PLOS | ONE

RESEARCH ARTICLE

Increased Mortality in Metal-on-Metal versus Non-Metal-on-Metal Primary Total Hip Arthroplasty at 10 Years and Longer Follow-Up: A Systematic Review and Meta-Analysis

B. G. Pijls[1]*, J. M. T. A. Meessen[1], J. W. Schoones[4], M. Fiocco[2,3], H. J. L. van der Heide[1], A. Sedrakyan[5,6], R. G. H. H. Nelissen[1]

1 Department of Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands, **2** Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands, **3** Mathematical Institute, Leiden University, Leiden, The Netherlands, **4** Walaeus Library, Leiden University Medical Centre, Leiden, The Netherlands, **5** FDA Medical Device Epidemiology (MDEpiNet) Science and Infrastructure Center, U.S. Food and Drug Administration, Silver Spring, MD, United States of America, **6** Department of Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States of America

* b.g.c.w.pijls@lumc.nl

CrossMark
click for updates

🔓 OPEN ACCESS

Abstract

Importance

There are concerns about increased mortality in patients with metal-on-metal bearings in total hip arthroplasty (THA).

Objective

To determine the mortality and the morbidity in patients with metal-on-metal articulations (MOM THA) compared to patients with non-metal-on-metal articulations (non-MOM THA) after primary total hip arthroplasty.

Data Sources

Search of PubMed, MEDLINE, EMBASE, Web of Science, Cochrane, CINAHL, Academic-SearchPremier, ScienceDirect, Wiley and clinical trial registers through March 2015, augmented by a hand search of references from the included articles. No language restrictions were applied.

Study Selection

Two reviewers screened and identified randomised controlled trials and observational studies of primary total hip arthroplasty comparing MOM THA with non-MOM THA.

Data Extraction and Synthesis

Two reviewers independently extracted study data and assessed risk of bias. Risk differences (RD) were calculated with random effect models. Meta-regression was used to explore modifying factors.

Main Outcomes and Measures

Difference in mortality and difference in morbidity expressed as revisions and medical complications between patients with MOM THA and non-MOM THA.

Results

Forty-seven studies were included, comprising 4,000 THA in randomised trials and over 500,000 THA in observational studies. For mortality, random effects analysis revealed a higher pooled RD of 0.7%, 95%, confidence interval (CI) [0.0%, 2.3%], I-square 42%; the heterogeneity was explained by differences in follow-up. When restricted to studies with long term follow-up (i.e. 10 years or more), the RD for mortality was 8.5%, 95%, CI [5.8%, 11.2%]; number needed to treat was 12. Further subgroup analyses and meta-regression random effects models revealed no evidence for other moderator variables (study level covariates, e.g. resurfacing vs. non-resurfacing MOM) than follow-up duration. The quality of the evidence presented in this meta-analysis was characterized as moderate according to the CLEAR-NPT (for non-pharmacological trials) and Cochrane risk of bias Table.

Conclusions and Relevance

Meta-analysis suggests there may be an increased long-term risk of mortality and revision surgery for patients with MOM THA compared to patients with non-MOM THA.

Registration

PROSPERO 2014:CRD42014007417

Introduction

Metal-on-metal bearings have been used since the early years of total hip arthroplasty (THA) development, and are still used today with 2.000 procedures in 2014 in the National Joint Registry alone [1]. Early historical prostheses from the 1960's 1970's and 1980s include the McKee Farrar hip and Ring hip prosthesis [2]. They can be considered the first generation of metal-on-metal total hip arthroplasty (MOM-THA). However, a recent long-term follow-up study of first generation MOM-THA reported increased mortality in patients with metal-on-metal bearings in total hip arthroplasty compared to patients with non-metal-on-metal bearings [3]. While this is an isolated report, metal-on-metal bearings in total hip arthroplasty are known to produce metallic particles due to wear and corrosion [4]. These metallic particles may lead to local and systemic adverse effects (e.g. nephrotoxicity, cardiotoxicity, carcinogenicity, and structural changes in the visual pathways and basal ganglia), which in turn could lead to increased mortality [5, 6]. These reports are in conflict with two recent registry-based studies of modern, second generation MOM-THA which do not report higher mortality associated with metal-on-metal hips [7, 8]. However, there are concerns that registry-based studies in this setting may be subject to residual confounding [9].

The purpose of this systematic review and meta-analysis is therefore to determine the overall mortality and morbidity in randomised controlled trials and observational studies for first- and second-generation metal-on-metal bearings compared to non-metal-on-metal bearings after primary total hip arthroplasty in patients with endstage primary and secondary osteoarthritis.

Materials and Methods

The reporting of this systematic review is in accordance with the PRISMA statement and a protocol has been registered a priori at the Prospero registry (PROSPERO 2014: CRD42014007417) S1 and S2 Files.[10]. After the PROSPERO protocol was registered, we also performed a systematic review of observational studies evaluating mortality and medical complications (i.e. cancer incidence, kidney failure or cardiomyopathy) for metal-on-metal bearings compared to non-metal-on-metal bearings in patients with total hip arthroplasty. This would allow us to compare the results from randomised controlled trials (RCTs) to the results from observational studies. The population of interest consisted of patients treated with primary total hip arthroplasty due to endstage primary and secondary osteoarthritis of the hip after failed conservative treatment. The intervention group consisted of patients who received metal-on-metal bearings, including total hip resurfacing with metal bearings: MOM THA. The control group consisted of patients with primary total hip arthroplasty with non-metal-on-metal bearings (e.g. metal-on-polyethylene, metal-on-ceramic, ceramic-on-ceramic, ceramic-on-polyethylene): non-MOM THA.

The primary outcome was mortality, expressed as the number of patients who died within the study period. The secondary outcome was morbidity, expressed as the number of surgical and medical complications experienced by the subjects within the study period.

Data Sources and Searches

The search strategy was composed in collaboration with a librarian experienced in the field of total hip arthroplasty, and included studies, abstracts, and trial registry records from the date of their their inception to the end of March 2015. The following databases were searched: PubMed, MEDLINE, EMBASE, Web of Science, Cochrane, CINAHL, Academic Search Premier. The following journal publisher databases were also searched: ScienceDirect and Wiley. References of included articles were screened for relevant studies. Finally, clinical trial registers (clinicaltrails.org; WHO InternationalClinicalTrialsRegistryPlatform; Multi-register; Dutch-TrialRegistry) were searched to identify any ongoing trials that were completed but not yet published. Contact persons of eligible trial registry records were contacted by e-mail, and at least two reminders were sent in case of no response.

The search strategy for the RCTs consisted of the following components, each defined by a combination of controlled vocabulary and free text terms:

1. implant type: metal-on-metal, resurfacing and brand names

2. total hip arthroplasty

3. randomised controlled trial.

   An example Pubmed search is provided in S3 File.

Study Selection

Initially, the literature was screened on title and abstract. This screening was performed by two reviewers (BP and JM) independently. Both reviewers recorded their findings in a pre-designed electronic database. Both databases were then compared and any disagreements were resolved by consensus or by consulting a referee. When the information in the abstract did not suffice, or if any doubt remained, the studies remained eligible.

The fulltext papers of eligible studies were independently evaluated by two reviewers (BP and JM). Both recorded their findings in a pre-designed electronic database. Any disagreements were resolved by consensus or by consulting a referee.

All bibliographic records identified through the electronic searches were collected in an electronic reference database and subjected to the following inclusion and exclusion criteria:

Inclusion criteria: 1) primary total hip arthroplasty

2) comparison of metal-on-metal bearing with non-metal–on-metal bearing

3) randomised controlled trial or quasi-randomised controlled trial (for RCTs)

4) follow-up of at least 3 months.

Exclusion criteria: 1) only bilateral cases with metal-on-metal and non-metal-on-metal in the same patient (this would not allow us to determine mortality for the groups separately)

2) no reporting/evaluation of mortality or morbidity.

Data Extraction and Quality Assessment

Two reviewers (BP and JM) independently extracted data and appraised the risk of bias from included studies regarding mortality and morbidity, patient demographics, study characteristics, and implant specifications in a pre-defined electronic data sheet. The data sheet was designed during the extraction of trial data on a random sample of eligible studies. Any disagreements were resolved by consensus or by consulting a referee.

Risk of bias was appraised at the level outcome using the CLEAR-NPT checklist and Cochrane risk of bias table [11]. The CLEAR-NPT checklist was specifically designed to appraise the methodological quality of non-pharmacological trials and contains items related to the standardization of the intervention, care provider influence, and additional measures to minimize the potential bias from lack of blinding of participants, care providers, and outcome assessors [11]. Any disagreements were resolved by consensus or by consulting a referee.

Data Synthesis and Analysis

A random effects model was employed to pool the risk difference of individual studies in order to estimate an overall risk difference and its associated confidence interval. The inverse variance method, which gives more weight to larger studies, was used to pool outcomes for different studies. The overall effects, corresponding to a random effects model, is reported in the forest plots along with its confidence intervals. The sizes of the square boxes on the forest plots are proportional to the total number of patients in the selected studies. An overall test on heterogeneity between studies was performed. To estimate between-study variance, DerSimonian-Laird's method was employed [12]. In case moderators are incorporated in the model, the weighted estimation gives an estimate of the weighted least squares relationship between the moderator variables and the true effect. All analyses were performed using Metafor Package R statistics [13]. The measure of interest chosen was risk difference (RD) to account for any "empty cells" for mortality or morbidity corresponding to a particular study.

Randomised controlled trials of first and second generation MOM THA and observational studies of first generation MOM THA (evolution of prosthesis development) were eligible for meta-analysis. Observational studies of second generation MOM were considered subject to strong selection bias [7–9], so they were not eligible for meta-analysis. The amount of heterogeneity was assessed through visual inspection of forest plots and by calculating tau-squared statistics (which is the amount of heterogeneity in the true RDs) and I-squared statistics. The latter estimates how much of the total variability in the effect size estimates is due to heterogeneity among the true effects. In the presence of heterogeneity, and if data allowed, random effects meta-regression on pre-defined factors (study level covariates) was employed. These factors were defined in the PROSPERO protocol: type of metal bearing (resurfacing vs. non-resurfacing), type of non-metal bearing, head size, fixation method (cemented vs. cementless), indication for THA (primary vs. secondary osteoarthritis), methodological items from CLEAR

NPT and Cochrane risk of bias Table, duration of follow-up, mean age at operation, gender distribution (% of females and males), and pre-operative health (American Society of Anesthesiologist (ASA) scores).

To assess for publication bias, we constructed a funnel plot for studies reporting the primary outcome. In the case of asymmetry in the funnel plot, or if publication bias was suspected based on the trial registries, a trim-and-fill method and cumulative meta-analysis was used to explore the magnitude and direction of publication bias.

Results

RCTs

The literature search yielded 686 hits and 30 studies (38 papers) published between 1975 and 2014 were included, for a total of 1,806 patients with MOM THA and 2,151 patients with non-MOM THA [2, 14–42]. Three studies were not published in peer reviewed journals (1 abstract, 2 trial registry reports) [19, 21, 41] and 27 studies [2, 14–18, 20, 22–40, 42] were published in 38 papers; 7 studies on the same RCT were published in more than one paper, including1 study that was published in 3 papers. These papers were mostly follow-up reports. For the analyses, we used the paper with the longest follow-up. Details of study selection and flow of the review are shown in Fig 1 and details of included studies are shown in Table 1.

The search of the trial registry reports yielded 111 hits, of which 12 were deemed eligible. The contact persons of these 12 trials were approached. Four did not respond, even after at least 2 reminders. Eight did respond, which resulted in the inclusion of 2 trials. One additional trial was already included as a journal version. Five trial registry reports were excluded because the study was not a randomised controlled trial (n = 4) or there was no information available on mortality or morbidity (n = 1).

Observational studies

The literature search yielded 288 hits and 9 studies were included, with a total of 78,110 patients with MOM THA and 451,605 patients with non-MOM THA, published between 1996 and 2014 [3, 7, 8, 43–48]. Details of study selection and flow of the review are shown in Fig 1 and details of included studies are shown in Table 2.
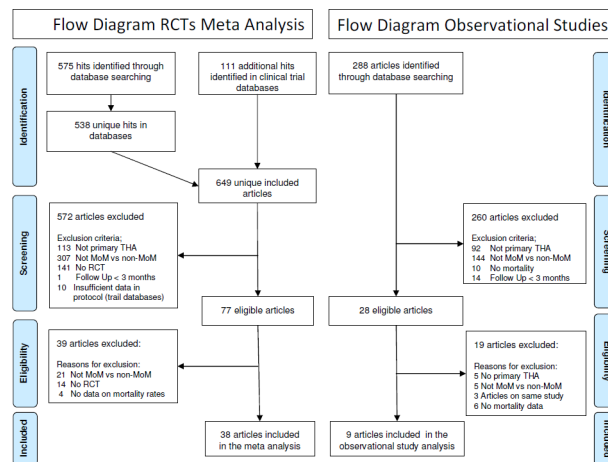

Fig 1. PRISMA flow chart.

doi:10.1371/journal.pone.0156051.g001

Table 1. Details of included RCTs.

Author	Publication year	MoM Generation	N patients	N hips	N deaths	N revision	Resurfacing	non-MoM				type non-MoM	followup time (year)
								N patients	N hips	N deaths	N revision		
Zagra	2013	2nd	20	20	0	0	no	40	40	0	0	Polyethylene—Ceramic	0,33
Grubl	2006	2nd	15	15	0	0	no	13	13	0	0	Ceramic—Ceramic	1
Schouten	2012	2nd	39	39	0	0	no	42	42	0	0	Ceramic—metal	1
Jensen	2011	2nd	21	21	0	0	yes	22	22	0	0	Polyethylene—Ceramic	1
Zijlstra	2011	2nd	25	25	0	0	no	25	25	0	0	Polyethylene—metal	1
Hanna	2012	2nd	28	28	0	0	no	23	23	0	0	Polyethylene—metal	2
Weissinger	2011	2nd	42	42	0	.	no	38	38	0	.	Ceramic—Ceramic	2
Tiusanen	2013	2nd	46	46	0	2	no	46	46	0	1	Polyethylene—metal	2
Penny	2012	2nd	21	21	0	0	yes	22	22	0	0	Polyethylene—metal	2
nct00208494		2nd	196	196	1	.	no	194	194	1	.	Ceramic—metal	2
Gauthier	2013	2nd	25	25	0	1	no	25	25	2	0	Polyethylene—metal	2
Malviya	2011	2nd	50	50	1	2	no	50	50	2	2	Polyethylene—metal	4
Brodner	2003	2nd	50	50	1	1	no	50	50	2	1	Polyethylene—Ceramic	5
Gustafson	2014	2nd	26	26	0	1	yes	26	26	0	0	Polyethylene—metal	5
Macdonald	2005	2nd	23	23	1	0	no	18	18	0	0	Polyethylene—metal	5,1
Wang	2012	2nd	37	37	0	0	yes	40	40	0	0	Ceramic—Ceramic	6
Engh	2014	2nd	68	68	2	1	no	37	37	2	1	Polyethylene—metal	6,5
Bjorgul	2013	2nd	123	129	6	8	no	251	268	16	4	mixed	7
Zerahn	2011	2nd	74	74	6	.	no	225	225	14	.	mixed	7,6
nct01422564		2nd	12	12	2	.	no	12	12	0	.	Polyethylene—metal	8
Hailer	2011	2nd	41	41	1	.	no	44	44	4	.	Polyethylene—metal	8
Howie	2005	2nd	11	11	0	8	yes	13	13	0	2	Polyethylene—metal	10
Desmarchelier	2013	2nd	111	125	19	3	no	116	125	13	1	Ceramic—Ceramic	10
Zijlstra	2010	2nd	101	102	30	4	no	97	98	23	2	Polyethylene—metal	10,7
Pabinger	2003	2nd	31	32	1	1	no	28	29	1	0	Polyethylene—Ceramic	.

doi:10.1371/journal.pone.0156051.t001

Table 2. Results from observational studies.

Outcome	Study	Resurfacing	MOM generation	IRR	CI	FU	n MOM	n non-MOM
All cause Mortality	Visuri 2010	No	1st	1.05	0.95–1.16	17	579	1585
	Lubbeke 2014	No	2nd	0.90*	0.70–1.20	9,6	883	2458
	Makela 2014	Mixed	2nd	0.78	0.69–0.88	4,6	10728	18235
	McMinn 2012a	Yes	2nd	0.61*	0.50–0.75	3,6	8352	53409
	McMinn 2012b	Yes	2nd	0.68*	0.55–0.84	3,6	8352	50529
	Kendal 2013a	Yes	2nd	0.51*	0.45–0.59	6	7437	22311
	Kendal 2013b	Yes	2nd	0.55*	0.47–0.65	5	8101	24303
Cancer Mortality	Visuri 2010	No	1st	1.27	0.98–1.63	17	579	1585
	Makela 2014	Mixed	2nd	0.78	0.63–0.97	4,6	10728	18235
Cardiac Mortality	Visuri 2010	No	1st	1.07	0.93–1.22	17	579	1585
	Makela 2014	Mixed	2nd	0.79	0.64–0.97	4,6	10728	18235
Cancer incidence	Visuri 1996	No	1st	1.25	0.99–1.58	13,5	698	1831
	Smith 2012	No	2nd	1.02*	0.93–1.12	3	21264	248995
	Lamohamed 2013	No	2nd	1.04*	0.70–1.56	3,2	988	9714
	Makela 2012	Mixed	2nd	0.92	0.81–1.05	4	10728	18235
	Smith 2012	Yes	2nd	0.72*	0.61–0.86	3	19312	248995

* hazard ratio. a = cemented. b = uncemented. IRR = incidence rate ratio. FU = follow up in years.

doi:10.1371/journal.pone.0156051.t002

Mortality

There were 25 RCTs (31 papers) that reported mortality [14, 16–27, 29, 31–38, 40–42]. These RCTs comprised 1,225 patients with MOM THA (71 mortalities) and 1,486 patients with non-MOM THA (80 mortalities). There were five observational studies that reported mortality: one with first generation MOM THA and four with second generation MOM THA [3, 7, 8, 43, 48].

Meta-analysis of RCTs and first generation MOM observational studies [3] showed a difference trend towards higher mortality for MOM THA: RD 0.7%, 95% CI [0.0%, 2.3%], I-square equal to 42%. Fig 2 shows the results of three different meta-analyses, including the RD of the MOM vs. non-MOM studies and the 95% CI associated to each individual study. The overall effect for each separate meta-analysis based on a random effects model is shown. This heterogeneity, I-square 42%, was explained by differences in follow-up, as shown in Fig 2. After correction for follow-up with random effects meta-regression, there was no residual heterogeneity, and I-square was equal to 0%.

When restricted to studies with long term follow-up (10 years or more) [3, 35, 36, 38], the RD was 8.5%, 95% CI [5.8%, 11.2%]; number needed to treat was 12. This analysis used the unadjusted data from Visuri et al. [3] When using adjusted data from Visuri et al [3], the RD was equal to 4.4%, 95% CI [1.4%, 7.4%]. Further subgroup analyses and meta-regression revealed no evidence for other modifying factors (e.g. resurfacing vs. non-resurfacing MOM). Sensitivity analyses with "leave one out" methodology indicated that the results were not significantly influenced by any single study.

Table 2 shows all-cause mortality and cause-specific mortality for first and second generation MOM observational studies. The first generation MOM observational study, which looked
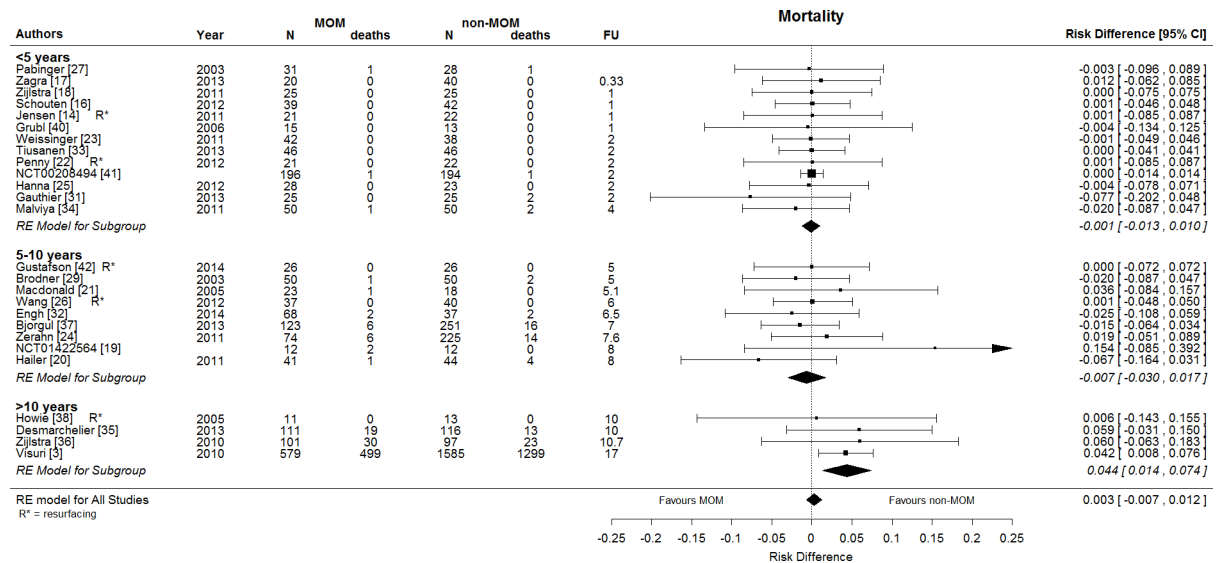
Fig 2. Forest plot showing the risk difference in mortality between MOM THA and non-MOM THA. Overall, there is no difference in mortality between MOM THA and non-MOM THA. After 10 years, there is an increased risk of mortality for MOM THA. Besides one observational study [3] of first generation MOM all other studies are RCTs. RE model = random effects model.

doi:10.1371/journal.pone.0156051.g002

at non-resurfacing MOM in patients with primary osteoarthritis, showed a trend towards increased risk of mortality for patients with MOM compared to non-MOM THA [3], Incidence Rate Ratio 1.05, which is in line with the long term results from the RCTs. The second generation MOM observational studies showed decreased risk of mortality for patients with MOM compared to non-MOM-THA, Hazard Ratios ranging from 0.51 to 0.90 [7, 8, 43, 48]. This is in contrast with the long-term results from RCTs and first generation observational study.

Morbidity: surgical complications

There were 26 RCTs (30 papers), all of second generation MOM THA, that reported revisions [14–17, 25–40, 42, 49–52]. These studies comprised 1,546 MOM THA (49 revisions) and 1,746 non-MOM THA (24 revisions). There were more revisions in MOM THA compared to non-MOM THA: RD 0.8%, 95% CI [-0.1%, 1.7%]; I-square 0%; random effects meta-analysis presented in Fig 3. This effect was stronger for cemented THA, with more revisions in MOM than non-MOM THA: RD 2.7%, 95% CI [0.1%, 5.3%]; number needed to treat was 37.

Regarding revision for aseptic loosening the RD was 0.6%, 95% CI [-0.3%, 1.4%], and regarding revision for septic loosening the RD was 0.3%, 95% CI [-0.3%, 0.9%].

Sensitivity analyses with "leave one out" methodology indicated that the results were not significantly influenced by any single study.

Morbidity: medical complications

There were four RCTs, all of second generation MOM THA, that reported medical complications, with maximum follow-up ranging from 2 to 10 years [19, 35, 41, 50]. Since there were only three or fewer RCTs that reported on each medical complication (nephrotoxicity, cardiotoxicity, carcinogenicity, and general medical complications [e.g. venous thrombosis]) meta-analysis was not considered appropriate. Data from single studies are reported in Table 3.

There were four observational studies that reported cancer incidence: one with first generation MOM THA and three with second generation MOM THA, see Table 2 [44–47]. The first
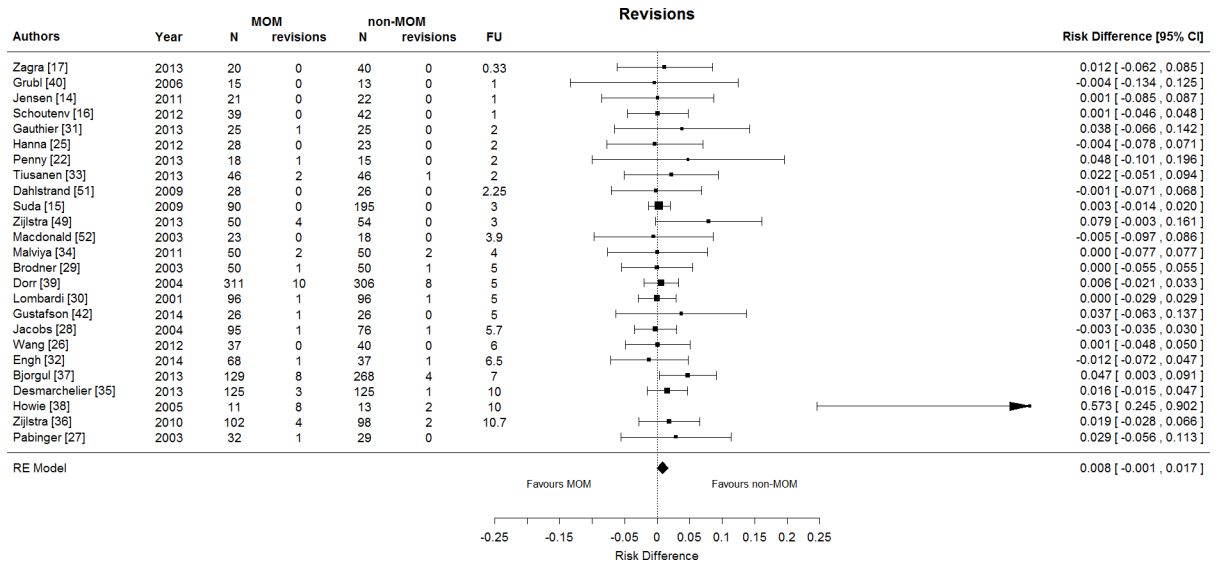
Fig 3. Forest plot showing the risk difference in revision surgery between MOM and non-MOM THA. There is significantly more revision surgery for MOM THA compared to non-MOM THA. RE model = random effects model.

doi:10.1371/journal.pone.0156051.g003

generation MOM observational study showed increased risk of cancer for patients with MOM compared to non-MOM THA [44]. The second generation MOM observational studies showed no difference in risk of cancer for patients with MOM compared to non-MOM THA [45–47].

Risk of bias

Risk of bias items from the CLEAR-NPT and Cochrane are presented in Fig 4. All studies suffered from problems with allocation concealment and blinding of patients, care givers, and outcome assessors.

The strong points of all studies were that compliance with the treatment was of course 100%, follow-up was similar for both MOM and non-MOM groups, and the skill/experience of the surgeons was similar for MOM and non-MOM THA (non-resurfacing).

The results from observational studies of second generation MOM THA were different from those of first generation MOM THA and those of the RCTs, suggesting strong confounding by indication for observational studies of second generation MOM THA [9].

Publication bias

The potential influence of publication bias is small, as shown by a nearly symmetrical funnel plot in Fig 5. Also, the trim-and-fit method and the cumulative meta-analysis showed small

Table 3. Medical complications for RCTs.

Author	Year	MOM					non-MOM				
		N patients	N cancer	N nephro	N cardio	N general	N patients	N cancer	N nephro	N cardio	N general
NCT00208494		196	2	1	4	35	194	3	3	5	37
NCT01422564		12	1	.	1	.	12	0	.	0	.
Desmarchelier	2013	111	.	.	.	2	116	.	.	.	5
Penny	2013	18	.	.	.	1	15	.	.	.	0

nephro = nephrotoxicity. cardio = cardiotoxicity.

doi:10.1371/journal.pone.0156051.t003
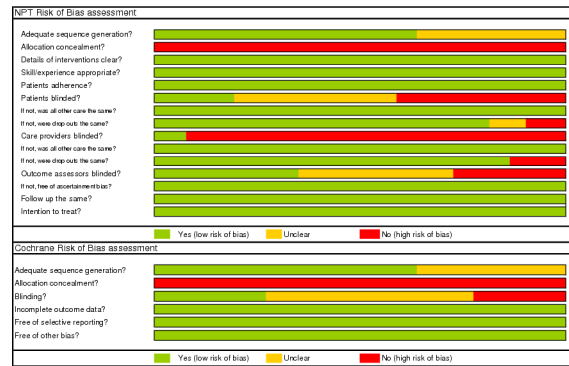
Fig 4. Risk of bias tables for CLEAR NPT and Cochrane.

potential influence of publication bias that would not influence the results. Furthermore, the results from the non-published RCTs (identified from the trial registries) were similar to those of published studies: RD for mortality in the non-published studies was -0.3%, 95% CI [-1.8%, 1.1%], and in the published studies was 0.1%, 95% CI [-1.3%, 1.5%].

Discussion

Principal findings

We found that when restricting to studies with long term follow-up (10 years and more), [3, 35, 36, 38] there was an increased risk of mortality in patients with MOM THA compared to patients with non-MOM THA: RD 8.5%, 95% CI [5.8%, 11.2%]. This finding, compared to a lack of difference between MOM and non-MOM THA patients with less than 10 years' follow-up, might indicate a dose-response association. The longer patients are exposed to MOM THA, the higher the risk of mortality is compared to non-MOM THA. Importantly, sensitivity analyses with meta-regression showed that duration of follow-up was the only effect modifier.

Regarding surgical morbidity, there were more revisions in MOM THA compared to non-MOM THA: RD 0.8%, 95% CI [-0.1%, 1.7%], based on 26 RCTs of second generation MOM THA. When restricted to cemented THA, this effect was stronger: RD 2.7%, 95% CI [0.1%, 5.3%].
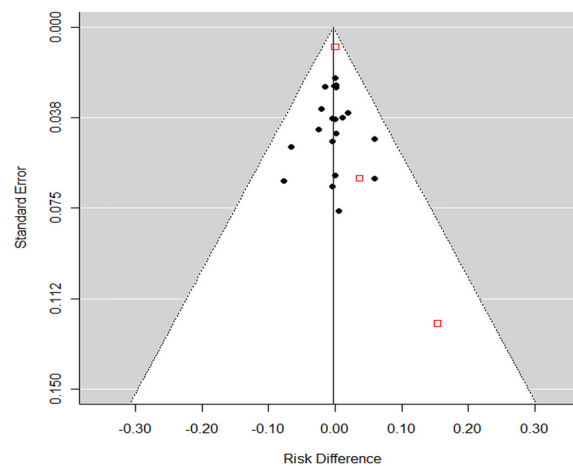

Fig 5. Funnel plot of RCTs. The red open boxes represent 1 abstract and 2 trial registry reports that have not been published.

Since data on post-operative medical complications were reported in only a few studies, no valid meta-analysis could be done on differences between the two THA groups. Regarding the observational studies, one first generation MOM study showed an increased risk of cancer for MOM patients compared to non-MOM THA patients[44]. The second generation MOM observational studies showed no difference in overall cancer risk. However, risk of soft-tissue sarcoma and basalioma was higher for MOM THA patients [48].

The risk of mortality for MOM THA from observational studies of second generation MOM THA was different from those of first generation MOM THA and RCTs between (non) MoM THA, suggesting confounding by indication in studies of second generation MOM THA as previously reported by Kandala et al [9].

In a recent review, Hartmann et al demonstrated that metal ion concentrations were persistently elevated after implantation of MOM bearings in whole blood, serum, plasma, erythrocytes and urine, irrespective of patient characteristics and study characteristics [6]. Of concern is that the same authors found very high serum cobalt concentrations in several of their included studies—above 50 μg/L, while the detection limit for serum cobalt is typically 0.3 μg/L. They found the highest metal ion concentrations in patients with a stemmed, large-head MOM implant and in patients with hip resurfacing arthroplasty. Our sensitivity analyses did not identify any association between MOM head size (either resurfacing or THA) and mortality or surgical complications. However the number (25) and size (2700 pts) of our included RCTs may have been too small to detect a difference.

Toxic and carcinogenic effects

Devlin et al and Bradberry et al have shown in a systematic review that patients with suspected Prosthetic Hip Associated Cobalt Toxicity (PHACT) had symptoms that fell in three categories: neuro-ocular toxicity, cardiotoxicity and thyroid toxicity [53, 54]. The signs and symptoms developed between 3 and 72 months (median 19 months) after the MOM THA, [53, 55]. The most common treatment of PHACT in literature was removal of the metal-containing prosthesis, which resulted in lowered cobalt concentration and improvement of symptoms [53–55]. Of great concern is also the fact that the International Agency for Research on Cancer (IARC) has classified cobalt as group 2B, *Possibly carcinogenic to humans"* [56]. Furthermore, Moulin et al have shown that metal workers exposed to cobalt have an increased mortality rate from lung cancer [57].

Although most emphasis in literature is on cobalt toxicity (PHACT), the effects of chronic exposure to elevated chromium or nickel levels should not be dismissed. The International Agency for Research on Cancer (IARC) has classified chromium and nickel as group 1, "*carcinogenic to humans"* [56]. Chromium(VI) in particular is carcinogenic through direct DNA damage after intra-cellular reduction to chromium(III), mutation, genomic instability, aneuploidy, and cell transformation [56]. Exposure to chromium by ingestion or inhalation is associated with increased risk of lung cancer, sinonasal cancer, and stomach cancer [56, 58–61]. The connection between chromium inhalation/ingestion and an increased risk of lung cancer, sinonasal cancer, stomach cancer, and possibly melanoma do not directly extrapolate to increased cancer risk due to increased plasma chromium levels in MOM THA. Briggs et al have shown a strong relationship between whole blood levels of chromium and total chromosomal aberration indices in peripheral lymphocytes of MOM patients. [62] Ladon et al have shown an increase of both chromosome translocations and aneuploidy in peripheral blood lymphocytes at 6, 12, and 24 months after MOM-THA [63]. Therefore the association of increased chromium plasma levels and increased risk of mortality through cancer warrants further research. The arguments for this association are the carcinogenic effect of chromium

through direct DNA-damage [56], strong relationship between whole blood levels of chromium and total chromosomal aberration indices in patients with MOM [62, 63], chronically increased chromium plasma levels in patients with MOM [6], and increased long-term mortality in MOM patients as shown by the present systematic review. Furthermore, patients with MOM THA are not only exposed to a single metal but to a "cocktail" of metal ions including chromium, cobalt, titanium, nickel, and molybdenum, of which at least two are potentially carcinogenic (chromium and nickel) and one is possibly carcinogenic (cobalt) [6, 56].

Strengths and limitations

Our search strategy was thorough and complete. We included studies published between 1975 and 2014. Also, after contacting corresponding persons, we were able to include additional RCTs (both peer-reviewed papers and clinical trial reports) from trial registries such as clinicaltrials.org. In total, we were able to include 47 papers, including several with follow-up of 10 years or more.

For non-resurfacing THA, the surgical procedure is almost identical for MOM and non-MOM THA. Even the implants are identical with respect to the femoral stem and outer shell of the cup. The only difference is the bearing (liner and femoral head) that is inserted during the procedure. Therefore the surgical skill/experience is the same for non-resurfacing MOM and non-MOM THA.

The fact that the results from observational studies of first generation MOM THA concur with those from the RCTs reinforces the conclusion that MOM patients have an increased risk of mortality in the long run compared to non-MOM patients.

We should consider some limitations. Most RCTs had problems with allocation concealment and blinding during follow-up. However, the primary outcome of mortality is an objective outcome measure and is therefore very unlikely to be misclassified due to problems with blinding. Lack of blinding could have resulted in intensified follow-up for patients with MOM THA once the issues with MOM became apparent. However, none of the included studies mentioned differences in follow-up. Also, if we were to assume intensified follow-up (due to public awareness) for patients with MOM, and that this follow-up would be successful in reducing mortality and morbidity, these effects would have led to an underestimation of the observed effect on mortality and surgical morbidity (revisions) in MOM THA. Thus, in this case the increased risk of long term mortality for MOM THA and the increased risk of revision for MOM THA would even be higher. These unlikely effects would thus not change our conclusions.

There was limited data from RCTs on medical complications. Future RCTs and new reports of existing RCTs should therefore report these complications in a systematic way.

Comparison with other studies

Visuri et al [3, 44] showed increased mortality and increased cancer incidence from MOM THA in an observational study of first generation MOM hip prostheses implanted between 1967 and 1973: the McKee-Farrar. This study is particularly interesting since the McKee-Farrar is part of the evolution of total hip prostheses and was not subject to modern marketing, nor was it labeled a "sports hip". The results from Visuri et al [3] are in accordance with the results of the RCTs of second generation (modern) MOM THA, therefore reinforcing our conclusion that MOM THA is associated with an increased risk of mortality in the long term.

Kendal et al found increased mortality in non-MOM THA in a registry based study of second generation MOM THA using propensity score matching [7]. Their results are in disagreement with the results of our meta-analysis, likely because registry-based studies are subject to

residual confounding by indication. Indeed, Kandala et al have shown that confounding by indication is likely for the Kendal study, since one-fifth of the metal-on-metal subjects are predicted to live beyond 100 years of age, making metal-on-metal total hip replacement more beneficial for longevity than any other known treatment [9]. This latter finding is highly unlikely, and confounding by indication for the Kendal study is the most likely reason for this predicted longevity.

Mäkela et al found at short-term follow-up no difference in cancer incidence and cause-specific mortality in patients with second generation MOM THA compared to non-MOM THA [48]. For the short-term follow-up, their results are in agreement with the results of our meta-analysis.

Conclusions and implications for clinicians and researchers

Studies with follow-up of greater than 10 years seem to suggest an increased risk of mortality in MOM THA compared to non-MOM THA. Additionally there is an increased risk of revision in MOM THA compared to non-MOM THA. In the light of these results, more long-term follow-up of RCTs reporting mortality is paramount. Also, future observational studies should address the dose-response association of person/hip years exposure to MOM THA and/or levels of metal ions to the risk of mortality and other medical complications e.g. cancer incidence, cardiomyopathy and renal failure.

There is currently no case for the use of MOM THA giving the increased risk of long-term mortality and revision without any proven major advantage. Considering the results discussed above, it is prudent to closely follow the patients that have already received a MOM THA, especially in the long-term.

Supporting Information

S1 File. Prospero Protocol.
(PDF)

S2 File. PRISMA Checklist.
(PDF)

S3 File. Search Strategy.
(DOC)

Acknowledgments

The authors would like to thank Emma Briggs for editing the paper.

Author Contributions

Conceived and designed the experiments: RN BP HH. Analyzed the data: BP AS MF. Wrote the paper: BP JM HH JS RN MF AS. Had the idea of the study: RN BP HH. Designed the search strategy for the literature search: JS. Performed the study selection and matching procedure: BP JM. Appraised the quality of the literature and performed the data extraction: BP JM. Analyzed the data: BP AS MF. Wrote the initial draft of the manuscript: BP JM HH JS. Critically reviewed and edited the manuscript: RN MF AS. Had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis: BP JM JS MF HH AS RN. Critical revision of the manuscript: BP JM JS MF HH AS RN. Read and approved the final manuscript: BP JM JS MF HH AS RN.

References

1. 12th Annual Report. National Joint Registry for England, Wales and Northern Island. 2016. Available: http://www.njrcentre.org.uk.

2. Convery FR, Gunn DR, Hughes JD, Martin WE. The relative safety of polymethylmethacrylate. A controlled clinical study of randomly selected patients treated with Charnley and ring total hip replacements. J Bone Joint Surg Am. 1975; 57(1):57–64. 161. PMID: 1123372

3. Visuri T, Borg H, Pulkkinen P, Paavolainen P, Pukkala E. A retrospective comparative study of mortality and causes of death among patients with metal-on-metal and metal-on-polyethylene total hip prostheses in primary osteoarthritis after a long-term follow-up. BMC Musculoskelet Disord. 2010; 11:78. PMID: 20416065. doi: 10.1186/1471-2474-11-78

4. Ishida T, Clarke IC, Donaldson TK, Shirasu H, Shishido T, Yamamoto K. Comparing ceramic-metal to metal-metal total hip replacements—a simulator study of metal wear and ion release in 32- and 38-mm bearings. J Biomed Mater Res B Appl Biomater. 2009; 91(2):887–96. PMID: 19598291. doi: 10.1002/jbm.b.31471

5. Clark MJ, Prentice JR, Hoggard N, Paley MN, Hadjivassiliou M, Wilkinson JM. Brain Structure and Function in Patients after Metal-on-Metal Hip Resurfacing. AJNR Am J Neuroradiol. 2014. PMID: 24722312.

6. Hartmann A, Hannemann F, Lutzner J, Seidler A, Drexler H, Gunther KP, et al. Metal ion concentrations in body fluids after implantation of hip replacements with metal-on-metal bearing—systematic review of clinical and epidemiological studies. PLoS One. 2013; 8(8):e70359. PMID: 23950923. doi: 10.1371/journal.pone.0070359

7. Kendal AR, Prieto-Alhambra D, Arden NK, Carr A, Judge A. Mortality rates at 10 years after metal-on-metal hip resurfacing compared with total hip replacement in England: retrospective cohort analysis of hospital episode statistics. Bmj. 2013; 347:f6549. PMID: 24284336. doi: 10.1136/bmj.f6549

8. McMinn DJ, Snell KI, Daniel J, Treacy RB, Pynsent PB, Riley RD. Mortality and implant revision rates of hip arthroplasty in patients with osteoarthritis: registry based cohort study. Bmj. 2012; 344:e3319. PMID: 22700782. doi: 10.1136/bmj.e3319

9. Kandala NB, Connock M, Pulikottil-Jacobs R, Mistry H, Sutcliffe P, Costa M, et al. Response to two recent BMJ papers on mortality after hip replacement: comparative modelling study. BMJ. 2014; 348 (Feb):g1506. doi: 10.1136/bmj.g1506 PMID: 24554171

10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009; 339:b2535. PMID: 19622551. doi: 10.1136/bmj.b2535

11. Boutron I, Moher D, Tugwell P, Giraudeau B, Poiraudeau S, Nizard R, et al. A checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) was developed using consensus. J Clin Epidemiol. 2005; 58(12):1233–40. PMID: 16291467.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–88. PMID: 3802833.

13. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010; 36(3):1–48.

14. Jensen C, Aagaard P, Overgaard S. Recovery in mechanical muscle strength following resurfacing vs standard total hip arthroplasty—a randomised clinical trial. Osteoarthritis Cartilage. 2011; 19(9):1108–16. 57. doi: 10.1016/j.joca.2011.06.011 PMID: 21749928

15. Suda AJ, Knahr K. Early results with the cementless Variall hip system. Expert Review of Medical Devices. 2009; 6(1):21–5. 284. doi: 10.1586/17434440.6.1.21 PMID: 19105776

16. Schouten R, Malone AA, Tiffen C, Frampton CM, Hooper G. A prospective, randomised controlled trial comparing ceramic-on-metal and metal-on-metal bearing surfaces in total hip replacement. J Bone Joint Surg Br. 2012; 94(11):1462–7. 31. doi: 10.1302/0301-620X.94B11.29343 PMID: 23109623

17. Zagra L, Anasetti F, Bianchi L, Licari V, Giacometti CR. No difference in gait recovery after THA with different head diameters: a prospective randomized study. Clin Orthop Relat Res. 2013; 471(12):3830–7. 15. doi: 10.1007/s11999-013-2926-6 PMID: 23640204

18. Zijlstra WP, van dA-SI, Zee MJ, van Raay JJ. No clinical difference between large metal-on-metal total hip arthroplasty and 28-mm-head total hip arthroplasty? Int Orthop. 2011; 35(12):1771–6. 63. doi: 10.1007/s00264-011-1233-7 PMID: 21373801

19. NCT01422564. Metal on Metal Versus Metal on Highly Crossed Linked Polyethylene Sytem. http://ClinicalTrials.gov/show/NCT01422564 38.

20. Hailer NP, Blaheta RA, Dahlstrand H, Stark A. Elevation of circulating HLA DR(+) CD8(+) T-cells and correlation with chromium and cobalt concentrations 6 years after metal-on-metal hip arthroplasty. Acta Orthop. 2011; 82(1):6–12. 66. doi: 10.3109/17453674.2010.548028 PMID: 21189110

21. MacDonald SJ, Bourne RB, Rorabeck CH, Cleland D, Chess DG, McCalden RW. Metal on metal versus metal on polyethylene in total hip arthroplasty—a prospective randomised clinical trial. The Journal of bone and joint surgery. 2005; 87-B:321–32b. 495.

22. Penny JO, Brixen K, Varmarken JE, Ovesen O, Overgaard S. Changes in bone mineral density of the acetabulum, femoral neck and femoral shaft, after hip resurfacing and total hip replacement: two-year results from a randomised study. J Bone Joint Surg Br. 2012; 94(8):1036–44. 35. doi: 10.1302/0301-620X.94B8.28222 PMID: 22844043

23. Weissinger M, Grubl A, Poll G. Serum-cobalt levels with metal-on-metal bearings in the cement-free total hip arthroplasty results covering two years; prospective study. Acta Chir Orthop TraumatolCech. 2011; 78(5):410–5. 51.

24. Zerahn B, Borgwardt L, Ribel-Madsen S, Borgwardt A. A prospective randomised study of periprosthetic femoral bone remodeling using four different bearings in hybrid total hip arthroplasty. Hip International. 2011; 21(2):176–86. 240. doi: 10.5301/HIP.2011.6527 PMID: 21484744

25. Hanna SA, Sewell MD, Sri-Ram K, Miles J, Aston WJ, Pollock RC, et al. The effect of femoral head size on functional outcome in primary total hip arthroplasty: a single-blinded randomised controlled trial. HipInt. 2012; 22(6):592–7. 28.

26. Wang Q, Zhang XL, Chen YS, Shen H, Shao JJ. Resurfacing arthroplasty for hip dysplasia: a prospective randomised study. J Bone Joint Surg Br. 2012; 94(6):768–73. 40. doi: 10.1302/0301-620X.94B6.28522 PMID: 22628590

27. Pabinger C, Biedermann R, Stockl B, Fischer M, Krismer M. Migration of metal-on-metal versus ceramic-on-polyethylene hip prostheses. Clin Orthop Relat Res. 2003;(412:):103–10. 137. PMID: 12838059

28. Jacobs M, Gorab R, Mattingly D, Trick L, Southworth C. Three- to six-year results with the Ultima metal-on-metal hip articulation for primary total hip arthroplasty. J Arthroplasty. 2004; 19(7 Suppl 2):48–53. 127. PMID: 15457418

29. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. J Bone Joint Surg Am. 2003; 85-A(11):2168–73. 133. PMID: 14630848

30. Lombardi AV Jr, Mallory TH, Alexiades MM, Cuckler JM, Faris PM, Jaffe KA, et al. Short-term results of the M2a-taper metal-on-metal articulation. J Arthroplasty. 2001; 16(8 Suppl 1):122–8. 141. PMID: 11742463

31. Gauthier L, Dinh L, Beaule PE. Peri-acetabular bone mineral densityin total hip replacement. Bone Joint Res. 2013; 2(8):140–8. 11. doi: 10.1302/2046-3758.28.2000173 PMID: 23913361

32. Engh CA, MacDonald SJ, Sritulanondha S, Korczak A, Naudie D, Engh C. Metal ion levels after metal-on-metal total hip arthroplasty: a five-year, prospective randomized trial. J Bone Joint Surg Am. 2014; 96(6):448–55. PMID: 24647500. doi: 10.2106/JBJS.M.00164

33. Tiusanen H, Makela K, Kiilunen M, Sarantsin P, Sipola E, Pesola M. The effect of different bearing surfaces on metal ion levels in urine following 28 mm metal-on-metal and 28 mm metal-on-polyethylene total hip arthroplasty. Scand J Surg. 2013; 102(3):197–203. 9. doi: 10.1177/1457496913491874 PMID: 23963035

34. Malviya A, Ramaskandhan JR, Bowman R, Hashmi M, Holland JP, Kometa S, et al. What advantage is there to be gained using large modular metal-on-metal bearings in routine primary hip replacement? A preliminary report of a prospective randomised controlled trial. J Bone Joint Surg Br. 2011; 93 (12):1602–9. 48. doi: 10.1302/0301-620X.93B12.27533 PMID: 22161921

35. Desmarchelier R, Viste A, Chouteau J, Lerat JL, Fessy MH. Metasul vs Cerasul bearings: a prospective, randomized study at 9 years. J Arthroplasty. 2013; 28(2):296–302. 37. doi: 10.1016/j.arth.2012.05.028 PMID: 22784488

36. Zijlstra WP, van Raay JJ, Bulstra SK, Deutman R. No superiority of cemented metal-on-metal over metal-on-polyethylene THA in a randomized controlled trial at 10-year follow-up. Orthopedics. 2010; 33 (3). 77.

37. Bjorgul K, Novicoff WN, Andersen ST, Ahlund OR, Bunes A, Wiig M, et al. High rate of revision and a high incidence of radiolucent lines around Metasul metal-on-metal total hip replacements: results from a randomised controlled trial of three bearings after seven years. Bone Joint J. 2013; 95-B(7):881–6. 13. doi: 10.1302/0301-620X.95B7.31067 PMID: 23814237

38. Howie DW, McGee MA, Costi K, Graves SE. Metal-on-metal resurfacing versus total hip replacement-the value of a randomized clinical trial. Orthop Clin North Am. 2005; 36(2):195–201, ix. 122. PMID: 15833457

39. Dorr LD, Long WT, Sirianni L, Campana M, Wan Z. The argument for the use of Metasul as an articulation surface in total hip replacement. Clin Orthop Relat Res. 2004;(429:):80–5. 126. PMID: 15577470

40. Grubl A, Weissinger M, Brodner W, Gleiss A, Giurea A, Gruber M, et al. Serum aluminium and cobalt levels after ceramic-on-ceramic and metal-on-metal total hip replacement. J Bone Joint Surg Br. 2006; 88(8):1003–5. 110. PMID: 16877596

41. NCT00208494. Metal on Metal Versus Ceramic on Metal Hip Replacement. http://ClinicalTrials.gov/show/NCT00208494 58.

42. Gustafson K, Jakobsen SS, Lorenzen ND, Thyssen JP, Johansen JD, Bonefeld CM, et al. Metal release and metal allergy after total hip replacement with resurfacing versus conventional hybrid prosthesis. Acta Orthop. 2014; 85(4):348–54. PMID: 24930546. doi: 10.3109/17453674.2014.922730

43. Lubbeke A, Gonzalez A, Garavaglia G, Roussos C, Bonvin A, Stern R, et al. A comparative assessment of small-head metal-on-metal and ceramic-on-polyethylene total hip replacement. Bone Joint J. 2014; 96-B(7):868–75. PMID: 24986938. doi: 10.1302/0301-620X.96B7.32369

44. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. Clin Orthop Relat Res. 1996;(329: Suppl):S280–9. PMID: 8769342.

45. Makela KT, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, et al. Risk of cancer with metal-on-metal hip replacements: population based study. British Medical Journal. 2012; 345. 445.

46. Smith AJ, Dieppe P, Porter M, Blom AW. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. Bmj. 2012; 344:e2383. PMID: 22490979. doi: 10.1136/bmj.e2383

47. Lalmohamed A, MacGregor AJ, de Vries F, Leufkens HG, van Staa TP. Patterns of risk of cancer in patients with metal-on-metal hip replacements versus other bearing surface types: a record linkage study between a prospective joint registry and general practice electronic health records in England. PLoS One. 2013; 8(7):e65891. PMID: 23861740. doi: 10.1371/journal.pone.0065891

48. Makela KT, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, et al. Cancer incidence and cause-specific mortality in patients with metal-on-metal hip replacements in Finland. Acta Orthop. 2014; 85(1):32–8. PMID: 24397743. doi: 10.3109/17453674.2013.878830

49. Zijlstra WP, van der Veen HC, van dA-SI, Zee MJ, Bulstra SK, van Raay JJ. Acetabular bone density and metal ions after metal-on-metal versus metal-on-polyethylene total hip arthroplasty; short-term results. HipInt. 2013:0. 5.

50. Penny JO, Ovesen O, Varmarken JE, Overgaard S. Similar range of motion and function after resurfacing large-head or standard total hip arthroplasty. Acta Orthop. 2013; 84(3):246–53. 20. doi: 10.3109/17453674.2013.788435 PMID: 23530872

51. Dahlstrand H, Stark A, Anissian L, Hailer NP. Elevated serum concentrations of cobalt, chromium, nickel, and manganese after metal-on-metal alloarthroplasty of the hip: a prospective randomized study. J Arthroplasty. 2009; 24(6):837–45. 96. doi: 10.1016/j.arth.2008.07.019 PMID: 18823744

52. MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, et al. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clinical orthopaedics and related research. 2003;(406:):282–96. Epub 2003/02/13. doi: 10.1097/01.blo.0000043066.62337.9d PMID: 12579029.

53. Devlin JJ, Pomerleau AC, Brent J, Morgan BW, Deitchman S, Schwartz M. Clinical features, testing, and management of patients with suspected prosthetic hip-associated cobalt toxicity: a systematic review of cases. J Med Toxicol. 2013; 9(4):405–15. PMID: 24222555. doi: 10.1007/s13181-013-0320-0

54. Bradberry SM, Wilkinson JM, Ferner RE. Systemic toxicity related to metal hip prostheses. Clin Toxicol (Phila). 2014; 52(8):837–47. PMID: 25132471.

55. Mao X, Wong AA, Crawford RW. Cobalt toxicity—an emerging clinical problem in patients with metal-on-metal hip prostheses? Med J Aust. 2011; 194(12):649–51. PMID: 21692725.

56. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009; 10(5):453–4. PMID: 19418618.

57. Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, et al. Lung cancer risk in hard-metal workers. Am J Epidemiol. 1998; 148(3):241–8. PMID: 9690360.

58. Beaumont JJ, Sedman RM, Reynolds SD, Sherman CD, Li LH, Howd RA, et al. Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. Epidemiology. 2008; 19(1):12–23. PMID: 18091413.

59. Binazzi A, Ferrante P, Marinaccio A. Occupational exposure and sinonasal cancer: a systematic review and meta-analysis. BMC Cancer. 2015; 15:49. PMID: 25885319. doi: 10.1186/s12885-015-1042-2

60. Smith AH, Steinmaus CM. Health effects of arsenic and chromium in drinking water: recent human findings. Annu Rev Public Health. 2009; 30:107–22. PMID: 19012537. doi: 10.1146/annurev.publhealth.031308.100143

61. Zhang JD, Li XL. [Chromium pollution of soil and water in Jinzhou]. Zhonghua Yu Fang Yi Xue Za Zhi. 1987; 21(5):262–4. PMID: 3443034.

62. Briggs TW, Hanna SA, Kayani B, Tai S, Pollock RC, Cannon SR, et al. Metal-on-polyethylene versus metal-on-metal bearing surfaces in total hip arthroplasty: a prospective randomised study investigating metal ion levels and chromosomal aberrations in peripheral lymphocytes. Bone Joint J. 2015; 97-B (9):1183–91. PMID: 26330583. doi: 10.1302/0301-620X.97B9.34824

63. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. J Arthroplasty. 2004; 19(8 Suppl 3):78–83. PMID: 15578558.