Self-reported neurotoxic symptoms in hip arthroplasty patients with highly elevated blood cobalt: a case-control study

Ilona Swiatkowska, PhD[1], Johann Henckel, MRCS[2], Shiraz A. Sabah, FRCS(Orth) BSc[2] and Alister J. Hart, FRCS(Orth)[1,2]

[1]Institute of Orthopaedics and Musculoskeletal Science, University College London, HA7 4LP Stanmore, UK
[2]Royal National Orthopaedic Hospital, Stanmore, HA7 4LP Stanmore, UK

Correspondence and requests for materials should be addressed to IS (email: ilona.swiatkowska.10@ucl.ac.uk, phone number: 020 8416 3412)

Conflicts of interest and source of funding

The authors declare no conflict of interest; AJH has been principal investigator on institutional projects funded from DePuy and Stryker. He also had a personal consultancy agreement with DePuy.

This study was sponsored by the Gwen Fish Orthopaedic Charitable Trust, which played no role in the study design, patient recruitment, collection or analysis of data, writing the report, or the decision to submit the paper for publication.

ABSTRACT

Objectives: To investigate the prevalence of self-reported neurotoxicity and cognitive defects in hip replacement patients with markedly raised blood cobalt.

Methods: Case group comprised 53 patients with metal-on-metal(MoM) implants and history of blood Co≥20 μg/L for a median of 3 years(IQR 2-5). Control group comprised 53 patients with ceramic-on-ceramic(CoC) prostheses and blood Co<1 μg/L. Median age was 67 years (IQR 60-74). The participants completed NSC-60, DNS, DN-10 and Systemic Symptom Checklist(SSC), and underwent MMSE.

Results: MoM vs CoC: NSC-60(median): cognitive defects(2.0 vs 1.9; p=0.002), chest complaints(1.3 vs 1.3; p=0.042), balance disturbances(1.3 vs 1.0; p<0.001), sleep disturbances(2.7 vs 2.0; p=0.004), mood disorders(2.0 vs 1.5; p=0.001), sensorimotor disorders(1.6 vs 1.2; p<0.001), physical complaints(2.0 vs 1.4; p=0.009), fatigue(2.0 vs 1.6; p=0.001), total score(108 vs 90; p<0.001). Abnormal DNS/DN-10(%): 60.3/13.2 vs 24.5/1.9(p<0.001/p=0.028). SSC(%): feeling cold(37.7 vs 17; p=0.01), weight gain(18.9 vs 1.9; p=0.008), metallic taste(26.4 vs 3.8; p=0.002), worsening eyesight(37.7 vs 15.1; p=0.008) and hearing(24.5 vs 7.5; 0.032), ankle swelling(32.1 vs 7.5; p=0.002), shortness of breath on exertion(9.4 vs 5.7; p=0.015), generalised rash(28.3 vs 7.5; p=0.01). MMSE(median): 29 vs 30; p=0.017. MoM group were aware of their high cobalt levels, and displayed a higher tendency to overreport symptoms(p<0.001), which could have contributed to the higher scores.

Conclusions: Frequency of reporting of a number of symptoms was markedly higher in MoM patients, but clinically significant neurotoxicity was not observed (possibly due to the short exposure to elevated cobalt). Patients with repeated blood Co≥20 μg/L measurements should be questioned about possible systemic health complaints at follow-up.

1. Introduction

Cobalt-chromium (CoCr) alloys are widely used in the manufacture of joint replacement implants. Their favourable mechanical properties are undermined by *in vivo* wear and corrosion, which release metal ions and nanoparticles into local tissue and systemic circulation. Systemic dissemination of metal debris, and the possibility of end-organ toxicity (arthroprosthetic cobaltism), is particularly concerning[1]. Symptoms including neuropathy, neurocognitive defects, visual and hearing impairment, hypothyroidism, skin changes and cardiomyopathy, are increasingly being reported in connection with highly elevated cobalt levels from failed hip replacements[2]. Since the initial report in 2001, more than 40 cases of arthroprosthetic cobaltism have been published, including 8 with a fatal outcome[3-10]. In most cases, the symptoms subsided over several months following removal of the offending prosthesis, although a few patients suffered irreversible damage[11-13].

The current Medicines and Healthcare products Regulatory Agency (MHRA) guidelines state that patients with blood cobalt/chromium level $\geq$7 μg/L are at an increased risk of local toxicity[14]. This threshold does not address the risk of systemic adverse effects. A systematic review of 25 published cases of arthroprosthetic cobaltism found that 17% had blood cobalt of <20 μg/L, and almost 50% had a level of <100 μg/L. While both blood cobalt and chromium were often elevated in those cases, cobalt is the more important contributor to metal ion toxicity. Its ability to disturb cellular energy production and kill many different cell types is known[15]. Additionally, adverse reactions (neurotoxicity, cardiomyopathy, hypothyroidism) resulting from occupational exposure, accidental ingestion and medicinal use are well-documented for cobalt[16-

[18], while no analogy exists in cases of chromium intoxication.

Even though metal bearing hip replacements are no longer widely used, over a million patients worldwide have a MoM prosthesis. It is important to understand the consequences of long-term exposure to elevated blood cobalt and raise awareness of the dangers involved, to facilitate the management of patients with high metal ion levels but no local symptoms. This study aimed to investigate the prevalence of neurotoxicity and cognitive defects in hip replacement patients with a history of markedly raised blood cobalt. Our secondary objective was to assess the frequency of reporting of other systemic toxicity symptoms.

2. Methods

The study protocol (**Figure 1**) was approved by Leeds East Research Ethics Committee (ref. 18/YH/0245). Written consent was obtained from all participants.

From our hospital database, we retrospectively identified 81 patients with a hip resurfacing, or a MoM total hip replacement (either indwelling or revised), *in situ* for $\geq$12 months, with a history of blood Co$\geq$20 μg/L. The rationale behind this threshold was that systemic toxicity symptoms were rarely reported in association with blood cobalt concentrations below 20 μg/L (1 published case[19]). We also felt that subjects with such highly elevated cobalt levels were underrepresented in previous studies[20-22]. The blood samples were collected following a recommended protocol[23] and analysed on an inductively-coupled plasma mass spectrometer. The control group consisted of 81 age-matched patients with ceramic-on-ceramic (CoC) hip implants. The participants were presented with a set of questionnaires:

1) The Neurotoxic Symptom Checklist-60 (NSC-60)[24] is a Dutch questionnaire validated to assess the incidence of neurotoxic sequelae in solvent workers[25]. It has since been extended to evaluating the neurobehavioral effects of occupational cadmium exposure[26] and symptoms of cobaltism in hip replacement patients[20,21]. The questionnaire lists 53 symptoms and 7 personality questions. The latter are designed to measure the participant's tendency to report more and/or more severe symptoms. Each question is answered as "Never" (1 point), "Seldom" (2 points), "Sometimes" (3 points) or "Often" (4 points). The 53 questions are grouped into 9 categories: cognitive defects, chest complaints, equilibrium (balance), sleep disturbances, mood disturbances, sensorimotor complaints, physical complaints, fatigue and solvent- specific neurotoxicity. The total score and mean category score were recorded for each participant.

2) Diabetic Neuropathy Score (DNS) is a scoring system validated for diabetic peripheral neuropathy, which has recently been used to screen for cobalt toxicity in hip replacement patients[20,21]. The questionnaire consists of 4 questions scored as "Yes" (1 point) or "No" (0 points), with a total score $\geq$1 suggesting peripheral neuropathy.

3) Douleur Neuropathique 10 (DN-10) is a validated tool used to help diagnose neuropathic pain. It consists of 10 questions answered "Yes" (1 point) or "No" (0 points), which aim to establish how the pain feels to the patient. A physical examination is needed to assess whether there is reduced sensation to touch or pinprick, and whether light brushing increases or causes pain. The test was administered if the participant indicated presence of chronic pain, and a total score $\geq$4 was considered abnormal.

4) Systemic Symptom Checklist (SSC) is a questionnaire written by the authors. It covers 12 of the most commonly reported symptoms associated with elevated blood cobalt levels, and is prefaced by asking whether the patient had been told that they had high metal ion levels (**Figure A.1**).

Following recent reporting of neurocognitive deficits in MoM patients[27], each participant also underwent the Mini Mental State Examination (MMSE)[28]. A total score $\geq$28 was considered normal for the studied population.

Participants were questioned about their current medications, oral supplements and their state of health. Those with abnormal scores were asked about their diet and alcohol intake. Diabetic patients were excluded due to peripheral neuropathy and vision/hearing disturbances that are commonly associated with the disease. One MoM patient with advanced dementia was excluded due to her inability to give informed consent. After exclusions, there were 53 patients in each group. Implant details are listed in **Table A.1.**

2.1. Statistical analysis

Total and mean cluster symptom scores of the NSC-60 followed a skewed distribution, and were analysed with Mann-Whitney U test. The prevalence of abnormal scores was compared using Pearson's Chi Squared test. Answers to the SSC questionnaire (Yes/No) were analysed separately for reporting frequency using Pearson's Chi Squared test or two-tailed Fisher's Exact test. Mean MMSE scores, which were normally-distributed, were compared with the independent samples T-test. SPSS 25.0 was employed for all statistical analyses, with $p \leq 0.05$

considered statistically significant.

3. Results

Baseline patient characteristics are summarised in **Table 1**.

In the case cohort, 28 (53%) patients have had their prosthesis revised to a non-MoM bearing at a median time of 38 months (IQR 26-62) before assessment. MoM patients were exposed to blood Co≥20 μg/L for a median of 3 years (IQR 2-5). In the control cohort, blood cobalt measurements were available for 13 participants (25%). Since the remaining subjects had no other metal implants, and disclosed no occupational or previous implant exposure to cobalt, it was assumed that they displayed similarly low concentrations (Co<1 μg/L). The distribution of peak recorded blood cobalt levels in the two groups is shown in **Figure 2**.

3.1. NSC-60

The median NSC-60 score was 108 (IQR 92.5-136.5) and 90 (IQR 79.5-105.0) in the MoM and CoC group, respectively (**Figure 3**). We observed a significantly higher prevalence of cognitive problems, chest complaints, balance disturbances, sleep disorders, mood changes, sensorimotor disorders, physical complaints and fatigue in the high cobalt group compared to control. None of the group median scores exceeded their respective clinically acceptable thresholds[29]. However, the upper limits of the IQR for sleep disorders and physical complaints were slightly above the threshold in the MoM group (**Table 2**). In the CoC group, the upper limit of the IQR for sleep disturbances was equal to the cut-off value. The total and cluster scores did not differ between the current MoM patients and those whose implants had been revised.

3.2. DNS and DN-10

We found a significantly higher frequency of abnormal DNS ($p<0.001$) and DN-10 ($p=0.028$) scores in the case group compared to control (**Table 3**).

3.3. SSC

The preliminary assessment revealed that 42 MoM patients (79%) were aware of their history of elevated blood metal levels and 7 (13%) were able to quote their most recent blood cobalt reading. There were significant differences in the frequency of reporting of 8 of the 12 symptoms (**Figure 4**), and in the total score ($p<0.001$). The number of SSC symptoms experienced by each patient is summarised in **Table A.2**. Symptom reporting frequency was similar in the current MoM patients and those whose implant had been revised.

3.4. MMSE

We observed a small, but statistically significant ($p=0.017$), difference in cognitive function between the high cobalt patients and controls (**Table 3**). There were no significant gender differences within each group.

4. Discussion

Despite increasing concerns, there is no universally accepted threshold level above which cobalt is likely to lead to systemic effects. The relationship between specific complaints and peak cobalt level, or length of exposure, is also unclear. It is thought that extreme symptoms, such as heart failure or blindness, do not generally occur at levels below 300 μg/L[30] though case reports describing severe cardiomyopathy associated with cobalt concentrations well below that threshold exist[8,31,32]. Cognitive decline, memory problems, tremor, vertigo, decreased exercise

tolerance, hearing loss and cardiomyopathy were reported in at least 5 patients with serum cobalt 15-50 μg/L[19,33-36]. Even lower concentrations subtly change brain structure and function after prolonged exposure[37].

In this study, hip replacement patients with a history of blood Co≥20 had a higher prevalence and severity of various self-reported systemic complaints. Additionally, cognitive function was significantly lower in the case group compared to control. The differences were statistically but not clinically significant, which could be due to the relatively short time that the patients had been exposed to blood Co≥20 μg/L. Chronic exposure to highly elevated blood cobalt levels might result in more pronounced adverse symptoms. We recommend further surveillance of this patient group.

4.1. Comparison with similar studies

NSC-60, DNS and DN-10 were previously used to assess the prevalence of systemic cobalt toxicity in Dutch MoM patients[20,21]. Van der Straeten and colleagues[20] noted a significant correlation between increasing blood cobalt levels and frequency of neurotoxic symptoms. The highest prevalence of adverse effects was found in the Co>20 μg/L group, with female gender and age <50 years acting as confounders. In contrast, van Lingen et al.[21] found no relationship between whole blood cobalt levels and neurotoxic symptoms in their cohort. The latter study only included 1 male and 18 females with blood Co>20 μg/L, and might have been underpowered to detect neurotoxic symptoms in that group. More recent work by Jelsma et al.[22] showed a trend, but no significance, for systemic complaints associated with high cobalt concentrations. The high cobalt group was, again, underrepresented (9 hips compared to 52

patients in the control group). Our study included 53 participants with blood Co≥20 μg/L, which makes it the largest investigation of patients with highly elevated blood cobalt levels to date. The median peak blood cobalt level was 48 μg/L- an order of magnitude higher than that observed in 95% of the MoM population. We found that the prevalence and severity of neurotoxic complaints (as assessed with NSC-60), and the frequency of abnormal DN-10 scores, were higher in the MoM group, which is in line with Van der Straeten's observations[20]. Additionally, we noted a significantly higher frequency of abnormal DNS scores in the case cohort, which is a novel finding.

The MMSE was previously used to assess the cognitive state of 10 recipients of the now-recalled Articular Surface Replacement (DePuy, Johnson and Johnson, Leeds, United Kingdom) hip replacement[27]. The participants (mean age 60.5 years, mean implant time in situ 4.4 years), had a history of toxic blood levels of cobalt and chromium (mean 39.5 and 17.6 μg/L, respectively). A mean MMSE score of 24.2 was noted, with short-term memory deficit in 70% of the sample. The assessment took place several years after revision surgery (when the blood metal levels were expected to have normalised), so the results were found to be unexpectedly low. The authors concluded that elevated blood metal levels might exert a long term impact on cognitive function, which "could have major, as yet unrecognised, implications for public health"[27]. A similar effect was not observed in our series. Even though there was a statistically significant difference between the two groups, all participants but one (score 27) passed the test. MMSE can be affected by a number of factors, such as age, education, cultural background and certain disease states[38], which might explain the conflicting findings. Additionally, Green's study had a much

smaller sample size, and might have been more prone to selection bias and random error than our investigation.

One patient with advanced dementia was excluded from our study due to her inability to give informed consent. Since this particular patient underwent hip replacement surgery after the onset of the condition, it is not thought that dementia was related to elevated blood cobalt.

4.2. Study strengths and limitations

The participants were required to attend a clinic visit, so that DN-10 and MMSE could be administered. The face-to-face approach helped to ensure that the questions were interpreted the same and that the forms were completed fully. The requirement for an outpatient visit reduced the number of participants we were able to assess. Despite relatively small sample size, the current study is the biggest investigation of patients with highly elevated blood cobalt levels to date. Additionally, we are the first to administer the MMSE to a large series of THA patients to evaluate the link between cobalt and cognitive function.

A significant limitation of our study is the heterogeneity of the case group. Since MoM constructs are no longer widely implanted, any new case-control studies of arthroprosthetic cobaltism have to rely on a finite existing pool of patients with MoM implants. These patients will have been exposed to varying blood cobalt levels for varying lengths of time, with 95% of the population displaying a steady-state blood cobalt concentration of ≤ 5 μg/L. It follows that the number of patients with blood cobalt content high enough to raise systemic toxicity concerns is very limited, and it is difficult to draw a homogenous sample of current MoM patients that is large enough to be sufficiently powered. The present study aimed to recruit all patients with a

history of elevated blood cobalt levels at our institution, both those with indwelling MoM hips and those whose implants had been revised to an alternative bearing, in order to study potential long-term adverse effects of cobalt exposure. This approach was intended to reduce selection bias and maximise sample size.

A total of 11 patients did not reply to the invitation letter, while 10 declined participation for undisclosed reasons, which could have distorted the sample population. Patients who thought they may have been harmed by metal implants, combined with prior knowledge of the suspected toxic effects of cobalt, could have been more drawn to taking part in our study and giving more negative answers. Two MoM patients (4%) admitted they had been involved in litigation against MoM implant manufacturers. The higher personality scores in the case cohort could have contributed to the higher symptom scores. Further, the MoM cohort knew that they were being evaluated for adverse effects of cobalt exposure, and 79% of the group were aware of their history of elevated blood metal levels, which could have influenced their answers. This was unavoidable, as not explaining the study to the participants, or not informing them of their blood cobalt levels, would have been unethical.

A further limitation of our study is the subjective nature of self-assessment questionnaires and lack of formal ophthalmological/audiometric screens, echocardiograms and thyroid function tests to confirm the reported symptoms. When 10 patients from Van Lingen's cohort (mean blood cobalt 46.8 μg/L; range 18–153) underwent formal screening, no symptoms of neurological dysfunction, cardiomyopathy or thyroid insufficiency could be identified at 3-6 years follow-up[39]. Notably, three patients in our MoM cohort sought neurological opinion prior to the study. Two were diagnosed with new-onset tremor. In the third case, the patient (indwelling bilateral

HR with blood Co of 20 μg/L) complained of mental fog and significant memory loss since surgery, but the neurological assessment found no abnormalities.

There are no validated questionnaires relating to the diagnosis of possible systemic toxicity in THA patients. The self-assessment questionnaires we employed, with the exception of the SSC, were not designed for cobalt toxicity, and include a number of non-specific symptoms that could be caused by other factors, such as advanced age or chronic diseases. We addressed this by excluding diabetic patients from the study and ensuring that the two cohorts were matched for age. Since heavy alcohol use and malnutrition are a major risk factor for systemic cobalt toxicity[40], we questioned the patients with abnormal scores about their diet and alcohol intake. None of the participants disclosed heavy alcohol use or poor diet.

NSC-60 was developed in 1992 to diagnose chronic solvent-induced encephalopathy (CSE) in Dutch painters[29]. At the time the questionnaire was written, there was only a small group of confirmed CSE patients in the Netherlands. For this reason, 80 uraemia patients under haemodialysis treatment (they can develop neuropsychological disorders similar to CSE) and an age-matched group of 93 bricklayers were chosen to validate the questionnaire. The validation study showed a considerable overlap between the uraemia patients and controls. To limit the number of false positives, the category thresholds were chosen to achieve a high specificity (0.9) and low sensitivity[41]. Spee et al.[41] screened 19,574 painters with a negative score on the NSC-60 and traced only one false negative. Nevertheless, the low sensitivity of NSC-60 thresholds might lead to patients affected by cobalt neurotoxicity being missed. Formal screening of those with normal cluster scores would have been useful to assess the questionnaire's sensitivity in THA

patients exposed to high cobalt levels. The two patients diagnosed with new-onset tremor displayed normal sensorimotor cluster scores, and might be considered as false negatives. On the other hand, the patient complaining of mental fog and significant memory loss since surgery produced an abnormal cognitive cluster score. Since the neurological assessment found no abnormality, the latter case could be regarded as a false positive.

5. Conclusion

The frequency of reporting of a number of systemic toxicity symptoms, including fatigue, sensorimotor problems, sleep disturbances, balance disturbances, ankle swelling, shortness of breath on exertion, worsening of hearing and eyesight, metallic taste, peripheral neuropathy, and neuropathic pain, was significantly higher in the MoM group. However, the differences fell below the clinically significant thresholds and the implants were generally well-functioning. The lack of clinical significance might be related to the relatively short exposure time to the elevated blood cobalt levels and low sensitivity of the NSC-60 questionnaire. It is possible that the severity of the symptoms will increase with chronic exposure to markedly elevated blood cobalt concentrations.

There were several sources of bias in this study. The MoM patients were aware of their history of high cobalt levels, displayed an increased tendency to overreport symptoms compared to the CoC patients, and underwent no formal testing to confirm the self-reported symptoms. Nevertheless, two patients from the case cohort had been diagnosed with new-onset tremor, which was believed to be related to the indwelling MoM devices. For this reason, we recommend further surveillance of this patient group. Individuals with a history of repeated high blood cobalt measurements (Co≥20 μg/L) ought to be questioned about possible systemic health complaints at

follow-up, and those reporting systemic sequalae should be offered formal screening, including neuro-cognitive testing.

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Table 1. *Summary of participant demographics.*

		Age[a]			**Max recorded blood cobalt (μg/L)**			**Blood cobalt at last follow up (μg/L)**		
		Overall (n=53)	**Males (n=18)**	**Females (n=35)**	**Overall (n=53)**	**Males (n=18)**	**Females (n=35)**	**Overall (n=53)**	**Males (n=18)**	**Females (n=35)**
MoM	**Median**	67	62	69	48.0	40.9	54.2	14.6	18.8	9.1
	p-value	0.306[a]	0.03[a]			0.34[b]			0.62[b]	
	IQR	60-74	53-73	61-74	26.9-78.8	25.8-69.5	27.2-84.3	1.6-30.4	2.85-36.4	1.4-29.3
		Overall (n=53)	**Males (n=23)[c]**	**Females (n=30)[c]**	**Overall (n=13)**	**Males (n=2)**	**Females (n=11)**	**Overall (n=13)**	**Males (n=2)**	**Females (n=11)**
CoC	**Median**	70	69	71	0.2	0.2	0.2	0.2	0.2	0.2
	p-value	0.306[a]	0.47[a]			n/a			n/a	
	IQR	64-74	62-74	65-74	0.1-0.2	n/a	0.1-0.2	0.1-0.2	n/a	0.1-0.2

[a]Student's T-test, [b]Mann-Whitney U test; MoM- metal-on-metal, CoC- ceramic-on-ceramic, IQR- interquartile range.

Table 2. *Comparison of median NSC category scores between MoM and CoC group.*

NSC-60 category	Threshold value (abnormal if >...)[28]	MoM (median (IQR))				CoC (median (IQR))
		Current (n=28)	Revised (n=25)	p-value[a]	Overall	
Cognitive	2.9	2.1 (1.7-2.6)	2.0 (1.7-2.9)	0.701	2.0 (1.7-2.6)	1.9 (1.4-2.1)
Chest	2.1	1.3 (1.0-2.0)	1.3 (1.0-2.0)	0.712	1.3 (1.0-2.0)	1.3 (1.0-1.4)
Equilibrium	2.0	1.3 (1.0-2.0)	1.3 (1.0-1.7)	0.650	1.3 (1.0-1.9)	1.0 (1.0-1.3)
Sleep	2.7	2.7 (2.0-3.0)	2.7 (2.2-3.0)	0.942	2.7 (2.0-3.0)	2.0 (1.7-2.7)
Mood	2.7	1.8 (1.3-2.5)	2.1 (1.5-2.9)	0.163	2.0 (1.5-2.7)	1.5 (1.2-1.8)
Sensorimotor	2.8	1.6 (1.3-2.2)	1.6 (1.1-2.1)	0.463	1.6 (1.2-2.1)	1.2 (1.0-1.3)
Physical	2.5	2.0 (1.4-2.6)	1.6 (1.4-2.5)	0.554	2.0 (1.4-2.5)	1.4 (1.2-2.0)
Fatigue	3.1	2.2 (1.6-2.6)	2.0 (1.7-2.8)	0.858	2.0 (1.6-2.6)	1.6 (1.2-2.2)
Personality	2.9	1.6 (1.3-2.0)	1.4 (1.3-2.0)	0.338	1.6 (1.3-2.0)	1.3 (1.0-1.6)

[a]Current vs revised, Mann-Whitney U test; NSC-60- Neurotoxic Symptom Checklist-60, MoM- metal-on-metal, CoC- ceramic-on-ceramic, IQR-interquartile range.

Table 3. *Summary of DNS, DN-10 and MMSE results in the two study groups.*

	MoM (n=53)	**CoC (n=53)**
N abnormal DNS scores (%)	32 (60.3)	13 (24.5)
N abnormal DN-10 scores (%)	7 (13.2)	1 (1.9)
N abnormal MMSE scores; median (IQR)	1; 29 (29-30)	0; 30 (29-30)

MoM- metal-on-metal, CoC- ceramic-on-ceramic, DNS- Diabetic Neuropathy Score, DN-10- Douleur Neuropathique-10, MMSE- Mini Mental State Examination, IQR- interquartile range.

Table A.1. *Implant types and duration of exposure to elevated blood cobalt levels in the MoM cohort.*

Patient number	Unilateral/ bilateral	Brand	Revised before assessment?[a]	MoM implant time in situ (y)	Co≥20 μg/L (y)	Year since blood Co<20 μg/L[b]
1	Unilateral	THA (brand unknown)	No	13	2	2018
2	Unilateral	BHR	Yes	18	14	2018
3	Unilateral	Cormet HR	No	11	2	2018
4	Unilateral	Birmingham/Synergy THA	Yes	8	1	2017
5	Bilateral	2 x BHR	No	16, 14	10	2018
6	Unilateral	BHR	No	18	10	>20 μg/L at TOA
7	Unilateral	Magnum/Taperloc THA	No	8	6	>20 μg/L at TOA
8	Unilateral	BHR	No	10	6	>20 μg/L at TOA
9	Bilateral	2 x BHR	No	20	3	>20 μg/L at TOA
10	Unilateral	BHR	Yes	15	2	2016
11	Unilateral	ASR XL/Corail THA	Yes	10	4	2015
12	Bilateral	2 x BHR	Yes	5, 5	3	2015
13	Bilateral	2 x BHR	Yes (one hip)	11	5	2014
14	Unilateral	Muller THA	Yes	6	3	2016
15	Unilateral	Pinnacle/Corail THA	Yes	9	1	2016
16	Unilateral	Adept/CLS Spotorno THA	No	13	4	2018
17	Unilateral	ASR/Corail THA	Yes	11	3	2016
18	Unilateral	BHR	Yes	8	6	2013
19	Bilateral	2 x Cormet HR	No	13	1	2018
20	Unilateral	Birmingham/Synergy THA	No	9	5	2018
21	Unilateral	BHR	Yes	12	3	2017
22	Bilateral	2 x BHR	No	14	3	>20 μg/L at TOA
23	Unilateral	ASR HR	No	13	3	>20 μg/L at TOA

24	Unilateral	BHR	No	15	3	>20 μg/L at TOA
25	Bilateral	Ultima C-stem THA; ASR/Corail THA	No	12, 12	1	>20 μg/L at TOA
26	Unilateral	ASR HR	Yes	10	6	2016
27	Unilateral	Magnum/Recap HR	Yes	7	3	2015
28	Unilateral	BHR	Yes	16	1	2016
29	Unilateral	Magnum/Taperloc THA	Yes	6	1	2014
30	Unilateral	Magnum/Taperloc THA	Yes	9	1	2018
31	Bilateral	2 x BHR	No	11, 6	4	>20 μg/L at TOA
32	Unilateral	BHR	Yes	12	1	2016
33	Unilateral	Magnum/Taperloc THA	No	11	1	>20 μg/L at TOA
34	Unilateral	HR (brand unknown)	No	7	1	>20 μg/L at TOA
35	Unilateral	Cormet THA	Yes	6	2	2016
36	Bilateral	2 x Pinnacle/Corail THA	Yes (one hip)	9	3	2016
37	Unilateral	Trident/Accolade THA	Yes	3	2	2014
38	Unilateral	BHR	Yes	11	2	2014
39	Unilateral	BHR	Yes	10	4	2017
40	Unilateral	Cormet HR	No	12	4	>20 μg/L at TOA
41	Unilateral	HR (brand unknown)	Yes	14	1	2018
42	Unilateral	BHR	No	6	1	2018
43	Unilateral	ASR HR	Yes	7	2	2012
44	Bilateral	THA (brand unknown), BHR	No	11, 9	4	>20 μg/L at TOA
45	Bilateral	2 x BHR	No	11	5	>20 μg/L at TOA
46	Unilateral	BHR	Yes	4	7	2012
47	Unilateral	THA (brand unknown)	Yes	7	3	2016
48	Unilateral	ReCap Magnum/Stanmore THA	No	11	5	>20 μg/L at TOA
49	Bilateral	2 x BHR revised to MoM THA in 2013 and 2015	No	12, 11	3	2015
50	Unilateral	MITCH/Accolade THA	Yes	9	2	2018

51	Unilateral	ReCap Magnum/Stanmore THA	Yes	9	3	2016
52	Unilateral	BHR	Yes	9	2	2017
53	Bilateral	BHR, Cormet HR	Yes (one hip)	12	5	2017

[a]In all revised cases, the indication was high metal ions associated with unexplained pain and/or adverse reaction to metal debris. All revised implants were replaced with a non-MoM bearing; [b]Year of study: 2018; MoM- metal-on-metal, TOA- time of assessment, THA- total hip arthroplasty, HR- hip resurfacing, ASR- Articular Surface Replacement (DePuy, Johnson and Johnson, Leeds, United Kingdom), BHR- Birmingham Hip Resurfacing (Smith and Nephew, Warwick, United Kingdom).

Table A.2. *The number of SSC symptoms experienced by each patient, and the total number of symptoms experienced by each study group.*

Patient number	**Number of experienced symptoms (out of 12)**	
	MoM	**CoC**
1	3	0
2	0	6
3	0	0
4	6	0
5	3	2
6	5	2
7	2	4
8	3	2
9	2	0
10	2	1
11	4	1
12	7	1
13	0	0
14	2	2
15	3	2
16	0	0
17	6	2
18	5	1
19	9	0
20	5	2
21	0	7
22	4	0
23	5	2
24	2	1
25	0	1
26	1	0
27	0	1
28	0	0
29	4	0
30	0	0
31	3	0
32	0	0
33	1	1
34	2	0
35	0	0
36	4	1
37	2	0

38	6	0
39	1	1
40	1	0
41	0	5
42	2	1
43	0	0
44	4	0
45	6	1
46	6	0
47	2	0
48	0	0
49	8	0
50	10	0
51	3	0
52	7	0
53	4	1
	Total number of experienced symptoms	
	88	37

SSC-Systemic Symptom Checklist, MoM- metal-on-metal, CoC- ceramic-on-ceramic.

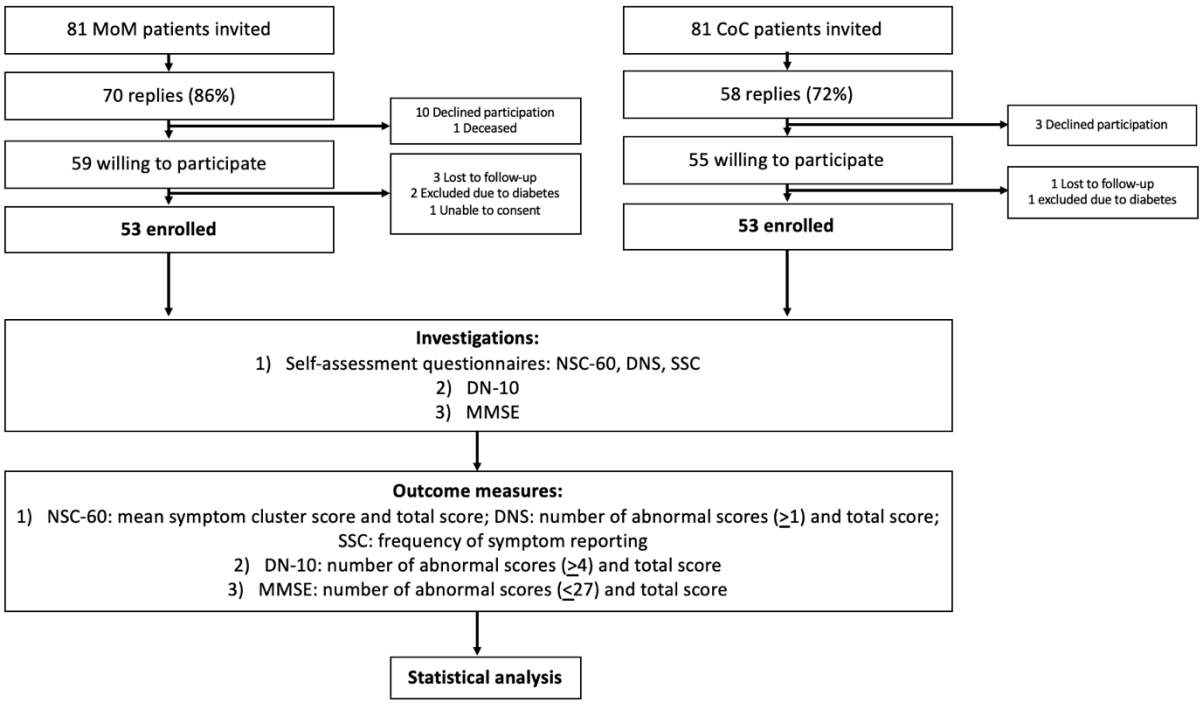

Figure 1. *Flow diagram of the study methods. MoM- metal-on-metal, CoC- ceramic-on-ceramic, NSC-60- Neurotoxic Symptom Checklist-60, DNS- Diabetic Neuropathy Score, SSC- Systemic Symptom Checklist, DN-10- Douleur Neuropathique-10, MMSE- Mini Mental State Examination.*

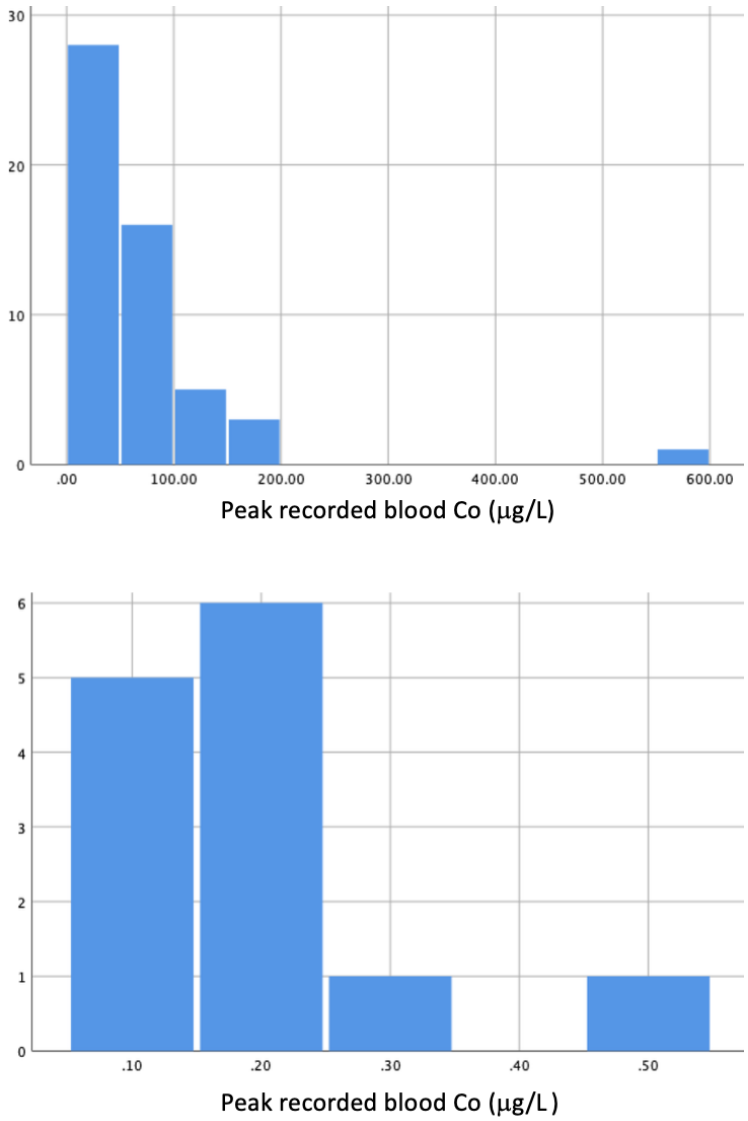

Figure 2*. The distribution of maximum recorded blood cobalt concentrations in the MoM group* ***(top)*** *and CoC group* ***(bottom)****.*

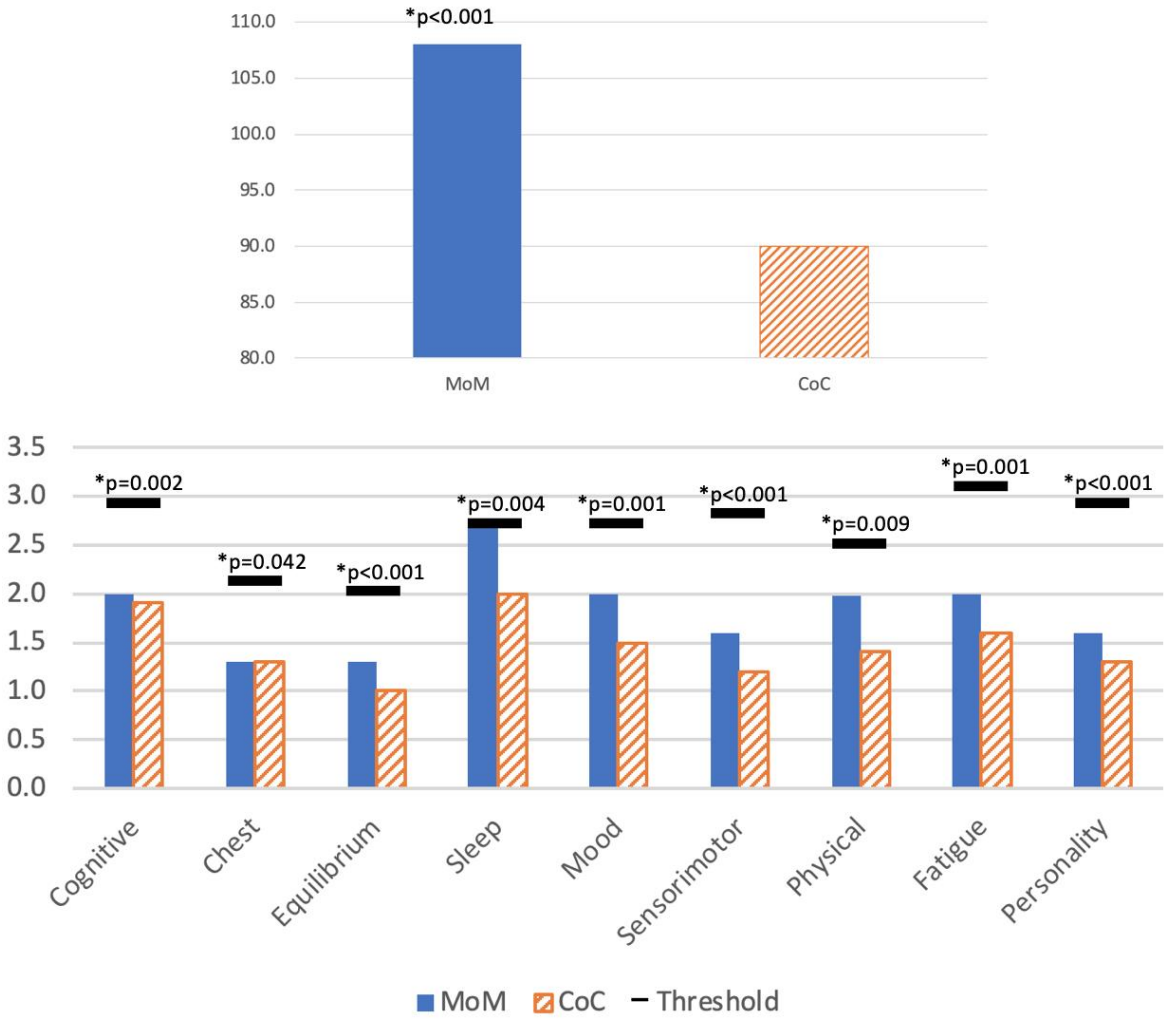

Figure 3. Top: *Median total NSC-60 scores (maximum score 240).* ***Bottom:*** *Median NSC-60 category scores (maximum score 4), with clinical thresholds denoted as horizontal lines. Asterisks indicate statistically significant differences. MoM- metal-on-metal, CoC- ceramic-on-ceramic, NSC-60- Neurotoxic Symptom Checklist-60.*

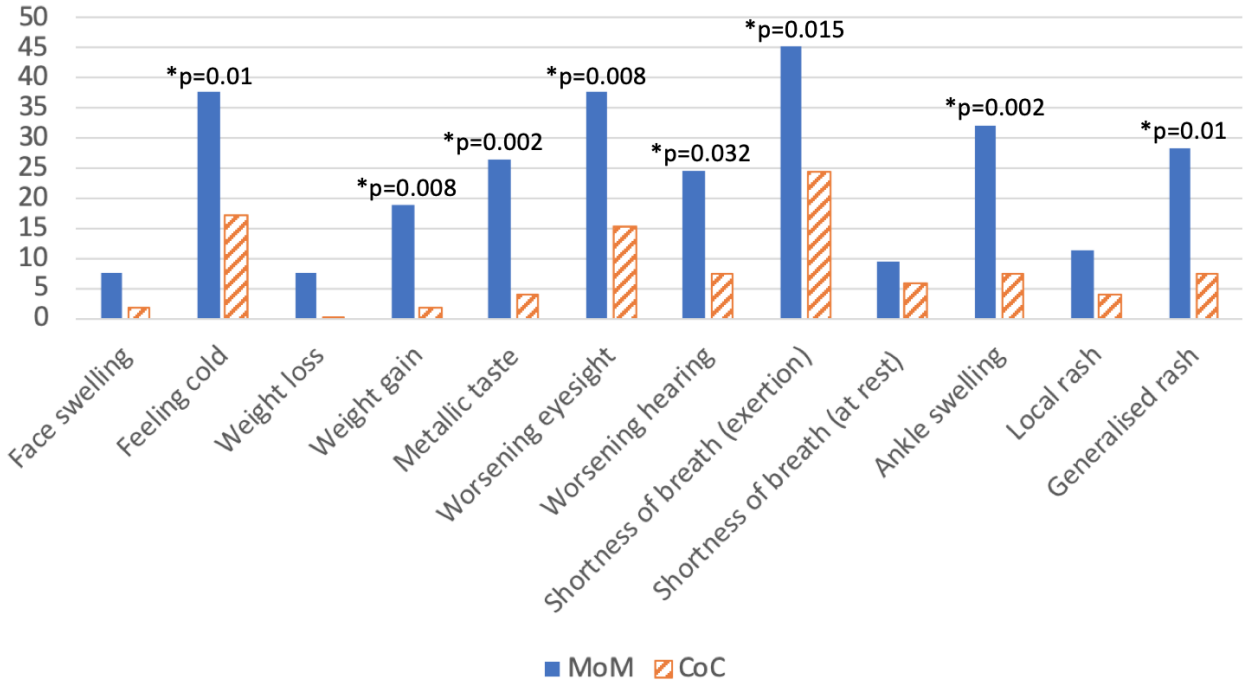

Figure 4. *Frequency of systemic toxicity symptoms reported in the two study groups (results are expressed as percentages). Asterisks denote statistically significant differences.*

Preliminary questions:

1. Do you know your blood metal level? ☐
2. Have you been told that you have high blood metal ion level? ☐

Since the day your implant was inserted:

1. Have you noticed any face swelling (particularly around the eyes)? ☐
2. Do you feel cold when others feel warm? ☐
3. Have you experienced:
   a) Significant unexplained weight loss? ☐
   b) Significant unexplained weight gain? ☐
4. Do you have a metallic taste in your mouth? ☐
5. Have you noticed that your eyesight has worsened significantly? ☐
6. Have you noticed that your hearing has worsened significantly? ☐
7. Are you often out of breath:
   a) On exertion? ☐
   b) When lying flat? ☐
8. Are your ankles swollen? ☐
9. Have you developed any permanent skin changes (e.g. rash or eczema):
   a) Localized to the implant site? ☐
   b) Not localized to the implant site (anywhere on your body)? ☐

Figure A.1. *Systemic Symptom Checklist (SSC).*