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**Long-Term Changes In Blood Metal Ion Levels In Patients
With Hip Resurfacing Implants: Implications for patient
surveillance after ten-years follow-up**

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Classifications:	Hip Replacement, Primary Arthroplasty, Biomaterials
Keywords:	metal-on-metal, hip resurfacing, metal ions, follow-up
Abstract:	<p>Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce.</p> <p>Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal ion measurements were identified at two large specialist European arthroplasty centres. After excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.</p> <p>Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%, chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar.</p> <p>Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.</p>

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4 1 **Long-Term Changes In Blood Metal Ion Levels In Patients With Hip**
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6 2 **Resurfacing Implants: Implications for patient surveillance after ten-**
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8 3 **years follow-up**

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47 25 **Conflict of interest**

49 26 The Author(s) declare(s) that there is no conflict of interest.

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56 30 for-profit sectors.

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3 31 **Abstract**
4

5 32 **Background:** Studies investigating changes in blood metal ion levels during the second decade of
6
7 33 the implant lifetime in MoM hip resurfacing patients are scarce.
8

9 34 **Methods:** Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface
10 35 Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal
11 36 ion measurements were identified at two large specialist European arthroplasty centres. After
12
13 37 excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an
14
15 38 increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt
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17 39 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.
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20 40 **Results:** We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and
21 41 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific
22 42 thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the
23
24 43 second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR
25
26 44 (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%,
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28 45 chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were,
29
30 46 however, uncommon during the second decade. Subgroup results with small diameter (<50 mm)
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32 47 implants were similar.
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34

35 48 **Conclusions:** We recommend less frequent blood metal-ion measurements are needed (every 3 to 5
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37 49 years) for hip resurfacing patients if initial values were below 7ppb.
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39 50 **Keywords:** metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt
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53 Introduction

54 High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip
55 replacements although some implants have demonstrated relatively good survival in the longer-term
56 in national joint registries (1,2) (3,4).

57
58 Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have
59 been published (2,5–7). The main issues for following up patients with MoM hips include the risk
60 stratification of patients, the frequency of follow-up assessments, and the actual screening methods
61 to use. In practice, the majority of patients receive blood metal ion testing with some form of hip
62 imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for
63 screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous
64 external validation which showed patients below these defined thresholds have a low risk of adverse
65 reaction to metal debris (ARMD) (8–10). The evidence-base for the guidelines are still limited, with
66 clear differences in the recommendations made by each regulatory authority (2). The cost-
67 effectiveness of these guidelines has also been questioned (11).

68
69 Most patients with their hip resurfacing (HR) still in situ are in the second decade of the implant
70 lifetime (4,5,13–15). However, no large studies have investigated how blood metal ion levels
71 change in the longer term, especially during the second decade after implantation. Most current
72 surveillance guidelines have no temporal stratification (3, 6, 8). Studies investigating changes in
73 blood metal ion levels during the second decade of the implant lifetime are needed to clarify the
74 specific role blood metal ion measurements play in the longer term follow-up of MoM HR patients.
75 Specifically, more research is needed on the patients with initially acceptable metal ion levels.
76 Patients with initially high metal ions are not an issue since these patients clearly need close
77 surveillance, more thorough diagnostic work-up and possible evaluation for revision (20).

78
79 We assessed patients with two commonly used MoM HR implant designs (Birmingham Hip
80 Resurfacing [BHR] and Articular Surface Replacement [ASR]) implanted at two specialist
81 arthroplasty centres. The study aims were to determine 1) the percentage of patients with initial
82 blood metal ion levels below previously devised thresholds whose subsequent metal ion levels were
83 above these thresholds during the second decade, 2) the prevalence of ± 2.15 parts per billion (ppb)
84 and ± 5.5 ppb changes in the long-term in serial whole blood metal ion levels, and 3) how blood
85 metal ion levels change with time in patients with repeated metal ion measurements.

86

87 **Materials**

89 *Study populations*

90 A cohort study of patients with BHR and ASR MoM HRs implanted at two large specialist
91 European arthroplasty centres was performed. All patients with either BHR or ASR implants and
92 three or more blood metal ion measurements during a follow-up of more than 10 years were
93 included for study analyses. From these patients we excluded those who had first metal ion levels
94 higher than 7 ppb (7). Focus in our study was patients with initially acceptable metal ion levels
95 since these patients are under frequent surveillance and in the need of repeated metal ion
96 measurements. Patients with initially elevated ion levels are usually referred for closer follow-up
97 and diagnostic work-up and changes in metal levels pose different kind of relevance compared to
98 patients with well-functioning implants. If a patient with bilateral implants had undergone a
99 unilateral revision we included only measurements taken whilst both implants were still in situ.
100 Selection of patients was based only on initial WB metal ion levels, follow-up time and availability
101 of measurements.

103 In center 1, 406 BHRs (357 patients) were implanted between January 2001 and February 2012. All
104 patients have been referred for whole blood (WB) cobalt (Co) and chromium (Cr) measurement and
105 clinical outcome was assessed using the Oxford Hip Score (OHS). All patients with elevated (>5
106 ppb) metal ion measurements or with any kind of hip related symptoms were referred for cross-
107 sectional imaging using MRI (16). Current protocol involves follow-up every two-years, which
108 includes WB Co and Cr, and OHS assessment. If the patient became symptomatic or metal ion
109 levels were above the 5 ppb threshold, patients underwent cross-sectional imaging and had an
110 appointment with a consultant orthopaedic surgeon.

112 Also in center 1, 497 ASR HRs (415 patients) were implanted between March 2003 and December
113 2009. Early surveillance and investigation of these patients has been described in detail previously
114 (17). After early intense screening, surveillance of ASR patients was changed in 2017 to that used
115 for BHR patients.

117 In center 2, there have been 3,990 BHRs (3,276 patients) implanted up until 30th April 2019. The
118 surveillance and investigation of these patients has been described in detail previously (9–11). In
119 summary, all symptomatic patients underwent WB metal ion sampling, radiographs and cross-
120 sectional imaging with either MRI and/or ultrasound. Asymptomatic patients with certain factors

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3 121 (such as female patients, males with small BHR head sizes, bilateral MoM implants, radiographic
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5 122 abnormalities) also underwent blood metal ion sampling, with targeted cross-sectional imaging used
6
7 123 if ions were raised and/or symptoms developed. All investigated patients remain under regular
8
9 124 surveillance, typically annually. No ASRs were implanted in center 2.
10 125

11 12 126 *Patient selection*

13
14 127 In center 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial Wb Co or Cr above
15 128 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore excluded. Of the remaining
16
17 129 patients, three or more blood metal ion level measurements were available for 194 BHR patients
18
19 130 (227 hips) with follow-up of more than 10 years (Figure 1). Similarly, of 415 ASR patients (497
20 131 hips), 54 patients (68 hips) had initial Wb Co or Cr above 7 ppb, (50 of 68 [74%] hips have been
21
22 132 revised since), and were excluded. Of the remaining patients, 216 (263 hips) have undergone three
23
24 133 or more metal ion measurements during follow-up of more than 10 years (Figure 2).
25
26 134

27 135 In center 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had undergone
28
29 136 any metal ion measurements. 418 patients (559 hips) had more than 3 measurements and 365
30
31 137 patients (481 hips) had initial measurement below 7 ppb. Of these 263 patients (328 hips) have
32
33 138 undergone three or more blood metal ion level measurements with follow-up of more than 10 years
34 139 (Figure 1).
35
36 140

37 38 141 *Assessment of metal ion level changes*

39 142 Previous studies have established implant specific thresholds in HR patients identifying those at low
40
41 143 risk of ARMD. The externally validated threshold for Co in unilateral patients is 2.15 ppb (11). We
42
43 144 applied the same threshold also for Cr in this study, although acknowledge this has not been
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45 145 formally validated, and therefore the findings for this study should focus on the Co levels in
46 146 unilateral patients. For bilateral patients externally validated threshold was 5.5 ppb for maximum of
47
48 147 Co or Cr (11). We applied this threshold also separately for both Co and Cr values. In this study, we
49
50 148 did two separate analyses to identify changes in metal ion measurements after 10 years or more
51
52 149 follow-up using these thresholds. Firstly, we investigated if each repeated measurement was more
53 150 than 2.15 ppb for unilateral patients while initial measurements in the first decade had been less
54
55 151 than 2.15 ppb. In bilateral patients we assessed change from below 5.5 ppb to above 5.5 ppb. This
56
57 152 was termed the absolute analysis since changes were assessed against the initial absolute level
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59 153 (Figure 3A). Secondly, we recorded relative changes or measurement-to-measurement change of
60 154 more than ± 2.15 ppb or ± 5.5 ppb for both implant groups. This was termed the relative analysis

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3 155 since we only assessed changes from measurement to measurement regardless of initial metal ion
4 156 level (Figure 3B). “Net change” was defined as the total sum of changes. This means that if the
5 157 patient had, for example, both -2.15 ppb and +2.15 ppb changes, there was no “net change”.
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8 158 Subgroup analysis was done in unilateral patients with a femoral head size under 50 mm.
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10 159

11 12 160 *Statistics*

13 161 Continuous variables were compared using Welch’s t-test when appropriate. Comparison of
14 162 continuous variables across three groups (BHRs in center 1, BHRs in center 2 and ASRs) was done
15 163 with analysis of variance. Proportions across two or three groups were compared using the Chi-
16
17 164 squared test with Yates correction. Association between time in-situ and metal ion levels was done
18
19 165 with generalized least squares linear model with random intercepts and fixed slopes. Full
20 166 description of this process is available in Supplement 1. Analysis was done with RStudio 1.2.5033.
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24 167

25 26 168 **Results**

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29 170 The final BHR study cohort included 359 patients with unilateral implants and 98 patients with
30 171 bilateral implants totaling 457 patients with 555 hips. There was a notable difference between the
31 172 institutions regarding distribution of femoral head size (Table 1). The ASR cohort included 169
32 173 patients with unilateral implants and 47 patients with bilateral implants totaling 263 hips. In total
33 174 there were 2743 WB metal ion measurements, of which 1645 had been done 10 or more years after
34 175 the index operation.
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40 41 177 *Absolute changes*

42 178 Absolute changes in relation to established implant specific thresholds are shown in Table 2. An
43 179 increase above implant specific threshold during second decade was seen in 10.8%-28.4% of the
44 180 unilateral patients. In bilateral patients increase was seen in 4.3%-11.8%.
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49 50 182 *Relative changes*

51 183 Table 3 shows the prevalence of ± 2.15 , ± 5.5 ppb measurement-to-measurement changes and “net
52 184 change” in metal ion levels performed after 10 years follow-up. Change of +2.15 ppb in either Co
53 185 or Cr levels was seen in 3.6-10% of unilateral BHR and ASR patients overall, however “net
54 186 change” was even less common. Change of +5.5 ppb were seen in 1.4-2.5% of unilateral BHR and
55 187 ASR patients overall, however “net change” was again even less common. In bilateral patients, +5.5
56 188 ppb change was also rarely seen (0 to 2.1%).
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Time effects

Population marginal effects are shown in Supplemental Figures 1-4. In center 1, Co levels reduced with time since index operation in patients with unilateral BHR implants and also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1A and 2A). Bilateral BHR patients also show metal ion levels reducing with time in the second decade (Supplemental Figure 4A). In center 2, metal ion levels increased with time since index operation in patients with unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table 1, Supplemental Figures 1B and 2B). Bilateral BHR patients showed a plateau (Supplemental figure 4B). In the ASR patients, increasing trends in metal ion levels with time were not seen (Supplemental Table 2, Supplemental Figure 3).

Discussion

Hundreds of thousands of patients with HRs are still in the need of regular follow-up. Studies assessing the roles for blood metal ion measurements and cross-sectional imaging are urgently needed to determine if regular monitoring for all HR patients is truly needed. We aimed to assess the population level changes in blood metal ion levels into the second decade. Patients at risk of failure and in need of closer follow-up, namely those with abnormal wear due to conditions such as edge-loading, are relatively straightforward to detect with initial screening. Our focus was especially on those patients having acceptable ion levels at initial screening and no abnormalities, who have been referred for more regular follow-up.

Generally, metal ion levels remained stable during the second decade of the implant lifetime. Relative changes (measurement-to-measurement) exceeding +5.5 ppb were uncommon. Major changes were not seen even in patients with small femoral head diameter implants. In center 2, one sixth (17.2%) of BHR patients had a relative increase of more than 2.15 ppb in WB Cr but only a few percent had an increase of greater than 5.5 ppb. A change in measurement-to-measurement in Wb Co was seen in 9.1% of BHR patients in center 2. Very similar results were reported by Van Der Straeten et al. who reported 4% prevalence with an increase of more than 2.5 ppb for serum Co at ten years follow-up (18). Overall prevalence in our study with a +2.15 ppb change in WB Co was 5%.

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3 222 Absolute changes in relation to fixed levels were similar to those seen in relative or measurement-
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5 223 to-measurement changes. We considered 2.15 ppb to be a clinically meaningful threshold for
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7 224 unilateral patients and 5.5 ppb for bilateral patients as per previous validation studies of these
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9 225 clinical thresholds (11). A change from below to above the threshold was seen in 4.3% to 28.4%
10 226 and this was most common in patients with unilateral implants. Up to a quarter of BHR patients had
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12 227 elevation of metal ion levels above the previously established threshold by the second decade,
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14 228 however the clinical significance of this requires further follow-up.

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17 230 Ion levels had negative association with time in one study center similar to that reported by Van Der
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19 231 Straeten et al, although they analyzed only unilateral patients (18). deSouza et al also reported
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21 232 results of serial metal ion measurements in a cohort of 53 patients with Corin HR implants (19).
22 233 They reported a slightly increasing trend in metal ion levels at ten-year follow-up. We noticed a
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24 234 decreasing trend also in bilateral patients which is a novel finding. These temporal effects were
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26 235 center dependent since associations were positive in our other study center. However, it is important
27 236 to see that these changes are negligible and even the upper limit of the confidence interval around
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29 237 these estimates remains below 5 ppb.

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33 239 Differences in metal ion trends between the study centers may be related to two separate reasons. It
34 240 is likely that the threshold for revision surgery due to ARMD differs between the study centers (20).
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36 241 Elevation in metal ion levels is always a relative indication for revision surgery but usually other
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38 242 factors such as symptoms and cross-sectional imaging findings are also considered as well. There
39 243 are no universal criteria for ARMD revision due to heterogeneity in clinical manifestation. It is
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41 244 therefore reasonable to assume that metal ion levels are valued differently in decision-making
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43 245 between study centers and hence different population trends are observed. It is of importance,
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45 246 however, that regardless of these varying indications the observed trends are not important from a
46 247 clinical perspective.

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50 249 ASR HR has been reported to have the poorest survival of all HR implant designs (4,5).
51 250 Interestingly, we observed decreasing population trends with time since index operation in metal
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53 251 ion levels in both unilateral and bilateral patients. Relative and absolute changes during the second
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55 252 decade were rare and similar to those seen in BHRs. The revision rate of ASR HRs in Center 1 has
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57 253 been approximately 30% at 10 years. Hence our results suggest that intense screening and high
58 254 revision rates have resulted in a situation where the majority of non-revised ASR HR patients have
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60 255 steady state wear and metal ion trends are similar to those seen in BHRs.

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5 257 The main strength of our multicenter study is the large number of patients with the largest number
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7 258 of analyzed metal ion measurements to date which extend into the second decade. The main
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9 259 limitation in our study is selection bias. All operated patients have not undergone regular metal ion
10 260 measurements and some patients have only one or two measurements. In Center 2 many BHR
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12 261 patients have no metal ion measurements at all. This is because Center 2 have a large cohort of male
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14 262 BHR patients who are asymptomatic and were not included in the recall for monitoring until 2017.
15 263 The BHR patients who have been monitored regularly at Center 2 are therefore the symptomatic
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17 264 patients, female patients and male patients with head sizes ≤ 46 mm, all of whom are at higher risk
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19 265 of ARMD than the unmonitored cohort of male asymptomatic patients who are likely to have low
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21 266 levels of metal ions. Metal ion trends were inferior in the BHR group which may seem
22 267 counterintuitive and biased. We did not, however, aim to predict theoretical behavior of metal ion
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24 268 levels. It is clear that implants with poor track-record have high revision rates, such as 30% in the
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26 269 ASR cohort in our study. Hence our results must be seen from pragmatic view: what is the behavior
27 270 of blood metal ion levels in well functioning implants not initially needing revision.
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31 272 Overall our results for BHR patients show that if initial blood metal ion measurements during the
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33 273 first decade are acceptable, the probability is high that ion levels will remain low in the second
34 274 decade. This also holds true for ASR patients, assuming a significant revision rate similar to the
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36 275 30% seen in our study group. These findings have major implications for the present worldwide
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38 276 regular surveillance for HR patients. Regular metal ion measurements (i.e. annual) therefore do not
39 277 seem reasonable if the initial values are below validated thresholds. We recommend less frequent
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41 278 blood metal-ion measurements are needed (every 3 to 5 years) for HR patients since only minor
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43 279 changes were seen after 10-year follow-up. Regulatory guidance stratifying implant surveillance
44
45 280 based solely on femoral head size does not seem useful with the BHR and ASR given temporal
46 281 metal ion changes.
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48 282 49 50 283 **References**

- 51
52 284 1. Reito A, Lainiala O, Elo P, Eskelinen A. Prevalence of Failure due to Adverse Reaction to
53
54 285 Metal Debris in Modern, Medium and Large Diameter Metal-on-Metal Hip Replacements--
55
56 286 The Effect of Novel Screening Methods: Systematic Review and Metaregression Analysis.
57 287 PLoS One. 2016 Mar 1;11(3):e0147872.
58
59
60

- 1
2
3 288 2. Lehtovirta L, Reito A, Parkkinen J, Peräniemi S, Vepsäläinen J, Eskelinen A. Association
4 between periprosthetic tissue metal content, whole blood and synovial fluid metal ion levels
5 289 and histopathological findings in patients with failed metal-on-metal hip replacement. PLoS
6 290 One. 2018 May 16;13(5):e0197614.
7 291
8
9
10
11 292 3. Pijls BG, Meessen JMTA, Tucker K, Stea S, Steenbergen L, Marie Fenstad A, et al. MoM
12 total hip replacements in Europe: a NORE report. EFORT Open Reviews. 2019 Jun
13 293 3;4(6):423–429.
14 294
15
16
17 295 4. National Joint Registry for England and Wales. NJR 16th Annual Report 2019.
18
19 296 5. Australian Orthopaedic Association National Joint Replacement Registry: Hip, Knee &
20 Shoulder Arthroplasty Annual Report 2019.
21 297
22
23 298 6. Information about Soft Tissue Imaging and Metal Ion Testing [Internet]. US Food & Drug
24 Administration; 2019 Mar [cited 2020 Jul 5]. Available from: [https://www.fda.gov/medical-](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
25 299 [devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
26 300 [testing](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
27 301
28 302
29
30
31 302 7. All metal-on-metal (MoM) hip replacements: updated advice for follow-up of patients' '.
32 Medicines and Healthcare products Regulatory Agency; 2017 Jun.
33 303
34
35 304 8. Metal-on-metal hip replacement implants: Information for general practitioners, orthopaedic
36 surgeons and other health professionals [Internet]. Therapeutic Goods Administration,
37 305 Australian Government; 2017 Jul [cited 2020 Jul 5]. Available from:
38 306 <https://www.tga.gov.au/metal-metal-hip-replacement-implants>
39
40 307
41
42 308 9. Matharu GS, Berryman F, Brash L, Pynsent PB, Dunlop DJ, Treacy RBC. Can blood metal
43 ion levels be used to identify patients with bilateral Birmingham Hip Resurfacings who are at
44 309 risk of adverse reactions to metal debris? Bone Joint J. 2016 Nov;98-B(11):1455–1462.
45
46 310
47
48 311 10. Matharu GS, Berryman F, Brash L, Pynsent PB, Treacy RBC, Dunlop DJ. The Effectiveness
49 of Blood Metal Ions in Identifying Patients with Unilateral Birmingham Hip Resurfacing and
50 312 Corail-Pinnacle Metal-on-Metal Hip Implants at Risk of Adverse Reactions to Metal Debris. J
51 Bone Joint Surg Am. 2016 Apr 20;98(8):617–626.
52 313
53 314
54
55
56 315 11. Matharu GS, Berryman F, Judge A, Reito A, McConnell J, Lainiala O, et al. Blood Metal Ion
57 316 Thresholds to Identify Patients with Metal-on-Metal Hip Implants at Risk of Adverse
58 Reactions to Metal Debris: An External Multicenter Validation Study of Birmingham Hip
59 317
60

- 1
2
3 318 Resurfacing and Corail-Pinnacle Implants. *J Bone Joint Surg Am.* 2017 Sep 20;99(18):1532–
4 1539.
5 319
6
7 320 12. Matharu GS, Mellon SJ, Murray DW, Pandit HG. Follow-Up of Metal-on-Metal Hip
8 Arthroplasty Patients Is Currently Not Evidence Based or Cost Effective. *J Arthroplasty.* 2015
9 321 Aug;30(8):1317–1323.
10 322
11 323 13. Moroni A, Miscione MT, Orsini R, Micera G, Mosca S, Sinapi F, et al. Clinical and
12 radiographic outcomes of the Birmingham Hip Resurfacing arthroplasty at a minimum
13 324 follow-up of 10 years: results from an independent centre. *Hip Int.* 2017 Mar 31;27(2):134–
14 325 139.
15 326
16 327 14. Matharu GS, McBryde CW, Pynsent WB, Pynsent PB, Treacy RBC. The outcome of the
17 328 Birmingham Hip Resurfacing in patients aged < 50 years up to 14 years post-operatively.
18 329 *Bone Joint J.* 2013 Sep;95-B(9):1172–1177.
19 330
20 331 15. Hunter TJA, Moores TS, Morley D, Manoharan G, Collier SG, Shaylor PJ. 10-year results of
21 332 the Birmingham Hip Resurfacing: a non-designer case series. *Hip Int.* 2018 Jan;28(1):50–52.
22 333
23 334 16. Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. Sensitivity and
24 335 specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal
25 336 hip replacement. *J Bone Joint Surg Br.* 2011 Oct;93(10):1308–1313.
26 337
27 338 17. Reito A, Puolakka T, Elo P, Pajamäki J, Eskelinen A. High prevalence of adverse reactions to
28 339 metal debris in small-headed ASR™ hips. *Clin Orthop Relat Res.* 2013 Sep;471(9):2954–
29 340 2961.
30 341
31 342 18. Van Der Straeten C, Van Quickenborne D, De Roest B, Calistri A, Victor J, De Smet K.
32 343 Metal ion levels from well-functioning Birmingham Hip Resurfacings decline significantly at
33 344 ten years. *Bone Joint J.* 2013 Oct;95-B(10):1332–1338.
34 345
35 346 19. deSouza RM, Parsons NR, Oni T, Dalton P, Costa M, Krikler S. Metal ion levels following
36 347 resurfacing arthroplasty of the hip: serial results over a ten-year period. *J Bone Joint Surg Br.*
37 348 2010 Dec;92(12):1642–1647.
38 349
39 350 20. Berber R, Skinner J, Board T, Kendoff D, Eskelinen A, Kwon YM, et al. International metal-
40 351 on-metal multidisciplinary teams: do we manage patients with metal-on-metal hip arthroplasty
41 352 in the same way? An analysis from the International Specialist Centre Collaboration on MOM
42 353 Hips (ISCCoMH). *Bone Joint J.* 2016 Feb;98-B(2):179–186.
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348 21. Matharu GS, Berryman F, Dunlop DJ, Judge A, Murray DW, Pandit HG. Has the threshold
349 for revision surgery for adverse reactions to metal debris changed in metal-on-metal hip
350 arthroplasty patients? A cohort study of 239 patients using an adapted risk-stratification
351 algorithm. *Acta Orthop.* 2019 Dec;90(6):530-536.

For Peer Review

353 **Table 1:** Comparison study groups between institutions.

		BHR cohort			ASR cohort	p-value for three group difference		
			Center 1	Center 2	p-value for difference			
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<.0001	54.3 (9.4)	<.0001	
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	.30	54.3 (8.3)	0.09	
	Bilateral - second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	.84	54.6 (8.4)	0.93	
Gender	Unilateral	Males	110	31	<.0001	117	<.0001	
		Females	51	167		52		
	Bilateral	Males	24	8	<.0001	36	<.0001	
		Females	9	57		11		
Femoral diameter	Unilateral	<43mm	3	48	<.0001	2	<.0001	
		44-45mm	1	0		7		
		46-47mm	28	100		25		
		48-49mm	1	0		14		
		50-51mm	51	38		24		
		52-53mm	58	11		46		
		54-55mm	19	1		26		
		56-57mm	0	0		18		
		58-59mm	0	0		5		
		≥60mm	0	0		2		
		Bilateral	<43mm	0		27		2
			44-45mm	0		3		4
			46-47mm	13		69		11
			48-49mm	0		0		9
50-51mm	25		24	11				
52-53mm	0		1	21				

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54-55mm	14	6	19
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56-57mm	0	0	9
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58-59mm	14	0	7
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>60mm	0	0	1

For Peer Review

357 **Table 2:** Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	Patients with at least one measurement above 2.15 ppb during 2nd decade
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	Patients with at least one measurement above 5.5 ppb during 2nd decade
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

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Table 3: Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. Small diameter means <50 mm head size.

			All BHR			Small diameter BHR			ASR	
			Overall	Center 1	Center 2	Overall	Center 1	Center 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb "net change"	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb "net change"	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
		Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)
-2.15 ppb change	10 (2.8%)		3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)	
+5.5 ppb change	6 (1.7%)		2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)	
-5.5 ppb change	1 (0.3%)		1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	
+2.15 ppb "net change"	31 (8.6%)		1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)	
+5.5 ppb "net change"	5 (1.4%)		1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)	
Bilateral	Cobalt		+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb "net change"	(0%)	(0%)	(0%)				1 (2.1%)	
		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)				2 (4.3%)
-2.15 ppb change	5 (5.1%)		0 (0%)	5 (7.7%)				0 (0%)		
+5.5 ppb change	1 (1%)		0 (0%)	1 (1.5%)				0 (0%)		
-5.5 ppb change	0 (0%)		0 (0%)	0 (0%)				0 (0%)		
+2.15 ppb "net change"	5 (5.1%)		0 (0%)	5 (7.7%)				2 (4.3%)		
+5.5 ppb "net change"	1 (1%)		0 (0%)	1 (1.5%)				0 (0%)		

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Figures

Figure 1: Flow chart for BHR patients

Figure 2: Flow chart for ASR patients

Figure 3: Explanation for A) absolute and B) relative change used in the analyses

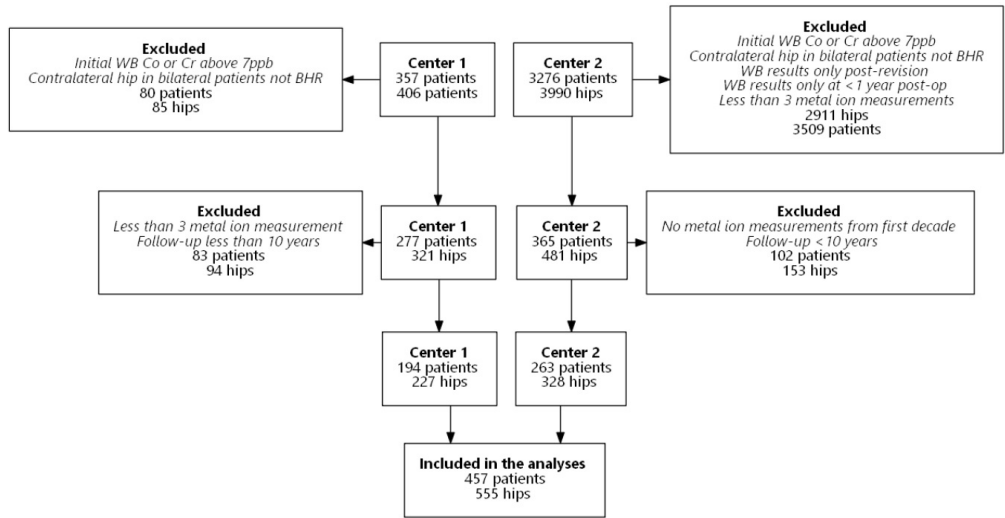
Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

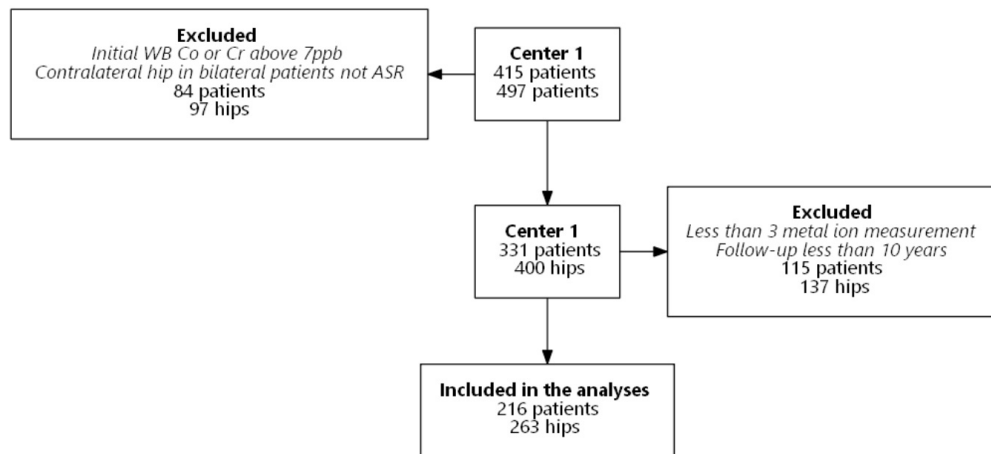
Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.

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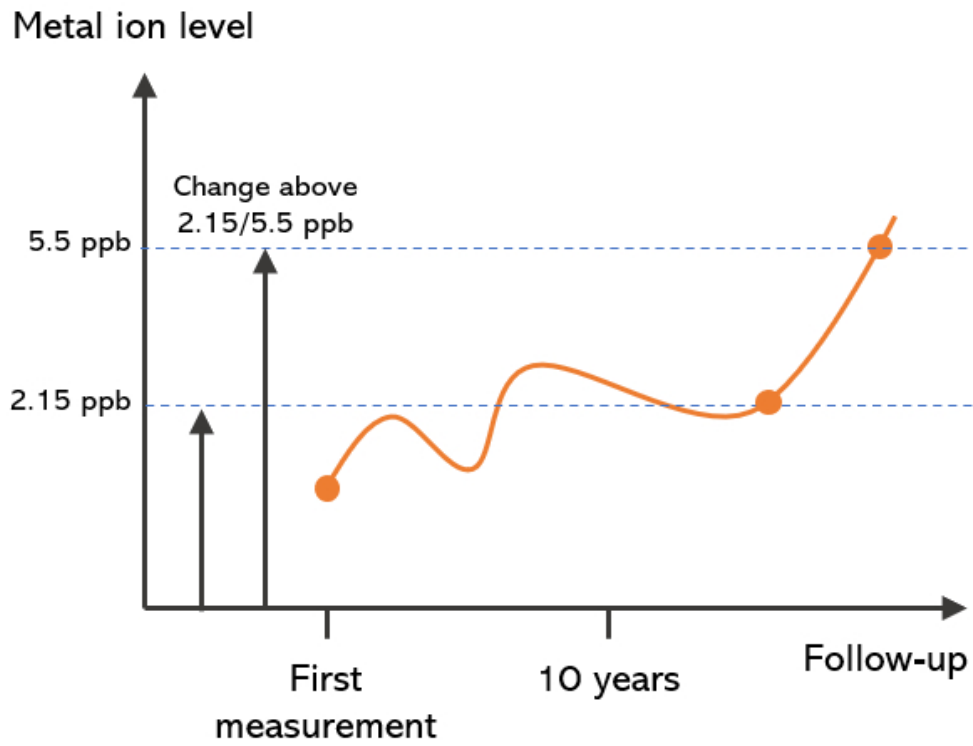
Flow chart for BHR patients
237x123mm (144 x 144 DPI)



Flow chart for ASR patients

237x109mm (144 x 144 DPI)

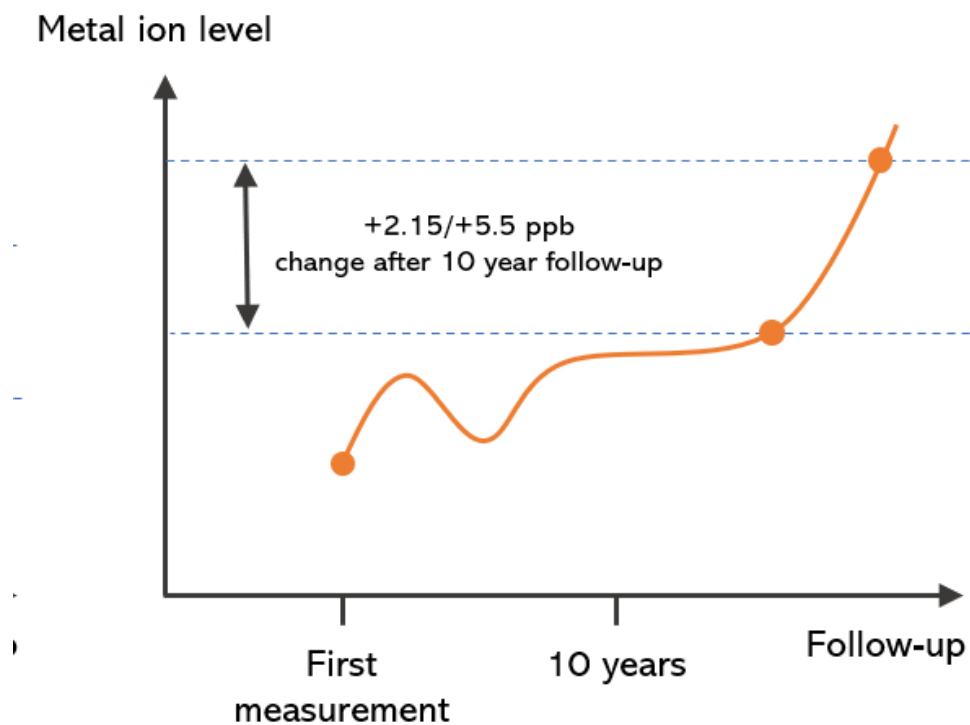
A) Absolute changes



Explanation for A) absolute and B) relative change used in the analyses

266x233mm (57 x 57 DPI)

B) Relative changes



Explanation for A) absolute and B) relative change used in the analyses

273x233mm (57 x 57 DPI)

Supplemental figures and tables

Supplemental Table 1: Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in BHR patients. AIC = Akaike's information criteria. Small diameter means <50 mm head size.

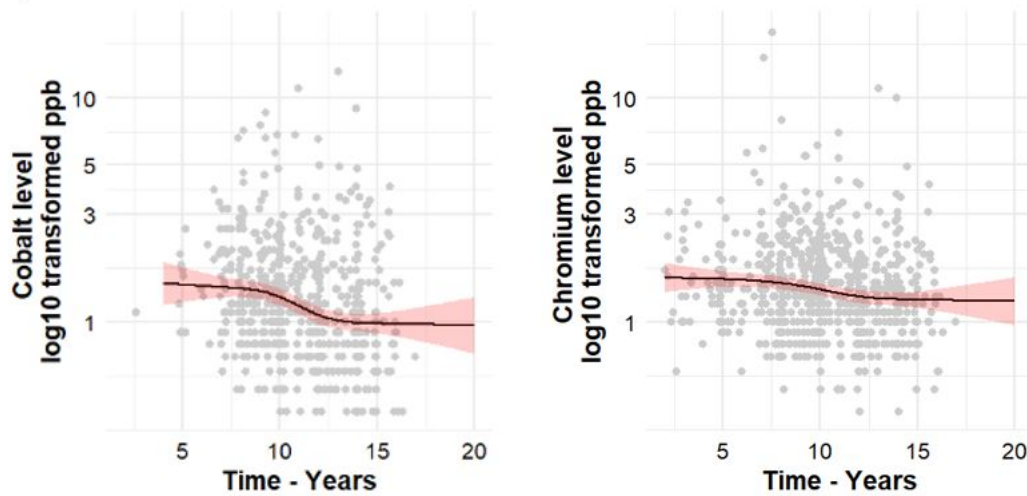
				Model 1	Model 2			
				β for time (95% CI)	AIC	AIC	p-value for nonlinearity	
Center 1	Unilateral	Cobalt	All patients	-0.020 (-0.026 to -0.014)	-366.5069	-327.75	0.013	
			Small diameter	-0.027 (-0.040 to -0.014)	-77.5	-86.30	0.64	
		Chromium	All patients	-0.010 (-0.016 to -0.0038)	-497.271	-492.11	0.006	
			Small diameter	-0.005 (-0.016 to -0.0069)	-115.34	-107.67	0.08	
	Bilateral	Cobalt	All patients	-0.015 (-0.024 to -0.0054)	-103.68	-91.42	0.70	
			Chromium	All patients	-0.097 (-0.021 to 0.0023)	-115.6838	-105.40	0.30
	Center 2	Unilateral	Cobalt	All patients	0.0094 (0.0036 to 0.015)	-113.8499	-87.48	0.010
				Small diameter	0.011 (0.0039 to 0.018)	-86.37	-87.48	0.0007
		Chromium	All patients	0.014 (0.008 to 0.020)	-153.152	-143.485	0.063	
			Small diameter	0.011 (0.004 to 0.018)	-147.172	-141.51	0.010	
Bilateral		Cobalt	All patients	0.0076 (0.0005 to 0.015)	-178.52	-199.16	0.14	
			Chromium	All patients	0.0015 (-0.0071 to 0.010)	-194.29	-209.3474	0.94

Supplemental Table 2 : Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in ASR patients. AIC = Akaike's information criteria. Small diameter means <50 mm head size.

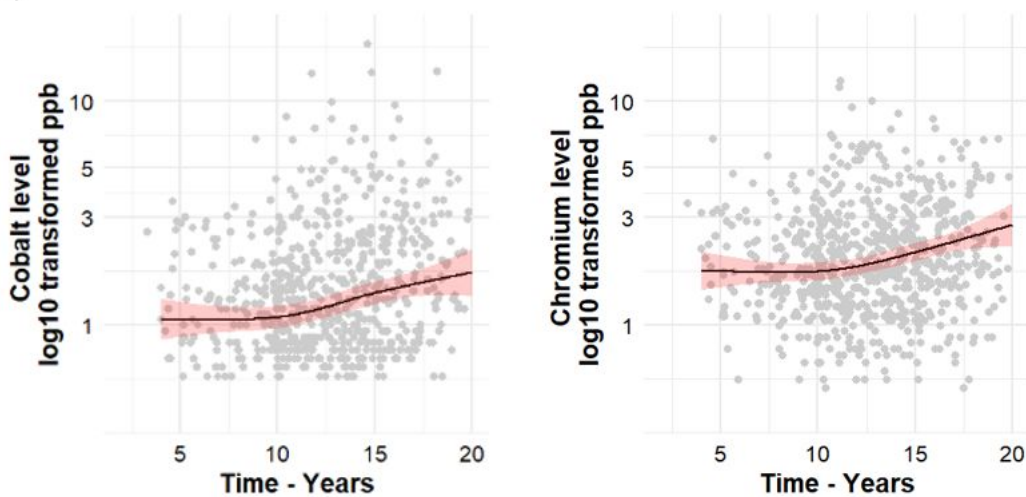
			Model 1	Model 2		p-value for model nonlinearity
			β for time (95% CI)	AIC	AIC	
Unilateral	Cobalt	All patients	-0.013 (-0.017 to -0.0090)	-179.74	-327.68	0.41
		Small diameter	-0.0036 (-0.010 to 0.0030)	-104.11	-94.95	0.72
	Chromium	All patients	-0.0048 (-0.0079 to -0.0017)	-656.01	-625.14	0.47
		Small diameter	0.0066 (0.0010 to 0.012)	-37.52	-34.23	0.08
Bilateral	Cobalt	All patients	-0.0088 (-0.015 to -0.0030)	-144.58	-137.48	0.28
	Chromium	All patients	-0.0057 (-0.011 to -0.0005)	-225.85	-171.27	0.27

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

A)



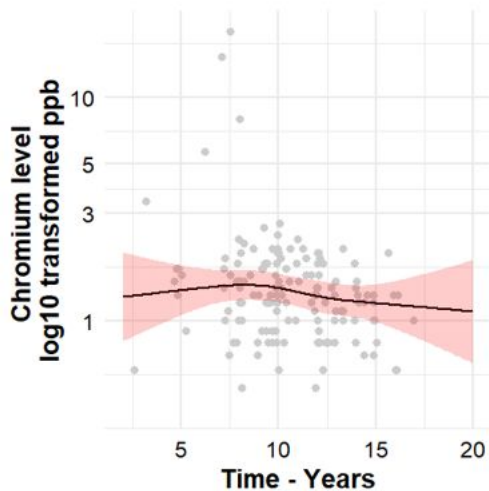
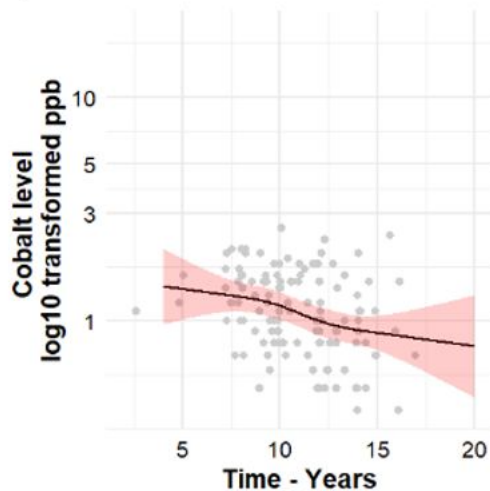
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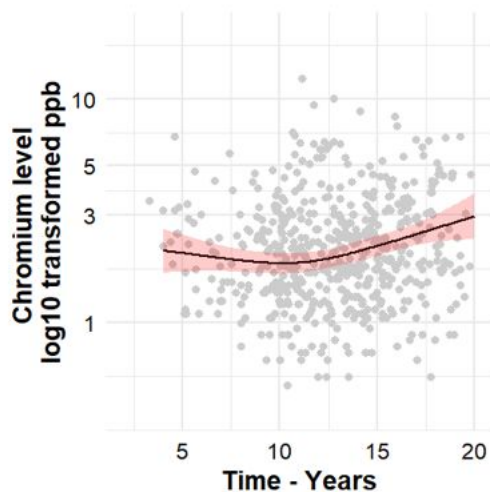
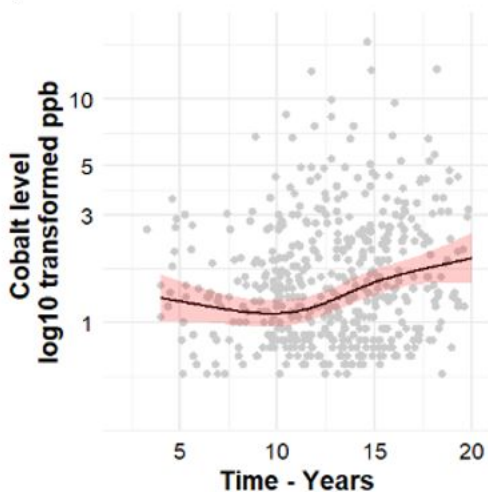
Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

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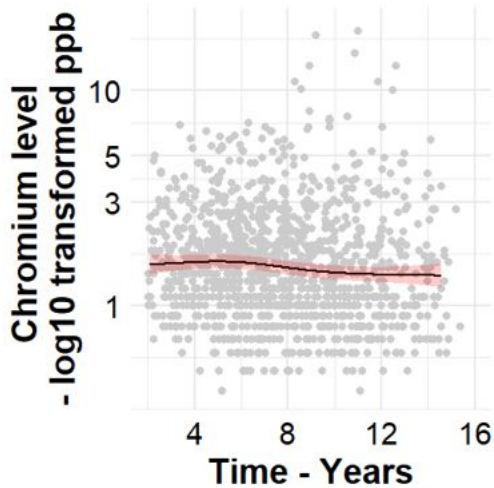
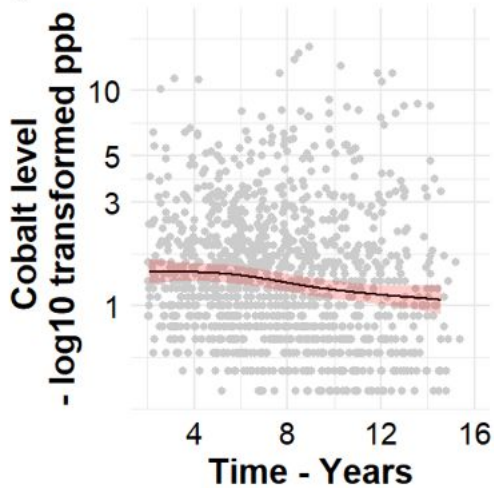


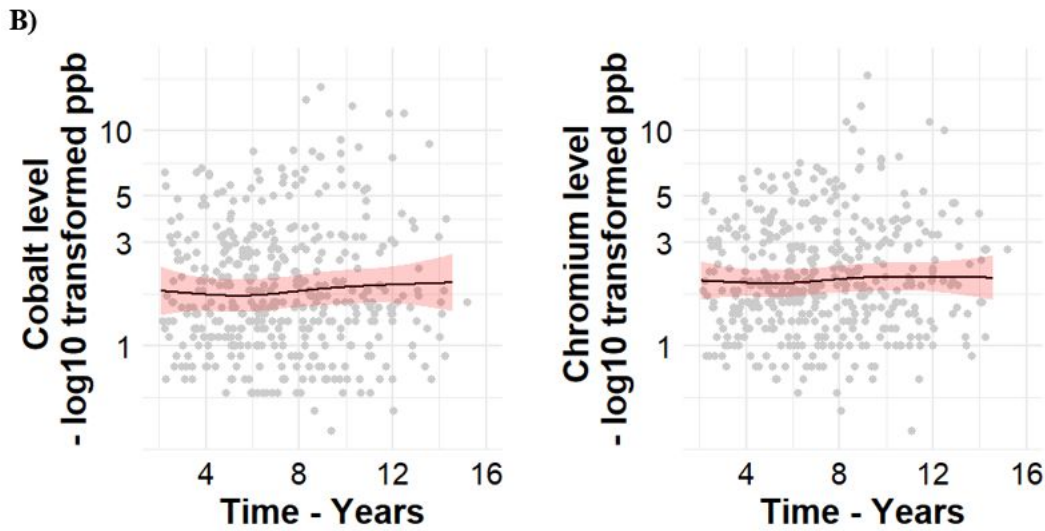
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Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in
A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

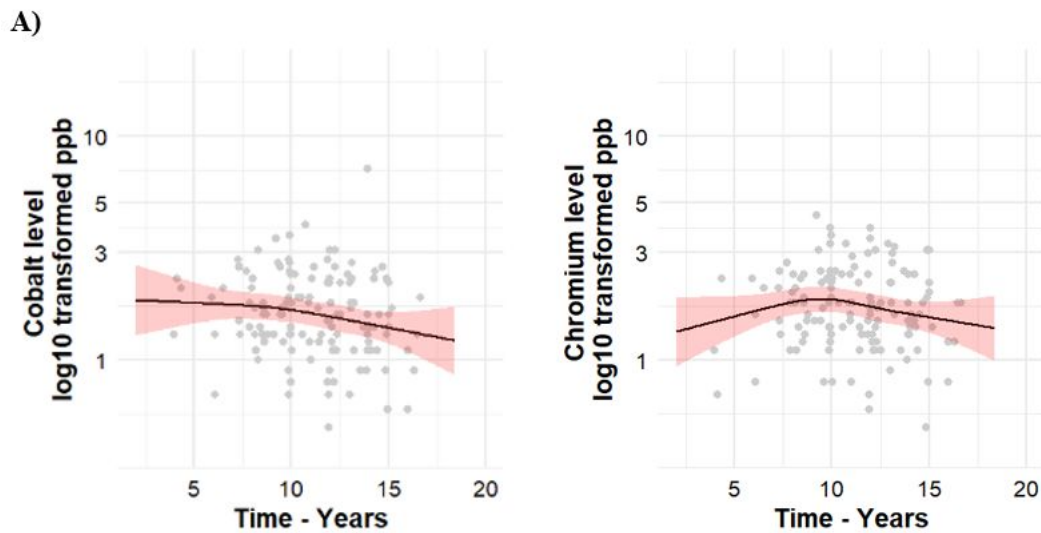
A)



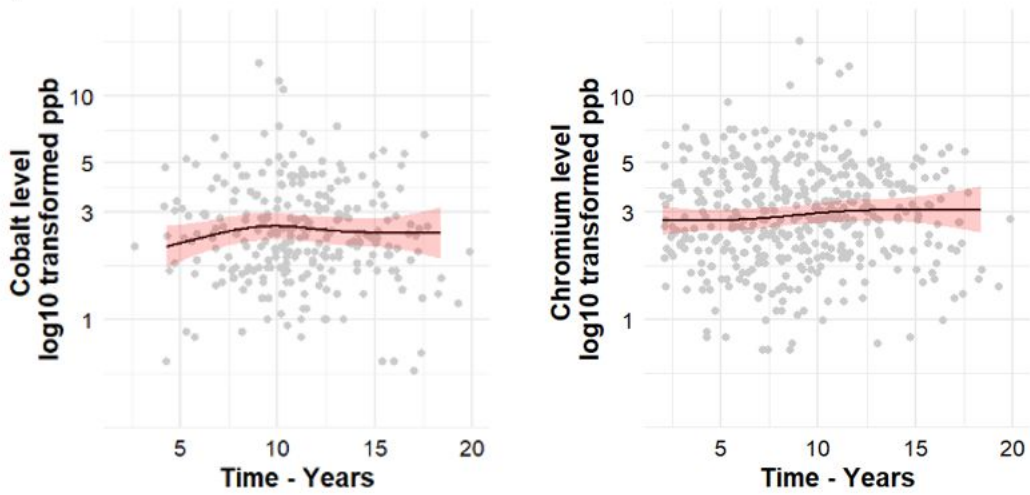


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Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.



B)



For Peer Review

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4 1 **Long-Term Changes In Blood Metal Ion Levels In Patients With Hip**
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6 2 **Resurfacing Implants: Implications for patient surveillance after ten-**
7
8 3 **years follow-up**

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1
2
3 **25 Abstract**
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5 **26 Background:** Studies investigating changes in blood metal ion levels during the second decade of
6
7 **27** the implant lifetime in MoM hip resurfacing patients are scarce.
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9
10 **28 Methods:** Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface
11 **29** Replacement (ASR) hip resurfacings with more than 10 years follow-up and repeated blood metal
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13 **30** ion measurements were identified at two large specialist European arthroplasty centres. After
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15 **31** excluding patients with initial metal ion levels above 7 ppb, the proportion of patients with an
16
17 **32** increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt
18
19 **33** 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.

20
21 **34 Results:** We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and
22
23 **35** 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific
24
25 **36** thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the
26
27 **37** second decade were seen as follows: unilateral BHR (cobalt=15.6%), unilateral ASR
28
29 **38** (cobalt=13.8%), bilateral BHR (cobalt=8.2%, chromium=11.8%), bilateral ASR (cobalt=8.5%,
30
31 **39** chromium=4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were,
32
33 **40** however, uncommon during the second decade. Subgroup results with small diameter (<50 mm)
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35 **41** implants were similar.

36
37 **42 Conclusions:** We recommend less frequent blood metal-ion measurements are needed (every 3 to 5
38
39 **43** years) for hip resurfacing patients if initial values were below 7ppb.

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41 **44 Keywords:** metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt
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47 **Introduction**

48 High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip
49 replacements although some implants have demonstrated relatively good survival in the longer-term
50 in national joint registries (1,2) (3,4).

51
52 Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have
53 been published (2,5–7). The main issues for following up patients with MoM hips include the risk
54 stratification of patients, the frequency of follow-up assessments, and the actual screening methods
55 to use. In practice, the majority of patients receive blood metal ion testing with some form of hip
56 imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for
57 screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous
58 external validation which showed patients below these defined thresholds have a low risk of adverse
59 reaction to metal debris (ARMD) (8–10). The evidence-base for the guidelines are still limited, with
60 clear differences in the recommendations made by each regulatory authority (2). The cost-
61 effectiveness of these guidelines has also been questioned (11).

62
63 Most patients with their hip resurfacing (HR) still in situ are in the second decade of the implant
64 lifetime (4,5,13–15). However, no large studies have investigated how blood metal ion levels
65 change in the longer term, especially during the second decade after implantation. Most current
66 surveillance guidelines have no temporal stratification (3, 6, 8). Studies investigating changes in
67 blood metal ion levels during the second decade of the implant lifetime are needed to clarify the
68 specific role blood metal ion measurements play in the longer term follow-up of MoM HR patients.
69 Specifically, more research is needed on the patients with initially acceptable metal ion levels.
70 Patients with initially high metal ions are not an issue since these patients clearly need close
71 surveillance, more thorough diagnostic work-up and possible evaluation for revision (20).

72
73 We assessed patients with two commonly used MoM HR implant designs (Birmingham Hip
74 Resurfacing [BHR, Smith & Nephew, London, United Kingdom] and Articular Surface
75 Replacement [ASR, DePuy/Johnson&Johnson, Leeds, United Kingdom]) implanted at two
76 specialist arthroplasty centres. The study aims were to determine 1) the percentage of patients with
77 initial blood metal ion levels below previously devised thresholds whose subsequent metal ion
78 levels were above these thresholds during the second decade, 2) the prevalence of ± 2.15 parts per
79 billion (ppb) and ± 5.5 ppb changes in the long-term in serial whole blood metal ion levels, and 3)
80 how blood metal ion levels change with time in patients with repeated metal ion measurements.

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Materials82
83*Study populations*

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85 A cohort study of patients with BHR and ASR MoM HRs implanted at two large specialist
86 European arthroplasty centres was performed. All patients with either BHR or ASR implants and
87 three or more blood metal ion measurements during a follow-up of more than 10 years were
88 included for study analyses. From these patients we excluded those who had first metal ion levels
89 higher than 7 ppb (7). Focus in our study was patients with initially acceptable metal ion levels
90 since these patients are under frequent surveillance and in the need of repeated metal ion
91 measurements. Patients with initially elevated ion levels are usually referred for closer follow-up
92 and diagnostic work-up and changes in metal levels pose different kind of relevance compared to
93 patients with well-functioning implants. If a patient with bilateral implants had undergone a
94 unilateral revision we included only measurements taken whilst both implants were still in situ.
95 Selection of patients was based only on initial WB metal ion levels, follow-up time and availability
96 of measurements.

97

98 In center 1, 406 BHRs (357 patients) were implanted between January 2001 and February 2012. All
99 patients have been referred for whole blood (WB) cobalt (Co) and chromium (Cr) measurement and
100 clinical outcome was assessed using the Oxford Hip Score (OHS). All patients with elevated (>5
101 ppb) metal ion measurements or with any kind of hip related symptoms were referred for cross-
102 sectional imaging using MRI (16). Current protocol involves follow-up every two-years, which
103 includes WB Co and Cr, and OHS assessment. If the patient became symptomatic or metal ion
104 levels were above the 5 ppb threshold, patients underwent cross-sectional imaging and had an
105 appointment with a consultant orthopaedic surgeon.

106

107 Also in center 1, 497 ASR HRs (415 patients) were implanted between March 2003 and December
108 2009. Early surveillance and investigation of these patients has been described in detail previously
109 (17). After early intense screening, surveillance of ASR patients was changed in 2017 to that used
110 for BHR patients.

111

112 In center 2, there have been 3,990 BHRs (3,276 patients) implanted up until 30th April 2019. The
113 surveillance and investigation of these patients has been described in detail previously (9–11). In
114 summary, all symptomatic patients underwent WB metal ion sampling, radiographs and cross-

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3 115 sectional imaging with either MRI and/or ultrasound. Asymptomatic patients with certain factors
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5 116 (such as female patients, males with small BHR head sizes, bilateral MoM implants, radiographic
6
7 117 abnormalities) also underwent blood metal ion sampling, with targeted cross-sectional imaging used
8
9 118 if ions were raised and/or symptoms developed. All investigated patients remain under regular
10 119 surveillance, typically annually. No ASRs were implanted in center 2.
11
12 120

13 121 *Patient selection*

15 122 In center 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial Wb Co or Cr above
16
17 123 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore excluded. Of the remaining
18
19 124 patients, three or more blood metal ion level measurements were available for 194 BHR patients
20
21 125 (227 hips) with follow-up of more than 10 years (Figure 1). Similarly, of 415 ASR patients (497
22 126 hips), 54 patients (68 hips) had initial Wb Co or Cr above 7 ppb, (50 of 68 [74%] hips have been
23
24 127 revised since), and were excluded. Of the remaining patients, 216 (263 hips) have undergone three
25
26 128 or more metal ion measurements during follow-up of more than 10 years (Figure 2).
27 129

29 130 In center 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had undergone
30
31 131 any metal ion measurements. 418 patients (559 hips) had more than 3 measurements and 365
32
33 132 patients (481 hips) had initial measurement below 7 ppb. Of these 263 patients (328 hips) have
34 133 undergone three or more blood metal ion level measurements with follow-up of more than 10 years
35
36 134 (Figure 1).
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38 135

39 136 *Assessment of metal ion level changes*

41 137 Previous studies have established implant specific thresholds in HR patients identifying those at low
42
43 138 risk of ARMD. The externally validated threshold for Co in unilateral patients is 2.15 ppb (11). We
44
45 139 applied the same threshold also for Cr in this study, although acknowledge this has not been
46 140 formally validated, and therefore the findings for this study should focus on the Co levels in
47
48 141 unilateral patients. For bilateral patients externally validated threshold was 5.5 ppb for maximum of
49
50 142 Co or Cr (11). We applied this threshold also separately for both Co and Cr values. In this study, we
51
52 143 did two separate analyses to identify changes in metal ion measurements after 10 years or more
53 144 follow-up using these thresholds. Firstly, we investigated if each repeated measurement was more
54
55 145 than 2.15 ppb for unilateral patients while initial measurements in the first decade had been less
56
57 146 than 2.15 ppb. In bilateral patients we assessed change from below 5.5 ppb to above 5.5 ppb. This
58
59 147 was termed the absolute analysis since changes were assessed against the initial absolute level
60 148 (Figure 3A). Secondly, we recorded relative changes or measurement-to-measurement change of

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2
3 149 more than ± 2.15 ppb or ± 5.5 ppb for both implant groups. This was termed the relative analysis
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5 150 since we only assessed changes from measurement to measurement regardless of initial metal ion
6
7 151 level (Figure 3B). “Net change” was defined as the total sum of changes. This means that if the
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9 152 patient had, for example, both -2.15 ppb and $+2.15$ ppb changes, there was no “net change”.
10 153 Subgroup analysis was done in unilateral patients with a femoral head size under 50 mm.
11

12 154

13 155 *Statistics*

15 156 Continuous variables were compared using Welch’s t-test when appropriate. Comparison of
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17 157 continuous variables across three groups (BHRs in center 1, BHRs in center 2 and ASRs) was done
18
19 158 with analysis of variance. Proportions across two or three groups were compared using the Chi-
20
21 159 squared test with Yates correction. Association between time in-situ and metal ion levels was done
22 160 with generalized least squares linear model with random intercepts and fixed slopes. Full
23
24 161 description of this process is available in Supplement 1. Analysis was done with RStudio 1.2.5033.
25

26 162

27 163 **Results**

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31 165 The final BHR study cohort included 359 patients with unilateral implants and 98 patients with
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33 166 bilateral implants totaling 457 patients with 555 hips. There was a notable difference between the
34 167 institutions regarding distribution of femoral head size (Table 1). The ASR cohort included 169
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36 168 patients with unilateral implants and 47 patients with bilateral implants totaling 263 hips. In total
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38 169 there were 2743 WB metal ion measurements, of which 1645 had been done 10 or more years after
39 170 the index operation.
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42 43 172 *Absolute changes*

44
45 173 Absolute changes in relation to established implant specific thresholds are shown in Table 2. An
46 174 increase above implant specific threshold during second decade was seen in 10.8%-28.4% of the
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48 175 unilateral patients. In bilateral patients increase was seen in 4.3%-11.8%.
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50 176

51 177 *Relative changes*

53 178 Table 3 shows the prevalence of ± 2.15 , ± 5.5 ppb measurement-to-measurement changes and “net
54
55 179 change” in metal ion levels performed after 10 years follow-up. Change of $+2.15$ ppb in either Co
56
57 180 or Cr levels was seen in 3.6-10% of unilateral BHR and ASR patients overall, however “net
58 181 change” was even less common. Change of $+5.5$ ppb were seen in 1.4-2.5% of unilateral BHR and
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3 182 ASR patients overall, however “net change” was again even less common. In bilateral patients, +5.5
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5 183 ppb change was also rarely seen (0 to 2.1%).
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9 185 *Time effects*

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11 186 Population marginal effects are shown in Supplemental Figures 1-4. In center 1, Co levels reduced
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13 187 with time since index operation in patients with unilateral BHR implants and also in patients with
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15 188 small headed BHR implants (Supplemental Table 1, Supplemental Figures 1A and 2A). Bilateral
16 189 BHR patients also show metal ion levels reducing with time in the second decade (Supplemental
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18 190 Figure 4A). In center 2, metal ion levels increased with time since index operation in patients with
19
20 191 unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table
21 192 1, Supplemental Figures 1B and 2B). Bilateral BHR patients showed a plateau (Supplemental figure
22
23 193 4B). In the ASR patients, increasing trends in metal ion levels with time were not seen
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25 194 (Supplemental Table 2, Supplemental Figure 3).
26
27 195

28 196 **Discussion**

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32 198 Hundreds of thousands of patients with HRs are still in the need of regular follow-up. Studies
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34 199 assessing the roles for blood metal ion measurements and cross-sectional imaging are urgently
35 200 needed to determine if regular monitoring for all HR patients is truly needed. We aimed to assess
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37 201 the population level changes in blood metal ion levels into the second decade. Patients at risk of
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39 202 failure and in need of closer follow-up, namely those with abnormal wear due to conditions such as
40 203 edge-loading, are relatively straightforward to detect with initial screening. Our focus was
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42 204 especially on those patients having acceptable ion levels at initial screening and no abnormalities,
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44 205 who have been referred for more regular follow-up.
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47 207 Generally, metal ion levels remained stable during the second decade of the implant lifetime.
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49 208 Relative changes (measurement-to-measurement) exceeding +5.5 ppb were uncommon. Major
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51 209 changes were not seen even in patients with small femoral head diameter implants. In center 2, one
52 210 sixth (17.2%) of BHR patients had a relative increase of more than 2.15 ppb in WB Cr but only a
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54 211 few percent had an increase of greater than 5.5 ppb. A change in measurement-to-measurement in
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56 212 Wb Co was seen in 9.1% of BHR patients in center 2. Very similar results were reported by Van
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58 213 Der Straeten et al. who reported 4% prevalence with an increase of more than 2.5 ppb for serum Co
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3 214 at ten years follow-up (18). Overall prevalence in our study with a +2.15 ppb change in WB Co was
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5 215 5%.

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8 217 Absolute changes in relation to fixed levels were similar to those seen in relative or measurement-
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10 218 to-measurement changes. We considered 2.15 ppb to be a clinically meaningful threshold for
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12 219 unilateral patients and 5.5 ppb for bilateral patients as per previous validation studies of these
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14 220 clinical thresholds (11). A change from below to above the threshold was seen in 4.3% to 28.4%
15 221 and this was most common in patients with unilateral implants. Up to a quarter of BHR patients had
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17 222 elevation of metal ion levels above the previously established threshold by the second decade,
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19 223 however the clinical significance of this requires further follow-up.

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22 225 Ion levels had negative association with time in one study center similar to that reported by Van Der
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24 226 Straeten et al, although they analyzed only unilateral patients (18). deSouza et al also reported
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26 227 results of serial metal ion measurements in a cohort of 53 patients with Corin HR implants (19).
27 228 They reported a slightly increasing trend in metal ion levels at ten-year follow-up. We noticed a
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29 229 decreasing trend also in bilateral patients which is a novel finding. These temporal effects were
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31 230 center dependent since associations were positive in our other study center. However, it is important
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33 231 to see that these changes are negligible and even the upper limit of the confidence interval around
34 232 these estimates remains below 5 ppb.

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37 234 Differences in metal ion trends between the study centers may be related to two separate reasons. It
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39 235 is likely that the threshold for revision surgery due to ARMD differs between the study centers (20).
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41 236 Elevation in metal ion levels is always a relative indication for revision surgery but usually other
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43 237 factors such as symptoms and cross-sectional imaging findings are also considered as well. There
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45 238 are no universal criteria for ARMD revision due to heterogeneity in clinical manifestation. It is
46 239 therefore reasonable to assume that metal ion levels are valued differently in decision-making
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48 240 between study centers and hence different population trends are observed. It is of importance,
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50 241 however, that regardless of these varying indications the observed trends are not important from a
51 242 clinical perspective.

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55 244 ASR HR has been reported to have the poorest survival of all HR implant designs (4,5).
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57 245 Interestingly, we observed decreasing population trends with time since index operation in metal
58 246 ion levels in both unilateral and bilateral patients. Relative and absolute changes during the second
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60 247 decade were rare and similar to those seen in BHRs. The revision rate of ASR HRs in Center 1 has

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3 248 been approximately 30% at 10 years. Hence our results suggest that intense screening and high
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5 249 revision rates have resulted in a situation where the majority of non-revised ASR HR patients have
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7 250 steady state wear and metal ion trends are similar to those seen in BHRs.

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10 252 The main strength of our multicenter study is the large number of patients with the largest number
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12 253 of analyzed metal ion measurements to date which extend into the second decade. The main
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14 254 limitation in our study is selection bias. All operated patients have not undergone regular metal ion
15 255 measurements and some patients have only one or two measurements. In Center 2 many BHR
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17 256 patients have no metal ion measurements at all. This is because Center 2 have a large cohort of male
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19 257 BHR patients who are asymptomatic and were not included in the recall for monitoring until 2017.
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21 258 The BHR patients who have been monitored regularly at Center 2 are therefore the symptomatic
22 259 patients, female patients and male patients with head sizes ≤ 46 mm, all of whom are at higher risk
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24 260 of ARMD than the unmonitored cohort of male asymptomatic patients who are likely to have low
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26 261 levels of metal ions. Metal ion trends were inferior in the BHR group which may seem
27 262 counterintuitive and biased. We did not, however, aim to predict theoretical behavior of metal ion
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29 263 levels. It is clear that implants with poor track-record have high revision rates, such as 30% in the
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31 264 ASR cohort in our study. Hence our results must be seen from pragmatic view: what is the behavior
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33 265 of blood metal ion levels in well functioning implants not initially needing revision.

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36 267 Overall our results for BHR patients show that if initial blood metal ion measurements during the
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38 268 first decade are acceptable, the probability is high that ion levels will remain low in the second
39 269 decade. This also holds true for ASR patients, assuming a significant revision rate similar to the
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41 270 30% seen in our study group. These findings have major implications for the present worldwide
42
43 271 regular surveillance for HR patients. Regular metal ion measurements (i.e. annual) therefore do not
44
45 272 seem reasonable if the initial values are below validated thresholds. We recommend less frequent
46 273 blood metal-ion measurements are needed (every 3 to 5 years) for HR patients since only minor
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48 274 changes were seen after 10-year follow-up. Regulatory guidance stratifying implant surveillance
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50 275 based solely on femoral head size does not seem useful with the BHR and ASR given temporal
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52 276 metal ion changes.

53 277 54 55 278 **References**

- 56
57 279 1. Reito A, Lainiala O, Elo P, Eskelinen A. Prevalence of Failure due to Adverse Reaction to
58
59 280 Metal Debris in Modern, Medium and Large Diameter Metal-on-Metal Hip Replacements--
60

- 1
2
3 281 The Effect of Novel Screening Methods: Systematic Review and Metaregression Analysis.
4 PLoS One. 2016 Mar 1;11(3):e0147872.
5 282
6
7 283 2. Lehtovirta L, Reito A, Parkkinen J, Peräniemi S, Vepsäläinen J, Eskelinen A. Association
8 between periprosthetic tissue metal content, whole blood and synovial fluid metal ion levels
9 284 and histopathological findings in patients with failed metal-on-metal hip replacement. PLoS
10 285 One. 2018 May 16;13(5):e0197614.
11 286
12
13 287 3. Pijls BG, Meessen JMTA, Tucker K, Stea S, Steenbergen L, Marie Fenstad A, et al. MoM
14 total hip replacements in Europe: a NORE report. EFORT Open Reviews. 2019 Jun
15 288 3;4(6):423–429.
16 289
17
18 290 4. National Joint Registry for England and Wales. NJR 16th Annual Report 2019.
19
20
21 291 5. Australian Orthopaedic Association National Joint Replacement Registry: Hip, Knee &
22 Shoulder Arthroplasty Annual Report 2019.
23 292
24
25 293 6. Information about Soft Tissue Imaging and Metal Ion Testing [Internet]. US Food & Drug
26 Administration; 2019 Mar [cited 2020 Jul 5]. Available from: [https://www.fda.gov/medical-](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
27 294 [devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
28 295 [testing](https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing)
29 296
30
31
32 297 7. All metal-on-metal (MoM) hip replacements: updated advice for follow-up of patients' '.
33 Medicines and Healthcare products Regulatory Agency; 2017 Jun.
34 298
35
36 299 8. Metal-on-metal hip replacement implants: Information for general practitioners, orthopaedic
37 surgeons and other health professionals [Internet]. Therapeutic Goods Administration,
38 Australian Government; 2017 Jul [cited 2020 Jul 5]. Available from:
39 300 <https://www.tga.gov.au/metal-metal-hip-replacement-implants>
40 301
41
42 302 9. Matharu GS, Berryman F, Brash L, Pynsent PB, Dunlop DJ, Treacy RBC. Can blood metal
43 ion levels be used to identify patients with bilateral Birmingham Hip Resurfacings who are at
44 303 risk of adverse reactions to metal debris? Bone Joint J. 2016 Nov;98-B(11):1455–1462.
45 304
46
47 305 10. Matharu GS, Berryman F, Brash L, Pynsent PB, Treacy RBC, Dunlop DJ. The Effectiveness
48 of Blood Metal Ions in Identifying Patients with Unilateral Birmingham Hip Resurfacing and
49 Corail-Pinnacle Metal-on-Metal Hip Implants at Risk of Adverse Reactions to Metal Debris. J
50 306 Bone Joint Surg Am. 2016 Apr 20;98(8):617–626.
51 307
52 308
53
54
55
56
57
58
59
60

- 1
2
3 310 11. Matharu GS, Berryman F, Judge A, Reito A, McConnell J, Lainiala O, et al. Blood Metal Ion
4 311 Thresholds to Identify Patients with Metal-on-Metal Hip Implants at Risk of Adverse
5 312 Reactions to Metal Debris: An External Multicenter Validation Study of Birmingham Hip
6 313 Resurfacing and Corail-Pinnacle Implants. *J Bone Joint Surg Am.* 2017 Sep 20;99(18):1532–
7 314 1539.
8
9
10
11
12 315 12. Matharu GS, Mellon SJ, Murray DW, Pandit HG. Follow-Up of Metal-on-Metal Hip
13 316 Arthroplasty Patients Is Currently Not Evidence Based or Cost Effective. *J Arthroplasty.* 2015
14 317 Aug;30(8):1317–1323.
15
16
17
18 318 13. Moroni A, Miscione MT, Orsini R, Micera G, Mosca S, Sinapi F, et al. Clinical and
19 319 radiographic outcomes of the Birmingham Hip Resurfacing arthroplasty at a minimum
20 320 follow-up of 10 years: results from an independent centre. *Hip Int.* 2017 Mar 31;27(2):134–
21 321 139.
22
23
24
25
26 322 14. Matharu GS, McBryde CW, Pynsent WB, Pynsent PB, Treacy RBC. The outcome of the
27 323 Birmingham Hip Resurfacing in patients aged < 50 years up to 14 years post-operatively.
28 324 *Bone Joint J.* 2013 Sep;95-B(9):1172–1177.
29
30
31
32 325 15. Hunter TJA, Moores TS, Morley D, Manoharan G, Collier SG, Shaylor PJ. 10-year results of
33 326 the Birmingham Hip Resurfacing: a non-designer case series. *Hip Int.* 2018 Jan;28(1):50–52.
34
35
36 327 16. Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. Sensitivity and
37 328 specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal
38 329 hip replacement. *J Bone Joint Surg Br.* 2011 Oct;93(10):1308–1313.
39
40
41
42 330 17. Reito A, Puolakka T, Elo P, Pajamäki J, Eskelinen A. High prevalence of adverse reactions to
43 331 metal debris in small-headed ASR™ hips. *Clin Orthop Relat Res.* 2013 Sep;471(9):2954–
44 332 2961.
45
46
47
48 333 18. Van Der Straeten C, Van Quickenborne D, De Roest B, Calistri A, Victor J, De Smet K.
49 334 Metal ion levels from well-functioning Birmingham Hip Resurfacings decline significantly at
50 335 ten years. *Bone Joint J.* 2013 Oct;95-B(10):1332–1338.
51
52
53
54 336 19. deSouza RM, Parsons NR, Oni T, Dalton P, Costa M, Krikler S. Metal ion levels following
55 337 resurfacing arthroplasty of the hip: serial results over a ten-year period. *J Bone Joint Surg Br.*
56 338 2010 Dec;92(12):1642–1647.
57
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51

52

53

54

55

56

57

58

59

60

- 339 20. Berber R, Skinner J, Board T, Kendoff D, Eskelinen A, Kwon YM, et al. International metal-
340 on-metal multidisciplinary teams: do we manage patients with metal-on-metal hip arthroplasty
341 in the same way? An analysis from the International Specialist Centre Collaboration on MOM
342 Hips (ISCCoMH). *Bone Joint J.* 2016 Feb;98-B(2):179–186.
- 343 21. Matharu GS, Berryman F, Dunlop DJ, Judge A, Murray DW, Pandit HG. Has the threshold
344 for revision surgery for adverse reactions to metal debris changed in metal-on-metal hip
345 arthroplasty patients? A cohort study of 239 patients using an adapted risk-stratification
346 algorithm. *Acta Orthop.* 2019 Dec;90(6):530-536.

For Peer Review

348 **Table 1:** Comparison study groups between institutions.

		BHR cohort			ASR cohort	p-value for three group difference		
			Center 1	Center 2	p-value for difference			
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<.0001	54.3 (9.4)	<.0001	
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	.30	54.3 (8.3)	0.09	
	Bilateral - second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	.84	54.6 (8.4)	0.93	
Gender	Unilateral	Males	110	31	<.0001	117	<.0001	
		Females	51	167		52		
	Bilateral	Males	24	8	<.0001	36	<.0001	
		Females	9	57		11		
Femoral diameter	Unilateral	<43mm	3	48	<.0001	2	<.0001	
		44-45mm	1	0		7		
		46-47mm	28	100		25		
		48-49mm	1	0		14		
		50-51mm	51	38		24		
		52-53mm	58	11		46		
		54-55mm	19	1		26		
		56-57mm	0	0		18		
		58-59mm	0	0		5		
		≥60mm	0	0		2		
		Bilateral	<43mm	0		27		2
			44-45mm	0		3		4
			46-47mm	13		69		11
			48-49mm	0		0		9
50-51mm	25		24	11				
52-53mm	0		1	21				

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>60mm	0	0	1

For Peer Review

352 **Table 2:** Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	Patients with at least one measurement above 2.15 ppb during 2nd decade
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	Patients with at least one measurement above 5.5 ppb during 2nd decade
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

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Table 3: Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. Small diameter means <50 mm head size.

			All BHR			Small diameter BHR			ASR	
			Overall	Center 1	Center 2	Overall	Center 1	Center 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb "net change"	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb "net change"	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
		Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)
-2.15 ppb change	10 (2.8%)		3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)	
+5.5 ppb change	6 (1.7%)		2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)	
-5.5 ppb change	1 (0.3%)		1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	
+2.15 ppb "net change"	31 (8.6%)		1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)	
+5.5 ppb "net change"	5 (1.4%)		1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)	
Bilateral	Cobalt		+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb "net change"	(0%)	(0%)	(0%)				1 (2.1%)	
		+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)				2 (4.3%)
-2.15 ppb change	5 (5.1%)		0 (0%)	5 (7.7%)				0 (0%)		
+5.5 ppb change	1 (1%)		0 (0%)	1 (1.5%)				0 (0%)		
-5.5 ppb change	0 (0%)		0 (0%)	0 (0%)				0 (0%)		
+2.15 ppb "net change"	5 (5.1%)		0 (0%)	5 (7.7%)				2 (4.3%)		
+5.5 ppb "net change"	1 (1%)		0 (0%)	1 (1.5%)				0 (0%)		

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Figures

361 **Figure 1:** Flow chart for BHR patients

362 **Figure 2:** Flow chart for ASR patients

363 **Figure 3:** Explanation for A) absolute and B) relative change used in the analyses

364 **Supplemental Figure 1:** Population marginal effect of time on log-transformed metal ion levels in
365 all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

366 **Supplemental Figure 2:** Population marginal effect of time on log-transformed metal ion levels
367 stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

368 **Supplemental Figure 3:** Population marginal effect of time on log-transformed metal ion levels in
369 A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

370 **Supplemental figure 4:** Population marginal effect of time on log-transformed metal ion levels
371 stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR
372 patients.

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3 **Long-term changes in blood metal ion levels in patients with hip**
4 **resurfacing implants: implications for patient surveillance after ~~ten~~10-**
5 **years follow-up**
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For Peer Review

Abstract

Background: Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime in MoM hip resurfacing patients are scarce.

Methods: Patients implanted with either Birmingham Hip Resurfacing (BHR) or Articular Surface Replacement (ASR) hip resurfacings with ~~more than~~ \geq 10 years follow-up and repeated blood metal ion measurements were identified at ~~two~~ \geq 2 large specialist European arthroplasty centres. After excluding patients with initial metal ion levels ~~above~~ \geq 7 ppb, the proportion of patients with an increase in blood metal ion levels above previously validated implant-specific thresholds (cobalt 2.15 ppb for unilateral implants, cobalt or chromium 5.5 ppb for bilateral) was assessed.

Results: We included 2743 blood metal ion measurements from 457 BHR patients (555 hips) and 216 ASR patients (263 hips). Of patients with initial metal ion levels below implant specific thresholds, increases in cobalt or chromium level, respectively, to above these thresholds during the second decade were seen as follows: unilateral BHR (cobalt = 15.6%), unilateral ASR (cobalt = 13.8%), bilateral BHR (cobalt = 8.2%, chromium = 11.8%), bilateral ASR (cobalt = 8.5%, chromium = 4.3%). Measurement-to-measurement changes exceeding +2.15 ppb or +5.5 ppb were, however, uncommon during the second decade. Subgroup results with small diameter (<50 mm) implants were similar.

Conclusions: We recommend less frequent blood metal-ion measurements are needed (every 3 to 5 years) for hip resurfacing patients if initial values were below 7ppb.

Keywords

~~Chrome, cobalt, follow-up, hip resurfacing, -metal-on-metal, hip resurfacing, metal ions, follow-up, chrome, cobalt~~

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For Peer Review

Introduction

High revision rates have resulted in gradual abandonment of metal-on-metal (MoM) hip replacements although some implants have demonstrated relatively good survival in the longer-term in national joint registries.¹⁻⁴ ~~(1,2) (3,4)~~.

Several follow-up guidelines regarding the surveillance of patients with MoM hip implants have been published.^{2,5-7} ~~(2,5-7)~~. The main issues for following up patients with MoM hips include the risk stratification of patients, the frequency of follow-up assessments, and the actual screening methods to use. In practice, the majority of patients receive blood metal ion testing with some form of hip imaging. While no single blood metal ion threshold offers both high sensitivity and specificity for screening MoM hip patients, certain previously reported ion thresholds have undergone rigorous external validation which showed patients below these defined thresholds have a low risk of adverse reaction to metal debris (ARMD).⁸⁻¹⁰ ~~(8-10)~~. The evidence-base for the guidelines are still limited, with clear differences in the recommendations made by each regulatory authority.² ~~(2)~~. The cost-effectiveness of these guidelines has also been questioned.¹¹ ~~(11)~~.

Most patients with their hip resurfacing (HR) still *in situ* are in the second decade of the implant lifetime.^{4,5,13-15} ~~(4,5,13-15)~~. However, no large studies have investigated how blood metal ion levels change in the longer term, especially during the second decade after implantation. Most current surveillance guidelines have no temporal stratification.^{3,6,8} ~~(3, 6, 8)~~. Studies investigating changes in blood metal ion levels during the second decade of the implant lifetime are needed to clarify the specific role blood metal ion measurements play in the longer-term follow-up of MoM HR patients. Specifically, more research is needed on the patients with initially acceptable metal ion levels. Patients with initially high

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3 metal ions are not an issue since these patients clearly need close surveillance, more
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5 thorough diagnostic work-up and possible evaluation for revision.²⁰ ~~(20)~~
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10 We assessed patients with ~~two~~2 commonly used MoM HR implant designs (Birmingham
11 Hip Resurfacing [BHR] and Articular Surface Replacement [ASR]) implanted at ~~two~~2
12 specialist arthroplasty centres. The study aims were to determine: (1) the percentage of
13 patients with initial blood metal ion levels below previously devised thresholds whose
14 subsequent metal ion levels were above these thresholds during the second decade; ~~(~~2)
15 the prevalence of ± 2.15 parts per billion (ppb) and ± 5.5 ppb changes in the long-term in
16 serial whole blood metal ion levels; ~~;~~3 and (3) how blood metal ion levels change with time in
17 patients with repeated metal ion measurements.
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33 **Materials**

34 *Study populations*

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38 A cohort study of patients with BHR and ASR MoM HRs implanted at ~~two~~2 large specialist
39 European arthroplasty centres was performed. All patients with either BHR or ASR
40 implants and ~~≥ 3 three or~~ more blood metal ion measurements during a follow-up of more
41 than 10 years were included for study analyses. From these patients we excluded those
42 who had first metal ion levels higher than 7 ppb.⁷ ~~(7)~~. Focus in our study was patients with
43 initially acceptable metal ion levels since these patients are under frequent surveillance
44 and in the need of repeated metal ion measurements. Patients with initially elevated ion
45 levels are usually referred for closer follow-up and diagnostic work-up and changes in
46 metal levels pose different kind of relevance compared to patients with well-functioning
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3 implants. If a patient with bilateral implants had undergone a unilateral revision, we
4 included only measurements taken whilst both implants were still *in situ*. Selection of
5 patients was based only on initial WB ([whole blood](#)) metal ion levels, follow-up time and
6 availability of measurements.
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14 In [Ceentreeer](#) 1, 406 BHRs (357 patients) were implanted between January 2001 and
15 February 2012. All patients have been referred for whole blood (WB) cobalt (Co) and
16 chromium (Cr) measurement and clinical outcome was assessed using the Oxford Hip
17 Score (OHS). All patients with elevated (>5 ppb) metal ion measurements or with any kind
18 of hip-related symptoms were referred for cross-sectional imaging using [magnetic](#)
19 [resonance imaging \(MRI\)](#).¹⁶-(16). Current protocol involves follow-up every ~~two~~ 2 years,
20 which includes WB Co and Cr, and OHS assessment. If the patient became symptomatic
21 or metal ion levels were above the 5 ppb threshold, patients underwent cross-sectional
22 imaging and had an appointment with a consultant orthopaedic surgeon.
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37 Also in [Ceentreeer](#) 1, 497 ASR HRs (415 patients) were implanted between March 2003
38 and December 2009. Early surveillance and investigation of these patients has been
39 described in detail previously.¹⁷-(17). After early intense screening, surveillance of ASR
40 patients was changed in 2017 to that used for BHR patients.
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49 In [eCentere](#) 2, there have been 3,990 BHRs (3,276 patients) implanted up until 30th April
50 2019. The surveillance and investigation of these patients has been described in detail
51 previously.⁹⁻¹¹-(9-11). In summary, all symptomatic patients underwent WB metal ion
52 sampling, radiographs and cross-sectional imaging with either MRI and/or ultrasound.
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58 Asymptomatic patients with certain factors (such as female patients, males with small BHR
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3 head sizes, bilateral MoM implants, radiographic abnormalities) also underwent blood
4 metal ion sampling, with targeted cross-sectional imaging used if ions were raised and/or
5 symptoms developed. All investigated patients remain under regular surveillance, typically
6 annually. No ASRs were implanted in eCentere r-2.

16 17 *Patient selection*

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19 In Ceentreeer 1, of the 357 BHR patients (406 hips), 26 patients (29 hips) had initial WBb
20 Co or Cr above 7 ppb, (23 of 29 [79%] hips have been revised since) and were therefore
21 excluded. Of the remaining patients, ≥3 three or more blood metal ion level measurements
22 were available for 194 BHR patients (227 hips) with follow-up of more than >-10 years
23 (Figure 1). Similarly, of 415 ASR patients (497 hips), 54 patients (68 hips) had initial WBb
24 Co or Cr above 7 ppb, (50 of 68 [74%] hips have been revised since), and were excluded.
25 Of the remaining patients, 216 (263 hips) have undergone ≥3 three or more metal ion
26 measurements during follow-up of more than >-10 years (Figure 2).

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42 [Figure 1. Flow chart for BHR patients.]

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47 [Figure 2. Flow chart for ASR patients.]

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51 In Ceentere 2, of 3276 BHR patients (3990 hips), a total of 1396 patients (1834 hips) had
52 undergone any metal ion measurements. 418 patietnspatients (559 hips) had more than >
53 3 measurements and 365 patients (481 hips) had initial measurement below ≤7 ppb. Of
54 these 263 patients (328 hips) have undergone ≥3 three or more blood metal ion level
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3 measurements with follow-up ~~of more than~~ \geq -10 years (Figure 1).
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10 *Assessment of metal ion level changes*

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13 Previous studies have established implant specific thresholds in HR patients identifying
14 those at low risk of ARMD. The externally validated threshold for Co in unilateral patients
15 is 2.15 ppb.~~11-(11)~~. We applied the same threshold also for Cr in this study, although
16 acknowledging this has not been formally validated, and therefore the findings for this
17 study should focus on the Co levels in unilateral patients. For bilateral patients externally
18 validated threshold was 5.5 ppb for maximum of Co or Cr.~~11-(11)~~. We applied this
19 threshold also separately for both Co and Cr values. In this study, we did ~~two~~ 2 separate
20 analyses to identify changes in metal ion measurements after 10 years or more follow-up
21 using these thresholds. Firstly, we investigated if each repeated measurement was ~~more~~
22 ~~than~~ \geq -2.15 ppb for unilateral patients while initial measurements in the first decade had
23 been ~~less than~~ \leq -2.15 ppb. In bilateral patients we assessed change from ~~below~~ \leq 5.5 ppb
24 to ~~above~~ \geq 5.5 ppb. This was termed the absolute analysis since changes were assessed
25 against the initial absolute level (Figure 3(A)). Secondly, we recorded relative changes or
26 measurement-to-measurement change of more than \pm 2.15 ppb or \pm 5.5 ppb for both
27 implant groups. This was termed the relative analysis since we only assessed changes
28 from measurement to measurement regardless of initial metal ion level (Figure 3(B)). “Net
29 change” was defined as the total sum of changes. This means that if the patient had, for
30 example, both -2.15 ppb and +2.15 ppb changes, there was no “net change”. Subgroup
31 analysis was done in unilateral patients with a femoral head size ~~under~~ \leq 50 mm.
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3 **[Figure 3. Explanation for (A) absolute and (B) relative change used in the analyses.]**
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10 **Statistics**

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16 Continuous variables were compared using Welch's *t*-test when appropriate. Comparison
17 of continuous variables across three groups (BHRs in Ceentere 1, BHRs in Ceentere 2 and
18 ASRs) was done with analysis of variance. Proportions across ~~two or three~~ 2 or 3 groups
19 were compared using the ~~c~~Chi-squared test with Yates correction. Association between
20 time *in-situ* and metal ion levels was done with generaliszed least squares linear model
21 with random intercepts and fixed slopes. Full description of this process is available in
22 Supplement 1. Analysis was done with RStudio 1.2.5033.
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37 **Results**

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41 The final BHR study cohort included 359 patients with unilateral implants and 98 patients
42 with bilateral implants totaling 457 patients with 555 hips. There was a notable difference
43 between the institutions regarding distribution of femoral head size (Table 1). The ASR
44 cohort included 169 patients with unilateral implants and 47 patients with bilateral implants
45 totaling 263 hips. In total there were 2743 WB metal ion measurements, of which 1645
46 had been done ≥ 10 ~~or more~~ years after the index operation.
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Absolute changes

Absolute changes in relation to established implant specific thresholds are shown in Table 2. An increase above implant specific threshold during second decade was seen in 10.8%–28.4% of the unilateral patients. In bilateral patients increase was seen in 4.3%–11.8%.

Relative changes

Table 3 shows the prevalence of ± 2.15 , ± 5.5 ppb measurement-to-measurement changes and “net change” in metal ion levels performed after 10 years follow-up. Change of +2.15 ppb in either Co or Cr levels was seen in 3.6–10% of unilateral BHR and ASR patients overall, however “net change” was even less common. Change of +5.5 ppb were seen in 1.4–2.5% of unilateral BHR and ASR patients overall, however “net change” was again even less common. In bilateral patients, +5.5 ppb change was also rarely seen (0 to 2.1%).

Time effects

Population marginal effects are shown in Supplemental Figures 1–4. In Center 1, Co levels reduced with time since index operation in patients with unilateral BHR implants and also in patients with small headed BHR implants (Supplemental Table 1) (Supplemental Figures 1(A) and 2(A)). Bilateral BHR patients also show metal ion levels reducing with time in the second decade (Supplemental Figure 4(A)). In Center 2, metal ion levels increased with time since index operation in patients with unilateral BHR implants and, also in patients with small headed BHR implants (Supplemental Table 1) (Supplemental

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3 Figures 1(B) and 2(B)). Bilateral BHR patients showed a plateau (Supplemental Figure
4 4(B)). In the ASR patients, increasing trends in metal ion levels with time were not seen
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6 (Supplemental Table 2;) (Supplemental Figure 3).
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14 Discussion

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19 Hundreds of thousands of patients with HRs are still in the need of regular follow-up.
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21 Studies assessing the roles for blood metal ion measurements and cross-sectional
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23 imaging are urgently needed to determine if regular monitoring for all HR patients is truly
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25 needed. We aimed to assess the population level changes in blood metal ion levels into
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27 the second decade. Patients at risk of failure and in need of closer follow-up, namely those
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29 with abnormal wear due to conditions such as edge-loading, are relatively straightforward
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31 to detect with initial screening. Our focus was especially on those patients having
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33 acceptable ion levels at initial screening and no abnormalities, who have been referred for
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35 more regular follow-up.
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42 Generally, metal ion levels remained stable during the second decade of the implant
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44 lifetime. Relative changes (measurement-to-measurement) exceeding +5.5 ppb were
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46 uncommon. Major changes were not seen even in patients with small femoral head
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48 diameter implants. In Ceentere 2, ~~1/6 one sixth~~ (17.2%) of BHR patients had a relative
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50 increase of ~~more than~~ \geq -2.15 ppb in WB Cr but only a few percent had an increase of
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52 ~~greater than~~ \geq -5.5 ppb. A change in measurement-to-measurement in WB Co was seen in
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54 9.1% of BHR patients in eCentere 2. Very similar results were reported by Van Der
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56 Straeten et al.¹⁸ who reported 4% prevalence with an increase of ~~more than~~ \geq 2.5 ppb for
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3 serum Co at ~~ten-10~~ years follow-up ~~(18)~~. Overall prevalence in our study with a +2.15 ppb
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5 change in WB Co was 5%.
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10 Absolute changes in relation to fixed levels were similar to those seen in relative or
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12 measurement-to-measurement changes. We considered 2.15 ppb to be a clinically
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14 meaningful threshold for unilateral patients and 5.5 ppb for bilateral patients as per
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16 previous validation studies of these clinical thresholds ~~.11-(11)~~. A change from below to
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18 above the threshold was seen in 4.3% ~~to~~ 28.4% and this was most common in patients
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20 with unilateral implants. Up to a ~~1/4quarter~~ of BHR patients had elevation of metal ion levels
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22 above the previously established threshold by the second decade, however the clinical
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24 significance of this requires further follow-up.
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30 Ion levels had negative association with time in ~~one-1~~ study center ~~e~~ similar to that reported
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32 by Van Der Straeten et al. ~~,18~~ although they analy~~s~~ed only unilateral patients ~~(18)~~.
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34 deSouza et al. ~~19~~ also reported results of serial metal ion measurements in a cohort of 53
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36 patients with Corin HR implants ~~(19)~~. They reported a slightly increasing trend in metal ion
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38 levels at ~~10-ten~~-year follow-up. We noticed a decreasing trend also in bilateral patients
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40 which is a novel finding. These temporal effects were center ~~e~~ dependent since
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42 associations were positive in our other study center ~~center~~. However, it is important to see
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44 that these changes are negligible and even the upper limit of the confidence interval
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46 around these estimates remains ~~below~~ ~~<~~5 ppb.
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53 Differences in metal ion trends between the study center ~~e~~s may be related to ~~two-2~~
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55 separate reasons. It is likely that the threshold for revision surgery due to ARMD differs
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57 between the study center ~~e~~s ~~.20-(20)~~. Elevation in metal ion levels is always a relative
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3 indication for revision surgery but usually other factors such as symptoms and cross-
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5 sectional imaging findings are also considered as well. There are no universal criteria for
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7 ARMD revision due to heterogeneity in clinical manifestation. It is therefore reasonable to
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9 assume that metal ion levels are valued differently in decision-making between study
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11 centeres and hence different population trends are observed. It is of importance, however,
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13 that regardless of these varying indications the observed trends are not important from a
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15 clinical perspective.
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21 ASR HR has been reported to have the poorest survival of all HR implant designs.^{4,5} ~~(4,5)~~.
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23 Interestingly, we observed decreasing population trends with time since index operation in
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25 metal ion levels in both unilateral and bilateral patients. Relative and absolute changes
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27 during the second decade were rare and similar to those seen in BHRs. The revision rate
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29 of ASR HRs in CCentere 1 has been approximately 30% at 10 years. Hence our results
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31 suggest that intense screening and high revision rates have resulted in a situation where
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33 the majority of non-revised ASR HR patients have steady state wear and metal ion trends
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35 are similar to those seen in BHRs.
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42 The main strength of our multicentere study is the large number of patients with the largest
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44 number of analyzsed metal ion measurements to date which extend into the second
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46 decade. The main limitation in our study is selection bias. All operated patients have not
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48 undergone regular metal ion measurements and some patients have only ~~one or two~~ 1 or 2
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50 measurements. In CenterCentre 2 many BHR patients have no metal ion measurements
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52 at all. This is because CenterCentre 2 have a large cohort of male BHR patients who are
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54 asymptomatic and were not included in the recall for monitoring until 2017. The BHR
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56 patients who have been monitored regularly at CenterCentre 2 are therefore the
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3 symptomatic patients, female patients and male patients with head sizes ≤ 46 mm, all of
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5 whom are at higher risk of ARMD than the unmonitored cohort of male asymptomatic
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7 patients who are likely to have low levels of metal ions. Metal ion trends were inferior in the
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9 BHR group which may seem counterintuitive and biased. We did not, however, aim to
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11 predict theoretical behaviour of metal ion levels. It is clear that implants with poor track-
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13 record have high revision rates, such as 30% in the ASR cohort in our study. Hence our
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15 results must be seen from pragmatic view: what is the behaviour of blood metal ion levels
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17 in well-functioning implants not initially needing revision.
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24 Overall, our results for BHR patients show that if initial blood metal ion measurements
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26 during the first decade are acceptable, the probability is high that ion levels will remain low
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28 in the second decade. This also holds true for ASR patients, assuming a significant
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30 revision rate similar to the 30% seen in our study group. These findings have major
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32 implications for the present worldwide regular surveillance for HR patients. Regular metal
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34 ion measurements (i.e. annual) therefore do not seem reasonable if the initial values are
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36 below validated thresholds. We recommend less frequent blood metal-ion measurements
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38 are needed (every 3-5 years) for HR patients since only minor changes were seen
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40 after 10-year follow-up. Regulatory guidance stratifying implant surveillance based solely
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42 on femoral head size does not seem useful with the BHR and ASR given temporal metal
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44 ion changes.
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Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

(Supplemental Figure 1. Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. (A) Centre 1, (B) Centre 2.)

(Supplemental Figure 2. Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. (A) Centre 1, (B) Centre 2.)

(Supplemental Figure 3. Population marginal effect of time on log-transformed metal ion levels in (A) unilateral ASR and (B) unilateral ASR with small femoral diameter (<50 mm).)

(Supplemental Figure 4. Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, (A) Centre 1, (B) Centre 2 and (C) bilateral ASR patients.)

(Supplemental Table 1. Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in BHR patients. AIC = Akaike's information criteria. Small diameter means <50 mm head size.)

(Supplemental Table 2. Values for fixed effect for time and comparison of simple linear mixed model and nonlinear mixed model using restricted cubic splines in ASR patients. AIC = Akaike's information criteria. Small diameter means <50 mm head size.)

References

1. Reito A, Lainiala O, Elo P, ~~Eskelinen A et al~~. Prevalence of failure due to adverse reaction to metal debris in modern, medium and large diameter metal-on-metal hip replacements--the effect of novel screening methods: systematic review and metaregression analysis. *PLoS One*. 2016 ~~Mar 1~~; 11(3): e0147872.
2. Lehtovirta L, Reito A, Parkkinen J, ~~Peräniemi S, Vepsäläinen J, Eskelinen A et al~~. Association between periprosthetic tissue metal content, whole blood and synovial fluid metal ion levels and histopathological findings in patients with failed metal-on-metal hip replacement. *PLoS One*. 2018 ~~May 16~~; 13(5): e0197614.
3. Pijls BG, Meessen JM~~TA~~, Tucker K, ~~Stea S, Steenbergen L, Marie Fenstad A~~, et al. MoM total hip replacements in Europe: a NORE report. *EFORT Open Reviews*. 2019 ~~Jun 3~~; 4(6): 423–429.
4. National Joint Registry for England, ~~and~~ Wales, ~~Northern Ireland and the Isle of Man~~. *NJR 16th annual report 2019*. *NJR (UK)*, 2019.
5. Australian Orthopaedic Association National Joint Replacement Registry (~~AOANJRR~~): *Hip, knee & shoulder arthroplasty: annual report 2019*. Adelaide, AOA, 2019.
6. Information about soft tissue imaging and metal ion testing ~~[internet]~~. US Food & Drug Administration, ~~;~~ 2019 Mar [cited 2020 Jul 5]. Available from: <https://www.fda.gov/medical-devices/metal-metal-hip-implants/information-about-soft-tissue-imaging-and-metal-ion-testing> (2019, accessed 05 July 2020).
7. ~~Medicines and Healthcare products Regulatory Agency~~. *All metal-on-metal (MoM) hip replacements: updated advice for follow-up of patients'* ~~;~~ ~~Medicines and Healthcare products Regulatory Agency (MDA/2017/018)~~. MHRA, ~~;~~ 2017 Jun.

- 1
2
3 8. Metal-on-metal hip replacement implants: ~~Information for general practitioners,~~
4 orthopaedic surgeons and other health professionals ~~[Internet].~~ Therapeutic Goods
5 Administration, Australian Government, ~~2017 Jul [cited 2020 Jul 5]. Available from:~~
6 ~~<https://www.tga.gov.au/metal-metal-hip-replacement-implants> (2017, accessed 05 July~~
7 ~~2020).~~
8
9
10
11
12
13
14 9. Matharu GS, Berryman F, Brash L, ~~Pynsent PB, Dunlop DJ, Treacy RBC~~ ~~et al.~~ Can
15 blood metal ion levels be used to identify patients with bilateral Birmingham Hip
16 Resurfacings who are at risk of adverse reactions to metal debris? ~~*Bone Joint J.* 2016~~
17 ~~Nov; 98-B(11): 1455–1462.~~
18
19
20
21
22
23
24 10. Matharu GS, Berryman F, Brash L, ~~Pynsent PB, Treacy RBC, Dunlop DJ~~ ~~et al.~~ The
25 effectiveness of blood metal ions in identifying patients with unilateral Birmingham Hip
26 Resurfacing and Corail-Pinnacle metal-on-metal hip implants at risk of adverse reactions
27 to metal debris. ~~*J Bone Joint Surg Am.* 2016 Apr 20; 98(8): 617–626.~~
28
29
30
31
32
33
34 11. Matharu GS, Berryman F, Judge A, ~~Reito A, McConnell J, Lainiala O,~~ et al. Blood
35 metal ion thresholds to identify patients with metal-on-metal hip implants at risk of adverse
36 reactions to metal debris: an external multicenter validation study of Birmingham Hip
37 Resurfacing and Corail-Pinnacle implants. ~~*J Bone Joint Surg Am.* 2017 Sep 20; 99(18):~~
38 ~~1532–1539.~~
39
40
41
42
43
44
45 12. Matharu GS, Mellon SJ, Murray DW, ~~Pandit H~~ ~~Get al.~~ Follow-up of metal-on-metal
46 hip arthroplasty patients is currently not evidence based or cost effective. ~~*J Arthroplasty.*~~
47 ~~2015 Aug; 30(8): 1317–1323.~~
48
49
50
51
52
53
54 13. Moroni A, Miscione MT, Orsini R, ~~Micera G, Mosca S, Sinapi F,~~ et al. Clinical and
55 radiographic outcomes of the Birmingham Hip Resurfacing arthroplasty at a minimum
56 follow-up of 10 years: results from an independent centre. ~~*Hip Int.* 2017 Mar 31; 27(2):~~
57 ~~134–139.~~
58
59
60

- 1
2
3 14. Matharu GS, McBryde CW, Pynsent WB, ~~Pynsent PB, Treacy RBC~~ et al. The
4
5 outcome of the Birmingham Hip Resurfacing in patients aged < 50 years up to 14 years
6
7 post-operatively. *Bone Joint J.* ~~2013-2013-Sep~~; ~~95-B(9)~~: 1172–1177.
8
9
- 10 15. Hunter TJA, Moores TS, Morley D, ~~Manoharan G, Collier SG, Shaylor P~~ Jet al. 10-
11
12 year results of the Birmingham Hip Resurfacing: a non-designer case series. *Hip Int.* 2018
13
14 ~~Jan~~; ~~28(1)~~: 50–52.
15
16
- 17 16. Hart AJ, Sabah SA, Bandi AS, ~~Maggiore P, Tarassoli P, Sampson B~~, et al.
18
19 Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of
20
21 metal-on-metal hip replacement. *J Bone Joint Surg Br.* 2011-~~Oct~~; ~~93(10)~~: 1308–1313.
22
23
- 24 17. Reito A, Puolakka T, Elo P, ~~Pajamäki J, Eskelinen A~~ et al. High prevalence of
25
26 adverse reactions to metal debris in small-headed ASR™ hips. *Clin Orthop Relat Res.*
27
28 2013-~~Sep~~; ~~471(9)~~: 2954–2961.
29
30
- 31 18. Van Der Straeten C, Van Quickenborne D, De Roest B, ~~Calistri A, Victor J, De Smet~~
32
33 ~~Ket al.~~ Metal ion levels from well-functioning Birmingham Hip Resurfacings decline
34
35 significantly at ten years. *Bone Joint J.* 2013-~~Oct~~; ~~95-B(10)~~: 1332–1338.
36
37
- 38 19. deSouza RM, Parsons NR, Oni T, ~~Dalton P, Costa M, Krikler S~~ et al. Metal ion levels
39
40 following resurfacing arthroplasty of the hip: serial results over a ten-year period. *J Bone*
41
42 *Joint Surg Br.* 2010-~~Dec~~; ~~92(12)~~: 1642–1647.
43
44
- 45 20. Berber R, Skinner J, Board T, ~~Kendoff D, Eskelinen A, Kwon YM~~, et al. International
46
47 metal-on-metal multidisciplinary teams: do we manage patients with metal-on-metal hip
48
49 arthroplasty in the same way? An analysis from the International Specialist Centre
50
51 Collaboration on MOM Hips (ISCCoMH). *Bone Joint J.* 2016-~~Feb~~; ~~98-B(2)~~: 179–186.
52
53
- 54 21. Matharu GS, Berryman F, Dunlop DJ, ~~Judge A, Murray DW, Pandit H~~ Get al. Has
55
56 the threshold for revision surgery for adverse reactions to metal debris changed in metal-
57
58
59
60

1
2
3 on-metal hip arthroplasty patients? A cohort study of 239 patients using an adapted risk-
4 stratification algorithm. *Acta Orthop*. 2019 Dec; 90(6): 530–536.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
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For Peer Review

Table 1: Comparison study groups between institutions.

		BHR cohort			ASR cohort	<i>P</i> -value for three group difference	
			Centre 1	Centre 2		<i>P</i> -value for difference	
Age	Unilateral	Mean (SD)	54.8 (8.7)	49.1 (11)	<0.0001	54.3 (9.4)	<0.0001
	Bilateral – first	Mean (SD)	53.2 (8.4)	51.6 (9.4)	0.30	54.3 (8.3)	0.09
	Bilateral – second	Mean (SD)	53.4 (8.8)	54.6 (9.7)	0.84	54.6 (8.4)	0.93
Gender	Unilateral	Males	110	31	<0.0001	117	<0.0001
		Females	51	167		52	
	Bilateral	Males	24	8	<0.0001	36	<0.0001
		Females	9	57		11	
Femoral diameter	Unilateral	<43 mm	3	48	<0.0001	2	<0.0001
		44–45 mm	1	0		7	
		46–47 mm	28	100		25	
		48–49 mm	1	0		14	
		50–51 mm	51	38		24	
		52–53 mm	58	11		46	
		54–55 mm	19	1		26	
		56–57 mm	0	0		18	
		58–59 mm	0	0		5	
		≥60 mm	0	0		2	

Bilateral	<43 mm mm	0	27	2
	44-45 mm mm	0	3	4
	46-47 mm mm	13	69	11
	48-49 mm mm	0	0	9
	50-51 mm mm	25	24	11
	52-53 mm mm	0	1	21
	54-55 mm mm	14	6	19
	56-57 mm mm	0	0	9
	58-59 mm mm	14	0	7
	>60 mm mm	0	0	1

BHR, Birmingham Hip Resurfacing; ASR, SD, standard deviation.

Table 2. Prevalence of absolute changes.

		Patients with initial value below 2.15 ppb	Patients with at least one 1 measurement above 2.15 ppb during 2nd decade
Unilateral BHR	Cobalt	301	47 (15.6%)
	Chromium	264	75 (28.4%)
Unilateral ASR	Cobalt	145	20 (13.8%)
	Chromium	139	15 (10.8%)
		Patients with initial value below 5.5 ppb	Patients with at least one 1 measurement above 5.5 ppb during 2nd decade
Bilateral BHR	Cobalt	98	8 (8.2%)
	Chromium	93	11 (11.8%)
	Cobalt or chromium	93	14 (15%)
Bilateral ASR	Cobalt	47	4 (8.5%)
	Chromium	47	2 (4.3%)
	Cobalt or chromium	47	4 (8.5%)

BHR, Birmingham Hip Resurfacing; ASR, Articular Surface Replacement.

Table 3: Prevalence of relative changes in repeated metal ion measurements performed beyond 10 years of follow-up. ~~Small diameter means <50 mm head size.~~

			All BHR			Small diameter BHR			ASR	
			Overall	Center 1	Center 2	Overall	Center 1	Center 2	Overall	Small diameter
Unilateral	Cobalt	+2.15 ppb change	18 (5%)	2 (1.2%)	18 (9.1%)	15 (8.3%)	0 (0%)	15 (10.1%)	9 (5.3%)	5 (10.4%)
		-2.15 ppb change	14 (3.9%)	6 (3.7%)	8 (4%)	7 (3.9%)	0 (0%)	7 (4.7%)	4 (2.4%)	2 (4.2%)
		+5.5 ppb change	9 (2.5%)	2 (1.2%)	7 (3.5%)	6 (3.3%)	0 (0%)	6 (4.1%)	4 (2.4%)	2 (4.2%)
		-5.5 ppb change	4 (1.1%)	2 (1.2%)	2 (1%)	2 (1.1%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
		+2.15 ppb “net change”	12 (3.3%)	0 (0%)	12 (6.1%)	9 (5%)	0 (0%)	9 (6.1%)	7 (4.1%)	4 (8.3%)
		+5.5 ppb “net change”	6 (1.7%)	1 (0.6%)	5 (2.5%)	4 (2.2%)	0 (0%)	4 (2.7%)	4 (2.4%)	2 (4.2%)
	Chromium	+2.15 ppb change	36 (10%)	2 (1.2%)	34 (17.2%)	28 (15.5%)	0 (0%)	28 (18.9%)	6 (3.6%)	2 (4.2%)
		-2.15 ppb change	10 (2.8%)	3 (1.9%)	7 (3.5%)	5 (2.8%)	0 (0%)	5 (3.4%)	1 (0.6%)	0 (0%)
		+5.5 ppb change	6 (1.7%)	2 (1.2%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	2 (1.2%)	0 (0%)
		-5.5 ppb change	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
		+2.15 ppb “net change”	31 (8.6%)	1 (0.6%)	30 (15.2%)	25 (13.8%)	0 (0%)	25 (16.9%)	5 (3%)	2 (4.2%)
		+5.5 ppb “net change”	5 (1.4%)	1 (0.6%)	4 (2%)	2 (1.1%)	0 (0%)	2 (1.4%)	1 (0.6%)	0 (0%)
Bilateral	Cobalt	+2.15 ppb change	6 (6.1%)	1 (3%)	5 (7.7%)				2 (4.3%)	
		-2.15 ppb change	3 (3.1%)	1 (3%)	2 (3.1%)				1 (2.1%)	
		+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)				1 (2.1%)	
		-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)				0 (0%)	
		+2.15 ppb “net change”	(0%)	(0%)	(0%)				1 (2.1%)	

	+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)	1 (2.1%)
Chromium	+2.15 ppb change	7 (7.1%)	0 (0%)	7 (10.8%)	2 (4.3%)
	-2.15 ppb change	5 (5.1%)	0 (0%)	5 (7.7%)	0 (0%)
	+5.5 ppb change	1 (1%)	0 (0%)	1 (1.5%)	0 (0%)
	-5.5 ppb change	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	+2.15 ppb "net change"	5 (5.1%)	0 (0%)	5 (7.7%)	2 (4.3%)
	+5.5 ppb "net change"	1 (1%)	0 (0%)	1 (1.5%)	0 (0%)

BHR, Birmingham Hip Resurfacing; ASR, Articular Surface Replacement.

Note: Small diameter means <50 -mm head size.

Figures

Figure 1: Flow chart for BHR patients

Figure 2: Flow chart for ASR patients

Figure 3: Explanation for A) absolute and B) relative change used in the analyses

Supplemental Figure 1: Population marginal effect of time on log-transformed metal ion levels in all unilateral BHR patients stratified by institution. A) Center 1, B) Center 2

Supplemental Figure 2: Population marginal effect of time on log-transformed metal ion levels stratified by institution in small headed (<50 mm) unilateral BHR hips. A) Center 1, B) Center 2

Supplemental Figure 3: Population marginal effect of time on log-transformed metal ion levels in A) unilateral ASR and B) unilateral ASR with small femoral diameter (<50 mm)

Supplemental figure 4: Population marginal effect of time on log-transformed metal ion levels stratified by institution in bilateral BHR hips, A) Center 1, B) Center 2 and C) bilateral ASR patients.