurfacings with evidence of a pseudotumour?

Abstract

Background

The role of radiographs in the follow-up of metal-on-metal hip resurfacing (MoMHR) patients is unclear. We investigated whether a combination of patient and radiological factors predicted MoMHRs with evidence of a pseudotumour.

Methods

We performed a retrospective single-centre case-control study (**384** MoMHRs). The pseudotumour group (n=**130**) all had symptomatic pseudotumours on cross-sectional imaging with the diagnosis confirmed at revision. The non-pseudotumour group (n=254; subgroup previously reported on) had normal cross-sectional imaging. Radiographs immediately prior to revision were assessed in the pseudotumour group and compared with radiographs performed at the time of normal cross-sectional imaging in the non-pseudotumour group. Two blinded independent observers analysed radiographs for signs of failure (excellent inter-observer agreement). Logistic regression modeling identified patient and radiological predictors of pseudotumour revision.

Results

Pseudotumour hips more commonly had abnormal radiographs (**80.0**% vs. 63.4%; p=**0.001**). Patient and radiological factors predicting pseudotumour revision in the multivariable model were: female gender (odds ratio (OR) **3.14** (95% CI **1.85-5.35**); p<0.001), high inclination

(OR 1.04 **per degree** (95% CI 1.01-1.07); p=**0.006**), acetabular osteolysis (OR **5.06** (95% CI **2.14-12.0**); p<0.001), femoral osteolysis (OR **17.8** (95% CI **5.09-62.2**); p<0.001), and acetabular loosening (OR **3.35** (95% CI **1.34-8.35**); p=**0.009**). Factors predicting being in the non-pseudotumour group were: anteversion $\geq 5^{o}$ (5^{o} to $<10^{o}$: OR **0.31** (**95% CI 0.12-0.77**), p=**0.012**; $\geq 10^{o}$: OR=**0.32** (**95% CI 0.15-0.70**), p=**0.004**) and heterotopic ossification (OR 0.19 (**95% CI 0.05-0.72**); p=**0.015**). The model was well calibrated (p=**0.589**) with good discriminatory ability (area under the curve (AUC)=**0.801**; sensitivity=**74.4**%, specificity=**71.7**%).

Conclusions

A combination of patient and radiological factors provided useful information for distinguishing between MoMHRs with and without evidence of pseudotumours. Surgeons may wish to consider these specific patient and radiological factors before proceeding with cross-sectional imaging. Radiographs are important when assessing MoMHR patients and should be included in all follow-up protocols.

Level of Evidence

Diagnostic Study (Level III)

Introduction

High short-term failure rates are reported for most metal-on-metal hip resurfacing (MoMHR) designs,[1-3] with many revisions performed for pseudotumours.[4,5] In an attempt to identify pseudotumours early, worldwide regulatory authorities recommend regular surveillance for most MoMHR patients.[6-8]

Radiographs are considered important when assessing MoMHR patients, providing information on component position, bone quality, and implant fixation.[9] Radiographs can identify signs suggestive of implant failure early, and in addition to blood metal ions and cross-sectional imaging, radiographs are currently recommended by most,[7,8] but not all[6] regulatory authorities. However, given that pseudotumours can be solid or cystic lesions associated with soft tissue damage and high wear,[4,5] clinicians prefer performing blood metal ions and cross-sectional imaging over radiographs.[6-8] Previous studies have reported radiological risk factors for pseudotumours that include implanting acetabular components outside an "optimal zone"[10-12] and significant reduction in the head-neck ratio following MoMHR.[13] However, these studies are limited by small numbers of pseudotumour revisions, and assessing relatively few radiological parameters.[10-13] Interpretation is also complicated by observations that pseudotumours can still occur in optimally positioned MoMHRs.[11,14] Furthermore, it remains unclear whether femoral neck narrowing is a normal "physiological" process following MoMHR or a clinically significant finding, given that neck narrowing is reported in both well-functioning MoMHRs[15,16] and pseudotumour revisions.[9,17]

The use of radiographs in the follow-up of MoMHR patients therefore remains unclear. However, it is important to establish the role of radiographs in MoMHR surveillance given

their wide availability, low costs, and the fact that current follow-up recommendations are not evidence-based but very costly.[18]

We investigated whether a combination of patient and radiological factors predicted MoMHRs with evidence of a pseudotumour. Using the factors identified, a clinical risk scoring tool was developed to predict a patient's risk of having a pseudotumour.

Patients and Methods

We performed a retrospective single-centre multi-surgeon case-control study including **384** MoMHRs implanted in **329** patients (Table 1). These hips were divided into pseudotumour (case) and non-pseudotumour (control) groups. All primary MoMHRs were performed between June 1999 and December 2009. During this interval 1,429 MoMHRs in 1,216 patients were implanted, with the outcomes for these patients previously described in detail.[19]

Pseudotumour group (130 hips)

Revision surgery of MoMHRs for pseudotumour has been performed since 2007 when this entity was first recognised.[4] By August 2015, 231 consecutive MoMHR revisions for any indication were recorded in our prospective clinical database. The pseudotumour group for the present study included all MoMHRs revised for pseudotumour (n=**130**; **56**% of all revisions). All patients undergoing revision for pseudotumour were symptomatic. Of the **130** hips revised for pseudotumour, 111 (**85**%) had their MoMHR at our institution with the remainder being referred to our centre after undergoing primary arthroplasty elsewhere. Prior to revision surgery patients were investigated using anteroposterior (AP) pelvic radiographs, blood metal ions, and ultrasound, with metal artefact reduction sequence magnetic resonance imaging (MARS-MRI) reserved for equivocal or complex cases.[4,20] The decision to perform revision was made by the patients' surgeon based on their symptoms and investigative findings.

All pseudotumours were diagnosed on cross-sectional imaging prior to revision surgery and subsequently confirmed intra-operatively. **Pseudotumours were defined as** cystic, solid, or mixed masses communicating with the hip joint.[4,21,22] The diagnosis of a pseudotumour was confirmed if there was also histological evidence of lymphocytic infiltrates (including aseptic

lymphocytic vasculitis and associated lesions) and a phagocytic macrophage response to metal wear debris, with or without tissue necrosis.[23-25]

Non-pseudotumour group (254 hips)

Following alerts in 2010 and 2012 from the Medical and Healthcare Products Regulatory Agency (MHRA), all symptomatic MoMHR patients underwent investigation with AP pelvic radiographs, blood metal ions, and cross-sectional imaging.[6,26] Prior to these alerts (in 2007/2008) we had investigated 201 asymptomatic MoMHRs with AP pelvic radiographs, blood metal ions, and cross-sectional imaging.[27]

The non-pseudotumour group for the present study included all non-revised MoMHR patients, regardless of symptoms, with normal cross-sectional imaging (no evidence of pseudotumours on ultrasound and/or MARS-MRI). The non-pseudotumour group included 254 MoMHRs, of which 128 were symptomatic (median Oxford Hip Score[28,29] (OHS)=32/48 (inter-quartile range=24-38)) and 126 were asymptomatic (median OHS=47/48 (inter-quartile range=45-48)). The asymptomatic patient subgroup has previously been reported on.[27]

Radiological analysis

Standardised AP pelvic radiographs for all patients were accessed using the hospitals' electronic picture archiving and communication system (PACS, GE Healthcare, Barrington, Illinois, USA). Apart from femoral neck narrowing (which also required the radiograph immediately following MoMHR), all radiological parameters were assessed using one single radiograph for each MoMHR. For the pseudotumour group the radiograph selected for assessment was the one performed closest to but immediately before the date of revision surgery. This represented a time when the hip was symptomatic and the pseudotumour had

already been diagnosed on cross-sectional imaging. In the non-pseudotumour group the radiograph selected for assessment was performed at the time cross-sectional imaging excluded a pseudotumour.

Each radiograph was systematically analysed for the presence or absence of abnormalities previously described in MoMHRs including component loosening (radiolucent line >2mm in any zone), osteolysis, femoral neck notching, fracture, dislocation, subluxation, impingement, and heterotopic ossification (HO).[9,30-32] Acetabular component inclination (relative to the pelvic interteardrop line) and anteversion were measured using ImageJ (National Institutes of Health, Berthesda, Maryland, USA).[33] Acetabular components were considered malpositioned if one or both parameters were outside the recommended optimal zone for MoMHR (inclination 35º-55º /anteversion 10º-30º).[11] Femoral neck narrowing was assessed as previously described.[34] Femoral neck diameter was measured in each radiograph at the junction of the neck and femoral component, and divided by the measured femoral component diameter (allowing correction for magnification). The difference between measurements from the most recent radiograph and the radiograph immediately following MoMHR allowed calculation of the degree of femoral neck narrowing since index surgery (expressed as a percentage of the initial neck diameter).

All radiographs were assessed by two independent observers (GSM and KD) in a random sequence, with both blinded to all clinical information including the study group. For the presence or absence of different radiographic abnormalities inter-observer agreement was almost perfect (Cohen's kappa statistic ranging from 0.88-1.00).[35] Any discrepancy regarding the presence or absence of abnormalities was settled by the senior author (HGP) with their final assessment used for analyses. For continuous radiographic data intra-class correlation

coefficients between observers were excellent: inclination=0.979 (95% confidence intervals (CI) 0.955-0.990), anteversion=0.968 (95% CI 0.947-0.988), femoral neck narrowing=0.941 (95% CI 0.861-0.987). The mean of the two observer measurements were used for continuous radiographic variables.

Statistical analysis

The study outcome of interest was a binary variable: MoMHR with or without a pseudotumour. The influence of patient (gender, age, implant design) and radiographic factors (above) were assessed between groups. Numerical data were compared between groups using either unpaired t-tests (parametric data) or the Wilcoxon rank-sum test (non-parametric data), with categorical data compared using either the Chi-squared test with Yates' correction or Fisher's exact test.

Logistic regression modeling was used to identify predictors of outcome. Univariable models explored the association between each predictor and outcome. For continuous predictors linearity was assessed using likelihood ratio tests, with data categorised if the relationship between a predictor and the outcome was non-linear. A multivariable logistic regression model was formulated using backward selection, with patient and radiographic predictors retained in the final model if $p<0.10$. Regression diagnostics were assessed to ensure all assumptions underlying the model were met.[36,37]

Internal validation of the final multivariable model was performed, including calibration, discrimination, and bootstrapping (Appendix).[37-39] Patient and radiographic factors from the final multivariable model were formulated into a clinical risk scoring tool with each factor assigned a weighting based on its respective regression coefficient.[38,40] The calculated overall

score represents a patient's risk of having evidence of a pseudotumour, with higher scores associated with increased risk (Appendix). P-values <0.05 were considered statistically significant.

Source of funding

The Royal College of Surgeons of England and Arthritis Research UK.

Results

Patient factors (Table 1)

Compared to the non-pseudotumour group, the pseudotumour group were younger (p=**0.0286**), more commonly female (**63.9**% vs. 38.2%; p<0.001), and had a longer follow-up time (mean 5.8 years vs. 4.8 years; **p<0.001**). There were significant differences in MoMHR implant design (p=**0.022**) between groups.

Radiographic factors (Table 2)

The pseudotumour group was significantly more likely to have radiographic abnormalities compared to the non-pseudotumour group (**80.0**% vs. 63.4%; p=**0.001**). Abnormalities more frequently observed in the pseudotumour group were: acetabular (21.5% vs. 4.3%; p<0.001) and femoral (20.0% vs. 1.6%; p<0.001) osteolysis, acetabular component loosening (**13.1**% vs. 4.7%; p=**0.003**), higher acetabular inclination (mean **49.5º** vs. 46.0º; p=**0.0013**), femoral fracture (p=**0.013**), dislocation (p=**0.038**), and subluxation (p=**0.038**). Acetabular component anteversion (p=**0.697**) and femoral neck narrowing (p=**0.556**) were not different between groups. The non-pseudotumour group was significantly more likely to have HO compared to the pseudotumour group (15.8% vs. **2.3**%; p<0.001).

Logistic regression (Table 3)

Five factors (female gender; high acetabular component inclination; acetabular osteolysis; femoral osteolysis; acetabular component loosening) significantly predicted being in the pseudotumour group in both the univariable and multivariable logistic regression analysis, and two factors (acetabular component anteversion $\geq 5^{o}$; HO) significantly predicting being in the non-pseudotumour group. Young age at radiograph (p=**0.044**) **was a** significant predictor

of being in the pseudotumour group in the univariable analysis, though **was** not significant in the multivariable analysis.

Internal validation of final multivariable model

The final multivariable model was well calibrated (p=**0.589**; Figure 1), and demonstrated good discriminatory ability with an AUC of **0.801** (95% CI **0.752**-**0.849**; sensitivity=**74.4**%, specificity=**71.7**%; Figure 2). Bootstrap validation of the final model provided a bias-corrected AUC of **0.784**.

Clinical risk scoring tool (Table 4)

A clinical points-based risk tool for identifying patients with evidence of a pseudotumour was developed using the final multivariable model. High overall scores represented an increased pseudotumour risk. Validation of the overall risk score model demonstrated it had good discriminatory ability (AUC=**0.796**; 95% CI **0.747**-**0.845**). The optimal risk score threshold for identifying MoMHRs with evidence of pseudotumours was **18**-points or more (95% CI **11.9**-**24.1**), which had **80.8**% sensitivity and **65.2**% specificity.

Discussion

The present large study demonstrated that a combination of patient and radiological factors provided useful information for distinguishing between MoMHRs with and without evidence of pseudotumours. Patient and radiographic factors predictive of MoMHRs with evidence of a pseudotumour included female gender, acetabular component malposition, osteolysis and acetabular loosening. Surgeons may wish to consider these factors before proceeding with cross-sectional imaging.

Our findings suggest radiographs form an important part of the assessment of MoMHR patients. The high AUC of the final model (**0.801**, and bias-corrected=**0.784**) confirms a combination of patient and radiographic factors were useful for distinguishing between MoMHRs with and without evidence of pseudotumours. Previous studies are limited by only assessing a few radiological factors, such as cup position or neck narrowing.[10-13,34] By contrast the current study assessed all major radiological parameters, and is further strengthened by having a large control group including both symptomatic and asymptomatic patients with no cross-sectional imaging evidence of pseudotumours. These non-revised MoMHR patients are typical of the many currently under regular surveillance worldwide.[18]

The final multivariable model identified female gender as the only patient factor significantly predicting MoMHRs with evidence of a pseudotumour. This finding is consistent with the literature[1,2,12,41] and further highlights the importance of stratifying MoMHR patients by gender for surveillance.[18,42] Although it is recognised that certain MoMHR designs have higher failure rates,[1,2,12] the present study did not identify implant design as a significant predictor of pseudotumour revision. This may reflect the limited different implant designs and small numbers of certain implant designs included in the present study. However, we

agree with previous recommendations that it is important to consider implant design when making clinical decisions about MoMHR patients.[18,42]

Similar to previous studies[10-12] we identified high inclination and inadequate anteversion (<5^{o}) as predictors of pseudotumour revision. Hard-on-hard bearings have low tolerances to acetabular component positioning outside an "optimal zone," with such malposition associated with edge loading, high bearing wear, and early failure.[11] However the relationship between acetabular component position and pseudotumours is complex. Our study and two others observed MoMHRs revised for pseudotumour more commonly have acetabular components positioned in inadequate anteversion,[10,11] though it is recognised other cohorts report excessive anteversion to be more important.[12] In addition, pseudotumours in patients with adequately positioned acetabular components have been reported in both our study (**46**% of pseudotumour group; Table 2) and previously.[11,12,43] Furthermore, a number of well-functioning MoMHR patients have malpositioned acetabular components.[15,16,44,45] Although 63% of our non-pseudotumour group had abnormal radiographs, which appears high, acetabular component malposition was the primary reason for these abnormalities. When all radiographic abnormalities apart from malposition were considered, only 19% of our non-pseudotumour group had abnormal radiographs. Other studies have similarly reported abnormal radiographs (excluding malposition) in up to 25% of non-revised MoMHRs.[15,16,44,45] These observations suggest pseudotumour development is multifactorial and not solely dependent on acetabular component malposition. It is therefore important to assess radiographs for other signs suggestive of failure.

Osteolysis (femoral and acetabular) and acetabular component loosening were highly predictive of MoMHRs with pseudotumours in this study. Previous reports observed intra-

operative osteolysis in up to 33% of pseudotumour revisions, and acetabular loosening in up to 28%.[17,46] Furthermore, extensive osteolysis can require complex reconstruction, which may contribute to poor short-term outcomes following pseudotumour revision.[20,47,48] Surgeons must therefore carefully inspect MoMHR radiographs for subtle osteolysis or acetabular loosening and arrange further investigations were necessary, as early identification of pseudotumours may improve patient outcomes following revision.

The clinical significance of femoral neck narrowing remains unclear. In well-functioning MoMHRs narrowing has been observed in up to 77% of cases, with up to 28% having greater than 10% narrowing.[15,16,30,34] Longitudinal studies report that neck narrowing stabilises in well-functioning MoMHR patients within 5 years.[16,30,34] Therefore it has been suggested that neck narrowing is a normal process reflecting early bone remodeling.[13,15] However, neck narrowing has also been reported in up to 26% of MoMHRs revised for pseudotumour.[9,17] We observed similar degrees of neck narrowing in MoMHRs with and without pseudotumours. This suggests femoral neck narrowing does not necessarily represent an underlying pseudotumour. However, if narrowing is observed it must be interpreted in the context of other abnormalities.

Radiographic HO was more common in MoMHRs without evidence of pseudotumours. The HO rate in the non-pseudotumour group (15.8%) was much lower than previous observations (up to 59%).[49] As HO is more common in males,[49] we suspect the higher rates observed in our non-pseudotumour group are related to significantly more males having well-functioning MoMHRs.[15,16,41] It is recognised other factors may also contribute to differences in HO rates, including surgical approach and drug use during the post-operative period. However these factors were not assessed due to lack of medication data and the risk of overfitting our

multivariable model. It is possible that patients with HO have a lower pseudotumour risk because the associated stiffness and reduced hip motion may decrease the risk of edge loading and subsequent pseudotumour formation, however this requires further investigation.

Current worldwide follow-up recommendations for MoMHR patients have recently been reported not to be evidence-based but very costly.[18] The use of radiographs during follow-up has been somewhat overlooked because of blood metal ions and cross-sectional imaging,[18] with some authorities not even specifying a role for radiographs.[6] The final study model and clinical risk scoring tool contained relevant patient and radiological factors which were useful for distinguishing between MoMHRs with and without evidence of pseudotumours. Our study therefore demonstrates that radiographs comprise an important part of the assessment of MoMHR patients, and we recommend all regulatory authorities include radiographs in their follow-up recommendations. Our findings may be particularly useful in centres where follow-up resources must be rationed given the costly nature of MoMHR surveillance,[18] and in centres where access to blood metal ion analysis and cross-sectional imaging is limited. However, radiographs should not be considered a substitute for performing blood metal ions and cross-sectional imaging, given **20%** of our revisions had normal radiographs despite having histologically confirmed pseudotumours. Furthermore, our findings require validation prior to any clinical implementation.[50]

This study has limitations, such as being retrospective and potentially not applicable to other MoMHR designs. Furthermore, the radiographs assessed in the pseudotumour group were performed significantly later from primary MoMHR compared to non-pseudotumour patients, which should be considered when interpreting our findings. Given limitations with radiographic data (49% of MoMHRs had adequate quality immediate post-operative

radiographs), this study cannot make conclusive statements about femoral neck narrowing. It is important to also acknowledge that this study only predicts the presence or absence of a pseudotumour at the time of radiographic assessment, and not the subsequent development of a pseudotumour which would require a longitudinal study. Our final model requires validation in an external cohort, however robust internal validation techniques were employed and the final model was not overfitted.

Conclusions

A combination of patient and radiological factors provided useful information for distinguishing between MoMHRs with and without evidence of pseudotumours. Surgeons may wish to consider these patient and radiological factors predictive of pseudotumour (including female gender, acetabular component malposition, osteolysis, and acetabular loosening) before proceeding with cross-sectional imaging. Radiographs are important when assessing MoMHR patients and should be included in the follow-up recommendations issued by all regulatory authorities.

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Figure Legends

Figure 1 Plot to assess calibration of the final multivariable model

Calibration measures how closely predicted risk (obtained from the final multivariable model) agrees with observed risk (0=non-pseudotumour group; 1=pseudotumour group). Calibration was assessed for each tenth of predicted risk using 10 equally sized groups. For each of the 10 groups the predicted risk was plotted against the mean observed risk for that particular group. The 'ideal' model has a line with a slope of 1 going through the graph origin. The 'apparent' line represents our final multivariable model and shows the model was well calibrated throughout the complete range of pseudotumour risk. The 'bias-corrected' line was obtained from 200 bootstrap repetitions to internally validate our model. The 'bias-corrected' line closely follows the 'apparent' line for our final multivariable model.

Figure 2 Receiver operating characteristic (ROC) curve to assess discrimination of the final multivariable model for identifying patients with evidence of a pseudotumour

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CME Questions Submission Form

Enter all questions on this form. A total of five questions are required.

Manuscript number: JBJS-D-16-00212
Article title: Can patient and radiological factors predict metal-on-metal hip resurfacings with evidence of a pseudotumour?

Question 1

(*staff use only* – question type_____)

I. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☐ Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☒ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

II. Intended Audience: Check as many categories as seem appropriate.

☒ Allied health personnel (minimum of one question)	☒MD, non-orthopaedic (minimum of one question)	☒ Orthopaedic generalist (minimum of one question)	☒ Orthopaedic subspecialist (minimum of one question)

III. Does this question have an image or images?

☐ Yes ☒ No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

IV. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

Which of the following cannot be determined from a pelvic radiograph of a hip resurfacing?

V. Options: *(in alphabetical or logical order)*

A.	Acetabular component inclination
B.	Acetabular component version
C.	Pseudotumour
D.	Femoral osteolysis
E.	Acetabular component loosening

VI. Answer: (must be *clearly* the best of the options)

☐ A. ☐ B. ☒ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Introduction

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☒ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions or sites).

Question 2

(*staff use only* – question type_____)

VII. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☐ Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☒ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

VIII. Intended Audience: Check as many categories as seem appropriate.

☒ Allied health personnel (minimum of one question)	☒MD, non-orthopaedic (minimum of one question)	☒ Orthopaedic generalist (minimum of one question)	☒ Orthopaedic subspecialist (minimum of one question)

IX. Does this question have an image or images?

☐ Yes ☒ No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

X. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

Which of the following tests is not routinely used to investigate hip resurfacing patients with a potential pseudotumour?

XI. Options: *(in alphabetical or logical order)*

A.	Radiographs
B.	CT scan
C.	Ultrasound
D.	Blood metal ions
E.	MARS MRI

XII. Answer: (must be *clearly* the best of the options)

☐ A. ☒ B. ☐ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Methods

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
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☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
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☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions or sites).

Question 3

(*staff use only* – question type_____)

XIII. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☐ Basic science	☐ Infection	☐ Shoulder
☐ Ethics	☐ Knee reconstruction, adult	☐ Spine
☐ Elbow	☐ Oncology	☐ Sports
☐ Foot and ankle	☐ Pain management	☐ Trauma
☐ Hand and wrist	☐ Pediatrics	☐ General interest/Does not fit

☒ Hip reconstruction, adult	☐ Rehabilitation	any other category

XIV. Intended Audience: Check as many categories as seem appropriate.

☐ Allied health personnel (minimum of one question)	☒MD, non-orthopaedic (minimum of one question)	☒ Orthopaedic generalist (minimum of one question)	☒ Orthopaedic subspecialist (minimum of one question)

XV. Does this question have an image or images?

☐ Yes ☒ No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

XVI. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

Which of the following patient factors was the only significant predictor of metal-on-metal hip resurfacings with evidence of pseudotumours?

XVII. Options: *(in alphabetical or logical order)*

A.	Body mass index
B.	Implant design
C.	Young age
D.	Female gender
E.	Bilateral hip implants

XVIII. Answer: (must be *clearly* the best of the options)

☐ A. ☐ B. ☐ C. ☒ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Results

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
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☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.
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Question 4

(*staff use only* – question type_____)

XIX. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☐ Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☒ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

XX. Intended Audience: Check as many categories as seem appropriate.

☐ Allied health personnel (minimum of one question)	☒MD, non-orthopaedic (minimum of one	☒ Orthopaedic generalist (minimum of one	☒ Orthopaedic subspecialist (minimum of one question)

	question)	question)	

XXI. Does this question have an image or images?

☐ Yes ☒ No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

XXII. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

Which of the following radiological factors was a significant predictor of metal-on-metal hip resurfacings with evidence of pseudotumours?

XXIII. Options: *(in alphabetical or logical order)*

A.	Femoral notching
B.	Femoral neck narrowing
C.	Heterotopic ossification
D.	Acetabular component retroversion
E.	Acetabular osteolysis

XXIV. Answer: (must be *clearly* the best of the options)

☐ A. ☐ B. ☐ C. ☐ D. ☒ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Results

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☒ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice

Improvement:	of medicine.
☐ **Interpersonal and Communication Skills:**	Demonstrate skills that result in effective information exchanges and teaming with patients, their families and professional associates (e.g. fostering a therapeutic relationship that is ethically sound, used effective listening skills with non-verbal and verbal communication; working as both a team member and at times a leader).
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Question 5

(*staff use only* – question type_____)

XXV. Question Category: Check as many categories as seem appropriate. Question category may differ from manuscript category.

☐ Basic science ☐ Ethics ☐ Elbow ☐ Foot and ankle ☐ Hand and wrist ☒ Hip reconstruction, adult	☐ Infection ☐ Knee reconstruction, adult ☐ Oncology ☐ Pain management ☐ Pediatrics ☐ Rehabilitation	☐ Shoulder ☐ Spine ☐ Sports ☐ Trauma ☐ General interest/Does not fit any other category

XXVI. Intended Audience: Check as many categories as seem appropriate.

☐ Allied health personnel (minimum of one question)	☒MD, non-orthopaedic (minimum of one question)	☒ Orthopaedic generalist (minimum of one question)	☒ Orthopaedic subspecialist (minimum of one question)

XXVII. Does this question have an image or images?

☐ Yes ☒ No

(If YES – upload image(s) separately using the "CME Question Figure" item option in the Attach Files screen of Editorial Manager. Include a one to two sentence description of each figure here. All figures should be at least 5x7 inches with a resolution of 300 ppi.)

XXVIII. Question: (A patient-care scenario is preferred when appropriate; see Guidelines)

Which of the following radiological factors was a significant predictor of metal-on-metal hip resurfacings with no evidence of pseudotumours?

XXIX. Options: *(in alphabetical or logical order)*

A.	Heterotopic ossification
B.	Femoral loosening
C.	Femoral neck narrowing
D.	Femoral notching
E.	Impingement

XXX. Answer: (must be *clearly* the best of the options)

☒ A. ☐ B. ☐ C. ☐ D. ☐ E.

VII. Answer Location: Please list the heading of the manuscript section where the correct answer is located (e.g. "Results" or "Anatomy and Physiology").

Results

VIII. Core Competencies addressed by this CME question:

☐ **Patient Care:**	Provide care that is compassionate, appropriate, and effective treatment for health problems and to promote health.
☒ **Medical Knowledge:**	Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
☐ **Practice-Based Learning and Improvement:**	Show and ability to Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve the practice of medicine.
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☐ **Professionalism:**	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a

	diverse patient population.
☐ **Systems-Based Practice:**	Demonstrate awareness of and responsiveness to the larger context and systems of health care. Be able to call on system resources to provide optical care (e.g. coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions or sites).

Table 1 Patient demographics for all metal-on-metal hip resurfacings (n=**384**)

Co-variate	All hips (n=384; 100%)	Non-pseudotumour group (n=254; 66.1%)	Pseudotumour group (n=130; 33.9%)	p-value
Gender				
Male	204 (53.1)	157 (61.8)	47 (36.2)	**<0.001**
Female	180 (46.9)	97 (38.2)	83 (63.9)	
Mean age at x-ray (range) in years	59.4 (30.3-88.2)	60.2 (30.3-88.2)	58.0 (37.5-77.6)	**0.0286**
Mean time from primary to x-ray (range) in years	5.1 (0.25-15.1)	4.8 (2.0-15.1)	5.8 (0.25-14.1)	**<0.001**
Mean time from primary to revision (range) in years	NA	NA	6.3 (0.31-14.8)	NA
Primary Implant				
BHR	180 (46.9)	117 (46.1)	63 (48.5)	**0.022**
Conserve	174 (45.3)	122 (48.0)	52 (40.0)	
Recap	26 (6.8)	15 (5.9)	11 (8.5)	
Cormet	4 (1.0)	0 (0)	4 (3.1)	
Median blood metal ion concentrations (IQR) in µg/l				
Cobalt	2.2 (1.5-4.6)	2.1 (1.4-3.6)	6.3 (3.1-22.5)	**<0.0001**
Chromium	2.4 (1.3-4.9)	2.2 (1.3-4.1)	7.6 (2.6-29.2)	**<0.0001**

BHR = Birmingham Hip Resurfacing; IQR = inter-quartile range; NA=Not applicable

Statistically significant results ($p<0.05$) highlighted in **bold text**

Table 2 Radiological features for all metal-on-metal hip resurfacings (n=**384**)

Co-variate	All hips (n=384; 100%)	Non-pseudotumour group (n=254; 66.1%)	Pseudotumour group (n=130; 33.9%)	p-value
Abnormal radiograph (≥1 abnormality)	265 (69.0%)	161 (63.4%)	104 (80.0%)	**0.001**
Normal radiograph	119 (31.0%)	93 (36.6%)	26 (20.0%)	
Cup position				
Mean inclination in ^{o} (range)	47.2 (21.3-83.5)	46.0 (21.3-67.6)	49.5 (24.3-83.5)	**0.0013**
Mean anteversion in ^{o} (range)	14.9 (1.2-40.3)	14.7 (1.2-40.3)	15.1 (1.2-39.5)	0.697
Malpositioned*	183 (47.7%)	113 (44.5%)	70 (53.8%)	0.062
Femoral neck narrowing				
Mean narrowing (range)	4.7% (0.3%-22.2%)	4.5% (0.3%-22.2%)	5.0% (0.3%-17.4%)	0.556
>10% narrowing	13 (3.4%)	7 (2.8%)	6 (4.6%)	0.377
Osteolysis				
Acetabular	39 (10.2)	11 (4.3)	28 (21.5)	**<0.001**
Femoral	30 (7.8)	4 (1.6)	26 (20.0)	**<0.001**
Loosening				
Acetabular	29 (7.6)	12 (4.7)	17 (13.1)	**0.003**
Femoral	13 (3.4)	7 (2.8)	6 (4.6)	0.377
Heterotopic ossification	43 (11.2)	40 (15.8)	3 (2.3)	**<0.001**
Femoral neck notching	12 (3.1)	9 (3.5)	3 (2.3)	0.758
Fracture				
Acetabular	0 (0)	0 (0)	0 (0)	NA
Femoral	4 (1.0)	0 (0)	4 (3.1)	**0.013**
Dislocation	3 (0.78)	0 (0)	3 (2.3)	**0.038**
Subluxation	3 (0.78)	0 (0)	3 (2.3)	**0.038**
Impingement	0 (0)	0 (0)	0 (0)	NA

NA = not applicable

***** Malposition was defined as one or both parameters outside the previously recommended optimal zone (inclination 35^{o}-55^{o} and anteversion 10^{o}-30^{o}).[11]

Statistically significant results ($p<0.05$) highlighted in **bold text**

Table 3 Logistic regression models identifying patient and radiographic factors predictive of pseudotumour revision

Co-variate	Univariable model Odds Ratio (95% CI)	p-value	Final multivariable model Odds Ratio (95% CI)	p-value
Gender				
Male	1.00	**<0.001**	1.00	**<0.001**
Female	3.00 (1.92-4.68)		3.14 (1.85-5.35)	
Age at radiograph (per year)	0.98 (0.95-1.00)	**0.044**	*	
Primary Implant				
BHR	1.00		*	
Conserve	0.79 (0.50-1.25)	0.309		
Other (Recap and Cormet)	1.89 (0.86-4.11)	0.111		
Cup position				
Inclination (per degree)	1.04 (1.02-1.07)	**0.001**	1.04 (1.01-1.07)	**0.006**
Anteversion				
<5°	1.00		1.00	
5° to <10°	0.37 (0.17-0.82)	**0.014**	0.31 (0.12-0.77)	**0.012**
≥10°	0.49 (0.25-0.94)	**0.033**	0.32 (0.15-0.70)	**0.004**
Femoral neck narrowing	1.03 (0.98-1.08)	0.259	*	
Osteolysis				
Acetabular	5.91 (2.82-12.4)	**<0.001**	5.06 (2.14-12.0)	**<0.001**
Femoral	14.4 (4.88-42.7)	**<0.001**	17.8 (5.09-62.2)	**<0.001**
Loosening				
Acetabular	3.15 (1.41-7.01)	**0.005**	3.35 (1.34-8.35)	**0.009**
Femoral	1.73 (0.57-5.26)	0.335	*	
Heterotopic ossification	0.13 (0.039-0.42)	**0.001**	0.19 (0.05-0.72)	**0.015**
Femoral neck notching	0.65 (0.17-2.45)	0.524	*	
Femoral fracture	1	NA	*	
Dislocation	1	NA	*	
Subluxation	1	NA	*	

BHR = Birmingham Hip Resurfacing; CI = confidence interval; NA = not applicable

*Final multivariable logistic regression model only includes patient and radiological factors where $p<0.10$.

Statistically significant results ($p<0.05$) highlighted in **bold text**

Impingement and acetabular fracture were not analysed as no events occurred in the whole cohort

The affect of acetabular component anteversion (p-value for non-linearity=0.0144) on outcome was non-linear, therefore this co-variate was categorised. The affect of both patient age at radiograph (p-value for non-linearity=0.937) and acetabular component inclination (p-value for non-linearity=1.0) on outcome were linear, therefore these co-variates were analysed as continuous variables.

Table 4 Clinical risk scoring tool for determining pseudotumour risk based on patient and radiological factors

Co-variate	Regression coefficient from final multivariable model	Risk score
Gender		
Male	Reference group	0
Female	1.14	11
Cup position		
Inclination	.041	
20^o to $<30^o$	Reference group	0
30^o to $<40^o$		14
40^o to $<50^o$		18
50^o to $<60^o$		23
60^o to $<70^o$		27
70^o to $<80^o$		31
80^o to $<90^o$		35
Anteversion		
$<5^o$	Reference group	0
5^o to $<10^o$	-1.18	-12
$\geq 10^o$	-1.13	-11
Acetabular osteolysis		
No	Reference group	0
Yes	1.62	16
Femoral osteolysis		
No	Reference group	0
Yes	2.88	29
Acetabular loosening		
No	Reference group	0
Yes	1.21	12
Heterotopic ossification		
No	Reference group	0
Yes	-1.64	-16

All baseline/reference groups for each category have a risk score of zero

Higher scores indicate increased risk of pseudotumour

Figure 1

Click here to download Figure Figure 1 - Model calibration.tif

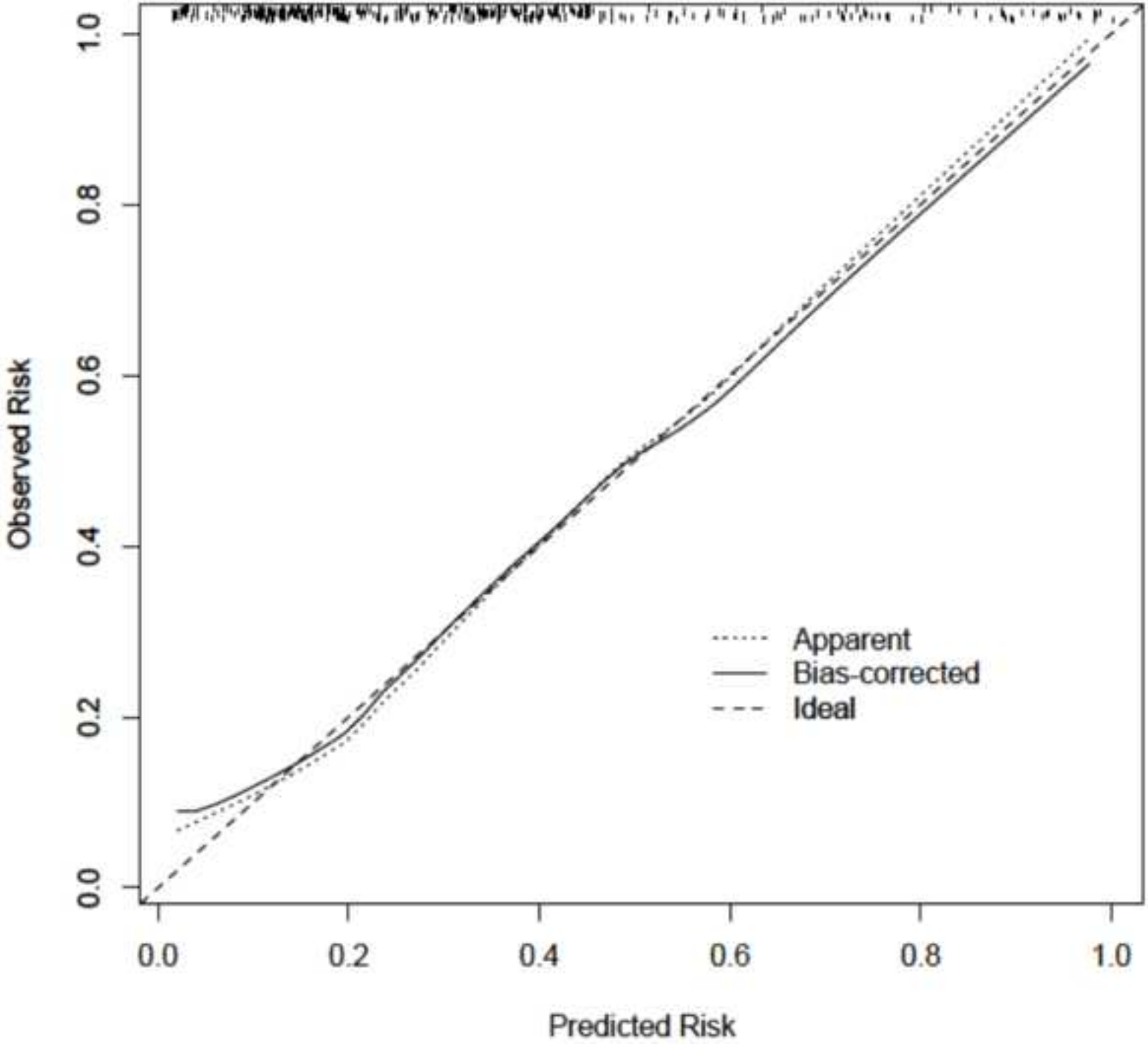
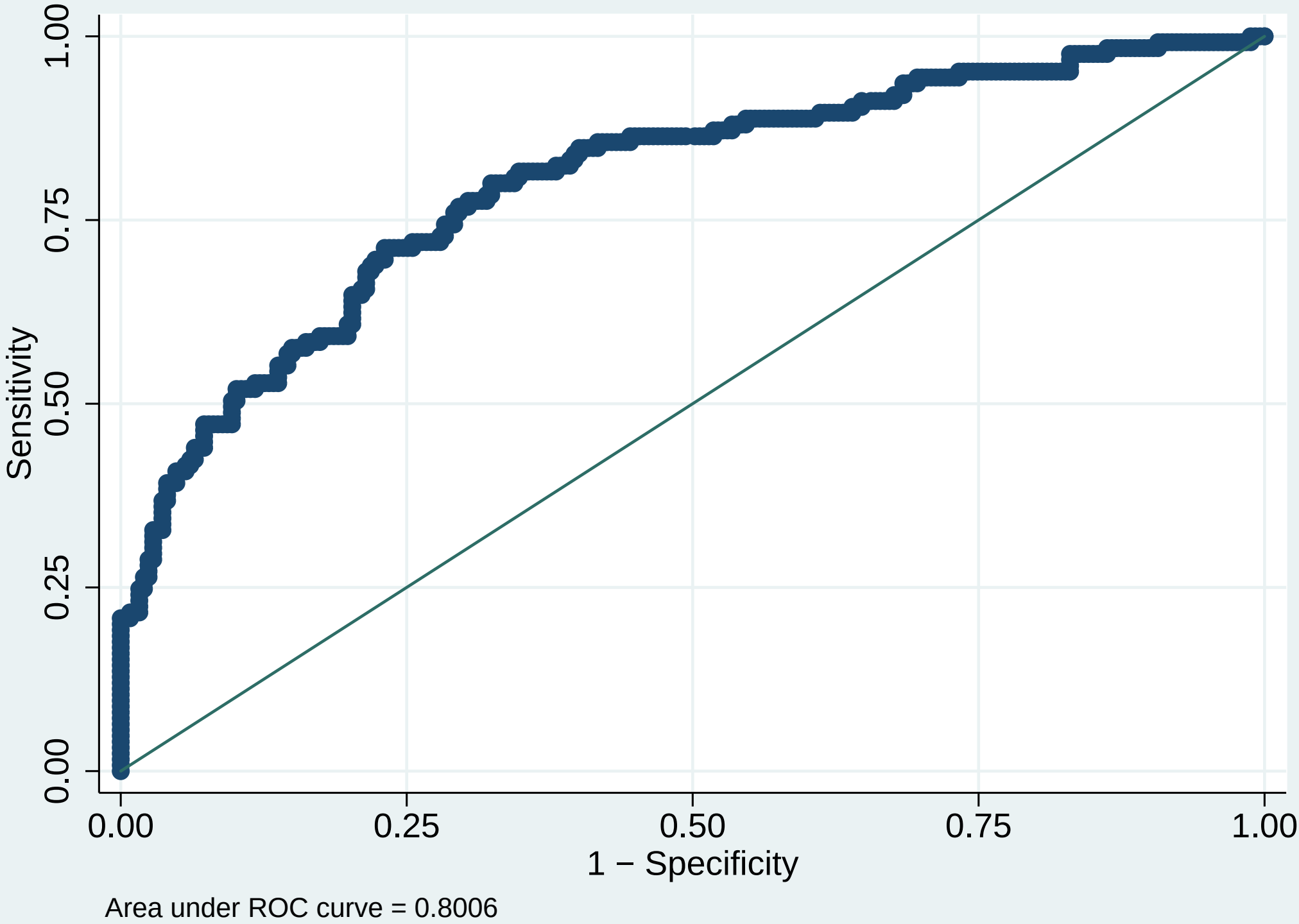


Figure 2


Sensitivity
0.00
0.25
0.50
0.75
1.00
1 − Specificity
0.00
0.25
0.50
0.75
1.00
Area under ROC curve = 0.8006

Appendix Detailed statistical methods

1. Internal validation of the final multivariable model

Robust internal validation of the final multivariable model was performed using calibration, discrimination, and bootstrapping techniques.[37-39] Calibration measures how closely predicted risk agrees with observed risk. Calibration was assessed for each tenth of predicted risk using 10 equally sized groups, with a Hosmer-Lemeshow goodness-of-fit test performed to quantify calibration (non-significant p-value indicates a well calibrated model). Discrimination is the models ability to differentiate between MoMHRs with and without evidence of a pseudotumour, which is assessed by calculating the area under the receiver operating characteristic curve (AUC). The AUC for a useful prognostic model is between 0.60-0.85.[38] The final multivariable regression model was further validated using bootstrapping with backward stepwise variable deletion.[37] Two-hundred bootstrap repetitions were performed to obtain a bias-corrected estimate of the AUC using a modified dataset.

2. Developing a clinical risk scoring tool

Using the patient and radiological predictors included in the final multivariable logistic regression model a clinical risk scoring tool was developed using previously described methods.[40] The calculated overall score represents a patients' risk of having evidence of a pseudotumour, with higher scores associated with increased pseudotumour risk. The respective regression coefficient for each predictor from the final multivariable model was converted to an integer risk score. The reference group for all variables was assigned a risk score of zero. For all variables apart from inclination the risk scores for non-reference groups were calculated by multiplying the respective regression coefficient by 10 and then rounding to the nearest whole number. Inclination data were grouped with the midpoint for each group

taken (midpoint of 30^{o} to 39^{o} group was 34.5^{o}). The midpoint for non-reference inclination groups was then multiplied by the respective regression coefficient, multiplied by 10, and then rounded to the nearest whole number. The discriminatory ability of the final overall risk score was assessed by calculating the AUC. The optimal risk score threshold for identifying MoMHRs with evidence of a pseudotumour was also calculated.

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Conflict of Interest AJ

Statement regarding need for ethical committee approval

This study did not require ethical approval and a letter from our National Research Ethics Service is attached to confirm this. Furthermore, metal-on-metal hip resurfacing patients were reviewed as part of the institution's routine follow-up arrangements, which have been adapted in response to published recommendations from the United Kingdom Medical and Healthcare Products Regulatory Agency (MHRA). Therefore no patients were specifically recalled for the study presented in the submitted manuscript, with all data obtained from the institution's clinical and imaging databases and from medical records.

IRB Approval letter

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National Research Ethics Service

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20 March 2009

Hemant Pandit
C/O OOEC
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Dear Hemant,

Full title of project: Prospective follow up of all hip and knee replacements.

Thank you for seeking the Committee's advice about the above project.

Following your discussion with the Chair, Janet Burton regarding the issue of regular follow up of patients (after joint replacement - clinical and radiological), she advised that the proposal is an audit. Therefore it does not require ethical review by a NHS Research Ethics Committee.

You can find a copy of our leaflet, "Defining Research", which explains how we differentiate research from other activities, at the following web address: http://www.nres.npsa.nhs.uk/rec-community/guidance/#researchoraudit.

You should check with the Oxford Radcliffe Hospitals NHS Trust what other review arrangements or sources of advice apply to projects of this type. Guidance may be available from the clinical governance office.

This letter should not be interpreted as giving a form of ethical approval to the project or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

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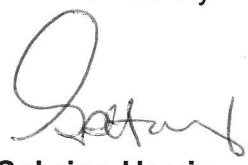
Yours sincerely



Sabrina Harris
Committee Co-ordinator