# Distributed Analysis of Hip Implants Using Six National and Regional Registries: Comparing Metal-on-Metal with Metal-on-Highly Cross-Linked Polyethylene Bearings in Cementless Total Hip Arthroplasty in Young Patients

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**Background:** The regulation of medical devices has attracted controversy recently because of problems related to metal-on-metal hip implants. There is growing evidence that metal-on-metal implants fail early and cause local and systemic complications. However, the failure associated with metal-on-metal head size is not consistently documented and needs to be communicated to patients and surgeons. The purpose of this study is to compare implant survival of metal on metal with that of metal on highly cross-linked polyethylene.

**Methods:** Using a distributed health data network, primary total hip arthroplasties were identified from six national and regional total joint arthroplasty registries (2001 to 2010). Inclusion criteria were patient age of forty-five to sixty-four years, cementless total hip arthroplasties, primary osteoarthritis diagnosis, and exclusion of the well-known outlier implant ASR (articular surface replacement). The primary outcome was revision for any reason. A meta-analysis of survival probabilities was performed with use of a fixed-effects model. Metal-on-metal implants with a large head size of >36 mm were compared with metal-on-highly cross-linked polyethylene implants.

**Results:** Metal-on-metal implants with a large head size of >36 mm were used in 5172 hips and metal-on-highly cross-linked polyethylene implants were used in 14,372 hips. Metal-on-metal total hip replacements with a large head size of >36 mm had an increased risk of revision compared with metal-on-highly cross-linked polyethylene total hip replacements with more than two years of follow-up, with no difference during the first two years after implantation. The results of the hazard ratios (and 95% confidence intervals) from the multivariable model at various durations of follow-up were 0.95 (0.74 to 1.23) at zero to two years ($p = 0.698$), 1.42 (1.16 to 1.75) at more than two years to four years ($p = 0.001$), 1.78 (1.45 to 2.19) at more than four years to six years ($p < 0.001$), and 2.15 (1.63 to 2.83) at more than six years to seven years ($p < 0.001$).

**Conclusions:** We conducted a comparison of large-head-size, metal-on-metal implants and metal-on-highly cross-linked polyethylene implants in younger patients with uncemented fixation. We found consistent and strong evidence worldwide that large-head-size, metal-on-metal implants were associated with increased risk of revision after two years compared with metal-on-highly cross-linked polyethylene implants, with the effect becoming more pronounced over time.

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The regulation of medical devices has attracted controversy due to recent problems related to metal-on-metal hip implants[1-5]. There is growing evidence that metal-on-metal implants fail early and cause local and systemic complications[1,6-14]. In a meta-analysis of bearing surfaces using five randomized studies comparing metal-on-metal total hip replacement with metal-on-polyethylene total hip replacement, the investigators found small but significantly better functional results in metal-on-polyethylene total hip replacement[4]. However, head size was not analyzed. Metal-on-metal articulation became popular because metal-on-conventional polyethylene articulation in uncemented cups showed poor results due to wear and osteolysis[15-17]. In vitro, large head sizes improve range of movement and, because of increased jump distance, decrease the risk of dislocation and component impingement[18]. These findings contributed to the increased interest in large-head, metal-on-metal total hip replacement. It has been well established that the ASR (articular surface replacement) metal-on-metal, large-head total hip replacement (DePuy, Leeds, England) had inferior results, and the company withdrew this prosthesis from the market in 2010[1,2,5]. There has been more uncertainty of the comparative effectiveness of other metal-on-metal total hip replacements[6]. In the Finnish registry study, uncemented, large-head, metal-on-metal total hip replacements had short-term results that were comparable with those of cemented hip implants[6], contrary to the findings of the National Joint Registry of England and Wales[1] and the Australian Orthopaedic Association National Joint Replacement Registry[3].

Highly cross-linked polyethylene inserts have shown promising results regarding wear in clinical studies with up to thirteen years of follow-up[19] and in radiostereometric analysis studies with up to ten years of follow-up[20,21].

The longevity of different bearing surfaces may also depend on the methods of fixation, design, femoral head size, and other operative or implant-related factors. National and regional registries have contributed substantially to detecting inferior implants and techniques[3,22-24]. Single registries might have too few patients or only a limited number of implants; therefore, combining data from several registries could increase power and could broaden inferences to a larger pool of prostheses and to countries around the world[4,25].

**TABLE I Results from the Fixed-Effects Model*†**

| | Hazard Ratio‡ | P Value§ |
|---|---|---|
| Time *(yr)* | | |
| One | Reference | — |
| More than one to two | 4.68 (3.86 to 6.12) | <0.001 |
| More than two to three | 5.76 (4.39 to 7.55) | <0.001 |
| More than three to four | 6.60 (5.02 to 8.69) | <0.001 |
| More than four to five | 7.18 (5.43 to 9.49) | <0.001 |
| More than five to six | 8.06 (6.07 to 10.72) | <0.001 |
| More than six to seven | 8.90 (6.64 to 11.94) | <0.001 |
| More than seven to eight | 11.44 (8.13 to 16.11) | <0.001 |
| More than eight to nine | 10.78 (7.95 to 15.29) | <0.001 |
| Sex | | |
| Male | Reference | — |
| Female | 1.13 (0.95 to 1.35) | 0.174 |
| Age *(yr)* | | |
| Forty-five to fifty-four | Reference | — |
| Fifty-five to sixty-four | 0.76 (0.62 to 0.93) | 0.009 |
| Bearing effects over time# | | |
| Metal on highly cross-linked polyethylene | Reference | — |
| Metal on metal | | |
| At zero to two years | 0.95 (0.74 to 1.23) | 0.698 |
| At more than two years to four years | 1.42 (1.16 to 1.75) | 0.001 |
| At more than four years to six years | 1.78 (1.45 to 2.19) | <0.001 |
| At more than six years to seven years | 2.15 (1.63 to 2.83) | <0.001 |

*Fixed registry effects were included in this model (five coefficients), but the results were omitted from this table because a precondition of data sharing was no reporting of between-registry comparisons. †The value of the estimate and the standard error of the intercept was given as $-5.257 \pm 0.171$. ‡The values are given as the hazard ratio, with the 95% CI, which is based on a normal distribution, in parentheses. §The p values are based on a normal distribution. #The effects over time are based on a combination of the main and interaction effects from the model.

**TABLE II Distribution of Non-ASR Metal-on-Metal and Metal-on-Highly Cross-Linked Polyethylene Cementless Total Hip Replacements in Patients with Osteoarthritis by Bearing Surface, Head Size, and Sex**

| Bearing Surface | Male Patients | No. of Total Hip Replacements* |
|---|---|---|
| Metal on highly cross-linked polyethylene | 6943 (48.3%)† | 14,372 (57.3%) |
| Metal on metal | 6258 (47.4%)† | 10,699 (42.7%) |
| Large head size, >36 mm | 3372 (65.2%)‡ | 5172 (20.6%) |
| Large head size, 36 mm | 1474 (55.2%)‡ | 2670 (10.6%) |
| Small head size, ≤32 mm | 1412 (49.4%)‡ | 2857 (11.4%) |
| Total | 13,201 (52.7%)‡ | 25,071 (100.0%) |

*The values are given as the number of total hip replacements, with the percentage in parentheses. †The values are given as the number of male patients, with the percentages, based on the total number of male patients, in parentheses. ‡The values are given as the number of male patients, with the row percentage based on the head size of the total hip replacement in parentheses.

The purpose of this study was to compare the implant survival of metal-on-metal total hip replacement with a large head size of >36 mm with that of metal-on-highly cross-linked polyethylene total hip replacement in a homogeneous population of young patients with one fixation type.

## Materials and Methods

Primary total hip arthroplasties were identified from six national and regional total joint arthroplasty registries. To ensure a homogeneous study population, we only included total hip arthroplasties in young patients with an age of forty-five to sixty-four years, uncemented (both acetabulum and femur) total hip replacement, and osteoarthritis as the underlying diagnosis. We excluded the ASR total hip replacement (DePuy) because this implant has been documented as inferior[2,5]. In a previous study, we found metal-on-metal implants with a head size of >36 mm to be associated with an increased risk of revision over time relative to metal-on-metal implants with a head size of <32 mm (results not published). With respect to the 36-mm head size, there was little evidence of a head-size effect (hazard ratio, 1.01 [95% confidence interval (95% CI), 0.31 to 3.27]; p = 0.980), but this estimate varied widely from registry to registry and the random effects variance was 0.326. On the basis of the examination of the deviation of each registry from the mean treatment effect (using empirical best linear unbiased predictions), the U.S. registry (Kaiser Permanente) provided the least evidence of a detrimental effect of the 36-mm head size, which may be attributed to its exclusive use of Pinnacle cups (DePuy), which perform very well at this head size[26]. Fitting a fixed-effects model increased the estimated effect but was still not significant (hazard ratio, 1.40 [95% CI, 0.88 to 2.24]; p = 0.155). In light of these findings, we chose to focus exclusively on metal-on-metal implants with a head size of >36 mm.

The primary outcome was revision for any reason. The definition of revision was the removal, exchange, or addition of any implant parts (including an exchange of inserts and heads only). Metal-on-metal implants with a large head size of >36 mm were compared with metal-on-highly cross-linked polyethylene implants. We analyzed the different highly cross-linked polyethylene head sizes together, as prior analyses have shown that there was no effect of head size on revision in the highly cross-linked polyethylene bearing surface group[27]. The inclusion of patients started on January 1, 2001, and ended on December 31, 2010. The patients were followed until they underwent revision or until the end of the study on December 31, 2010. Death and health plan member terminations were treated as censored cases. A study protocol was developed by investigators, and syntax was sent from the coordinating center located jointly at the Surgical Outcomes & Analysis Department, Kaiser Permanente, San Diego, California, and Weill Cornell Medical College, New York, NY, to each participating registry. In the study, we used a distributed health data network that does not require centralized data storage[4]. Each registry categorized its implants according to bearing surface, fixation, age, and sex. Each registry identified the highly cross-linked polyethylene inserts and metal-on-metal implants according to the information from the implant companies. Survival probabilities and their standard errors based on a cross-classification of bearing surface, head size, age category, and sex were extracted from each registry and were sent back to the coordinating center where the data were analyzed. No personal identifiable data were sent from the registry, only aggregated data.

### Statistical Analysis

A multivariate meta-analysis was performed using linear mixed models comparing metal-on-metal total hip replacement with a large head size of >36 mm with metal-on-highly cross-linked polyethylene total hip replacements of all head sizes, with survival probability as the unit of analysis[28]. The models estimate the residual covariances using the precise method of Dear[29] and implement a transformation[30,31] to ensure that the models can be fit with existing software (SAS version 9.2; SAS Institute, Cary, North Carolina). Survival probabilities and their standard errors were extracted from each registry for each unique combination of the covariates listed above at each distinct event time, and each unique combination was grouped into yearly time intervals, with only the earliest observation in that interval retained. We fit two models, one that treated registry as a set of fixed effects and another that treated registry as random effect(s). Although the random-effects model offers some inferential advantage[32,33], with few observational data or registries, the estimated between-registry variation in the random-effects model can be quite inaccurate. Further, the absence of randomization for bearing and head-size groups could lead to confounding due to registry-level effects, which is addressed by the fixed-effects model but not by the random-effects model[34,35]. Therefore, preference would be given to interpretation of the fixed-effects model, particularly if the parameter estimates are substantially different in the fixed-effects model compared with the random-effects model[34,35]. Hence, we present the results of the fixed-effects model in Table I and include the results of the random-effects model in the Appendix. SAS version 9.2 (SAS Institute) was used for all analyses.

## Results

The study cohort was based on six national and regional registries and consisted of 19,544 cementless total hip arthroplasties, in which metal-on-metal implants with a large head size of >36 mm were used in 5172 hips (26.5%) and metal-on-highly cross-linked polyethylene implants were used in 14,372 hips (73.5%) (Table II). Six registries contributed data to the study: the Australian Orthopaedic Association National Joint Replacement Registry (n = 12,482), the Kaiser

**TABLE III Distribution of Cementless Metal-on-Metal and Metal-on-Highly Cross-Linked Polyethylene Total Hip Replacements Included in Analyses by Registry, Bearing Surface, Head Size, Age, and Sex**

| | Registry* | | | | | |
|---|---|---|---|---|---|---|
| | United States (Kaiser Permanente) | Australia | Italy (Emilia-Romagna Region) | United States (HealthEast) | Norway | Spain (Catalan Region) |
| Metal on highly cross-linked polyethylene, <32-mm head size | | | | | | |
| Age | | | | | | |
| Forty-five to fifty-four years | 194 (23.0%) | 1109 (24.3%) | 26 (10.4%) | 56 (32.9%) | 33 (22.1%) | 30 (30.9%) |
| Fifty-five to sixty-four years | 648 (77.0%) | 3462 (75.7%) | 224 (89.6%) | 114 (67.1%) | 116 (77.9%) | 67 (69.1%) |
| Sex | | | | | | |
| Male | 275 (32.7%) | 2110 (46.2%) | 121 (48.4%) | 63 (37.1%) | 51 (34.2%) | 61 (62.9%) |
| Female | 567 (67.3%) | 2461 (53.8%) | 129 (51.6%) | 107 (62.9%) | 98 (65.8%) | 36 (37.1%) |
| Metal on highly cross-linked polyethylene, 32-mm head size | | | | | | |
| Age | | | | | | |
| Forty-five to fifty-four years | 347 (18.6%) | 554 (21.2%) | 1 (12.5%) | 23 (30.3%) | 3 (21.4%) | 14 (25.5%) |
| Fifty-five to sixty-four years | 1516 (81.4%) | 2062 (78.8%) | 7 (87.5%) | 53 (69.7%) | 11 (78.6%) | 41 (74.5%) |
| Sex | | | | | | |
| Male | 723 (38.8%) | 1253 (47.9%) | 1 (12.5%) | 42 (55.3%) | 6 (42.9%) | 28 (50.9%) |
| Female | 1140 (61.2%) | 1363 (52.1%) | 7 (87.5%) | 34 (44.7%) | 8 (57.1%) | 27 (49.1%) |
| Metal on highly cross-linked polyethylene, >32-mm head size | | | | | | |
| Age | | | | | | |
| Forty-five to fifty-four years | 352 (19.3%) | 367 (22.2%) | 6 (22.2%) | 15 (14.2%) | 2 (40.0%) | 7 (14.3%) |
| Fifty-five to sixty-four years | 1471 (80.7%) | 1284 (77.8%) | 21 (77.8%) | 91 (85.8%) | 3 (60.0%) | 42 (85.7%) |
| Sex | | | | | | |
| Male | 1020 (56.0%) | 1060 (64.2%) | 23 (85.2%) | 71 (67.0%) | 5 (100.0%) | 30 (61.2%) |
| Female | 803 (44.0%) | 591 (35.8%) | 4 (14.8%) | 35 (33.0%) | 0 (0.0%) | 19 (38.8%) |
| Non-ASR metal on metal, >36-mm head size | | | | | | |
| Age | | | | | | |
| Forty-five to fifty-four years | 326 (37.1%) | 1228 (33.7%) | 126 (29.0%) | 27 (31.0%) | 12 (52.2%) | 30 (28.3%) |
| Fifty-five to sixty-four years | 552 (62.9%) | 2416 (66.3%) | 308 (71.0%) | 60 (69.0%) | 11 (47.8%) | 76 (71.7%) |
| Sex | | | | | | |
| Male | 629 (71.6%) | 2261 (62.0%) | 296 (68.2%) | 80 (92.0%) | 19 (82.6%) | 87 (82.1%) |
| Female | 249 (28.4%) | 1383 (38.0%) | 138 (31.8%) | 7 (8.0%) | 4 (17.4%) | 19 (17.9%) |

*The values are given as the number of hip implants, with the percentage, within the age and sex for each registry, in parentheses.

Permanente Total Joint Registry (United States) (n = 5406), the HealthEast Joint Replacement Registry (United States) (n = 439), the Emilia-Romagna Joint Registry R.I.P.O. (Registro dell'implantologia Protesica Ortopedica [Registry of the Orthopaedic Prosthetic Implants]) (Italy) (n = 719), the Norwegian Arthroplasty Register (n = 191), and the Catalan Arthroplasty Register (Spain) (n = 307). The distribution of bearing surfaces, sex, and age in each registry is shown in Table III.

The results of a fixed-effects model comparing metal-on-metal total hip replacements with a head size of >36 mm with metal-on-highly cross-linked polyethylene total hip replacements are presented in Table I, which consists of treating registry membership as a set of fixed effects. The advantage of this approach is that it controls for all registry-level confounding. The results of a random-effects model are presented in the Appendix with details of how these models were selected. Most relevant in Table I are the entries for bearing surface effects over time, showing that there is no evidence of a difference between the bearings at zero to two years (hazard ratio, 0.95 [95% CI, 0.74 to 1.23]; p = 0.698), but there is a greater

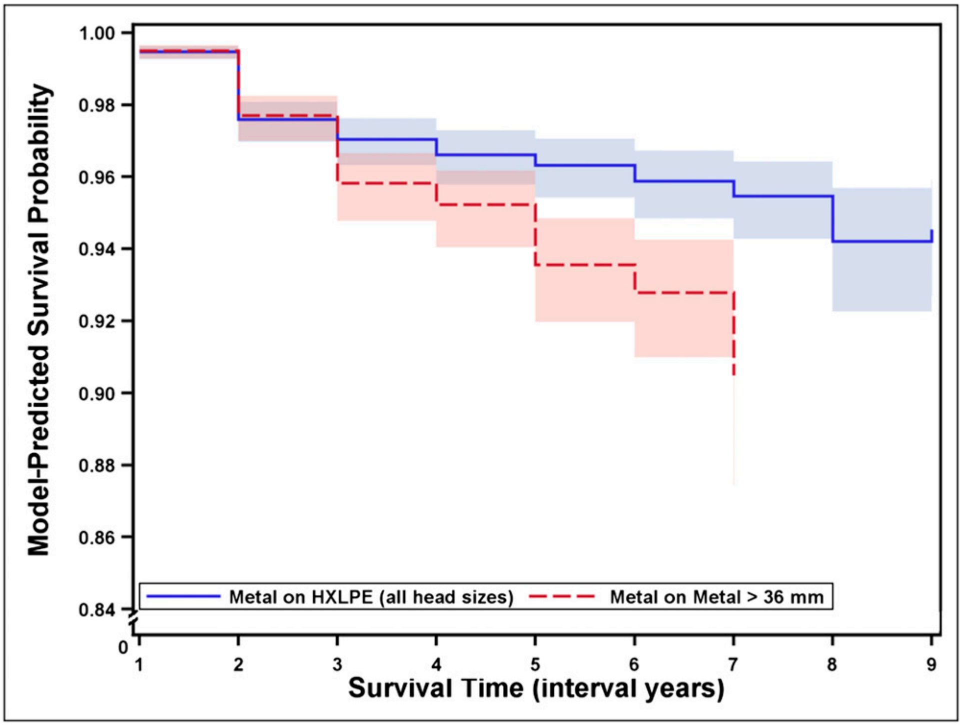


Fig. 1

Model-predicted survival of the results of Table I comparing metal-on-metal implants with a head size of >36 mm with metal-on-highly cross-linked polyethylene (HXPLE) implants of all head sizes. The x-axis values of 1 to 9 correspond to the interval years of zero to one year to more than eight years to nine years.

risk of metal-on-metal failures appearing thereafter at more than two years to four years (hazard ratio, 1.42 [95% CI, 1.16 to 1.75]; $p = 0.001$), at more than four years to six years (hazard ratio, 1.78 [95% CI, 1.45 to 2.19]; $p < 0.001$), and at more than six years to seven years (hazard ratio, 2.15 [95% CI, 1.63 to 2.83]; $p < 0.001$). These effects were similar for the random-effects model. Figure 1 displays the model-predicted survival for each head-size group from the fixed-effects model.

## Discussion

With the exclusion of the ASR implant, we provided a comprehensive analysis of the metal-on-metal total hip replacement implant outcomes in younger osteoarthritic patients using uncemented fixation. Metal-on-metal implants with a large head size of >36 mm were associated with a higher risk of revision when compared with metal-on-highly cross-linked polyethylene implants. There was no difference in the first two years, but revision risk increased thereafter to greater than a twofold risk at a follow-up of six to seven years.

### *Evidence from the Literature*

With increasing diameter of the head, the wear of large-head, metal-on-metal implants decreases, but the taper damage increases[2]. The resulting wear causes high metal ion levels and pseudotumors[7,11,12]. It also explains why, when compared with small-head resurfacing hip implants, large-head resurfacing metal-on-metal hip implants have less risk of revision[24,26] and large-head metal-on-metal total hip replacements have more risk of revision[1,26]. Our study confirms these findings. In a meta-analysis of four randomized studies[36] comparing metal-on-metal and metal-on-polyethylene hip replacements, Voleti et al. found no difference in functional outcome, but a 3.37 times higher complication rate in the metal-on-metal total hip replacement group. In a meta-analysis of five studies on metal-on-metal total hip replacements compared with metal-on-polyethylene total hip replacements, Sedrakyan and coworkers found a small but significantly lower functional score using the Harris hip score in metal-on-metal total hip replacement[4]. However, head size was not analyzed in that meta-analysis, and three of the included studies compared 28-mm metal-on-metal components with 28-mm metal-on-polyethylene components. In that same study, three national registries reported more revision in metal-on-metal total hip replacement compared with metal-on-polyethylene total hip replacement. In a large study from the National Joint Registry of England and Wales[24], one type of stem (the Corail stem) used in total hip arthroplasty was studied, and risk factors for revision were investigated. Those investigators found that metal-on-metal total hip replacement had a hazard ratio of 1.93 at a follow-up duration of 7.5 years compared with metal-on-polyethylene replacement, which is in accordance with our findings.

The brand of metal-on-metal total hip replacement is important. The Finnish Arthroplasty Register found that the cementless Spotorno (CLS) stem combined with the Durom cup had a 2.9 times increased revision risk compared with the cementless Synergy stem combined with the Birmingham Hip Resurfacing (BHR) cup[6]. The Finnish study could not demonstrate a difference in revision risk between cementless metal-on-metal total hip replacement compared with cemented metal-on-polyethylene total hip replacement[6] with a maximum seven-year follow-up. Our study compared only cementless total hip replacement, which makes it less prone to confounding by indication. However, in a recent study from a Finnish hospital[6], 54% of eighty patients followed for a mean duration of six years had definite, probable, or possible adverse reaction to metal debris, but only three of the patients had undergone revision. In the selection model using random head size outlined in the Appendix, we did not find a head-size effect comparing metal on metal at 36 mm and at ≤32 mm, but there was substantial variation between registries. However, we advocate caution in the use of small head size in metal-on-metal implants. A randomized study of 397 hips from Norway comparing small-head (28 mm) Metasul metal-on-metal implants, small-head metal-on-conventional polyethylene implants, and ceramic-on-conventional polyethylene implants with seven years of follow-up showed no advantage of the metal-on-metal bearing with a higher revision rate and greater incidence of radiolucent lines in the metal-on-metal group than with the two other articulations[37].

Several governmental medical regulatory agencies, including the Medicines and Healthcare Products Regulatory Agency, have issued warnings and have recommended regular follow-up for metal-on-metal total hip replacements and hip resurfacing, and the number of metal-on-metal total hip replacements has decreased substantially. Our study should dispel uncertainty related to large-head-size, metal-on-metal total hip replacements. The increased risk of large-head-size, metal-on-metal total hip replacements needs to be communicated to regulators, clinicians, and patients.

### *Strengths and Limitations*

The strengths of this study were the homogeneous study population of young patients with only uncemented implants with osteoarthritis as diagnosis, the comparison with highly cross-linked polyethylene (and not a mixture of standard polyethylene and highly cross-linked polyethylene), and the use of data from six national and regional registries. The external validity of the study can therefore be regarded as good. Another strength was the number of implants studied, with 5172 metal-on-metal total hip replacements compared with 14,372 metal-on-highly cross-linked polyethylene hip implants in younger age groups, thus being, to our knowledge, the largest registry-based study for this age group reported. A limitation of the study was that the maximum follow-up was short to mid-term (up to nine years). Currently, the harmonization of implant databases across registries has not been completed and there is no comparison of implant designs across countries. While the average follow-up rate in the registries is >90%, there are limitations of observational data collected by registries. Therefore, such data would not be sufficient to support a marketing application in the U.S. Larger registries with longer follow-up would likely have a stronger influence on estimates, and differential follow-up time and implant brands used in the registries also could have influenced the results.

The case of confidentiality of the patients from each registry was not an issue because we used a standardized syntax to extract aggregated data from each registry. This approach did not necessitate institutional ethical board review as each registry's legal approval could be used. The method is less flexible because changes in the syntax require new analysis to be conducted by each registry, but it protects registry data and participation. Another approach used in the Nordic Arthroplasty Register Association (NARA)[25] might be more flexible as it creates one file for analysis with anonymous data on which researchers can do repeated analysis, but it requires a higher level of agreement by the registries and a continuous update of the main analytic file as new data are accumulating. A limitation of our study was that it was based on a minimal data set, limited by the data available from each registry. Currently, the harmonization of implant databases across registries is under development, and in the future we can validate the implants in each group. Larger registries with longer follow-up would likely have had a stronger influence on estimates, and differential follow-up time and implant brands used in the registries also could have influenced the results.

### *Future Research*

The effect of the different head sizes in large-head, metal-on-metal total hip replacements will be studied in the future, as well as various bearing surfaces in individual age groups, including a number of brands of highly cross-linked polyethylene. An important step in international registry studies will be the harmonization of different implants in a standardized implant database across registries and categorization of implants. Inclusion of new registries in the project is ongoing, providing a larger number of patients with longer durations of follow-up.

In conclusion, we demonstrated the potential of the international research network and conducted a robust study using advanced harmonized distributed analyses of six national and regional joint replacement registries. We provided a comprehensive analysis of the metal-on-metal implant outcomes in younger patients using uncemented fixation, with a well-known outlier implant excluded. We found consistent and strong evidence worldwide that large-head-size, metal-on-metal implants were associated with a higher risk of revision when compared with the metal-on-highly cross-linked polyethylene bearing. Higher revision occurs later in time rather than early after surgery.

## Appendix—Details of the Model Fitting

### *Data Inclusion*

For the models described here, we chose to retain observations with standard errors of <0.025, given simulations indicating increased bias, root mean squared error, and poorer coverage when observations with large degrees of imprecision (resulting from sparse data for certain covariate combinations) are retained. This particular threshold was based on both the simulation results and a sensitivity analysis comparing the effect on model parameters when different levels of restriction (0.05, 0.025, and 0.0125) are applied.

**TABLE IV Random-Effects Model for Metal-on-Metal Implants at a >36-mm Head Size Compared with Metal-on-Highly Cross-Linked Polyethylene Implants at All Head Sizes***

| | Hazard Ratio† | P Value |
|---|---|---|
| Time *(yr)* | | |
| Zero to one | Reference | — |
| More than one to two | 4.446 (3.415 to 5.789) | <0.001 |
| More than two to three | 5.474 (4.188 to 7.155) | <0.001 |
| More than three to four | 6.272 (4.786 to 8.218) | <0.001 |
| More than four to five | 6.826 (5.189 to 8.979) | <0.001 |
| More than five to six | 7.666 (5.798 to 10.137) | <0.001 |
| More than six to seven | 8.449 (6.337 to 11.265) | <0.001 |
| More than seven to eight | 10.856 (7.766 to 15.175) | <0.001 |
| More than eight to nine | 10.232 (7.256 to 14.429) | <0.001 |
| Sex | | |
| Male | Reference | — |
| Female | 1.127 (0.943 to 1.349) | 0.187 |
| Age *(yr)* | | |
| Forty-five to fifty-four | Reference | — |
| Fifty-five to sixty-four | 0.781 (0.637 to 0.957) | 0.018 |
| Bearing effects over time‡ | | |
| Metal on highly cross-linked polyethylene§ | Reference | — |
| Metal on metal# | | |
| At zero to two years | 0.964 (0.747 to 1.243) | 0.773 |
| At more than two to four years | 1.424 (0.993 to 2.043) | 0.053 |
| At more than four to six years | 1.814 (1.478 to 2.227) | <0.001 |
| At more than six to seven years | 2.207 (1.670 to 2.917) | <0.001 |

*The estimate and the standard error were $-5.238 \pm 0.165$ for the intercept and $0.003 \pm 0.059$ for the random effect of a metal-on-metal implant at a time of more than two years to four years. The random effect is based on the coefficient corresponding to the interaction effect for this time interval. Results are based on an iterative solution that updates the residual covariances until convergence. The random-effects model is estimated using the restricted maximum likelihood. Our simulations indicate that an optimal strategy for confidence interval construction in the presence of random effects is to use $t_{K-1}$ for fixed parameters with corresponding random effects and $t_{n-p}$ otherwise (where $K-1$ and $n-p$ indicate the degrees of freedom for the t distribution, $n$ is the number of observations, $p$ is the number of fixed effects, and $k$ is the number of registries). †The values are given as the hazard ratio, with the 95% CI in parentheses. ‡The effects over time are based on a combination of the main and interaction effects from the model. In this table, only the bearing effect at a time of more than two years to four years uses $t_{K-1}$ for confidence intervals and p values; all others use $t_{n-p}$. §Metal-on-highly cross-linked polyethylene bearings are all head sizes. #Metal-on-metal bearings have head sizes of >36 mm and exclude ASR implants.

### *Model Selection*

The fixed-effects model was based on the random-effects model selected. Details related to the selection of the random-effects model are provided below.

**Metal-on-Metal Implants with Head Sizes of 36 mm and ≤32 mm**

Prior to making comparisons of metal-on-metal implants with metal-on-highly cross-linked polyethylene implants, we conducted analyses of metal-on-metal implants (excluding ASR implants) with a head size of 36 mm compared with a head size of ≤32 mm. We fitted a model with an intercept, head size, age, sex, piecewise constant function of time, random head-size effect, and residual variance fixed at 1. For the comparison of metal-on-metal head sizes of 36 mm and ≤32 mm, the interaction terms were based on the following intervals of time in years: zero to two years, more than two years to four years, and more than four years to six years. There was no evidence of a significant interaction in this model ($\chi^2(2) = 0.56$; p = 0.754), and these terms were subsequently removed. From this model, there was no evidence of a fixed head-size effect, with a β (and a standard error) of 0.011 ± 0.388 (p = 0.977), but there was substantial between-registry variation across head size, with a $\sigma^2_{head\ size}$ (and standard error) of 0.326 ± 0.375. An examination of the empirical best linear unbiased predictions (estimate of the deviation of each registry from the average head-size effect) indicates that the registry for the United States (Kaiser Permanente) produced the least evidence for the harmful effect of a 36-mm head size at −0.61, followed by those for Italy (Emilia-Romagna) at 0.01, Australia at 0.30, and again the United States (HealthEast) at 0.31. Therefore, we focus on the >36-mm metal-on-metal head sizes for this analysis.

**Metal-on-Metal Implants with a Head Size of >36-mm Compared with Metal-on-Highly Cross-Linked Polyethylene Implants at All Head Sizes**

Including an interaction is motivated by findings that the risk for failure increases with large head size, metal-on-metal implants over time (see Table IV). The interaction terms were based on intervals of time: zero to two years, more than two years to four years, more than four years to six years, and more than six years to seven years. The intervals of time were constructed in this way to improve precision in estimation relative to the use of single-year intervals. The last interval contains only one year because there is no survival information for the metal-on-metal implants in this data set after seven years. There was improvement in model fit with the inclusion of the interaction terms $\chi^2(3) = 33.70$ and $p < 0.001$. Lastly, we considered the addition of random effects for the bearing effect for each of these time intervals. These effects were estimated to be near zero ($<1.0 \times 10^{-10}$) or would not converge for all but the interaction term corresponding to the interval of time at more than two years to four years. The addition of this random effect led to a near-zero random-effects variance estimate for the intercept; as a result, the latter effect was subsequently removed from the model. ■

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