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Influence of implant design on blood metal ion concentrations in metal-on-metal total hip replacement patients

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Abstract
Purpose Most factors considered to affect blood metal ions
following metal-on-metal hip replacement are based on hip
resurfacing patients. The study aims were to determine which
factors affect blood metal ion concentrations following metal-
on-metal total hip replacement (MoM THR).
Methods All unilateral MoM THR patients at one centre with
whole-blood cobalt (Co) and chromium (Cr) concentrations
measured up to May 2013 were included. Blood sampling was
at a mean of 4.5 years (range 1.1–11.8 years) postoperatively.
Results Of 496 patients (mean age 59.1 years; 52.8 % male),
blood metal ions >7 μg/l were observed in 9.7 % (*n*=48).
Large femoral head sizes (≥38 mm) had significantly higher
(*p*<0.0001) blood metal ions than smaller sizes (28/36 mm).
Corail–Pinnacle implants produced significantly lower blood
metal ions compared to other implant designs (*p*<0.01 Co and
Cr). Univariate linear regression demonstrated the only sig-
nificant predictors of both blood Co and Cr concentra-
tions were femoral head size (R^2=8.6 % Co and R^2=3.3 %
Cr, both *p*<0.0001) and implant design (R^2=8.8 %,
p=0.005 Co and R^2=5.1 %, *p*=0.003 Cr). When the
three THR implant design groups (Corail–Pinnacle, Synergy,
Other) were analysed separately, femoral head size no longer
significantly affected blood metal ions in any of the three
implant design groups.
Conclusions Implant design was the most important factor
affecting blood metal ion concentrations. We recommend the
regularity of follow-up be tailored to survival rates of various
MoM THR designs rather than according to femoral head size.

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Introduction

Large-diameter metal-on-metal total hip replacement (MoM
THR) became popular for treating patients with hip arthritis
over the last decade [1–4], with more than 1 million patients
worldwide receiving MoM hip bearings [5]. A number of
patients with MoM THRs have developed adverse reactions
to metal debris (ARMD), resulting in high short-term revision
rates [6–8]. The risk of ARMD is greater in THRs compared
with hip resurfacings given the additional metal wear debris,
which can be generated at the taper–head interface and other
modular junctions [2, 7, 9]. This has led to withdrawal from
the market of poorly performing devices [10] and the opinion
that MoM THR should no longer be performed [2].

In light of these problems, the Medical and Healthcare
Products Regulatory Agency (MHRA) recommend annual
follow-up for the life of the implant of all MoM THR patients
with femoral head diameters of ≥36 mm and those with
recalled implants, regardless of symptoms [11]. This follow-
up includes blood metal ion sampling, which is both an ac-
cepted surrogate marker of MoM bearing wear and useful in
identifying patients with ARMD [12]. Although little is
known about the natural history of ARMD [13, 14], it is pos-
sible that not all MoM THR patients will develop it [15].
Therefore, it remains unclear how patients should be followed
up, especially in the long term.

If MoM THR patients at highest risk of ARMD were iden-
tified, resources could be distributed efficiently, allowing
more clinically and cost-effective patient care. Risk factors
associated with ARMD development include female gender,

small femoral component size and acetabular component mal-position [8, 16–19]. However, these risk factors were identified in predominantly hip resurfacing populations and therefore may not necessarily apply in MoM THR patients due to the additional taper and modular junctions [20, 21]. Indeed, few studies have analysed factors affecting blood metal ion concentrations in modern MoM THRs, with the findings from those studies being less conclusive compared with reports in hip resurfacings [22–25].

This study aimed to determine which patient, surgeon and implant factors affect blood metal ion concentrations following modern MoM THR. It was expected this would identify which patient subgroup(s) are at greatest risk of developing ARMD, which will have implications for rationalising future clinical follow-up.
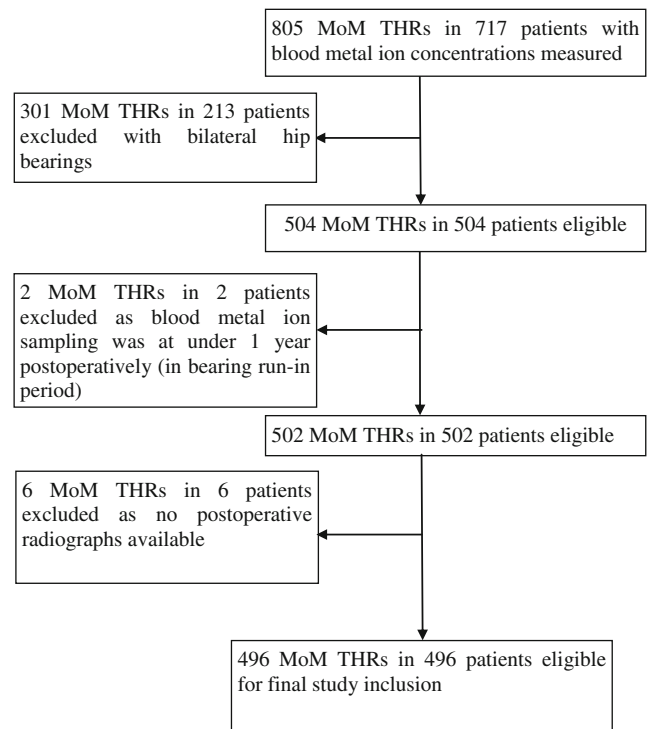
Patients and methods

Study design and patient demographics

This prospective cohort study was undertaken at one specialist arthroplasty centre and was approved and registered with the institutional review board. All patients undergoing primary MoM THR implanted at this centre since January 2001 with blood metal ion concentrations measured up to May 2013 were eligible for inclusion (805 MoM THRs in 717 patients). As renal impairment is an established contraindication for MoM hip arthroplasty, all patients considered suitable for MoM THR at this centre had normal renal function confirmed prior to bearing implantation. Patients with bilateral hip replacements, regardless of bearing type, were excluded from this analysis due to difficulties associated with interpreting raised blood metal ions in the presence of two hip bearings [26]. After other exclusions (Fig. 1), 496 MoM THRs in 496 patients were included in the final cohort, with a mean follow-up of 4.5 years (range 1.1–11.8 years) since the index arthroplasty (Table 1).

Operations were performed by 13 surgeons, with two surgeons performing half of the cases (n=251; 50.1 %). Each operation was performed in a clean-air laminar flow operating theatre using a posterior (n=386) or an anterolateral (n=110) surgical approach. Five different MoM THR designs were used according to surgeon preference (Table 1). All components were uncemented, with each implanted as for a routine THR but in line with the manufacturer's instructions.

Description of follow-up routine

All patients were invited for clinical review at six weeks, six months and one year postoperatively, with invitations for annual clinical review thereafter. Each consultation included clinical examination, anteroposterior pelvic radiographs and

completion of the Oxford Hip Score (OHS) questionnaire [27]. Blood metal ion sampling was not performed in patients reviewed prior to 2010. After the 2010 MHRA alert highlighting concerns with MoM hips [10], this institution contacted all MoM THR patients by post to explain the situation at the time ("Electronic Supplementary Material"). All patients, regardless of symptoms, were offered an appointment for clinical review and blood metal ion sampling.

Blood metal ion sampling

Whole blood was collected from patients and transported to a laboratory approved by the MHRA for blood metal ion analysis (City Hospital, Birmingham, UK). Cobalt (Co) and chromium (Cr) concentrations were measured in all samples using an inductively coupled plasma mass spectrometer (Agilent 7500cx, Agilent Technologies Inc., Santa Clara, CA, USA). Detection and reporting limits were 0.06 μg/l and 0.6 μg/l, respectively. Blood metal ions were considered raised if Co and/or Cr concentrations were greater than the MHRA upper limit of 7 μg/l [11].

Description of outcome measures

All study data except for acetabular inclination angle were extracted from the institution's prospectively maintained

MoM THR = metal-on-metal total hip replacement

Fig. 1 Study inclusion criteria for metal-on-metal total hip replacements

Table 1　Summary of the study cohort

		Total cohort (n=496)	Cohort for Oxford Hip Score analysis (n=298)
Gender	Male	261 (52.6 %)	146 (49.0 %)
	Female	235 (47.4 %)	152 (51.0 %)
Age at index arthroplasty	Mean (range); years	59.1 (18.3−89.1)	60.2 (21.8−89.1)
Diagnosis	Primary osteoarthritis	421 (84.9 %)	256 (85.9 %)
	Developmental dysplasia	10 (2.0 %)	3 (1.0 %)
	Avascular necrosis	20 (4.0 %)	10 (3.4 %)
	Inflammatory arthritis	3 (0.6 %)	2 (0.7 %)
	SUFE	3 (0.6 %)	2 (0.7 %)
	Perthes	5 (1.0 %)	2 (0.7 %)
	Hip trauma	18 (3.6 %)	9 (3.0 %)
	Other causes	16 (3.2 %)	14 (4.7 %)
Follow-up time	Mean (range); years	4.5 (1.1−11.8)	4.5 (1.1−8.4)
Blood metal ion concentration	Median (IQR); μg/l	Co 2.12 (0.88−4.01)	Co 2.06 (0.77−3.71)
		Cr 1.35 (0.82−2.13)	Cr 1.30 (0.78−2.03)
Implant design	Corail–Pinnacle (DePuy International Limited, Leeds, UK)	300 (60.5 %)	208 (69.8 %)
	Synergy/modular head (Smith & Nephew, Warwick, UK)	150 (30.2 %)	61 (20.5 %)
	Caparo Amoda (Comis Orthopaedics, Birmingham, UK)	43 (8.7 %)	28 (9.4 %)
	Conserve (Wright Medical UK Limited, Letchworth, UK)	2 (0.4 %)	1 (0.3 %)
	Adept (Finsbury Orthopaedics Limited, UK)	1 (0.2 %)	0 (0 %)
Femoral component size	28 mm	7 (1.4 %)	4 (1.3 %)
	36 mm	293 (59.1 %)	204 (68.5 %)
	38 mm	2 (0.4 %)	0 (0 %)
	40 mm	1 (0.2 %)	0 (0 %)
	42 mm	27 (5.4 %)	11 (3.7 %)
	44 mm	16 (3.2 %)	5 (1.7 %)
	46 mm	32 (6.5 %)	20 (6.7 %)
	48 mm	17 (3.4 %)	9 (3.0 %)
	50 mm	57 (11.5 %)	21 (7.0 %)
	52 mm	18 (3.6 %)	10 (3.4 %)
	54 mm	21 (4.2 %)	10 (3.4 %)
	56 mm	3 (0.6 %)	3 (1.0 %)
	58 mm	2 (0.4 %)	1 (0.3 %)
Acetabular component inclination	Mean inclination	43.0° (20.6°−65.0°)	43.6° (21.1°−63.5°)
	<30°	16 (3.2 %)	6 (2.0 %)
	30–50°	412 (83.1 %)	248 (83.2 %)
	>50°	68 (13.7 %)	44 (14.8 %)
Oxford Hip Score	Median (IQR); as % and 0–48	Not applicable	10.4 % (2.1−33.3)
			43.0/48 (32.0−47.0)

Co cobalt, *Cr* chromium, *SUFE* slipped upper femoral epiphysis, *IQR* interquartile range

database (MySQL database, Oracle Corporation, Redwood Shores, CA, USA). Acetabular component inclination was measured in each anteroposterior pelvic radiograph using the teardrop line for reference, as previously described [28]. Two authors (GSM and DJD) each measured acetabular inclination in half of the cohort after interobserver and intraobserver reliability had been evaluated on a random sample of 30

radiographs (intra-observer and interobserver 95 % limits of agreement were −2.2° to 1.6° and −2.5° to 3.5°, respectively, and 95 % confidence intervals (CI) for intraclass coefficients were 0.994–0.998 and 0.984–0.994, respectively [29, 30]).

The OHS was used to assess postoperative pain and disability following MoM THR [27]. At this institution, the OHS is expressed as a percentage (0 % = healthy joint and 100 % =

worst possible joint) [31]. However, as the OHS is frequently scored on a scale of 0–48 points (0 = worst possible joint and 48 = healthy joint) [32], these scores have also been provided for comparison with previous reports.

Statistical analysis

Data were extracted from the outcomes database and analysed using the R statistical programming language [33]. Summary statistics were calculated for all variables. Linear regression and t tests were performed to investigate relationships between the base 10 logarithm of blood metal ion concentrations and the different patient, surgeon and implant covariates. Similar to previous studies [25, 34, 35], the logarithm was necessary to transform the asymmetric blood metal ion concentration distributions so that the residuals in the regression models were more normally distributed. Adjusted R^2 was also calculated to give the percentage of variance in the logarithm blood metal ion concentrations explained by the models.

Not all 496 patients submitted an OHS at the time of blood sampling. Therefore, all covariates apart from OHS were analysed in the cohort of 496 patients, whilst the OHS analysis was only performed in the 298 patients providing eligible questionnaires (Table 1). For completeness, all covariates analysed in the full cohort were also assessed in the subgroup of 298 patients.

Femoral head sizes were grouped into small (28/36 mm, $n=300$) and large (38–58 mm, $n=196$) for t testing with multiple comparisons. Similarly, acetabular inclination angles were grouped ($<30°$ ($n=16$), $30°-50°$ ($n=412$), $>50°$ ($n=68$)) using the previously described safe inclination zone for THR [36]. The five different MoM THR implant designs were grouped as follows: Corail–Pinnacle ($n=300$), Synergy ($n=150$), and Other (Caparo Amoda, Conserve and Adept; $n=46$). The Holm method was used for adjusting the p values in this t

testing to allow for multiple comparisons. A p value <0.05 was considered statistically significant.

Results

Blood metal ions >7 μg/l for either Co or Cr were observed in 9.7 % ($n=48$). The large femoral head-size group had significantly higher blood metal ion concentrations than the small head-size group (Table 2, Fig. 2). Blood metal ion concentrations >7 μg/l were observed in 4.3 % (13/300) of small-head MoM THRs compared with 17.9 % (35/196) of large-head THRs. The small head-size group all had Corail–Pinnacle implants, so further analysis was performed by implant design. Patients with Corail–Pinnacle implants had significantly lower log blood metal ion concentrations compared with both the Synergy and Other groups, but there were no significant differences between the Synergy and Other implant groups (Table 2, Fig. 3). No other variables significantly affected both blood Co and Cr concentrations (Table 2).

Univariate linear regression analysis demonstrated that most variables, including the OHS (Fig. 4), had no significant effects on log Co or Cr (Table 3). Femoral head size (Fig. 5) and implant design were the only factors significantly affecting both log blood Co and Cr concentrations. When linear regression analysis was repeated separately for the three implant design groups (Corail–Pinnacle, Synergy, Other), femoral head size did not significantly affect log blood metal ion concentrations.

Multivariate linear regression modeling demonstrated the best fitting model was one combining femoral head size, gender and time since index arthroplasty (R^2 13.6 % for log Co and 7.5 % for log Cr). When this modeling was repeated separately for the three implant design groups, the only significant covariates were gender and time since index

Table 2 Patient, surgeon and implant factors affecting log blood metal ion concentrations following metal-on-metal total hip replacement

Variable	Comparison of mean differences	P values: Co (t test)	P values: Cr (t test)
Age (years)	under 60>over 60	0.309	0.039
Gender	female>male	0.968	0.055
Femoral head size	large>small	<0.0001	<0.0001
Implant design	Synergy>CP	<0.0001	< 0.0001
	Other>CP	0.009	0.006
	Synergy>Other	0.153	0.890
Acetabular inclination angle	under 30°>over 50°	All pairs>0.8	All pairs>0.2
	under 30°>30°-50°		
	over 50°>30°-50°		
High-volume surgeon 1 with implant design	Synergy>CP	0.033	0.139
High-volume surgeon 2 with implant design	Synergy>CP	0.006	0.213
Indication for primary	other indications>OA	0.458	0.643

All tests were carried out on log_{10} metal ion concentrations; when multiple comparisons were made, correction to the p value was made using the Holm method

CP Corail–Pinnacle, *OA* osteoarthritis

Fig. 2 Log_{10} blood **a** cobalt and **b** chromium concentrations for small (28 mm and 36 mm) and large (38–58 mm) femoral head sizes following metal-on-metal total hip replacement. The Medical and Healthcare Products Regulatory Agency (MHRA) upper limit of 7 μg/l is indicated by the *dashed red horizontal line*. *Box widths* are proportional to the number of hips in the group; *notch size* is an indication of the 95 % confidence interval around the median of the distribution
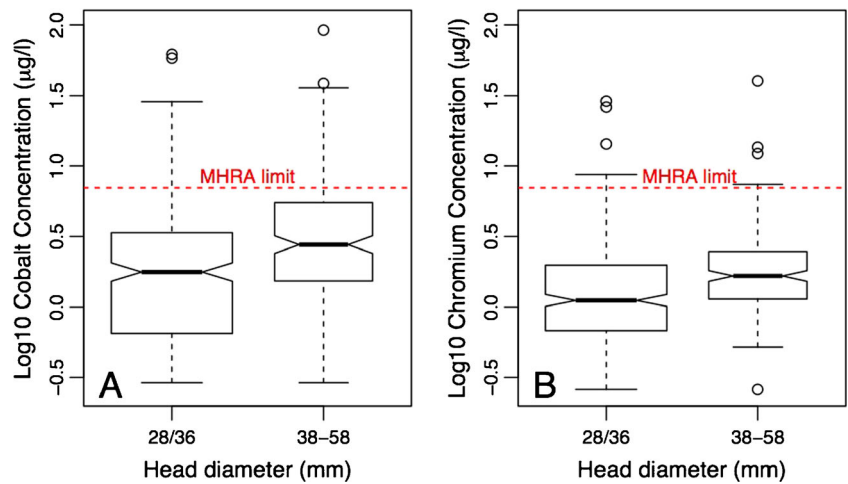
arthroplasty in an additive model for Co in the Corail–Pinnacle group (R^2=8.3 %) and for Cr in the Synergy group (R^2=9.2 %). When repeating all statistical analysis in patients with eligible postoperative OHSs (*n*=298), although there were some minor differences in *t* test results and R^2 values, the conclusions reached were the same as those for the entire cohort (*n*=496).

Of the 48 patients with blood metal ions >7 μg/l, there have been 15 revisions (13 ARMD; one infection; one periprosthetic stem fracture). The remaining 33 patients with high blood metal ions remain under regular clinical surveillance. Sixteen further MoM THRs were revised (13 ARMD, and one each for unexplained pain, acetabular loosening and femoral loosening) where blood metal ion levels were ≤7 μg/l. Mean time from index MoM THR to revision in these 31 cases was 4.5 years (range 1.6−12.2 years).

Discussion

Most risk factors for developing ARMD have been identified in hip resurfacing populations [8, 16–19]. These factors have

frequently and possibly incorrectly been assumed to apply in modern MoM THR patients, given that few studies have formally analysed factors affecting blood metal ion concentrations in MoM THR patients [22–25]. Such studies are limited by short-term follow-up as well as the inclusion of hip resurfacing patients and those with bilateral MoM hip bearings. Our study provides a comprehensive analysis of the affect of patient, surgeon and implant factors on blood metal ion concentrations using the largest cohort of modern MoM THRs with the longest follow-up reported to date.

The main findings were that although larger femoral head sizes appear to be associated with higher blood metal ion concentrations, this was no longer the case when implant design was controlled for. In addition, there were significant differences in blood metal ion concentrations between implant designs, with Corail–Pinnacle THRs having lower levels compared with other implants. This remained the case when individual surgeon was controlled for (Table 2). Therefore, implant design was the most important factor affecting blood metal ion concentrations in MoM THR patients.

Fig. 3 Log_{10} blood **a** cobalt and **b** chromium concentrations for different implant designs following metal-on-metal total hip replacement. The Medical and Healthcare Products Regulatory Agency (MHRA) upper limit of 7 μg/l is indicated by the *dashed red horizontal line*. *Box widths* are proportional to the number of hips in the group; *notch size* is an indication of the 95 % confidence interval around the median of the distribution
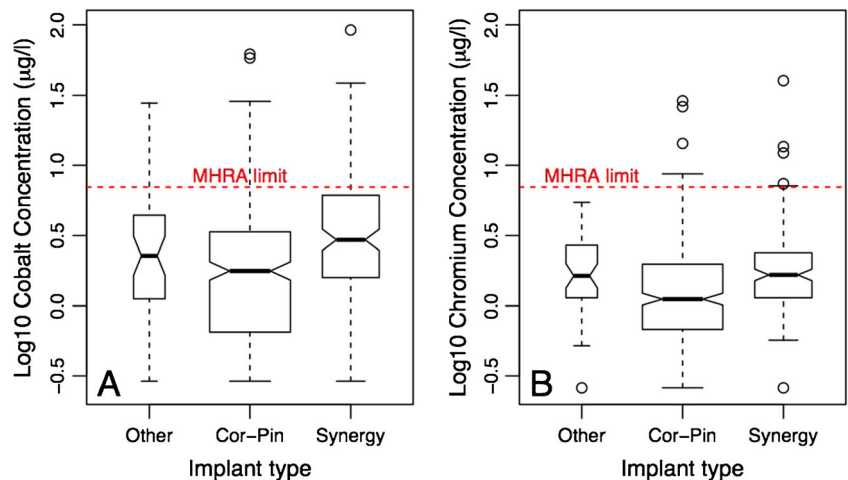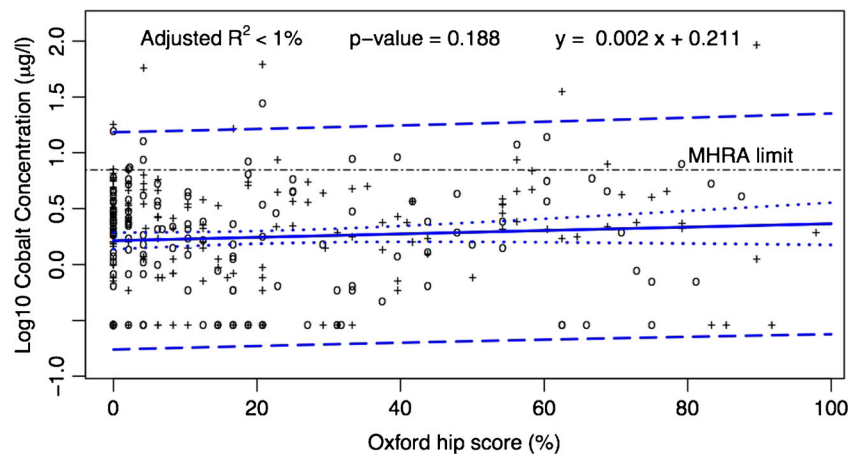
Fig. 4 Log$_{10}$ whole blood cobalt concentration modelled on Oxford Hip Score with regression line (*solid*), 95 % confidence limits (*dotted*) and 95 % prediction limits (*dashed*). Medical and Healthcare Products Regulatory Agency (MHRA) upper limit of 7 μg/l is indicated by the *dot–dashed horizontal line*. Hips from women are indicated by + and from men by *o*. Similar results were obtained for log$_{10}$ blood chromium concentrations (adjusted $R^2 < 1$ %, *p* value=0.442, $y=0.0007x+0.075$)

The serious concerns raised regarding high failure rates of all modern MoM THR devices [2, 6–8, 11] suggest there is a universal design problem. However, registry-reported revision rates of various MoM THR designs range from 11.1 % to 43.3 % at eight years [37]. Our findings support these observations, with evidence suggesting the risk of wear-related problems differs between implant designs. A smaller study of 144 MoM THRs with four different implant designs also demonstrated significant differences in blood Co between designs [23].

As well as the bearing surface, MoM THRs have a taper junction with or without modular junctions, which are subject

to wear debris and/or corrosion [38, 39]. It has been observed that taper wear produces Co in preference to Cr [20]. Our findings suggest the taper is the main source of metal ions generated, given that blood Co concentrations were nearly twice that of Cr (Table 1). The number and nature of taper and modular junctions vary between implants, which may be responsible for differences observed in blood metal ions between MoM THR designs and the risk of failure. It is clear by comparing hip resurfacing patients with stemmed MoM THRs with identical bearing designs that adding a taper junction increases blood metal ions [7, 40, 41]. In addition, different MoM THR designs from the same

Table 3 Univariate linear regression models for whole blood log cobalt (Co) and chromium (Cr) concentrations

Ion	Variable	Estimate (slope)	Standard error	t value	Pr>|t|	Adj. R^2
Co	Age	−0.002	0.002	−1.016	0.310	<1 %
	Gender	M: −0.002	0.044	−0.040	0.968	<1 %
	Head size	0.022	0.003	6.884	<0.0001	8.6 %
	Implant design	CP: −0.209	0.073	−2.850	0.005	8.8 %
		Syn: 0.112	0.078	1.432	0.153	
	Inclination angle	−0.001	0.003	−0.203	0.839	<1 %
	Time since index arthroplasty	0.028	0.013	2.111	0.035	<1 %
	Surgeon volume	0.000	0.002	0.204	0.842	<1 %
	OHS	0.002	0.001	1.320	0.188	<1 %
Cr	Age	−0.004	0.002	−2.560	0.011	1.1 %
	Gender	M: −0.064	0.033	−1.940	0.053	<1 %
	Head size	0.010	0.002	4.259	<0.0001	3.3 %
	Implant design	CP: −0.170	0.056	−3.003	0.003	5.1 %
		Syn: 0.008	0.060	0.138	0.890	
	Inclination angle	0.000	0.002	−0.162	0.871	<1 %
	Time since index arthroplasty	−0.004	0.010	−0.371	0.711	<1 %
	Surgeon volume	0.000	0.001	0.246	0.813	<1 %
	OHS	0.001	0.001	0.769	0.442	<1 %

Cr chromium, *Co* cobalt, *CP* Corail–Pinnacle, *M* male, *OHS* Oxford Hip Score, *Syn* Synergy
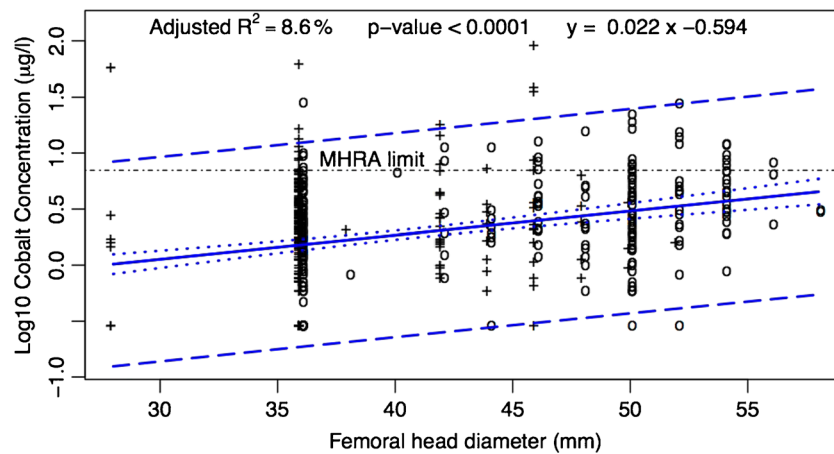
Fig. 5 Log$_{10}$ whole blood cobalt concentration modelled on femoral head size with regression line (*solid*), 95 % confidence limits (*dotted*) and 95 % prediction limits (*dashed*). Medical and Healthcare Products Regulatory Agency (MHRA) upper limit of 7 µg/l is indicated by the *dot–dashed horizontal line*. Hips from women are indicated by + and from men by *o*. Similar results were obtained for log$_{10}$ blood chromium concentrations (adjusted R^2=3.3 %, p value<0.0001, y=0.010x−0.302)

manufacturer have been observed to have significantly different volumetric and linear wear rates [39].

This study provides evidence that variations in implant design can affect blood metal ion concentrations. Excluding the bearing surface and the interface between the cup and liner, the Corail–Pinnacle has one modular junction (taper–head). By contrast, implants with significantly higher blood metal ion concentrations had additional design features. The later Synergy device has an adapter sleeve applied to the stem taper, whilst the Caparo Amoda THR has a modular junction between the stem and neck. Furthermore, cobalt concentration was significantly higher (p=0.008) in Synergy devices with an adapter sleeve (n=98; 65%) compared with the pre-2006 sleeveless femoral-component design (n=52; 35%). Similar metal ion levels were observed in the sleeveless Synergy design and Corail-Pinnacle THRs (p=0.187). Similar to previous authors [39], we were unable to obtain more detailed information on implant metallurgy and design from the manufacturers, given this is sensitive data and these implants are no longer used. However, we suspect variations in taper design, tolerance, and metallurgy between THR designs play an important role in metal ion generation.

Although registry data suggests larger MoM femoral head sizes have higher failure rates, this has not yet been stratified according to implant design [2, 37]. Similar to our findings, other studies have not demonstrated significant relationships between femoral head size and blood metal ions when analysing single MoM THR brands [7, 22, 24]. Furthermore, a retrieval analysis observed increasing femoral head size was only weakly associated with MoM THR taper wear rates [39]. It would therefore be interesting to use registry data to determine whether large femoral head size remains a risk factor for failure when implant design is controlled for.

Despite female gender and acetabular component malposition being risk factors for raised blood metal ions and hip resurfacing failure [8, 16–19], these factors did not affect blood metal ions in MoM THRs in this cohort. Previous studies have almost universally demonstrated that gender and acetabular component position do not significantly affect blood metal ions following MoM THR [23–25, 42]. In one study assessing 213 ASR XL MoM THRs, the authors concluded that acetabular inclination was not a meaningful determinant of blood metal ions and that the high failure rates were design related [25]. By assessing large numbers of different THR designs, our findings provide further evidence that implant design, and not modifiable factors, is the major factor affecting blood metal ion levels. It is suspected that risk factors associated with hip resurfacing are not apparent in THRs given that wear predominantly arises from taper and modular junctions; therefore, failure may be inevitable regardless of patient selection and surgical technique.

Symptoms assessed using the OHS did not reflect blood metal ion concentrations. This supports previous findings of ARMD in asymptomatic patients [43, 44] and the MHRA recommendations that follow-up of large-head MoM THRs is irrespective of symptoms [11]. Symptoms alone should therefore not be used to decide on blood sampling.

This study has some recognised limitations. Factors such as acetabular anteversion and combined anteversion, which may affect blood metal ion concentrations, were not assessed, as they could not be measured accurately using the available software. Furthermore, some patients may develop ARMD with normal blood metal ions [45, 46] and therefore would not be identified in our analysis. Renal function was not assessed at metal ion sampling; however, all patients had normal renal function prior to MoM THR.

Conclusions

Implant design was the most important factor affecting blood metal ion concentrations following MoM THR. Follow-up regularity should therefore be tailored according to registry

survival rates of the various THR designs rather than according to femoral head size [11]. This should allow more effective distribution of clinical resources, with implants known to have higher failure rates reviewed more frequently.

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