# METAL-ON-METAL HIP ARTHROPLASTY:

# INDICATIONS FOR CONTINUED USE IN LIGHT OF ADVERSE REACTION TO METAL DEBRIS

**by**

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A thesis submitted to the University of Birmingham for the degree of

MASTERS OF RESEARCH IN CLINICAL RESEARCH

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October 2014

## ABSTRACT

Adverse reaction to metal debris (ARMD) represents a recently recognised mode of failure of metal-on-metal (MoM) hip resurfacings (HRs) and total hip replacements (THRs). ARMD often requires revision surgery which can have poor outcomes, therefore questioning the future role of MoM hip bearings. The 14-year survival of 447 HRs implanted by a designing surgeon was 94.1% (95% CI 84.9%-97.3%) with the best outcomes in males with primary osteoarthritis. The 8-year survival of 578 MoM THRs was 88.9% (95% CI 78.5%-93.4%) with 44% (17 of 39) of revisions performed for ARMD. A systematic review identified six studies reporting short-term outcomes following 216 ARMD revisions with variable complication (4%-68%) and re-revision (3%-38%) rates. Analysis of outcomes following 64 ARMD revisions demonstrated comparable complication (20.3%) and re-revision (12.5%) rates at a mean 4.5 year follow-up. The 5-year survival following ARMD revision was 87.9% (95% CI 78.9%-98.0%) with revision to another MoM bearing having significantly higher re-revision rates (p=0.046). Male patients with primary osteoarthritis may undergo HR in the future, however designing surgeons may also consider females for HR. There is no future role for MoM THR. Limited evidence exists regarding outcomes following ARMD revision, though exchange to a non-MoM bearing surface is advised.

## DEDICATION

I would like to dedicate this thesis to my grandfather, Mr Amar Singh Bilkhu, who inspired me to work hard and achieve my dream of becoming a doctor.

In loving memory.

## ACKNOWLEDGEMENTS

First of all I would like to acknowledge my supervisor, Professor Paul B. Pynsent. He has been an excellent supervisor and friend to me since we initially met six-years ago. Professor Paul B. Pynsent has provided me with invaluable guidance and support during this time for which I am eternally grateful. I would like to thank all the co-authors of the research work presented in this thesis. In particular, I wish to give special thanks to Mr Ronan B.C. Treacy, Mr Matthew P. Revell, and Mr David J. Dunlop who have all voluntarily contributed their time and expertise as consultant surgeons, and provided their ideas and support with the research presented. I would also like to thank all of the other surgeons and staff at The Royal Orthopaedic Hospital in Birmingham for supporting this research. I am grateful to Ann Weaver and The Royal Orthopaedic Hospital Charity for their help and support, which has included financial assistance with attending international scientific meetings to disseminate the research findings. Finally, I would like to thank all the patients who have participated in the research contained within this thesis and without whom none of this work would have been possible.

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## LIST OF ABBREVIATIONS

ALTR = adverse local tissue reaction

ARMD = adverse reaction to metal debris

ASR = Articular Surface Replacement

ALVAL = aseptic lymphocytic vasculitis associated lesion

AVN = avascular necrosis of the femoral head

BHR = Birmingham Hip Resurfacing

CoC = ceramic-on-ceramic

CoP = ceramic-on-polyethylene

Cr = chromium

Co = cobalt

CT = computerised tomography

CI = confidence interval

DDH = developmental dysplasia of the hip

F = female

HHS = Harris Hip Score

HR = hip resurfacing

IQR = interquartile range

LLD = leg length discrepancy

MRI = magnetic resonance imaging

M = male

MHRA = Medical and Healthcare Products Regulatory Agency

MoM = metal-on-metal

MoP = metal-on-polyethylene

NJR = National Joint Registry

NICE = National Institute for Health and Clinical Excellence

NOF = neck of femur fracture

NS = not stated

OA = osteoarthritis

OHS = Oxford Hip Score

OxP = oxinium-on-polyethylene

RA = rheumatoid arthritis

SUFE = slipped upper femoral epiphysis

TLO = tertiary lymphoid organ

THR = total hip replacement

USS = ultrasonography scan

UCLA = University of California, Los Angeles Activity Score

WOMAC = Western Ontario and McMaster Universities Arthritis Index

# CHAPTER 1

# INTRODUCTION

## 1.1 Metal-on-metal hip arthroplasty

Total hip replacement (THR) is well established as the most successful surgical procedure for the long-term alleviation of pain and disability in patients with hip joint arthritis [1]. Over 75,000 primary THRs were performed in England, Wales, and Northern Ireland during 2012 [2]. Metal-on-polyethylene (MoP) bearings were traditionally used for THR. The production of polyethylene wear debris can lead to periprosthetic osteolysis resulting in aseptic component loosening, which remains the most frequent cause of MoP THR failure [3,4]. As bearing wear has been demonstrated to be related to usage and not time in-situ [5], MoP THR is a satisfactory option for elderly patients with lower demands [6-8]. In contrast, using this bearing surface in more active younger patients (under 60 years of age) has been associated with unsatisfactory outcomes and high failure rates [9,10].

Over the years metal-on-metal (MoM) bearings have been perceived as an attractive option for hip arthroplasty. This type of bearing surface has significantly lower wear rates compared to MoP articulations [11]. In addition, larger femoral head sizes can be used with MoM bearings compared to MoP. This increases the femoral head-neck ratio, which importantly increases hip range of motion, reduces the risk of impingement of the

femoral neck on the acetabulum, and reduces the risk of dislocation [12,13]. Therefore MoM bearings appear an attractive alternative to MoP articulations in young active patients requiring a hip replacement.

Interestingly MoM hip bearings have been around for some time. Although hip resurfacing (HR) as recognised today was originally a concept described by Sir John Charnley in the 1950s using Teflon-on-Teflon bearings [14], MoM HR was first attempted by Edward Haboush in 1953 [15] and Maurice Müller in 1965 [16]. This technique failed to gain acceptance and was subsequently abandoned. Further attempts at HR during the 1970s by Michael Freeman [17], Heinz Wagner [18], and Harlan Amstutz [19] using various combinations of MoP articulation were largely unsuccessful compared to conventional THR. This led to HR being temporarily abandoned [20]. However it was later observed that some of the MoM HRs originally implanted by Müller lasted over 25 years before requiring revision [21]. In addition, the McKee-Farrar and Ring were two types of large-diameter MoM THR first implanted in the 1950s to 1960s which demonstrated good long-term outcomes [22,23]. During the late 1980s Derek McMinn, a surgeon in Birmingham at the time, recognised the promising long-term results of MoM THR and considered the poor results observed with earlier attempts at HR to be a failure of materials rather than a failure in concept [24]. Convinced that MoM bearings were a viable option to treat young and active patients with hip arthritis Derek McMinn's pioneering work during the late 1980's and early 1990's led to the rebirth of modern MoM HR.

The technique of modern MoM HR gradually gained acceptance from hip arthroplasty surgeons with promising results published at five-years with certain HR devices from designing surgeons and independent centres [25-32]. Unique problems related to HR prompted the development of large-diameter MoM THRs. First, a device was required to manage HR patients with isolated femoral component failure (femoral neck fracture or avascular necrosis of the femoral head) occurring in the presence of a well-fixed and adequately positioned acetabular component [24,30]. Second, HR is a technically demanding procedure for the surgeon with a much steeper learning curve than for performing a THR [24-28]. The use of large-diameter MoM THRs would therefore allow low volume hip surgeons to obtain the benefits of a MoM bearing for their patients but without needing to perform a technically challenging surgical procedure.

Subsequently there was a steep increase in the implantation of MoM hip bearings (HR and THR) worldwide. Between 2005 and 2006, 35% of all primary THRs implanted in the United States had a MoM bearing [33]. It has been estimated that over one million MoM hip arthroplasties have been implanted worldwide [34].

### 1.2 Adverse reaction to metal debris

In recent years concerns have mounted regarding abnormal periprosthetic tissue reactions associated with MoM hip arthroplasties [35-38]. These reactions can lead to early implant failure requiring revision surgery. Numerous terms have been used in the literature to describe these abnormal reactions associated with MoM hips [13]. Aseptic

lymphocytic vasculitis and associated lesions (ALVAL) was first described in 2005 by Willert *et al.* [39]. ALVAL refers to a specific histological reaction associated with MoM hip bearings, which is characterised by perivascular lymphocytes, lymphoid aggregates containing follicles with B and T cells, plasma cells, tissue necrosis, fibrin exudation, high endothelial venules, and the accumulation of macrophages [39]. In 2008, Pandit *et al*. described non-neoplastic, non-infective, solid or semi-liquid soft-tissue periprosthetic masses associated with MoM HRs, which the authors termed "pseudotumours" [35]. Interestingly this term had originally been used in 1987 to describe similar periprosthetic tissue reactions to debris released from MoP articulations [40]. Although the term "pseudotumour" described a specific clinical problem related to MoM hips, it was considered by many to be emotive. In addition, not all patients with abnormal reactions have a periprosthetic mass which may be considered to be a "pseudotumour." Therefore this term only accounted for a subset of patients with abnormal reactions. In 2010, Langton *et al*. described the entity "adverse reaction to metal debris" (ARMD) [36]. This is now considered the most accepted term in the literature [13] and will be used to refer to these abnormal periprosthetic tissue reactions associated with MoM hips throughout the thesis. ARMD is an umbrella term, which includes both clinical and histological features, namely metallosis (macroscopic soft-tissue staining associated with abnormal wear), pseudotumour, ALVAL (histological diagnosis only), and macroscopic tissue necrosis (observed at revision surgery and initial histopathological analysis) [36,41]. ARMD is the sequelae of large amounts of metal debris released from MoM hip articulations due to wear and corrosion [42].

In theory all MoM hips are at risk of ARMD. However it is becoming increasingly apparent the outcomes of MoM hip replacements are dependent on various patient, surgeon, and implant factors [13]. Factors associated with an increased risk of developing ARMD include female gender, small femoral component sizes in HR, malpositioning of the acetabular component, and patients with hip dysplasia [36,41,43-45]. In addition, it appears the risk of ARMD is greater in THRs compared to HRs given that additional metal wear debris can be generated at the taper-head interface and other modular junctions [2,37,38]. This is supported by clinically significant differences in short-term failure rates for MoM THRs (48.8% at six-years) and HRs (25% at six-years) with identical bearing surfaces produced by the same manufacturer [38].

The subsequent local tissue reactions can result in the formation of destructive soft-tissue masses often requiring revision surgery [35]. At the time of revision findings can include significant bone loss and muscle damage [35,36]. Limited evidence exists regarding clinical outcomes following ARMD revision surgery, however this suggests short-term outcomes are poor with a number of patients experiencing recurrence of these lesions and requiring further surgery [46]. These unsatisfactory outcomes are concerning given most MoM hip patients are young and active [25-32]. Furthermore in England, Wales, and Northern Ireland the prevalence of ARMD revision surgery is increasing with ARMD accounting for 13% (n=1,330) of all revisions performed in 2012 [2].

In light of MoM hips developing ARMD in recent years the Medical and Healthcare Products Regulatory Agency (MHRA) have withdrawn certain devices with unacceptably high failure rates and issued guidance regarding the investigation and

management of these periprosthetic reactions [47,48]. There has subsequently been a significant decrease in MoM hip usage worldwide. In England, Wales, and Northern Ireland, MoM THR and HR once accounted for 10.9% and 10.8% of all primary THRs performed respectively [2]. By contrast in 2012 MoM THR and HR accounted for 0.1% and 1.3% of all primary THRs performed respectively [2].

### 1.3 Research rationale

Despite the increasing awareness regarding ARMD over the last five-years a number of reports have subsequently confirmed earlier results regarding HR [25-32]. Specifically good ten-year outcomes have been achieved by designing and independent surgeons in certain patient subgroups when using HR implants with an established record [49-54]. This suggests select patients will benefit from MoM HR and if these subgroups can clearly be identified these patients could be considered for HR in the future. However long-term follow-up studies into the second decade and particularly in younger patient populations are still lacking. In contrast evidence currently suggests MoM THR should not be used in the future [55], though not all MoM THR designs have results published from independent centres.

Due to the more intense clinical surveillance and investigations recommended for patients with MoM hip arthroplasties it is expected the number of patients requiring revision surgery for ARMD will continue to increase [2,48]. Although there is limited evidence currently available [46] it is important that surgeons are aware of the likely clinical outcomes following ARMD revision surgery. This will allow patients to be

more effectively counselled regarding the risks of undergoing such surgery. Given ARMD has been observed in a number of asymptomatic MoM hip patients [56,57] it is expected improved awareness of the risks of revision surgery may be of increasing importance when counselling these individuals. In addition, only one study has examined factors affecting outcome following ARMD revision [58]. Determining prognostic factors of outcome following ARMD revision is important as this will help identify the thresholds for performing revision surgery.

## 1.4 Research objectives

1. To determine the long-term clinical outcomes following primary metal-on-metal hip resurfacing and explore factors affecting outcomes.
2. To determine the medium-term clinical outcomes following primary metal-on-metal total hip replacement.
3. To determine the clinical outcomes following revision of metal-on-metal hip resurfacings and total hip replacements for adverse reaction to metal debris and identify factors predictive of clinical outcomes.

## 1.5 Structure of the thesis

The thesis will initially describe two prospective cohort studies which assess the long-term clinical outcomes following MoM HR (Chapter 2) and the medium-term clinical outcomes following MoM THR (Chapter 3). Outcomes following revision of MoM HRs

and THRs for ARMD will be assessed using a systematic review (Chapter 4) followed by a retrospective cohort study (Chapter 5) with the latter also exploring factors predictive of outcomes. Finally the important findings and conclusions of the work presented will be summarised and considered in the context of the present literature, with recommendations for future research proposed (Chapter 6).

# CHAPTER 2

# LONG-TERM OUTCOMES OF METAL-ON-METAL HIP RESURFACING

## 2.1 Declaration

The work detailed in this chapter has been published in a peer reviewed journal. As first author of this work my role involved input with study design, data collection including all radiographic analysis, involvement with statistical analysis and data interpretation, and the writing of all versions of the paper submitted to the journal as well as this chapter.

Matharu GS, McBryde CW, Pynsent WB, Pynsent PB, Treacy RB. The outcome of the Birmingham Hip Resurfacing in patients aged < 50 years up to 14 years post-operatively. *The Bone and Joint Journal* 2013; **95**(9): 1172-1177.

## 2.2 Introduction

The long-term survival reported for conventional THR in young and active patients with hip arthritis has been unsatisfactory [9,10,59,60]. A report from the Finnish Arthroplasty Register on 3668 THRs implanted in patients under 55 years of age highlights this problem, with a 15-year survival of 71% for cemented implants, and as low as 58% for some uncemented THRs [10].

Resurfacing of the hip is a recognised treatment for young and active patients with painful primary or secondary hip joint arthritis [50]. The Birmingham Hip Resurfacing (BHR; Smith & Nephew, Warwick, United Kingdom) was introduced in July 1997 and remains one of the most commonly used MoM HR devices with an estimated 125,000 implanted worldwide [61]. The BHR is produced from an as-cast high carbon cobalt-chromium-molybdenum alloy (Figure 2.1) [24]. The actetabular component is hemispherical with a hydroxyapatite coating which allows uncemented fixation. Component sizes range from 44 mm to 66 mm (available in 2 mm increments) for the acetabular implant. The femoral component requires cement for fixation and is available in sizes from 38 mm to 58 mm (available in 2 mm increments). For the BHR the acetabular component implanted must always be 6 mm or 8 mm larger than the femoral component used.

**Figure 2.1** The Birmingham Hip Resurfacing

Despite concerns regarding MoM hips developing ARMD (Chapter 1.2), good clinical outcomes have been reported for the BHR at up to ten-years by both the designing surgeons [50,51] and independent centres [52-54]. It is also becoming apparent that females and patients with small femoral component head sizes are factors associated with higher failure rates in HR [44,50,52-54].

The study aims were to determine the long-term survival and functional outcome of primary BHR in a large cohort of patients less than 50 years of age at operation, and to explore factors affecting outcome.

## 2.3 Methods

### 2.3.1 Study design and patient cohort

Between August 1997 and April 2006, data were prospectively collected on all consecutive BHRs (447 hips in 393 patients) implanted in patients under 50 years of age (Table 2.1). All operations were performed by one designing surgeon at a specialist arthroplasty centre (The Royal Orthopaedic Hospital, Birmingham). Information regarding patient selection and operative technique for the BHR has previously been described in detail [50,62]. Briefly patients with end-stage hip arthritis were considered suitable candidates for BHR if they were under the age of 65 years, maintained an active lifestyle which included sports participation, and had normal bone stock on pre-

operative pelvic radiographs. All operations were performed in a clean-air laminar flow operating theatre using a posterior surgical approach to the hip joint [27,63].

**Table 2.1** Summary of the study cohort

| **Characteristic** | | **Study cohort (n=447 hips)** |
|---|---|---|
| **Gender** | Male | 267 (59.7%) |
| | Female | 180 (40.3%) |
| **Age** | Mean (range) in years | 41.5 (14.9 to 49.9) |
| **Bilateral hips** | Total patients | 54 (108 hips) |
| | Single-stage bilateral procedures | 15 (30 hips) |
| | Two-stage bilateral procedures | 39 (78 hips) |
| **Diagnosis** | Primary osteoarthritis | 304 (68.0%) |
| | Developmental dysplasia | 46 (10.3%) |
| | Avascular necrosis | 41 (9.2%) |
| | Inflammatory arthritis | 21 (4.7%) |
| | Slipped upper femoral epiphysis | 13 (2.9%) |
| | Other causes | 22 (4.9%) |
| **Follow-up time** | Mean (range) in years | 10.1 (5.2 to 14.7) |
| **Femoral component size** | 38 mm | 3 (0.7%) |
| | 42 mm | 47 (10.5%) |
| | 46 mm | 125 (28.0%) |
| | 50 mm | 169 (37.8%) |
| | 54 mm | 92 (20.6%) |
| | 58 mm | 11 (2.5%) |

### 2.3.2 Data collection and follow-up after BHR

Data were extracted from the institution's prospectively maintained database (MySQL database, Oracle Corporation, Redwood Shores, California). The database contains a vast amount of information including patient demographics, primary indication for surgery, and component sizes implanted. This study was approved and registered with the relevant hospital department.

A number of methods were used to determine the final outcome of the BHR [64]. The surgeon's routine practice was to review patients at six-weeks post-operatively in the out-patient clinic, and thereafter at an invitational annual clinical review. All consultations included clinical examination, anteroposterior pelvic radiographs, and completion of the Oxford Hip Score (OHS) questionnaire [27,50]. The OHS is a commonly used patient-reported outcome measure assessing pain and disability following hip arthroplasty which has been demonstrated to be a reliable, responsive, and valid outcome measure [65]. In addition, all patients were sent a postal questionnaire (detailed below). The questionnaire was sent up to four times to any non-responding patients. Those failing to respond to all postal questionnaires were subsequently contacted by telephone to complete data collection.

The questionnaire requested details on any further surgical intervention, including revision, the patient may have had on the ipsilateral hip (Appendix 1). If revision was performed, details of the location of the surgery, the revision indication, and the

findings at surgery were obtained from the treating surgeon or hospital. As part of the questionnaire patients were asked to complete the OHS [65] (Appendix 2) and the University of California, Los Angeles (UCLA) Activity Score [66] (Appendix 3).

All deaths occurring during the study period were recorded. In each case assessment was made using the patient case notes and details held by the general practitioner to identify whether the death was related to the BHR surgery, and whether the hip had been revised or remained in-situ at the time of death.

Consideration was given to obtaining study data from the NJR. Given all primary and revision hip arthroplasty procedures should be recorded in the NJR, registry data has the advantage of capturing revisions performed at other centres. However, the institutional database was considered more appropriate given the study aims were to determine the long-term outcomes of BHRs performed between August 1997 and April 2006. The NJR commenced in April 2003 with poor compliance and procedure linkability reported in the early years [2]. Although patient reported outcome measure scores are collected nationally at six-months following primary hip replacement, a recent study observed significant changes occur in these scores during the first twelve-months following hip arthroplasty [67]. Using the institutional database therefore has the advantage of obtaining serial functional outcome scores at long-term follow-up [67].

### 2.3.3 Functional outcomes

The OHSs were expressed as a percentage (healthy joint scoring 0% and worst possible joint 100%) with questionnaires considered valid if they met the minimum inclusion criteria previously described [68,69]. As the OHS is currently most commonly scored in the literature on a scale of 0 to 48 points (0 being the worst possible joint and 48 representing a healthy joint) [70], these scores have also been provided to assist comparison with other reports. However, the percentage method used at this institution includes methods for dealing with missing and multiple responses to questions [68], therefore direct conversion to an OHS on the 48-point scale may not be completely representative. Pre-operative OHSs for the cohort were also available for analysis. The UCLA activity score ranged from 1 (wholly inactive) to 10 (regular participation in impact sports).

### 2.3.4 Radiological analysis

All pelvic radiographs available at the time of most recent follow-up were analysed for signs suggestive of implant failure. The femoral component was considered to have evidence of loosening if there was a radiolucent line > 2 mm in any of the three zones described by Amstutz *et al.* [25]. Acetabular loosening was defined as a radiolucent line > 2 mm in two or more zones as described by DeLee and Charnley [71]. Any osteolysis around the femoral or acetabular components was recorded. Acetabular component inclination and femoral stem-shaft angles were measured as previously described [72].

### 2.3.5 Statistical analysis

All statistical analysis was performed using the program R (R Foundation for Statistical Computing, Vienna, Austria) [73]. Cumulative BHR survival was determined using the Kaplan–Meier method, with the Peto method used to calculate the lower 95% confidence interval (CI) [74]. The endpoint for survival analysis was revision surgery, defined as removal or exchange of either the femoral or acetabular component, or both. Patients not undergoing revision surgery were censored after their last contact with the hospital, whether it was in clinic or by completion of the postal or telephone questionnaire, or after death.

A Cox-proportional hazards model was used to compare the differences in BHR survival distributions for each of the covariates recorded [75]. A multivariate model was constructed, and then covariates that were not significantly influential were systematically removed from the model to identify those having the greatest influence on survival. A Mann-Whitney test was used to compare functional outcomes (OHS and UCLA score) between males and females. A Shapiro-Wilk test was performed on the relevant data to test for normality, and where appropriate the median and interquartile range (IQR) were used rather than the mean and range. The level of significance was set at 95% ($p<0.05$) and CIs were also at the 95% level.

## 2.4 Results

### 2.4.1 Survival analysis and factors affecting survival

The final outcome of the BHR was obtained in all patients during this study, with no patient lost to follow-up. There were 11 patient deaths (13 hips), all unrelated to BHR surgery, and none of these patients underwent implant revision. A total of 16 BHRs (3.6%) in 15 patients were revised (Table 2.2) at a mean of 6.2 years (range 0.5-11.8 years) from primary BHR. All revisions were performed at this institution with some described in detail previously [27,50]. Excluding revisions, no patient underwent any further surgical interventions on the ipsilateral BHR.

**Table 2.2** Details of 16 Birmingham Hip Resurfacings requiring revision surgery

| Revision | Sex | Age (years) | Primary diagnosis | Femoral head size (mm) | Time to revision (years) | Revision indication |
|---|---|---|---|---|---|---|
| 1 | F | 49 | OA | 46 | 0.5 | Aseptic acetabular loosening |
| 2 | M | 44 | OA | 54 | 0.5 | Deep infection |
| 3 | F | 49 | OA | 42 | 0.7 | Neck fracture |
| 4 | F | 49 | OA | 46 | 1.8 | Undiagnosed pain |
| 5 | F | 48 | OA | 46 | 2.2 | Deep infection |
| 6 | F | 43 | OA | 42 | 5.3 | Deep infection |
| 7 | M | 42 | AVN | 50 | 5.9 | Aseptic femoral loosening |
| 8 | F | 26 | DDH | 42 | 6.3 | Aseptic femoral loosening |
| 9 | F | 42 | OA | 42 | 6.7 | Aseptic femoral |

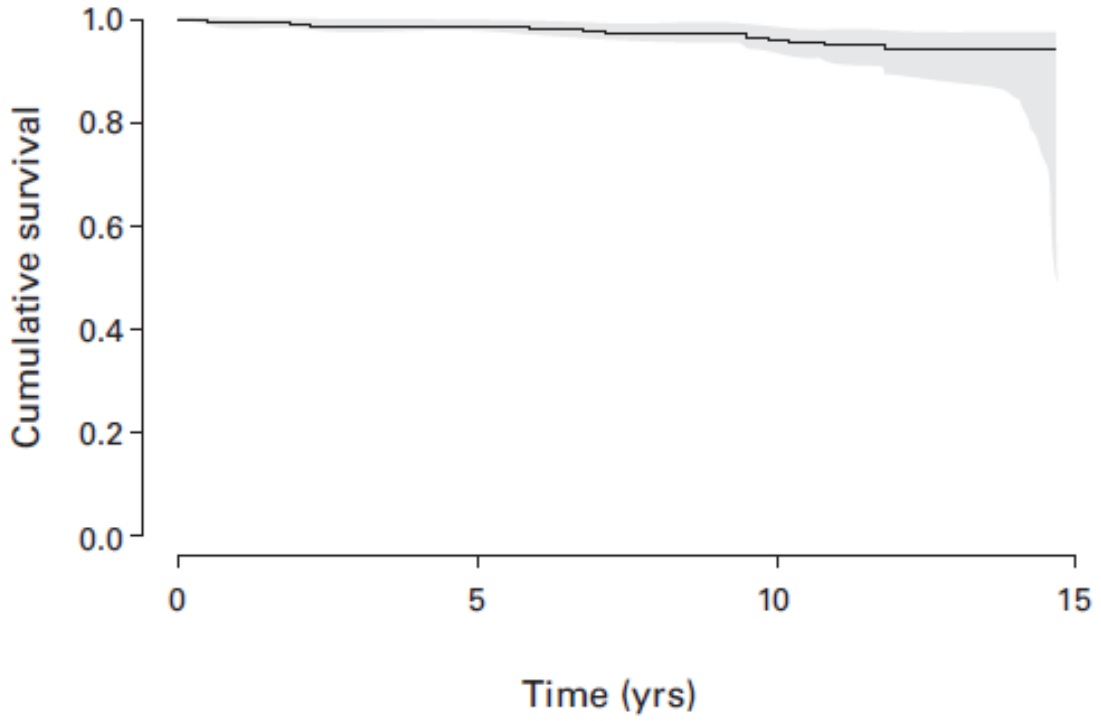
| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | loosening |
| 10 | M | 30 | RA | 46 | 7.1 | Undiagnosed pain |
| 11 | F | 17 | Inflammatory arthritis | 42 | 9.4 | Aseptic femoral loosening |
| 12 | M | 30 | AVN | 50 | 9.5 | Aseptic femoral loosening |
| 13 | F | 17 | AVN | 42 | 9.9 | AVN |
| 14 | F | 49 | OA | 50 | 10.2 | Undiagnosed pain |
| 15 | F | 36 | OA | 46 | 10.8 | Implant fracture |
| 16 | M | 43 | Perthe's | 50 | 11.8 | Aseptic femoral loosening |

AVN = avascular necrosis of the femoral head; DDH = developmental dysplasia of the hip; F = female; M = male; OA = osteoarthritis; RA = rheumatoid arthritis

Revisions number 1 and 5 were performed in the same patient who had bilateral hip resurfacings.

The cumulative survival rate for all BHRs (n=447) at 10-years was 96.3% (95% CI 93.7%-98.3%; 202 hips at risk) and at 14-years was 94.1% (95% CI 84.9%-97.3%; 23 hips at risk) (Figure 2.2).

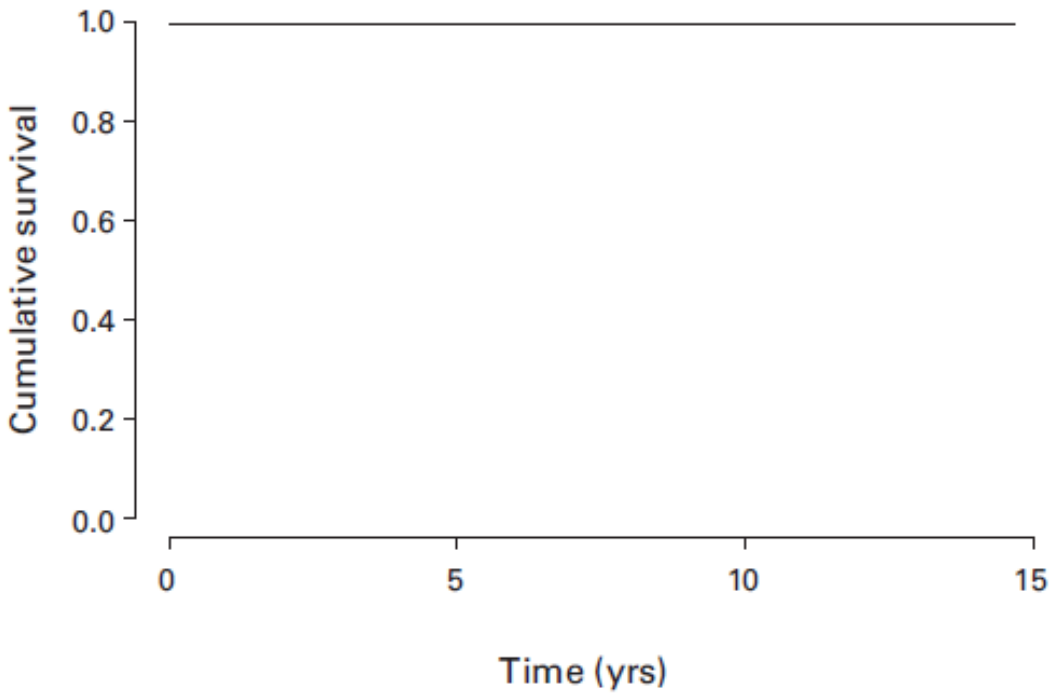
**Figure 2.2** Kaplan-Meier survival curve for all Birmingham Hip Resurfacings (n=447)




Revision for any indication was used as the endpoint for survival, with 16 hips revised in total. Shaded area represents the upper and lower limits of the 95% confidence intervals.

The cumulative survival for 195 BHRs implanted in males with primary osteoarthritis and aseptic revision used as the endpoint was 100% (95% CI 100%-100%) at both 10-years (89 hips at risk) and 14-years (16 hips at risk), with no hips requiring revision (Figure 2.3).

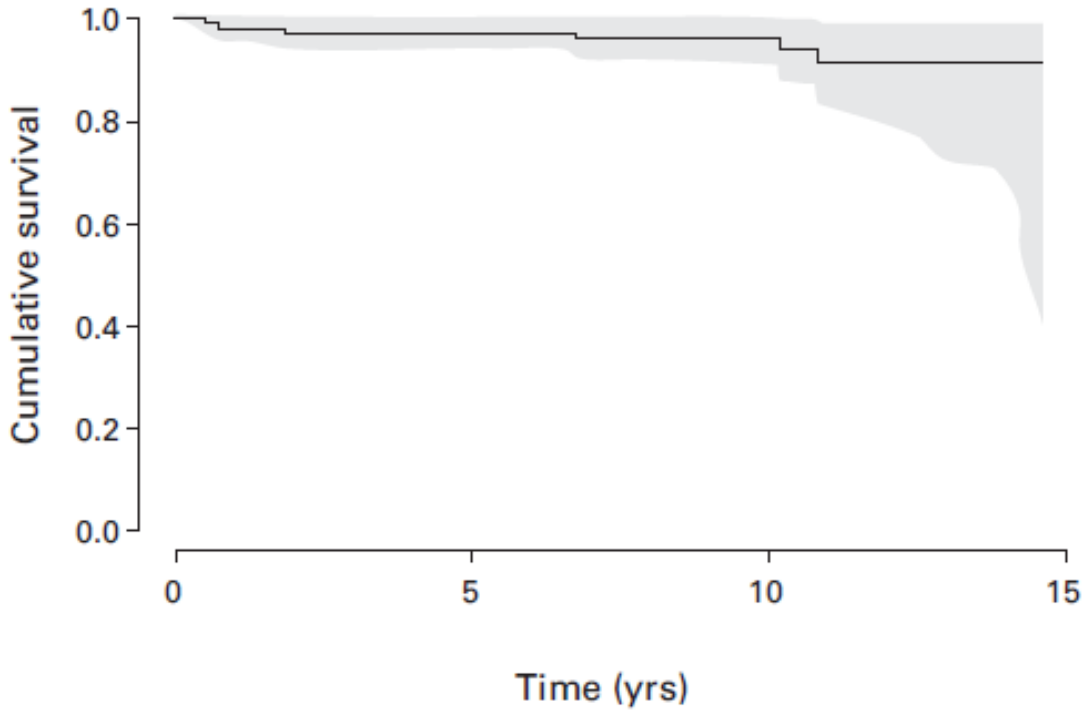
**Figure 2.3** Kaplan-Meier survival curve for Birmingham Hip Resurfacings implanted in males for primary osteoarthritis with aseptic revision as the endpoint (n=195)




No aseptic revisions were performed during follow-up.

The cumulative survival for 109 BHRs implanted in females with primary osteoarthritis and aseptic revision used as the endpoint was 96.1% (95% CI 90.1%-99.9%; 52 hips at risk) at 10-years and 91.2% (95% CI 68.6%-98.7%; 6 hips at risk) at 14-years (Figure 2.4), with six hips requiring revision.

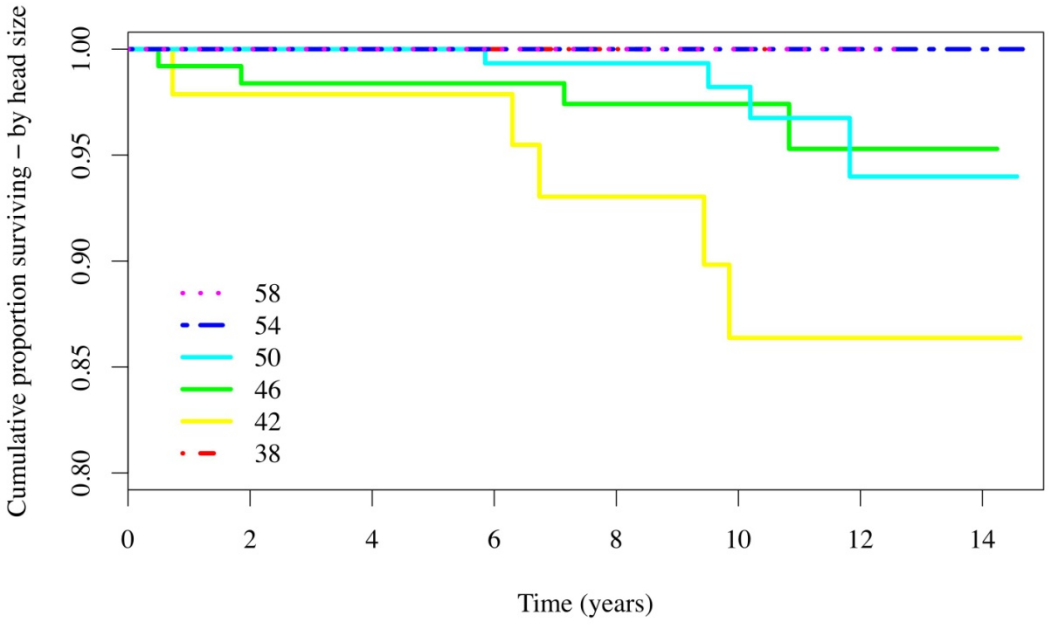
**Figure 2.4** Kaplan-Meier survival curve for Birmingham Hip Resurfacings implanted in females for primary osteoarthritis with aseptic revision as the endpoint (n=109)




Shaded area represents the upper and lower limits of the 95% confidence intervals. There were six aseptic revisions performed during follow-up.

Females had a significantly increased risk of revision over males (p=0.047). Decreasing femoral head size was significantly associated with an increased risk of revision (p=0.044) (Figure 2.5).

**Figure 2.5** Kaplan-Meier survival curve for Birmingham Hip Resurfacings in relation to femoral head size with aseptic revision as the endpoint (n=447)




Femoral head size given in millimetres. Confidence intervals have not been included for clarity. The survival for femoral head sizes 58, 54 and 38 overlap at a cumulative proportion surviving level of 1.00, as no aseptic revisions occurred in these three femoral head size groups.

The designing surgeon has performed over 4000 BHRs to date. To assess the validity of the survival data obtained from the institutional database, the designing surgeon has provided a survivorship funnel plot based on NJR data. This plot compares his BHR results to other surgeons implanting any MoM hip device (Figure 2.6). The NJR data confirms the designing surgeons exceptional survival results for all BHRs implanted, with the surgeon lying more than three standard deviations (>99.8%) from his peers.

**Figure 2.6** National Joint Registry standardised revision ratio funnel plot for all metal-on-metal hip procedures (including hip resurfacing)

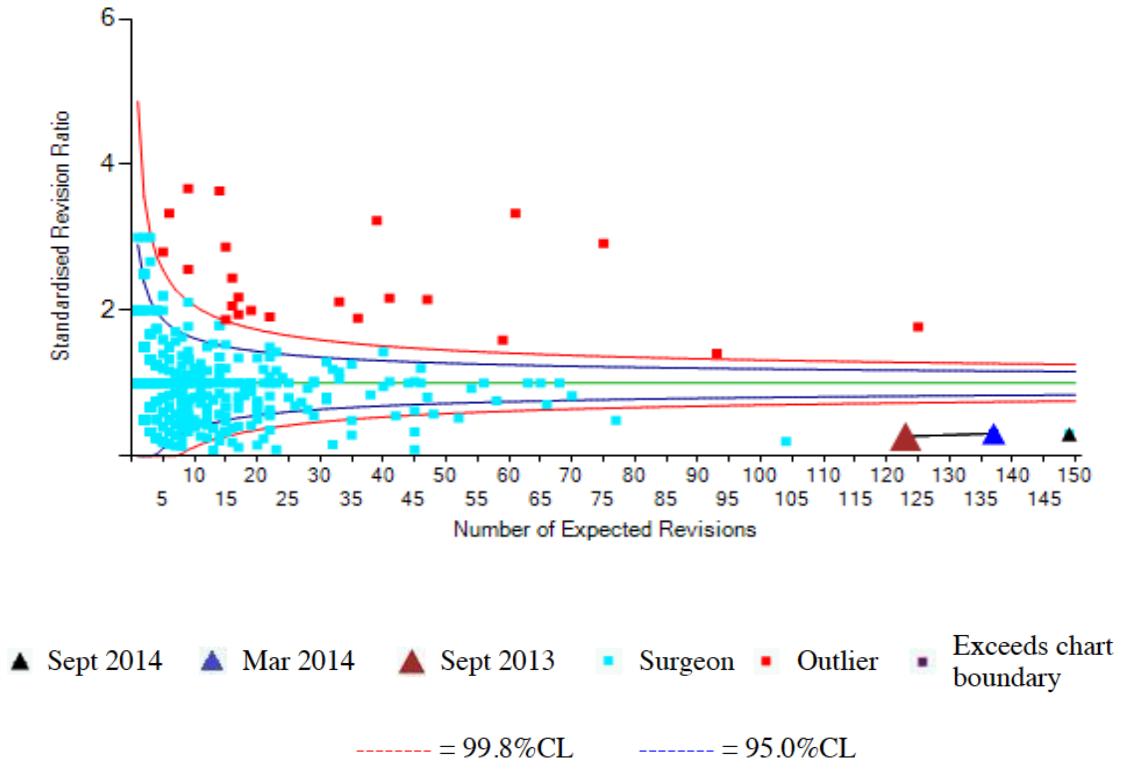



Figure kindly reproduced courtesy of Mr Ronan Treacy. Funnel plot produced on the 17th March 2015 and includes NJR data from April 2003 to December 2014. The plot confirms the surgeons' excellent survival results with hip resurfacing which correlate well with the outcomes recorded in the institutional database.

### 2.4.2 Functional outcomes

The median OHS was 60% (IQR 46%-73%) pre-operatively and 4.2% (IQR 0%-24%) at latest follow-up. Using the 48-point OHS, this equated to a median pre-operative OHS of 19.2 (IQR 13.0-25.9) which improved to 46.0 (IQR 36.5-48.0) at latest follow-up. Males had significantly better OHSs than females (median 3.1% (46.5/48) vs. 6.3% (45.0/48); p=0.02). The median UCLA score was 6.0 (IQR 5-8) at latest follow-up, with males scoring significantly higher than females (median 7.0 vs. 5.0; p=0.01).

### 2.4.3 Radiological analysis

At the time of BHR the mean acetabular component inclination angle for the cohort was 47.1° (range 31°-67°) as measured from the initial post-operative radiographs, and the mean femoral stem–shaft angle was 138.6° (range 125°-152°). Pelvic radiographs were available for review at the time of latest follow-up in 196 of the 431 hips (45%) not requiring BHR revision surgery. In these follow-up radiographs there was no change in the acetabular component inclination angle (mean 48.2°; range 31°-67°) or the femoral stem–shaft angle (mean 138.8°; range 126°-152°) from the initial post-operative radiographs. None of the radiographs available at the time of latest follow-up demonstrated any evidence of osteolysis, loosening of the femoral or acetabular components, or any femoral neck thinning.

## 2.5 Discussion

The study findings demonstrate that the BHR provides excellent survival and functional results in young males with primary osteoarthritis into the second decade, with good survival achieved in appropriately selected female patients. With no patient loss to follow-up, overall BHR survival was 94.1% (95% CI 84.9%-97.3%) at 14-years (Table 2.3).

**Table 2.3** Comparison of the present study results with independent series reporting ten-year survival of the Birmingham Hip Resurfacing

| | **Present study** | **Coulter *et al.* [52]** | **Holland *et al.* [53]** | **Murray *et al.* [54]** |
|---|---|---|---|---|
| BHRs (n) | 447 | 230 | 100 | 646 |
| Patients (n) | 393 | 213 | 90 | 554 |
| Mean age (range) in years | 41.5 (14.9-49.9) | 52.1 (18-82) | 51.3 (21-68) | 51.9 (16.5-81.5) |
| Male (n) | 59.7% (267) | 66% (140) | 74% (74) | 59% (379) |
| Primary osteoarthritis (n) | 68% (304) | NS | 79% (79) | 81% (526) |
| Mean (range) follow-up time in years | 10.1 (5.2-14.7) | 10.4 (9.6-11.7) | 9.6 (0.2-13) | 8.0 (1-12) |
| BHRs lost to follow-up (n) | 0% (0) | 7% (16) | 2% (2) | 2% (12) |
| Overall survival | | | | |
| 10-year | 96.3% | 94.5% | 92% | 87.1% |
| 14-year | 94.1% | NS | NS | NS |

| | | | | |
|---|---|---|---|---|
| BHRs revised (n) | 3.6% (16) | 4.8% (11) | 8% (8) | 8.4% (54) |
| BHR revision vs. Female gender | p=0.047 | p=0.019 | p=0.240 | Not significant (value not stated) |
| BHR revision vs. Decreasing femoral head size | p=0.044 | p=0.123 | p=0.030 | p=0.030 |

BHR = Birmingham Hip Resurfacing; NS = not reported

Recent reports from independent centres have demonstrated good survival for the BHR at ten-years [52-54], which are comparable to that reported by the designing surgeons [50,51]. HR is recognised as a more technically demanding procedure for surgeons than conventional THR [76], therefore the reproducibility of 10-year results from independent centres is encouraging. The present study provides the longest reported survival of the BHR prosthesis in young patients and is comparable to that reported from another designing surgeon series of 96% at 13-years [51]. Although the present long-term survival results compare favourably to registry reports detailing long-term THR survival in young patients with traditional MoP bearings [10], ceramic-on-ceramic (CoC) bearings are beginning to show promise [77]. Two recent studies have reported 10-year survival rates of 95.6% (n=218; mean age 60 years) [78] and 97.9% (n=73; mean age 55 years) [79] with CoC THR, which are comparable to the present results. Although this THR bearing may appear attractive in treating young patients, it is recommended longer term follow-up studies are performed in larger and younger patient cohorts to define the role of CoC THR in this patient population.

In recent years accelerated failure of some MoM hip implants have been reported (Chapter 1.2). However no revisions for ARMD were performed in the present study. In addition, no patient in this series is currently under investigation for a painful BHR with suspected ARMD. It is worth considering this study comprised of a very young patient cohort (mean age 41.5 years) compared to previous studies (mean age of 48.3-53.0 years) [26,51-54]. These young active patients with hip arthritis have traditionally been difficult to treat, with unsatisfactory long-term outcomes with conventional THR [9,10,59,60]. The findings from this study therefore support the continued use of the BHR in this patient population, provided they meet the other selection criteria for HR [50,62].

Young male patients undergoing BHR for primary osteoarthritis were the best performing subgroup, with only one revision for deep infection and 100% survival at 14-years with aseptic revision as the endpoint. These excellent results are comparable to a recent independent report demonstrating a 10-year BHR survival of 99% in males under 50 years of age with primary osteoarthritis [54]. In contrast, the results of HR in females have proved to be more controversial.

Two recent independent studies have reported significantly inferior survival in females compared to males at 10-years following BHR, and therefore have recommended against performing HR in females [52,54]. Indeed, our previously reported experience [27] and findings from this study similarly demonstrate significantly better survival in

males. However the inferior survival reported in females is likely to be complex and multifactorial [69]. Female patients usually require smaller implants, and both this study and previous reports have demonstrated increased failure rates with decreasing femoral component head sizes [50,52-54,69]. The present study findings at long-term follow-up (Figure 2.5) confirm the earlier work of McBryde *et al*., which demonstrated that femoral head size was the best predictor of revision in 2123 BHRs at a mean of 3.5 years follow-up [69]. In addition, young women more commonly have hip dysplasia, and such pathology has been demonstrated to be associated with a relatively inferior survivorship [51]. In this study, of the 16 revised hips 7 (44%) were in patients with diagnoses other than primary osteoarthritis, although only 143 (32%) of all BHRs were implanted for these indications. More recently, observations from independent centres have suggested females are at increased risk of ARMD with certain MoM hip implants, which has led to many surgeons avoiding performing HR in women [36,44,54]. Taking all of this into account the present study demonstrated that in females under 50 years of age with primary osteoarthritis and aseptic revision used as the endpoint, cumulative survival was 96.1% at 10-years and 91.2% at 14-years. This is well within the acceptable limits quoted in published guidelines from the National Institute for Health and Clinical Excellence (NICE), which recommends a revision rate of 10% or less at 10-years for continued implant usage [80]. These results also exceed the long-term survival reported by registries following THR in a similar young patient group [10]. In light of this, we support the continued use of the BHR in young women, provided they have primary osteoarthritis, have adequate femoral anatomy to allow the use of a femoral head size of typically above 46 mm, and meet all the other established indications for HR [50,62].

The functional outcome following BHR for this cohort was excellent. At latest follow-up the majority of patients were almost completely asymptomatic, with a median OHS of 4.2% (or 46/48) and the 25$^{th}$ percentile scoring 0% (or 48/48). These results are similar to both our previously reported findings [50,69] and those from other centres [52,54]. In an earlier analysis including 2123 BHRs significant improvement in the OHS was observed for the first 12-months post-operatively, with the score maintained for the duration of follow-up [69]. As the OHS may not have a sufficiently demanding scale to reveal limitations in very active patients, the UCLA score was also used which demonstrated levels of function similar to those previously reported after BHR [50,52-54].

This study has some recognised limitations. This consecutive series was performed by one designing HR surgeon with excellent BHR survival confirmed by independent NJR data (Figure 2.6), therefore the results achieved may not be reproducible when the surgery is performed by others. However the series includes the surgeon's learning experience with this implant and also spans a period when subtle nuances of anteversion, combined anteversion, and aiming for an acetabular inclination of under $45^0$ were not fully appreciated when performing HR [81], some of which may have been responsible for early failures. Radiographic analysis at latest follow-up was not possible for a number of hips as not all patients attended for clinical review. They were instead assessed using questionnaires. Therefore despite determining the final implant outcome in all patients as well as obtaining functional outcome scores, it remains possible some

hips may have radiological evidence suggestive of implant failure. Other studies reporting 10-year BHR survival have similarly encountered difficulties in obtaining complete radiological review [52,54]. However it is established that survival analysis into the second-decade is important to determine the long-term outcomes of any implant [82], and as such this study adds valuable information to the literature regarding the BHR. Blood metal ion levels and cross-sectional implant imaging were not routinely available for analysis in this cohort, as these investigations are not required in asymptomatic patients with well-functioning HRs [48]. Such investigations would have allowed an assessment of component wear to be made.

In conclusion, this designing surgeon series has demonstrated that the BHR provides excellent survival and functional results into the second decade in males under 50 years of age with primary osteoarthritis. Good survival was also achieved in appropriately selected young females, and was within the recommended thresholds proposed by NICE even at 14-years. It is therefore recommended the BHR can be used in females with primary osteoarthritis and an adequately sized femoral head, provided they fulfill all the other established indications for HR.

# CHAPTER 3

# MEDIUM-TERM OUTCOMES OF METAL-ON-METAL TOTAL HIP REPLACEMENT

## 3.1 Declaration

The work detailed in this chapter has been published in a peer reviewed journal. As first author of this work my role involved input with study design, data collection including all radiographic analysis, involvement with statistical analysis and data interpretation, and the writing of all versions of the paper submitted to the journal as well as this chapter.

Matharu GS, Theivendran K, Pynsent PB, Jeys L, Pearson AM, Dunlop DJ. Outcomes of a metal-on-metal total hip replacement system. *Annals of The Royal College of Surgeons of England* 2014; **96**(7): 530-535.

## 3.2 Introduction

The use of MoM bearings in THR has been considered an attractive option for treating young active patients with hip joint arthritis given the lower wear rates of MoM bearings compared to MoP (Chapter 1.1). This resulted in an increased usage of large-diameter MoM hip bearings during the last decade with over one million MoM hips implanted worldwide [34]. Recently reports have observed high short-term failure rates

due to ARMD for a number of MoM THR designs (Chapter 1.2). This has led to the MHRA issuing guidance regarding the investigation and management of MoM hip patients, the withdrawal of devices with unacceptably high failure rates, and a significant decrease in MoM hip usage worldwide [2,47,48].

The study aims were to determine the medium-term clinical outcomes for one commonly used primary MoM THR system. Outcomes of interest were implant survival, function, blood metal ion concentrations, and radiological analysis.

## 3.3 Methods

### 3.3.1 Study design and patient cohort

Between January 2004 and December 2010, data were prospectively collected on all consecutive MoM THRs (578 hips in 511 patients) implanted at one specialist arthroplasty centre (The Royal Orthopaedic Hospital, Birmingham). All MoM THRs consisted of the Corail femoral stem and the Pinnacle acetabular component (both manufactured by DePuy Ltd, Leeds, United Kingdom). Since 2010 this MoM THR system has not been implanted due to reports of high failure rates with similar implants and various device recalls [37,38,47,48]. Patients were selected for MoM THR if they had end-stage hip arthritis and wished to maintain a reasonably active lifestyle. All operations were performed in a clean-air laminar flow operating theatre by ten surgeons with three surgeons performing the majority (n=459; 79.4%). Data on patient

demographics, primary indication for THR, and components implanted were extracted from the institution's prospectively maintained database (Table 3.1). This study was approved and registered with the relevant hospital department.

**Table 3.1** Summary of the study cohort

| **Characteristic** | | **Study cohort (n= 578 hips)** |
|---|---|---|
| **Gender** | Female<br>Male | 340 (58.8%)<br>238 (41.2%) |
| **Age** | Mean (range) in years | 60.0 (19.8-88.0) |
| **Bilateral hips** | Total patients<br>Single-stage bilateral procedures<br>Two-stage bilateral procedures | 67 (134 hips)<br>1 (2 hips)<br>66 (132 hips) |
| **Diagnosis** | Primary osteoarthritis<br>Developmental dysplasia<br>Avascular necrosis<br>Inflammatory arthritis<br>Neck of femur fracture<br>Slipped upper femoral epiphysis<br>Other causes | 533 (92.2%)<br>12 (2.1%)<br>10 (1.7%)<br>5 (0.9%)<br>5 (0.9%)<br>3 (0.5%)<br>10 (1.7%) |
| **Follow-up time** | Mean (range) in years | 5.0 (1.0-9.1) |
| **Surgical approach** | Posterior<br>Anterolateral | 537 (92.9%)<br>41 (7.1%) |
| **Grade of surgeon** | Consultant<br>Specialist registrar | 559 (96.7%)<br>19 (3.3%) |
| **Femoral head size** | 28 mm<br>36 mm | 14 (2.4%)<br>564 (97.6%) |
| **Acetabular component size** | Median<br>Range | 52 mm<br>48-66 mm |

**Figure 3.1** The Corail, Pinnacle, Ultamet metal-on-metal total hip replacement system

### 3.3.2 Implant design

The Corail femoral stem is a fully hydroxyapatite coated titanium alloy stem designed for insertion without cement (Figure 3.1). The stem is available in a range of sizes (6-20) with all but the smallest sizes available with either a collar or collarless option. Three different options of neck geometry are available (standard, high offset, and coxa vara) but the neck itself is not modular. All stem options have a 12/14 taper onto which, in this series, a 36 mm or 28 mm diameter cobalt chromium alloy metal femoral head (Articul/eze, DePuy Ltd, Leeds, United Kingdom) was impacted. The Pinnacle acetabular component is a hemispheric porous-coated titanium shell which is inserted without cement and can accommodate a polyethylene, ceramic, or metal liner (Figure

3.1). In this series metal liners were used (Ultamet, DePuy Ltd, Leeds, United Kingdom). The acetabular component is available in a range of diameters (38-66 mm) and includes solid backed, spiked solid back, three-hole, and multi-hole cup varieties.

Similar to most other large-diameter MoM THRs, the Corail, Pinnacle, Ultamet MoM THR system has three interfaces: (1) stem taper and femoral head, (2) femoral head and acetabular liner, and (3) acetabular liner and acetabular component. By contrast, MoM HR devices do not have a modular femoral head or acetabular liner. Therefore the only interface in HRs is the single articulation between the femoral and acetabular components (Figure 2.1).

### 3.3.3 Data collection and follow-up after THR

Patients underwent clinical review at six-weeks, six-months, and one-year post-operatively with invitations for annual clinical review thereafter. All consultations included clinical examination, anteroposterior pelvic radiographs, and completion of the OHS questionnaire [65]. After the 2010 MHRA alert which highlighted concerns regarding ARMD associated with MoM hip replacements [47] all patients with MoM THRs were recalled to this institution for clinical review and blood metal ion sampling (Appendix 4). In line with MHRA recommendations, cross-sectional periprosthetic imaging was performed in all symptomatic patients and any asymptomatic patients with high blood metal ion concentrations [48]. Patients with high blood metal ion concentrations and periprosthetic effusions on further imaging were considered to have ARMD. ARMD was subsequently confirmed intra-operatively at revision and after histopathological analysis.

Data were collected on all revision THR surgery performed up until 31st October 2013 with details obtained from other hospitals if revisions were performed elsewhere. Data from the NJR was also used to confirm no revisions performed elsewhere were missed. All deaths were recorded and assessed as previously described (Chapter 2.3.2).

### 3.3.4 Blood metal ion sampling

Blood metal ion sampling was performed at a minimum of one-year following arthroplasty to avoid taking measurements during the running-in phase [83]. Whole blood was obtained from each patient with cobalt and chromium concentrations measured using inductively-coupled plasma mass spectrometry as previously described [84]. Whole blood metal ions were considered raised if cobalt and/or chromium concentrations were greater than 7 μg/l as per MHRA recommendations [48]. Although the stem is made of titanium alloy, titanium concentrations were not measured because this is not recommended in the current MHRA guidelines [48]. Other authors have measured blood titanium concentrations in non-MoM THR patients with well-functioning hips [85], and in patients with failure due to corrosion at the femoral head-neck taper requiring revision surgery [86]. Interestingly both patient groups had low blood titanium concentrations [85,86] suggesting this particular metal ion may not be useful for identifying failing MoM THRs.

### 3.3.5 Functional outcomes and radiological analysis

The OHS questionnaire (Appendix 2) was used to assess pain and disability before and after MoM THR [65]. This questionnaire was scored as already described (Chapter

2.3.3). All anteroposterior pelvic radiographs available at the time of most recent follow-up were analysed for signs suggestive of implant failure. Analysis of radiographs was performed as previously described (Chapter 2.3.4), which included assessing the femoral stem for evidence of component loosening [87] or subsidence [88].

### 3.3.6 Statistical analysis

All statistical analysis was performed using the program R [73]. Cumulative implant survival analysis and Cox-proportional hazards modelling was performed as described earlier (Chapter 2.3.5). Mood's test was used to compare OHSs between males and females. The level of significance was set at 95% ($p<0.05$) and CIs were also at the 95% level.

## 3.4 Results

### 3.4.1 Survival analysis

All patients were reviewed following the institutions recall therefore no patient was lost to follow-up. The mean follow-up time since index THR was 5.0 years (range 1.0-9.1 years) with 92% (529 of 578 THRs) having a minimum follow-up of three-years. There were 22 patient deaths (22 hips) during follow-up which occurred at a mean of 2.7 years (range 1.4-6.5 years) from the index procedure. All deaths were unrelated to surgery.

During follow-up 39 hips (6.7%) in 38 patients underwent revision surgery (Table 3.2) with all revisions performed at this institution. All 39 hips revised had an initial femoral component head size of 36 mm. Mean time from index THR to revision arthroplasty was 3.5 years (range 0.01-8.3 years) with 30 revisions (77%) performed in females.

**Table 3.2** Clinical details of the 39 revised metal-on-metal total hip replacements

| Revision | Age (years) / sex | Time to revision (years) | Cup size (mm) | Primary indication | Revision indication | Revision bearing | Operative time (min) | Outcome after revision |
|---|---|---|---|---|---|---|---|---|
| 1 | 78.2 M | 0.01 | 52 | OA | Dislocation | MoM | 60 | Died after 3.2 yr |
| 2 | 32.7 F | 0.02 | 50 | DDH | Dislocation | MoM | 67 | 4.9 yr no complications |
| 3 | 56.2 F | 0.69 | 52 | OA | Recurrent dislocation | MoP | 40 | 0.1 yr re-revised for dislocation (liner exchange) |
| 4* | 49.1 F | 1.00 | 54 | OA | Aseptic loosening femur | OxP | 185 | 4.3 yr no complications |
| 5 | 59.9 F | 1.05 | 52 | OA | Stem subsidence with LLD | MoM | 109 | 0.1 yr re-revised for periprosthetic stem fracture. Subsequent evacuation haematoma 2 weeks later |
| 6 | 58.6 F | 1.25 | 54 | OA | Aseptic loosening cup | MoM | 60 | 0.2 yr re-revision for aseptic cup loosening |
| 7* | 67.4 M | 1.37 | 56 | OA | Deep infection | 1st stage | 103 | 4.0 yr no complications |
| 8 | 78.7 M | 1.69 | 54 | OA | ARMD | MoP | 80 | 2.1 yr no complications |
|  | 66.9 M | 1.81 | 60 | OA | Aseptic loosening | MoP | 305 | 2.2 yr stem lucency but |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9* | | | | | femur | | | not re-revised |
| 10 | 71.3 F | 1.86 | 52 | OA | LLD | MoM | 97 | 4.1 yr re-revised for aseptic femoral loosening |
| 11* | 70.6 F | 1.96 | 52 | OA | Deep infection | MoP | 124 | 3.6 yr no complications |
| 12 | 46.4 F | 1.97 | 50 | OA | Unexplained pain | CoP | 60 | 1.0 yr no complications |
| 13* | 48.3 F | 2.00 | 52 | AVN | Deep infection | MoM | 90 | 6.8 yr no complications |
| 14* | 63.6 F | 2.03 | 52 | OA | Recurrent dislocation | CoP | 48 | 3.3 yr no complications |
| 15 | 73.4 F | 2.25 | 52 | OA | LLD | MoP | 65 | 3.6 yr no complications |
| 16 | 59.5 F | 2.29 | 50 | SUFE | ARMD | CoP | 81 | 1.4 yr no complications |
| 17 | 63.2 F | 2.97 | 52 | OA | Aseptic loosening femur | MoP | 106 | 2.3 yr no complications |
| 18* | 63.1 F | 3.53 | 50 | OA | Peri-prosthetic stem fracture | MoP | 128 | 1.1 yr no complications |
| 19 | 70.3 F | 3.66 | 52 | OA | ARMD | CoP | 60 | 1.8 yr no complications |
| 20* | 68.3 M | 3.66 | 58 | OA | Deep infection | 1st stage | 114 | 3.1 yr no complications |
| 21 | 58.1 F | 3.69 | 50 | OA | ARMD | CoP | 66 | 1.5 yr no complications |
| 22* | 68.2 F | 4.01 | 52 | DDH | Deep infection | 1st stage | 81 | 1.4 yr no complications |
| 23 | 69.6 M | 4.06 | 54 | OA | Aseptic loosening femur | MoP | 259 | 0.9 yr no complications |
| 24* | 60.7 F | 4.08 | 52 | OA | Aseptic loosening femur | MoP | 117 | 4.1 yr no complications |
| 25 | 67.8 F | 4.20 | 52 | OA | ARMD | CoP | 81 | 1.3 yr no complications |
| | 73.0 F | 4.22 | 52 | OA | ARMD | MoP | 183 | 1.0 yr lucency around |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 26 | | | | | | | | acetabular component but not revised |
| 27 | 60.9 F | 4.24 | 52 | OA | ARMD | CoP | 92 | 0.9 yr no complications |
| 28* | 61.6 F | 4.43 | 52 | OA | ARMD | CoP | 90 | 0.6 yr no complications |
| 29* | 62.7 M | 4.51 | 58 | OA | ARMD | CoP | 103 | 0.7 yr no complications |
| 30* | 72.7 F | 4.83 | 52 | OA | Aseptic loosening cup | MoP | 106 | 0.5 yr no complications |
| 31 | 70.5 M | 5.01 | 54 | AVN | ARMD | CoP | 62 | 0.3 yr no complications |
| 32* | 72.3 F | 5.23 | 54 | OA | ARMD | OxP | 118 | 1.4 yr no complications |
| 33 | 65.1 F | 5.32 | 52 | OA | Aseptic loosening femur | MoP | 127 | 1.5 yr no complications |
| 34* | 69.5 F | 5.84 | 52 | OA | ARMD | CoP | 46 | 0.5 yr no complications |
| 35* | 69.8 F | 6.06 | 52 | OA | ARMD | CoP | 65 | 0.2 yr no complications |
| 36* | 63.7 F | 6.28 | 54 | OA | ARMD | CoP | 85 | 0.1 yr no complications |
| 37* | 67.2 F | 7.33 | 52 | OA | ARMD | CoP | 110 | 0.2 yr no complications |
| 38* | 46.3 M | 8.13 | 56 | OA | ARMD | MoP | 206 | 0.1 yr no complications |
| 39 | 78.7 F | 8.26 | 52 | OA | ARMD | CoP | 75 | 0.1 yr no complications |

ARMD = adverse reaction to metal debris; AVN = avascular necrosis; CoP = ceramic-on-polyethylene; DDH = developmental dysplasia of the hip; F = female; LLD = leg length discrepancy; M = male; MoM = metal-on-metal; MoP = metal-on-polyethylene; OA = osteoarthritis; OxP = oxinium-on-polyethylene; SUFE = slipped upper femoral epiphysis

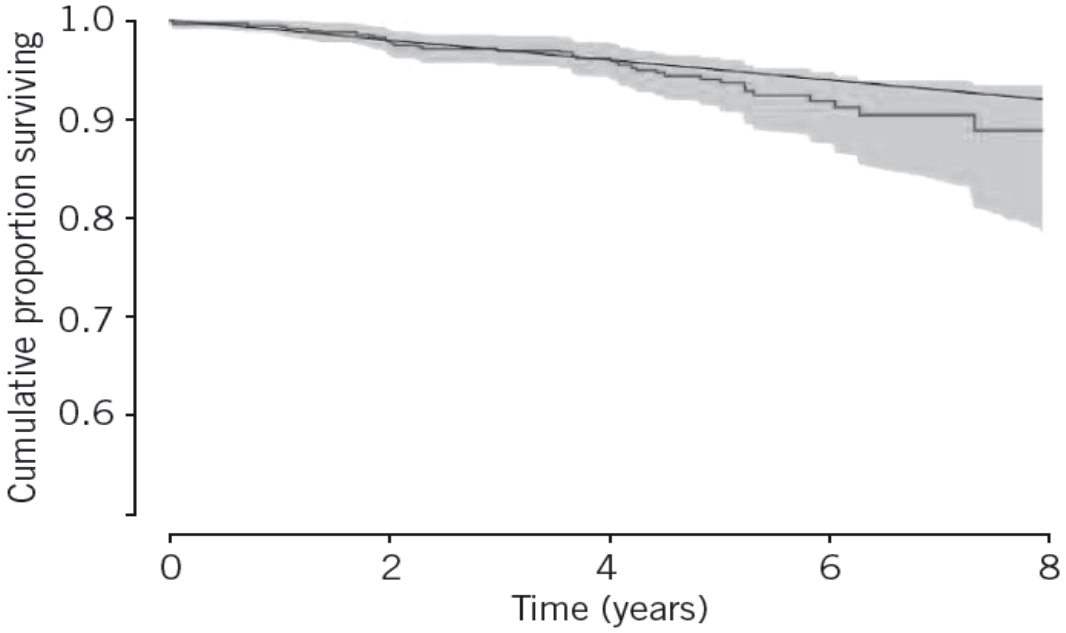
*Bilateral metal-on-metal hip bearing (total hip replacement or hip resurfacing).

Revision 7 and 20 were in the same patient requiring bilateral revision arthroplasty.

All first-stage revisions performed for deep infection underwent successful second-stage revision total hip arthroplasty using a metal-on-polyethylene bearing.

The cumulative survival for all THRs (n=578) was 94.1% (95% CI 91.3%-96.3%) at 5-years (257 hips at risk) and 88.9% (95% CI 78.5%-93.4%) at 8-years (31 hips at risk) (Figure 3.2). Cumulative survival for male patients (n=238) was 96.3% (95% CI 92.4%-99.1%) at 5-years (84 hips at risk) and 95.2% (95% CI 84.2%-98.7%) at 8-years (14 hips at risk) with nine hips requiring revision. Cumulative survival for female patients (n=340) was 92.7% (95% CI 89.0%-95.7%) at 5-years (173 hips at risk) and 85.3% (95% CI 70.2%-92.1%) at 8-years (17 hips at risk) with 30 hips requiring revision. Gender did not significantly affect implant survival (p=0.053).

**Figure 3.2** Kaplan-Meier survival curve for all total hip replacements (n=578)



Revision for any indication was used as the endpoint for survival, with 39 hips revised in total. The shaded area represents the upper and lower limits of the 95% confidence intervals. The diagonal line represents the National Institute for Health and Clinical Excellence recommendations for implant survival (acceptable implant failure rate of up to 1% per year).

ARMD was the commonest indication for revision surgery accounting for 44% (17 of 39) of all revisions performed (Table 3.3). The mean acetabular inclination prior to ARMD revision for the 17 cases was 45.0° (range 37.5°-55.5°). The five hips (29%) with intraoperative evidence of macroscopic bearing wear all had acetabular components with excessive anteversion. Taper wear was observed macroscopically in six cases (35%) with four undergoing femoral component revisions and the other two less severe cases retaining their well-fixed femoral stems. There were no documented cases of wear or corrosion at the interface between the acetabular liner and acetabular component. All cases of ARMD were revised to a non-MoM articulation with no complications recorded at a mean of 0.8 years (range 0.1-2.1 years) following revision surgery (Table 3.2). Blood metal ions normalised following revision in all but the five most recently performed ARMD revisions. The mean acetabular inclination following ARMD revision was 45.7° (range 40.4°-51.6°). At the time of writing, none of the surviving 539 MoM THRs were awaiting revision surgery.

**Table 3.3** Details of 17 patients undergoing revision for adverse reaction to metal debris

| Revision | Initial cup inclination (degrees) | Pre-revision blood metal ion levels (µg/l) | Imaging | Revision performed | ARMD intra-operative findings | Histo-pathology |
|---|---|---|---|---|---|---|
| | 49.0 | Not | USS + CT large joint | Head, cup | Milky effusion; granulomatous | ARMD |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | | performed | effusion | and liner | infiltration; cup over anteverted | |
| 16 | 55.5 | Co 64.4<br>Cr 36.3 | USS normal | Head, cup and liner | Metallosis; cup with excessive inclination and anteversion | ARMD with prominent peri-vascular lymphocytic infiltrate |
| 19 | 39.7 | Not performed | USS small effusion<br>X-ray proximal femoral osteolysis | Head and liner | Milky effusion; granulomatous infiltration; cup over anteverted | ALVAL |
| 21 | 39.9 | Co 9.7<br>Cr 6.7 | USS effusion | Head and liner | Necrotic tissue in trochanteric bursa; free light brown watery fluid | ALVAL |
| 25 | 42.4 | Co 1.8<br>Cr 1.3 | USS effusion | Head and liner | Thickened trochanteric bursa with fluid content; thickened capsule with watery effusion | ARMD with lymphocytic infiltrate |
| 26 | 40.1 | Co 8.6<br>Cr 2.8 | X-ray acetabular osteolysis with medial migration of socket<br>MRI two large effusions | Stemmed acetabular component and long femoral stem | Abductor detachment; pelvic discontinuity; significant osteolysis of femur | ARMD |
| 27 | 49.6 | Co 5.5<br>Cr 1.0 | USS effusion | Head, cup and liner | 15ml black stained fluid; metallosis; cup open and in 30 degrees of anteversion | ARMD |
| 28* | 37.5 | Co 26.1<br>Cr 16.3 | USS + MRI small effusion | Head and liner | Metallosis of abductors and trochanteric bursa | ARMD |
| | 45.5 | Co 0.7<br>Cr 1.4 | USS effusion | Stem, head and liner | Extensive inflammatory haemorrhagic tissues; proximal femoral osteolysis exposing upper | ARMD |

| | | | | | | |
|---|---|---|---|---|---|---|
| 29* | | | | | 3/4 of stem; osteolysis around cup | |
| 31 | 45.7 | Co 3.8<br>Cr 0.6 | CT and MRI moderate effusion | Head and liner | 100 ml thick white fluid / metal debris; hip dislocating easily; anterior scar tissue | ARMD |
| 32* | 44.5 | Co 1.8<br>Cr 1.2 | USS normal | Stem, head, cup, and liner | Metallosis; neutral cup; well fixed but proud stem | ARMD |
| 34* | 38.5 | Co 10.2<br>Cr 1.3 | MRI effusions | Head and liner | Mild effusion; necrotic tissue within capsule taper corrosion | ARMD |
| 35* | 43.2 | Co 8.9<br>Cr 2.3 | USS + MRI small effusion | Head and liner | 20 ml black stained metal debris fluid; taper stained black | ARMD |
| 36* | 46.3 | Co 8.7<br>Cr 9.6 | USS + MRI moderate effusion | Head and liner | Breakdown of previous repair with black/grey fluid communicating with joint; metallosis | ARMD |
| 37* | 46.6 | Co 15.5<br>Cr 10.1 | USS normal | Head and liner | Metallosis; well fixed components | ARMD |
| 38* | 51.7 | Co 62.5<br>Cr 37.2 | X-ray – femoral osteolysis<br>USS large effusion | Long modular femoral stem and cup | Large green/brown fluid collection; extensive metallosis; cup open and anteverted | ARMD |
| 39 | 49.3 | Co 13.7<br>Cr 8.1 | MRI normal | Head and liner | Metallosis | ARMD |

Revision numbers correspond to those in Table 3.2

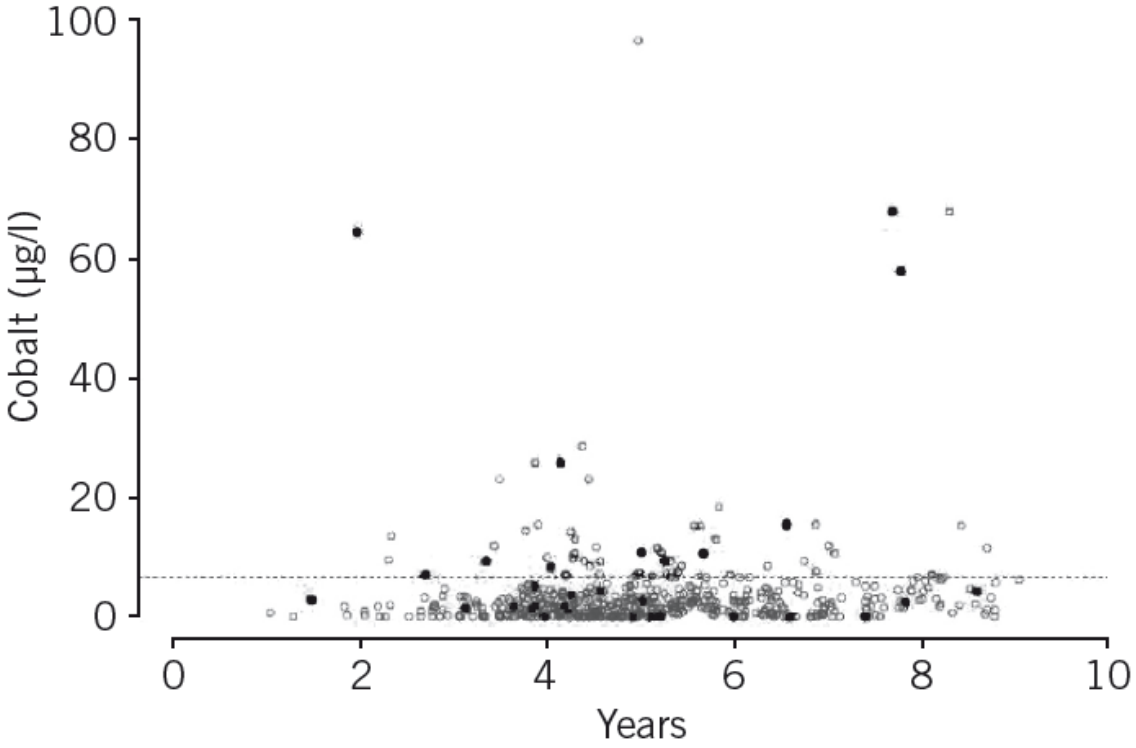
ARMD = adverse reaction to metal debris; ALVAL = aseptic lymphocytic vasculitis associated lesion; Cr = chromium; Co = cobalt; CT = computerised tomography; MRI = magnetic resonance imaging; USS = ultrasonography scan

*Bilateral metal-on-metal hip bearing (total hip replacement or hip resurfacing)

### 3.4.2 Blood metal ion analysis

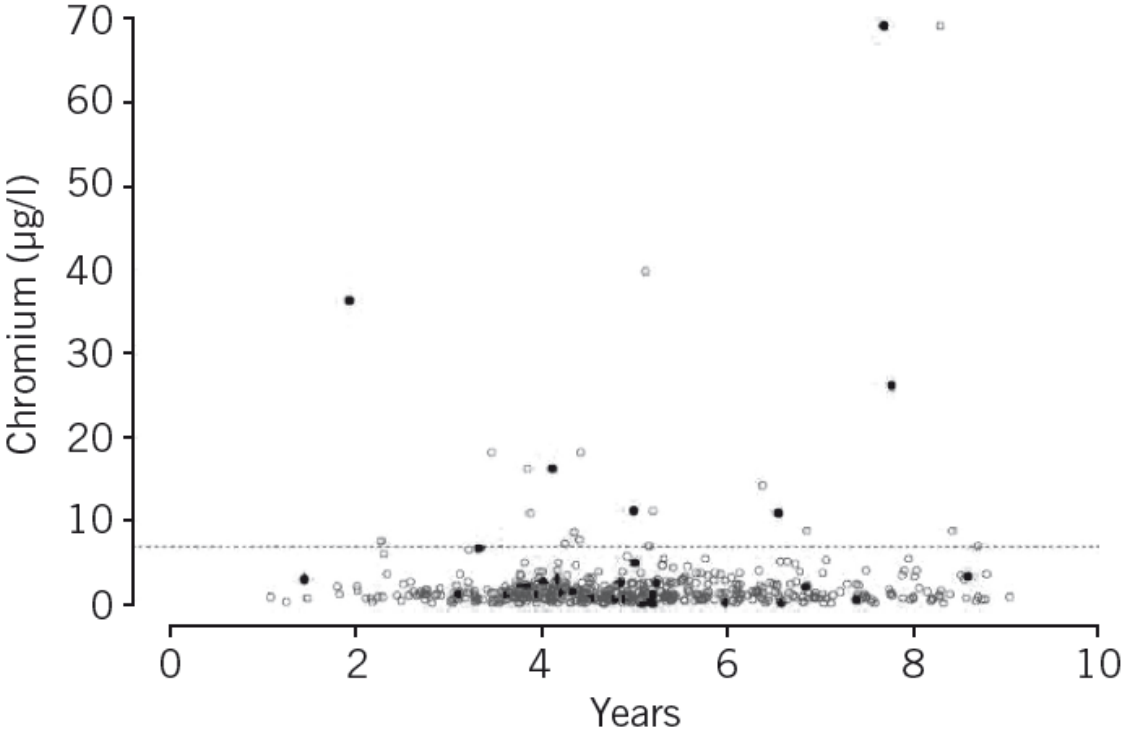
The median maximum blood metal ion concentrations recorded were 2.06 µg/l (IQR 0.83-3.71 µg/l) for cobalt and 1.25 µg/l (IQR 0.83-2.03 µg/l) for chromium. Excluding revisions (n=39), 36 patients with 47 MoM THRs (8.7% of the non-revised cohort) had blood metal ion concentrations above 7 µg/l (Figures 3.3 and 3.4). Fifteen hips had raised blood cobalt and chromium concentrations and 32 hips had raised blood cobalt concentrations with normal chromium levels.

**Figure 3.3** Maximum whole blood cobalt concentration following metal-on-metal total hip replacement




Dashed line = Medicines and Healthcare products Regulatory Agency safe level of 7 µg/l; filled circles = hips which have been revised.

**Figure 3.4** Maximum whole blood chromium concentration following metal-on-metal total hip replacement




Dashed line = Medicines and Healthcare products Regulatory Agency safe level of 7 µg/l; filled circles = hips which have been revised.

Of the 25 unilateral MoM THRs with raised blood metal ion concentrations, 23 hips had normal hip ultrasonography and/or magnetic resonance imaging (under annual clinical follow-up) and two hips had periprosthetic fluid collections of variable sizes (under more regular review). Of the 11 patients (22 hips) with bilateral MoM THRs with raised blood metal ion concentrations, 17 hips had normal hip ultrasonography and/or magnetic resonance imaging (under annual clinical follow-up) and five hips had periprosthetic fluid collections of variable sizes (under more regular review).

### 3.4.3 Functional outcomes and radiological analysis

Pre-operative and post-operative OHS data are summarised in Table 3.4. There was no statistically significant difference in absolute post-operative OHSs between males and females ($p = 0.608$).

Excluding cases with initial femoral stem subsidence there were no changes in femoral or acetabular component position in hips not undergoing revision (n=539). All femoral (n=19) and acetabular (n=3) radiolucent lines observed during follow-up were non-progressive (Table 3.4). There were no cases of femoral or acetabular osteolysis.

**Table 3.4** Functional and radiological outcomes following the 539 non-revised metal-on-metal total hip replacements

| **Functional outcome** | **Median pre-operative OHS (IQR)** | |
|---|---|---|
| | Overall | 66.7% (54.2%-79.2%)<br>16/48 (10-22) |
| | Female | 70.8% (58.3%-81.3%)<br>14/48 (9-20) |
| | Male | 62.5% (50.0%-72.9%)<br>18/48 (13-24) |
| | **Median post-operative OHS (IQR)** | |
| | Overall | 6.3% (0%-27.1%)<br>45/48 (35-48) |
| | Female | 6.8% (0%-27.1%)<br>44.7/48 (35-48) |
| | Male | 6.3% (0%-25.5%)<br>45/48 (36-48) |

| | | |
|---|---|---|
| **Radiological outcome** | Mean acetabular component inclination (range) | 44.0° (21.1°-58.3°) |
| | Mean femoral stem subsidence (range) | 1 mm (0-7 mm) |
| | Femoral radiolucent lines (zones 1 and 7) | 19 hips (3.5% of non-revised hips) |
| | Acetabular radiolucent lines (zone 1) | 3 hips (0.6% of non-revised hips) |

IQR = interquartile range; OHS = Oxford Hip Score (provided as a percentage and on a scale of 0-48)

### 3.5 Discussion

This represents one of the largest single centre studies reporting medium-term outcomes on any modern MoM THR system [37,38,89]. Furthermore, we are unaware of any independent reports on outcomes for this particular THR system.

The present findings demonstrated lower than expected implant survival at eight-years (88.9%). Although survival was not significantly different between genders it was below that expected in published guidelines from NICE [80]. The survival curve appears to diverge from these guidelines at the four-year point (Figure 3.2), which is most likely due to 13 of 17 ARMD revisions occurring after this time. However good functional outcomes were reported in non-revised patients, which are comparable to those reported in young patients following HR [50-54,90]. ARMD was the commonest cause of failure requiring revision with this THR system. In light of recent findings from registry data confirming stemmed MoM hip replacements have significantly

higher revision rates than non-MoM articulations [55,91], it is advised that MoM THRs should not be implanted in the future with regular surveillance recommended for patients with these bearings in-situ.

Although ARMD was the commonest indication for revision, it only accounted for 44% of all revisions performed. More traditional modes of THR failure (such as aseptic loosening, dislocation, and deep infection) were responsible for the remaining revisions performed. In contrast, previous studies reporting on MoM THRs observed that ARMD accounted for nearly all the revisions performed (at least 82%) [37,38]. One potential explanation for this relates to differences in implant metallurgy, with studies demonstrating that subtle differences in HR design can have a significant impact on failure rates [36,41].

Another reason may relate to femoral head size. Recent observations suggest that larger femoral head sizes are associated with increasing failure rates in MoM THRs [55,92]. Potential explanations for these findings include higher wear at the taper-head interface due to increased mechanical stress on the taper with larger heads [37,38], failure to achieve optimum lubrication, and/or early loosening due to increased transmitted torque when using larger femoral heads [55]. The femoral head sizes implanted in this cohort (median 36 mm) were smaller than those used in previous studies reporting higher failure rates (range 38-58 mm) [37,38]. No 28 mm femoral heads used in the present series have required revision.

The lower failure rates for ARMD observed in this study compared to previous reports [37,38] may also be related to cases being performed by surgeons experienced in HR [50,69,90]. The mean acetabular component inclination in this series was acceptable at $44.0^{o}$ with 10 of 17 ARMD revisions also having acceptable acetabular component inclination.

It is important MoM THR patients undergo regular clinical surveillance as they may eventually develop ARMD. In this cohort, 8.7% of non-revised hips had blood metal ion concentrations above MHRA thresholds. The subgroups in which management remains unclear are patients with: (1) high blood metal ion levels and normal imaging findings (n=40), and (2) raised metal ion levels (most with bilateral MoM bearings) and periprosthetic fluid collections of variable sizes (n=7). Repeat blood metal ion sampling and cross-sectional imaging may assist in identifying ARMD [13,48], however the natural history of ARMD is not well understood [93,94]. Decisions relating to revision surgery must therefore be considered on a case-by-case basis. This should include thorough discussion with the patient about the potential risks of further surveillance as well as the risks associated with revision surgery [46]. More detailed investigative and treatment algorithms should be developed for patients with suspected ARMD as new evidence becomes available regarding its natural history.

In addition to the common findings of metallosis and acetabular component malposition, a variety of other intra-operative findings were observed in the 17 ARMD revisions performed. These included effusions of variable sizes and consistencies,

granulomas, tissue necrosis, and osteolysis. This heterogeneity of findings in hips revised for ARMD was also observed in an earlier report from this centre on HRs [95] as well as by other authors [35,96], and is likely to be related to the complex and incompletely understood pathogenesis of this condition.

The macroscopic implant analysis and opinions of the surgeons revising the MoM THRs in this study were that failure for ARMD with this particular device was due to wear at the stem taper and femoral head interface, combined with excessive wear from the bearing surface (femoral head and acetabular liner interface) in cases of acetabular component malpositioning. Taper junction failure requiring revision for large-diameter MoM THRs has certainly been implicated previously as the main failure mechanism for these implants [37,38]. There is evidence that significant volumetric material loss occurs at the taper junction which exceeds that taking place at the bearing surface [92]. Furthermore, a recent retrieval analysis of 20 failed 36mm MoM THRs demonstrated significantly greater femoral head taper material loss from Corail stems compared to S-ROM stems [97]. The rougher and shorter Corail stem taper design was considered responsible for this finding [97]. However, other recent reports have identified the interface between the acetabular liner and acetabular component as a source of significant metal wear and corrosion for a number of large-diameter MoM THR designs, including the Pinnacle cup [98,99]. Therefore it is suspected the failure mechanism of modern large-diameter MoM THRs is multifactorial and requires more detailed investigation.

All revisions for ARMD in the present series underwent bearing exchange to non-MoM articulations with subsequent normal blood metal ion concentrations and no complications reported at short-term follow-up. Nevertheless, given the poor outcomes reported following revision arthroplasty for ARMD [46] these patients will continue to have regular follow-up.

This study has some recognised limitations. The follow-up period may be considered relatively short. However this THR system was only implanted from 2004, therefore it is not possible to determine long-term outcomes at this stage. Other studies reporting on these devices have similar follow-up periods [37,38]. In addition, although all patients were reviewed after the institutions recall 8% have a follow-up of less than three years. This reflects the logistical challenge of reviewing large numbers of patients in clinic with over 4000 MoM hips implanted at this centre. Understandably it has taken time to achieve complete follow-up after the recall, therefore some patients are yet to reach their second clinical review. It was not possible to accurately measure anteversion of the acetabular component from pelvic radiographs. This study also spans a time when subtle nuances of anteversion and combined anteversion were not fully appreciated [81] and which may have been responsible for some ARMD failures. Although it was not routine practice during the study, some surgeons did send a selection of implants for forensic explant analysis (maximum of ten). These reports would provide more detail regarding the mechanisms of implant failure. However they were not easily available for further analysis given some forensic reports were obtained for medico-legal reasons, whilst others were analysed externally and therefore annonymised for confidentiality.

In conclusion, the medium-term results of this MoM THR system demonstrated good functional outcomes in non-revised patients with less dramatic failure rates compared to similar devices [37,38]. However survival was still below that recommended in published guidelines from NICE [80]. On the basis of the available evidence it is recommended large-diameter MoM THRs are not implanted in the future. Patients who currently have these implants should have regular clinical surveillance so that ARMD can be identified and treated early.

# CHAPTER 4

# A SYSTEMATIC REVIEW OF OUTCOMES FOLLOWING REVISION OF METAL-ON-METAL HIP RESURFACINGS AND TOTAL HIP REPLACEMENTS FOR ADVERSE REACTION TO METAL DEBRIS

## 4.1 Declaration

The work detailed in this chapter has been published in a peer reviewed journal. As first author of this work my role involved designing the systematic review, and providing significant input in performing the review, data collection, statistical analysis, data interpretation, and the writing of all versions of the paper submitted to the journal as well as this chapter.

Matharu GS, Pynsent PB, Dunlop DJ. Revision of metal-on-metal hip replacements and resurfacings for adverse reaction to metal debris: a systematic review of outcomes. *Hip International* 2014; **24**(4): 311-320.

## 4.2 Introduction

In recent years ARMD has become a recognised mode of failure of MoM HRs and THRs with this condition often requiring revision arthroplasty (Chapter 1.2). Between 2003 and 2012, 67,363 MoM hips (35,470 HRs and 31,893 THRs) were implanted in England, Wales, and Northern Ireland [2]. Failure rates at 9-years have been reported as

12.3% for all HRs and up to 21.4% for stemmed MoM THRs [2]. Overall ARMD has accounted for 7.4% of all revision hip replacements performed in England, Wales, and Northern Ireland, however this is increasing with ARMD responsible for 13.2% of all hip revisions performed in 2012 [2].

As ARMD is a relatively new mode of hip failure little is currently known about the outcomes following revision arthroplasty. Both the MHRA [48] and orthopaedic experts [13] recommend early surgical intervention for ARMD based on a small study of 16 HRs revised for pseudotumour which experienced high short-term complication (50%) and re-revision (38%) rates [46]. These unsatisfactory outcomes are concerning given most patients are young and active [25-32]. Importantly this study did not report on patients with MoM THRs which can have additional problems related to taper wear [37,38]. Given the large number of MoM hips implanted worldwide it is important surgeons are aware of the likely outcomes following ARMD revision surgery so patients can be appropriately counselled pre-operatively regarding the risks of revision.

The aim of this systematic review was to assess the clinical outcomes following revision of MoM HRs and THRs for ARMD.

## 4.3 Methods

### 4.3.1 Search strategy

A systematic literature review was conducted to assess the evidence on clinical outcomes following revision of MoM HRs and THRs for ARMD. The search was performed independently by two reviewers (GSM and PBP) using PubMed, Medline, Embase, and the Cochrane Central Register of Controlled Trials to identify relevant articles published between 1st January 2009 and 1st July 2013. The search started from 2009 as this was when the first study reporting outcomes following ARMD revision was published [46].

Combinations of the following search terms were used in each electronic database: 'adverse reaction to metal debris (ARMD)', 'adverse local tissue reaction (ALTR)', 'aseptic lymphocytic vasculitis associated lesions (ALVAL)', 'pseudotumour', 'pseudotumor', 'metal-on-metal', 'hip resurfacing', 'total hip replacement', 'total hip arthroplasty', 'failure', 'revision surgery', 'outcomes', 'clinical outcomes', and 'functional outcomes'. There was no restriction on language, study type, or publication status. Full text articles were obtained of all potentially relevant studies and assessed independently by both reviewers. Additional review was performed of pertinent references from the bibliographies of these publications not found in the electronic search but fitting the inclusion criteria.

### 4.3.2 Study inclusion and exclusion criteria

Studies were included if they specifically reported on clinical outcomes following revision of MoM HRs and/or THRs for ARMD. Only studies reporting cohorts with more than ten MoM HRs and/or more than ten MoM THRs undergoing revision for ARMD were included. This was to eliminate small case series which may be influenced by learning curves, and to minimise any selection and publication bias of "positive" results. No restrictions were placed on the minimum follow-up period of patients following revision in the studies identified. Any duplicate publications identified were excluded. If multiple publications from centres reporting on the same cohort were found, only the most recent article was included.

### 4.3.3 Quality of included studies

The methodological quality of each study was independently assessed by two reviewers using the Oxford Centre for evidence-based medicine levels of evidence [100]. Any disagreement was resolved by discussion and consensus with the third author (DJD).

### 4.3.4 Data collection and outcomes of interest

Studies were categorised into those reporting on clinical outcomes of MoM HRs following revision arthroplasty for ARMD and those reporting on MoM THRs revised for ARMD. All study data were independently extracted and recorded in relevant data tables by two reviewers. Data extracted included: patient demographics (age and gender), implants requiring revision, time from index arthroplasty to revision, follow-up

time, and clinical outcomes (complications, further surgery including re-revision, and functional outcomes) after ARMD revision.

Defined outcomes of interest following ARMD revision surgery were: (1) complication rates, (2) re-revision rates, including re-revisions performed for recurrent ARMD or pseudotumour, (3) surgical intervention other than re-revision, (4) functional outcomes. If studies reported functional outcomes following revision arthroplasty, the specific instrument and scoring method used was extracted from the original report and recorded to assist comparison between studies. Meta-analysis of the pooled data was not performed due to the heterogeneity between studies in terms of implants used and data reported.

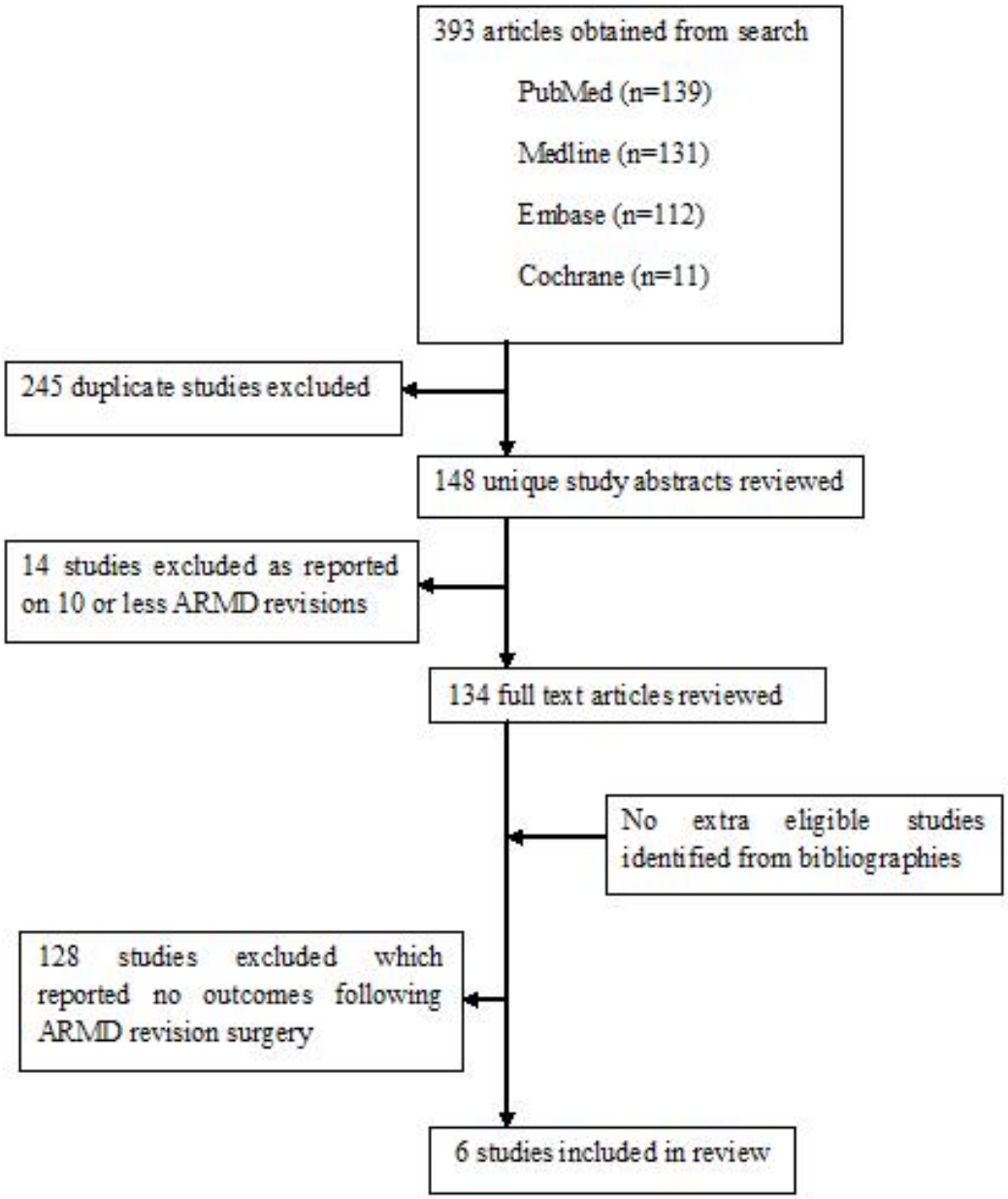
## 4.4 Results

### 4.4.1 Studies for review

The systematic review identified 393 articles with six studies [46,58,101-104] meeting the inclusion criteria for analysis (Figure 4.1). Of the six studies reviewed, one was a retrospective case-control study [46] and the remaining five were either prospective or retrospective case-series' [58,101-104]. All six studies were graded as level 4 evidence [100]. Two studies [58,101] reported on clinical outcomes following ARMD revision of both MoM HRs and THRs. Although both studies reported outcomes of more than ten HR revisions which were included in this review, they also reported the outcomes of

either two [101] or seven [58] THR revisions for ARMD which were excluded from further analysis.

**Figure 4.1** PRISMA flow diagram showing article selection for the systematic review




ARMD = adverse reaction to metal debris

### 4.4.2 Patient demographics

Relevant patient demographic data from the six studies is summarised in Table 4.1. From the six studies a total of 216 MoM hip bearings were revised for ARMD (197 HRs and 19 THRs) with clinical outcome data. Mean age at revision in the six studies ranged from 49.8 years to 57.7 years with between 36% and 100% of patients being female. Mean time from primary arthroplasty to ARMD revision ranged from 19.0 months to 51.4 months.

**Table 4.1** Demographics of patients revised for adverse reaction to metal debris from the six studies

| Study and year of publication | Mean age (range) at revision in years | Female hips (%) | Hips revised for ARMD (patients) | Prostheses revised | Mean time to ARMD revision (range) in months |
|---|---|---|---|---|---|
| Grammatopoulos 2009 [46] | 51.3 (20-71) | 16/16 (100) | 16 (16) HR | Included BHR, Cormet, Conserve Plus, and Re Cap (exact numbers NS) | 19.0 (0.1-80)* |
| Rajpura 2011 [101] | 53.5 (22-67) | 4/11 (36) | 11 (11) HR | 8 BHR, 2 Cormet, 1 ASR | 46.0 (15-87) |
| De Smet 2011 [102] | 52.5 (18-71)* | 69 (61)* | 48 (45) HR | Included BHR, McMinn, Conserve Plus, ASR, Durom, Adept, | 32.5 (4-101) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Cormet, and Re Cap* | |
| Liddle 2013 [58] | 57.7 (25-74) | 26/32 (81) | 32 (29) HR | 20 BHR, 5 Cormet, 4 ASR, 2 Biomet, 1 Mitch | 51.4 (11-131) |
| Pritchett 2013 [104] | 49.8 (32-71) | 43/90 (48) | 90 (89) HR | 35 BHR, 32 Conserve Plus, 8 ASR, 7 Cormet, 4 Re Cap, 4 Durom | 33.3 (16-59) |
| Munro 2013 [103] | 57.5 (46-76)* | NS (37)* | 19 (NS) THR* | 19 Durom | 34.0 (7-59)* |

ARMD = adverse reaction to metal debris; ASR = Articular Surface Replacement; BHR = Birmingham Hip Resurfacing; HR = hip resurfacing; NS = not stated; THR = total hip replacement

*Studies did not provide the relevant data specifically for the cohort of patients undergoing revision for adverse reaction to metal debris (but rather for the whole cohort of revisions they reported on).

### 4.4.3 Outcomes following ARMD revision surgery

All six studies reported data on complications, re-revision surgery, and functional outcomes (Table 4.2 and 4.3). Only one study specifically reported on performing further surgery other than re-revision during follow-up [103]. In one study complications and re-revisions were reported for the whole cohort rather than just for ARMD revisions [102]. In another study [58] it was not possible to determine whether the complications and re-revisions occurred in the 32 HRs included in this review, or the seven MoM THRs excluded from further analysis. Therefore complication and re-

revision rates for both studies [58,102] have been provided as ranges rather than absolute values.

**Table 4.2** Clinical outcomes reported in five studies following revision of metal-on-metal hip resurfacings for adverse reaction to metal debris

| | **Grammatopoulos 2009 [46]** | **Rajpura 2011 [101]** | **De Smet 2011 [102]** | **Liddle 2013 [58]** | **Pritchett 2013 [104]** |
|---|---|---|---|---|---|
| **Revision bearing used (%)** | CoC 8/16 (50)<br>CoP 6/16 (38)<br>MoP 2/16 (12) | CoC 9/11 (82)<br>MoP 1/11 (9)<br>Pseudo-arthrosis 1/11 (9) | CoC (67)*<br>MoM (33) | CoC 24/32 (75)<br>MoP 6/32 (19)<br>MoM 2/32 (6) | MoP 47/90 (52)<br>MoM 43/90 (48) |
| **Mean (range) follow-up time from revision in months** | 36 (10-86)* | 21 (12-40) | 43 (3-121)* | Median 30 (12-54)* | 61 (36-118) |
| **Total complications (%)** | 8/16 (50)<br>Dislocation (n=3)<br>Nerve palsy (n=3)<br>Aseptic cup loosening (n=2) | 2/11 (18)<br>ARMD recurrence (n=2) | <11/48 (<23)*<br>Dislocation (n=5)<br>Deep infection (n=3)<br>Component loosening (n=2)<br>Metal sensitivity (n=1) | <2/32 (<6)*<br>Dislocation (n=1)<br>Recurrent pseudo-tumour / aseptic cup loosening (n=1) | 4/90 (4)<br>ARMD recurrence (n=1)<br>Deep infection (n=1)<br>Aseptic cup loosening (n=1)<br>Acetabular fracture (n=1) |
| **Hips requiring re-** | 6/16 (38) | 2/11 (18)<br>ARMD | <6/48 (<13)* | <2/32 (<6)*<br>Dislocation | 3/90 (3)<br>ARMD |

| | | | | | |
|---|---|---|---|---|---|
| **revision (%)** | Dislocation (n=3)<br><br>Aseptic cup loosening (n=2)<br><br>NS (n=1)<br><br>3 of these re-revised hips also had evidence of recurrent pseudotumour | recurrence (n=2) | Component loosening (n=2)<br><br>Deep infection (n=2)<br><br>Dislocation (n=1)<br><br>Metal sensitivity (n=1) | (n=1)<br><br>Recurrent pseudo-tumour / aseptic cup loosening (n=1) | recurrence (n=1)<br><br>Deep infection (n=1)<br><br>Aseptic cup loosening (n=1) |
| **Surgery other than re-revision (%)** | 0/16 (0) | 0/11 (0) | 0/48 (0) | 0/32 (0) | 0/90 (0) |
| **Functional outcome scores following revision** | Mean OHS = 20.9 (/48)<br><br>48 = best outcome | Mean OHS = 35.3 (/48)<br><br>48 = best outcome | Mean HHS = 93.1* (/100)<br><br>100 = best outcome | Median OHS = 36.5 (/48)<br><br>48 = best outcome | Mean HHS = 93.2 (/100)<br><br>100 = best outcome |
| **Additional study findings and comments** | Significantly worse clinical and functional outcomes compared to:<br><br>(1) HRs revised for other indications<br><br>and<br><br>(2) Patients undergoing primary total hip replacement | Pseudo-arthrosis patient had satisfactory function so no re-revision planned<br><br>3 of 11 patients had no OHS before and/or after revision | Presence of soft-tissue fluid collection did not affect outcome after revision | Patients with solid pseudo-tumours and those revised to MoM bearings had worse functional outcomes | All hips had only one HR component revised for ARMD<br><br>All re-revisions were in those retaining a MoM hip bearing |

ARMD = adverse reaction to metal debris; CoC = ceramic-on-ceramic; CoP = ceramic-on-polyethylene; HHS = Harris Hip Score; HR = hip resurfacing; MoM = metal-on-metal; MoP = metal-on-polyethylene; OHS = Oxford Hip Score; NS = not stated

*Studies did not provide the relevant data specifically for the cohort of patients undergoing revision for adverse reaction to metal debris (but rather for the whole cohort of revisions they reported on).

**Table 4.3** Clinical outcomes reported in one study following revision of metal-on-metal total hip replacements for adverse reaction to metal debris

| | **Munro 2013 [103]** |
|---|---|
| **Revision bearing used*** | Metal-on-polyethylene 75%<br>Ceramic-on-polyethylene 25% |
| **Mean (range) follow-up time from revision in months*** | 25 (10-48) |
| **Total complications (%)** | 13/19 (68)<br>Dislocation (n=5)<br>ARMD recurrence (n=3)<br>Aseptic cup loosening (n=3)<br>Nerve injury (n=2) |
| **Hips requiring re-revision (%)** | 4/19 (21)<br>Dislocation and / or aseptic cup loosening (n=3)<br>ARMD recurrence (n=1) |
| **Surgery other than re-revision (%)** | 5/19 (26)<br>Dislocations reduced under anaesthesia |
| **Functional outcome scores following revision*** | Mean WOMAC (pain) 78 (/100)<br>Mean WOMAC (function) 83 (/100)<br>0 = best outcome |
| **Additional study findings and comments** | High failure rate of 'fiber' metal cups<br>High dislocation rate despite using large heads |

ARMD = adverse reaction to metal debris; WOMAC = Western Ontario and McMaster Universities Arthritis Index

*Study did not provide the relevant data specifically for the cohort of patients undergoing revision for adverse reaction to metal debris (but rather for the whole cohort of revisions they reported on).

### 4.4.4 Outcomes following HR revision for ARMD

Five [46,58,101,102,104] of the six included studies reported outcomes following ARMD revision in HR patients (Table 4.2). Mean follow-up time from ARMD revision ranged from 21 months to 61 months. During this time the complication and re-revision rates reported were between 4% to 50% and 3% to 38% respectively. The commonest complications were dislocation (n=9 amongst the five studies), ARMD and/or pseudotumour recurrence (n=8), and aseptic acetabular component loosening (n=6). These three complications were also the commonest indications for re-revision surgery. All five studies reported between one and three cases of ARMD and/or pseudotumour recurrence during follow-up. ARMD and/or pseudotumour recurrence accounted for between 17% (1/6) and 100% (2/2) of all re-revisions performed.

Functional outcomes following ARMD revision were reported in all studies using one of two different instruments. In one study three of eleven revised hips did not have pre-operative and/or post-operative functional outcomes available [101]. Another study only reported post-operative functional outcomes therefore change in score could not be determined [46]. Functional outcomes following ARMD revision were good or satisfactory in all but one study [46].

### 4.4.5 Outcomes following THR revision for ARMD

One [103] study reported outcomes following ARMD revision in THR patients (Table 4.3). At a mean follow-up time of 25 months from ARMD revision the complication

rate was 68% and the re-revision rate was 21%. The commonest complications were dislocation (n=5), ARMD recurrence (n=3), and aseptic acetabular component loosening (n=3). These were also the commonest indications for re-revision surgery. In addition to re-revision, 26% of patients required closed reductions for dislocated THRs. Post-operative functional outcomes following ARMD revision were reported, however no pre-revision scores were available to determine change in score. Functional outcomes following ARMD revision were generally poor.

### 4.5 Discussion

It is important for arthroplasty surgeons to have a good understanding of the clinical outcomes which can be expected in patients following revision of MoM hips for ARMD. With the revision burden for ARMD increasing, especially in specialist centres [58,102], it is vital patients receive appropriate pre-operative counselling regarding the likely outcomes following ARMD revision surgery. This is perhaps of even greater importance when counselling asymptomatic individuals with clinically well functioning prostheses in whom revision for ARMD is recommended based on other investigations.

This systematic review has demonstrated that since an initial report in 2009 observing poor short-term outcomes following revision of HRs for pseudotumour [46], few studies have been published on outcomes following ARMD revision [58,101-104]. Furthermore, all studies reviewed were graded as low-quality evidence (level 4) with most limited by reporting on small cohorts with short-term follow-up [46,58,101,103]. It is recognised that given the potential ethical issues of not revising patients with

ARMD and the heterogeneity between patients with this diagnosis [58] it is unlikely better quality evidence, such as from randomised trials, will be obtained in the future.

Outcomes following ARMD revision in the studies reviewed were variable. Complication rates ranged from 4% to 68% and re-revision rates between 3% and 38% [46,58,101-104]. These generally high complication rates are of concern given they are reported at largely short-term follow-up. In addition, for HR patients who often comprise a young and active group [25-32] these outcomes appear significantly inferior to those reported following HRs revised for other indications [105-107]. Interestingly one study reporting on 48 HRs revised for ARMD and 65 HRs revised for other indications demonstrated outcomes were not affected by the presence of a soft-tissue fluid collection [102]. However the authors acknowledge their outcomes following ARMD revision have improved with increasing experience [102].

Of further concern is the high complication (68%) and re-revision (21%) rates observed in the short-term in the only study reporting on MoM THRs revised for ARMD [103]. All but one hip revised retained their well-fixed femoral stem, therefore these complication rates do not even reflect the additional problems which can be associated with removing a stemmed femoral component [108,109]. In addition the morbidity following ARMD revision in some studies may have been underestimated [46,58,101,102,104] given only one study specifically reported on further surgery performed other than re-revision [103]. Not all dislocations and deep infections reported as a complication underwent re-revision. It is possible such patients underwent further

procedures, such as closed prosthetic reductions or wound washouts, which were not recorded but would add to overall morbidity.

Three complications were common to most studies following ARMD revision, namely dislocation, ARMD and/or pseudotumour recurrence, and acetabular component loosening. Dislocation was the commonest complication with most cases requiring re-revision. This complication is predisposed to by a combination of stretching and damage to the hip abductors and/or short external rotators caused by the adverse reaction itself, and the subsequent excision of periprosthetic tissues affected by ARMD which may include the hip capsule [102]. Two studies did not report any dislocations following ARMD revision [101,104], which may reflect these patients had less severe soft-tissue destruction at revision. Studies reporting on patients with more severe soft-tissue destruction observed poorer outcomes [46,58]. Grammatopoulos *et al*. reported significantly worse clinical and functional outcomes in patients with HRs revised for pseudotumour than matched patients undergoing primary THR, and compared to HRs revised for other indications [46]. In another study the only two re-revisions performed occurred in the subgroup of four patients with solid pseudotumours [58]. This subgroup also experienced significantly inferior functional outcomes compared to other patients [58]. If the degree of soft-tissue destruction is time-dependent these findings would support early and aggressive surgical intervention for ARMD.

All six studies reported at least one case of ARMD and/or pseudotumour recurrence during follow-up [46,58,101-104]. Incomplete initial resection and leaving substantial

amounts of metal wear debris may explain such recurrence [46,58]. In addition, incomplete initial debridement may increase the risk of secondary infection [58,103]. We recommend that excision of ARMD lesions is considered an oncological procedure with clear resection margins required to reduce the risk of recurrence [110]. However these intentions may become compromised when surgeons attempt to preserve soft-tissue for hip joint stability. As these lesions may involve vital neurovascular structures and/or extend into the pelvis it is important to perform detailed pre-operative imaging and enlist the appropriate expertise when performing revision surgery, such as vascular surgeons and specialists in pelvic and soft-tissue reconstruction. The management algorithm proposed by Liddle *et al*. highlights the heterogeneity of findings encountered at revision in patients with MoM hips and provides a good basis for surgical planning [58].

Recurrence of ARMD can also be caused by the bearing implanted at revision. Poorer clinical and/or functional outcomes were observed in ARMD patients revised using MoM articulations [58,104]. It is suspected the persistence of a MoM bearing provides a source of metal wear debris which can continue to cause periprosthetic tissue reactions. It is therefore recommended that non-MoM bearings are used for ARMD revisions with CoC and ceramic-on-polyethylene (CoP) articulations currently most popular [46,58,101-104]. In one study two of the three patients developing ARMD recurrence had initially been revised to MoP bearings [103]. It was postulated these recurrences were due to wear debris generated from the metal femoral head articulating with the metal stem taper and that in these instances the use of ceramic heads with titanium sleeves may be appropriate, though requires further research [103].

The best outcomes reported following ARMD revision were from a study performing 90 one-component HR revisions (complication rate 4% and re-revision rate 3%) [104]. Although this study described an interesting and novel method of managing ARMD associated with HRs [104], this approach cannot be recommended without longer-term follow-up in light of current evidence. Registry data reports unacceptably high revision rates following acetabular component only HR revisions [111] with surgeons experienced in HR also reporting inferior outcomes following single component revisions [102]. After observing inferior outcomes in ARMD patients revised to MoM bearings Liddle *et al*. recommended revision of MoM hips for any reason should always include both sides of the bearing surface and result in a non-MoM articulation [58]. We agree with this recommendation in the current climate of uncertainty about the use of MoM hip bearings in any context apart from carefully selected patients undergoing HR [50-52,90]. Indeed all three re-revisions performed by Pritchett *et al*. were in patients retaining MoM bearings with one re-revision performed for ARMD recurrence [104].

In conclusion, limited evidence is presently available regarding clinical outcomes following revision of MoM hips for ARMD, especially for large-diameter THRs. This must be addressed in future studies so surgeons can better inform their patients pre-operatively about the risks of undergoing revision for ARMD. Such information will especially by important when counselling asymptomatic individuals in whom revision for ARMD is recommended, and may also be informative in protecting arthroplasty surgeons from a medico-legal perspective.

# CHAPTER 5

# OUTCOMES FOLLOWING REVISION OF METAL-ON-METAL HIP RESURFACINGS AND TOTAL HIP REPLACEMENTS FOR ADVERSE REACTION TO METAL DEBRIS

## 5.1 Declaration

The work detailed in this chapter was accepted for publication in a peer reviewed journal on 22nd August 2014. As first author of this work my role involved input with study design, data collection including all radiographic analysis, involvement with statistical analysis and data interpretation, and the writing of all versions of the paper submitted to the journal as well as this chapter.

Matharu GS, Pynsent PB, Sumathi VP, Mittal S, Buckley CD, Dunlop DJ, Revell PA, Revell MP. Predictors of time to revision and clinical outcomes following revision of metal-on-metal hip replacements for adverse reaction to metal debris. *The Bone and Joint Journal* 2014 (In Press).

## 5.2 Introduction

A number of patients with MoM HRs and THRs who develop ARMD eventually require revision surgery (Chapter 1.2). For these patients it is a pivotal time in their care. The surgeon has a number of decisions to make both pre-operatively, using results

from blood tests and radiological examinations to plan surgery, and intra-operatively, based on the findings at revision. These findings include bone loss and muscle damage, which can both vary from minimal to catastrophic, and periprosthetic effusions which range from negligible to large solid or semi-solid pseudotumours [35,36,95].

The few studies reporting outcomes following revision of MoM hips for ARMD suggest outcomes are generally poor with short-term complication and re-revisions rates up to 68% and 38% respectively (Chapter 4). Because of the need for caution in a condition where there is tissue destruction and some uncertainty about the natural history, early surgical intervention is often recommended [13,46,48]. Knowledge of prognostic factors of outcome would be useful for surgeons in making decisions related to revision surgery. Only one study has specifically examined any factors affecting outcome following ARMD revision which observed poorer outcomes in patients with solid pseudotumours and those revised to stemmed MoM hips [58].

In addition, it is possible the specific histopathological response in local tissues may affect outcomes following ARMD revision. Recent work demonstrated a subgroup of ARMD patients exhibited an immune reaction with local appearances of tertiary lymphoid organs (TLOs) [112]. These TLO structures have been observed in several autoimmune conditions [113], therefore it is possible patients with such structures have more aggressive disease.

The study aims were to determine the clinical outcomes following revision of MoM HRs and THRs for ARMD, and identify factors predictive of outcomes following ARMD revision. It was hypothesised poorer outcomes would be observed in (1) patients with TLO structures, and (2) patients retaining MoM bearings following ARMD revision, either as a contralateral MoM bearing or revision to another MoM articulation. The second hypothesis is particularly relevant at revision because it may influence the surgeon's choice of bearing surface.

## 5.3 Methods

### 5.3.1 Study design and patient cohort

This retrospective study was approved and registered with the relevant hospital department. Between January 1998 and March 2012, 64 MoM hips in 63 patients underwent revision for ARMD (Table 5.1). All revisions were performed at one specialist arthroplasty centre (The Royal Orthopaedic Hospital, Birmingham). Operations were performed in a clean-air laminar flow operating theatre by nine surgeons. Sixty-one operations were performed through a posterior surgical approach with the remaining three hips revised using an anterolateral approach.

**Table 5.1** Summary of the study cohort

| Characteristic | Whole cohort | HR | THR |
|---|---|---|---|
| Number of hips (%) | 64 (100) | 46 (72) | 18 (28) |
| Female (%) / Male (%) | 46 (72) / 18 (28) | 34 (74) / 12 (26) | 12 (67) / 6 (33) |
| Mean age at revision in years (range) | 57.8 (31.0-78.8) | 55.8 (31.0-71.2) | 63.2 (48.3-78.8) |
| Indication for metal-on-metal HR or THR (%) | OA 49 (77)<br>DDH 5 (8)<br>SUFE 5 (8)<br>AVN 4 (6)<br>NOF 1 (1) | OA 34 (74)<br>DDH 5 (11)<br>AVN 4 (9)<br>SUFE 3 (6) | OA 15 (83)<br>SUFE 2 (11)<br>NOF 1 (6) |
| Previous hip surgery prior to index arthroplasty (%) | 12 (19) | 8 (17) | 4 (22) |
| Contralateral metal-on-metal hip bearing at revision (%) | Total = 26 (41)<br>19 (73) HR<br>7 (27) THR | Total = 21 (46)<br>16 (76) HR<br>5 (24) THR | Total = 5 (28)<br>3 (60) HR<br>2 (40) THR |
| Prosthesis revised (%) | | BHR 32 (70)<br>Corin McMinn 11 (24)<br>Conserve Plus 2 (4)<br>Other 1 (2) | Corail / Pinnacle 7 (39)<br>Modular BHR 6 (33)<br>Other 5 (28) |
| Median femoral component head size in millimetres (range) | | 46 (38-52) | 36 (36-50) |
| Mean time from primary arthroplasty to revision in years (range) | 5.5 (1.1-13.8) | 5.8 (1.1-13.8) | 4.7 (1.7-11.6) |
| Mean time from primary arthroplasty to symptoms in years (range) | 3.9 (0-13.6) | 4.1 (0-13.6) | 3.2 (0-10.9) |
| Mean time from symptoms to revision in years (range) | 1.6 (0.02-7.2) | 1.7 (0.02-7.2) | 1.6 (0.14-5.4) |
| Index metal-on-metal HR or THR performed at another institution (%) | 20 (31) | 12 (26) | 8 (44) |

AVN = avascular necrosis of the femoral head; BHR = Birmingham Hip Resurfacing; DDH = developmental dysplasia of the hip; HR = hip resurfacing; NOF = neck of femur fracture; OA= Osteoarthritis; SUFE = slipped upper femoral epiphysis; THR = total hip replacement

### 5.3.2 Definition for adverse reaction to metal debris

ARMD was originally described as an umbrella term which includes the presence of metallosis, pseudotumour, aseptic lymphocytic vasculitis associated lesions, and macroscopic tissue necrosis [36,41]. In the present study a diagnosis of ARMD was made if on review of both the clinical and histopathological information there were features compatible with those consistently reported in the literature. This included clinical evidence of periprosthetic joint effusions or solid masses, metallosis, macroscopic tissue necrosis or foreign body granulomas, and histopathological evidence of aseptic foreign body or phagocytic reactions, significant metal wear debris, lymphocytic reactions and tissue necrosis [114]. Three patients (three hips) were initially deemed eligible for inclusion but subsequently demonstrated evidence of infection from the samples sent at the time of revision surgery for microbiological and histopathological analysis. These three patients were excluded leaving a final cohort of 64 MoM hips in 63 patients revised for ARMD.

### 5.3.3 Data collection

Cases of ARMD were identified from prospectively maintained clinical and histopathological databases. Data were collected from the institutional databases and patient case notes using a standard proforma. The pre-operative variables collected were: patient age and gender, any previous surgery on the ipsilateral hip, the indication for index MoM arthroplasty and components implanted, the presence of a contralateral MoM hip bearing, the institution at which the index arthroplasty was performed, the date of presentation with symptoms, radiological findings prior to revision (Chapter

2.3.4 and 3.3.5), and the date of revision. Acetabular component inclination was measured in each radiograph. The intra-operative variables were: the macroscopic features at revision, the specific components revised including the revision bearing used, and operative time. Data were also collected on relevant outcomes of interest following ARMD revision surgery (Chapter 5.3.6).

### 5.3.4 Histopathological analysis

All histopathological sections from the periprosthetic tissue of hips revised for ARMD were reviewed by two consultant histopathologists (PAR and VPS). Both were blinded to the clinical details and cellular pathology diagnostic reports in all cases. Categorisation was performed using previously described criteria [112]. On the basis of this review all cases were assigned to one of four histopathological categories: (1) no lymphocytic infiltrate; (2) diffuse lymphocytic infiltrate (with T cells but no aggregates); (3) lymphocyte aggregates containing T cells; (4) TLO structures containing both T and B cell aggregates.

### 5.3.5 Follow-up after revision surgery

Following revision patients were seen in the outpatient clinic at six-weeks, six-months, and one-year post-operatively. Thereafter review was according to clinical need, usually annually. All consultations included clinical examination, anteroposterior pelvic radiographs, and completion of the OHS questionnaire (Appendix 2) [65]. All radiographs were analysed for signs suggestive of implant failure as previously

described (Chapter 2.3.4 and 3.3.5). The OHS questionnaire was scored as described (Chapter 2.3.3).

Patients not reviewed in clinic within 12 months of study commencement were sent a postal questionnaire to determine their OHS and identify whether they had any further surgery on the revised hip (Appendix 1). Patients failing to respond to the postal questionnaire were subsequently contacted by telephone to complete data collection. All deaths were recorded and assessed as previously described (Chapter 2.3.2).

### 5.3.6 Outcomes of interest

The defined clinical outcomes of interest following revision hip arthroplasty for ARMD were: (1) any complication related to revision surgery, (2) re-revision surgery, and (3) post-revision OHS.

### 5.3.7 Statistical analysis

All statistical analysis was performed using the program R [73]. Cumulative implant survival analysis was performed as described (Chapter 2.3.5). The endpoint for survival analysis was re-revision surgery, defined as removal or exchange of any component. A Cox-proportional hazards model was used to determine the affect of (1) histopathological category, and (2) patients with a contralateral MoM bearing, on the risk of re-revision surgery.

Pre-operative and intra-operative variables were analysed in relation to the three outcomes of interest (Chapter 5.3.6). Chi-squared test with Yeates's correction was used to compare proportions between single variables, though in instances where less than five hips were in any subgroup a Fisher's exact test was performed instead. Unpaired t-tests were used for analysing numerical data. Mood's test was used to compare medians for the OHS data. The level of significance was set at 95% ($p<0.05$) and CIs were also at the 95% level.

## 5.4 Results

### 5.4.1 Clinical outcomes following revision

No patients were lost to follow-up. At a mean follow-up time from revision of 4.5 years (range 1.0-14.6 years) there have been 13 (20.3%) complications related to surgery. The five complications not requiring re-revision were: superficial wound infection (n=1; treated with oral antibiotics), deep vein thrombosis (n=1; treated with oral anticoagulation), permanent sciatic nerve palsy (n=1), dislocation (n=1; 4.5 months after revision treated by closed reduction with no subsequent dislocations), and hip haematoma (n=1; resolved following conservative treatment).

Eight hips (12.5%) required re-revision with all further surgery performed at this institution (Table 5.2). In addition four patients (four hips) died at a median time of 2.7 years from revision arthroplasty. None of the deaths were related to surgery and no

patient had undergone re-revision surgery. The cumulative survival for revision hip arthroplasty performed for ARMD was 87.9% (95% CI 78.9%-98.0%) at 5-years (19 hips at risk) and 83.0% (95% CI 71.0%-97.1%) at 10-years (4 hips at risk). At the time of writing, no other patients in this cohort were awaiting re-revision surgery.

**Table 5.2** Details of 8 hips undergoing re-revision during follow-up

| Age / Sex / Implant | Femoral head size (mm) | Time to re-revision (years) | Indication for re-revision | Re-revision performed | Outcome after re-revision |
|---|---|---|---|---|---|
| 48F THR (MoP) | 32 | 0.27 | Recurrent dislocation | Head + liner (constrained) exchange (MoP) | No complications at 4.3 yr |
| 65F THR (OxP) | 36 | 0.31 | Deep infection | Washout with head + liner exchange (OxP) | Girdlestone at 0.5 yr due to persistent infection |
| 65F THR (MoM) | 42 | 0.83 | Recurrent dislocation | Head + liner (constrained) exchange (MoP) | No complications at 5.9 yr |
| 40M HR (MoM) | 50 | 1.3 | Component mismatch causing impingement | Revised to uncemented THR (MoM) | No complications at 0.5 yr with normal blood metal ion levels |
| 56F HR (MoM) | 46 | 2.0 | Unexplained pain (no significant findings at revision to explain pain and normal histology) | Revised to uncemented THR (CoC) | No complications at 1.3 yr |
| 38F HR (MoM) | 50 | 4.0 | Recurrent ARMD | Revised to uncemented THR (OxP) | No complications at 0.5 yr |

| | | | | | |
|---|---|---|---|---|---|
| 70M THR (MoM) | 48 | 6.4 | Recurrent ARMD | Revised to uncemented THR (CoP) | No complications at 0.5 yr |
| 53F THR (MoP) | 28 | 11.4 | Aseptic acetabular loosening | Revised to uncemented cup and cemented stem (MoP) + femoral head allograft | No complications at 1.9 yr |

ARMD = adverse reaction to metal debris; CoC = ceramic-on-ceramic; CoP = ceramic-on-polyethylene; F = female; HR = hip resurfacing; M = male; MoM = metal-on-metal; MoP = metal-on-polyethylene; OA = osteoarthritis; OxP = oxinium-on-polyethylene; THR = total hip replacement

Excluding hips undergoing re-revision (n=8) the median OHS in patients revised for ARMD at latest follow-up was 18.8% (IQR 7.8%-48.3%). This equates to a median OHS of 39.0/48 (IQR 24.8/48-44.3/48). Excluding re-revisions the mean acetabular component inclination in the remaining 56 hips was 45.1° (range 31.1°-57.1°) at latest follow-up with no change in these angles from the initial post-revision radiographs. Three hips had evidence of non-progressive acetabular radiolucencies in zone 2 following ARMD revision. There were no femoral component radiolucencies observed. In addition there was no evidence of neck narrowing or femoral component loosening in the three HRs which underwent acetabular only revisions, therefore retaining the original femoral resurfacing component.

### 5.4.2 Factors predictive of outcomes following revision

The analyses of pre-operative and intra-operative factors and their affect on clinical outcomes following ARMD revision surgery are detailed in Table 5.3.

**Table 5.3** Affect of pre-operative and intra-operative factors on clinical outcomes following revision surgery for adverse reaction to metal debris

| | | | **Complications** | | | **Re-revision** | | |
|---|---|---|---|---|---|---|---|---|
| | | **Whole cohort (n=64)** | **Hips without complications (n=51)** | **Hips with complications (n=13)** | **P value** | **Hips not re-revised (n=56)** | **Hips re-revised (n=8)** | **P value** |
| **Pre-operative factors** | | | | | | | | |
| Gender | F (%)<br>M (%) | 46 (72)<br>18 (28) | 35 (69)<br>16 (31) | 11 (85)<br>2 (15) | 0.424 | 40 (71)<br>16 (29) | 6 (75)<br>2 (25) | 1.0 |
| Mean age at revision | Years (range) | 57.8 (31.0-78.8) | 59.3 (31.0-78.8) | 52.2 (34.2-66.9) | 0.171 | 58.8 (31.0-78.8) | 51.1 (34.2-64.6) | 0.192 |
| Type of hip arthroplasty | HR (%)<br>THR (%) | 46 (72)<br>18 (28) | 35 (69)<br>16 (31) | 11 (85)<br>2 (15) | 0.480 | 39 (70)<br>17 (30) | 7 (88)<br>1 (12) | 0.574 |
| Previous surgery on ipsilateral | Number (%) | 12 (19) | 8 (16) | 4 (31) | 0.333 | 9 (16) | 3 (38) | 0.398 |
| Presence of contralateral metal-on-metal hip bearing at revision | Number (%) | 26 (41) | 23 (45) | 3 (23) | 0.260 | 25 (45) | 1 (13) | 0.178 |
| Mean time from index arthroplasty to symptoms* | Years (range) | 3.9 (0-13.6) | 4.1 (0-13.6) | 3.1 (0.1-13.0) | 0.513 | 4.2 (0-13.6) | 1.2 (0.1-6.8) | 0.260 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mean time from symptoms to revision | Years (range) | 1.6 (0.02-7.2) | 1.5 (0-6.1) | 2.3 (0.1-7.2) | 0.513 | 1.5 (0-6.1) | 2.6 (0.1-7.2) | 0.260 |
| Index metal-on-metal HR or THR performed at another institution (%) | Number (%) | 20 (31) | 17 (33) | 3 (23) | 0.706 | 17 (30) | 3 (38) | 1.0 |
| *Radiological factors* | | | | | | | | |
| Mean acetabular component inclination | Degrees (range) | 49.9 (23.6-75.0) | 50.0 (23.6-75.0) | 49.4 (30.6-67.0) | 0.704 | 49.7 (23.6-75.0) | 51.2 (30.6-67.0) | 0.692 |
| Loose stem | Number (%) | 16 (25) | 13 (25) | 3 (23) | 1.0 | 14 (25) | 2 (25) | 1.0 |
| Loose cup | Number (%) | 13 (20) | 11 (22) | 2 (15) | 0.410 | 12 (21) | 1 (13) | 0.272 |
| Femoral neck thinning in HRs | Number (%) | 12 (19) | 10 (20) | 2 (15) | 1.0 | 11 (20) | 1 (13) | 1.0 |
| | | | | | | | | |
| **Intra-operative factors** | | | | | | | | |
| *Histo-pathological category* | | | | | | | | |
| No lymphocytic infiltrate | Number (%) | 13 (20) | 10 (20) | 3 (23) | 1.0 | 11 (20) | 2 (25) | 1.0 |
| Diffuse lymphocytic infiltrate | Number (%) | 26 (41) | 19 (37) | 7 (54) | 0.441 | 21 (38) | 5 (63) | 0.336 |
| Lymphocyte aggregates containing T cells | Number (%) | 7 (11) | 5 (10) | 2 (15) | 0.938 | 7 (13) | 0 (0) | 0.650 |
| Tertiary lymphoid organ structures | Number (%) | 18 (28) | 17 (33) | 1 (8) | 0.136 | 17 (30) | 1 (13) | 0.528 |
| | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mean operation time | Minutes (range) | 91 (40-185) | 91 (45-165) | 90 (40-185) | 0.241 | 90 (40-165) | 98 (60-185) | 0.855 |
| | | | | | | | | |
| *Revision performed* ** | | | | | | | | |
| Acetabular and femoral components | Number (%) | 42 (66) | 36 (71) | 6 (46) | 0.272 | 39 (70) | 3 (38) | 0.323 |
| Acetabulum only | Number (%) | 11 (17) | 7 (14) | 4 (31) | 0.322 | 8 (14) | 3 (38) | 0.734 |
| Femoral component only | Number (%) | 6 (9) | 4 (8) | 2 (15) | 0.410 | 4 (7) | 2 (25) | 0.548 |
| | | | | | | | | |
| *Bearing implanted* | | | | | | | | |
| Metal-on-polyethylene | Number (%) | 32 (50) | 28 (55) | 4 (31) | 0.196 | 30 (54) | 2 (25) | 0.376 |
| Metal-on-metal | Number (%) | 16 (25) | 10 (20) | 6 (46) | 0.102 | 11 (20) | 5 (63) | 0.046 |
| Ceramic-on-polyethylene | Number (%) | 8 (13) | 8 (16) | 0 (0) | 0.441 | 8 (14) | 0 (0) | 0.693 |
| Oxinium-on-polyethylene | Number (%) | 6 (9) | 3 (6) | 3 (23) | 0.410 | 5 (9) | 1 (13) | 1.0 |
| Ceramic-on-ceramic | Number (%) | 2 (3) | 2 (4) | 0 (0) | 1.0 | 2 (4) | 0 (0) | 1.0 |
| | | | | | | | | |
| *Intra-operative findings* | | | | | | | | |
| Metallosis | Number (%) | 31 (48) | 25 (49) | 6 (46) | 0.854 | 27 (48) | 4 (50) | 0.925 |
| Peri-prosthetic effusion*** | Number (%) | 24 (38) | 20 (39) | 4 (31) | 0.438 | 23 (41) | 1 (13) | 0.179 |
| Osteolysis | Number (%) | 21 (33) | 16 (31) | 5 (38) | 0.627 | 18 (32) | 3 (38) | 0.763 |
| Loose cup | Number (%) | 18 (28) | 16 (31) | 2 (15) | 0.424 | 17 (30) | 1 (13) | 0.528 |
| Soft-tissue damage | Number (%) | 14 (22) | 11 (22) | 3 (23) | 1.0 | 12 (21) | 2 (25) | 1.0 |
| Foreign body granuloma | Number (%) | 12 (19) | 10 (20) | 2 (15) | 1.0 | 11 (20) | 1 (13) | 1.0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Loose stem | Number (%) | 7 (11) | 6 (12) | 1 (8) | 1.0 | 7 (13) | 0 (0) | 0.650 |
| Fracture | Number (%) | 5 (8) | 4 (8) | 1 (8) | 1.0 | 4 (7) | 1 (13) | 1.0 |
| Infection | Number (%) | 5 (8) | 4 (8) | 1 (8) | 1.0 | 5 (9) | 0 (0) | 0.860 |
| Tissue necrosis | Number (%) | 2 (3) | 1 (2) | 1 (8) | 0.191 | 2 (4) | 0 (0) | 0.823 |

F = female; HR = hip resurfacing; M = male; THR = total hip replacement

*2 hips revised were asymptomatic

**The remaining 5 hips initially underwent a first stage revision. They all had no histopathological or microbiological evidence of infection and subsequently all underwent revision to metal-on-polyethylene bearings.

***Includes effusions on pre-operative imaging

#### 5.4.2.1 Pre-operative predictive factors

There was no difference in the risk of re-revision between patients with unilateral and bilateral MoM hip bearings (p=0.178). No other pre-operative factors significantly affected the risk of complications or re-revision following ARMD revision (Table 5.3). No pre-operative factor significantly affected the absolute post-revision OHS (p-values ranged from 0.110-0.993 for the variables listed in Table 5.3).

#### 5.4.2.2 Intra-operative predictive factors

The choice of revision bearing was the only intra-operative factor which predicted the risk of re-revision. Patients retaining MoM bearings were significantly more likely to require re-revision than those revised to different articulations (p=0.046). No intra-

operative factor significantly affected the absolute post-revision OHS (p-values ranged from 0.090-0.939 for the variables listed in Table 5.3).

Of the 64 ARMD revisions, 16 (25%) continued with a MoM bearing. All 16 hips were initially MoM HRs and were revised for persistent pain with or without cup malposition. As these 16 revisions were performed before ARMD was described as a clinical entity, no patient had pre-revision blood metal ions measured. Patients either underwent an acetabular component revision (n=6) or revision to a large diameter stemmed MoM THR (n=10). The 16 hips were subsequently classified as revised for ARMD based on the recorded intra-operative and histopathological findings.

Five of the 16 hips (31%) retaining a MoM bearing have been re-revised (Table 5.2) and two patients (two hips) have died. The median OHS at latest follow-up for the nine patients with a MoM hip in-situ was 14.6% (IQR 4.2%-50.0%) which equates to 41.0/48 (IQR 24.0/48-46.0/48). Median blood cobalt and chromium concentrations were 6.1 µg/l (IQR 3.4 µg/l-8.2 µg/l) and 4.7 µg/l (IQR 3.8 µg/l-5.5 µg/l) respectively. Four of these nine MoM hips have bilateral MoM hip bearings and these are the four patients with the highest blood metal ion concentrations. None of these patients have demonstrated ARMD lesions on cross-sectional imaging, however all remain under regular clinical surveillance.

#### 5.4.2.3 Histopathological response

No significant difference was demonstrated in the risk of re-revision in patients with TLO structures (n=18) compared to those with non-TLO responses (n=46) (p=0.436). An additional model including the four histopathological categories as separate covariates (no lymphocytic infiltrate vs. diffuse lymphocytic infiltrate vs. lymphocyte aggregates containing T cells vs. TLOs) was similarly not significant (p=0.879). The post-operative absolute OHS was not significantly different between histopathological categories.

#### 5.4.2.4 Subgroup analysis

Given 5 of the 8 re-revisions performed were in ARMD patients retaining a MoM hip bearing, it is possible that including the 16 hips revised to MoM bearings in the analysis could influence the results. Therefore a subgroup analysis (containing 48 MoM hips revised for ARMD with 3 re-revisions) was performed which excluded these 16 MoM hips.

The cumulative survival for revision hip arthroplasty performed for ARMD in this subgroup was 91.0% (95% CI 77.0%-100%) at 5-years (11 hips at risk). Further analysis demonstrated there were no significant pre-operative or intra-operative variables predictive of clinical outcomes following ARMD revision (for the variables listed in Table 5.3, p-values ranged from 0.105-1.00 for complications and from 0.070-1.00 for re-revision). Cox-proportional hazards models performed in the whole cohort

(n=64) were repeated for this subgroup (n=48). However in all instances the models were unstable due to only three re-revisions occurring during follow-up.

## 5.5 Discussion

Few studies have reported on outcomes following revision of MoM hip bearings for ARMD with most involving small cohorts limited by short-term follow-up (Chapter 4). The present study contributes to the literature by reporting clinical outcomes following 64 ARMD revisions at a mean 4.5 year follow-up. This study is also the first to attempt to support clinical decision-making in the management of ARMD patients by comprehensively examining factors available to clinicians around the time of revision.

Complication (20.3%) and re-revision rates (12.5%) in the present study are comparable to other studies reporting outcomes of revised ARMD hips (complication rates 4%-68% and re-revision rates 3%-38%) with similar indications for performing re-revisions [46,58,101-104]. One previous study had a longer follow-up time (61 months) and a larger cohort (90 hips) than the present report, with this study reporting the best clinical outcomes following ARMD revision [104]. These more promising results may be related to the performance of single component HR revisions which were associated with less surgical morbidity and shorter operative times [104]. Five-year survival for ARMD revision was 87.9% in the present study with no known radiological failures. Although these results may be considered acceptable after THR revision, they are less favourable compared to results for HR revisions performed for other indications [105-

107]. It is important surgeons are aware of the expected outcomes when counselling patients prior to ARMD revision surgery.

Functional outcomes were satisfactory in this series (median OHS 18.8% or 39.0/48) and comparable to our historical results for primary THR (median OHS 14.6% or 41.0/48) [67]. An earlier study reported significantly worse clinical and functional outcomes in HRs revised for pseudotumour compared to matched HRs revised for other indications and primary THR patients [46]. Liddle *et al.* also observed inferior outcomes in patients revised with solid pseudotumours [58]. In contrast, studies not observing such significant soft-tissue destruction at ARMD revision have reported more favourable outcomes [102,104], with one study finding the presence of soft-tissue fluid collections did not affect outcomes following revision [102]. The present study similarly failed to demonstrate worse outcomes in the presence of periprosthetic effusions, osteolysis, metallosis, soft-tissue damage, and tissue necrosis.

Contrary to the study hypothesis, ARMD patients with TLO structures did not have significantly worse outcomes following revision compared to patients revised with other histopathological responses. This remained the same when all four histopathological categories were analysed separately (rather than TLO vs. non-TLO hips). This additional analysis was performed to determine if there were any differences in clinical behaviour between categories. Therefore despite TLO structures observed in revised ARMD hips appearing similar histologically to those seen in other autoimmune

conditions [112], the clinical behaviour of these TLO structures appears to be different to that expected.

Retention of a MoM bearing was significantly more likely to require re-revision in this series than ARMD hips revised to non-MoM articulations. This was consistent with the study hypothesis that the persistence of MoM bearings following ARMD revision would adversely affect clinical outcomes. Some authors have observed good survival in patients receiving MoM bearings for ARMD [115]. However, most studies [39,58,104] support the present findings that MoM bearings are associated with higher re-revision rates. It is suspected the persistence of a MoM bearing provides a potential source of metal wear debris which perpetuates local tissue reactions. A recent study recommended revision of MoM hips for any indication should always include both sides of the bearing surface and result in a non-MoM bearing couple [58]. The present study observations support this recommendation.

The ARMD hips revised to MoM articulations were performed early in this series before ARMD was an established clinical entity [35,36,41]. The relevance of exchanging the articulating surfaces is highlighted by the fact that two of eight re-revisions performed in this series were for recurrent ARMD in which a MoM bearing was retained at the initial ARMD revision with no resolution of symptoms until the hips were re-revised to non-MoM articulations (Table 5.2). The remaining patients in this series with MoM hips in-situ are asymptomatic with good functional outcomes. Although the median blood cobalt concentration is raised in this subgroup, four patients

have bilateral MoM hip bearings with no ARMD lesions demonstrated on cross-sectional imaging. However these patients remain under regular clinical surveillance. Given that ARMD recurrence has been documented in patients revised to a MoP bearing [103], it is important to consider this condition in patients with MoP bearings not progressing as expected following ARMD revision. Of the 32 hips revised to MoP bearings, 28 remain in-situ (2 re-revisions and 2 deaths). There have been no complications in this subgroup, with no concerns about ARMD recurrence at latest follow-up (median OHS 25%). However, it is recognised these patients have not routinely undergone blood metal ion sampling and cross-sectional imaging which are required to diagnose ARMD recurrence.

Contralateral MoM hip bearings did not adversely affect outcomes following ARMD revision which was contrary to the study hypothesis. These findings are at variance with previous case reports demonstrating patients with bilateral MoM bearings can develop bilateral ARMD requiring revision surgery, with suggestion that a type IV immune response is responsible for these bilateral failures which develop after the implantation of the second MoM hip [116,117].

This study has some recognised limitations. As a retrospective study, it was subject to limitations such as data collection from the operative notes being dependent on the accuracy and terminology used by the recording individual. In addition some important pre-revision data were not available for analysis, namely acetabular component anteversion, blood metal ion concentrations, and OHSs, the latter of which would have

provided an assessment of change in function over time following revision surgery. It was also not routine practice at this centre to perform forensic analysis of explanted bearings which would have allowed an assessment of component wear to be made. Finally, although this case series is relatively large compared to previous studies (Chapter 4) it is recognised there was inadequate statistical power for some of the comparisons made. However obtaining larger patient cohorts would require a large multi-centre study with registry data not sufficient to answer the questions posed given the limited data set collected on each patient.

In conclusion, the present study demonstrated the short-term morbidity in a large cohort of patients undergoing ARMD revision at a single specialist centre was comparable to previous reports. Although revision to a MoM bearing provided good functional outcomes in non-revised patients, there was an association with higher re-revision rates when using this articulation in ARMD revision surgery. It is therefore recommended caution is exercised in the choice of bearing when revising MoM hip arthroplasties for ARMD.

# CHAPTER 6

# CONCLUSIONS

## 6.1 The role of metal-on-metal hip arthroplasty

The use of MoM bearings for hip arthroplasty in young and active patients has been an attractive concept due to low wear rates [11], greater range of hip motion, and a lower risk of dislocation [12,13]. Furthermore MoM HR has additional benefits including femoral bone conservation permitting easier revision in cases of HR failure, more normal gait patterns, and increased activity levels compared to conventional THR [118]. Recently the role of MoM hip arthroplasty has been questioned in light of ARMD and the high failure rates of certain MoM hip implants [35-38,41,55,119]. The present research aimed to determine the medium-term to long-term clinical outcomes following MoM HR and THR (Chapters 2 and 3).

Although a number of studies reported promising early clinical results following modern MoM HR [25-32], one of the designing surgeons acknowledged caution was needed with HR until long-term results were available [26]. Since these early reports it has become increasingly apparent that outcomes following HR are dependent on various patient, surgeon, and implant factors [13]. When these factors are optimised excellent long-term survival and functional outcomes can be achieved with MoM HR in young and active patients with hip arthritis (Chapter 2). This subgroup of patients has

traditionally experienced unsatisfactory long-term results with conventional THR [9,10, 59,60].

What has also become clear over recent years is that the indications for MoM HR are actually narrower than originally described [62]. Following a review of outcomes in 3095 BHRs McMinn *et al*. observed inferior 10-year survivorship in patients with a pre-operative diagnosis of developmental dysplasia of the hip (94%) and avascular necrosis of the femoral head (93%) compared to all other indications for HR (98%) [51]. These findings have recently been confirmed at 15-years following BHR, leading the authors to modify their indications for performing HR [51,120]. Although the present research confirms the promising outcomes following BHR extend into the second decade (94.1% survival at 14-years) the best results were achieved in patients with primary osteoarthritis (Chapter 2). Nearly half of all revised hips were in patients with diagnoses other than primary osteoarthritis, although only 32% of all BHRs were implanted for these indications (Chapter 2). On the basis of the results obtained by experienced surgeons when using the BHR for indications other than primary osteoarthritis and the findings that HRs performed for hip dysplasia are associated with an increased risk of ARMD [44], it is recommended arthroplasty options other than HR are considered for treating this subgroup of patients.

The BHR is one of the most commonly used MoM HR devices worldwide [61]. Its continued use is supported by reports from independent centres demonstrating good 10-

year survival of up to 94.5% (total of 1487 BHRs between the five studies) [52-54, 121,122]. The Conserve Plus (Wright Medical, Arlington, Tennessee, United States of America) is the only other HR device that has an established track record with the promising 10-year survivorship from the designing surgeon (88.5%) [123] supported by a recent independent report [124]. Contrary to the findings from designing HR surgeons [50,51,90,120,123], some reports from independent centres have suggested against performing HR in female patients [52,54]. When performed by the two designing surgeons BHR survival in females was 91.2% at 14-years (109 hips with primary osteoarthritis) (Chapter 2) and 91.5% at 15-years (335 hips with all diagnoses) [120]. The 10-year survival of BHRs implanted in females at independent centres ranges from 73.9% to 89.1% [52-54,121,122]. As these independent results in females are inferior to both the proposed revision rates from NICE for continued implant usage [80] and the results achieved with conventional THR in this patient subgroup [2], it is recommended HR is not performed in females at independent centres.

In light of the present evidence regarding the medium-term to long-term outcomes following MoM HR it is possible to define the indications for continued use. The implant must either be a BHR or Conserve Plus device. The surgeon must have sufficient experience with implanting HRs given the procedure is more technically demanding than conventional THR [76]. The patient must meet the previously described indications for HR (young and active, with adequate proximal femoral bone quality, and no renal function impairment) [62], but also have primary osteoarthritis and adequate femoral anatomy to allow the use of head sizes typically above 46 mm.

Surgeons at independent centres should only perform HR on male patients whilst designing surgeons may perform HR on both genders meeting the aforementioned selection criteria. On occasions experienced surgeons may wish to consider older patients for HR provided they are active and meet all other proposed indications. This is because chronological age was not originally cited as an absolute contraindication to HR [62], with good medium-term to long-term outcomes reported by designing surgeons in patients aged over 60-years [120,125].

Finally all patients considered appropriate for MoM HR must undergo thorough pre-operative counselling. This should include explanation of: (1) the unique complications of HR (such as femoral neck fracture), (2) the potential for wear related complications associated with MoM bearings requiring investigation with blood metal ion sampling and cross-sectional imaging with revision surgery needed in certain cases, and (3) the unknown potential long-term adverse risks of systemic metal ion exposure. Such comprehensive counselling will allow patients suitable for MoM HR to make informed decisions regarding their treatment.

By contrast there is sufficient evidence to suggest MoM THRs should not be implanted in the future. The NJR of England, Wales, and Northern Ireland reported cumulative 8-year survival of all uncemented MoM THRs of 84.5%, however for different implant designs this ranged from 56.7% to 88.9% [2]. Although the 8-year survival of 88.9% from the present research (Chapter 3) appears favourable compared to other MoM THR

designs, it is below NICE recommendations for continued implant usage [80]. The suboptimal outcomes of all modern large-diameter MoM THRs suggests although the concept is fundamentally flawed variations in implant design between devices can significantly affect survivorship. Further analysis of registry data demonstrated MoM THRs have increasing failure rates with larger femoral head sizes and significantly inferior survivorship compared to MoP and CoC THR [55]. The authors therefore recommended against the future use of stemmed MoM THRs [55]. Given the poor outcomes of modern MoM THR it is advised all patients with these devices remain under regular clinical surveillance according to published protocols [48]. It is suggested more frequent surveillance may be needed in patients with the poorest performing implant designs with surgeons also having a lower threshold for revision surgery in these cases.

Given the only future role of MoM hip arthroplasty is for a subgroup of patients meeting the refined selection criteria for HR, it follows that consideration is needed regarding the type of THR patients who would have previously undergone MoM hip arthroplasty should receive. Popular bearing surfaces include ceramic femoral heads with ceramic or highly cross-linked polyethylene liners or metal heads with highly cross-linked polyethylene liners. Although these THR bearing surfaces have promising outcomes at up to 10-years [78,79,126-128] they must be used with caution until long-term results are established given late modes of failure may occur which could alter the indications for bearing usage. Recently, the use of large-diameter CoC bearings has been recommended in place of poorly performing MoM THRs [55]. However in light of concerns that taper junction failures seen in MoM articulations may occur in non-MoM

large-diameter THRs [129], the widespread usage of large femoral head sizes is not recommended in this time of uncertainty.

Finally consideration should be given to modular THRs. A range of head-neck, neck-stem, and mid-stem modular THR systems are available to treat patients with complex anatomy. Almost all of the 460,000 primary and revision THRs performed in the United States in 2011 involved head-neck modularity with up to 8% involving both head-neck and neck-stem or mid-stem modularity [130]. Metal ion release and corrosion may occur at these modular junctions resulting in ARMD, even when using non-MoM bearing surfaces [86,131-133]. Modular implants should therefore not be recommended for routine primary THR, with guidance regarding patient follow-up in light of ARMD recently published [134].

### 6.2 Revision surgery for adverse reaction to metal debris

In 2009 poor short-term clinical outcomes were reported following revision of MoM HRs for pseudotumours [46]. With the revision burden for ARMD associated with MoM hips continuing to increase [2,58,102] and more recent observations that ARMD can occur in modular THRs with non-MoM bearings [86,132,133], it is important surgeons are aware of the expected outcomes following ARMD revision. The present research aimed to determine the clinical outcomes following revision of MoM HRs and THRs for ARMD, and identify factors predictive of outcomes (Chapters 4 and 5).

A systematic review demonstrated few studies have been published on outcomes following ARMD revision**,** especially for large-diameter MoM THRs, with outcomes variable between studies (Chapter 4). To supplement current evidence, outcomes were assessed in 64 MoM hips revised for ARMD at one centre, with similar complication (20.3%) and re-revision rates (12.5%) observed to previous studies at a mean 4.5 year follow-up (Chapter 5). Comprehensive analysis of pre-operative and intra-operative factors predictive of outcome demonstrated only revision to another MoM bearing was associated with significantly higher re-revision rates (Chapter 5). It is therefore recommended non-MoM bearings are used when performing ARMD revisions. Although the work presented is the first to attempt to support clinical decision-making in managing ARMD patients it is recognised it was limited by inadequate statistical power. For the Cox-proportional hazards model assessing the affect of a contralateral MoM bearing on re-revision risk (Chapter 5.4.2.1), it is estimated a minimum of 210 hips are needed in each group to have 80% statistical power (assuming an equal number of events in each group, an alpha of 0.05, and the null hypothesis that the hazard rates are equal). However such patient numbers can only be obtained in large multi-centre studies.

In addition to the present research (Chapter 5), repeating the systematic review up until 16$^{th}$ September 2014 with the same study inclusion criteria (Chapter 4.3.2) identified three further studies reporting outcomes following ARMD revision [135-137]. Su *et al*. assessed outcomes at a mean of 2.3 years following 55 HR revisions of which 22 were performed for ARMD or unexplained pain [135]. Short-term outcomes following revision were generally good, though patients revised for metal sensitivity and

unexplained pain had the poorest functional outcomes [135]. A more recent report of 35 HRs revised for ARMD demonstrated significant improvement in functional outcomes by six-months post-revision, though outcomes were not related to the severity of the histopathological response [136]. The third study assessed outcomes following revision of 114 monoblock MoM THRs with 51% of these performed for ARMD [137]. By contrast to the HR studies [135,136], complication (20%) and re-revision rates (16%) were high at only a mean follow-up of 14 months with greater morbidity observed in older patients [137]. The only study identified in the initial systematic review reporting outcomes following MoM THR revision for ARMD [103] similarly reported high complication and re-revisions rates at short-term follow-up (Table 4.3). Therefore, it is suspected outcomes following MoM THR revision for ARMD are inferior to those following HR revision for ARMD. This may be due to modular THR junctions having the potential to produce wear debris and the challenges which can be associated with femoral component removal and reconstruction. However further studies are needed to assess this in more detail.

There are two strategies which may reduce morbidity following ARMD revision. The first is considering all patients with MoM hips for early revision surgery. Previous recommendations for early surgical intervention were based on the premise that soft-tissue destruction is time-dependent [13,46,48]. Studies reporting on patients with more severe soft-tissue destruction [46,58] observed poorer outcomes compared to those not reporting significant soft-tissue problems [102,104]. However applying a strategy of early revision universally is not advisable as little is known about the natural history of

ARMD [93,94]. Therefore patients with MoM hip bearings may never develop ARMD but could be unnecessarily subjected to further surgery which itself is not without risk.

The second strategy to reduce morbidity following ARMD revision is to consider methods for reducing the risks of the main post-revision complications, namely dislocation, ARMD recurrence, and acetabular component loosening (Chapter 4). De Smet *et al*. observed a reduction in morbidity following HR revisions with the routine use of hip abduction braces and large non-metallic femoral heads [102]. However with concerns about taper wear with femoral head sizes over 36 mm it is recommended 36 mm may provide the best option [92,103]. Dual-mobility cups provide another option for dislocation prevention though long-term results are needed [138,139]. ARMD recurrence can be minimised by thorough debridement of all macroscopic metal wear debris and exchange to non-MoM bearings. The former may require specialists in pelvic and soft-tissue reconstruction which highlights the importance of thorough pre-revision planning. The extent of bone loss needs to be considered when planning acetabular reconstruction with revision implants chosen accordingly. However, given some patients have extensive bone loss at revision, newer implants which achieve better fixation in such situations require development.

### 6.3 Recommendations for future research

Further long-term clinical studies are required in patients undergoing HR, especially from independent centres. These studies should include the BHR and Conserve Plus

devices given that these two implant designs have the best reported results to date and therefore have potential for future use. Establishing survival and functional outcomes at over 15-years follow-up will assist in refining patient selection for HR and also identify if late modes of implant failure differ from those following THR.

Given the numerous reports relating to ARMD and MoM hip bearings it is recommended centres publish their outcomes following ARMD revision surgery, especially after MoM THR revision. It would be preferable to use a standard set of outcome measures in these reports such as those used in this systematic review (Chapter 4.3.4). More uniform reporting of outcomes would allow meta-analysis to be performed in the future. This will provide the large cohort of ARMD revisions with sufficient statistical power to identify prognostic factors of outcome, and therefore define the thresholds for performing ARMD revision surgery. Arthroplasty surgeons would subsequently have an evidence based tool for clinical decision making in patients with MoM hip replacements.

**APPENDIX 1** Further surgery questionnaire

Date .../ .../ .....  Hospital No. C201920

The Royal Orthopaedic Hospital NHS

NHS Trust

Research and Teaching Centre, Royal Orthopaedic Hospital,
Northfield, Birmingham, B31 2AP

# Further Surgery and Email

It would help us to know if you have had further surgery to your hip(s) after the first resurfacing operation.
Please circle the 'Yes / No' for each hip and tell us at which hospital this further surgery took place, even if this was at the Royal Orthopaedic Hospital.
Please return this form together with the *Hip Questionnaire* in the provided **pre-paid** envelope.

| **Left side** | |
|---|---|
| Have you had your left hip resurfaced? | Yes / No |
| If yes, have you had further surgery to your left hip after the resurfacing? | Yes / No |
| If yes, at which hospital did you have this further surgery? | ..... |

| **Right side** | |
|---|---|
| Have you had your right hip resurfaced? | Yes / No |
| If yes, have you had further surgery to your right hip after the resurfacing? | Yes / No |
| If yes, at which hospital did you have this further surgery? | ..... |

Also, if you have an email address and are happy for us to contact you by this method, please give the address in the space below.
Thank you.

My email address is _____

**APPENDIX 2** Oxford Hip Score questionnaire

**APPENDIX 3** University of California, Los Angeles Activity Score

Date .../ .../ ..... Hospital No..... Surname .....

## Royal Orthopaedic Hospital
## Birmingham

**APPENDIX 4** Letter sent to patients with metal-on-metal THRs

The Royal Orthopaedic Hospital NHS
NHS Foundation Trust

Date

(Name and address)

Dear (Patient),

Re: Metal-on-Metal Total Hip Joint Replacements

You may be aware of the recent media discussions about the safety of metal-on-metal hip replacements and resurfacings.

One type of hip resurfacing, the DePuy ASR, has had a higher than anticipated failure rate and as a consequence was withdrawn from use in September 2010. This resurfacing has never been used at the Royal Orthopaedic Hospital.

The Medicines and Healthcare Regulatory Authority (MHRA) has raised concerns regarding both metal on metal hip replacements and some resurfacings based on the poor results of some designs. Our records show that you have a DePuy Corail/Pinnacle total hip replacement.

If you already have a follow-up outpatient appointment booked within the next three months, you do not need to take any further action. If you do not have a follow-up appointment in the next three months please complete the enclosed forms and return them in the pre-paid envelope.

We will then make arrangements for you to have a blood test and updated x-ray and subsequent review appointment as appropriate. We are reviewing patients in accordance with national standards which have recently been changed to recommend an annual review and blood test.

We are committed to providing the best possible service for our patients. If you have any questions or queries about your hip surgery, please use the comments box on the questionnaire and we will be happy to address your concerns.

Yours sincerely

Mr xxxx xxxx FRCS

Individual surgeon

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