Metal Ion Concentrations in Body Fluids after Implantation of Hip Replacements with Metal-on-Metal Bearing – Systematic Review of Clinical and Epidemiological Studies

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Abstract

Introduction: The use of metal-on-metal (MoM) total hip arthroplasty (THA) increased in the last decades. A release of metal products (i.e. particles, ions, metallo-organic compounds) in these implants may cause local and/or systemic adverse reactions. Metal ion concentrations in body fluids are surrogate measures of metal exposure.

Objective: To systematically summarize and critically appraise published studies concerning metal ion concentrations after MoM THA.

Methods: Systematic review of clinical trials (RCTs) and epidemiological studies with assessment of metal ion levels (cobalt, chromium, titanium, nickel, molybdenum) in body fluids after implantation of metalliferous hip replacements. Systematic search in PubMed and Embase in January 2012 supplemented by hand search. Standardized abstraction of pre- and postoperative metal ion concentrations stratified by type of bearing (primary explanatory factor), patient characteristics as well as study quality characteristics (secondary explanatory factors).

Results: Overall, 104 studies (11 RCTs, 93 epidemiological studies) totaling 9,957 patients with measurement of metal ions in body fluids were identified and analyzed. Consistently, median metal ion concentrations were persistently elevated after implantation of MoM-bearings in all investigated mediums (whole blood, serum, plasma, erythrocytes, urine) irrespective of patient characteristics and study characteristics. In several studies very high serum cobalt concentrations above 50 μg/L were measured (detection limit typically 0.3 μg/L). Highest metal ion concentrations were observed after treatment with stemmed large-head MoM-implants and hip resurfacing arthroplasty.

Discussion: Due to the risk of local and systemic accumulation of metallic products after treatment with MoM-bearing, risk and benefits should be carefully balanced preoperatively. The authors support a proposed ‘time out’ for stemmed large-head MoM-THA and recommend a restricted indication for hip resurfacing arthroplasty. Patients with implanted MoM-bearing should receive regular and standardized monitoring of metal ion concentrations. Further research is indicated especially with regard to potential systemic reactions due to accumulation of metal products.

Introduction

Total hip arthroplasty (THA) for patients with osteoarthritis is one of the most successful surgical interventions in general inducing substantial improvement of health-related quality of life of affected patients [1]. Aseptic loosening is a typical long-term complication that significantly determines implant survival. Compared to regular bearings with conventional polyethylene, one advantage of metal-on-metal (MoM) bearings is that they produce less volumetric wear [2]. However, MoM hip replacements may release metallic products (i.e. particles, ions, metallo-
Despite the current uncertainty a systematic review on the safety of MoM-hip replacements is missing. We systematically appraised published clinical and epidemiologic studies to clarify the following issues related to the safety of MoM-hip replacement:

- What are median and maximum metal ion concentrations following MoM-hip replacement?
- Which patient and implant related risk factors exist for elevated metal ion concentrations following MoM-hip replacement?
- To what extent does the metal ion concentration after MoM-hip replacement predict local and systemic adverse reactions?

### Methods

We undertook a systematic review to identify, summarize, and critically appraise the clinical and epidemiological evidence concerning the impact of metallic/ferrous hip replacements on metal ion levels in body fluids. In addition to the type of bearing as the hypothesized determinant of metal ion concentrations we were particularly interested in patient characteristics as well as study quality characteristics as potential secondary determinants of metal ion concentrations after THR, and in the clinical consequences resulting from increased metal ion concentrations.

### Inclusion criteria

All randomized controlled trials (RCTs) and epidemiological studies (cohort, case-control and cross-sectional studies, case series) with metal ion measurement (cobalt, chromium, titanium, nickel, molybdenum) in body fluids (full blood, serum, plasma, erythrocytes, synovia, urine) after implantation of metallic/ferrous hip replacements in at least 20 patients were considered eligible. Studies were required to be published as an original article in English, German, or French language to be included.

### Literature search

Systematic electronic literature searches were conducted in PubMed and EMBASE (until January 19, 2012). Combinations of MeSH-terms were used to identify relevant trials with a high sensitivity. The exact search string used is provided in table 1. Systematic electronic search was supplemented by hand search in...

| # | Suchstring |
|---|------------|
| 1 | "Arthroplasty, Replacement, Hip"[Mesh] OR "Hip Prosthesis"[Mesh] |
| 2 | total hip arthroplast*[All Fields] OR "THA"[All Fields] OR hip arthroplast*[All Fields] OR total hip replacement*[All Fields] OR hip replacement*[All Fields] OR "hip prosthetics"[All Fields] |
| 3 | "surface replacement"[All Fields] OR "hip resurfacing"[All Fields] OR hip resurfacing arthroplast*[All Fields] OR "HRA"[All Fields] OR surface replacement arthroplast*[All Fields] OR "articulare surface replacement"[All Fields] OR "ASR"[All Fields] OR surface arthroplast*[All Fields] OR "Birmingham Hip Resurfacing"[All Fields] OR "BHR"[All Fields] |
| 4 | #1 OR #2 OR #3 |
| 5 | "Chromium"[Mesh] OR "Chromium Alloys"[Mesh] OR "Cobalt"[Mesh] OR "Molybdenum"[Mesh] OR "Titanium"[Mesh] OR "Nickel"[Mesh] |
| 6 | "Chromium"[All Fields] OR "Cr"[All Fields] OR Titanium[All Fields] OR "Ti"[All Fields] OR Nickel*[All Fields] OR Cobalt*[All Fields] OR "Co"[All Fields] OR Molybdenum*[All Fields] OR "Mo"[All Fields] |
| 7 | #5 OR #6 |
| 8 | "Blood"[Mesh] OR "Urine"[Mesh] OR "Tissues"[Mesh] |
| 9 | "blood"[All Fields] OR "serum"[All Fields] OR "plasma"[All Fields] OR "urine"[All Fields] OR "tissue"[All Fields] OR "tissues"[All Fields] |
| 10 | #8 OR #9 |
| 11 | #4 AND #7 AND #10 |
| 12 | #11 NOT letter[pt] OR editorial[pt] OR comment[pt] OR review[pt] OR meta-analysis[pt] |
| 13 | #12 NOT (animals[MeshNoExp] NOT (humans[Mesh])) |
| 14 | #12 NOT (animals[MeshNoExp] NOT (humans[Mesh])) Limits: only items with abstracts |

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the reference lists of the papers included, as well as all articles published in the "Journal of Bone and Joint Surgery British" between 2007 and 2011. Screening of titles and abstracts as well as full-text articles was done independently by two reviewers (F.H., A.H.). Disagreements were resolved by discussing within the whole team of reviewers.

Data abstraction
The following information was abstracted from the studies included using standardized and beta tested evidence tables:

- study characteristics (e.g. author, geographical region, study design, time points of assessment, follow-up period).
- Patient characteristics (e.g. number of patients included and followed up to each point of assessment of metal ion level, UCLA – University of California Los Angeles score [26], body mass index).
- Implant characteristics (type of bearing material and head size in three different groups of implants: small head (SH-)THA with head diameter ≤32 mm, stemmed large-head (LH-)THA with head diameter ≥36 mm, HRA).
- Implant position (inclination of acetabular cup in the frontal plane).
- Details on metal ion assessment, i.e. type of metal ions assessed (cobalt, chromium, titanium, nickel, molybdenum), the medium of assessment, method of analysis, metal ion levels (median, mean, interquartile range (IQR), outliers, definition of outliers).
- Clinical results, i.e. local adverse reactions such as ARMD – "adverse reactions to metal debris", systemic adverse reactions.

Rating of methodological study quality
Standardized study quality assessment was based on the CASP und SIGN Checklists [27,28]. Based on consented and a priori defined study quality criteria the risk of bias was rated for each study with the following categories:

- very low risk of bias: "++"
- low risk of bias: "+"
- high risk of bias: "−"

We considered the following criteria to increase the risk of bias:

- no consideration of confounding and/or explanatory factors such as other metallic implants, type, size, and position of implant.
- missing information on the methods used to measure metal ion levels.
- missing reference group without THR.
- missing preoperative (baseline) metal ion assessment.

Figure 1. Study flow chart of in- and excluded studies. Figure 1 summarizes the yield of systematic search and study selection [31]. Overall, 104 studies (11 RCTs, 14 cohort studies, 1 case-control study, 55 cross-sectional studies, 2 case series) were identified and analyzed. doi:10.1371/journal.pone.0070359.g001
| Reference | Study design | Geographical region | Number of patients\(^1\) | Age (mean)\(^2\) | Proportion women (%) | BMI\(^3\) | THA\(^4\) \(\%\) | HRA\(^5\) \(\%\) | MoM | MoP | CoC | CoP | Small\(^6\) | Large\(^7\) | Both | Zimmer** | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
|-----------|-------------|---------------------|---------------------------|-----------------|----------------------|---------|----------------|----------------|-----|-----|-----|-----|---------|---------|------|----------|----------|-------|---------------|----------------|--------------|
| Brodner 1997 | RCT | Austria | 27/35 | 66/69 | 100 | * | * | * | * | * | * | * | * | * | Zimmer** | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Brodner 2003 | RCT | Austria | 50/100 | 56/70 | 100 | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Dahlstrand 2009 | RCT | Sweden | 54 | 65 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Engh 2009 | RCT | USA | 91 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Gribi 2006 | RCT | Austria | 13/28 | 77/64 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Hailer 2011 | RCT | Sweden | 85 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| MacDonald 2003 | RCT | Canada | 41 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Smolders 2011b | RCT | Netherlands | 71 | 46 | 54 | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Vendittoli 2007+2010 | RCT | Canada | 117 | 45 | 55 | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Weissinger 2011 | RCT | Austria | 42/80 | 67 | 67| 68 | 100 | * | * | * | * | * | * | * | * | * | * | Others | Indication | Anteversion | UCLA Activity Score | Study quality |
| Zijlstra 2009+2010 | RCT | Netherlands | 43 | 100 | * | * | * | * | * | * | * | * | * | * | * | * | * | DePuy*** | Others | Indication | Anteversion | UCLA Activity Score | Study quality |

Gathered information refer to patients with at least one metallic part of the bearing being investigated on metal ions. Studies were summarized due to multiple reporting of identical patient population.

RCT: randomised controlled trial; comparison of 2 interventions, being different regarding e.g. bearing or type of implant; incl. metal ion measurement for all groups.

1: Number of patients (with at least one metallic part of the bearing) being investigated on metal ions.
2: Rounded mean age of patients with at least one metallic part of the bearing/rounded mean age of total number of patients being investigated.
3: BMI = Body Mass Index.
4: THA = Total hip replacement.
5: HRA = Hip resurfacing arthroplasty.
6: Femoral head size 28–32 mm; small head.
7: Femoral head size ≥36 mm; large head.

**incl. Protek, AlloPro, Sulzer Orthop., Centerpulse, Zimmer.
**incl. Landander.

UCLA: Activity Score, University of California, Los Angeles.

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Table 3. Points of time, investigated mediums, methods of analysis, and reporting of results of metal ion measurement in included RCTs.

| Reference          | Metal ion measurement¹ | Metal ions | Medium | Technique      | Outcome reported |
|--------------------|------------------------|------------|--------|----------------|------------------|
| Brodner 1997       | •                      |            | •      |                | mean, median, IQR |
| Brodner 2003       | •                      | •          | •      |                | median, IQR      |
| Dahlstrand 2009    | •                      | •          |        |                | mean, median, IQR |
| Engh 2009          | •                      | •          | •      |                | median, IQR      |
| Grubl 2006         | •                      |            | •      |                | median, IQR, range |
| Hailer 2011        | •                      | •          |        |                | mean             |
| MacDonald 2003     | •                      | •          | •      |                | median, IQR      |
| Smolders 2011b     | •                      | •          |        |                | median, range    |
| Vendittoi 2007+2010| •                      | •          | •      |                | mean, SD, range, median, IQR |
| Weissinger 2011    | •                      |            | •      |                | mean, median, IQR |
| Zijstra 2009+2010  | •                      | •          | •      |                | median, range    |

Studies were summarized due to multiple reporting of identical patient population.
2: Incl. all kinds of metal ion measurement in urin, e.g. 12- or 24 h urine.
3: AAS = All procedures of atomic absorption spectrometry.
4: ICP-MS = all procedures of inductively coupled plasma mass spectrometry.
n. r. = Not reported
SD: Standard deviation; SEM: Standard error of the mean; IQR: Interquartile range.
Metal ion concentration in RCTs.
doi:10.1371/journal.pone.0070359.t003
| Reference        | Intervention | Medium       | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) | 120 Months |
|------------------|--------------|--------------|--------------|---------------|----------------|----------------|----------------|------------|
| Brodner 1997     | CoP SH-THA   | Serum        | 0.15; 0.15–0.15; 28 | 0.15; 0.15–0.15; 28 | 0.15; 0.15–0.15; 28 | 0.15; 0.15–0.15; 28 | 0.15; 0.15–0.15; 37 |           |
| Brodner 2003     | CoP SH-THA   | Serum        | 0.15; 0.15–0.15; 50 | 0.15; 0.15–0.15; 50 | 0.15; 0.15–0.15; 50 | 0.15; 0.15–0.15; 50 | 0.15; 0.15–0.15; 37 |           |
| Dahlstrand 2009  | MoP SH-THA   | Serum        | 0.1; 0.05–0.25; 26 | 0.1; 0.05–0.26; 26 | 0.15; 0.06–0.3; 26 | 0.25; 0.1–0.4; 26 | 0.15; 0.15–0.15; 37 |           |
| Engh 2009        | MoP SH-THA   | Serum        | 0.15; 0.10–0.20; 30 | 0.15; 0.11–0.17; 31 | 0.12; 0.10–0.17; 31 | 0.14; 0.09–0.19; 28 | 0.15; 0.15–0.15; 37 |           |
| Grübli 2006      | CoC SH-THA   | Serum        | 0.15; 0.15–0.15; 15 | 0.15; 0.15–0.15; 15 | 0.40; 0.15–0.70; 15 | 0.24; 0.17; 15 | 0.24; 0.17; 15 |           |
| Hailer 2011      | MoP SH-THA   | Serum        | 0.16; 0.44**    | 0.16; 0.44**    | 0.24; 0.17; 15 | 0.24; 0.17; 15 | 0.24; 0.17; 15 |           |
| MacDonald 2003   | MoP SH-THA   | Erythrocytes | 0.11; 0.09–0.15; 18 | not reported | not readable | 0.17; 0.12–0.23; 18 |           |
| Smolders 2011b   | MoM SH-THA   | Whole blood  | 0.1; 0.05–0.6; 29*** | 0.05–0.6; 29*** | 0.85; 0.1–4.0; 29*** | 1.0; 0.1–4.2; 28*** | 0.9; 0.1–7.2; 17*** |           |
| Vendittoli 2007+2010 | MoM SH-THA | Whole blood  | 0.15; 0.06–0.42; 36*** | 0.06–0.42; 36*** | 0.87; 0.25–3.57; 33*** | 1.0; 0.23–2.09; 31*** | 0.94; 0.24–4.89; 24*** |           |
| Weissinger 2011  | CoC SH-THA   | Serum        | 0.15; 0.38*     | not reported | 0.15; 0.15–0.4 | 0.15; 0.15–0.4 | 0.15; 0.15–0.4 |           |
| Zijlstra 2009+2010 | MoM SH-THA | Serum        | 0.24; 0.18–0.65; 19**** | 0.18; 0.18–0.65; 19**** | 0.30; 0.29–1.65; 14**** | 0.50; 0.40–1.30; 13**** |           |

| Reference        | Intervention | Medium       | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) | 120 Months |
|------------------|--------------|--------------|--------------|---------------|----------------|----------------|----------------|------------|
| Brodner 2003     | MoM SH-THA   | Serum        | 0.15; 0.15–0.15; 27 | 1.0; 0.35–1.35; 27 | 1.1; 0.65–2.6; 27 | 0.75; 0.4–2.85; 50 | 0.9; 0.4–1.7; 36 |           |
| Dahlstrand 2009  | MoM SH-THA   | Serum        | 0.05; 0.05–0.1; 28 | 0.75; 0.5–1.05; 28 | 0.8; 0.5–1.05; 28 | 0.85; 0.65–1.3; 28 | 0.85; 0.65–1.3; 28 |           |
| Engh 2009        | MoM SH-THA   | Serum        | 0.16; 0.09–0.29; 24 | 0.72; 0.49–0.98; 21 | 0.72; 0.48–1.02; 22 | 0.77; 0.48–1.19; 21 | 0.77; 0.48–1.19; 21 |           |
| Grübli 2006      | MoM SH-THA   | Serum        | 0.15; 0.15–0.15; 13 | 1.4; 0.5–10.5; 13**** | 1.0; 0.65–2.6; 27 | 0.75; 0.4–2.85; 50 | 0.9; 0.4–1.7; 36 |           |
| Hailer 2011      | MoM SH-THA   | Serum        | 0.09; 0.09** | not reported | not readable | 1.10; 0.66–2.43; 223 |           |
| MacDonald 2003   | MoM SH-THA   | Erythrocytes | 0.14; 0.09–0.17; 23 | not reported | not readable | 1.10; 0.66–2.43; 223 |           |
| Smolders 2011b   | HRA          | Whole blood  | 0.1; 0.1–0.8; 33*** | 1.3; 0.1–23; 33*** | 1.25; 0.6–8.3; 33*** | 1.2; 0.5–22; 16*** | 1.2; 0.5–22; 16*** |           |
| Vendittoli 2007+2010 | HRA     | Whole blood  | 0.16; 0.06–1.05; 44*** | 0.78; 0.25–1.61 51*** | 0.67; 0.23–2.09; 57*** | 0.16; 0.20–2.89; 48*** |           |
| Weissinger 2011  | MoM SH-THA   | Serum        | 0.15; 0.42*     | not reported | 1.2; 0.8–2.74 | 1.2; 0.8–2.74 | 1.2; 0.8–2.74 |           |
| Zijlstra 2009+2010 | MoM SH-THA | Serum        | 0.18; 0.18–1.77; 24*** | 0.77; 0.18–15.57; 24*** | 0.88; 0.29–7.02; 19**** | 1.10; 0.50–11.0; 17****6 |           |

**Metal Ion Concentrations Following MoM THA/HRA**

Table 4. Concentrations of Co in μg/L for several interventions in RCTs.
Evidence-synthesis

The qualitative evidence-synthesis included a comparison of the pre- vs. postoperative metal ion concentrations (median, alternatively: mean, IQR, maximum values) stratified by type of bearing as the primary explanatory factor. Patient characteristics (mean age, sex ratio) and implant characteristics (bearing size and position) were considered as secondary explanatory factors. Additionally, the definition of cut-off levels of metal ion concentrations in different studies was compared.

RCTs and epidemiological studies were analyzed separately. The detection limit of metal ions depends on the method and device used. The range of the detection limits reported and the handling of values below the detection rate was also part of the qualitative synthesis of the published evidence.

The course of metal ions in body fluids over time was assessed based on studies reporting baseline serum Co-values and at least 2 postoperative Co-measurements. In these studies, we investigated the course of median serum Co-concentration after implantation of hip replacements with different kinds of metal-on-metal bearings.

Metal ion concentrations in all tables and figures below generally relate to patients with unilateral THR, unless stated differently. We initially planned to conduct a quantitative summary (meta-analysis) of the results of qualitatively homogeneous studies with very low or low risk of bias.

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Table 5. Summary of study characteristics of included epidemiological studies.

| Study design         | N |
|----------------------|---|
| Cohort study         | 14|
| Case-control study   | 1 |
| Cross-sectional study| 55|
| Case series          | 23|

| Geographical region  | n |
|----------------------|---|
| Europe               | 63|
| North America        | 23|
| Asia                 | 6 |
| Australia            | 1 |

| Patients characteristics | |
|-------------------------|---|
| number of patients (range) | 20–789|
| mean age (n = 70 studies) | 37–70|
| distribution of sex (n = 68 studies) | 19–90% female|
| BMI* (n = 29 studies) | |
| mean** (range of means, n = 25 studies) | 22.8–28.5|
| range of extreme values (n = 11 studies) | 17–56.6|
| median (range of medians, n = 9 studies) | 26–28|
| range of extreme values (n = 6 studies) | 19–42|

| Implant characteristics | |
|-------------------------|---|
| Intervention            | n = 70 |
| THA                     | |
| MoM LH-THA              | 26 |
| MoM SH-THA              | 42 |
| MoP                     | 17 |
| MoC                     | 1 |
| CoC                     | 4 |
| CoP                     | 2 |
| HRA                     | 47 |
| Manufacturer            | |
| Zimmer                  | 56 |
| DePuy                   | 26 |
| Smith&Nephew            | 34 |
| Corin Group             | 12 |
| Wright Medical Technology | 12 |
| others                  | 27 |
| not reported            | 3 |

| Study quality           | n |
|-------------------------|---|
| ++ (very low risk of bias) | 0 |
| + (low risk of bias)     | 7 |
| - (high risk of bias)    | 86 |

*Including both sexes and different points of measurement (e.g. preoperative, or at follow up).
**Including weighted means for several study cohorts.

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- missing outcome data, i.e. loss to follow-up >10% [29].
## Table 6. Study characteristics of included epidemiological studies.

| Reference          | Study design | Geographical region | Number of patients | Age (mean) | Females (%) | BMI | Interventions | Bearing | Head size | Manufacturer | Inclination | Anteverision | UCLA Activity Score | Study quality |
|--------------------|--------------|---------------------|--------------------|------------|-------------|-----|---------------|----------|------------|--------------|-------------|---------------|---------------------|--------------|
| Antonioi 2008      | CO Canada    | 174                 | 58*               | 43         | 60          | 40  | -             | -        | -         | THA           |             |               |                     |              |
| Beauché 2011       | CO Canada    | 52                  | 57*               | 25         | 50          | 50  | -             | -        | -         | THA           |             |               |                     |              |
| Bernstein 2011a    | CO Canada    | 104                 | 61                | 48         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Boyer 2009         | CO France    | 109                 | 54                | 49         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| De Souza 2010      | CO Great Britain | 56             | 52                | 48         | 100         | -   | -             | -        | -         | THA           |             |               |                     | +            |
| Garbuz 2010        | CO Canada    | 26/104              | n. r.             | 50         | 50          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Isaac 2009a        | CO Great Britain | 60              | 54                | 65         | 100         | -   | -             | -        | -         | THA           |             |               |                     | +            |
| Jacobs 1998        | CO USA       | 55                  | 61*               | 33         | 100         | -   | -             | -        | -         | THA           |             |               |                     | +            |
| Lavigne 2011       | CO Canada    | 137                 | 54*               | 38         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Lazennec 2009      | CO France    | 109                 | 54                | 49         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Pattyn 2011        | CO Belgium   | 52/70               | 51^/52*           | 35         | 40          | 60  | -             | -        | -         | THA           |             |               |                     | +            |
| Smolders 2011a     | CO Netherlands | 92               | 39                | 35         | 63          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Sunderman 1989     | CO USA       | 32                  | 100               | -          | n. r.       | -   | -             | -        | -         | THA           |             |               |                     |              |
| Wittek 2006        | CO Germany   | 185                 | 49                | 40         | 60          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Hart 2011a         | CC Great Britain | 176              | 50                | n. r.      | n. r.       | -   | -             | -        | -         | THA           |             |               |                     |              |
| Bernstein 2011b    | CS Canada    | 34                  | 60                | 50         | 59          | 41  | -             | -        | -         | THA           |             |               |                     |              |
| Bisseling 2011     | CS Netherlands | 57               | 40                | 63         | 37          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Rolland 2011       | CS Great Britain | 185              | 58                | 60         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Brauns 1986        | CS France    | 24                  | 100               | -          | -           | -   | -             | -        | -         | THA           |             |               |                     |              |
| Brodrner 2004      | CS Austria   | 60                  | 62                | 55         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Campbell 2010      | CS USA       | 519                 | 100               | -          | n. r.       | -   | -             | -        | -         | THA           |             |               |                     |              |
| Clarke 2003        | CS USA       | 44                  | 57                | 50         | 50          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Damie 2004         | CS France    | 48                  | 70                | 38         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| Daniel 2006        | CS Great Britain | 135             | 54*               | 38         | 62          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Daniel 2008        | CS Great Britain | 56              | 60*               | 100        | -           | -   | -             | -        | -         | THA           |             |               |                     |              |
| Daniel 2010        | CS Great Britain | 426             | 55                | 10         | 90          | -   | -             | -        | -         | THA           |             |               |                     |              |
| Dardas 2011        | CS Great Britain | 92              | 60                | 67         | 10          | 90  | -             | -        | -         | THA           |             |               |                     |              |
| De Haan 2008       | CS Belgium   | 214                 | 51                | 42         | 100         | -   | -             | -        | -         | THA           |             |               |                     |              |
| De Smet 2008       | CS Belgium   | 26                  | 53                | 33         | 23          | 77  | -             | -        | -         | THA           |             |               |                     |              |
| Reference | Study design | Geographical region | Number of patients (mean) | Proportion women (%) | Age (mean) | BMI | Intervention | Bearing | Head size | Manufacturer | Inclination | Anteverision | UCLA Activity Score | Study quality |
|-----------|--------------|---------------------|--------------------------|----------------------|------------|-----|--------------|---------|-----------|--------------|-------------|-------------|---------------------|---------------|
| Gleizes 1999 | CS | France | 41 | 54 | 51 | 100 | • | • | • | • | • | • | • | • |
| Hallows 2011 | CS | USA | 46 | 57* | 54 | 100 | • | • | • | • | • | • | • | • |
| Hart 2006 | CS | Great Britain | 68 | 59* | 48 | 50 | 50 | • | • | n. r. | • | • | • | • |
| Hart 2008 | CS | Great Britain | 26 | 53 | 42 | 100 | • | • | • | • | • | • | • | • |
| Hart 2009a | CS | Great Britain | 26 | 52 | 68 | 100 | • | • | • | • | • | • | • | • |
| Hart 2009b | CS | Great Britain | 139/164 | 34 | 35 | 65 | • | • | • | • | • | • | • | • |
| Jacobs 1991 | CS | USA | 42 | 59* | 48 | 100 | • | • | • | • | • | • | • | • |
| Karamat 2005 | CS | Austria | 50/75 | 46 | 100 | • | • | • | • | • | • | • | • | • |
| Khan 2008 | CS | Great Britain | 21 | 54 | 31 | 100 | • | • | • | • | • | • | • | • |
| Kwon 2010 | CS | Great Britain | 70 | 55* | 56 | 100 | • | • | • | • | • | • | • | • |
| Kwon 2011 | CS | USA | 178 | 56 | 34 | 11 | 89 | • | • | • | • | • | • | • | • |
| Langton 2008-2009 | CS | Great Britain | 160 | 53* | 40 | 100 | • | • | • | • | • | • | • | • |
| Langton 2010 | CS | Great Britain | 247 | 8 | 92 | • | • | • | • | • | • | • | • | • |
| Langton 2011a | CS | Great Britain | 789 | | | | | | | | | | | | |
| Langton 2011b | CS | Great Britain | 723 | 53* | 31 | 100 | • | • | • | • | • | • | • | • |
| Langton 2011c | CS | Great Britain | 257 | 20 | 80 | • | • | • | • | • | • | • | • | • |
| Lhotka 2003 | CS | Austria | 259 | 55* | 65 | 100 | • | • | • | • | • | • | • | • |
| Maclean 2010 | CS | Great Britain | 30 | | | | | | | | | | | | |
| Marzawa 2002 | CS | Japan | 75 | 67* | 84 | 100 | • | • | • | • | • | • | • | • |
| Matthews 2011a | CS | Great Britain | 120 | 57* | 67 | 50 | 50 | • | • | • | • | • | • | • | • |
| Matthews 2011b | CS | Great Britain | 105 | 72 | 34 | 66 | • | • | • | • | • | • | • | • |
| Migaud 2011 | CS | France | 30/62 | 40/40* | 17 | 100 | • | • | • | • | • | • | • | • |
| Milosev 2005 | CS | Slovenia | 43 | 56* | 72 | 100 | • | • | • | • | • | • | • | • |
| Moroni 2008 | CS | Italy | 46 | 48* | 52 | 57 | 43 | • | • | • | • | • | • | • | • |
| Moroni 2011 | CS | Italy | 95 | 54* | 48 | 63 | 37 | • | • | • | • | • | • | • | • |
| Patzold 1983 | CS | Italy | 20 | 69 | | | | | | | | | | | | |
| Petk 2011 | CS | USA | 39 | 56* | 44 | 100 | • | • | • | • | • | • | • | • |
| Pilger 2002 | CS | Austria | 46/53 | 58*/n. r. | 54 | 100 | • | • | • | • | • | • | • | • |
| Raquind 2006 | CS | USA | 30/40 | 58*/58* | 100 | • | • | • | • | • | • | • | • | • |

* Denotes statistically significant differences.
Table 6. Cont.

| Reference | Study design | Geographical region | Number of patients | Age (mean) | Proportion women (%) | BMI | Intervention | Bearing | Head size | Manufacturer | Inclination | Anteverision | UCLA Activity Score | Study quality |
|-----------|--------------|----------------------|--------------------|------------|----------------------|-----|--------------|----------|-----------|--------------|-------------|---------------|-------------------|---------------|
| Saito 2006 | CS | Japan | 50/90 | 55/n. r. | 90 | 100 | * | • | • | • | • | • | • | • |
| Sammiento-Gonzalez 2008 | CS | Spain | 22 | 46 | 100 | • | n. r. | • | • | • | • | • | • | • |
| Savarino 2002 | CS | Italy | 41 | 54* | 68 | 100 | • | • | • | • | • | • | • | • |
| Savarino 2003 | CS | Italy | 41 | 49* | 59 | 100 | • | • | • | • | • | • | • | • |
| Savarino 2006 | CS | Italy | 42/65 | 57/59* | 48 | 100 | • | • | • | • | • | • | • | • |
| Schaffer 1999 | CS | Austria | 76 | 58* | 61 | 100 | • | n. r. | • | • | • | • | • | • |
| Tkaczuk 2010 | CS | Canada | 127 | 55* | 68 | 100 | • | • | • | • | • | • | • | • |
| Tridot 2009 | CS | France | 30/39 | 40 | 100 | • | • | • | • | • | • | • | • | • |
| Underwood 2011 | CS | Great Britain | 130 | 56* | 65 | 100 | • | • | • | • | • | • | • | • |
| Walter 2008 | CS | Australia | 29 | 40 | 100 | • | • | • | • | • | • | • | • | • |
| Williams 2011 | CS | Canada | 75 | 73 | 27 | 100 | • | • | • | • | • | • | • | • |
| Akihiko 2001 | CA | Japan | 20 | 51 | 100 | • | • | • | • | • | • | • | • | • |
| Allian 2007 | CA | USA | 35 | 51 | 43 | 100 | • | • | • | • | • | • | • | • |
| Castelli 2011 | CA | Italy | 53 | 50 | 100 | • | • | • | • | • | • | • | • | • |
| Conradi 2011 | CA | Great Britain | 31 | 62 | 23 | 100 | • | • | • | • | • | • | • | • |
| Daniel 2007a | CA | Great Britain | 26 | 53 | 100 | • | • | • | • | • | • | • | • | • |
| Daniel 2007b | CA | Great Britain | 262 | 56 | 28 | n. r. | n. r. | • | • | • | • | • | • | • | • |
| Desaunay 2000 | CA | France | 58 | 60 | 36 | 100 | • | • | • | • | • | • | • | • | • |
| Desaunay 2004 | CA | France | 89 | 60 | 37 | 100 | • | • | • | • | • | • | • | • | • |
| Drey 2011 | CA | Canada | 91 | 53 | 19 | 100 | • | • | • | • | • | • | • | • | • |
| Girard 2011 | CA | France | 22 | 44 | 73 | 100 | • | • | • | • | • | • | • | • | • |
| Grubl 2007 | CA | Austria | 22/98 | n. r/56 | 100 | • | • | • | • | • | • | • | • | • | • |
| Hart 2011b | CA | Great Britain | 100 | 51 | 100 | • | • | • | • | • | • | • | • | • | • |
| Imanishi 2010 | CA | Japan | 33 | 60 | 88 | 100 | • | • | • | • | • | • | • | • | • |
| Isaac 2009b | CA | Great Britain | 77 | 27 | 100 | • | • | • | • | • | • | • | • | • | • |
| Kim 2011 | CA | Canada | 97 | 48 | 22 | 100 | • | • | • | • | • | • | • | • | • |
| Ladon 2004 | CA | Great Britain | 95 | 100 | • | • | • | • | • | • | • | • | • | • | • |
| Maczewska 2004 | CA | Japan | 44 | 63 | 80 | 100 | • | • | • | • | • | • | • | • | • |

THA**: THA (n%), HRA**: HRA (n%), MoM: MoM, MoP: MoP, MoC: MoC, CoC: CoC, CoP: CoP, Small**: Small, Large**: Large, Zimmer**: Zimmer, DePuy**: DePuy, Smith & Nephew**: Smith & Nephew, Corin: Corin, Wright Medical Technology: Wright Medical Technology, Others: Others.
Table 6. Cont.

| Reference  | Study design | Geographical region | Number of patients1 | Age (mean)2 | Proportion women (%) | BMI1 | Intervention | Bearing | Head size | Manufacturer | Inclination | Anteverision | UCLA Activity Score | Study quality |
|------------|--------------|---------------------|---------------------|-------------|---------------------|------|--------------|---------|-----------|--------------|-------------|--------------|------------------|--------------|
| Markle 2008 | CA Austria    | 70/98 n. r./56       | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |
| Maise 2003  | CA Italy      | 30 52 67             | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |
| Nikolaou 2011 | CA Canada   | 166 50 46            | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |
| Skipor 2002 | CA USA        | 25 49 32             | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |
| Vendritoli 2011 | CA Canada | 29 50 48             | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |
| Yang 2011   | CA China      | 25 37                | 100                 | •           | •                   |      |              |         |           |              |             |              |                  |              |

Gathered information refer to patients with at least one metallic part of the bearing being investigated on metal ions.

Studies were summarized due to multiple reporting of identical patient population.

Study design:

CO: Cohort study, examination on metal ions at 2 or more points of time, reference group being different regarding state of surgery, implant type, bearing, or the like is necessary; incl. metal ion measurement for all groups.

CC: Case-control study, cases with elevated metal ion concentrations, controls with not elevated metal ions concentrations, retrospective detection of exposition (bearing, implant typ); incl. metal ion measurement for all groups.

CS: Cross-sectional study, examination on metal ions at one point of time, reference group being different regarding state of surgery, implant type, bearing or the like is necessary; incl. metal ion measurement for all groups.

CA: Case series, examination of 2 or more persons on metal ions, at one or more points of time; incl. metal ion measurement.

1: Number of patients (with minimum one metallic part of the bearing) being examined on metal ions/total number of patients being examined on metal ions.

2: Rounded mean age of patients with minimum one metallic part of the bearing/rounded mean age of total group of examined patients.

*: Rounded weighted mean.

3: BMI = Body Mass Index.

4: THA = Total hip arthroplasty.

5: HRA = Hip resurfacing arthroplasty.

MoM: Metal-Metal bearing.

MoP: Metal-Polyethylene bearing.

MoC: Metall-Ceramic bearing.

CoC: Ceramik-Ceramik bearing.

CoP: Ceramik-Polyethylene bearing.

n. r.: Not reported.

6: Femorale head size 28–32 mm; small head.

7: Femorale head size ≥ 36 mm; large head.

**Incl. Protek, AlloPro, Sulzer Orthop., Centerpulse, Zimmer.

***Incl. Midland med. Technologies, Medizintechnik Wien, Endo Plus.

UCLA: University of California, Los Angeles.

$ distribution was not reported for the whole group.

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Table 7. Points of time, investigated mediums, methods of analysis, and reporting of results of metal ion measurement in included epidemiological studies.

| Reference           | Metal ion measurement | Metal ions | Medium | Technique | Outcome reported |
|---------------------|-----------------------|------------|--------|-----------|------------------|
| Antoniou 2008       | Preoperative ≤6 Months | Co, Cr     | Whole blood | AAS  | median, IQR     |
| Beaule 2011         | Preoperative >6–12 Months | Co, Cr | Erythrocytes | ICP-MS | mean, range, median, IQR |
| Bernstein 2011a     | Preoperative >12–≤24 Months | Co, Cr | Serum | AAS  | mean |
| Boyer 2009          | Preoperative >24 Months | Co, Cr    | Urine  | ICP-MS | median, IQR     |
| De Souza 2010       | Preoperative | Co, Cr | Erythrocytes | AAS  | median, IQR     |
| Gaibuzzi 2010       | Preoperative | Co, Cr | Serum | AAS  | median, IQR     |
| Isaac 2009a         | Preoperative | Co, Cr | Erythrocytes | AAS  | median, IQR     |
| Jacobs 1998         | Preoperative | Co, Cr | Serum | AAS  | mean |
| Lavigne 2011        | Preoperative | Co, Cr | Erythrocytes | AAS  | mean, range, median |
| Lazennec 2009       | Preoperative | Co, Cr | Serum | AAS  | mean, range |
| Pattyn 2011         | Preoperative | Co, Cr | Erythrocytes | AAS  | mean, range, SD, median, IQR |
| Smolders 2011a      | Preoperative | Co, Cr | Serum | AAS  | mean, range |
| Sunderman 1989      | Preoperative | Co, Cr | Erythrocytes | AAS  | mean, SEM, range |
| Witzleb 2006        | Preoperative | Co, Cr | Serum | AAS  | median, IQR |
| Hart 2011a          | Preoperative | Co, Cr | Erythrocytes | AAS  | median, range |
| Bernstein 2011b     | Preoperative | Co, Cr | Erythrocytes | AAS  | median, IQR |
| Bisseling 2011      | Preoperative | Co, Cr | Erythrocytes | AAS  | median, range |
| Bolland 2011        | Preoperative | Co, Cr | Erythrocytes | AAS  | median, range |
| Braun 1986          | Preoperative | Co, Cr | Erythrocytes | AAS  | median, range |
| Brodner 2004        | Preoperative | Co, Cr | Erythrocytes | AAS  | median |
| Campbell 2010       | Preoperative n. r. | Co, Cr | Erythrocytes | ICP-MS | median, SEM, range |
| Clarke 2003         | Preoperative | Co, Cr | Erythrocytes | ICP-MS | median, IQR |
| Dame 2004           | Preoperative | Co, Cr | Erythrocytes | ICP-MS | median |
| Daniel 2006         | Preoperative | Co, Cr | Erythrocytes | ICP-MS | median |
| Daniel 2008         | Preoperative | Co, Cr | Erythrocytes | ICP-MS | median |
| Daniel 2010         | Preoperative n. r. | Co, Cr | Erythrocytes | ICP-MS | median, IQR |
| Davda 2011          | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, range, median, IQR |
| De Haan 2008        | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, range, IQR |
| De Smet 2008        | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, range, IQR |
| Gleizes 1999        | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, SD, range |
| Hallows 2011        | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, range |
| Hart 2006           | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean |
| Hart 2008           | Preoperative | Co, Cr | Erythrocytes | ICP-MS | mean, SD |
| Hart 2009a          | Preoperative n. r. | Co, Cr | Erythrocytes | ICP-MS | median, range, IQR |
| Reference                  | Metal ion measurement | Metal ions | Medium | Technique | Outcome reported |
|---------------------------|-----------------------|------------|--------|-----------|------------------|
| Hart 2009b                | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, IQR |
| Jacobs 1991               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range |
| Karamat 2005              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range |
| Khan 2008                 | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range, SD |
| Kwon 2010                 | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range, IQR |
| Kwon 2011                 | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range, IQR |
| Langton 2008+2009         | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range, median, IQR |
| Langton 2010              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range, median, IQR |
| Langton 2011a             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range, IQR |
| Langton 2011b             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median |
| Langton 2011c             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | n. r. |
| Lhotka 2003               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM |
| Maclean 2010              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | n. r. |
| Maezawa 2002              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | n. r. |
| Matthies 2011a            | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range |
| Matthies 2011b            | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, median, range |
| Migaud 2011               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD, range |
| Milosev 2005              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD, range, median, IQR |
| Moroni 2008               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM, median, range |
| Moroni 2011               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD, median, range |
| Pazzaglia 1983            | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD |
| Pelt 2011                 | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, IQR, range |
| Pilger 2002               | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, range |
| Ramosinha 2006            | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD, range, median |
| Saito 2006                | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SD, range |
| Sarmiento-González 2008   | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM, IQR |
| Savarino 2002             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM, median, range |
| Savarino 2003             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM, median, range |
| Savarino 2006             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, SEM, median, range |
| Schaffer 1999             | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range, IQR |
| Tkaczyk 2010              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | median, IQR |
| Triclot 2009              | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean |
| Underwood 2011            | Preoperative ≤6 Months | ≤6–≤12 Months | >12–≤24 Months | Whole blood | Co Cr | Erythrocytes | Serum | Urine² | AAS³ | ICP-MS⁴ | mean, range |
| Reference          | Metal ion measurement | Metal ions | Medium       | Technique | Outcome reported |
|-------------------|-----------------------|------------|--------------|-----------|------------------|
|                   | Preoperative          | ≤6 Months  | >6–<12 Months | >12–<24 Months | >24 Months | Co | Cr |
| Walter 2008       |                      |            |              |           |                  |    |    |
| Williams 2011     |                      |            |              |           |                  |    |    |
| Akihiko 2011      |                      |            |              |           |                  |    |    |
| Allan 2007        |                      |            |              |           |                  |    |    |
| Castelli 2011     |                      |            |              |           |                  |    |    |
| Corradi 2011      |                      |            |              |           |                  |    |    |
| Daniel 2007a+2009 |                      |            |              |           |                  |    |    |
| Daniel 2007b      |                      |            |              |           |                  |    |    |
| Delaunay 2000     |                      |            |              |           |                  |    |    |
| Delaunay 2004     |                      |            |              |           |                  |    |    |
| Desy 2011         |                      |            |              |           |                  |    |    |
| Girard 2011       |                      |            |              |           |                  |    |    |
| Grübl 2007        |                      |            |              |           |                  |    |    |
| Hart 2011b        |                      |            |              |           |                  |    |    |
| Imanishi 2010     |                      |            |              |           |                  |    |    |
| Isaac 2009b       |                      |            |              |           |                  |    |    |
| Kim 2011          |                      |            |              |           |                  |    |    |
| Ladon 2004        |                      |            |              |           |                  |    |    |
| Maezawa 2004      |                      |            |              |           |                  |    |    |
| Marker 2008       |                      |            |              |           |                  |    |    |
| Masse 2003        |                      |            |              |           |                  |    |    |
| Nikolaou 2011     |                      |            |              |           |                  |    |    |
| Skipor 2002       |                      |            |              |           |                  |    |    |
| Vendittoli 2011   |                      |            |              |           |                  |    |    |
| Yang 2011         |                      |            |              |           |                  |    |    |

Studies were summarized due to multiple reporting of identical patient population.
2: Incl. all kinds of metal ion measurement in urine, e.g. 12- or 24 h urine.
3: AAS = All procedures of atomic absorption spectrometry.
4: ICP-MS = all procedures of inductively coupled plasma mass spectrometry.

SD: Standard deviation; SEM: Standard error of the mean; IQR: Interquartile range.
doi:10.1371/journal.pone.0070359.t007
Data on all relevant metal ions (cobalt, chromium, titanium, nickel, molybdenum) was extracted from the studies included. In the results section, we present cobalt levels as the proposed reference metal ion concentration after THR, as suggested by an international, multiprofessional expert panel [30].

Results

Figure 1 summarizes the yield of systematic search and study selection [31]. Overall, 104 studies (11 RCTs, 14 cohort studies, 1 case-control study, 55 cross-sectional studies, 23 case series) totaling 9,957 patients with measurement of metal ions in body fluids were identified and analyzed. The majority of studies were performed in Europe (n = 71) and North America (n = 26).

Study characteristics RCTs

Table 1 summarizes the characteristics of the 11 RCTs included. RCTs were generally small and included between 13 and 117 patients. Two RCTs examined MoM vs. ceramic-polyethylene (CoP) [32,33], five studies MoM vs. metal-polyethylene (MoP) [34,35,36,37,38,39], two studies examined MoM vs. ceramic-ceramic (CoC) [26,40,41], and two MoM vs. hip resurfacing arthroplasty (HRA) [42,43,44]. LH-THA was investigated in one US-American study [35]. All other RCTs investigated MoM SH-THA.

Despite some methodological limitations such as missing description of patient recruitment/randomization, incomplete information on patient characteristics, and incomplete outcome data, all RCTs were considered as having low risk of bias (Table 2).

Determination of metal ions in RCTs

Table 3 presents details of metal ion assessment in the RCTs included. All RCTs reported pre- and postoperative Co-concentrations. Nine [32,33,34,35,36,39,40,41,43,44] RCTs preferred serum as medium for metal ion assessment. Long-term measurement ≥24 months were reported in five RCTs [33,34,35,41].

As detailed in table 4, median Co-concentrations were elevated at each postoperative assessment after implantation of MoM SH-THA, MoM LH-THA, and HRA compared to THA with only one or without metallic part of the bearing. Following MoM SH-THA median serum Co-concentrations varied between 0.66–1.0 μg/L at 6 months [32,33,34,35] and 0.73–1.2 μg/L at 2 years [33,34,35,41] after surgery. After MoM LH-THA median serum Co-levels of 0.66 μg/l and 0.73 μg/L were reported at 6-month and 2-year follow-up, respectively [35]. After HRA, median whole blood Co-concentrations varied between 0.78 and 1.3 μg/L up six months and between 0.16 and 1.2 μg/L two years postoperatively [42,43,44]. The only direct comparison between MoM SH- and LH-THA revealed no relevant differences in the median serum Co-concentration [35].

Two RCTs directly compared MoM SH-THA vs. HRA and revealed qualitatively different results: While Smolders et al. [42] observed higher median and maximum Co-concentrations following HRA compared to MoM SH-THA, Vendittoli et al. [43,44] did not observe relevant differences in mean Co-concentrations following HRA and MoM SH-THA. THA with only one metallic part of the bearing resulted in not or only slightly elevated serum Co-concentrations (Table 4).
Table 9. Co concentration in μg/L in serum/whole blood for MoM LH-THA or HRA vs. MoM SH-THA in epidemiological studies.

| Reference | Intervention | Medium | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------|--------------|--------|--------------|---------------|---------------|---------------|---------------|
| Antoniou 2008 | MoM LH-THA | Whole blood | 18; 58* | 2.3; 58* | | | |
| Pattyn 2011 | HRA | Whole blood | 0.45; 22* | 1.1; 22* | 0.95; 0.7-1.2; 22 | 16; 0.6-0.9; 21 |
| HRA_1 | Whole blood | 0.45; 20* | 1.5; 20* | 1.7; 1-2.4; 18 | | |
| HRA_2 | Whole blood | 0.1; 0.1-26; 60** | 1.2; 0.1-11.4; 51** | 1.3; 0.1-11.4; 42** | 1.5; 0.7-17.6; 21** |
| Witzleb 2006 | HRA | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | |
| HRA_1 | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | | |
| HRA_2 | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | | |
| Smolders 2011a | HRA | Serum | 0.1; 0.1-26; 60** | 1.2; 0.1-11.4; 51** | 1.3; 0.1-11.4; 42** | 1.5; 0.7-17.6; 21** |
| Witzleb 2006 | HRA | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | |
| HRA_1 | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | | |
| HRA_2 | Serum | 0.1; 0.1-0.2; 13 | 5.09; 3.0-7.5; 13 | 5.38; 3.5-7.2; 13 | | | |

Values of the given studies were reported, if they fitted to the fixeds timeframes; if several measurements fitted to one timeframe, those values were reported being nearest to the timeframes given above; e.g. values were reported 3 months and 5 months postoperatively, the values postoperatively are shown in this table.

*Median; n.
**Median; range; n.
***Mean; n.
1 metal ion measurement at mean 73 months postoperatively.
2 metal ion measurement mean 5 years postoperatively.
3 metal ion measurement at mean 73 months postoperatively.
doi:10.1371/journal.pone.0070359.t009
Table 10. Co concentration in serum/whole blood for MoM SH-THA, MoM LH-THA or HRA vs. MoP, CoP, CoC, MoC THA in epidemiological studies.

| Reference       | Intervention | Medium         | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------------|--------------|----------------|--------------|---------------|---------------|---------------|---------------|
| Antoniou 2008   | HRA          | Whole blood    |              | 2.3; 70*      | 2.4; 70*      | 2.4; 70*      | 2.4; 70*      |
| MoM LH-THA      | Whole blood  |                |              | 1.8; 58*      | 2.3; 58*      | 2.3; 58*      | 2.3; 58*      |
| MoM SH-THA      | Whole blood  |                |              | 2.5; 28*      | 2.6; 28*      | 2.6; 28*      | 2.6; 28*      |
| Hart 2006       | HRA          | Whole blood    |              | 4.18; 34***   |               |               |               |

| Reference       | Comparison   | Medium         | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------------|--------------|----------------|--------------|---------------|---------------|---------------|---------------|
| Karamat 2005    | MoM SH-THA   | Whole blood    |              | 0.69; 0.19-3.7; 25** |               |               |               |
| Savarino 2002   | MoM SH-THA   | Serum          |              | 0.97; 0.34-5.32; 26** |               |               |               |
| Hallows 2011    | MoM SH-THA   | Serum          |              | 1.0; 0.3-14.0; 10**4 |               |               |               |
| MoM LH-THA      | Serum        |                |              | 0.7; 0.0-14.0; 10**4 |               |               |               |
| Rasquinha 2006  | MoM SH-THA   | Serum          |              | 1.55; 0.58-7.93; 10**4 |               |               |               |

| Reference       | Comparison   | Medium         | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------------|--------------|----------------|--------------|---------------|---------------|---------------|---------------|
| Pattyn 2011     | MoP THA      | Whole blood    |              | 0.45; 22*     | 1.1; 22*      | 0.95; 0.73-1.2; 22 | 0.8; 0.6-0.9; 21 |

| Reference       | Comparison   | Medium         | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------------|--------------|----------------|--------------|---------------|---------------|---------------|---------------|
| Hart 2009b      | HRA          | Whole blood    |              | 1.71; 1.29-2.33; 88 |               |               |               |
| Isaac 2009      | MoM SH-THA   | Whole blood    |              | 0.45; 19*     | 0.51; 19*     | 0.83; 19*     | 1.0; 19*      |

Cobalt µg/L - Comparison (Median; IQ-Range; n)

| Reference       | Intervention | Medium         | Preoperative | 6 Months (±3) | 12 Months (±3) | 24 Months (±6) | 48 Months (±6) |
|-----------------|--------------|----------------|--------------|---------------|---------------|---------------|---------------|
| Antoniou 2008   | MoP THA      | Whole blood    |              | 1.8; 18*      | 1.7; 18*      |               |               |
| Hart 2006       | MoP THA      | Whole blood    |              |               |               | 2.48; 34***   |               |
| Karamat 2005    | MoP SH-THA   | Whole blood    |              | 0.19; 0.19-1.07; 25** |               |               |               |
| Savarino 2002   | MoP SH-THA   | Serum          |              | 0.62; 0.19-1.45; 15** |               |               |               |
| Hallows 2011    | MoP SH/LH-THA| Serum          |              | 0.35; 0.1-0.9; 10**4 |               |               |               |
| Rasquinha 2006  | MoP SH-THA   | Serum          |              | 0.26; 0.15-3.91; 10**4 |               |               |               |
| Pattyn 2011     | CoC SH-THA_1 | Whole blood    |              | 0.6; 8*       | 0.5; 8*       | 0.5; 8*       | 0.45; 8*      |
Study characteristics epidemiological studies

Table 5 summarizes aggregated characteristics of the epidemiological studies included. Table 6 provides details of the characteristics of each epidemiological study included. Metal ion concentrations following HRA were reported in 48 studies (52%). Information on inclination and anteversion were reported in 30 studies (32%) and in 16 (17%) studies, respectively. Information on mean age was reported in 60 studies (71%). The sex distribution of patients was reported in 64 studies (69%) and varied substantially with 19 to 90% of the study populations being female.

The vast majority of studies (n = 86; 83%) had significant methodological shortcomings such as a lack of reference group, lack of preoperative baseline assessment, lack of essential information on implant characteristics or metal ion measurement, and/or insufficient follow-up rates and were therefore considered as having a high risk of bias.

Determination of metal ions in epidemiological studies

87 and 85 epidemiological studies reported Co and Cr values following hip replacement, respectively. No study differentiated between Cr(III) and Cr(VI). Metal ion concentration was most often measured in whole blood (n = 51), serum (n = 47), and urine (n = 19). Few studies investigated ion levels in erythrocytes (n = 2), plasma (n = 5), or in synovia (n = 3). Inductively coupled plasma mass spectrometry (ICP-MS) was used in 56 studies (60%), atomic absorption spectrometry (AAS) in 33 studies (36%), and inductively coupled plasma atomic emission spectrometry (ICP-AES) resp. inductively coupled plasma optical emission spectrometry (ICP-OES) in three studies for metal ion detection. Only 24 studies (26%) reported preoperative (baseline) metal ion concentrations. For more details on metal ion assessment in the epidemiological studies included please refer to table 7.

Metal ion concentrations in epidemiological studies

Table 8 summarizes median serum Co-concentrations, 75th percentiles, and maximum values of Co-concentrations before and after hip replacement stratified by the type of intervention (MoM SH-THA, MoM LH-THA, HRA). After MoM SH-THA median Co-concentrations varied between 0.65 and 1.5 µg/L at six months and between 0.7 and 1.7 µg/L two years postoperatively [42,45,46]. After HRA, median serum Co-concentrations varied between 1.12 and 3.7 µg/L six months and between 0.54 and 4.28 µg/L two years postoperatively indicating higher Co-levels after HRA vs. MoM SH-THA [45,46,47,48,49,50]. Median Co-concentrations after MoM LH-THA varied between 0.7 and 3.26 µg/L six months and between 3.77 and 5.38 µg/L two years postoperatively [48,49,51].

One important result of our systematic review is that the maximum serum Co-levels were consistently higher at all postoperative assessments in patients who received MoM LH-THA and HRA [13,48,49,51,52,53,54,55] compared to patients who received MoM SH-THA [45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60] (Table 8).

Tables 9 and 10 summarize the results of comparative epidemiological studies. In accordance with these indirect comparisons from epidemiological studies, median Co-concentrations following MoM LH-THA and HRA tended to be higher compared to MoM SH-THA. Consistently, MoM LH-THA, MoM SH-THA, and HRA resulted in higher metal ion concentrations than THA with CoP, CoC, and MoP-implants.

Conclusions on the role of patient characteristics (age, sex) on metal ion concentration could not be drawn due to a lack of
standardization in the design and reporting of the epidemiological studies included.

The levels of Cr and other metal ions showed similar distributions and lead to the same conclusions as the Co-ion levels reported (data available on request from the corresponding author).

Course of metal ion concentration pre- vs. postoperative

Figure 2 provides an overview of the course of metal ion concentrations in studies reporting baseline serum Co-values and at least 2 postoperative Co-measurements. All MoM-interventions showed an increase in median serum Co-concentration. Again, highest median levels were observed in patients with HRA or MoM LH-THA. In some studies median Co-concentrations peaked at 12 months follow-up and declined thereafter. Other studies showed stable (increased) median serum Co-concentrations until 4-years follow-up.

Maximum Co-concentrations in epidemiological studies

Authors applied different definitions of outlier/extreme values of Co-concentration ranging between 0.25 and 124.9 µg/L for all bearings. Details on the reported maximum Co-concentrations in epidemiological studies are provided in table 11. MoP THA generally resulted in lower extreme values than MoM hip replacements. In studies investigating MoM SH-THA maximum Co-concentrations ranged between 0.72 and 26.0 µg/L. The highest Co-concentrations were observed after MoM LH THA (range of maximum values: 1.8–79.3 µg/L) and after HRA (range of maximum values: 1.4–124.9).

Due to substantial differences in the design, interventions, methods of metal ion assessment, study populations and study reporting, we considered statistical meta-analysis not to be indicated.

Local clinical reactions

Local metal-related adverse reactions were reported in 9 epidemiological studies [5,6,13,19,20,53,55,68,69]. As summarized in table 12 ARMD, metallosis and pseudotumors were the most frequently reported metal-related adverse reactions. Six studies reported Co-concentrations in well and poorly functioning implants [5,18,19,20,53]. Cases with local metal-related adverse reactions (poorly functioning implants) had consistently higher metal ion concentrations than patients with well-functioning THA (Figure 3).

Systemic clinical reactions

Five studies [61,62,70,71,72] examined possible associations between metal ion concentrations and nephrotoxicity. Daniel et al. [71] examined renal clearance and renal concentrating efficiency of cobalt. The renal efficiency, i.e. the ratio of urine cobalt concentration to plasma cobalt concentration, was 0.9 (IQR 0.7–1.6) for preoperative controls and 3.2 (IQR 1.7–5.1) in patients with MoM THA or HRA. No threshold was endorsed at which renal capacity is overextended. Corradi et al. [70] examined metal ion concentrations in whole blood and renal markers in patients with HRA and in healthy controls. The median Co-excretion in patients with HRA was 12.9 µg/24-h urine (range 6.1–71.5 µg). No elevated renal markers were found in comparison with controls. Grued et al. and Marker et al. [61,62] investigated serum metal ions, blood urea nitrogen, and serum creatinine in overlapping cohorts of patients with MoM THA. The median (range) serum creatinine value preoperatively and at 10 years follow-up was 0.88 mg/dL (0.63–1.21 mg/dL) and 0.86 mg/dL (0.55–1.51 mg/dL), respectively. Evidence for or against further systemic toxicity or carcinogenicity could not be revealed from the studies included.

Discussion

As highlighted in this comprehensive systematic review, there is substantial and consistent evidence that patients receiving hip replacement with a MoM-bearing are at increased risk for systemic accumulation of metallic products. In the 104 studies analyzed, median metal ion concentrations were persistently elevated after implantation of MoM-bearings in all investigated mediums (whole blood, serum, plasma, erythrocytes, urine), irrespective of patient characteristics and study characteristics.

Overall, metal ion concentrations in body fluids were assessed in 9,957 patients in the 11 RCTs and 93 epidemiological studies.
### Table 11. Maximal postoperative Co-concentrations after THA in RCTs and epidemiological studies.

| Reference     | Intervention                  | Outlier                                                                 |
|---------------|-------------------------------|-------------------------------------------------------------------------|
| Brodner 2003  | not reported                  | overall postoperative: 2 outlier with Co-concentrations in serum of 24 and 119.2 µg/L |
| Brodner 2004  | MoM THA                       | overall postoperative: 3 outlier with Co-concentrations in serum of 4.9–12.9 µg/L |
| Dahlstrand 2009 | MoM SH-THA                  | overall postoperative: 7 outlier with Co-concentrations in serum up to >9 µg/L |
|               | MoP THA                       | overall postoperative: 9 outlier with Co-concentrations in serum up to approx. 1.3 µg/L |
| Engh 2009     | MoM LH-THA                    | overall postoperative: 2 outlier with Co-concentrations in serum of approx. 1.8 and approx. 3.4 µg/L |
|               | MoM SH-THA                    | overall postoperative: 2 outlier with Co-concentrations in serum of approx. 2.0 and approx. 2.8 µg/L |
|               | MoP THA                       | overall postoperative: 8 outlier with Co-concentrations in serum of approx. 0.25–approx. 2.75 µg/L |
| Zijlstra 2009,2010 | MoM SH-THA                  | 2 years postoperative: 2 outlier with Co-concentrations in serum of 7.0 and 15.6 µg/L |
|               | not reported                  | 5 years postoperative: 1 outlier with Co-concentration in serum of 7.0 µg/L |
|               | not reported                  | 10 years postoperative: 1 outlier with Co-concentrations in serum of 11 µg/L |
| Allan 2007    | HRA                           | outlier: 1.5-fold boxwidth above 75th percentile                          |
|               |                               | overall postoperative: 6 outlier Co-concentrations in serum of 13.6–124.9 µg/L |
| Antoniou 2008 | MoM SH-THA                    | overall postoperative: 5 outlier with Co-concentrations in whole blood of approx. 4–approx. 6.5 µg/L |
|               | MoM LH-THA                    | overall postoperative: 9 outlier with Co-concentrations in whole blood of approx. 2.5–approx. 10 µg/L |
|               | HRA                           | overall postoperative: approx. 11 outlier with Co-concentrations in whole blood of approx. 3.3–approx. 11.7 µg/L |
| Bernstein 2011a | MoM SH-THA                   | overall postoperative: 6 outlier with Co-concentrations in whole blood of approx. 2.5–approx. 19 µg/L |
|               | MoM LH-THA                    | overall postoperative: 3 outlier with Co-concentrations in whole blood of approx. 24.0–approx. 37.5 µg/L |
| Bernstein 2011b | MoM SH-THA + MoM LH-THA + HRA | whole cohort consists of outlier with Co-concentrations in whole blood ≥10 µg/L |
| Daniel 2010   |                               | outlier: values above upper quartile + 3-fold IQ-range                  |
| De Haan 2008  | HRA (steep)                   | overall postoperative: 14 outlier with Co-concentrations in plasma of approx. 8.8–approx. 14.5 µg/L |
|               | HRA (non-steep)               | overall postoperative: approx. 12 outlier with Co-concentrations in serum of approx. 5–approx. 30 µg/L |
| Delauanay 2000 | MoM SH-THA                  | overall postoperative: 6 patients with Co-concentrations in whole blood >5 µg/L |
| Delauanay 2004 | MoM SH-THA                   | laboratory reference value value 5 µg/L for Co in whole blood            |
|               |                               | overall postoperative: 15 outlier with Co-concentrations in whole blood >5 µg/L with max. 36 µg/L |
| Reference     | Intervention                  | Outlier                                                                 |
| De Smet 2008  | MoM (unilateral)              | overall postoperative: 1 outlier with Co-concentration in serum of approx. 93 µg/L |
|               | MoM (bilateral)               | overall postoperative: 1 outlier with Co-concentration in serum of approx. 62 µg/L |
| Garbuz 2010   | HRA                           | overall postoperative: 2 outlier with Co-concentrations in serum of approx. 1.5+1.8 µg/L |
| Grübl 2007    | MoM LH-THA                    | overall postoperative: 1 outlier with Co-concentrations in serum of approx. 2.4 µg/L |
| Hallows 2011  | MoM SH-THA                    | overall postoperative: 2 outlier with Co-concentrations in serum of approx. 8.4 resp. 50.1 µg/L |
| Imanishi 2010 | MoM LH-THA                    | overall postoperative: 1 outlier with Co-concentration in serum of approx. 79.3 µg/L |
| Isaac 2009a   | MoM SH-THA + CoC SH-THA       | overall postoperative: 8 outlier with Co or Cr-concentrations in whole blood >0 µg/L |
| Isaac 2009b   | HRA                           | overall postoperative: 6 outlier with Co-concentrations in whole blood >10 µg/L |
| Kim 2011      | HRA                           | overall postoperative: approx. 14 outlier with Co-concentrations in serum approx. 3.0–approx. 49 µg/L |
| Kwon 2010     | HRA (no pseudotumor)          | overall postoperative: 3 outlier with Co-concentrations in serum approx. 7.0–approx. 9.5 µg/L |
| Kwon 2011     | MoP THA                       | overall postoperative: 1 outlier with Co-concentration in serum of approx. 3.8 µg/L |
|               | HRA (no pseudotumor)          | overall postoperative: 4 outlier with Co-concentrations in serum approx. 6.0–approx. 10.5 µg/L |
| Langton 2011a | HRA (incl. ASR)               | overall postoperative: several outlier with Co-concentrations in serum approx. 20 µg/L–240 µg/L |
| Langton 2011b | HRA – DePuy (ASR)             | overall postoperative: 56 outlier (23 %) with Co-concentrations in serum >7 µg/L |
|               | HRA – Smith&Nephew/Wright Medical Technology | overall postoperative: 29 outlier (6 %) with Co-concentrations in serum >7 µg/L |
| Langton 2011c | HRA – DePuy (ASR); MoM LH-THA – DePuy | overall postoperative: 67 outlier (26,1 %) with Co- or Cr-concentrations in serum >7 µg/L |
| Reference | Intervention | Outlier |
|-----------|--------------|---------|
| Lavigne 2011 | MoM LH-THA – Zimmer | overall postoperative: 2 outlier with Co-concentrations in whole blood of approx. 6.3 and approx. 6.8 μg/L |
| | MoM LH-THA – Biomet | overall postoperative: 14 outlier with Co-concentrations in whole blood of approx. 1.5– approx. 13.0 μg/L |
| | MoM LH-THA – DePuy | overall postoperative: 9 outlier with Co-concentrations in whole blood of 2.2–approx. 8.4 μg/L |
| | MoM LH-THA – Smith&Nephew | overall postoperative: 5 outlier with Co-concentrations in whole blood of approx. 3.0– approx. 5.2 μg/L |
| Lazennec 2009 | MoM LH-THA | overall postoperative: 1 outlier with highest Co-concentration in serum of 47 μg/L |
| Pelt 2011 | MoM LH-THA | overall postoperative: 4 outlier (unilateral) with Co-concentrations in serum of approx. 1.2– approx. 5.6 μg/L |
| Pilger 2002 | MoM THA | overall postoperative: 16 outlier with Co-concentration in whole blood of >5 μg/L |
| Savarino 2002 | MoM THA | reference value for Co of 0.72 μg/L (Italian health agency) |
| | MoM SH-THA | overall postoperative: 17 outlier (65 %) with Co-concentrations in serum > reference value |
| | MoP THA | overall postoperative: 90% with Co-concentrations in serum > reference limit 0.4 μg/L |
| Savarino 2003 | MoM SH-THA | overall postoperative: 24 outlier with Co-concentrations in serum > median reference value of 0.29 μg/L for Co |
| Savarino 2006 | MoM SH-THA | overall postoperative: 5 outlier (33 %) with Co-concentrations in serum > reference value of 0.4 μg/L for Co |
| Schaffer 1999 | MoM THA | overall postoperative: 12 outlier with Co-concentration in whole blood of >5 μg/L |
| Smolders 2011b | MoM SH-THA | overall postoperative: 5 outlier with Co-concentration in whole blood of approx. 2.1– approx. 4.2 μg/L |
| Tkaczyk 2010 | MoM SH-THA | overall postoperative: 12 outlier with Co-concentrations in whole blood of approx. 4.0– approx. 8.2 μg/L |
| Vendittoli 2007+2010 | MoM SH-THA | outlier: 1.5–3 boxwidth above 3. quartile; extreme values: >3 boxwidth above 3. quartile |
| | HRA | overall postoperative: 9 outlier with Co-concentration in whole blood of approx. 3.0– approx. 6.5 μg/L |
| Vendittoli 2011 | MoM LH-THA | overall postoperative: 2 outlier with Co-concentrations in whole blood approx. 5.8– approx. 7.0 μg/L |
| Williams 2011 | MoM LH-THA | overall postoperative: 1 outlier with Co-concentration in serum >50 μg/L |
| Witzleb 2006 | MoM SH-THA | overall postoperative: 4 outlier with Co-Concentrations in serum approx. 5.5– approx. 9.5 μg/L |

**Table 11. Cont.**

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included in this review. Despite heterogeneity in the study designs, techniques and medium of metal ion assessment, investigators consistently observed elevated median/mean metal ion concentrations after MoM THA and HRA compared to baseline, i.e. before surgery. Metal-free hip replacements did not result in increased metal ion levels. Metal ion concentrations following MoP and MoC THA were much lower compared to MoM THA or HRA.

One important finding from this review is that stemmed large-head MoM-implants and HRA tended to result in higher Co-concentrations than small-head MoM-implants. In several studies very high serum cobalt concentrations above 50 μg/L were measured in patients who had received large-head MoM-implants or HRA.

These findings have significant clinical relevance, as increased metal ion concentrations translate into increased risk for the development of local adverse reactions such as ARMD. In many cases ARMD results in the indication for the revision of MoM-implants.[13] One current issue of debate is the definition of a cutoff cobalt level, above which revision should be considered.

Hart et al. [8,18,30] recommend a serum cobalt threshold level of 4.97 μg/L based on ROC-curve analyses. However, no explicit advice is given on how to treat patients above this value. Recommendations of present literature currently state Co-

Table 12. Documentation of local metal-related adverse reactions.

| Reference   | local clinical reactions                                                                 |
|-------------|-----------------------------------------------------------------------------------------|
| Bolland 2011 | 14 patients (7.6 %) with revision due to ARMD                                           |
| DeSmet 2008  | 10 patients (38.5 %) with metallosis                                                     |
| Kwon 2010    | 10 patients (14.3 %) with pseudotumors diagnosed by MRI                                  |
| Kwon 2011    | 7 patients (4 %) with pseudotumors diagnosed by MRI                                      |
| Langton 2010 | 16 patients with ASR, revision due to ARMD                                              |
| Langton 2011a| 60 failures related to ARMD, incl. patients with ASR                                    |
| Langton 2011c| 82 failures (31.9 %) related to ARMD, patients with ASR HRA and ASR THA                |
| Matthies 2011b| 72 patients (68.6 %, incl. patients with ASR) with pseudotumors diagnosed by MARS-MRI |
| Williams 2011| 15 patients (20 %) with pseudotumors diagnosed by ultrasound                            |

ARMD = adverse reaction to metal debris.
ASR = Articular Surface Replacement, Firma DePuy.
MRI = Magnetic Resonance Imaging.
MARS-MRI = Metal Artifact Reduction Sequence-Magnetic Resonance Imaging.
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Figure 3. Summarizes six studies which reported Co-concentrations in well and poorly functioning implants [55,18,19,20,53]. Cases with local metal-related adverse reactions (poorly functioning implants) had consistently higher metal ion concentrations than patients with well-functioning THA.
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concentrations in serum or plasma greater 2 up to 7 µg/L as a predictor for a subjectively adverse outcome and an increased risk of MoM-specific complications [8,18,30,73].

While MoM SF THA (head diameter ≤32 mm) seem to show similar long-term survival rates as hip replacement with other bearings [61,74,75,76,77], the implantation of stemmed LH-THA (head diameter ≥36 mm) is associated with significantly higher short-term revision rates in clinical studies as well as arthroplasty registries [15,16,17,44,45,48,68,78,79]. The elevated release of metal products in these stemmed LH-implants may be due to fretting corrosion at the head-taper-junction in addition to a metal particle release from bearing surfaces.

Besides local tissue damages, it is important to gain better understanding about the potential systemic adverse effects induced by metal ion accumulation, i.e. toxicity, carcinogenicity, teratogenicity. The degree to which increased metal ion concentrations after MoM THA translate into increased risk for systemic toxicity cannot be sufficiently answered based on the studies identified and analyzed in this review. Until now, epidemiological studies have not revealed clinically relevant toxic damages of the kidney, heart or nervous system after MoM THA [45,58-60]. Case reports, however, indicate the possibility of metal-induced cardiomyopathy [21,22]. An elevated risk of incident cancer following hip replacements with MoM bearing could not be identified yet [80,81,82], but studies may have been underpowered.

There is substantial evidence that occupational metal exposure is related to increased cancer risk. It has to be noted, however, that bioavailability of Cr(III) compounds is substantially lower than those of Cr(VI) compounds. Cr(VI) compounds are able to infiltrate into cells due to transmembrane motion and to operate genotoxic following reduction to Cr(III). Carbid metal workers exposed to Co are at increased risk for fatal lung cancer [83]; the 'International Agency for Research on Cancer (IARC)’ classified Co to be possibly carcinogenic. Persons being occupationally exposed to Co have higher Co urine concentrations when compared to the general population. It should be noted that specific attentiveness was laid on possibly elevated Cr(VI) in body fluids due to ascertained carcinogenicity of Cr(VI) compounds. Due to considerable differences in exposure routes, the effects of increased metal ion concentrations as a consequence of MoM hip replacement cannot be directly compared with the systemic effects of occupationally acquired (mainly inhaled) metals.

Strengths and weaknesses of this review

This systematic review was conducted in accordance with the PRISMA checklist [31]. Systematic literature search and assessment of eligibility of studies identified was done independently by two reviewers. Study quality assessment was based on a priori defined criteria. Due to methodological limitations in most of the studies included and due to substantial qualitative differences in the study design, conduct, and reporting, quantitative meta-analysis was not indicated. However, as highlighted above, the qualitative results are consistent despite the heterogeneity of the studies included so that we consider the conclusions drawn to be robust and generalizable.

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Implications for clinical practice and future research

After hip replacement with contemporary MoM bearings the release of metal ions is highest in stemmed implants with large heads followed by resurfacing devices and also — but on a lower level — small heads. As the deposition of metal products may not only lead to local but possibly also systemic adverse health outcomes, the conclusions of this review have high relevance not only for orthopaedic surgeons, but also for other medical disciplines.

Due to the risk of systemic accumulation of metal ions following implantation of hip replacements with MoM bearing, consideration on risks and benefits should be done carefully and individually for every patient prior to surgery.

The authors support a “time out” of stemmed large-head MoM-THA and recommend a restricted indication for hip resurfacing arthroplasty to patients without risk factors such as small implant size, female gender, and renal insufficiency [5,79].

Patients with status post implantation of MoM should be followed by standardized monitoring. Especially examined ions, medium and analysis technique should be standardized to allow comparability of results and further analysis. Close interdisciplinary cooperation is necessary in case of potential systemic reactions due to increased metal ion concentrations.

An approach to this unresolved difficulty was one of the main objectives of an international and interdisciplinary expert conference, which took place in our institution. In April 2012, we hosted an international multi-disciplinary expert conference endorsed by the “European Federation of National Associations of Orthopaedics and Traumatology” (EORT), “European Hip Society” (EHS), and the “German Osteoarthritis Society” in order to provide clinically-relevant advice on how to treat and monitor current and future patients with MoM THR. Beside orthopaedic surgeons being experienced with MoM hip endoprosthetics, epidemiologists, toxicologists, biomechanics, and pathologists as well as a patients representative and regulatory agency representative from 7 European countries and the US participated.

The statement resulting from this consensus initiative is published in detail on web sites of European [30] and German [84,85] orthopaedic societies [86]. Beside detailed recommendations on monitoring of MoM hip replacements and metal ion measurement the statement also summarizes prioritized questions for future research. One research issue that needs to be prioritized is the investigation of potential systemic risks due to accumulation of metal ions.

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Author Contributions

Analyzed the data: AH FH JL AS HD KPG JS. Wrote the paper: AH FH JL AS HD KPG JS.
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