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The risk of all-cause mortality, heart outcomes, cancer, and neurodegenerative disorders with cobalt-chrome containing total hip replacement implants: an analysis of the National Joint Registry

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Abstract

Aims

A recent report from France suggested an association between the use of cobalt-chrome femoral heads in total hip replacements (THRs) and an increased risk of dilated cardiomyopathy and heart failure. Cobalt-chrome is a commonly used material in orthopaedic implants. If the reported association is causal the consequences would be significant given the millions of joint replacements and other orthopaedic procedures in which cobalt-chrome is used annually. We examined whether cobalt-chrome containing THRs were associated with an increased risk of all-cause mortality, heart outcomes, cancer or neurodegenerative disorders in a large national database.

Methods

Data from the National Joint Registry was linked to NHS English hospital inpatient episodes for 374,359 primary THRs with up to 14.5 years follow-up. We excluded any patients with (i) bilateral THRs, (ii) knee replacements, (iii) indications other than osteoarthritis, (iv) under 55 years, and (v) diagnosis of one or more outcome of interest before THR. Implants were grouped as either containing cobalt-chrome or not containing cobalt-chrome. The association between implant construct and the risk of all-cause mortality and incident heart failure, cancer, and neurodegenerative disorders was examined.

Results

There were 158,677 individuals (42.4%) with an implant containing cobalt-chrome. There were 47,963 deaths, 27,332 heart outcomes, 35,720 cancers and 22,025 neurodegenerative disorders. There was no evidence of an association that patients with cobalt-chrome implants had higher rates of any of the outcomes.

Conclusions

Cobalt-chrome containing THRs did not have an increased risk of all-cause mortality, or clinically meaningful heart outcomes, cancer or neurodegenerative disorders into the second decade post-implantation. Our findings will help reassure clinicians and the increasing number of patients receiving primary THR worldwide that the use of cobalt-chrome containing implants is not associated with significant adverse systemic effects.

Introduction

A recent observational study of 255,350 patients from the French national database suggested an association between the use of metal femoral heads (metal-on-metal and metal-on-polyethylene bearings) in primary total hip replacements (THRs) and an increased risk of subsequent cardiomyopathy and heart failure. They attributed this to the release of cobalt metal ions released from the metal heads (the most commonly used head material worldwide) and compared outcomes with THRs using ceramic femoral heads.[1]

If this association with cardiomyopathy was causal, this may present a significant public health and economic problem as over 2 million THRs are performed annually worldwide with numbers rising.[2] Cobalt-chrome is a common material in orthopaedic implants,[1, 3, 4] and monitoring of cardiac function in THR patients, as recommended,[1] would lead to a significant clinical and economic burden.

A number of large observational studies have assessed systemic effects (heart failure, cancer, mortality) following THR, comparing metal-on-metal bearings (rarely used now due to high failure rates for adverse local tissue reactions)[5, 6] with alternatives.[7-11] Most show no increased risk of systemic effects from metal-on-metal THRs compared with alternatives.[7-11]

The problem with previous studies is that both patient groups (metal-on-metal and alternative bearing THRs) have prosthesis containing cobalt-chrome, making interpretation of the findings difficult if cobalt-chrome is the potentially deleterious exposure. The recent French study was the first to consider the composition of the bearing surface according to whether or not it contained cobalt-chrome.[1] This work has now raised valid and urgent patient safety concerns about the systemic toxicity of THRs containing cobalt-chrome alloys.[12] Furthermore a recent review reported half of all cases with cobalt-induced cardiomyopathy occurred in non-metal-on-metal THRs.[13]

However the French study[1] is limited by only focusing on femoral head composition (metal or ceramic), as did the recent review.[13] Femoral stem composition is equally important, given ceramic heads may be coupled with cobalt-chrome stems, which may generate metal ion release through fretting and corrosion at the head-neck junction.[14] Failure to consider this may induce substantial mis-classification. Furthermore, given concerns that metal ion release from implants may lead to more widespread systemic effects,[15] it is important to consider other conditions linked to exposure of heavy metals, like cancer,[16, 17] and neurodegenerative disorders.[18, 19]

Using the world's largest and mandatory joint replacement registry, we aimed to determine whether cobalt-chrome containing primary THRs are associated with an increased risk of all-cause mortality, heart outcomes, cancer or neurodegenerative disorders when compared to non-cobalt-chrome containing THRs within 14.5 years of implantation. We hypothesised that cobalt-chrome containing primary THRs would not be associated with an increased risk of all-cause mortality, heart outcomes, cancer or neurodegenerative disorders when compared to non-cobalt-chrome containing THRs.

Methods

Study design and participants

In this retrospective cohort analysis, of prospectively collected observational data, we have reported on primary total hip replacements (THRs) implanted between 1st April 2003 and 31st December 2018 collected by the National Joint Registry (NJR) for England, Wales, Northern Ireland and the Isle of Man. NJR data were linked to English Hospital Episode Statistics Admitted Patient Care data (HES) and to data from the Office for National Statistics (ONS). The former provides secondary care admission records and the latter was used to obtain time to and cause of death. Patients with a primary THR with a successful link to their HES data (and ONS data where applicable) using a unique NHS number were included in this study. Patient consent was obtained for data collection by the NJR and all data were anonymised.

Exposure

The NJR data included information about the components used in the THR construct. The exposure of interest was binary, namely whether or not the THR implant construct, including the femoral head and/or stem, contained any cobalt-chrome. Implants were grouped as cobalt-chrome containing and non-cobalt-chrome containing THR constructs.

Several exclusions were made prior to analysing the outcomes of those with a primary THR (Figure 1): (i) Any patients with bilateral THRs, and any patients with a total knee replacement recorded within the NJR to avoid any misclassification from any other potential cobalt-chrome producing hip or knee replacements; (ii) Any primary THRs performed for any indication other than osteoarthritis[4] (over 90% of THRs are performed for osteoarthritis in this setting, given patients with other indications, such as inflammatory arthritis may have different comorbidity profiles or be on treatments that predispose to outcomes of interest, we decided *a priori* to limit to patients with osteoarthritis); (iii) Records without complete data

for all covariates; (iv) Patients younger than 55 years of age (in line with the selection criteria in the previous study)[1]; (v) Patients who had a diagnosis of one or more of our outcomes (prevalent cases) prior to the primary operation date.

Outcomes and other covariates

There were four groups of outcomes: all-cause mortality, incident heart outcomes, cancer and neurodegenerative disorders. The latter 3 were defined using appropriate International Classification of Diseases 10th revision (ICD-10) records diagnoses (Appendix), which were either recorded in HES to indicate a related hospital episode and/or in ONS to confirm a disease-related cause of death. Time to each event was calculated in days from the date of the primary operation.

The following covariates were extracted from either the NJR or HES datasets as potential confounders as they may influence choice of implant and subsequent risk of the outcomes of interest: age, American Society of Anesthesiologists (ASA) grade, ethnicity, sex, deprivation index and a Summary Hospital-level Mortality Indicator (SHMI) variable.[20] ASA grade was in 5 categories; grade 1 - fit and healthy; grade 2 - mild disease, not incapacitating; grade 3 - incapacitating systemic diseases; grade 4 - life threatening disease; grade 5 - expected to die within 24 hours without an operation. The reference ASA category was set as ASA grade 2, which is reflective of the population that undergo elective THR. The SHMI was categorised into 5 categories: a score of zero; 1 to 5; 6 to 11; 12 to 20; >20; with the baseline equal to a score of 0. Ethnicity was categorised as white (baseline group), non-white and unknown. The first quintile of the deprivation index score was the baseline (1=most deprived and 5=least deprived), and the sex baseline was set as female. For each of the outcome (heart outcome, cancer or neurodegenerative disorder) analyses we created a modified Summary Hospital-level Mortality Indicator (SHMI) variable that excluded scoring related to the outcome of the

analysis.

Statistical analysis

We included age as a continuous variable (using a restricted cubic spline transformation centred on average age, with 5 evenly distributed knots). We used flexible parametric survival models to analyse the effects of cobalt-chrome containing THR constructs on the time-to-event for the outcomes of interest. The decision to use flexible parametric models was made *a priori* as we did not expect proportionality between cobalt and/or chromium release over time and the outcomes of interest i.e. we would expect little to no immediate effect, with the effect increasing with a systemic exposure or accumulation over time. For each outcome in our analyses, the crude Kaplan-Meier survival data was plotted, dichotomised by our cobalt-chrome exposure variable, and a model was fitted to the data. Patients who underwent implant revision were not censored as we made the assumption that once patients were exposed to cobalt-chrome from a primary implant, the effect of the exposure could not subsequently be removed given the outcomes of interest. Patients were censored at death or administratively at the end of follow-up. Given the expected lack of proportionality in outcomes, it would be inappropriate to present a single hazard ratio. We therefore preferred the use of standardized restricted mean survival time.[21] This may be defined as the area under the survival curve up to a prespecified time horizon, and represents either the loss or gain of life expectancy if everyone was exposed to cobalt-chrome compared to not being exposed to cobalt-chrome.

Models were adjusted for potential confounders and our final model was adjusted for age, ASA grade, ethnicity, sex, deprivation index and SHMI variable.

Pre-specified sub-group analyses and test for interaction

As well as analysing the four main outcome groups (all-cause mortality, heart outcomes, cancer and neurodegenerative disorders) we repeated the analysis for specific sub-categories of each of the main outcomes for which there have been specific aetiological interest around metal toxicity. For example, as well as a model to assess the effect of cobalt-chrome on overall incident cancer, we also performed separate analysis on outcomes such as urinary cancer and haematological cancer, or Parkinson's disease[22] (which included Parkinson's dementia) as a sub-group of the neurodegenerative outcome. In addition, after assessing all heart outcomes together, we looked at specific heart outcomes as separate endpoints, such as cardiomyopathy, heart failure, and hypertension. Given our lack of data on smoking habit, which could be a confounder, we specifically looked at lung cancer (as a proxy for smoking). We also pre-specified one test of interaction between cobalt-chrome exposure and age. As a further subgroup analysis we assessed the mortality rate using the methods described above, with the cobalt-chrome implant group subdivided into those with and those without metal-on-metal bearing surfaces. This was done to determine if metal-on-metal bearings were responsible for driving any potential systemic effects seen. All analyses were performed using Stata version 15.1 (StataCorp, Texas, USA) utilising the stpm2 command.[23]

Results

There were 374,359 individuals with a primary THR eligible for inclusion with a maximum follow-up period of 14.5 years (mean 5.1 years, standard deviation 3.5 years, range 1 day to 14.5 years) (Table 1 and Figure 1). There were 158,677 (42.4%) with a cobalt-chrome containing THR implant. In the subsequent analyses, the number of patients included for each analysis was variable given the number of patients excluded due to having a pre-existing diagnosis varies for each outcome of interest.

Mortality

Prior to the mortality analysis we excluded all observations with a pre-existing diagnosis of heart outcomes, cancer, or neurodegenerative disorders as defined by ICD-10 codes from the HES data. This resulted in 316,120 observations (132,145 (41.8%) with cobalt-chrome containing implants) with 47,963 (15.2%) deaths.

All-cause mortality

The fully adjusted flexible parametric model showed similar mortality rates (Figure 2 which displays adjusted rates and Table 2 which displays crude rates) (restricted mean survival analysis=6.9 days, 95% CI 0.1, 13.7 days, p=0.05). We performed separate analyses for heart based mortality (6,239 (2.0%) heart deaths), cancer mortality (16,106 (5.1%) cancer deaths), and mortality related to neurodegenerative disorders (6,704 (2.1%) neurodegenerative related deaths). Each analysis resulted in similar findings.

Incident heart outcomes

There were 354,190 observations (149,544 (42.2%) with cobalt-chrome containing implants) and 27,332 (7.7%) incident heart outcomes. The failure variable in this analysis was a diagnosis of a defined heart outcome during the study period and/or a fatal heart outcome from the mortality data. Our model showed no difference in incident heart outcomes between

the implant groups (Figure 3 which displays adjusted rates and Table 2 which displays crude rates). The restricted mean survival analysis found no difference for the exposed group (-2.0 days, 95% CI -8.0, 4.0 days, p=0.52). Similar findings were seen with the different heart outcomes (including cardiomyopathy, heart failure and hypertension).

Incident cancer outcomes

There were 331,320 observations (139,221 (42.0%) with cobalt-chrome containing implants) with 35,720 (10.8%) incident cancer diagnoses. The failure variable in this analysis was a diagnosis of cancer during the study period and/or a cancer related death. Our model showed no clinically meaningful difference in incident cancer outcomes between the implant groups (Figure 4 which displays adjusted rates and Table 2 which displays crude rates) (restricted mean survival analysis= -9.0 days, 95% CI -16.3, -1.7 days, p=0.02). Similar results were seen in separate analyses with urinary cancer, haematological cancer, melanoma type cancers, prostate cancer, and lung cancer.

Incident neurodegenerative disorders

There were 361,728 observations (152,828 (42.3%) with cobalt-chrome containing implants) with 22,025 (6.1%) incident neurodegenerative disorder diagnoses. The failure variable in this analysis was a diagnosis of a neurodegenerative disorder during the study period and/or death from a neurodegenerative disorder. Our model showed no clinically meaningful difference in incident neurodegenerative diagnoses between cobalt-chrome implants and non-cobalt-chrome implants, however there was a possibility of a divergence in rates after around 11 years with higher rates for cobalt-chrome (Figure 5 which displays adjusted rates and Table 2 which displays crude rates) (restricted mean survival analysis at 10 years= -6.9 days, 95% CI -12.3, -1.5 days, p=0.01). Similar results were seen when analyses were performed on sub-categories of neurodegenerative disorders, such as dementia, Alzheimer's and

Parkinson's disease (the latter both with and without the inclusion of Parkinson's dementia).

There was no evidence of any interaction between exposure and age.

In our subgroup analysis, no difference in mortality rates were observed between patients with cobalt-chrome implants that were metal-on-metal bearing surfaces (n=13,621), cobalt-chrome implants that did not have metal-on-metal bearing surfaces (n=118,524), and non cobalt-chrome containing implants (n=183,975) (Figure 6).

Discussion

Cobalt-chrome is used in many orthopaedic implants, including THR. If implants containing cobalt-chrome were demonstrated to cause harmful systemic implant effects, this would cause a major worldwide public health problem. A recent study linking the French national health insurance databases to the national hospital discharge database observed an increased risk of cardiomyopathy and heart failure in patients with metal femoral heads compared with ceramic heads (hazard ratio (HR) for hard-on-soft bearings=1.08, 95% CI=1.05-1.12; HR for hard-on-hard bearings=1.11, 95% CI=1.03-1.19), which was attributed to metal heads containing cobalt-chrome.[1] This study had a number of important limitations as previously described.[14] Limitations included focus only on the femoral head composition (metal or ceramic) and not the stem composition, and only considering cardiac related systemic effects, rather than other conditions linked with exposure to heavy metals (such as cancer,[16, 17] and neurodegenerative disorders[18, 19]). Furthermore the increased risk of cardiomyopathy and heart failure was only small. However, the findings of the French study have raised concerns, and if validated, they would suggest a widespread problem for orthopaedic patients, given metal is the commonest head material used in THR implants worldwide.

Our large nationwide cohort study of 374,359 THRs demonstrated that cobalt-chrome containing primary THRs did not have an increased risk of all-cause mortality, or a clinically meaningful difference in heart outcomes, cancer, and neurodegenerative disorders into the second decade after implantation compared with non-cobalt-chrome containing primary THRs. These findings remained consistent in numerous robust sensitivity analyses, including when metal-on-metal bearings were separated from the cobalt-chrome implants without metal-on-metal bearings. Therefore, on the basis of current evidence, we believe that cobalt-chrome containing THRs are safe for continued use and do not cause major systemic effects to patients.

Metal-on-metal THRs have higher circulating cobalt and chromium ion concentrations compared with non-metal-on-metal bearing surfaces, which could cause systemic effects.[24] Previous reports document a wide range of blood metal ion concentrations occur in metal-on-metal THR patients who have systemic effects,[25] and there have even been reports of death due to cardiac failure secondary to cobalt toxicity in metal-on-metal THR patients.[26, 27] For this reason over the past decade a number of large observational studies have assessed systemic effects (heart failure, cancer, mortality) following THR, comparing metal-on-metal bearings with alternatives.[7-11] Most observational studies show no increased risk of systemic effects from metal-on-metal THRs compared with alternatives.[7-11] One small study showed older males with one type of metal-on-metal implant had a three-fold increased risk of hospital admission due to cardiac failure, though this study had a number of limitations.[28] A small cross-sectional study found a 7% lower cardiac ejection fraction in metal-on-metal THRs,[29] although studies to the contrary exist.[30] Therefore to date there is no robust evidence supporting an increased risk of systemic effects of metal-on-metal THRs compared with alternative bearings.

Previous studies are limited in the current context by comparing exposure and control groups both exposed to cobalt-chrome. Interpretation of these findings is therefore difficult if cobalt-chrome is the potentially deleterious exposure. Although the French study observed an increased risk of cardiomyopathy and heart failure in patients with metal femoral heads compared with ceramic heads,[1] it is not possible to directly compare these results to our study given the former was limited by not considering the femoral stem material in the analysis. Therefore any differences in the findings between the studies may relate to misclassification of the material composition of the implants or failure to consider the entire construct. Our work is consistent with observations regarding other commonly used orthopaedic implants, such as knee and shoulder replacements and internal fixation devices used in trauma, in that

patients with these implants do not commonly experience systemic effects.[31] Furthermore our subanalyses highlighted that mortality rates were not different between patients with cobalt-chrome implants that were metal-on-metal bearing surfaces, cobalt-chrome implants that did not have metal-on-metal bearing surfaces, and non cobalt-chrome containing implants. This analysis importantly isolated those patients with implants containing no cobalt-chrome in the construct, with those containing cobalt-chrome as part of the construct, which has been a limitation of previous work in which both groups analysed had cobalt-chrome within their implants. The findings provide further support that cobalt-chrome THR implants are not associated with clinically significant adverse systemic effects.

Strengths and limitations

This large study with extended follow-up is the first to assess this important issue given the recent concerning French study findings. Robust methodology were used to define the exposure group, with patients grouped according to whether or not they had cobalt-chrome in their THR (not just the femoral head), which has limited previous analyses.[1] Furthermore patients with non-hip cobalt-chrome implants were excluded. Potential systemic effects of concern were assessed given previous studies focussed on few endpoints. We used linked data from the world's largest arthroplasty registry with excellent levels of data completion and accuracy,[32, 33] and the unselected population improved the generalisability of the findings, with THR patients broadly similar to other high income populations.[3] Our findings remained consistent in multiple sensitivity analyses, which validates the observations presented.

Limitations include the use of observational data which limits our ability to infer causality.

However, this question cannot be answered by conventional randomised trials given the very large sample sizes and long follow-up period required. Therefore, the best evidence to inform practice will come from well-conducted observational data. Whilst the linked datasets include many variables that adjust for case-mix/comorbidity, residual confounding remains a possibility. Although we used consistent methods for identifying heart outcomes, cancer and neurodegenerative disorders, some may have been missed given not every diagnosis will result in hospital admission and/or will contribute to the cause of death. Coding errors may have occurred and/or practices may have changed over time though it is unlikely that this is systematically biased by prosthesis type. Incident outcomes may vary between countries, therefore there may be a baseline difference in risk between populations, although this is unlikely. Although our analysis extends into the second decade after implantation for some patients (maximum 14.5 year follow-up, mean 5.1 year follow-up, and over 40,000 patients with over 10 years follow-up), there may be an accumulative effect over time. This, in combination with the long latency period for the development of some cancers and the potential divergence in neurodegenerative outcomes beyond 11 years warrants longer term follow-up of those outcomes, although the latter finding was consistent with chance. A small proportion of cases without complete data available were excluded (0.62% of NJR-HES-ONS data) and we assume data is either missing completely at random or missing at random, and therefore unbiased estimates should be obtained following complete case analysis.[34, 35]

Conclusions

Data from the world's largest joint replacement registry demonstrates that cobalt-chrome containing THRs do not have an increased risk of all-cause mortality, or clinically meaningful heart outcomes, cancer, and neurodegenerative disorders into the second decade after implantation compared with non-cobalt-chrome containing primary THRs. Our findings

will help reassure clinicians and the increasing number of patients receiving primary THR worldwide that the procedure is safe and not associated with significant systemic implant effects.

Ethics approval and consent to participate

With support under Section 251 of the NHS Act 2006, the Ethics and Confidentiality Committee (ECC), (now the Health Research Authority Confidentiality Advisory Group) allows the NJR to collect patient data where consent is indicated as 'Not Recorded'.

References

1. Lassalle M, Colas S, Rudnichi A, Zureik M, Dray-Spira R. Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res*. 2018;**476**(7):1441-1451.

2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;**89**(4):780-785.

3. AOANJRR. Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) Hip, Knee & Shoulder Arthroplasty Annual Report. 2018:https://aoanjrr.sahmri.com/annual-reports-2018.

4. National Joint Registry (NJR) for England, Wales, Northern Ireland and the Isle of Man 16th Annual Report. 2019:https://reports.njrcentre.org.uk/Portals/0/PDFdownloads/NJR 16th 20Annual 20Report 2019.pdf.

5. Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW, National Joint Registry of E, Wales. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. *Lancet*. 2012;**379**(9822):1199-1204.

6. Smith AJ, Dieppe P, Howard PW, Blom AW, National Joint Registry for E, Wales. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. *Lancet*. 2012;**380**(9855):1759-1766.

7. Makela KT, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, Junnila M, Pukkala E. Risk of cancer with metal-on-metal hip replacements: population based study. *BMJ*. 2012;**345**:e4646.

8. Smith AJ, Dieppe P, Porter M, Blom AW, National Joint Registry of E, Wales. 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.

9. 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.

10. Goodnough LH, Bala A, Huddleston J, III, Goodman SB, Maloney WJ, Amanatullah DF. Metal-on-metal total hip arthroplasty is not associated with cardiac disease. *Bone Joint J*. 2018;**100-B**(1):28-32.

11. Sabah SA, Moon JC, Jenkins-Jones S, Morgan CL, Currie CJ, Wilkinson JM, Porter M, Captur G, Henckel J, Chaturvedi N, Kay P, Skinner JA, Hart AJ, Manisty C. The risk of cardiac failure following metal-on-metal hip arthroplasty. *Bone Joint J*. 2018;**100-B**(1):20-27.

12. Kremers HM. CORR Insights®: Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res*. 2018;**476**(7):1452-1454.

13. Umar M, Jahangir N, Faisal Khan M, Saeed Z, Sultan F, Sultan A. Cobalt cardiomyopathy in hip arthroplasty. *Arthroplast Today*. 2019;**5**(3):371-375.

14. Matharu GS, Whitehouse MR. Letter to the Editor: Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res*. 2018;**476**(12):2459-2461.

15. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br*. 2007;**89**(5):567-573.

16. Iarmarcovai G, Sari-Minodier I, Chaspoul F, Botta C, De Meo M, Orsiere T, Berge-Lefranc JL, Gallice P, Botta A. Risk assessment of welders using analysis of eight metals by

ICP-MS in blood and urine and DNA damage evaluation by the comet and micronucleus assays; influence of XRCC1 and XRCC3 polymorphisms. *Mutagenesis*. 2005;**20**(6):425-432.

17. Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. *Regul Toxicol Pharmacol*. 2005;**43**(3):225-231.

18. Tan EK, Tan C, Fook-Chong SM, Lum SY, Chai A, Chung H, Shen H, Zhao Y, Teoh ML, Yih Y, Pavanni R, Chandran VR, Wong MC. Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. *J Neurol Sci*. 2003;**216**(1):163-167.

19. Olivieri G, Novakovic M, Savaskan E, Meier F, Baysang G, Brockhaus M, Muller-Spahn F. The effects of beta-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and beta-amyloid secretion. *Neuroscience*. 2002;**113**(4):849-855.

20. NHS Digital. About the Summary Hospital-level Mortality Indicator (SHMI). 9th July 2020:https://digital.nhs.uk/data-and-information/publications/ci-hub/summary-hospital-level-mortality-indicator-shmi.

21. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;**13**:152.

22. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol*. 2011;**26 Suppl 1**:S1-58.

23. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *The Stata Journal*.**9**(2):265-290.

24. Cheung AC, Banerjee S, Cherian JJ, Wong F, Butany J, Gilbert C, Overgaard C, Syed K, Zywiel MG, Jacobs JJ, Mont MA. Systemic cobalt toxicity from total hip arthroplasties:

review of a rare condition Part 1 - history, mechanism, measurements, and pathophysiology. *Bone Joint J*. 2016;**98-B**(1):6-13.

25. Zywiel MG, Cherian JJ, Banerjee S, Cheung AC, Wong F, Butany J, Gilbert C, Overgaard C, Syed K, Jacobs JJ, Mont MA. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 2. measurement, risk factors, and step-wise approach to treatment. *Bone Joint J*. 2016;**98-B**(1):14-20.

26. Martin JR, Spencer-Gardner L, Camp CL, Stulak JM, Sierra RJ. Cardiac cobaltism: a rare complication after bilateral metal-on-metal total hip arthroplasty. *Arthroplast Today*. 2015;**1**(4):99-102.

27. Gilbert CJ, Cheung A, Butany J, Zywiel MG, Syed K, McDonald M, Wong F, Overgaard C. Hip pain and heart failure: the missing link. *Can J Cardiol*. 2013;**29**(5):639 e631-632.

28. Gillam MH, Pratt NL, Inacio MC, Roughead EE, Shakib S, Nicholls SJ, Graves SE. Heart failure after conventional metal-on-metal hip replacements. *Acta Orthop*. 2017;**88**(1):2-9.

29. Prentice JR, Clark MJ, Hoggard N, Morton AC, Tooth C, Paley MN, Stockley I, Hadjivassiliou M, Wilkinson JM. Metal-on-metal hip prostheses and systemic health: a cross-sectional association study 8 years after implantation. *PLoS One*. 2013;**8**(6):e66186.

30. Berber R, Abdel-Gadir A, Rosmini S, Captur G, Nordin S, Culotta V, Palla L, Kellman P, Lloyd GW, Skinner JA, Moon JC, Manisty C, Hart AJ. Assessing for Cardiotoxicity from Metal-on-Metal Hip Implants with Advanced Multimodality Imaging Techniques. *J Bone Joint Surg Am*. 2017;**99**(21):1827-1835.

31. Biological Responses to Metal Implants. September 2019.:https://www.fda.gov/media/131150/download.

32. Sabah SA, Henckel J, Cook E, Whittaker R, Hothi H, Pappas Y, Blunn G, Skinner JA, Hart AJ. Validation of primary metal-on-metal hip arthroplasties on the National Joint Registry for England, Wales and Northern Ireland using data from the London Implant Retrieval Centre: a study using the NJR dataset. *Bone Joint J*. 2015;**97-B**(1):10-18.

33. Sabah SA, Henckel J, Koutsouris S, Rajani R, Hothi H, Skinner JA, Hart AJ. Are all metal-on-metal hip revision operations contributing to the National Joint Registry implant survival curves? : a study comparing the London Implant Retrieval Centre and National Joint Registry datasets. *Bone Joint J*. 2016;**98-B**(1):33-39.

34. Schafer JL, Graham JW. Missing Data: Our View of the State of the Art. *Psychological Methods*. 2002;**7**(2):147-177.

35. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;**338**:b2393.

Table 1. Baseline demographic characteristics of the study population

	non Cobalt-Chrome		Cobalt-Chrome		Total	
Total, N (%)	215,682	(57.6)	158,677	(42.4)	374,359	(100.0)
Sex, N (%)						
Male	86,514	(40.1)	64,457	(40.6)	150,971	(40.3)
Female	129,168	(59.9)	94,220	(59.4)	223,388	(59.7)
Age, mean (SD)	70.5	(8.5)	72.5	(8.2)	71.4	(8.4)
Age, range (min, max)	55.0	(8.5)	55.0	(8.2)	55.0	(8.4)
ASA grade, N (%)						
1	29,055	(13.5)	16,988	(10.7)	46,043	(12.3)
2	151,114	(70.1)	111,370	(70.2)	262,484	(70.1)
3	34,431	(16.0)	29,266	(18.4)	63,697	(17.0)
4	1,052	(0.5)	1,030	(0.6)	2,082	(0.6)
5	30	(<0.1)	23	(<0.1)	53	(<0.1)
Ethnicity, N (%)						
White	205,613	(95.3)	151,745	(95.6)	357,358	(95.5)
non-White	2,146	(1.0)	1,598	(1.0)	3,744	(1.0)
Other/Unknown	7,923	(3.7)	5,334	(3.4)	13,257	(3.5)
Deprivation index quintile, N (%)						
1st (least deprived)	39,568	(18.3)	29,591	(18.6)	69,159	(18.5)
2nd	48,327	(22.4)	35,823	(22.6)	84,150	(22.5)
3rd	51,212	(23.7)	36,681	(23.1)	87,893	(23.5)
4th	43,646	(20.2)	33,138	(20.9)	76,784	(20.5)
5th (most deprived)	32,929	(15.3)	23,444	(14.8)	56,373	(15.1)
SHMI quintile, N (%)						
1st (lowest score)	126,471	(58.6)	87,030	(54.8)	213,501	(57.0)
2nd	38,593	(17.9)	28,490	(18.0)	67,083	(17.9)
3rd	26,254	(12.2)	21,507	(13.6)	47,761	(12.8)
4th	17,629	(8.2)	15,126	(9.5)	32,755	(8.7)
5th (highest score)	6,735	(3.1)	6,524	(4.1)	13,259	(3.5)

ASA grade 1 - fit and healthy; grade 2 - mild disease, not incapacitating; grade 3 - incapacitating systemic diseases; grade 4 - life threatening disease; grade 5 - expected to die within 24hrs without an operation. SHMI stands for Summary Hospital-level Mortality Indicator. Test of homogeneity by Cobalt-Chrome status gave a p-value of <0.001 in all groups, except Sex where the p-value was 0.002.

Table 2 Estimated crude rates of each outcome of interest based on whether or not the primary total hip replacement contained cobalt-chrome

Outcome of interest	Exposure group	Crude rate of outcome of interest per 1,000 person-years (95% confidence intervals)
All-cause mortality	Non-cobalt-chrome	28.98 (28.65 - 29.32)
	Cobalt-chrome	28.91 (28.51 - 29.32)
Incident heart outcomes	Non-cobalt-chrome	15.15 (14.92 - 15.39)
	Cobalt-chrome	16.03 (15.74 - 16.32)
Incident cancer outcomes	Non-cobalt-chrome	21.23 (20.94 - 21.52)
	Cobalt-chrome	22.50 (22.15 - 22.87)
Incident neurodegenerative disorders	Non-cobalt-chrome	11.98 (11.77 - 12.18)
	Cobalt-chrome	12.51 (12.26 - 12.76)

Figure Legends

Figure 1. Participant flow diagram

Figure 2. Estimated adjusted baseline mortality rates by cobalt-chrome exposure status

Figure 3. Estimated adjusted baseline hazard for incident heart outcomes by cobalt-chrome exposure status

Figure 4. Estimated adjusted baseline hazard for incident cancer outcomes by cobalt-chrome exposure status

Figure 5 Estimated adjusted baseline hazard for incident neurodegenerative disorders by cobalt-chrome exposure status

Figure 6 Estimated adjusted baseline mortality rates by cobalt-chrome exposure status, with the cobalt-chrome group subdivided into those with and those without a metal-on-metal bearing

Appendix: ICD-10 codes for outcomes of interest

	Included ICD 10 codes (any code beginning with)	**Notes**
Any cancer	C	Including C792 but excluding C44
	D00 to D09 inclusive	Excluding D04
	D37 to D48 inclusive	
Any haematological cancer (lymphoma, leukaemia, myeloma)	C81 to C86 inclusive	
	C88 to C96 inclusive	
	D45 to D47 inclusive	
	C77	Unspecified malignant neoplasm of lymph nodes
Any malignant melanoma	C43	
	D03	Melanoma in situ
Any prostate cancer	C61	In men
	D075	
	D400	
Any urinary cancer (bladder, ureter, kidney)	C64 to C68 inclusive	
	C790 to C791 inclusive	
	D090 to D091 inclusive	
	D41	

ICD-10 Heart outcome codes

Cardiomyopathy:

I-420: Dilated cardiomyopathy

I-429: Cardiomyopathy (unspecified)

Heart failure:

I-500: Congestive heart failure

I-501: Left ventricular failure

I-502: Systolic (congestive) heart failure

I-503: Diastolic (congestive) heart failure

I-504: Combined systolic and diastolic heart failure

I-509: Heart failure, unspecified

Hypertension:

I-110: hypertensive heart disease with (congestive) heart failure

I-119: hypertensive heart disease without (congestive) heart failure

I-130: hypertensive heart and renal disease with (congestive) heart failure

I-131: hypertensive heart and renal disease with renal failure

I-132: hypertensive heart and renal disease with both (congestive) heart failure and renal failure

I-139: hypertensive heart and renal disease, unspecified

Ischaemic cardiomyopathy:

I-255: Ischaemic cardiomyopathy

Cirrhotic complications:

K-761: Heart failure complication - cirrhosis, cirrhotic (hepatic) - cardiac (of liver)

Odema:

J-81X: Heart failure complication - oedema

ICD-10 Neurodegenerative disease codes

Dementia:

F00 Dementia in AD

F01 Vascular dementia

F02 other dementias

F03 unspecified dementia

F051 delirium superimposed on dementia

F067 Mild cognitive disorder

Parkinson's dementia:

F023 Parkinson's disease dementia

Alzheimer's disease:

G30 Alzheimer's Disease

G31-G32 Other degenerative diseases

Parkinson's Disease:

G20 PD

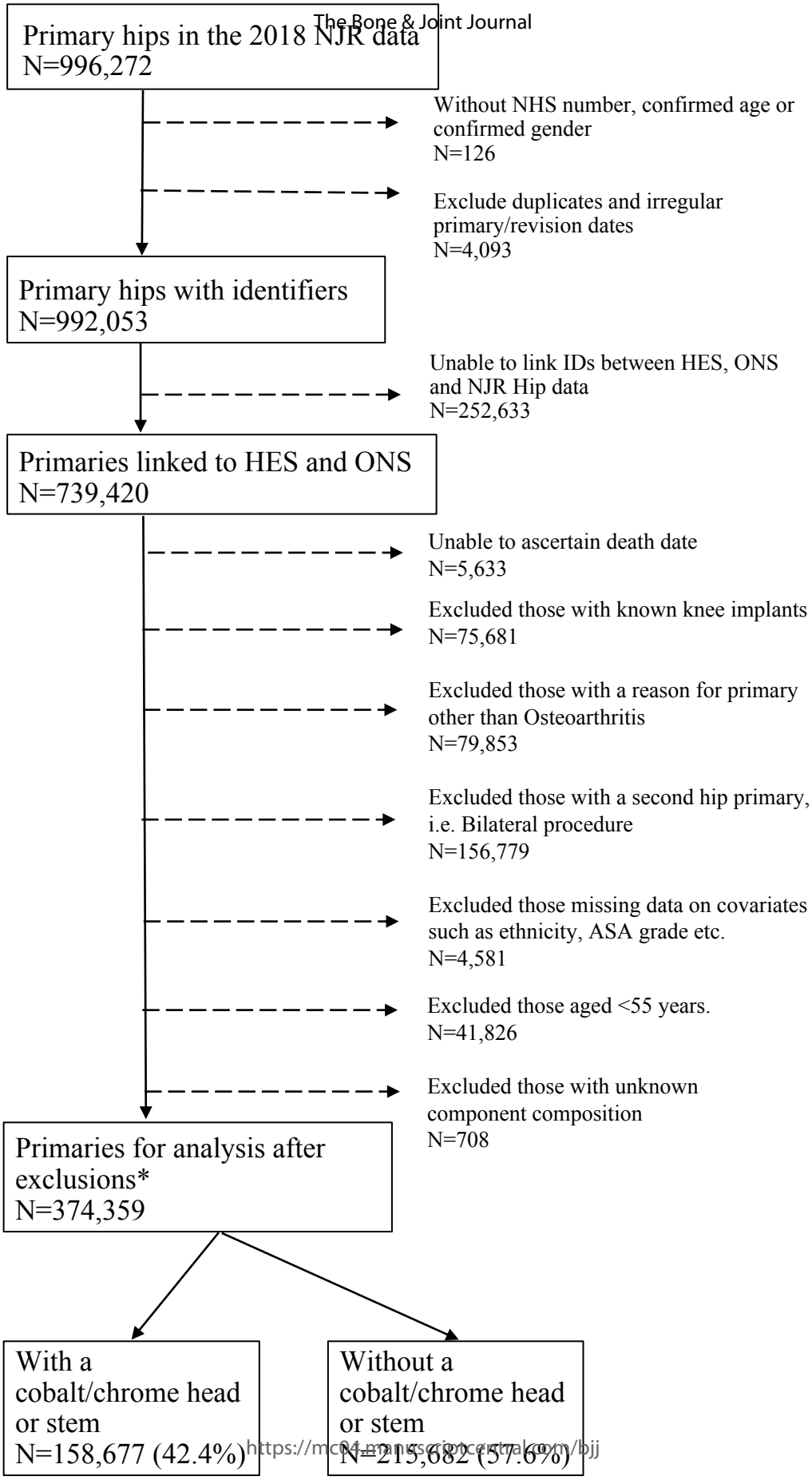
G21 secondary PD

G22 PD classified elsewhere

G23 other degenerative basal ganglia

Motor neurone disease:

G122 Motor Neurone Disease



*After this point there were analysis specific exclusions based on prior history of analysis outcomes.

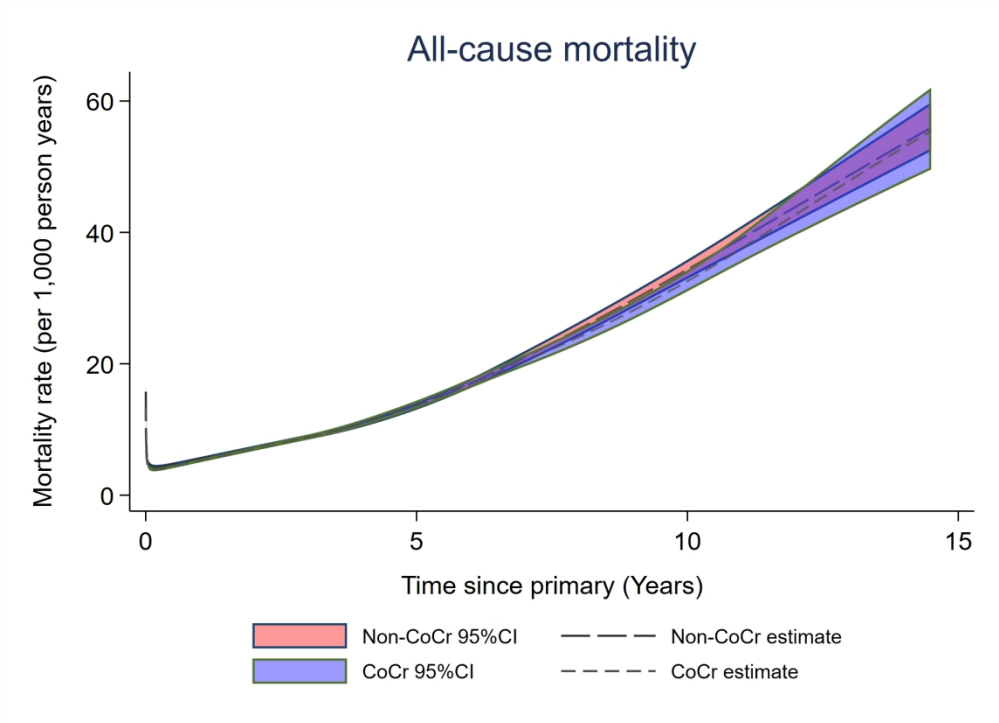


Fig 2: Estimated adjusted baseline mortality rates by cobalt-chrome exposure status

186x135mm (300 x 300 DPI)

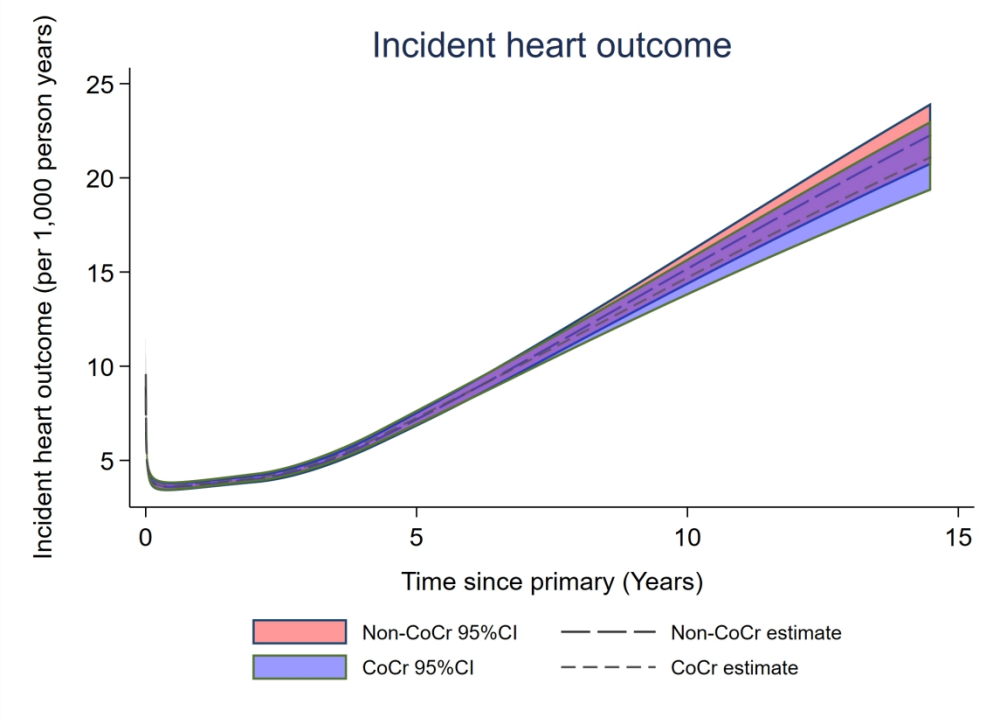


Fig 3: Estimated adjusted baseline hazard for incident heart outcomes by cobalt-chrome exposure status

186x135mm (300 x 300 DPI)

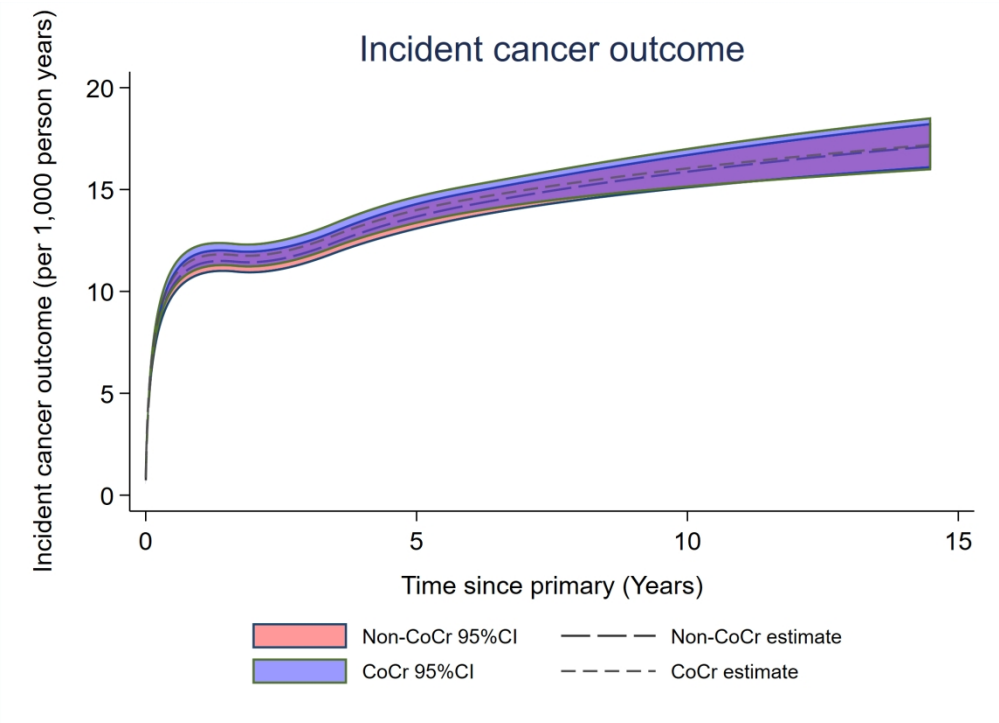


Fig 4: Estimated adjusted baseline hazard for incident cancer outcomes by cobalt-chrome exposure status

186x135mm (300 x 300 DPI)

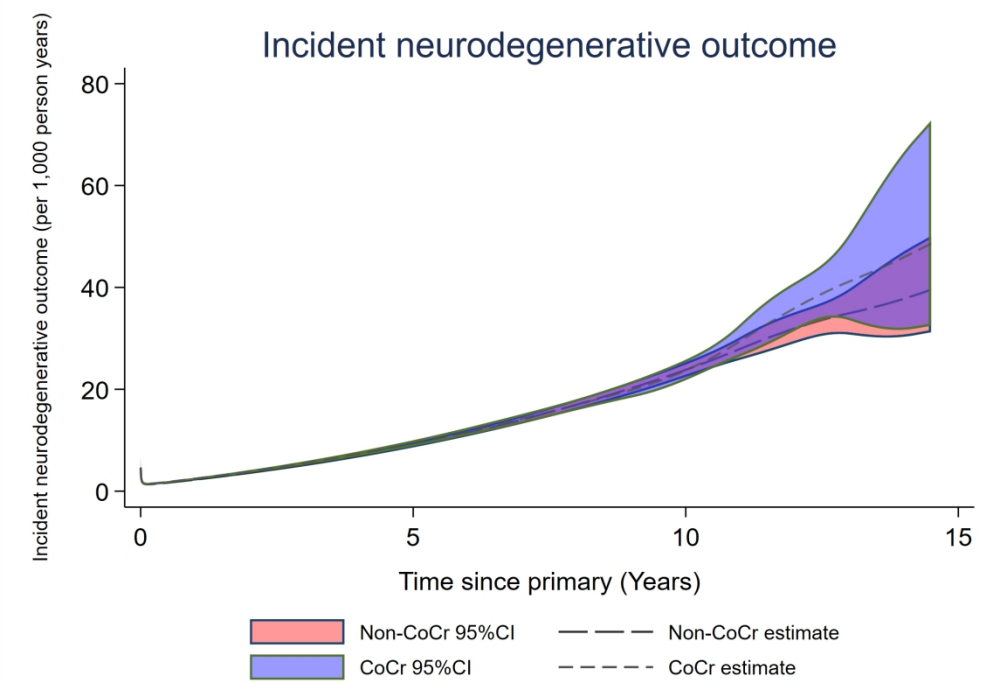


Fig 5: Estimated adjusted baseline hazard for incident neurodegenerative disorders by cobalt-chrome exposure status

186x135mm (300 x 300 DPI)

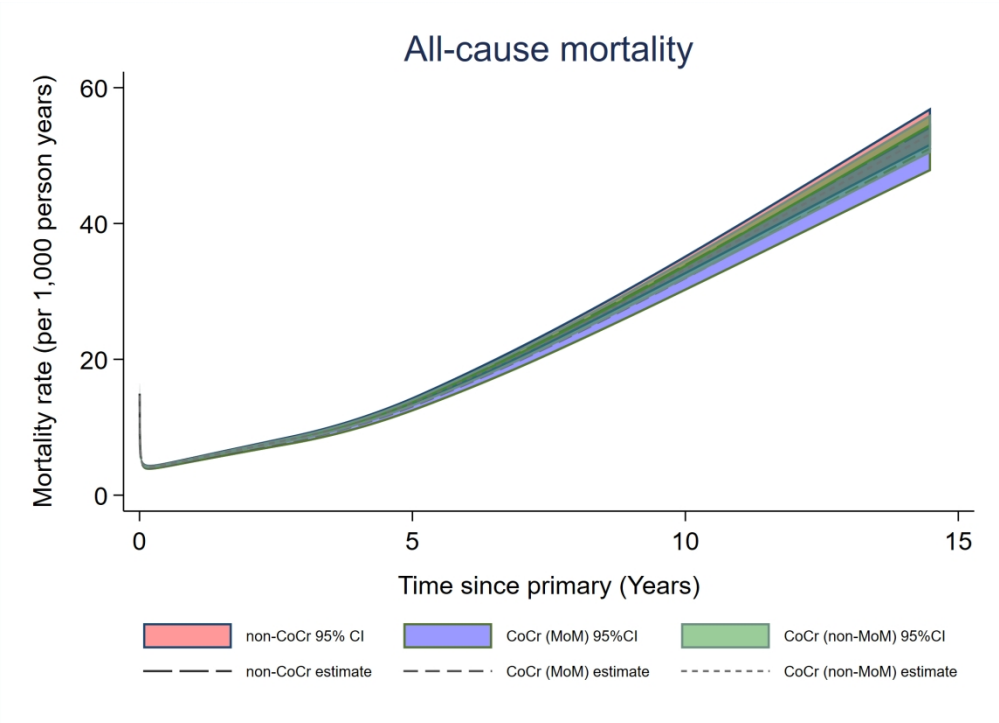


Fig 6: Estimated adjusted baseline mortality rates by cobalt-chrome exposure status, with the cobalt-chrome group subdivided into those with and those without a metal-on-metal bearing

186x135mm (300 x 300 DPI)