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Toxicity after Metal-on-metal Hip Replacement

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A Centre for Research Excellence funded by the Australian Government National Health and Medical Research Council

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Toxicity after Metal-on-metal Hip Replacement

- Metal-on-metal (MOM) prostheses are associated with increased risk of revision compared to hip prostheses with bearings of other material
  - Articular Surface Replacement (ASR) was recalled from the Australian market in December 2009 after the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) documented a comparatively high risk of revision.
  - In December 2010 a worldwide recall was issued

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What's the problem?

- Wear debris from hip prostheses with metal-on-metal (MOM) bearings may have adverse local and systemic health effects
- MOM wear debris consists of metallic particles produced by mechanical wear and metal corrosion
- The metallic particles may cause local adverse effects and dissolve to metal ions
- Increased blood levels of metal ions (especially cobalt) may have systemic adverse effects

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Effects of metal toxicity

- Local:
  - Peri-prosthetic tissue inflammation causing loosening, bone loss and tissue damage, pseudotumor, metalosis, aseptic lymphocytic vasculitis-associated lesion (ALVAL), pain, dislocation, nerve palsy, adverse reaction to metal debris (ARMD)
- Systemic:
  - Cardiomyopathy, neuropathies (auditory, visual impairment, polyneuropathy), depression, cognitive impairment, thyroid dysfunction (hypothyroidism), skin rash, renal function impairment, infections
- Cobalt and chromium are possibly mutagenic and carcinogenic

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The Quebec Beer Drinkers Epidemic

- Unusual type of cardiomyopathy, characterized by pericardial effusion, elevated hemoglobin concentrations, and congestive heart failure in Quebec City between 1965 and 1966
- This epidemic was directly related the consumption of a popular beer containing cobalt sulfate.
  - The epidemic appeared 1 month after cobalt sulfate was added to the specific brewery, and no further cases were seen a month after this specific chemical was no longer used in making this beer.

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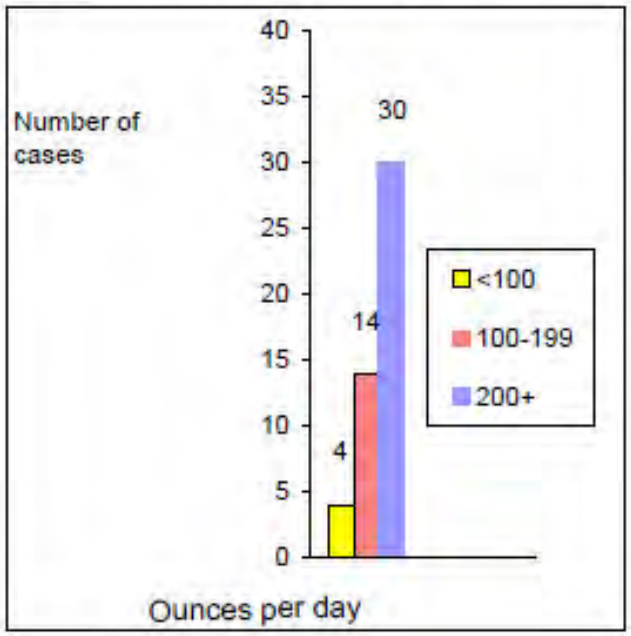
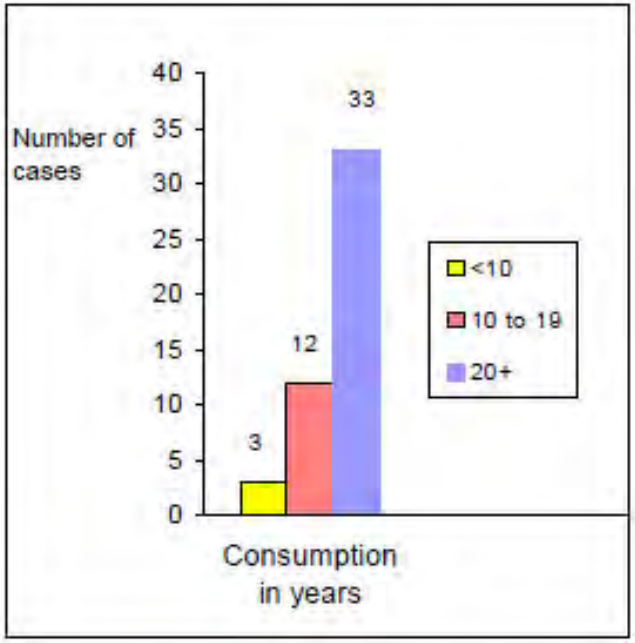
The Quebec Beer Drinkers Epidemic

- Incidence of cardiomyopathy related to consumption and duration (dose-response)

Figures 8 and 9: Distribution of Cases According to Daily Quantity of Beer Consumed and Duration of Consumption





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Evidence from the AOA NJRR

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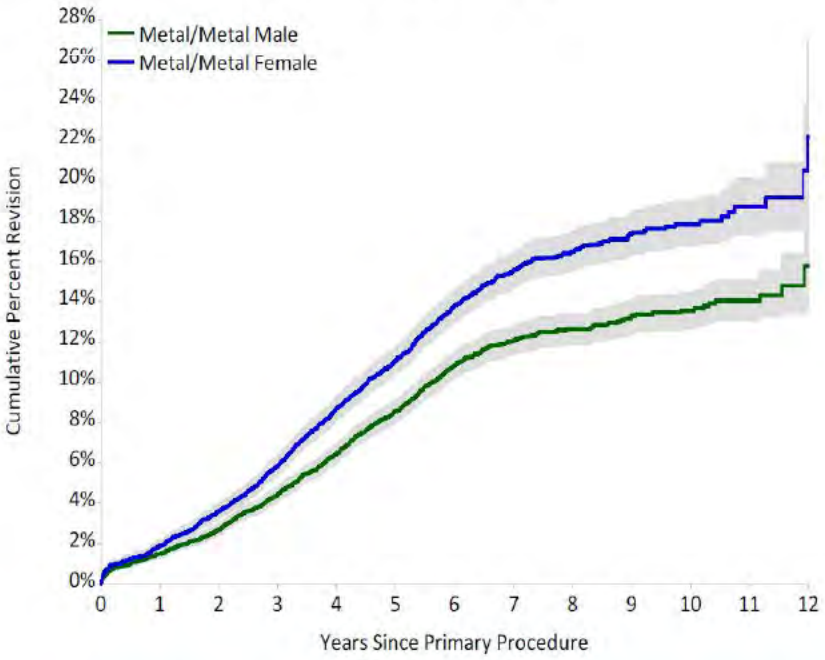
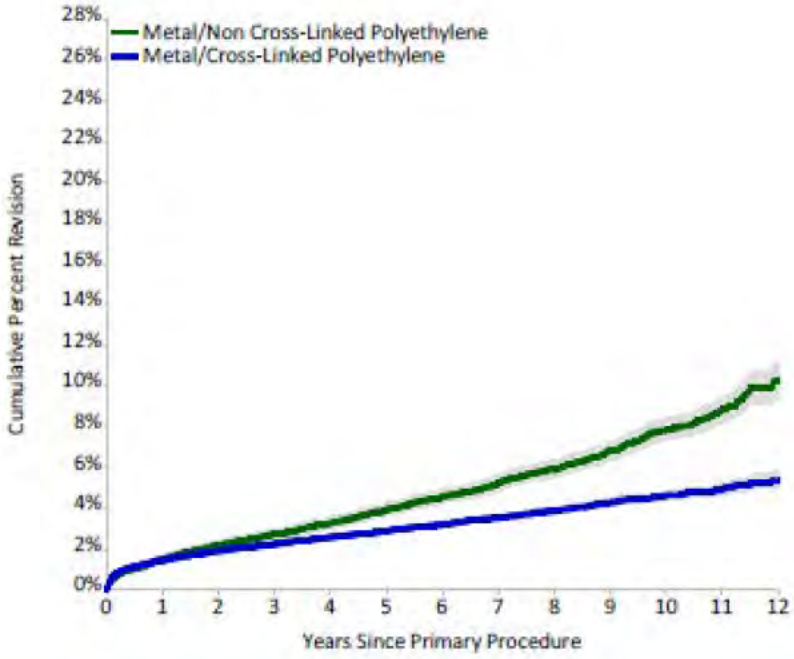
AOA NJRR 2013: Revision Rates

Figure MM5: Cumulative Percent Revision of Metal/Metal Primary Total Conventional Hip Replacement by Gender (Primary Diagnosis OA)





Metal-on-Metal

Metal-on-Poly

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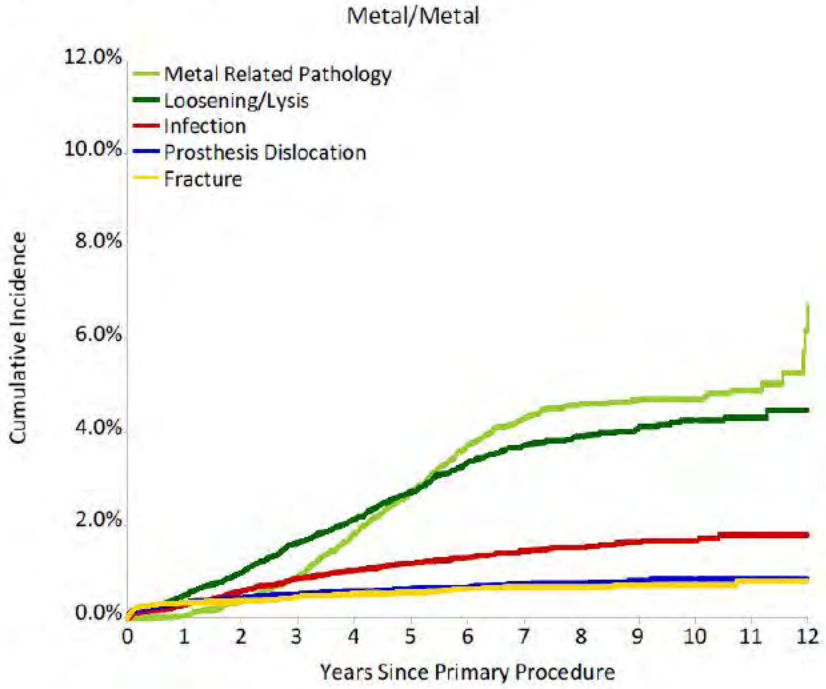
AOA NJRR 2013: Reason for Revision

Figure MM1: Cumulative Incidence Revision Diagnosis of Metal/Metal Primary Total Conventional Hip Replacement (Primary Diagnosis OA)



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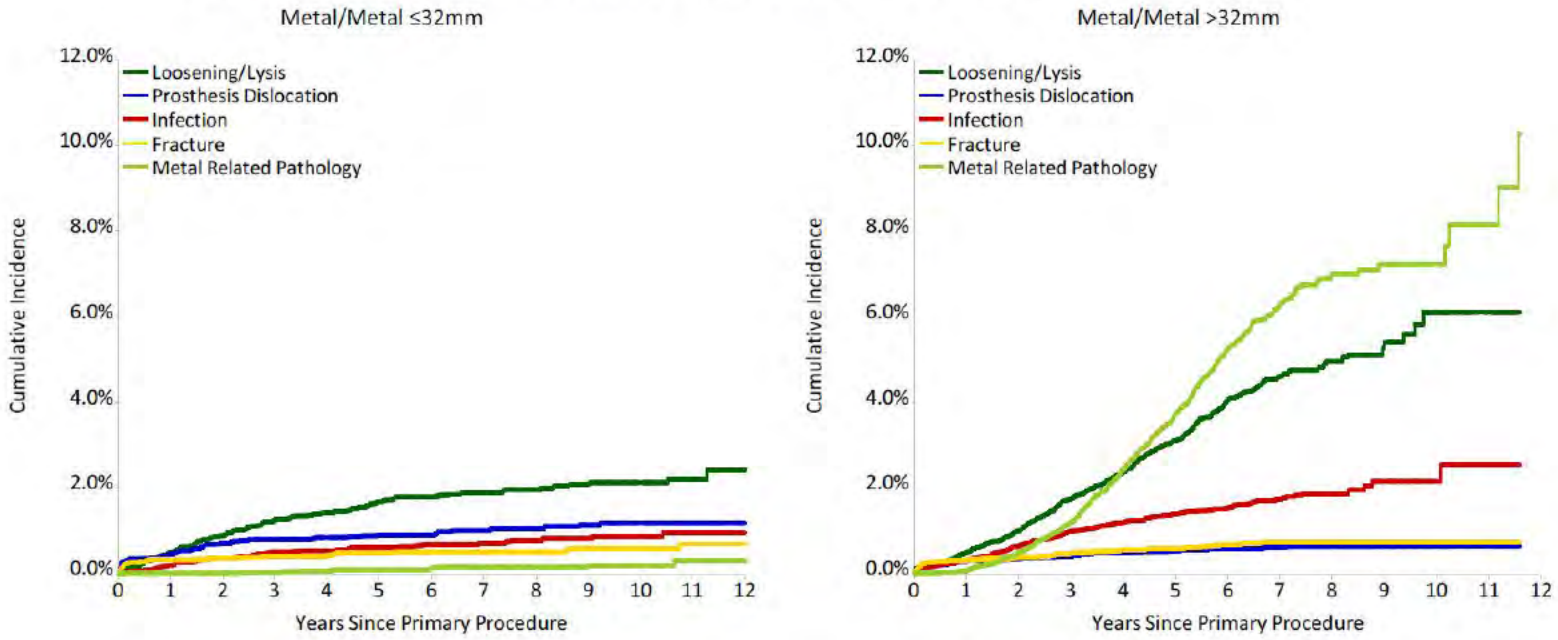
AOA NJRR 2013: Reason for Revision by headsize

Figure MM8: Revision Diagnosis Cumulative Incidence of Metal/Metal and Metal/Polyethylene Primary Total Conventional Hip Replacement by Head Size (Primary Diagnosis OA)



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Aim

- This study seeks to determine if there is an association between MOM prostheses and adverse *systemic* effects

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Data Source

- Department of Veterans' Affairs Health Claims Database
  - Treatment population of 233,800 veterans; median age is 82 years, with 5 co-morbidities
  - Prescription records
  - Medicare and allied health records (GP visits, radiology, pathology etc)
  - Hospital records (public and private)
    - Devices listed and the benefits payable for them on Part A of the Prostheses List maintained by Prostheses List Advisory Committee (PLAC)

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Prostheses List

- 10,000 products
  - cardiac pacemakers and defibrillators, cardiac stents, hip and knee replacements and intraocular lenses, as well as human tissues such as human heart valves, corneas, bones (part and whole) and muscle tissue.
  - The List does not include external legs, external breast prostheses, wigs and other such devices, only surgically implanted prostheses

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Product Category	Product Group
11 - Hip	11.01.01 - Cemented
11 - Hip	11.01.02 - Cemented, Long Lengths (≥200mm)
11 - Hip	11.01.03 - Uncemented
11 - Hip	11.01.04 - Uncemented, HA Coated
11 - Hip	11.01.05 - Uncemented, Long Lengths (≥200mm)
11 - Hip	11.01.06 - Uncemented, Long Lengths, HA Coated (≤200mm)
11 - Hip	11.01.07 - Uncemented, Modular
11 - Hip	11.01.08 - Uncemented, Modular, HA Coated
11 - Hip	11.01.09 - Uncemented, Modular, Long Lengths (Stem ≥200mm; Body ≥75mm; Cone ≥70mm; Spacer/Sleeve ≥50mm)
11 - Hip	11.01.10 - Uncemented, Modular, HA Coated, Long Lengths (Stem ≥200mm; Body ≥75mm; Cone ≥70mm; Spacer/Sleeve ≥50mm)
11 - Hip	11.01.11 - Calcar Replacement
11 - Hip	11.01.13 - Monoblock Hemis
11 - Hip	11.01.14 - Femoral Neck
11 - Hip	11.02.01 - Conventional Femoral Heads, ≤32mm
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11 - Hip	11.02.03 - Metal on Metal Heads
11 - Hip	11.02.04 - Resurfacing, Cemented
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11 - Hip	11.02.06 - Bipolar/Multipolar
11 - Hip	11.03.01 - Cups, Cemented
11 - Hip	11.03.02 - Shells, Uncemented
11 - Hip	11.03.03 - Shells, Uncemented, HA
11 - Hip	11.03.04 - Insert/Liner
11 - Hip	11.03.05 - Bonded Shell/Liner

MEDICINE & DEVICE SURVEILLANCE
CRE

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11 - Hip	11.02.02 - Conventional Femoral Heads, >32mm	11.02.02.02 - Cobalt Chrome
11 - Hip	11.02.02 - Conventional Femoral Heads, >32mm	11.02.02.03 - Alumina
11 - Hip	11.02.02 - Conventional Femoral Heads, >32mm	11.02.02.05 - Ceramic Mix
11 - Hip	11.02.02 - Conventional Femoral Heads, >32mm	11.02.02.06 - Ceramicised Metal

Product Sub-Group	Billing Code	Sponsor	Product Name	Size
11.02.02.02 - Cobalt Chrome	AX099	Austofix	F2 Large Femoral Head	Diameter 36mm, -4, 0, +4, +8
11.02.02.02 - Cobalt Chrome	AX103	Austofix	U2 Femoral Head	Size 42 - 56mm
11.02.02.02 - Cobalt Chrome	BI875	Biomet Australia Pty Ltd	Endo II Head	41 mm through 61mm
11.02.02.02 - Cobalt Chrome	BI877	Biomet Australia Pty Ltd	Freedom 36 mm Modular Head	36mm, -6mm to +9mm
11.02.02.02 - Cobalt Chrome	BI974	Biomet Australia Pty Ltd	Modular Head Implants	36mm diameter , - 6 to + 12mm neck, collared, no collar
11.02.02.02 - Cobalt Chrome	CR084	Corin Australia Pty Ltd	Unipolar Modular Head, CoCr	38 - 60mm, short, standard and long necks
11.02.02.02 - Cobalt Chrome	DD038	DJO Australasia Pty Ltd	R120 Metal Femoral Head	36mm
11.02.02.02 - Cobalt Chrome	DD049	DJO Australasia Pty Ltd	Foundation Unipolar System - CoCr Unipolar Femoral Heads	40mm to 64mm in 2mm increments
11.02.02.02 - Cobalt Chrome	DY026	Johnson & Johnson Medical Pty Ltd	Elite Unipolar Femoral Head	42 - 60 mm
11.02.02.02 - Cobalt Chrome	DY402	Johnson & Johnson Medical Pty Ltd	Cathcart Unipolar Head	41 to 60mm
11.02.02.02 - Cobalt Chrome	EX003	Exactech Australia	L-Series Unipolar Head	unipolar head: 42mm, 43mm, 44mm, 45mm, 46mm, 47mm, 48mm,
11.02.02.02 - Cobalt Chrome	GM066	Global Manufacturing Technology Pty Ltd	BioBall Femoral Head	36mm to 58mm
11.02.02.02 - Cobalt Chrome	LC157	Lima Orthopaedics Australia Pty Ltd	Modular Head	36mm Diameter Small to XXXLarge
11.02.02.02 - Cobalt Chrome	MA542	Mathys Orthopaedics Pty Ltd	Mathys CoCr Femoral Head	36mm, S to XXL
11.02.02.02 - Cobalt Chrome	MU097	Medacta Australia Pty Ltd	Femoral Head	Ø 36mm & Ø 40mm: both of sizes S-M-L-XL-XXL
11.02.02.02 - Cobalt Chrome	SF025	Signature Orthopaedics	Unipolar Femoral head	40-62mm
11.02.02.02 - Cobalt Chrome	SF047	Signature Orthopaedics	Signature Delta Femoral Head >=36mm	Offsets S, M, L & XL
11.02.02.02 - Cobalt Chrome	SK405	Stryker Australia Pty Ltd	LFIT Femoral Heads	36mm-72mm
11.02.02.02 - Cobalt Chrome	SN308	Smith & Nephew Surgical Pty Ltd	Unipolar Head	12/14 42 - 61mm
11.02.02.02 - Cobalt Chrome	SN809	Smith & Nephew Surgical Pty Ltd	Femoral head	>32mm
11.02.02.02 - Cobalt Chrome	ST570	Stryker Australia Pty Ltd	UNITRAX	38-64mm OD 2mm increments
11.02.02.02 - Cobalt Chrome	TO155	Tornier Pty Ltd	Tornier CoCr Femoral Head – Femoral Head >32mm	Dia 36mm, Short, Medium, Long and Extra-Long Necks
11.02.02.02 - Cobalt Chrome	WR129	Wright Medical Australia	Gladiator Bipolar Hip System Bipolar CoCR Head	36mm Short Medium Long
11.02.02.02 - Cobalt Chrome	WR265	Wright Medical Australia	Transcen/Lineagte Articulation System	28mm- 36mm, 4 lengths
11.02.02.02 - Cobalt Chrome	ZI054	Zimmer Pty Ltd	Femoral Head	38 - 63mm
11.02.02.02 - Cobalt Chrome	ZI347	Zimmer Pty Ltd	Femoral Head	42 to 60
11.02.02.02 - Cobalt Chrome	ZI359	Zimmer Pty Ltd	Large Zimmer Femoral Heads	34 - 38mm
11.02.02.02 - Cobalt Chrome	ZI500	Zimmer Pty Ltd	Femoral Head	36mm, 38mm

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Methods

- Retrospective cohort study using Private Hospital Admissions
  - Males only
  - No prior hospitalisation for heart failure
- Primary Total Hip Replacement
  - Metal-on-Poly (MOP)
  - ASR XL
- Outcome
  - Hospitalisation for heart failure
- Statistical Analysis
  - Cox proportional hazards model (reference MOP)

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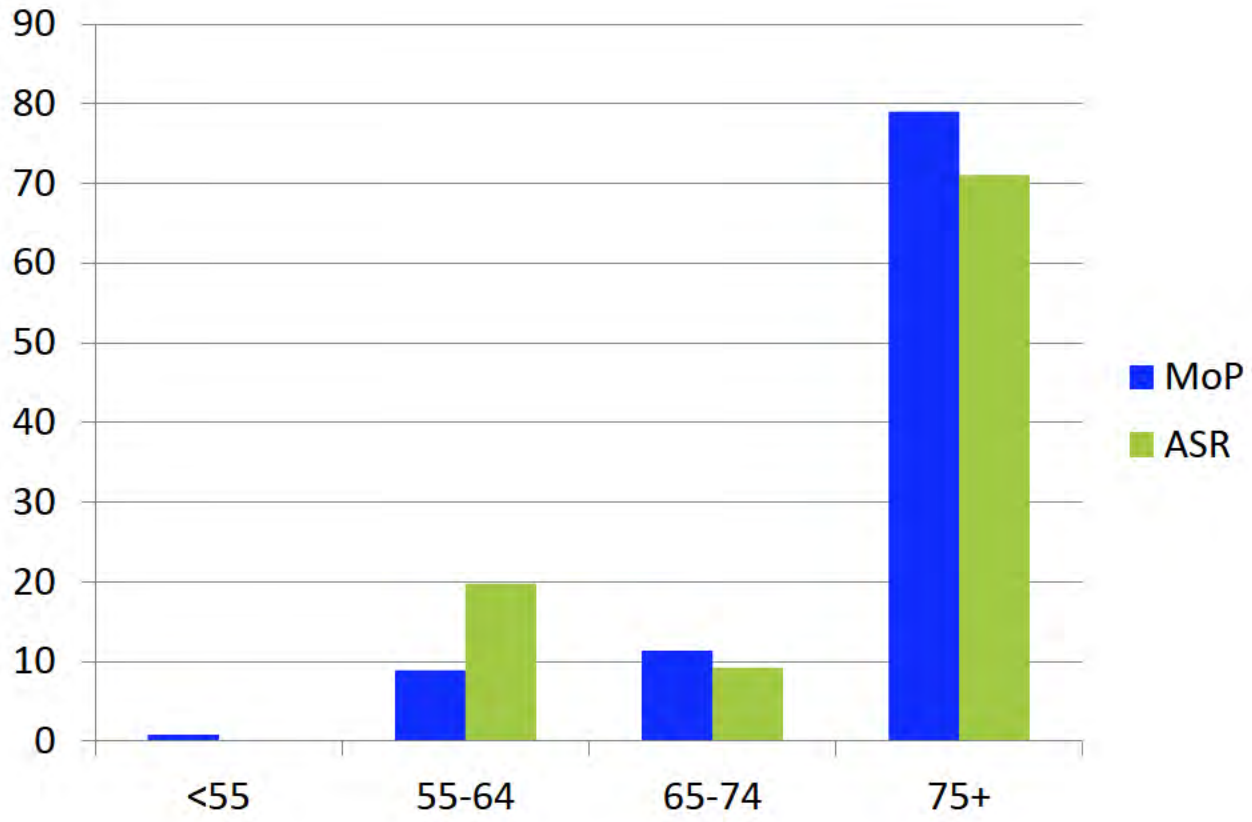
Total Hip Replacement – Bearing Surface



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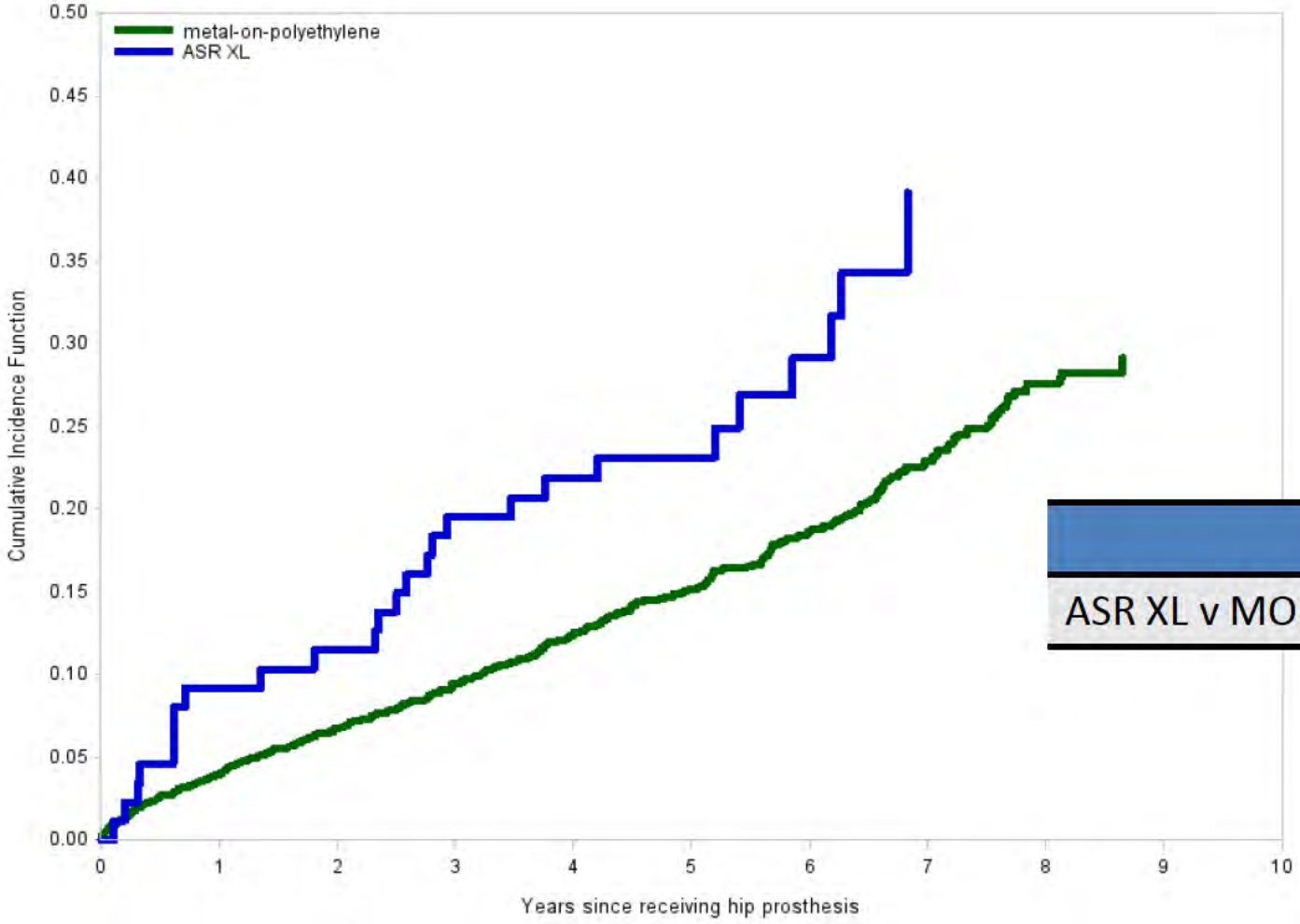
Time to hospitalisation for Heart failure



	HR (95% CI)
ASR XL v MOP	1.9 (1.3 – 2.8)

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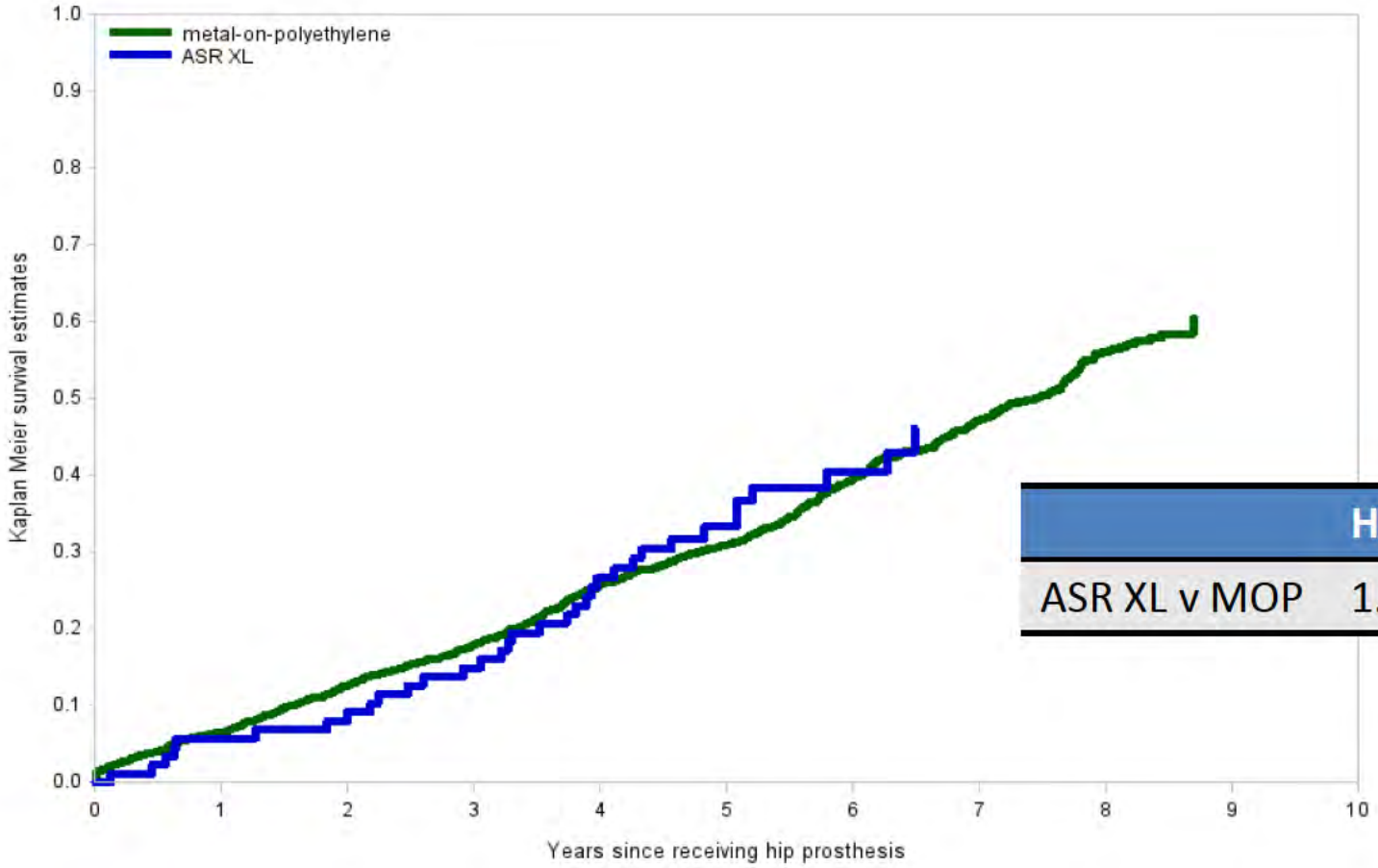
No Difference in time-to-death



	HR (95% CI)
ASR XL v MOP	1.1 (0.8 – 1.6)

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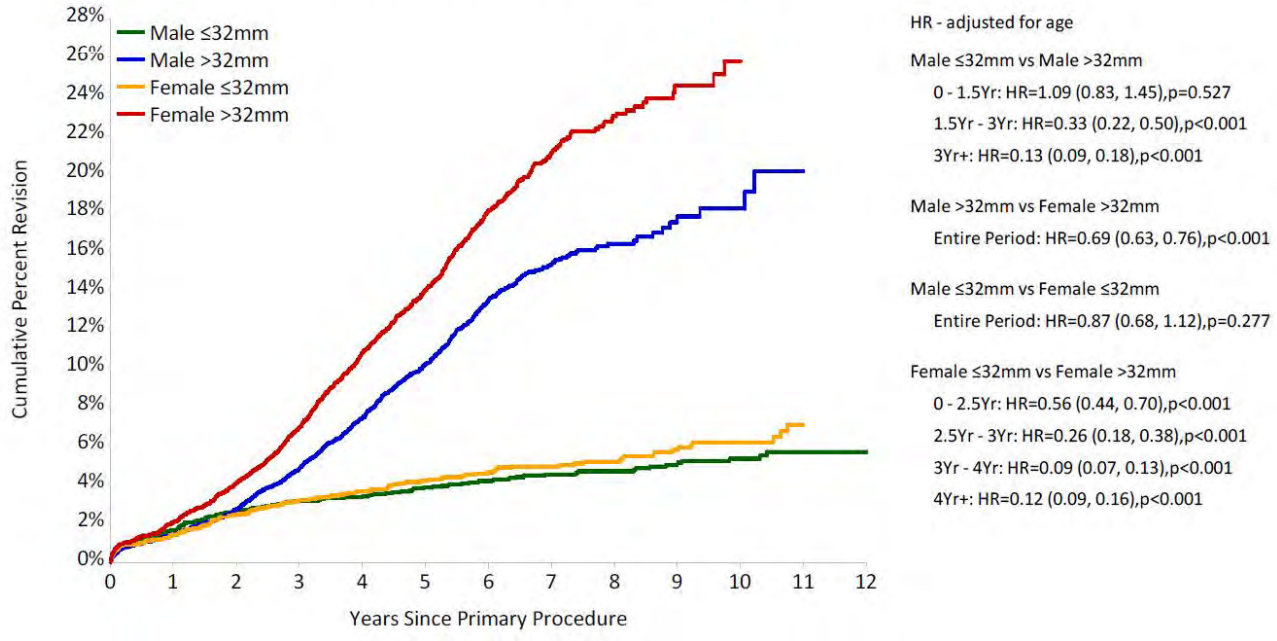
Limitations

- Generalisability of results
  - Can only look at males (too few females)

Figure MM6: Cumulative Percent Revision of Metal/Metal Primary Total Conventional Hip Replacement by Gender and Head Size (Primary Diagnosis OA)



HR - adjusted for age

Male ≤32mm vs Male >32mm

0 - 1.5Yr: HR=1.09 (0.83, 1.45),p=0.527

1.5Yr - 3Yr: HR=0.33 (0.22, 0.50),p<0.001

3Yr+: HR=0.13 (0.09, 0.18),p<0.001

Male >32mm vs Female >32mm

Entire Period: HR=0.69 (0.63, 0.76),p<0.001

Male ≤32mm vs Female ≤32mm

Entire Period: HR=0.87 (0.68, 1.12),p=0.277

Female ≤32mm vs Female >32mm

0 - 2.5Yr: HR=0.56 (0.44, 0.70),p<0.001

2.5Yr - 3Yr: HR=0.26 (0.18, 0.38),p<0.001

3Yr - 4Yr: HR=0.09 (0.07, 0.13),p<0.001

4Yr+: HR=0.12 (0.09, 0.16),p<0.001

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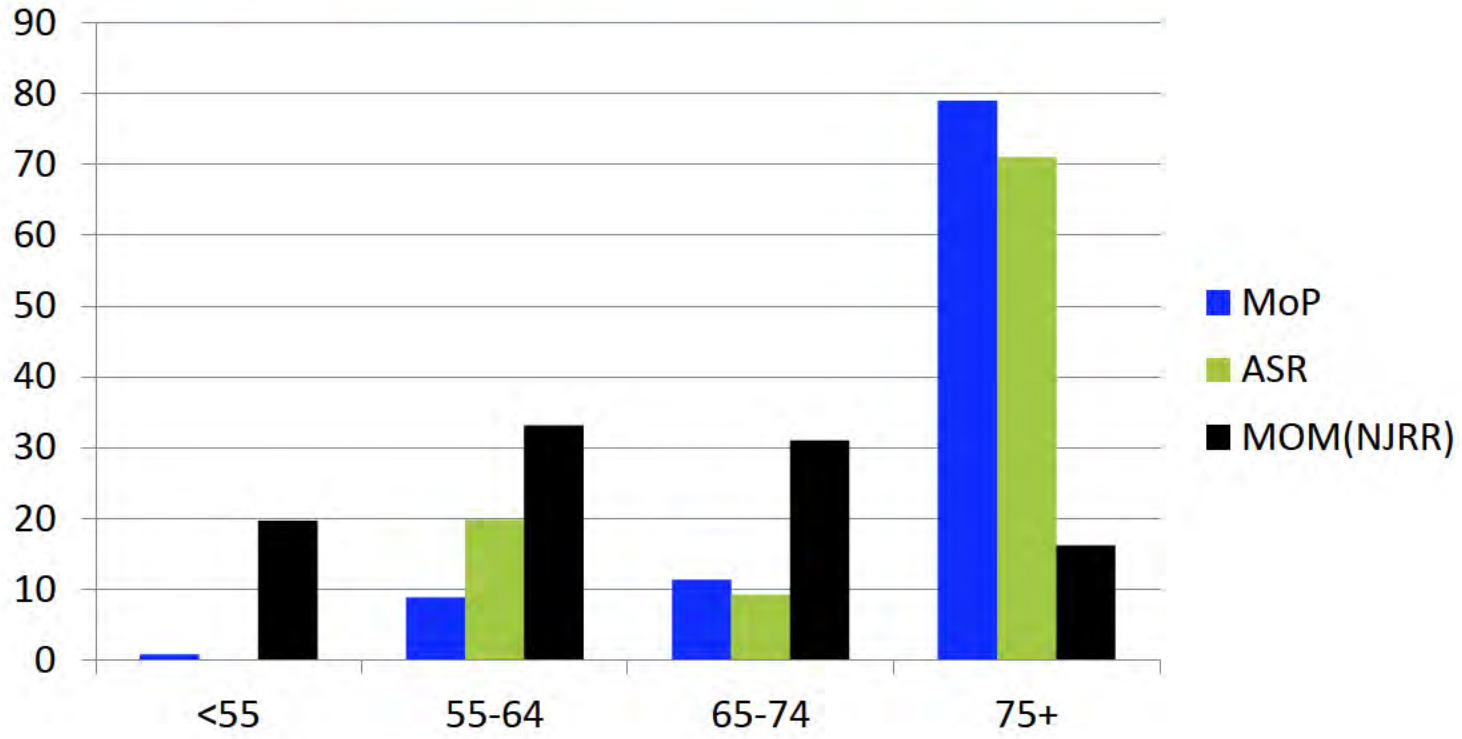
Limitations

- Generalisability of results
  - Older population than used in Australia



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Limitations

- Unable to determine actual size of the femoral head component used. PLAC lists head size range for the model only (<=32, >32)
  - all ASR head sizes > 32mm
- Unable to fully adjust for potential differences between MOM and MOP group
  - Similar rate of death between groups so MOM not ‘sicker’ than MOP
  - MOM group younger than MOP group so baseline risk of heart failure should be lower

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Conclusions

- Using a computerised claims database we were able to show that the risk of heart failure was significantly higher with the ASR procedure compared to patients with MOP procedures,
- There have been case reports of patients with ASR prostheses who have developed heart failure, but this is the first cohort study to indicate an association between the development of heart failure with the ASR prosthesis
- Our results are in line with the AOA NJRR which shows a rise in the rate of revisions due to metal related pathology after 2-3 years

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Toxicity after Metal-on-metal Hip Replacement

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Toxicity after Metal-on-metal Hip Replacement

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What's the problem?

- Wear debris from hip prostheses with metal-on-metal (MOM) bearings may have adverse local and systemic health effects
- MOM wear debris consists of metallic particles produced by mechanical wear and metal corrosion
- The metallic particles may cause local adverse effects and dissolve to metal ions
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Effects of metal toxicity

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- Systemic:
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- Cobalt and chromium are possibly mutagenic and carcinogenic

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The Quebec Beer Drinkers Epidemic

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- This epidemic was directly related the consumption of a popular beer containing cobalt sulfate.
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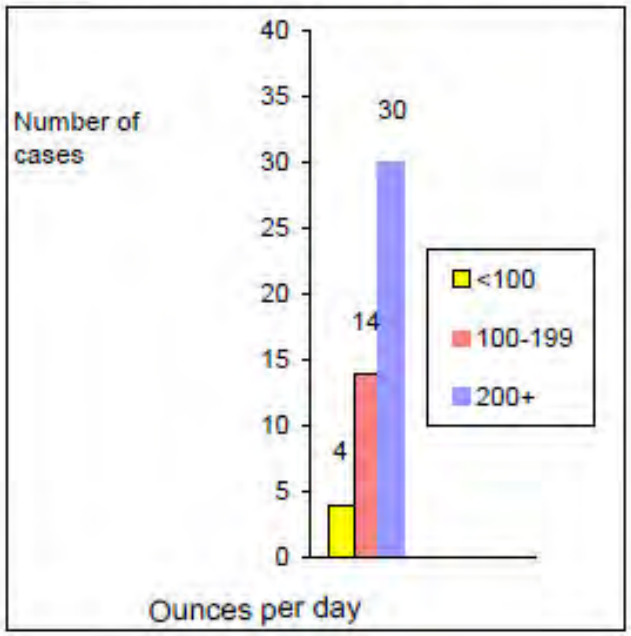
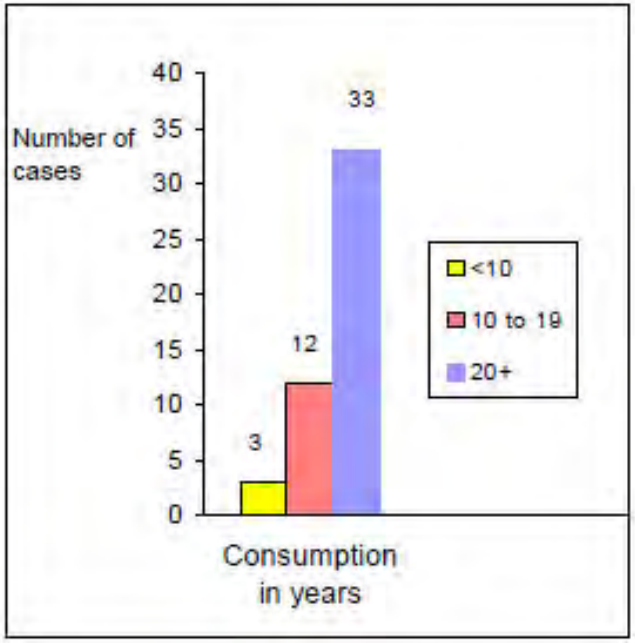
Figures 8 and 9: Distribution of Cases According to Daily Quantity of Beer Consumed and Duration of Consumption





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Evidence from the AOA NJRR

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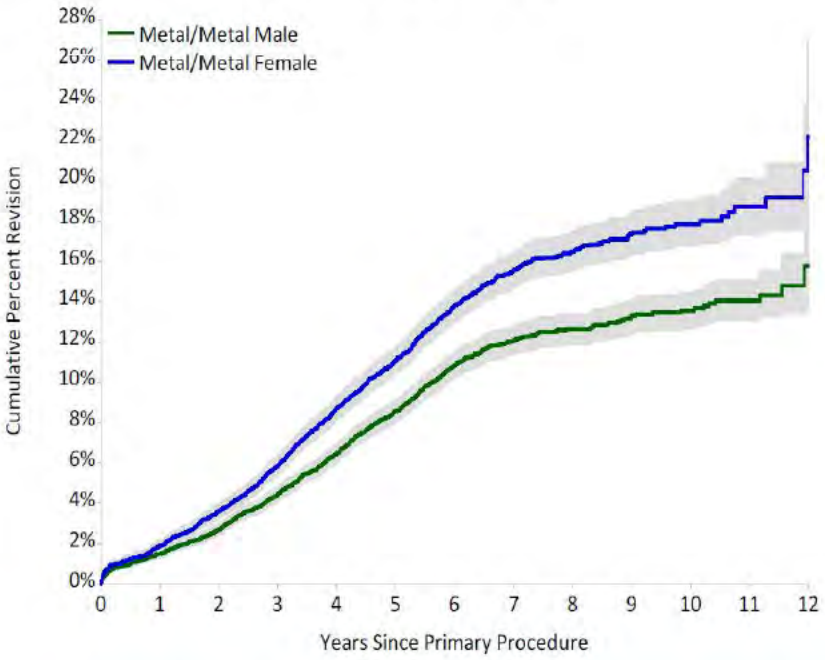
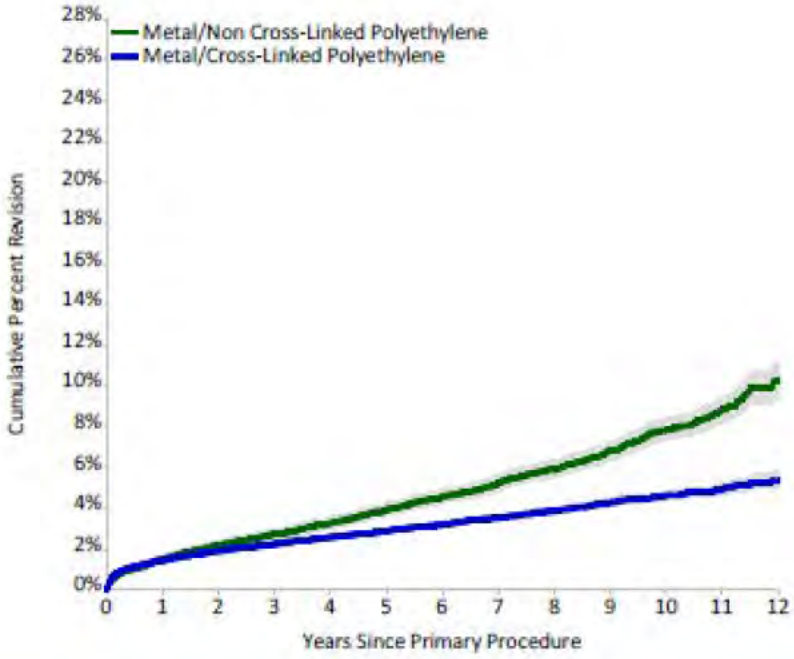
AOA NJRR 2013: Revision Rates

Figure MM5: Cumulative Percent Revision of Metal/Metal Primary Total Conventional Hip Replacement by Gender (Primary Diagnosis OA)





Metal-on-Metal

Metal-on-Poly

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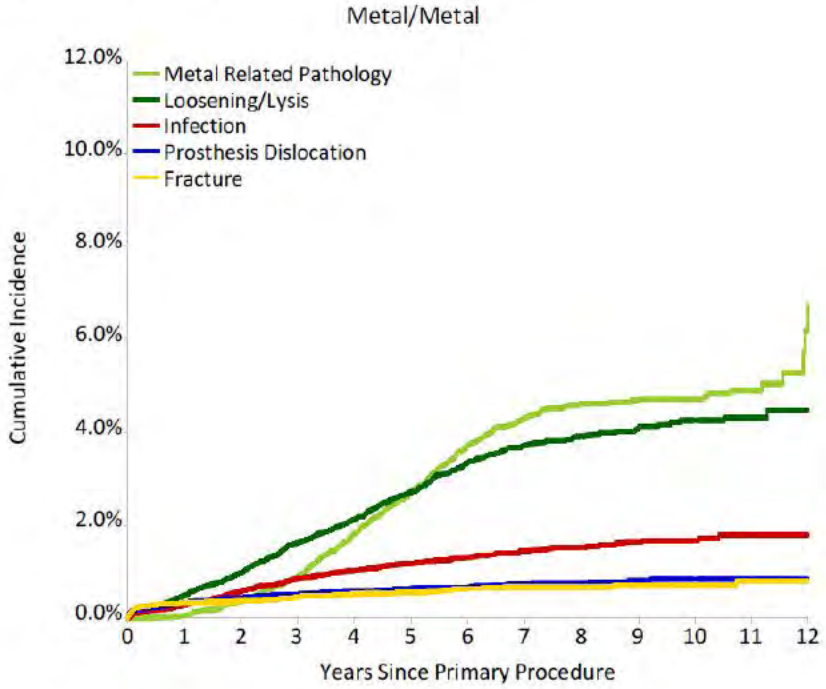
AOA NJRR 2013: Reason for Revision

Figure MM1: Cumulative Incidence Revision Diagnosis of Metal/Metal Primary Total Conventional Hip Replacement (Primary Diagnosis OA)



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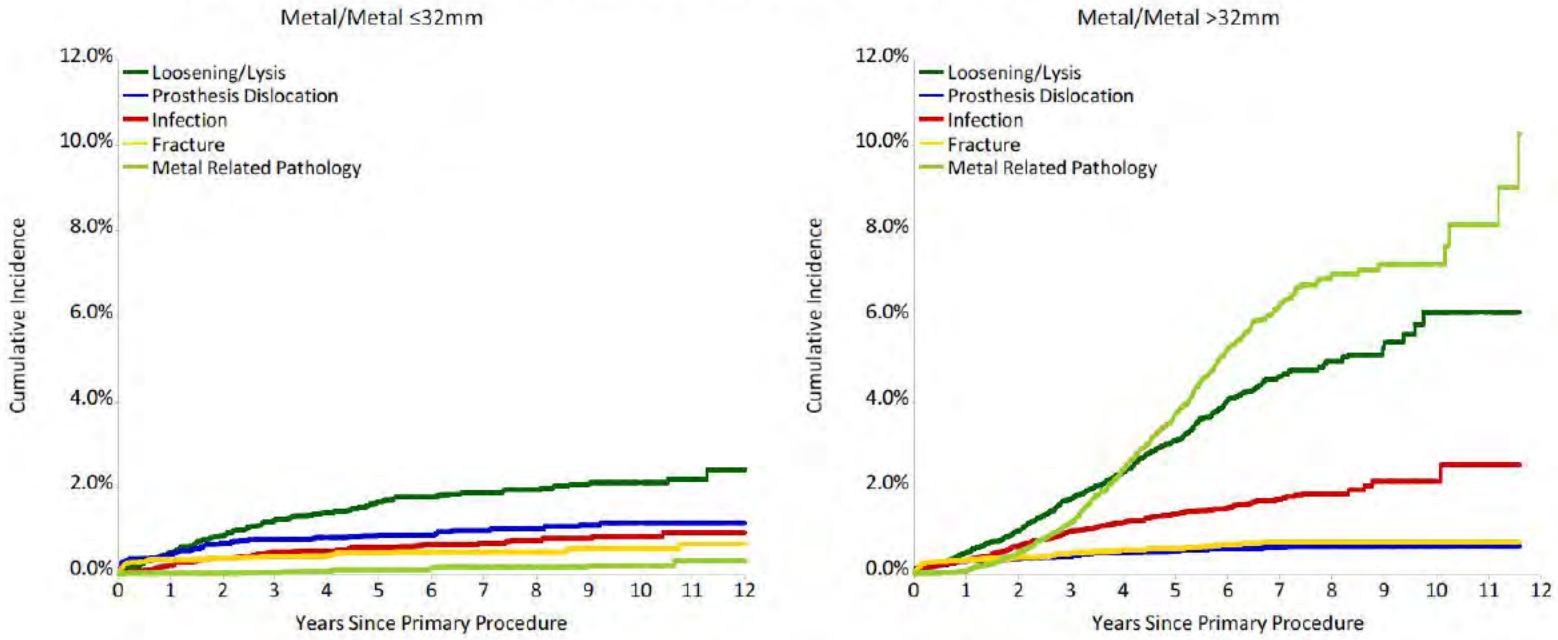
AOA NJRR 2013: Reason for Revision by headsize

Figure MM8: Revision Diagnosis Cumulative Incidence of Metal/Metal and Metal/Polyethylene Primary Total Conventional Hip Replacement by Head Size (Primary Diagnosis OA)



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11.02.02.02 - Cobalt Chrome	AX103	Austofix	U2 Femoral Head	Size 42 - 56mm
11.02.02.02 - Cobalt Chrome	BI875	Biomet Australia Pty Ltd	Endo II Head	41 mm through 61mm
11.02.02.02 - Cobalt Chrome	BI877	Biomet Australia Pty Ltd	Freedom 36 mm Modular Head	36mm, -6mm to +9mm
11.02.02.02 - Cobalt Chrome	BI974	Biomet Australia Pty Ltd	Modular Head Implants	36mm diameter , - 6 to + 12mm neck, collared, no collar
11.02.02.02 - Cobalt Chrome	CR084	Corin Australia Pty Ltd	Unipolar Modular Head, CoCr	38 - 60mm, short, standard and long necks
11.02.02.02 - Cobalt Chrome	DD038	DJO Australasia Pty Ltd	R120 Metal Femoral Head	36mm
11.02.02.02 - Cobalt Chrome	DD049	DJO Australasia Pty Ltd	Foundation Unipolar System - CoCr Unipolar Femoral Heads	40mm to 64mm in 2mm increments
11.02.02.02 - Cobalt Chrome	DY026	Johnson & Johnson Medical Pty Ltd	Elite Unipolar Femoral Head	42 - 60 mm
11.02.02.02 - Cobalt Chrome	DY402	Johnson & Johnson Medical Pty Ltd	Cathcart Unipolar Head	41 to 60mm
11.02.02.02 - Cobalt Chrome	EX003	Exactech Australia	L-Series Unipolar Head	unipolar head: 42mm, 43mm, 44mm, 45mm, 46mm, 47mm, 48mm,
11.02.02.02 - Cobalt Chrome	GM066	Global Manufacturing Technology Pty Ltd	BioBall Femoral Head	36mm to 58mm
11.02.02.02 - Cobalt Chrome	LC157	Lima Orthopaedics Australia Pty Ltd	Modular Head	36mm Diameter Small to XXXLarge
11.02.02.02 - Cobalt Chrome	MA542	Mathys Orthopaedics Pty Ltd	Mathys CoCr Femoral Head	36mm, S to XXL
11.02.02.02 - Cobalt Chrome	MU097	Medacta Australia Pty Ltd	Femoral Head	Ø 36mm & Ø 40mm: both of sizes S-M-L-XL-XXL
11.02.02.02 - Cobalt Chrome	SF025	Signature Orthopaedics	Unipolar Femoral head	40-62mm
11.02.02.02 - Cobalt Chrome	SF047	Signature Orthopaedics	Signature Delta Femoral Head >=36mm	Offsets S, M, L & XL
11.02.02.02 - Cobalt Chrome	SK405	Stryker Australia Pty Ltd	LFIT Femoral Heads	36mm-72mm
11.02.02.02 - Cobalt Chrome	SN308	Smith & Nephew Surgical Pty Ltd	Unipolar Head	12/14 42 - 61mm
11.02.02.02 - Cobalt Chrome	SN809	Smith & Nephew Surgical Pty Ltd	Femoral head	>32mm
11.02.02.02 - Cobalt Chrome	ST570	Stryker Australia Pty Ltd	UNITRAX	38-64mm OD 2mm increments
11.02.02.02 - Cobalt Chrome	TO155	Tornier Pty Ltd	Tornier CoCr Femoral Head – Femoral Head >32mm	Dia 36mm, Short, Medium, Long and Extra-Long Necks
11.02.02.02 - Cobalt Chrome	WR129	Wright Medical Australia	Gladiator Bipolar Hip System Bipolar CoCR Head	36mm Short Medium Long
11.02.02.02 - Cobalt Chrome	WR265	Wright Medical Australia	Transcen/Lineagte Articulation System	28mm- 36mm, 4 lengths
11.02.02.02 - Cobalt Chrome	ZI054	Zimmer Pty Ltd	Femoral Head	38 - 63mm
11.02.02.02 - Cobalt Chrome	ZI347	Zimmer Pty Ltd	Femoral Head	42 to 60
11.02.02.02 - Cobalt Chrome	ZI359	Zimmer Pty Ltd	Large Zimmer Femoral Heads	34 - 38mm
11.02.02.02 - Cobalt Chrome	ZI500	Zimmer Pty Ltd	Femoral Head	36mm, 38mm

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Methods

- Retrospective cohort study using Private Hospital Admissions
  - Males only
  - No prior hospitalisation for heart failure
- Primary Total Hip Replacement
  - Metal-on-Poly (MOP)
  - ASR XL
- Outcome
  - Hospitalisation for heart failure
- Statistical Analysis
  - Cox proportional hazards model (reference MOP)

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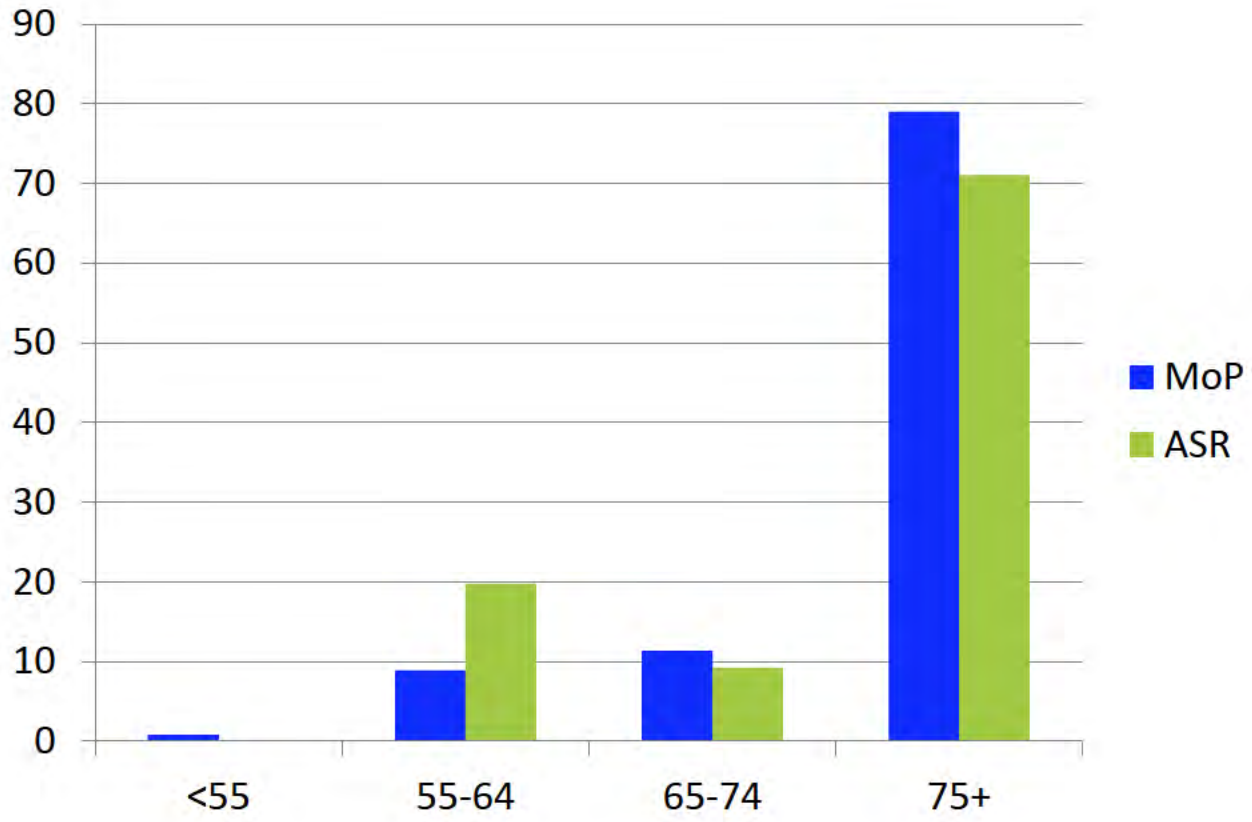
Total Hip Replacement – Bearing Surface



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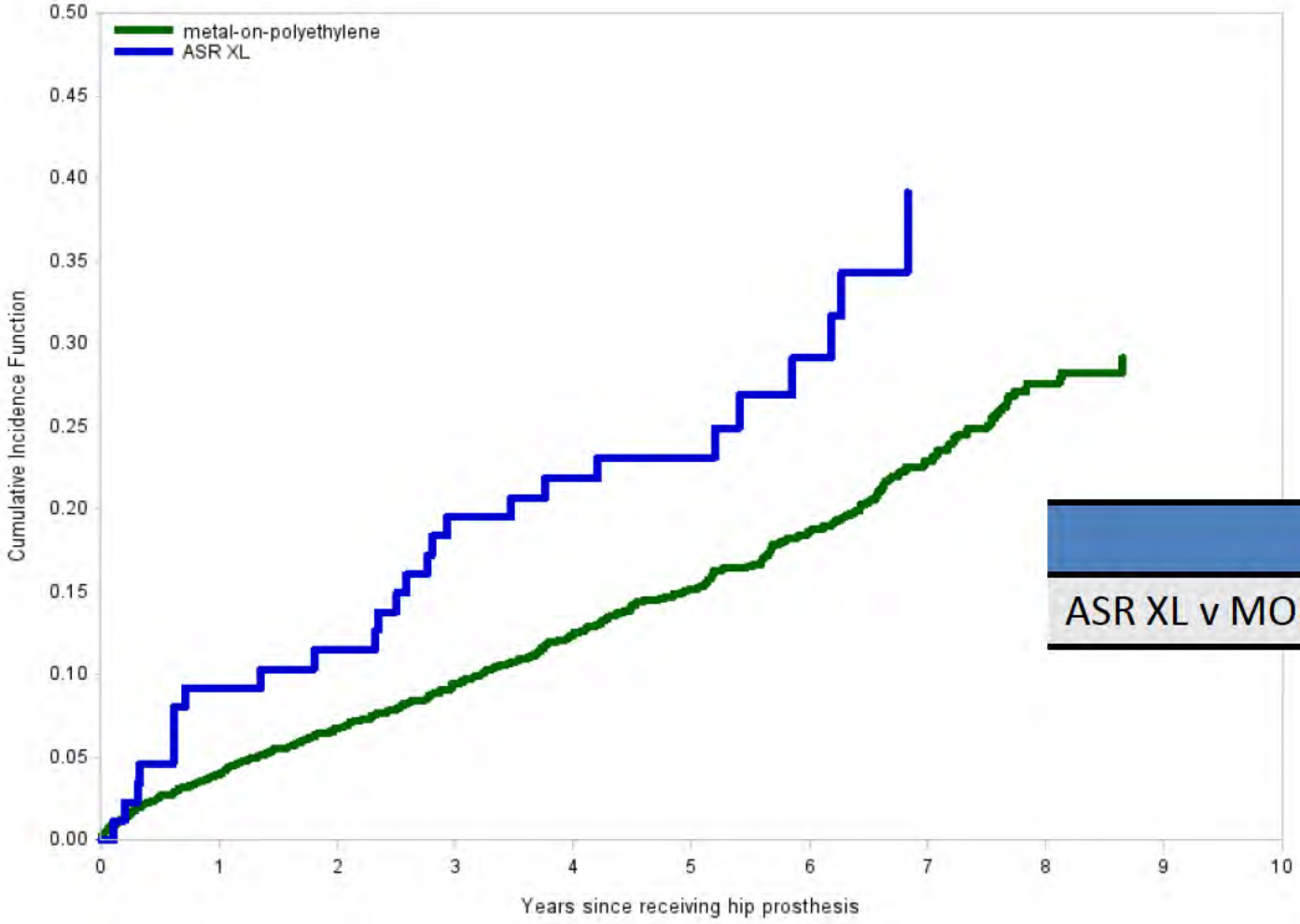
Time to hospitalisation for Heart failure



	HR (95% CI)
ASR XL v MOP	1.9 (1.3 – 2.8)

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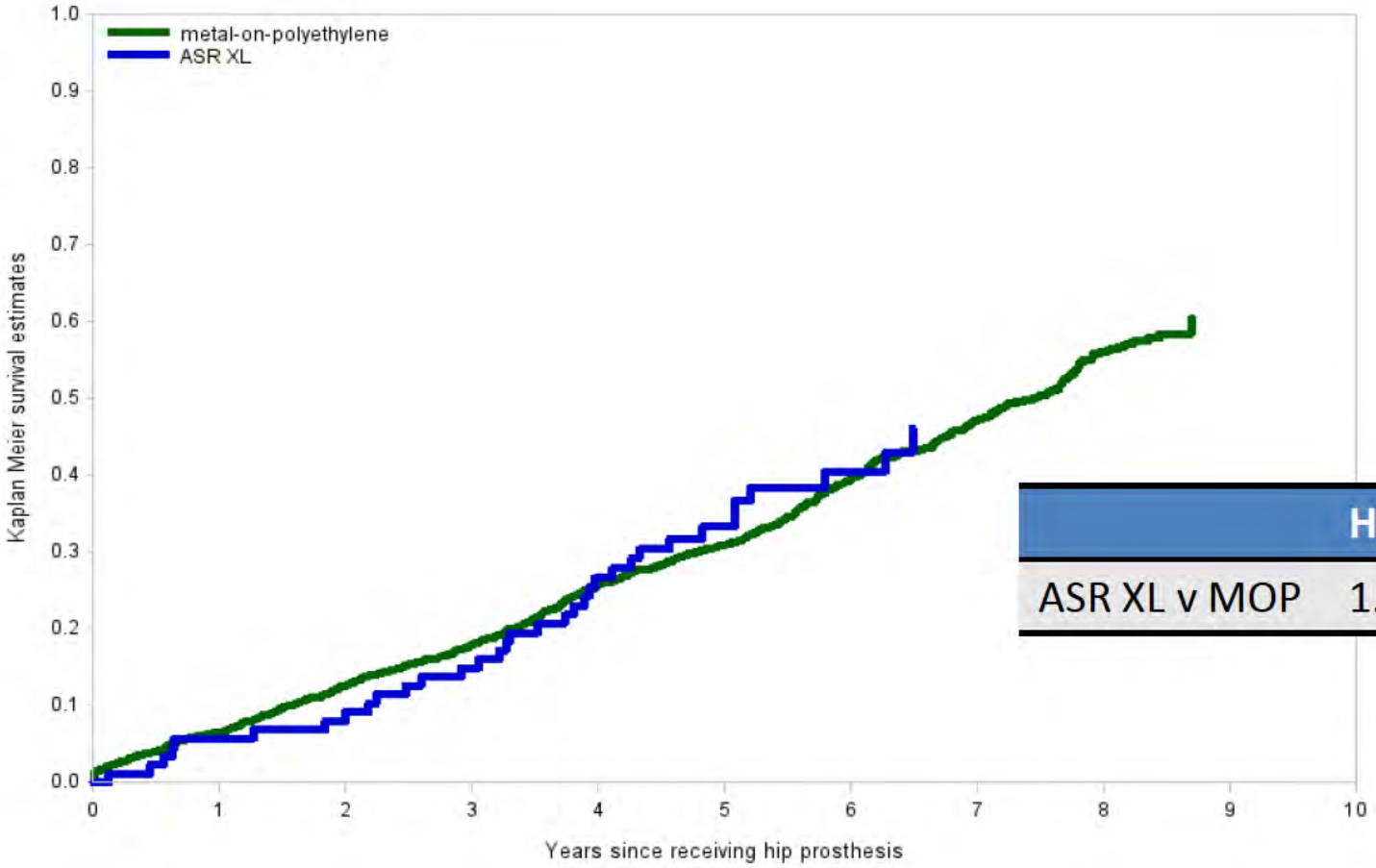
No Difference in time-to-death



	HR (95% CI)
ASR XL v MOP	1.1 (0.8 – 1.6)

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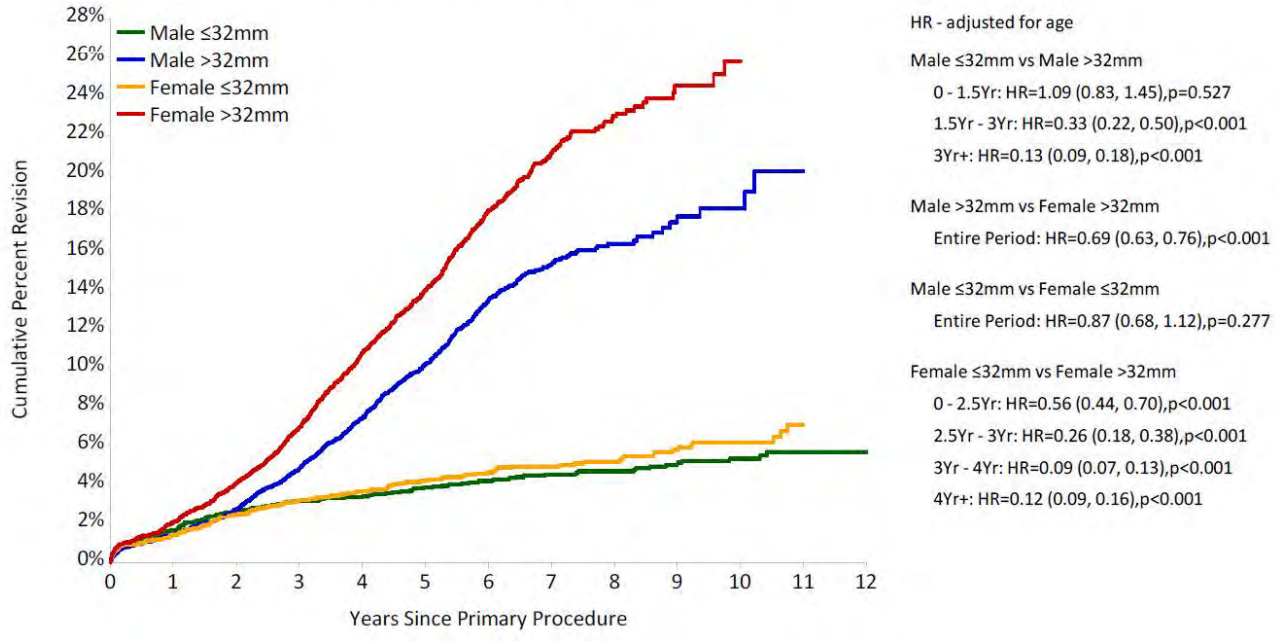
Limitations

- Generalisability of results
  - Can only look at males (too few females)

Figure MM6: Cumulative Percent Revision of Metal/Metal Primary Total Conventional Hip Replacement by Gender and Head Size (Primary Diagnosis OA)



HR - adjusted for age

Male ≤32mm vs Male >32mm

0 - 1.5Yr: HR=1.09 (0.83, 1.45),p=0.527

1.5Yr - 3Yr: HR=0.33 (0.22, 0.50),p<0.001

3Yr+: HR=0.13 (0.09, 0.18),p<0.001

Male >32mm vs Female >32mm

Entire Period: HR=0.69 (0.63, 0.76),p<0.001

Male ≤32mm vs Female ≤32mm

Entire Period: HR=0.87 (0.68, 1.12),p=0.277

Female ≤32mm vs Female >32mm

0 - 2.5Yr: HR=0.56 (0.44, 0.70),p<0.001

2.5Yr - 3Yr: HR=0.26 (0.18, 0.38),p<0.001

3Yr - 4Yr: HR=0.09 (0.07, 0.13),p<0.001

4Yr+: HR=0.12 (0.09, 0.16),p<0.001

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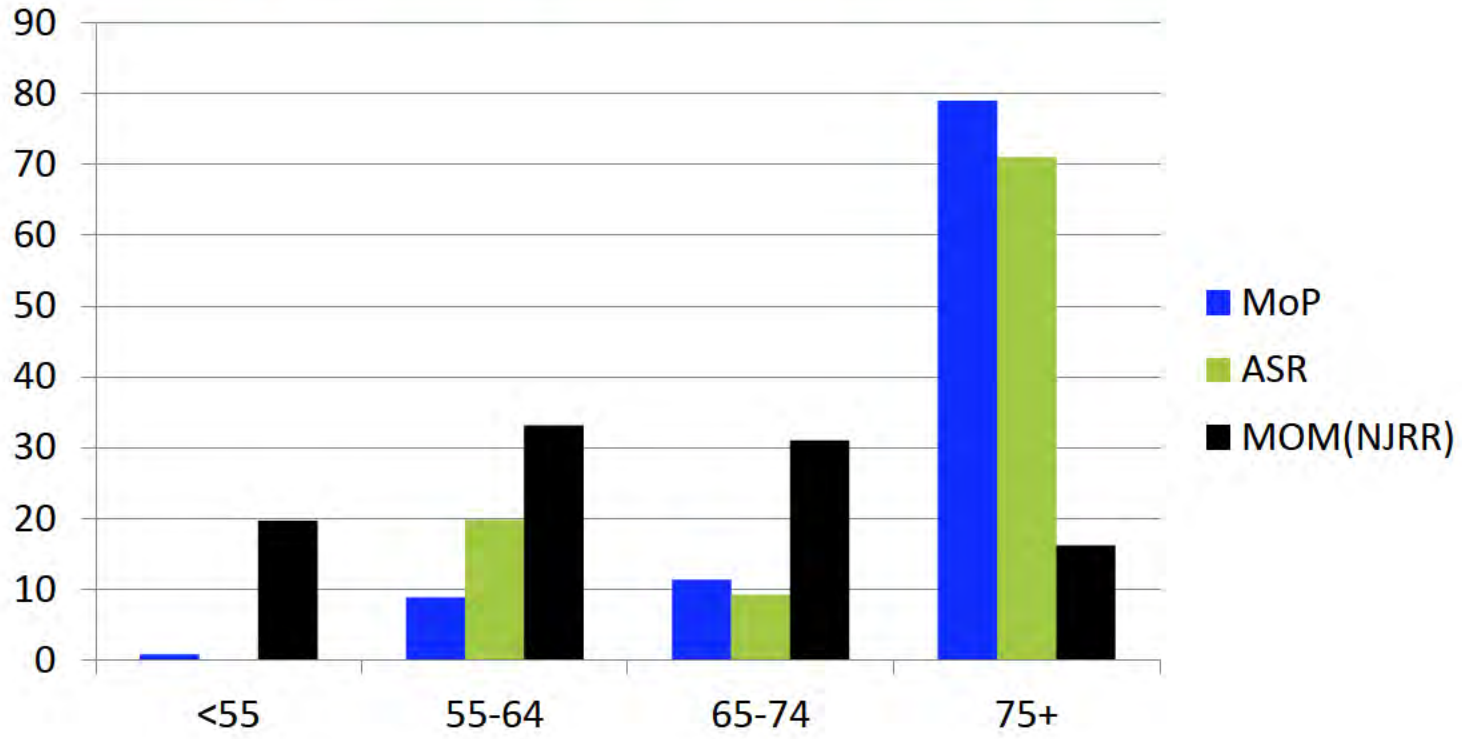
Limitations

- Generalisability of results
  - Older population than used in Australia



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Limitations

- Unable to determine actual size of the femoral head component used. PLAC lists head size range for the model only (<=32, >32)
  - all ASR head sizes > 32mm
- Unable to fully adjust for potential differences between MOM and MOP group
  - Similar rate of death between groups so MOM not ‘sicker’ than MOP
  - MOM group younger than MOP group so baseline risk of heart failure should be lower

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Conclusions

- Using a computerised claims database we were able to show that the risk of heart failure was significantly higher with the ASR procedure compared to patients with MOP procedures,
- There have been case reports of patients with ASR prostheses who have developed heart failure, but this is the first cohort study to indicate an association between the development of heart failure with the ASR prosthesis
- Our results are in line with the AOA NJRR which shows a rise in the rate of revisions due to metal related pathology after 2-3 years

Abstract:

HEART FAILURE AFTER CONVENTIONAL LARGE HEAD METAL-ON-METAL HIP REPLACEMENTS IN MEN

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Background: Metal particles and ions from wear and corrosion of hip prosthesis with metal-on-metal (MoM) articulations may cause systemic adverse effects [1]. Cobalt levels have been found to be high in patients with MoM total hip arthroplasties (THA) [2]. Historically increased levels of cobalt have been associated with heart failure [3].The aim of the study was to examine the association between conventional stemmed large head metal-on-metal (MoM) THA and heart failure.

Methods: Using the Australian Government Department of Veterans' Affairs health claims database, a retrospective cohort study was conducted on men who received conventional THA from 2003 to 2012. Men with a record of hospitalisation with heart failure or heart failure medication in the year prior to the hip replacement were excluded. The ASR XL Acetabular Hip System, a large head MoM prosthesis, which has one of the highest revision rates of MoM prostheses, was grouped separately. The cumulative incidence function was used to estimate risk of being hospitalised with heart failure and the Cox Proportional Hazards model was used to estimate hazard rate ratios (HR).

Results: A total of 825 men were included in the study; 671 received Metal-on-Polyethylene (MoP), 72 received ASR XL and 82 received other large head MoM prostheses. In men aged 75 years and over, 20.4% with ASR XL, 5.7% with other large head MoM prostheses and 6.4% with MoP prostheses had a hospitalisation for heart failure. The number needed to harm after three years for ASR XL compared to MoP was 7 (95% CI 4-44), indicating that there was one excess heart failure hospitalisation for every seven men treated with an ASR XL rather than with a MoP prosthesis. The age adjusted rate of hospitalisation for heart failure was almost three times higher for men with ASR XL compared to MoP prostheses (HR 2.85, 95% CI 1.39-5.83). No significant difference in risk of heart failure hospitalisation was found for other large head MoM compared to MoP prostheses.

Conclusion: Our results suggest that there is an association between ASR XL prostheses and risk of developing heart failure. Prior to this research there have been only case reports on people with MoM prostheses who have developed heart failure [4]. The results have implications for people who have received ASR XL prostheses and

potentially also other large head MoM prostheses. Close monitoring and measures to prevent serious complications should be a priority in this group of people.

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3. Morin, Y. and P. Daniel, *Quebec beer-drinkers' cardiomyopathy: etiological considerations.* Can Med Assoc J, 1967. **97**(15): p. 926-8.
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TITLE PAGE

Heart failure after conventional metal-on-metal hip replacements: a retrospective cohort study

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Abstract

Background and purpose: It is unclear if metal particles and ions produced by mechanical wear and corrosion of hip prostheses with metal-on-metal (MoM) bearings cause systemic adverse health effects. We examined the risk of heart failure in patients with conventional MoM total hip arthroplasty (THA) compared to those with metal-on-polyethylene (MoP) THA.

Patients and methods: We conducted a retrospective cohort study using data from the Australian Government Department of Veterans' Affairs health claims database on patients who received conventional THA for osteoarthritis between 2004 and 2012. The MoM THAs were classified into groups: Articular Surface Replacement (ASR) XL Acetabular System, other large head (LH) (>32mm) MoM and small head (SH) (≤ 32mm) MoM. Primary outcome was hospitalization for heart failure after THA.

Results: 4019 patients with no history of heart failure (56% women) were included. Men with an ASR XL THA had a higher rate of hospitalization for heart failure compared to men with MoP THA (hazard ratio: 3.2 95% CI: 1.6 - 6.5). No statistically significant difference in rate of heart failure was found with the other LH MoM or SH MoM compared to MoP in men. No statistically significant difference in heart failure rate between exposure groups was found in women.

Interpretation: An association between ASR XL and hospitalisation for heart failure was found in men. While causality between ASR XL and heart failure could not be established in this study, it highlights an urgent need for further studies to explore the potential for systemic effects associated with MoM THA.

Introduction

It has been reported that more than 1 million metal-on-metal (MoM) bearing total hip arthroplasties (THA) have been performed globally (Kwon et al. 2014). While MoM hips were generally recommended by companies for young and active patients, these devices became popular among orthopedic surgeons and were used in a wide range of patients. The advantage of the MoM hip design, which allowed for the use of a large femoral head, was a lower risk of dislocation and an improved range of movement compared to other bearings.

MoM hip prostheses with components made of cobalt-chromium alloys are known to produce high levels of metal particle and metal ions from wear and corrosion (Lavigne et al. 2011, Chang et al. 2013, Jantzen et al. 2013). Resultant damage to local soft tissues and periprosthetic bone with subsequent increased rates of revision surgery have been commonly reported (Pandit et al. 2008, Langton et al. 2010, Fary et al. 2011, Sampson and Hart 2012, Hug et al. 2013, Langton et al. 2013). The revision rates vary by class of MoM prostheses (Graves et al. 2011). For example, conventional stemmed large head (LH) MoM (>32mm diameter) prostheses have the highest rate of revision compared to both small head (SH) MoM (≤32mm diameter) and resurfacing hip replacement (AOANJRR 2015).

The risk of revision also varied within class. The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) reported that the cumulative percent revision at 7 years for the 13 most commonly used conventional LH MoM ranged from 4.3% to 36.7% (AOANJRR SR 2015). The highest of these was the Articular Surface Replacement (ASR) XL Acetabular System (DePuy). This device was withdrawn from the market in Australia in 2009 and was the subject of a worldwide recall in 2010. The high rate of revision for this

prosthesis is due mainly to metal ion related pathology and is almost certainly related to design and manufacturing differences compared to other LH MoM prostheses.

In addition to the reported local effects there has been increasing concern that the dissemination of wear particles and increased blood levels of metal ions, especially cobalt, may be associated with systemic adverse health effects (Campbell and Estey 2013). There is no doubt that high levels of serum cobalt are associated with systemic adverse effects. This was demonstrated by the 1960's heart failure epidemic among people who drank beer that contained cobalt added as a foam stabilizer (Morin and Daniel 1967).

To date there have been a number of case reports of suspected systemic adverse health effects following the use of MoM THA (Cheung et al. 2016, Zywiel et al. 2016). In a case study of a patient with bilateral ASR XL prostheses who developed heart failure in both native and transplanted heart, Allen et al. (2014) found signs of mitochondrial injury and elevated cobalt level in heart tissue, supporting the diagnosis of cobalt-induced cardiomyopathy. There have also been case reports of neuropathies (auditory, optic, polyneuropathy), depression, cognitive impairment, hypothyroidism and renal function impairment associated with MoM bearings (Tower 2010, Mao et al. 2011, Cohen 2012, Machado et al. 2012, Devlin et al. 2013, Gessner et al. 2015). Furthermore, a cross-sectional study of patients with resurfacing MoM hip arthroplasties identified reduced cardiac ejection fraction in asymptomatic patients who had cobalt levels above cobalt levels in patients in a matched reference group, but below what was previously thought to be the threshold concentration for prosthesis malfunction (Prentice et al. 2013).

Although current evidence suggests that MoM THA may be associated with detrimental systemic health effects, the incidence of this remains unknown. The aim of this study was to determine if conventional MoM THA is associated with a higher rate of developing heart failure compared to a reference cohort who received THA with the commonly used bearing of metal-on-polyethylene (MoP). An additional aim was to examine whether MoM THA was associated with higher mortality compared to the reference cohort.

Methods

Study Sample

A retrospective cohort study using data from the Australian Government Department of Veterans' Affairs (DVA) health claims database was conducted. The database contains comprehensive data on prescription medicines, hospital admissions in both public and private hospitals, procedures and medical devices for all Australian veterans and their spouses. The database has a current treatment population of 233,800 veterans with a median age of 82 years. Veterans, widowers/widows or dependents of veterans were included if they were full entitlement holders of all DVA services. The DVA provide funding for all treatment related to all medical conditions for these patients.

The study sample consisted of patients who underwent primary THA for treatment of osteoarthritis in private hospitals between 1 January 2004 and 31 December 2012. Primary THA procedures were identified using the Australian Classification of Health Interventions (ACHI/ICD-10-AM) procedure codes: 49318-00, 49319-00. For those patients who received more than 1 primary hip procedure during the study period, only the initial primary THA undertaken in the study period was used in the analysis.

Patients who had a record of hospitalization for heart failure (either primary or any secondary discharge diagnoses ICD-10-AM codes I50.0-I50.9) in the year prior to the THA were excluded (n=273). In addition, those who were dispensed heart failure medication in the year prior were also excluded (n=762)(see Table 1). Specification of heart failure medication was based on the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines for management of chronic heart failure (2011) and included angiotensin-converting-enzyme inhibitor plus a loop diuretic, heart specific beta blocker, spironolactone or loop diuretics plus an angiotensin II receptor blocker.

Exposure of interest

Exposure groups were created based on the THA bearing surface used in the primary procedure. Bearing surface was ascertained through matching product codes associated with the hip procedure with the Australian Government's Prosthesis List (2016), which contains a unique billing code for individual prostheses. As MoP bearing is the most common articulation in THA this was used as the comparator for MoM THAs. Based on the literature on varying performance and revision rates by MoM types (Graves et al. 2011), three groups of MoM THAs of interest were identified; ASR XL, which has the highest rate of revision of all large head (LH) MoM THA (AOANJRR SR 2015), other LH MoM THA and all small head (SH) MoM THA.

Outcome of interest

The main outcome of interest was first hospitalization for heart failure after the primary THA (ICD-10-AM codes I50.0-I50.9 as primary discharge diagnosis). A secondary outcome was all cause mortality. A sensitivity analysis was performed for the primary analysis in

which we identified heart failure events as hospitalizations with the specified discharge diagnosis codes as either a primary or a secondary diagnosis.

Effect Modifiers and Confounders

Patient age and sex are associated with development of heart failure. Therefore, age and sex were evaluated as confounders and as effect modifiers. Only sex was identified as an effect modifier for the primary outcome (hospitalization for heart failure as a primary diagnosis), hence all analyses were stratified by sex. Other covariates considered as possible confounders included type of fixation of the prosthesis (cementless/cement) and comorbidities at baseline identified by RxRisk-V(Sloan et al. 2003). RxRisk-V is a prescription based comorbidity measure with 45 disease categories, which has been validated as a measure of co-morbidity burden (Vitry et al. 2009) (Appendix 1, see supplementary data).

Statistics

Medians, interquartile ranges, frequencies and proportions were used to describe the study sample. Survival analyses were conducted for time to first heart failure hospitalization and for time to death after the primary THA. Patients were censored at time of death, revision of the hip prosthesis or admission to hospital for a second primary hip prosthesis. Cumulative incidence curves were used to describe the estimated cumulative probabilities of heart failure stratified by exposure groups and sex, accounting for informative censoring. Cox proportional hazards (PH) models were used to estimate the cause specific hazard ratio (HR) for hospitalization for heart failure by exposure group. Time at risk of hospitalization for heart failure was measured from day of discharge from the hospital after the THA operation until first hospital admission for heart failure or end of the study period (June 30th, 2014).

The Cox PH model was used to examine all-cause mortality by exposure group, stratified by sex and adjusted for age and comorbidities Confounders were included based on clinical knowledge and bias assessment using the method for directed acyclic graphs (DAG) outlined by Shrier and Platt (2008) and a DAG graphical tool (Textor et al. 2011) combined with a change in estimate approach. The assumption of proportional hazards for the Cox PH model was confirmed using interactions with time and covariates. SAS (version 9.4) was used for all analyses. A 2-tailed P value below 0.05 was considered to be statistically significant.

Results

4019 patients were included in the study; 3546 (88%) received MoP prostheses, 121 (3%) received ASR XL prostheses, 231 (6%) received other LH MoM and 121 (3%) received SH MoM prostheses. Baseline characteristics of the cohorts are presented in Table 1 and baseline RxRisk-V in Appendix 1, see supplementary data.

Crude incidences of the main and secondary outcomes are presented in Table 2. In men, the proportion who experienced a hospitalization with a primary diagnosis of heart failure was 10/63, 10/124, 4/75 and 114/1506in patients who had ASR XL prostheses, other LH MoM prostheses, SH MoM prostheses and MoP prostheses respectively. For women the proportion with heart failure was 2/58 with ASR XL, but otherwise the incidence of heart failure was similar to men (6/107 with LH MoM, 2/46 with SH MoM and 162/2044 with MoP).

The cumulative probability of hospitalization for heart failure after receiving a THA is provided in Figures 1 and 2. For men, there was a higher rate of hospitalization for heart failure with ASR XL compared to MoP (hazard ratio (HR) 3.2, 95% CI: 1.6 - 6.5) (Table 3). No

statistically significant difference in the rate of heart failure hospitalization for men receiving other LH MoM or SH MoM THA compared to MoP was observed. There was no significant difference in rates for heart failure for women with ASR XL compared to MoP (HR 0.5, 95% CI: 0.1 - 1.9) or for any other type of MoM THA (Table 3).

Results were similar to the main analysis in the sensitivity analysis, in which both primary and secondary diagnoses were used to identify heart failure hospitalizations (Appendix 2, see supplementary data).

Mortality was high for all bearing groups, and higher for men than for women (Table 2). No statistically significant difference in mortality was observed for any MoM bearing compared to MoP bearings (Table 3).

Discussion

To our knowledge this is the first observational cohort study to identify an association between an adverse systemic health effect, in this case hospital admission for heart failure, and the use of MoM THA. This effect was only observed in one type of prosthesis (i.e. ASR XL (DePuy)) and was only evident in men. Based on our results, we estimate that after 3 years 1 additional heart failure hospitalization would have occurred for every 11 (95%CI:6-109) men treated with an ASR XL rather than a MoP prosthesis.

The higher rate of hospitalization for heart failure with ASR XL only is consistent with previous research that demonstrates that the ASR XL has the highest rate of revision of any LH MoM prosthesis (AOANJRR SR 2015). The higher revision rate with the ASR XL has been attributed to higher occurrence of metal related pathology compared to similar prostheses (AOANJRR SR 2015). The identification of a higher rate of heart failure that is specific to this

high risk prosthesis and not to other MoM THA supports that the association between heart failure and the use of the ASR XL is real. An important potential implication of these findings is that it remains uncertain if other MoM prostheses will also be associated with increased risk of developing heart failure as time progresses.

There are a number of possible explanations as to why the higher heart failure rate was only observed in men. It is known that heart failure increases with age and that men have a higher incidence (Bui et al. 2011). It has been reported that among the DVA population, men experienced higher rates of hospitalization than women, consistent with that most women with full-entitlement benefits are likely to be war widows without service-related injuries and diseases (Lloyd and Anderson 2008). In our study cohort mortality for men was higher than for women in all exposure groups. Hence, the sex difference may reflect that the male cohort in this study are a more vulnerable group and as such are more susceptible to developing heart failure following exposure to MoM prostheses than women. This is consistent with our results where the hospitalization rate for heart failure was statistically significantly higher for men with MoM hips compared to women with MoM hips, whereas there was no significant sex difference in the rate of heart failure hospitalization for patients with MoP hips (data not shown). In the Quebec heart failure epidemic, the majority of heart failure reported following exposure to beer with added cobalt occurred in men (Morin et al. 1967, Kesteloot et al. 1968, Sullivan et al. 1969, Alexander 1972). Although it is possible that this is due to preferential exposure or other contributing factors such as poor nutritional status, the possibility of greater male susceptibility to the toxic effects of cobalt remains.

While we were unable to link occurrence of heart failure directly to raised serum cobalt ion levels in this study our identification of higher rate of admision for heart failue being isolated to the most at risk prosthesis is strong circumstantial evidence of a link to raised serum cobalt. Patients with the ASR XL prostheses as well as other large head MoM THA have been identified as having raised blood levels of cobalt ions (Hart et al. 2011, Gill et al. 2012, Chang et al. 2013, Hartmann et al. 2013, Jantzen et al. 2013, Randelli et al. 2013) with levels normalizing after the hip prostheses have been removed (Allen et al. 2014). Blood levels of cobalt are related to wear rate and corrosion of the prostheses (Vendittoli et al. 2011, Hart et al. 2013). An increase in revision has been associated with increasing blood levels of cobalt (Hart et al. 2014). In patients with ASR XL THA a positive correlation with blood levels of cobalt and femoral head size has been reported (Langton et al. 2011). The ASR XL THA has also been associated with a higher rate of revision compared to other LH MoM prostheses (de Steiger et al. 2011) indicating a greater problem with metal products in the ASR XL prosthesis.

We found no statistically significant difference in rates of heart failure hospitalization between patients with other MoM hips compared to MoP hips, however, we cannot rule out an association with these prostheses as only a small number of each type of design and combinations was used in the other MoM groups. There is large variability in femoral design, femoral head sizes, metallurgy, modularity and acetabular components between implanted MoM prostheses and consequently revision rates and potential for metal particle and ion production vary between MoM prostheses (Cheung et al. 2016).

We were not able to adjust for a number of potential confounding factors associated with heart failure events, such as tobacco and alcohol use, obesity, and pre-existing cardiac dysfunction (with preserved or reduced ejection fraction), however, we did exclude patients who had been hospitalized previously for heart failure or were on medicines likely to be indicative of heart failure. These factors are unlikely to be associated with the type of prostheses selected by the surgeon and therefore we have no reason to believe this would systematically bias our results. Our cohort has a higher median age than the general population who received MoM prostheses, and as such one of the limitations of our study is that the results are generalizable only to an older patient population. We did adjust for age and baseline comorbidities using the validated co-morbidity burden RxRisk-V; the hazard ratio for admission for heart failure following the use of the ASR XL compared to MoP was increased compared to the unadjusted result (Table 3). Importantly, heart failure was not an identified risk at the time the treatment decision was made, therefore it is unlikely that patients were selected to receive a particular bearing surface due to this perceived risk. However, even if confounding by indication did occur, indications for MoM hips were for younger patients and so patients who received MoM hips would likely have lower risk of developing heart failure than patients who received MoP hips. It might be expected that there should also be an increased mortality risk. Our study population is an older cohort and consequently the mortality for all groups was high. This may be the explanation for no observed difference. It is also possible that longer follow up may be required before any difference in mortality is observed. The observation that there was no statistically significant difference in mortality between the exposure groups also suggests that the groups were not different in their over-all health status at the time of their primary THA suggesting that the

observed increased heart failure rate is not due to selection of the ASR XL to sicker patients more at risk of experiencing this event.

We used the end point of primary discharge diagnosis of heart failure to identify incident heart failure, which would predominantely identify patients with the most severe heart failure. This approach may have underestimated the incidence of heart failure (Pfister et al. 2013) resulting in potential missclassification of outcomes, however, there is no reason to suspect that this misscalssification would differ between the exposure groups and would have introduced bias to our results. Our sensitivity analysis including both primary and secondary diagnoses of heart failure resulted in an increased proportion of heart failure outcomes while estimates of relative hazards were similar to the main analysis. Because only a 1-year look back period for a history of heart failure was used to exclude patients, it is possible that patients with a history of heart failure that were not on medication in the year prior to surgery were not captured. However, if the history of heart failure is under-ascertained in our patients we have no reason to believe that it is different between the patients with MoM or MoP and therefore not likely to bias our estimations.

Our study has a number of major strengths. The most important is the quality of the data source. Veterans' adminstrative health data in Australia are comprehensive and have enabled the examination of a potential temporal relationship between development of heart failure and receiving a THA. Data are available for the type of hip replacement procedure, types of hip prostheses, heart failure hospitalizations, mortality, and dispensed medications. The comorbidities of the different groups could be identified and compared using a validated comorbidity measure based on prescribed medicines (RxRisk-V). The

totality of the available information was important in avoiding potential bias and confounding in this analysis.

In summary, our study shows that men with ASR XL THA with no recorded history of heart failure at the time of surgery had a higher rate of hospital admission for heart failure following the THA compared to men with MoP THA. Further studies are needed to investigate whether the association also can be found in a younger cohort of patients with these prostheses. While the causality of the relationship remains uncertain, our findings highlight an urgent need for further research to explore this possibility. It may also have potential implications for the long term monitoring of people who have received ASR XL and possibly other MoM hip prostheses.

MHG drafted the manuscript, managed and analysed the data. NLP extracted the data. All authors were responsible for the design of the study, interpretation of the data, revising the work critically for important content and final approval of the version to be published.

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review, or approval of the manuscript; and decision to submit the manuscript for publication. None of the author report conflicts of interest that are directly relevant to the content of this study.

Appendices 1 and 2 are available on the web-site of Acta Orthopaedica (http://www.actaorthop.org/) identification number 10562.

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Table 1. Study Sample Characteristics by Hip Bearing Surface and Sex, 2004-2012

	Men				*Women*			
Bearing surface	**MoP**	**ASR XL**	**LH MoM (>32mm)**	**SH MoM (≤32mm)**	**MoP**	**ASR XL**	**LH MoM (>32mm)**	**SH MoM (≤32mm)**
Pre-exclusion cohort:	***Men (N=2384)***				***Women (N=3213)***			
Total Patients, No. (%)	2026 (85)	87 (3.6)	171(7.2)	100 (4.2)	2907 (90.5)	79 (2.5)	159 (5)	68 (2.1)
Heart failure medication[b]	268	12	18	11	413	12	21	7
Heart failure admission[b]	122	3	8	2	126	3	7	2
Study cohort:	***Men (N=1764)***				***Women (N=2255)***			
Total Patients, No. (%)	1502 (85.1)	63 (3.6)	124 (7)	75 (4.3)	2044 (90.1)	58 (2.6)	107 (4.7)	46 (2)
Age, median (IQR), years	82.3 (75.6-85.6)	81.6 (68.3-85.1)	77.8 (64.2-83.2)	77.3 (69.9-82.7)	82.2 (78.9-85.2)	80.6 (77.9-83.6)	80.2 (76.3-84.5)	79.4 (76.3-81.2)
Age groups, No. (%)								
<55	12 (0.8)	0 (0)	7 (5.6)	2 (2.7)	1 (0)	0 (0)	0 (0)	1 (2.2)
55-64	156 (10.4)	13 (20.6)	27 (21.8)	20 (26.7)	13 (0.6)	1 (1.7)	6 (5.6)	2 (4.3)
65-74	193 (12.8)	8 (12.7)	21 (16.9)	13 (17.3)	190 (9.3)	5 (8.6)	14 (13.1)	5 (10.9)
75-84	705 (46.9)	26 (41.3)	46 (37.1)	36 (48)	1292 (63.2)	40 (69)	64 (59.8)	35 (76.1)
85+	436 (29)	16 (25.4)	23 (18.5)	4 (5.3)	548 (26.8)	12 (20.7)	23 (21.5)	3 (6.5)
Fixation, No. (%)								
Uncemented	605 (40.3)	61 (96.8)	73 (58.9)	69 (92)	656 (32.1)	53 (91.4)	61 (57)	32 (69.6)
Cemented	897 (59.7)	2 (3.2)	51 (41.1)	6 (8)	1388 (67.9)	5 (8.6)	46 (43)	14 (30.4)
Co-morbidities[a]**, median (IQR)**	4.0 (3.0-6.0)	4.0 (2.0-6.0)	4.0 (3.0-6.0)	4.0 (2.0-5.0)	5.0 (3.0-6.0)	4.0 (2.0-6.0)	5.0 (3.0-6.0)	4.0 (1.0-6.0)
Co-morbidities, No. (%)								
0	75 (5)	5 (7.9)	5 (4)	5 (6.7)	132 (6.5)	3 (5.2)	4 (3.7)	6 (13)
1	108 (7.2)	6 (9.5)	8 (6.5)	9 (12)	111 (5.4)	7 (12.1)	1 (0.9)	6 (13)
2	181 (12.1)	6 (9.5)	16 (12.9)	9 (12)	185 (9.1)	6 (10.3)	10 (9.3)	5 (10.9)
3	204 (13.6)	11 (17.5)	26 (21)	10 (13.3)	281 (13.7)	9 (15.5)	18 (16.8)	4 (8.7)
≥4	934 (62.1)	35 (55.6)	69 (55.6)	42 (56)	1335 (65.5)	33 (56.9)	74 (69.3)	25 (54.4)

Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on -Metal; IQR, Interquartile Range. [a]Co-morbidities based on RxRisk-V. [b]Record of admission/dispensed medication in the year prior to the primary THA.

Table 2. Incidence of Hospitalization for Heart Failure, Death, Revision Surgery, and Second Total Hip Replacement by Hip Bearing Surface and Sex

Bearing surface	*Men*				*Women*			
	MoP (N=1502)	**ASR XL (N=63)**	**LH MoM (>32mm) (N=124)**	**SH MoM (≤32mm) (N=75)**	**MoP (N=2044)**	**ASR XL (N=58)**	**LH MoM (>32mm) (N=107)**	**SH MoM (≤32mm) (N=46)**
Heart failure hospitalization– primary diagnosis, No. (%)	114 (7.6)	10 (15.9)	10 (8.1)	4 (5.3)	162 (7.9)	2 (3.4)	6 (5.6)	2 (4.3)
Heart failure hospitalization– primary or secondary diagnosis, No. (%)	270 (18.0)	18 (28.6)	18 (14.5)	12 (16.0)	322 (15.8)	11 (19.0)	13 (12.1)	5 (10.9)
Death, all causes, No. (%)	558 (37.2)	26 (41.3)	34 (27.4)	22 (29.3)	544 (26.6)	11 (19.0)	23 (21.5)	11 (23.9)
Revision surgery, No. (%)	79 (5.3)	5 (7.9)	12 (9.7)	7 (9.3)	80 (3.9)	4 (6.9)	8 (7.5)	3 (6.5)
Second Primary Total Hip Replacement, No. (%)	146 (9.7)	9 (14.3)	13 (10.5)	11 (14.7)	199 (9.7)	12 (20.7)	11 (10.3)	7 (15.2)
Follow up time, median (IQR)[a], years	6.8 (6.4-7.2)	7.2 (6.4-8.0)	6.7 (6.1-7.1)	7.4 (6.3-8.6)	6.5 (6.3-6.7)	6.6 (6.1-7.3)	6.3 (6.0-7.1)	9.0 (8.5-9.4)

Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on -Metal; IQR, Interquartile Range. [a]Censored: death, heart failure hospitalization, 2nd total hip arthroplasty, and revision.

Table 3. Association between Bearing Type and Heart Failure and Death for Men and Women.

	Men			*Women*		
Heart failure hospitalization*– primary diagnosis						
	Crude HR (95%CI)	Adjusted[a] HR (95%CI)	p value	Crude HR (95%CI)	Adjusted[c] HR (95%CI)	p value
MoP	Reference	Reference		Reference	Reference	
ASR XL	2.28 (1.19-4.37)	3.21 (1.59-6.47)	0.001	0.47 (0.12-1.88)	0.46 (0.12-1.88)	0.28
LH MoM (>32mm)	0.88 (0.43-1.81)	1.20 (0.58-2.48)	0.62	0.75 (0.33-1.70)	0.89 (0.39-2.02)	0.79
SH MoM (≤32mm)	0.52 (0.16-1.63)	0.94 (0.29-3.06)	0.93	0.44 (0.11-1.76)	0.67 (0.17-2.73)	0.58
Death, all causes						
	Crude HR (95%CI)	Adjusted[b] HR (95%CI)	p value	Crude HR (95%CI)	Adjusted[b] HR (95%CI)	p value
MoP	Reference	Reference		Reference	Reference	
ASR XL	0.95 (0.64-1.41)	1.15 (0.76-1.72)	0.51	0.65 (0.36-1.19)	0.69 (0.38-1.28)	0.24
LH MoM (>32mm)	0.65 (0.46-0.92)	0.88 (0.62-1.24)	0.45	0.80 (0.53-1.21)	0.93 (0.61-1.42)	0.75
SH MoM (≤32mm)	0.55 (0.36-0.85)	0.85 (0.55-1.32)	0.48	0.59 (0.33-1.08)	0.79 (0.43-1.43)	0.44

*Note: Cause specific hazard ratios censored for death, revision and 2nd hip. Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on -Metal; IQR, Interquartile Range; HR, hazard ratio.

[a]Adjusted for (RxRisk-V) age, cement, arrhythmia, hypertension, ischemic heart disease angina, ischemic heart disease hypertension.

[b]Adjusted for (RxRisk-V) age and cement.

[c]Adjusted for (RxRisk-V) age, arrhythmia, hypertension, IHD hypertension

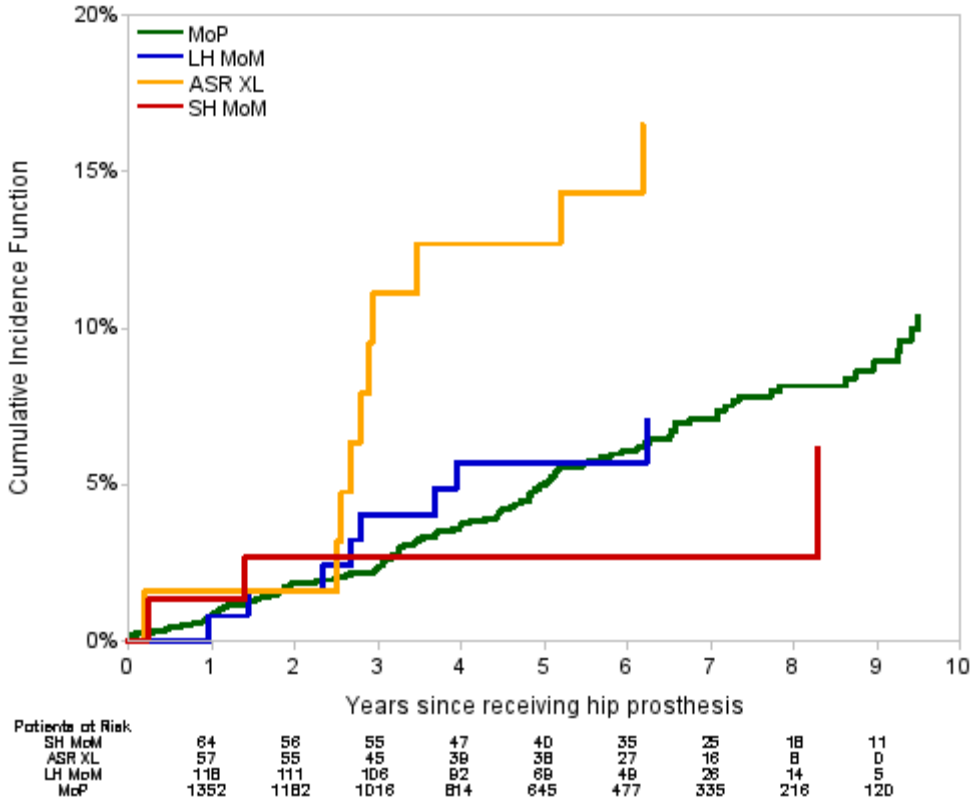

Figure 1. Cumulative Probabilities of Heart Failure Hospitalization in Men

Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on -Metal

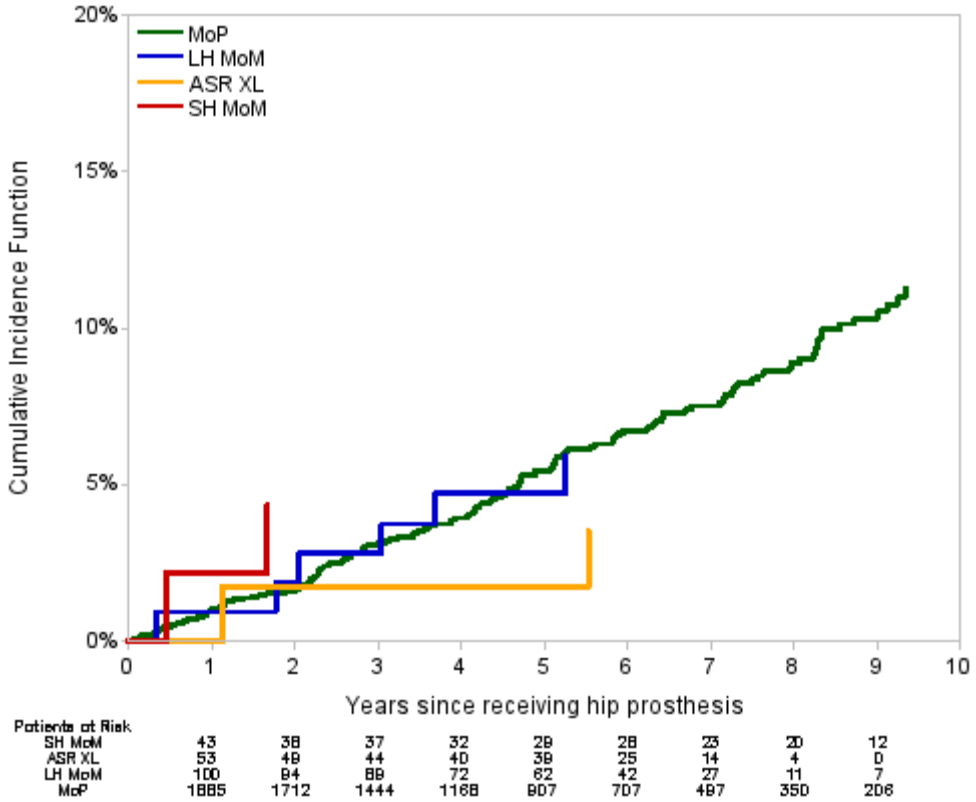

Figure 2. Cumulative Probabilities of Heart Failure Hospitalization in Women

Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on -Metal

Appendix 1. RxRisk-V Patient Co-morbidities by Hip Bearing Surface and Sex

	Men								Women							
	MoP, N, %		ASR XL, N, %		LH MoM, N, %		SH MoM, N, %		MoP, N, %		ASR XL, N, %		LH MoM, N, %		SH MoM, N, %	
Alcohol dependence	3	0.2	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0	0	0.0	0	0.0
Allergies	157	10.5	3	4.8	8	6.5	9	12.0	167	8.2	6	10.3	10	9.3	5	10.9
Anticoagulation	274	18.2	7	11.1	25	20.2	9	12.0	287	14.0	11	19.0	14	13.1	8	17.4
Antiplatelets	489	32.6	18	28.6	31	25.0	20	26.7	577	28.2	17	29.3	36	33.6	14	30.4
Anxiety	131	8.7	3	4.8	9	7.3	3	4.0	242	11.8	3	5.2	16	15.0	5	10.9
Arrhythmia	95	6.3	3	4.8	7	5.6	1	1.3	126	6.2	2	3.4	6	5.6	2	4.3
Benign Prostatic Hyperplasia	49	3.3	0	0.0	2	1.6	2	2.7	0	0.0	0	0.0	0	0.0	0	0.0
Bipolar	4	0.3	0	0.0	0	0.0	0	0.0	5	0.2	0	0.0	1	0.9	0	0.0
Dementia	6	0.4	0	0.0	2	1.6	1	1.3	25	1.2	0	0.0	2	1.9	0	0.0
Depression	323	21.5	16	25.4	25	20.2	16	21.3	451	22.1	9	15.5	20	18.7	6	13.0
Diabetes	110	7.3	8	12.7	9	7.3	9	12.0	122	6.0	3	5.2	9	8.4	4	8.7
End stage renal disease	7	0.5	0	0.0	0	0.0	0	0.0	29	1.4	1	1.7	2	1.9	0	0.0
Epilepsy	74	4.9	2	3.2	7	5.6	3	4.0	69	3.4	3	5.2	7	6.5	1	2.2
GORD	613	40.8	25	39.7	59	47.6	31	41.3	895	43.8	24	41.4	52	48.6	17	37.0
Glaucoma	130	8.7	8	12.7	9	7.3	5	6.7	220	10.8	7	12.1	12	11.2	1	2.2
Gout	181	12.1	5	7.9	13	10.5	11	14.7	67	3.3	2	3.4	3	2.8	1	2.2
Hyperlipidaemia	590	39.3	28	44.4	44	35.5	24	32.0	806	39.4	21	36.2	44	41.1	14	30.4
Hypertension	765	50.9	29	46.0	58	46.8	28	37.3	1193	58.4	31	53.4	66	61.7	21	45.7
Hypothyroidism	32	2.1	3	4.8	3	2.4	1	1.3	231	11.3	4	6.9	8	7.5	4	8.7
IHD angina	124	8.3	7	11.1	8	6.5	2	2.7	150	7.3	5	8.6	6	5.6	4	8.7
IHD hypertension	470	31.3	17	27.0	34	27.4	18	24.0	742	36.3	23	39.7	41	38.3	14	30.4

IBS hydrocortisone prednisolone salazines	15	1.0	1	1.6	1	0.8	0	0.0	16	0.8	0	0.0	0	0.0	0	0.0
Liver failure	35	2.3	1	1.6	1	0.8	1	1.3	49	2.4	1	1.7	4	3.7	1	2.2
Malignancies	45	3.0	1	1.6	4	3.2	1	1.3	42	2.1	0	0.0	4	3.7	0	0.0
Malnutrition	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0
Migraine	2	0.1	0	0.0	1	0.8	0	0.0	3	0.1	0	0.0	0	0.0	0	0.0
Osteoporosis Paget's	73	4.9	2	3.2	8	6.5	1	1.3	425	20.8	9	15.5	25	23.4	7	15.2
Pain	619	41.2	27	42.9	62	50.0	28	37.3	851	41.6	22	37.9	49	45.8	12	26.1
Inflammation pain	794	52.9	34	54.0	68	54.8	42	56.0	939	45.9	23	39.7	53	49.5	21	45.7
Pancreatic insufficiency	0	0.0	0	0.0	0	0.0	0	0.0	3	0.1	0	0.0	0	0.0	0	0.0
Parkinson's	24	1.6	2	3.2	1	0.8	0	0.0	24	1.2	1	1.7	4	3.7	2	4.3
Psoriasis	5	0.3	0	0.0	0	0.0	0	0.0	3	0.1	1	1.7	0	0.0	1	2.2
Psychotic illness	27	1.8	0	0.0	1	0.8	0	0.0	16	0.8	0	0.0	1	0.9	0	0.0
Chronic airways disease	256	17.0	14	22.2	16	12.9	12	16.0	319	15.6	11	19.0	15	14.0	2	4.3
Smoking cessation	20	1.3	0	0.0	0	0.0	0	0.0	11	0.5	0	0.0	0	0.0	0	0.0
Steroid responsive diseases	167	11.1	3	4.8	12	9.7	8	10.7	235	11.5	5	8.6	10	9.3	3	6.5

Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on –Metal; GORD, Gastro-oesophageal reflux disease; IHD, Ischemic Heart Disease; IBS, Irritable Bowel Syndrome. No patients in this cohort had the co-morbidities of: transplant organs, tuberculosis, hepatitis C, HIV, or hyperkalaemia.

Appendix 2. Sensitivity Analysis, association between Bearing Type and Heart Failure for Men and Women.

Heart failure hospitalization– primary and secondary diagnoses	*Men*			*Women*		
	Crude HR (95%CI)	Adjusted[a] HR (95%CI)	p value	Crude HR (95%CI)	Adjusted[a] HR (95%CI)	p value
MoP	Reference	Reference		Reference	Reference	
ASR XL	1.41 (0.84-2.38)	1.83 (1.06-3.17)	0.03	1.12 (0.58-2.18)	1.20 (0.61-2.39)	0.59
LH MoM (>32mm)	0.64 (0.37-1.09)	0.85 (0.49-1.47)	0.57	0.68 (0.37-1.24)	0.82 (0.45-1.51)	0.53
SH MoM (≤32mm)	0.66 (0.34-1.28)	1.14 (0.57-2.25)	0.72	0.33 (0.11-1.04)	0.47 (0.15-1.47)	0.20

Note: Cox PH model censored for death, revision and 2nd hip. Abbreviations: MoP, Metal-on-Polyethylene; ASR, Articular Surface Replacement; LH MoM, Large Head Metal-on-Metal; SH MoM, Small Head Metal-on-Metal; HR, hazard ratio.

[a]Adjusted for (RxRisk-V) age, cement, arrhythmia, hypertension, ischemic heart disease angina, ischemic heart disease hypertension