From the Orthopaedic departments at Odense University Hospital and Næstved Hospital

METAL-METAL ARTICULATIONS VERSUS STANDARD CERAMIC-POLYETHYLENE CEMENTLESS TOTAL HIP ARTHROPLASTY IN YOUNGER PATIENTS.

PhD Thesis

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Preface:

The thesis is based on work conducted during my full-time employment at Orthopaedic Research Unit, Clinical Institute, Faculty of Health, University of Southern Denmark and Dept.of Orthop. Surg., Region Zealand, Hospital South, Naestved from 2006 to 2010 and along side residency elsewhere during 2010-2011.
The thesis comprises a review of the resurfacing concept, with special focus on design, pros and cons.
The methods chosen for evaluation of implant are presented and discussed.
Summaries of the 6 individual papers comprising the thesis are presented, followed by a general discussion and conclusion.

The PhD thesis is based on the following papers:

1:Penny J, Ovesen O, Varmarken JE, Overgaard S. Clinical outcome after resurfacing, large head or standard total hip arthroplasty in patients with osteoarthrosis. Two year results from a randomised clinical trial. *In review.*

2:Penny J, Nielsen C, Ovesen O, Varmarken JE, Overgaard S. Metal ion levels and Lymphocyte subset counts. Randomised 2 year results for the ASR hip resurfacing prosthesis vs. a standard Bimetric THA. *In review.*

3:Penny J, Overgaard S. Serum chromium levels sampled with steel needle versus plastic IV cannula. Does method matter? *J.Biomed.Mater.Res.B Appl.Biomater.* 2010; 92:1-4

4: Penny J, Brixen K, Ovesen O, Varmarken JE, Overgaard S. Changes in bone mineral density at the femoral neck, gruen zones and the acetabulum following total and resurfacing hip arthroplasty. Two year results from a randomized study. *Accepted for publication in JBJS Br.*

5: Penny J, Ovesen O, Brixen K, Varmarken JE, Overgaard S. Bone mineral density of the femoral neck in resurfacing hip arthroplasty. *Acta Orthop.* 2010; 81:318-32

6:Penny J, Ding M, Ovesen O, Varmarken JE, Overgaard S. Early micro motion of the ASR™ femoral component. 2 year radiostereometry (RSA) results. *Accepted for publication in JBJS Br.*

Contents

Abbreviations

ARMD	adverse reaction to metal debris
BMD	bone mass density
Co	cobalt
Cr	chromium
DXA	dual energy X-ray absorptiometry
EQ-5D	Euro Qol- 5d
HHS	Harris hip score
MoM	metal on metal
MoPE	metal on polyethylene
UCLA	University of California Los Angeles activity scale
PE	polyethylene
RHA	resurfacing hip arthroplasty
ROM	range of motion
RSA	radiostereometry
SD	standard deviation
SDdiff	standard deviation on the difference
THA	total hip arthroplasty
Trans	translation
WOMAC	Western Ontario McMaster osteoarthritis questionnaire

1. Introduction

1.1.General introduction to standard THA

Traditional total hip arthroplasty (THA), consisting of a socket with a polyethylene inlay and a 28-32 mm head mounted on a femoral stem inserted into the femoral canal, has long been the gold standard for treatment of osteoarthrosis in the hip. The past few years have seen a rise in the use of slightly larger heads in combination with more wear resistant highly cross linked/ or vitamin E enriched polyethylene liners.

In 2009, 9408 primary THA were carried out in Denmark (170/100.000 inhabitants). The below 60 year old account for 20 % of all primary procedures, and the incidence in this age group has risen from proportionally with other age groups.
In Denmark the most common type of articulation is uncemented THA which account for 67% of all primary THA and the majority of THA in younger patients due to the more favourable outcome of uncemented implants in this age group(Overgaard, Pedersen, 2011a).
THA is a very successful treatment that eases pain, restores a good functional level and greatly improves quality of life(Garellick et al., 2011b).

1.2 Standard uncemented THA - special issues for the young patient

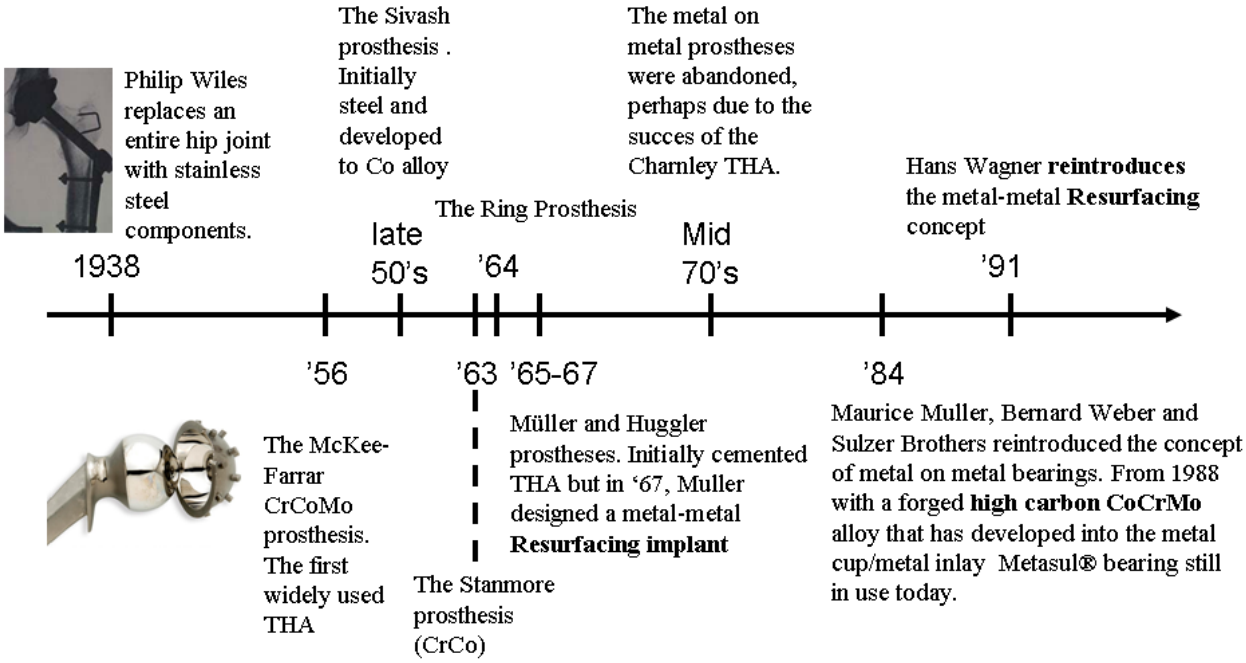
There are however some disadvantages, which include postoperative restrictions such as limited range of motion (ROM) due to the risk of dislocation (Bozic et al., 2009) and the recommendations of a moderate activity level (Klein et al., 2007).
The younger patient have a higher activity level (Bohannon, 2007), which leads to increased polyethylene wear (Schmalzried et al., 2000). The polyethylene debris induces osteolysis (Hallan et al., 2006; Wilkinson et al., 2005; Dowd et al., 2000), a contributing factor to aseptic loosening. Ultimately it leads to poor implant survival. The Danish hip arthroplasty register have an overall 14 year implant survival of 87% (88.6 - 89.7) %, but the group of patients below 50 years at primary operation fare significantly worse with approximately 20 % of the patients reoperated within 14 years(Overgaard, Pedersen, 2011a), and the findings are confirmed form other hip registres (Table 1). So while the senior patients generally can expect their primary arthroplasty to last them for the rest of their life, the younger patients are likely to face one or more revision surgeries in their lifetime.

Table 1	Annual report	Definition of young	Cumulative revision freq. young	Definition of old	Cumulative revision freq. average	Cumulative revision freq. old	Ref.
Australia	2009	<65	4.6%/8 y	>65		3.6%/8 y	(Graves et al., 2009)
Sweden	2008	<60	26%/17 y		17%/17 y		(Garellick, 2009)
New Zealand	2010	<55	0.87/100 component years		0.67/100 component years		(Rothwell et al., 2011)

It is assumed that bony support is required for the stability of the implant and that a solid bone stock will be an advantage to the patient.
The bone around a traditional uncemented THA remodels as the load and stress to the proximal femoral bone occurs via the femoral anchoring of the THA rather than via the femoral neck. This stress shielding causes the supportive bony matrix in the calcar region to decrease over time, expressed as a loss of Bone mineral density (BMD) measured by Dual energy X-ray absorptiometry (DXA) (Arabmotlagh et al., 2008; Kim et al., 2007; Tanzer et al., 2001) and although debated, (Karachalios et al., 2004) it may lead to a poorer bony support for a future revision THA.
Large generalized BMD loss has been observed around unstable THAs (Boden et al., 2004) and THAs ready for revision, (Venesmaa et al., 2000) whereas a stable implant seems bone conserving. A link between stress shielding related osteopenia and prosthesis failure seems plausible, but currently no causality has been established.
The bottom line is, that there is room for improvement in hip arthroplasty for the younger patients in particular with regard to survival, stability and BMD preservation. Resurfacing hip arthroplasty (RHA) is one proposal to address some of the problems.

1.3 A short history of Metal-on-Metal (MoM) hip articulations

Fig 1



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MoM and RHA today:
Todays metal on metal articulations all are manufactured from a high carbon CoCrMo alloy that allows for a low friction surface. The THAs comes with both non-solid or solid cups (ie. with or without a metal inlay, but articulating with a smaller metal head) and the RHA cups as solid only. Different manufacturers have developed a variety of RHAs, where some of the most widely used

are the *Cormet* ™, the *Birmingham Hip Resurfacing system (BHR),* the *CONSERVE® PLUS*, the *ReCap*, the *Durom*™ and the *DePuy ASR*™ *System* (Durom was recalled in 2008 and ASR in 2010 due to above average revision rates).
The (small) proportion of uncemented implants have increased slightly the past years (Graves et al., 2011), but most of the RHA systems are designed for hybrid fixation with a cemented head and a press-fit uncemented acetabular component.
The different brands differ mainly on design, heat treatment and the surface coating. Along with the resurfacing concept the companies also supply compatible large-head stemmed femoral components for revision of femoral neck fractures or as primary large articulation metal-on-metal articulation THAs.

For the first years after the introduction to the marked the RHA use was steadily increasing every year reaching as much as 10% of primary hip implants in 2006 (Porter et al., 2012), but within the past years, and increasing awareness of potential harmful effects, their proportion has declined to 2-5% of primary hip implants(Overgaard, Pedersen, 2011a; Porter et al., 2012).
Apart from the resurfacings a number of patients will also have MoM articulations of varying head size. In 2008 7% of all UK primary THA were large head MoM procedures, and in Canada just above 6%.(Canadian Institute for Health Information, 2009) - a proportion that has also declined the last few years.
The following chapters will focus on RHA, but the metallurgy and many aspects of the design are shared with Large head MoM THA

1.4 Materials/Metallurgi

The wear profile of an articulation is a combination of the hardness of the material, head size, regularity and roundness of the surface, clearance and coverage or impingement of the articulating parts.

The metallurgy is very important and the current MoM implants are made of a Cobalt-28 Chromium-6 Molybdenum Alloy (ASTM-F75-07 and ASTM F1537-08) This alloy nominally contains 30% chromium, 7% molybdenum, 1% manganese, 1% nickel, 0.75% iron, 0.35% carbon, and the balance cobalt.
Most current implanted components are made from an alloy with a high carbon content ≥ 0.15%. The carbon increased hardness and strength of the alloy and thereby reduces the wear (Dowson et al., 2004a), but at the same time causes a rougher surface.
One way of reducing the size and number of the carbides is using wrought metal instead of “as cast” or by heat treating, either during the sintering process used for porous coated acetabular implants or in hot isostatic pressure (HIP = 103 MPa) or Solution annealing (SA = vaccum). Despite the different heat treatment regimes and wrought versus cast, the major brands all generally have very low surface roughness of about 0.03µm (Heisel et al., 2008a; Dowson et al., 2004a).

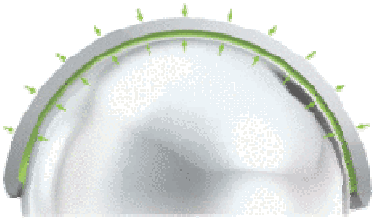
1.5. Design

Design features like roundness of the surface and clearance may also affect the wear. A bearing has to be round to avoid collision and all brands aim for a high surface sphericity. The deviation from roundness varies to some extent (Table 2), but it is unknown if this variety results in a difference of wear. Generally the deviation is larger for the femoral component than the cup, as the thinner structure results in more deformation more during cooling.

Table 2 Implant	**Mean deviation of roundness – head (µm)**	**Mean deviation of roundness – cup (µm)**
ReCap	3.2	1.9
BHR	0.9	0.9
Conserve plus	3.2	3.2
Durom	6.1	2.5
ASR	3.4	3.8
Cormet	7.3	3.8
All measured on a 44 mm head apart from Cormets 46 mm (Heisel et al., 2008a). Ideal roundness = every part of the surface or the circumference is equidistant from the center		

Ex vivo research has suggested that femoral head size and radial clearance (the distance of the gap between the articulating surfaces (Fig.2, Table 3)) of the articulation is of importance for the wear. A large femoral component has a large contact area and will, during a given movement, have more sliding distance/greater speed than a small component. In contrast to metal on polyethylene articulations, where increasing head size leads to increased wear, the greater speed in MoM articulations helps promote fluid film formation where the irregularities of the articulating surface (Fig 3)) are kept apart. A minimal radial clearance may further promotes this film, and by keeping the articulation surfaces apart we get a theoretical low-friction slide keeping the wear at a minimum.(Dowson et al., 2004b)
In support of this theory several clinical studies have demonstrated that wear assessed as whole blood and serum chromium (Cr) and cobalt (Co) concentrations are inversely related to the size of the femoral head (Langton et al., 2009; Langton et al., 2008; Vendittoli et al., 2007), but the theory is debated, as others haven't been able to find the same effect of size.(Daniel et al., 2008; Engh, Jr. et al., 2008; Witzleb et al., 2006)

(Fig 2)



(Fig 3)

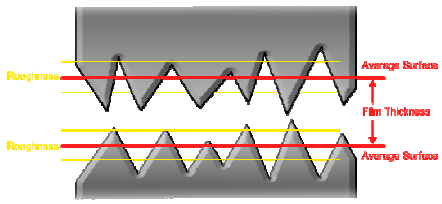


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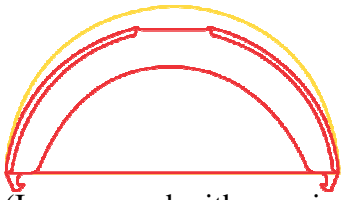
Table 3 Implant	Radial clearance (µm)	
ReCap	120	High (100-125 µm)
BHR	105	
Cormet	98	Medium (75-100 µm)
Conserve plus	79	
Durom	68	Low (50-75 µm)
ASR	49	
All measured on a 44 mm head apart from Cormets 46 mm (Heisel et al., 2008a)		

The disadvantage of low radial clearance lies in the risk of deformation. If the components are distorted during impaction there are fewer microns to spare before low clearance becomes a collision zone with accelerated wear. Design, in the choice of acetabular component thickness (Table 4), may also affect clearance as a thick wall will see less deforming during cooling and also be more resistant to deformation during impaction.(Lin et al., 2006)

Table 4 Implant	Wall thickness for cup at rim (mm)
ReCap	3.4
BHR	3.6
Conserve plus	3.8
Durom	4.6
ASR	3.1
Cormet	5.6
All measured on a 44 mm head apart from Cormets 46 mm (Heisel et al., 2008a)	

But choosing a thicker wall will logically require more bone to be removed on either the acetabular or femoral side.



The ASR™ acetabular component was designed thin-walled, and sub-hemispherical in order to both conserve bone and increase impingement-free range of movement. An instep was created at the egde to further prevent impingement.

(Images used with permission by DePuy)

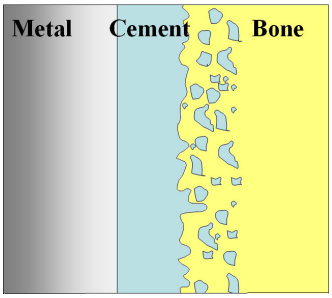
The design of the ASR™ acetabular component therefore carries the risk of deforming an already low clearance, but perhaps more importantly – results in a lower arch of cover than the more hemispheric designs. With less than a full hemisphere, the contact area with the head will be located closer to the edge of the cup, and in a steeply placed or overly anteverted cup, the reduced component cover can lead to increased edge loading and thereby to increased wear (De et al., 2008; Hart et al., 2008; Langton et al., 2008).

The arch of cover decreases with the size of the components, and a clinical study of the BHR and ASR™, focusing on suboptimal placed components, found that large resurfacing components

demonstrated less wear if they had a small clearance, whereas the opposite was true for the smaller (head < 51 mm) components (Langton et al., 2009).
The results would suggest that a large clearance and greater arc of coverage is more forgiving of component misplacement and if the head size is large enough the small clearance may work as an advantage, where the larger slide distance promotes a protective fluid film that protects against the egde loading.

1.6. Fixation

The inner surface differs is where the femoral heads differ in design. Most are designed for cement fixation and come with or without coating, the inner surface-to-bone gap varies in size depending on the desired cement mantle and the inner shape also varies from cylindrical to tapered to allow excess cement to be pressed out and removed during surgery, thus hoping to minimise the thickness of the polar cement mantle.



The cement is divided between the mantle, i.e the bone-component interface, and the penetration zone, where the cement interdigitates with the bone structure (Fig 4).
The cement used for fixation of the femoral component can be either high or low viscosity. Both however will heat up during the polymerization process, with the risk of necrosis in the surrounding bone.

Fig 4.
Using the *low viscosity cement technique*, developed by McMinn, cement is poured into the femoral component and rolled around its axis before rapid application to the femoral head. It requires some practise but the low viscosity allows for good interdigitation with the femoral bone.
The femoral components using low viscosity cement are designed to have a tight fit to the reamed femur; thus allowing the hip to be reduced once the excess cement is cleared away.
The drawback is that it is difficult to control (Morlock, 2010), can lead to increased depth of cement penetration/risk of heat damage to deeper parts of the femoral head (Bitsch et al., 2010; Campbell et al., 2006), the cement can leak into the pin canal, thus allow load transfer along the pin and induced stress shielding in the proximal femur (Radcliffe, Taylor, 2007).

The *high/normal viscosity technique*, developed by Amstutz, uses a more putty-like cement that is applied to the prepared femoral bone. It is easier to control, but is designed to give a thicker cement mantle, and the cement has to cure before the femoral component becomes secure and can be reduced.
So one type of cementation may increase penetration and the other may increase the mantle thickness. Which is more damaging is debatable.

Gill et al. found a trend towards higher bone temperatures, reaching up to 67.9°C, with increased cement penetration, but with only 4 femoral heads it was not statistically significant. If the implant

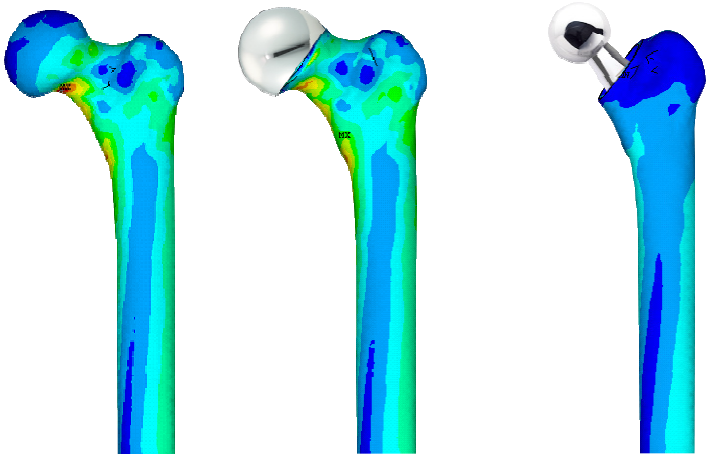
was cooled with pressure lavage during polymerization the temperature could be held at a non-damaging level. (Gill et al., 2007)
Bitsch et al reported similar findings using composite femoral models (Bitsch et al., 2010), and so did Campbells Finite element study where higher cement volume/deeper penetration lead to higher temperatures sufficient to cause bone necrosis.(Campbell et al., 2006)
Conversely, cadaver studies found the use of high viscosity cement technique to low viscosity technique (small bone component clearance) to increase the temperature in the head, implying that a thick mantle causes necrosis.(Little et al., 2008) But the study is limited as it did not measure the cement penetration or the mantle thickness.

The concerns regarding the cementation regime primarily focused on the development of damaging heat as a possible cause of early loosening and inside-head fractures, but the cementation regime may also bring about the risk of micro fractures.
Using the low viscosity designs, the bone-component gap is designed to be a snug fit to promote interdigitation and the femoral head may need impaction to be seated properly. An excessive cement mantle, more likely using the normal viscosity cement but also possible if too much low viscosity cement is applied, will leave the component proud, and the risk of leaving uncovered reamed bone as a possible weak spot for fractures may lead the surgeon to apply extra impaction force to seat the component (Campbell et al., 2006).
These impaction forces can be quite large and histology have found that fractures which were completely inside the head had a high rate of pseudarthrosis or 'two time' fracture patterns, that indicated that the fractures beneath the head developed from an earlier event like a high implantation trauma (Morlock et al., 2006).

The desired cement thickness differ according to manufacturer's instructions, but should be approximately 0-2 mm for the mantle (thin for a low viscosity cement) and about 2-3 mm for penetration.
Failed femoral implants shows major deviations from the desired situation, primarily exceeding the recommendations (Morlock et al., 2006; Campbell et al., 2006) .That would imply that failed implants are improperly cemented, but as we have very limited knowledge of the cementation in well functioning resurfaced heads we cannot be sure of this.
That reservation was highlighted in a study where 4 femoral heads were resurfaced prior to a planned conversion to THA. The retained heads all had far more cement penetration than optimal, ranging from 26.2% to 81.7% of a transverse section (Gill et al., 2007), and evidence of the advantages and drawbacks of the different cementation regimes must still be considered inconclusive.

1.7. Pros

Bone preservation:
Compared to the stemmed THA, a RHA preserves the femoral head and neck. The bone reserve is assumed to be an advantage at future revision surgery, where the proximal femur may be free of the osteolytic laesion often encountered at revision surgery.(Bradley, Freeman, 1983; Capello et al., 1982; Thomas, Amstutz, 1982; McGrath et al., 2008)
By maintaining a natural anatomy of the femoral head and neck, loading forces and tensile stresses are theoretically transferred naturally to the femoral neck (Fig 5), thus avoiding the stress shielding phenomena and resulting bone mineral density (BMD) loss seen following standard THA.(Gupta et al., 2006; Harty et al., 2005; Hayaishi et al., 2007; Kishida et al., 2004; Lian et al., 2007).



(Fig 5. Image used with permission by DePuy)

Wear:
The alloy used is extremely hard and scratch resistant. Compared to the acetabular polyethylene, the use of a metal inlay reduces the volumetric debris dramatically by more than a factor 100. (Anissian et al., 1999) The more modern highly cross linked polythylene only have an eight of the traditional wear , but still that is 50 timers higher than the steady state wear for a MoM articulation (Fisher et al., 2006). The particles released from the MoM articulations are mainly in the sub micron size range, and does not seem to stimulate the macrophages in the way seen with the larger polyethylene particles, (Ingham, Fisher, 2000) so theoretically the MoM articulations should reduce the occurrence af osteolysis and thereby the associated early loosening risk.

Head size:
The option of a large femoral head does not only improve the wear characteristics, it also increases the stability,(Beaule et al., 2002; Burroughs et al., 2005; Padgett et al., 2006) as the larger jump distance (Fig 6) for a large head require a substantial movement out of the cup before dislocation.

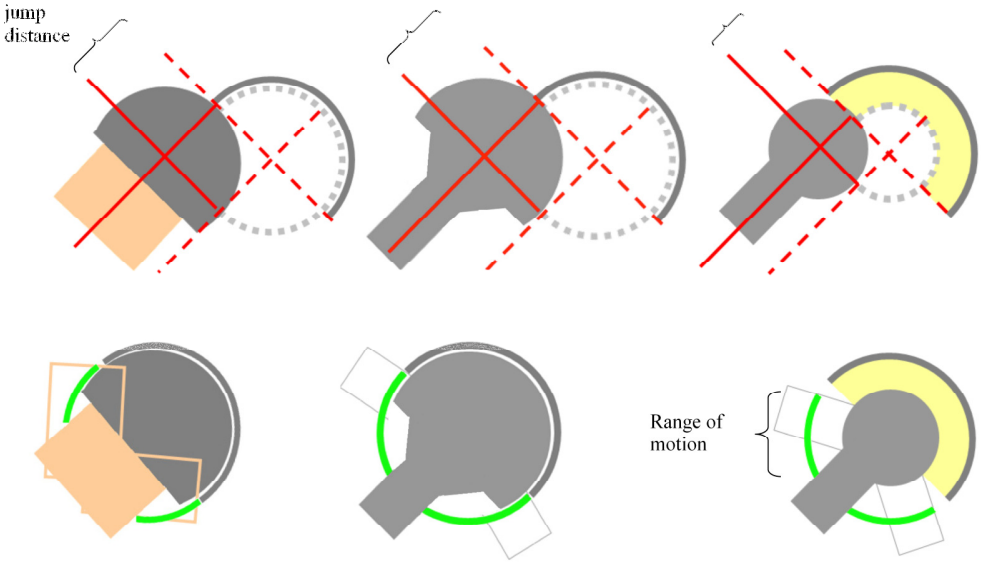


Fig 6

With dislocations being an unlikely event the patients are not subjected to the same postoperative restrictions as the standard 28/32 mm THA patient. The unrestricted movement regime allows for a more intensive training effort and could potentially lead to a faster recovery.
An early recovery is not only important for the well-being of the patient. The length of sick absence is highly associated to expulsion from the work force (The Danish ministry of Occupation, 2001) and as the majority of our focus group are still active in the work force, a speedy recovery becomes an important aspect of returning to the job and continued professional/economical success.

Some have argued that the large head improves range of motion (ROM),(la Rosa et al., 2007; Vail et al., 2006; Burroughs et al., 2005) and thus facilitate a better function(Davis et al., 2007), but it may be that an improved ROM only applies to the combination of a large head and a slim neck, (Bader et al., 2004) like the large-head MoM articulation. Simulation studies indicates that the small head/neck ratio found in RHA causes neck/rim impingement,(Kluess et al., 2008) and that Resurfacing prostheses may even have a lover ROM than traditional THAs.(Bengs et al., 2008) (Fig 6). To our present knowledge this has not been tested in clinical randomized studies. A cross sectional study of patients with resurfacing on one side and large head THA articulations on the other found no difference between the clinical ROM, suggesting the individual patient has an inherent flexibility, depending not only on bony impingement and the head neck ratio, but also on the soft tissue. In time, we will return to this ROM after hip replacement, independent from the type of implant design. (Le Duff et al., 2009)

Joint mechanics:
Biomechanically the resurfacing patients have demonstrated higher speed as well as gait characteristics closer to normal than standard THA, (Mont et al., 2007) and as a blinded randomised trail between a resurfacing and a large head MoM THA group didn't differ, (Lavigne et al., 2009) the large head articulations have been proposed to restore normal joint function, amongst other things by preserving the abductor and extensor moment arm distances. But as both resurfacing and standard THA was reconstructed to roughly the same off set postoperatively the theory is flawed, and the different gait kinematics could be caused by a biased design with a younger and more motivated resurfacing group. A randomised study between all 3 concepts is called for.

1.8. Cons

Wear and corrosion products:
The RHA articulations releases Chromium and Cobalt to the body both locally and systemically (Fig 7).

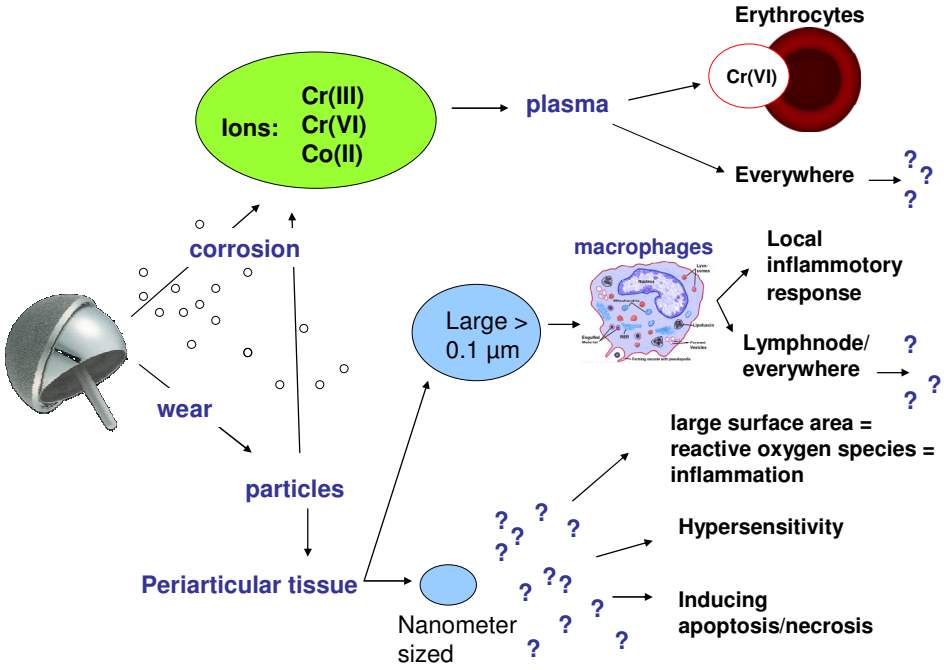


Fig 7

Metal ions:
Systemically Cobalt (Co) and Chromium (Cr) ions are released by corrosion of the surgical implant, or by secondary corrosion from wear particles.
Trivalent chromium (Cr(III)) is required in trace amounts for sugar and lipid metabolism in humans and Cobalt is an essential trace element in the formation of vitamin B-12. Hexavalent chromium (Cr(VI)) however is toxic and has been linked to cancer (lung, bladder) and genotoxicity. Co can accumulate in the heart and cause cardiomyopathy, it may cause a highly inflammatory response and can inhibit the uptake of iodine in thyroxine thus causing hypothyroidisme. Co and Cr can accumulate in the kidneys and cause local damage and in vitro test has demonstrated the capacity of both metals to be phagocytosed and induce apoptosis and cytotoxicity in a number of cells (Keegan et al., 2007; Keegan et al., 2008; Oldenburg et al., 2009). The majority of these links however are found in studies of industrial exposure - where Cr and Co often aren't the only metals in the environment, and furthermore, with an orthopaedic implants we have internal exposure compared to the lungs, GI or skin exposure often seen in the work environment and it makes it difficult to translate the results from the industry to surgical exposure.

Accumulation of metal ions:
Cr may be more likely to stay in the joint and synnivium where as Co diffuses systemically(Davda et al., 2011). The kidneys are responsible to excrete some, but not all of the Cr and Co ions. Patients with kidney failure demonstrate 100 fold higher Co levels compared with normal kidney function, but the picture is not so clear for Cr. (Hur et al., 2008). High intensity activity may,(De et al., 2007) or may not (Heisel et al., 2005) increase the renal Cr but not Co excretion, suggesting that there could be many ways the body regulates metal ion homeostasis. In the interest of the patients, the MoM articulations are reserved for patients with normal kidney function.

Adverse effects of Cr Co ions in arthroplasty patients:

A very small number of patients experience Cr above 50 parts per billion (ppb) and co above 100 ppb. These patients have demonstrated neurological, cardiac, skin and endocrine effects (Oldenburg et al., 2009; Steens et al., 2006), but most patients with a MoM articulation have levels around a few ppb. Increased translocations and aneuploidy in peripheral whole blood following MoM surgery has been demonstrated in well functioning hips with Cr Co levels below 2 ppb, but the metal ion concentration did not correlate with the chromosomal aberrations (Ladon et al., 2004).Whether the aberrations were increased by soluble or particulate metal in the bone or to some other aspects related to joint arthroplasty surgery is not known, but a study of 9 MoM patients initially operated for tumors, indicates that metal ions cause chromosomal damage and that this effect is reversible when the MoM is removed (Dunstan et al., 2008).
The possible ability of the ions to affect the DNA has lead to caution against implanting the devices in, particularily, fertile women. The studies are naturally scarce as very few uses MoM articulation on this group of patients, but the data suggests that the placenta blocks or exerts a modulatory effect on the rate of metal ion transfer (Ziaee et al., 2007; Brodner et al., 2004). Sperm parameters are not affected by ion concentrations around 2 ppb (Petit et al., 2010).
In vivo very few adverse effects have been demonstrated from systemic, THA related, metal ion exposure.
There may be a slight increase in haemopoetic cancers, but overall no risk of cancer have been demonstrated.(Visuri et al., 2006; Tharani et al., 2001) Those conclusions however are based on a limited material. Only few of the MoM patients have been followed with ion measurements, the side effects we're looking for are rare and may take some time to develop. There's a risk that we've missed an adverse effect because our follow up is not long enough and because many countries lack the national registers that links the individual to a medical history/possibly adverse effects.

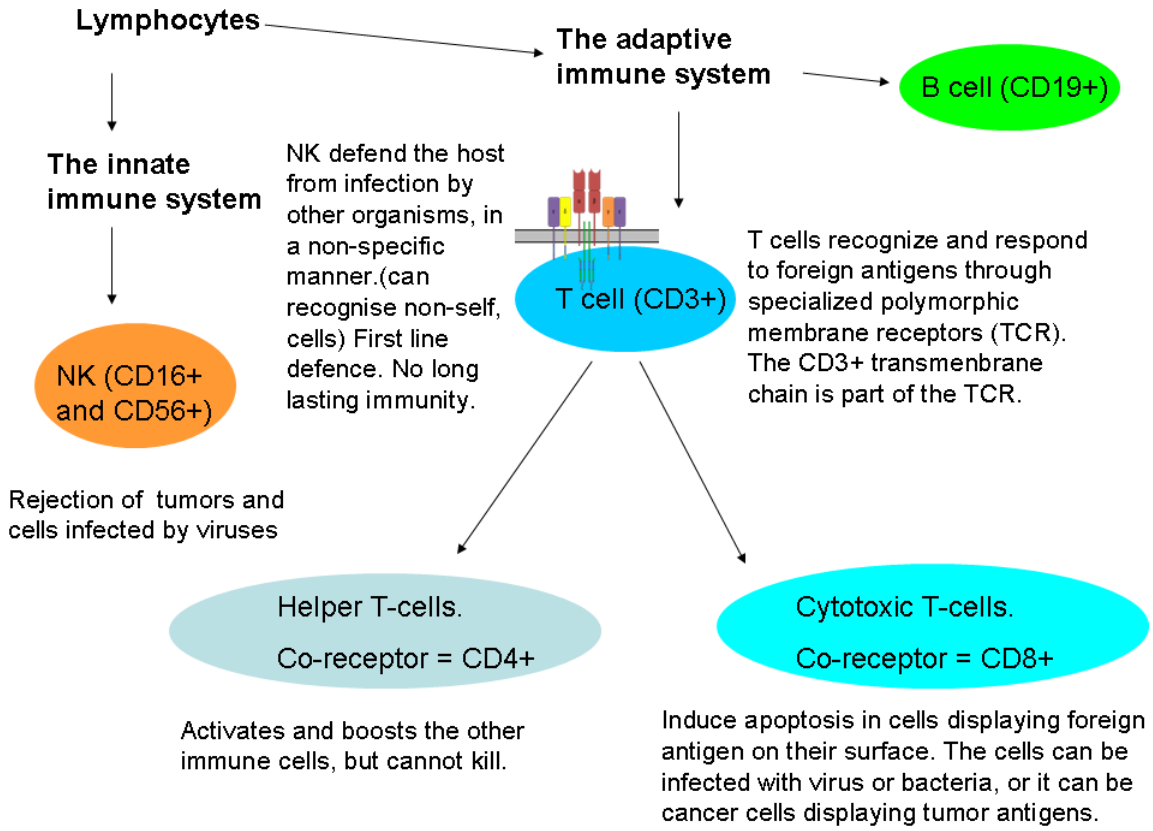
But where the ions may or may not be cause of concern, the metal particles may pose a problem.

Local effects – Pseudotumors or Adverse reaction to metal debris (ARMD):
During the last half decade reports of cystic and/or solid pseudotumors around the hip joint have emerged. Characteristic histological features have initially been reported as diffuse and perivascular infiltrates of T and B lymphocytes, plasma cells, high endothelial venules, massive fibrin exudation, accumulation of macrophages with droplike inclusions, and infiltrates of eosinophilic granulocytes and necrosis – an Aseptiv lymphocyte-dominated vasculitis–associated–laesion (ALVAL) (Willert et al., 2005; Thomas et al., 2009). Albeit not typical,with the B-lymphocytes and plasma cells, the histiological picture with abundant T-lymphocytes are indicative of a type IV hypersensitivity reaction and several pathways for this have been discussed (Mabilleau et al., 2008). There is a link between in vivo metal exposure and lymphocyte reactivity (LTT)(Hallab et al., 2004), but it may just reflect a general systemic reaction to the presence of a metal implant – primarily the minute traces of nickel. Kwon et al. found that patients with pseudotumors did **not** display an overall systemic lymphocyte reaction towards metal compared to well functioning resurfacing patients (as measured by Lymphocyte transformation test), despite having significantly higher median levels of metal ions in the blood. It lead the authors to conclude that the pseudotumors are associated with a reaction to a higher metal wear, but it does not appear to be mediated by a systemic hypersensitivity type IV reaction. A *local* hypersensitivity reaction cannot be ruled out from this study nor can a toxic reaction(Kwon et al., 2009b). Pandit et al found many macrophages and extensive necrosis rather than the typical ALVAL picture and suggests that the local metal wear particles are taken up by machrophages induce cytotoxicity and kills off the machrophages thus causing the necrosis seen (Pandit et al., 2008b). It has been suggested that the higher surface area of the nanometer size of the metal particles may allow for an increased number of chemical reactions at the particle surface, thus

generating reactive oxygen species (ROS) able to initiate an inflammatory response.(Papageorgiou et al., 2007)
Whichever the underlying mechanism for an activation of the immune system, the end result is likely to weaken the tissue and thus the stability of the implant.

The incidence of the pseudotumors is not well founded but is reported to be around 1% in symptomatic (Pandit et al., 2008a), and 8% in asymptomatic MoM hips(Kwon et al., 2009a). Albeit not malignant they can be locally infiltrative and following revision leaves the patient with a functional status similar to that of an primary arthritic hip *before* surgery(Grammatopolous et al., 2009).
There is no clear international consensus of either the underlying ethiology of or the diagnosis of ALVAL/ARMD/Pseudotumor, but commonly used indicators are hip pain, a non malignant tumor around the hip joint, systemic Cr Co ion whole blood levels above 7 ppb and histology with a more or less typical ALVAL appearance.

Systemic affects of the immune system:
Apart from the already mentioned local hypersensitivity response, the lymphocytes of the immune system may also be systemically affected by MoM articulations. Locally in the hip joint the macrophages will digest wear particles and bring them to the lymph nodes, but wear particles also travel periferally in the lymph nodes and ions and soluble metal nano particles reach all parts of the bloodstream, thus exposing lymphocytes/lymphocyte subgroups (Fig 8) everywhere to Cr and Co.



(Fig 8)

The peripheral Cr Co concentration will likely reflect the magnitude of the wear (Langton et al., 2010; De Smet K. et al., 2008), and Cr and Co ions has been associated with decreased levels of CD3+CD8+, CD3+CD4+, CD16+ and possible CD19+ cells (Hart et al., 2009b; Hart et al., 2006; Savarino et al., 1999) Fifteen percent presented with Laboratory-defined T-cell lymphopenia but none displayed actual side effects. The finding are debatable as others have failed to find a correlation with the ion level (Granchi et al., 2003; Hailer et al., 2011). A common problem is the comparison with a "healthy"control group rather than prospective data.

Gender/head size:
A small head size/female gender is a confounder to early failure (Marker et al., 2007; Graves et al., 2011; Porter et al., 2010) possibly due to less arch of cover and difficulty of placing the cup optimally in these patients, leading to excessive wear (Hart et al., 2008; Langton et al., 2008). The small components are often used in women, and the problems are reflected in a larger revision rate for women (Graves et al., 2011; Porter et al., 2010; Johanson et al., 2010). The implantation of the monobloc acetabular component can be difficult – especially in the smaller women - and result in less than full bony coverage of the cup, thus causing irritation and groin pain where the psoas tendon rubs against the metal(Bin et al., 2009).

Early revision risk predictors:
Femoral neck fractures/femoral head necrosis is the predominant reason for early revision(Graves et al., 2011). Patients with large cysts in the femoral head may be predispose to femoral head necrosis from heat damage emerging from excessive amounts of bone cement.(Campbell et al., 2006; Marker et al., 2007) The anatomy of the femoral head and neck disqualifies a number of the patients for RHA as a suboptimal shape of the neck, by nature or former fracture, can lead to notching which, although debated,(Steffen et al., 2008; Hing et al., 2007) some has found to be associated with neck fracture (Siebel et al., 2006; Shimmin et al., 2005).

Learning curve and surgical technique:
The RHA surgery takes longer than THA and demands a larger surgical incision, occasionally requiring release of the gluteus maximus tendon. The operation is technically demanding, has a substantial learning curve and probably requires to be maintained regularly to keep the failure rate low.(Marker et al., 2007; Klein et al., 2008; Siebel et al., 2006)

Limited indications:
The RHA cannot adjust leg length differences and femoral head and neck morphology has to meet certain demands.

1.9. Survival rates for RHA

The bottom line for success will be the survival of the implant.
As the current generation of RHA are new to the marked, 10 year survival rates are not yet available to compare to those of the standard THA.

Combining the Scandinavian countries the 2 years relative risk of revision was 2.7 (95% CI:1.9-3.7) compared to THA (Johanson et al., 2010). In Denmark, the hip register reports a 5 year failure rate of 6% (Overgaard, Pedersen, 2011a), and Sweden finds that the risk of revision is increased by

2.9 (2.1-4.1) times compared to primary standard THA (an overall 9 year RHA survival rate of 89%)(Garellick, 2009).
The New Zealand hip register observed a resurfacing revision rate/100-component years of 0.9, which was not statistically different from THA (Rothwell et al., 2009).
Australia and the UK has substantially more RHA patients in their registries, and The Australian registry reports a 9 year cumulative percent revision of 7.2% for the RHA compared to 5.2% for the standard THA (Graves et al., 2011). Finally in the UK there is a 7 year revision rate of 5.5% (95% CI: 5.09%-5.85%) for un-cemented THAs and 11.81% (10.80%-12.90%) for the RHAs. Even excluding the ASR RHAs the revision rate is roughly 10% and statistically clearly higher than THA(Porter et al., 2012).
The large head MoM THAs experience similar problems as the RHAs with revision rates slightly higher than RHA(Porter et al., 2012).

1.10. Motivation

RHA and large head MoM THA, may have many advantages that are attractive to the patient but the initial failure rate and the metal released from the components raises a new range of questions, unknown to us when the study was first initiated.
The motivation for initiating this RCT was the potential promise of the RHA to improve bone preservation, decrease wear, allow free movement and possible increased ROM for the younger active patients compared to the standard THA. The specific RHA – the ASR™ was chosen as hip simulator studies indicated decreased wear related to the low clearance in this component (Dowson et al., 2004b).
The early and intermediate RHA, and in particular the ASR™ RHA, failure rates emphasizes that is very important to validate the new methods and component designs, in a prospective controlled study, in order to establish a positive effect of the methods before stepwise introduction at a large scale(malchau H, 1995), and this study aimed to be a part of that process. Reality overtook the ph.D study when the ASR™ was voluntary recalled from the marked in 2010 due to above average failure rates.

2 Aims of the thesis

The overall aim of this thesis was to evaluate the ASR resurfacing prosthesis. It was chosen for use at Odense university hospital due to low wear rates in simulator studies, the prospect of avoiding stress shielding, and increase in range of motion and the hope of a better function due to anatomical restoration of the joint.

The specific aims of the papers were:

2.1. To evaluate the clinical function the first two years following surgery for 3 different prosthesis concepts that differs in head and incision size.

2.2. To compare the ASR RHA and a 28 mm Ceramic on polyethylene THA with regards to metal ion concentrations and lymphocyte subset counts for 2 years following surgery.

2.3. To asses the magnitude of metal ion contamination from the steel needle used to draw the blood samples for metal ion analysis.

2.4. To determine weather rotation of the limb affects the reliability of the bone mineral density measurements in the femoral neck surrounding a RHA.

2.5. To compare maintenance of bone mineral density around the ASR RHA and a 28 mm THA over a period of two years.

2.6. To asses the initial stability of the ASR femoral head component, using radiostereometry to determine subsidence and rotation indicative of early failure.

3. Methodological considerations.

3.1. Design.

A randomized study design was chosen in an attempt to create homogenous groups for comparison. Bias is a big problem when comparing different concepts. Before embarking on the study the authors discussed the blinding issue. If we allowed all free range of motion the 28 mm THA would risk dislocations, but if all groups had to apply to a standard THA protocol, we would impose unnecessary restrictions on the large articulation group and deprive them of the potential benefits of their implant, so an un-blinded design was agreed on despite the drawbacks. Inclusion to RCT's can be lengthy and by including at two departments we increased the uptake population, but added the bias of a more rural and slightly older population versus a more urban, which may have biased the sick leave patterns. All technical examinations (RSA, DXA, blood samples) were performed using the same equipment, which meant transporting Næstved patients to Odense for follow-up. It was costly and as we already had a standard THA control group in Odense, the standard THA group from Næstved did not participate in the metal ion, DXA and RSA examinations, where only small sample sizes were needed. The large head THA group did, due to financial limitations, not participate in the metal ion study – regrettable - in light of the high revision rates seen for this type of articulations today.
The patients were followed preoperatively, at 2 and 6 months and after 1 and 2 years. Appendix 1 depicts the investigations undertaken at different group at different times.
The trail is registered at http://clinicaltrials.gov NCT01113762. The randomized and the method studies has regional ethical committee approval from Funen County, Denmark (VF-20050133, S-20070118 and VF-20060090.

3.2. Inclusion of the patients

All patients included had to be eligible for a RHA according to the manufactures guidelines. As we also wished to examine BMD, we excluded patients with metabolical diseases or medication that could affect the BMD. Other gait affecting ailments were also ground for exclusion as the patients also had gait analysis performed in a separate study. Finally patients that were suspected not to comply with follow-up protocol were excluded. In- and exclusion criteria in Appendix 2.
Appendix 3 depicts the inclusion/exclusion process of the randomized study that took place in both Odense and Næstved, and there is a discrepancy between the numbers of assessments in each department as the Næstved secretary screened the GP referrals prior to assignment to the project. If the referral mentioned one of the exclusion criteria they were never assessed. An extensive review was undertaken of all the 40-65 year olds referred to Odense/Middelfart during the inclusion period and we found that 65% of the patients fell for the exclusion criteria. The relatively large number reflects exclusion of contra lateral hip implants as metal ion analysis was undertaken and exclusion of moderate and severe hip dysplasia as they were non eligible for RHA at our institution. The interpretation of our results should therefore bear in mind that we're addressing a selected sub segment of the osteoarthritis patients and the results may not be extrapolated to all.

3.3. Dual X-ray Absorbtiometry (DXA)

DXA scans are low in radiation dose and are used to assess the bone mineral density (BMD). Compared to bone without metal implants, the precision is slightly reduced as the pixels near the bone/implant interface may be excluded by the "metal remove" software during analysis, but it still provide a reliable method of monitoring the changes in bone mass density that occurs after total hip arthroplasty, when performed under standardized positioning of the patients pelvis (Wilkinson et

al., 2001; Laursen et al., 2006) and femur (Murray et al., 2005; Rosenthall, 2004; Smart et al., 1996).

Regions of interest (ROI):

Using DXA, we estimated the BMD around the metal cup in the regions described by Wilkinson and modified by Laursen (Laursen et al., 2005; Wilkinson et al., 2001) (Fig 9a).
BMD around the proximal femur in regions described by Gruen (Gruen et al., 1979) (Fig. 9b), and BMD of the femur neck in the ASR group was analyzed in a 6 zone model (Fig 9c). described by Kishida et Al.(Kishida et al., 2004).

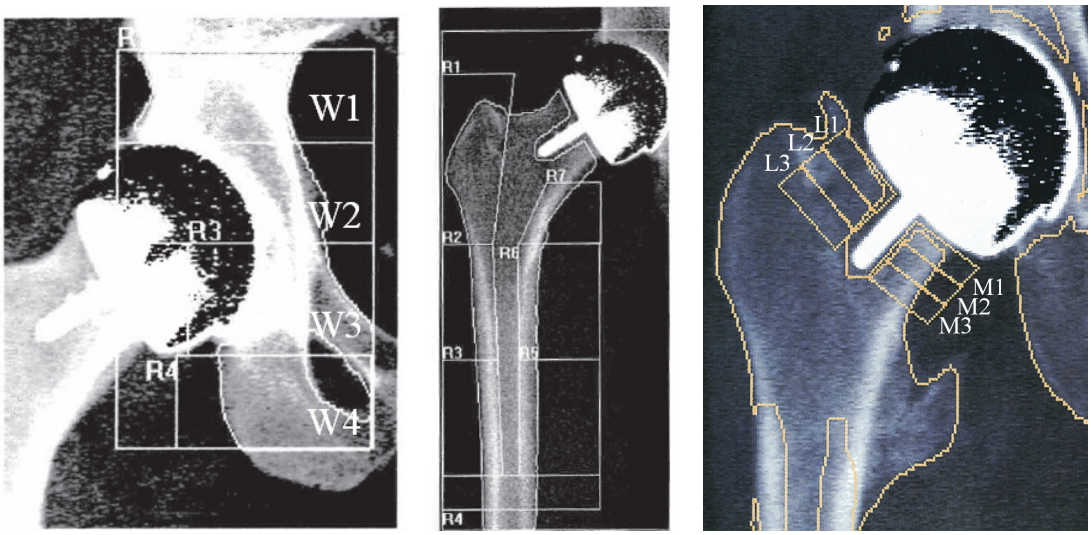


Fig. 9 a,b and c

Precision of DXA in the femoral neck:

There is no commonly accepted femoral neck model and Kishidas was chosen as it excludes the Gruen zones, is detailed and has a constant numbers of regions independent of femoral collum length. The anteversion of the femoral neck means that rotations of the hip alter the neck length of the screen-image and may cause a change in region size that could affect the BMD results.
As the average neck is anteverted 15 degrees, a 15 degree internal rotation of the hip was assumed to provide the best AP (anterior-posterior) image of the neck region. The reproducibility was tested on 15 ASR patients operated prior to the RCT, in 3 positions of 15 degrees in, neutral and 15 degrees out, and in 3 different sized analyzing regions (study 5). All had low acceptable coefficients of variation (CV), averaging 4.6% for the Kishida model, when the hip was scanned in the same position. The 15°externally rotated position tended to be less reproducible than others. One explanation could be that the area was slightly smaller (as seen by the higher BMD) in external rotation leading to some difficulty in placing the ROIs.
As expected (Gehrchen, 1999), a declining reproducibility was observed with smaller-size regions. Despite subdividing the femoral neck into 6 small regions, individual BMD changes below 9% could be detected with 95% confidence. That reproducibility compares with the Gruen zones (Cohen, Rushton, 1995; Kroger et al., 1996; Sabo et al., 1998; Yamaguchi et al., 2000), so the detailed model seems reasonable to use when evaluating longitudinal bone changes around a RHA. The use of the detailed model however, required the hip to be held in the same position at each scan. Rotation of the leg in increments of 15º and 30º increased the variability in all models, and had dramatic effects in the distal part of the 6 ROI model, where the CV was increased to unacceptable levels reaching up to 36%.

The neutral positions did, in most regions, demonstrate a slightly better reproducibility than the internally rotated position and may reflect a more relaxed position with minimal movement. By the time this information was available the randomised study had already begun with the hip 15 degrees inward rotated. As the method study demonstrated that that was acceptable for our purpose, we maintained our protocol, but the results suggest choosing the neutral position in future studies.
Our longitudinal study tested the reproducibility in the internal rotation after 1 year, and compared to the method study (study 5) the reproducibility had increased (Table 5).

Table 5: CV %	**M1**	**M2**	**M3**	**L1**	**L2**	**L3**
Rotational study (%)	4.6	2.8	2.9	5.1	6.1	4.6
Longitudinal study (%)	2.5	4.4	3.8	3.1	3.8	3.3

We're dealing with the same type of patients, but perhaps the increased routine for the technical staff in positioning the patient and marking the regions improved during the course of the study, and the ability to detect BMD change increased.

The set-up:

All scans were performed with the patient supine and with the femur 15° inward rotated, and held in place in a plastic shell from toes to upper thigh (Fig 10a). The plastic shells were molded for both left and right in 3 sizes, and could be adjusted to fit with Velcro straps. A peg from the heel of the shell, fitted into a goniometer, custom made to lock at 0° or 15° in or out (Fig 10b). If 15° in was not possible, the achieved rotation was noted (Fig 10c).

Fig. 10 a, b & c

BMD was measured using a Hologic 4500A (Waltham, MA, USA) DXA-scanner, applying the Hologic "metal-removal" software (version V8.26A/3). Scans were performed with a resolution of 0.5 line pair/mm and a speed of 2.5 mm/sec. Radiation dosage was 20 mSv per examination.
Quality controls for the DXA equipment were undertaken daily according to the manufacturer's guidelines to verify the stability of the system, and no drift was observed in the study periode.
For repeated measurements, shell and goniometer was removed and repositioned whilst the patient walked around for a few minutes.

Sources of error:

We did not control the pelvic tilt in the supine position, but dynamic(Parratte et al., 2009) and static studies (Nishihara et al., 2003) have established that only 10% have pelvic tilt changes exceeding the 10° Laursen et Al found acceptable regarding BMD precision around the acetabular cup (Laursen et al., 2005), and no changes above 14°.

Without the femoral stem in the RHAs, our software could not create identical Gruen zones to those of the THAs, so they had to be created manually, with the inbuilt risk of human error. Double markings as well as double examinations were undertaken, which found the manual marking of the fictional Gruen accurate.

3.4. Radiostereometry (RSA)

RSA relies on marking one or more segments of the bone with tantalum markers to create "a rigid body" and to compare the position relative to another rigid body – the implant. Simultaneous two-directional x-ray images projected over a calibration cage, creates stereo images with projections of the markings from both the calibration cage and the implant/bone markers. Software will translate these projections into a 3D coordinate system, calculation the distance between the rigid bodies (bone and implant). Changes, during follow-up between the relative position of bone and implant, mean that the implant is moving.
Evaluation of primary fixation of prosthetic components by Radiostereometry (other accepted names are Radiostereometric analysis, Roentgen stereophotogrammetric analysis or RSA for short) is important, as it can be used as a short-term surrogate indicator for future survival of the implant. For THA, early and continuous migration is one of the most important predictors of early implant loosening (Karrholm et al., 1994b; Rohrl et al., 2006). There is no definite limit for acceptable early migration/rotation, but continuous motion following the first year is a poor prognostic sign. Traditionally, migration has been focused on subsidence, where Kärrholms studies on mixed primary and revision cemented stems originally predicted that a migration/subsidence below 1.2 mm/2 years would be indicative of a good long term result (Karrholm et al., 1994a), it is now known that a low subsidence is not a guarantee for longevity, the rotation may also have to be small (Hauptfleisch et al., 2006).
Different implants seem to have different "safe" migration patterns. In uncemented implants, a small gap persists between the bone and the stem enabling minor subsidence to occur. Ideally the initial press fit at surgery provides adequate stability for bony ingrowth for permanent fixation of the stem, within the first year (often after the first 3 months). After this point, a well functioning uncemented stem stops migrating. Maximal total point motion of 3.8 mm seems to be well tolerated for the uncemented stem (Soballe et al., 1993). Some uncemented implants may quite safely, subside 1 mm before the implant settles (Strom et al., 2007; Campbell et al., 2011), whereas others hardly move (Karrholm et al., 2002; Thien et al., 2007). Cemented Total hip arthroplasties (THA) also differ in their migration. Some benefits from compressing in the cement (faro-Adrian et al., 2001) and some are stable in their cement immediately (Strom et al., 2006; Karrholm et al., 2002) without this influencing the final stability and survival. (Garellick et al., 2011a; Overgaard, Pedersen, 2011b). RSA has successfully been applied to migration studies on resurfacing femoral components as well as the cup, with good precision (Baad-Hansen et al., 2011b; Glyn-Jones et al., 2004; Gulati, 2008; Itayem et al., 2007; Itayem et al., 2005), and with minimal micro movement. Despite revision rates above standard THA, none of the RHA brands investigated has had alarming early loosening rates, thus supporting the use of the method on RHA, but weather we can apply the same criteria for poor prognostic signs to RHA as THA is not yet known.

Marking:
To mark points on the proximal femur and around the acetabulum, we used spherical 0.8 mm radio opaque tantalum markers inserted by an UmRSA® Injector™ during surgery.
The implants can be marked, either by injecting markers into cement or the polyethylene liner, or by soldering tantalum markers onto the implant during manufacturing. In the present study, the

supplier modified the femoral ASR components, to fit them with 4 tantalum markers on the peg. A special cutting tool was designed to create a groove in the pin-hole, and in that way slightly altering the implant from the original. A theoretical disadvantage would be if the larger hole carried a risk of cementing the stem with the possibility of load transfer along the pin and induction of stress shielding in the proximal femur (Radcliffe, Taylor, 2007). As normal viscosity cement was used and care was taken to avoid the groove, we believe the alteration to be harmless. The cup was designed to cement less, press fit insertion so no markers could be attached.
For both bone markers (reference segment) and implant markers, it is very important to use enough markers and to scatter them, as markers too close are less accurate.

Radiographic Examination: Two ceiling mounted x-ray tubes are used for simultaneous exposure of the patient (Fig 11a). The exposure is set for 130 mV and 20 mAs. The tubes are angulated so that their beams cross at the object of interest (in present case the hip with the tantalum markers). The rays then continue towards 2 separate film cassettes stored below a marker filled calibration cage (in present study the 43 UmRSA® Calibration Cage™ Fig. 11b). These markers are placed very accurate, the vertical markers act as control points and will be captured on both sets of images, and the horizontal (fiducial) markers only appear on one image. Each X-ray image will contain the marked bone and implant but with different calibration markers for images 1 and 2 (Fig 12).

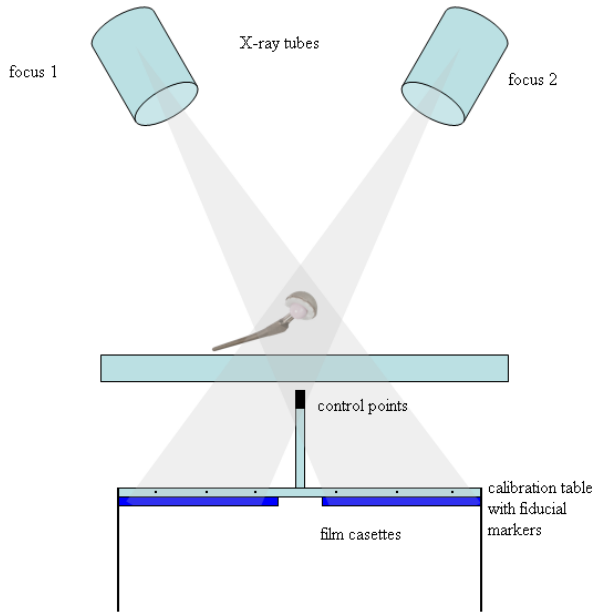


Fig 11a

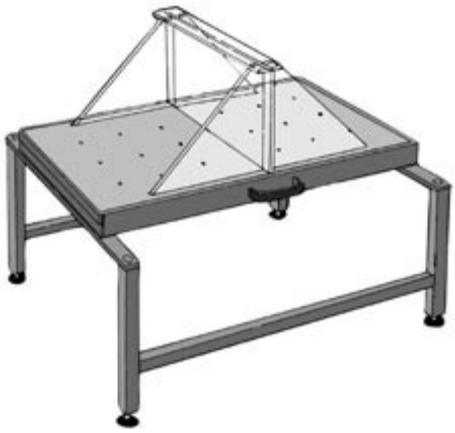
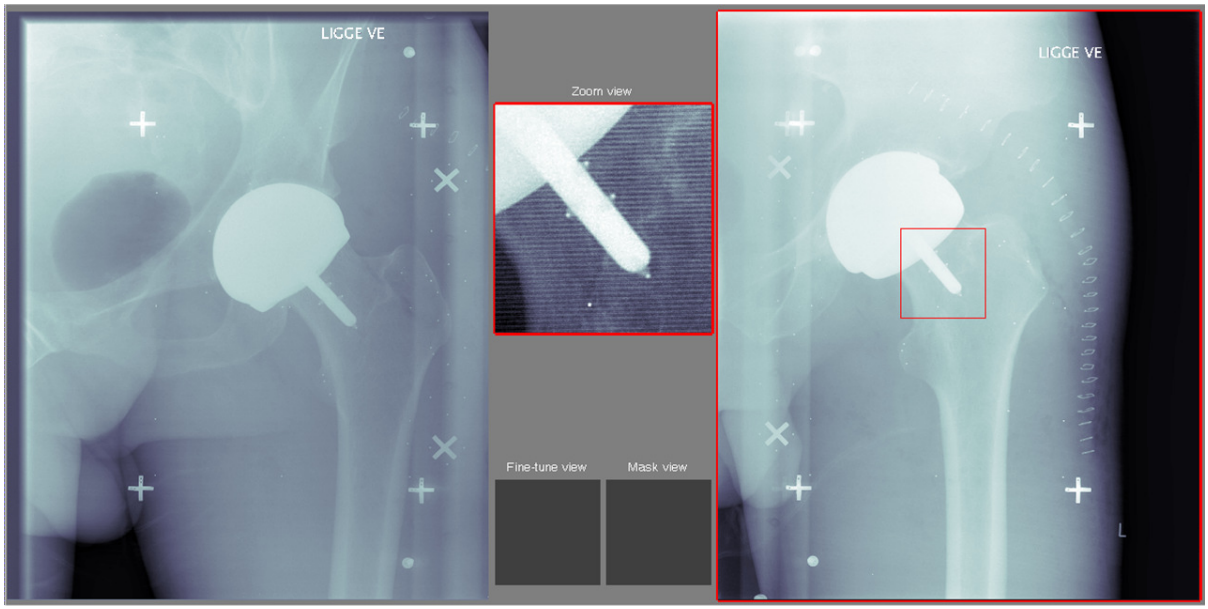


Fig 11b Image used with permission by UmRSA Biomedical



(Fig. 12)

Analysis:
Following import of the images into the system via DICOM Link, a few fiducial and control markers are manually indentified, and the UmRSA® Digital Measure™ (Software v6) automatically identifies the rest of the markers from the table. Some manual identifying, marking and adjustment is necessary though to make sure they are centred. The bone markers followed by the implant markers (the rigid body) are then marked and adjusted. The UmRSA® Digital Analysis (Software v6) then was used to calculate the 3D positions with high precision. The placements of the bone markers are assumed constant (any movement will be detected and the marker excluded) so they will be used as the reference segment. The position of the implant markers will be related to the reference segment, and any difference over time will be expressed as 3D motion of the implant. In the present study, the position of the implant is defined as the centre of gravity between all the implant markers, but a single implant marker can also be used.

The linear movements (translations) and rotations of the pin in a X,Y, Z co-ordinate system, are presented as mean (sd) signed values in mm and degrees. The right-hand side of the body is used as anatomical reference point, with a positive X being a medial motion, positive Y being superior and positive Z being anterior movement. Left hip reverses the sign for the lateral-medial translation as well as the internal rotation and adduction to compare right and left hips (Fig. 13).

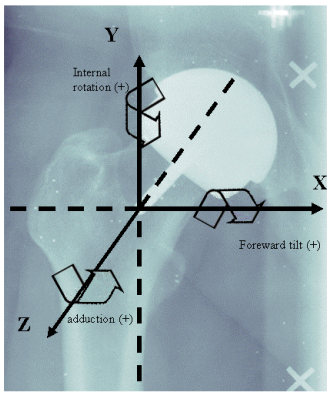


Fig. 13

Sources of error:
Mean error of rigid body fitting, is the difference between the relative distances of the markers of a segment on two separate examinations. If a marker is moving the mean error increases, and a maximum of 0.35 mm is acceptable (Valstar et al., 2005).
If the markers are too few or too closely spaced the precision drops. The condition numbers reflects the spread of the markers and above 150 around a hip implant generally leads to exclusion of the image (Valstar et al., 2005). In smaller joints where scattering is impossible a higher conditioning number may be acceptable if the mean error of rigid body fitting is small.
The implant may shadow the bone markers, so it is important to have enough markers.
The markers on the implant may not all be visible in an image. It is very important to make sure all are visible, as loss of a marker will alter the centre of gravity, and wrongly count as motion of the implant.

3.5. Conventional radiographs

Conventional standardised AP and lateral oblique view radiographs were used to evaluate cup position.
The inclination angle was measured twice on the AP images at the intersection of a line following the acetabular cup opening and a line between the ischial tuberosities. An average was used for the analyses. The anteversion angle was measured between the projected long axis of the acetabular opening and a line at a right angle to the horizontal line parallel with the ischial tuberosity (Yao et al., 1995)
For some patients the radiographs were not standardized before discharge. In those cases the patients with a metal on metal articulation were x-rayed again.
We assumed the cups to be stable, but the different follow-up time for the cup radiographs could introduce a bias if the cup has moved.
Conventional radiographs are not the best way to obtain the anteversion angle. EBRA (Ein Bild Roentgen Analysis) or Computer tomography (CT) would have been more accurate, but also yet another method to be mastered or an increase of radiation. Cup anteversion was not a primary investigation point and EBRA and CT were therefore abandoned.

Questionnaires:
All were administrated preoperative, at 8 weeks, 6 months, 1 and 2 years. The WOMAC was also filled out at home at 3 and 6 weeks, and the pain component of WOMAC was completed daily during hospitalization. (Appendix 1)

3.6. University of California Los Angeles activity score (UCLA activity)
The orthopaedic field suffers from a general lack of properly validated questionnaires to evaluate function. UCLA activity score (Amstutz et al., 1984) is a simple score from 1-10 (Appendix 4) often used to rate physical activity after a hip arthroplasty .
The UCLA score is based on participation in the highest-rated activity, regardless of the frequency or intensity of participation and is found to correlate well to pedometer data in a population but for individual patients with the same UCLA score, in whom the difference in the average steps per day could vary by as much as a factor of 15. (Zahiri et al., 1998). Naal et al has tested it in a THA population using the International Physical Activity Questionnaire (IPAQ) as gold standard. They found UCLA to have high construct validity it was reliable in re-test and also had very few floor and ceiling patients (Naal et al., 2009).UCLA activity outcome can be biased by both patient selection and the surgeon asking the THA patients to refrain from certain activities due to both risk

of dislocation and increased wear. Our randomized design should disperse with the selection bias, but the problem with patient information persists.
As the questionnaire wasn't translated into Danish, the investigator interviewed and rated the patient according to the original language version.

3.7. Harris Hip Score (HHS)/ Range of motion (ROM)

Harris Hip Score was originally developed to evaluate long term outcomes after traumatic hip dislocation(Harris, 1969), and was chosen as it is the most widespread method to evaluate the function of an arthritic hip/arthroplasty. It combines some objective measures (Range of motion, leg length discrepancies and limp) with patient reported estimates of walking-distance, pain, difficultes performing activities and discomfort. (Appendix 5)
It's a valid tool with regards to test-re-test as well as interobserver reliability, but suffers from a high ceiling effect in operated patients and most ROM measurements are not very reliable with the exception of hip flexion. But as the ROM only accounts for a minor part of the HHS the score is recommended to evaluate hip arthroplasties (Soderman, Malchau, 2001).
The Danish version of the HHS was used. It has not been validated but was translated by Henrik Malchau from the above mentioned Swedish register.
The score was calculated according to the original algorithm.

Range of motion (ROM = flexion+extension+adduction+abduction+internal and external rotation)

A single intern orthopaedic surgeon (JØP) performed the measurements, aiming to control the pelvic tilt. A clear18 cm plastic goniometer with broad arms and three linear stripes for limb centering and alignment was used. Movement to the nearest 5° was recorded. Extension was tested in the prone position. Flexion, abduction, adduction, internal and external rotation in the supine position - the latter two with the hip and knee flexed in 90°. The drawback of range of motion is the lack of accuracy. Repeated ROM measurement by single investigators have a standard deviation of 42 degrees,(Holm et al., 2000) due to bias such as pelvic movement, variable joint laxity, pain, caution by the investigator (fear of dislocating the joint) and inaccuracies in aligning the goniometer. Accuracy can be improved by use of an assistant(Hakkinen et al., 2010; Holm et al., 2000), but the logistic demands surpassed our resources.

3.8. Western Ontario and McMaster University questionnaire (WOMAC)

The WOMAC scoring system is a patient reported outcome measure describing the perceived pain, stiffness and difficulty performing daily activities, using a visual analogue scale (VAS) on a lickert scale developed by Bellamy in 1988 (Bellamy, 2002; Bellamy, 1989; Bellamy et al., 1988b).
The scale is developed specifically to OA and is one of the few scales for hip OA that is validated. Content validity was established by treating with NSAID(Bellamy et al., 1988a) and the VAS scale found to be slightly higher test-retest reliability for the VAS scale, and in addition it has high test-retest and interobserver reliability (Soderman, Malchau, 2001).
The WHO and the American Academy of Orthopaedic Surgeons recommend WOMAC as tool for following patient rated function in longitudinal hip OA studies, (Dieppe, 1995) but the questionnaire have some problems regarding construct validity, as some studies have found that patients may have a problem separating pain from function , hence an objective measure for function is recommended.(Lindemann et al., 2006; Stratford, Kennedy, 2006; Stratford, Kennedy, 2004)
Our institution has permission to use the WOMAC scoring system. A Danish questionnaire was used (Appendix 6). It has been translated according to international guidelines (personal correspondance w. N Bellamy, WOMAC) but has not been validated.

3.9. The EuroQol 5d (EQ-5d)

Quality of life measures are not routinely used in orthopaedic papers. The EuroQol 5d, a generic instrument for assessing quality of life, identifies 243 possible health states. It is based on 5 questions about mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Perfect health and death have values of 1 and zero respectively, and states worse than death (<0) are possible. The EQ-5d is created from a large European material (The euroqol group, 1990), translated to Danish, and validated in a large sample of Danes (Wittrup-Jensen et al., 2009). The present study only uses the tick-box options, and EQ-5d score calculated accordingly (Appendix 7). Not being specific for hip surgery the EQ-5d may not be as sensitive for change as a specific hip questionnaire (Dawson et al., 2001; Ostendorf et al., 2004), but EQ-5d has the advantage of converting to quality adjusted years of living (QALYs), and thereby assist in choosing the treatment with the best cost/benefit profile for society as a whole.

3.10. Sick leave

Patients available for the work force were asked their occupations and the date for returning to their job (not necessarily full time).
The job description was coded using the "search on occupation" function at "DISCOLØN" (http://www.dst.dk/Vejviser/Portal/loen/DISCO/discoloen.aspx) from Statistics Denmark. DISCO is the Danish version of the **ISCO-88** (**I**nternational **S**tandard **C**lassification of **O**ccupations, Geneva, 1990).
The classifications were grouped into self-employed, employee, or unemployed (we had no Assisting spouses) according to SOCIO (Spieker F, Plougsing J, 1997), a tool used for defining socio-economical groups (Appendix 8).

3.11. Pedometer

As a simple measure for objective function we chose to let the patients measure their steps/day during the week prior to the control visits. A Yamax (YX200) is very simple to operate and is found accurate in several studies.(Schneider et al., 2003; Le Masurier, Tudor-Locke, 2003). The downside is that a pedometer is inaccurate for obese patients as well as during non-walking activities like cycling, stair walking and will underestimate the activity for the patients engaging more active forms of exercise (Shepherd et al., 1999).

3.12. Metal ions

To evaluate long term effects of metal ions, a consensus paper has suggested uniform guidelines for future studies measuring metal ions in metal-on-metal Arthroplasties (MacDonald et al., 2004). As the blood concentrations of Co and Cr ions often are very low (below the part per billion level) the major concern in sampling and handling is the risk of contamination from dust or containers. Sempercare Vinyl, powder free vinyl gloves (Sempermed, Vienna, AU) were used during sampling and handling and all pipettes and vials had been soaked for a week in 0.14 M HNO_3 and verified contamination free.

The frozen serum samples for the methodological study were analysed for Co and Cr content on a Perkin-Elmer, Elan 6100 DRC FI-ICP-MS (PerkinElmer, Massachusetts, USA)(Fig. 14) in a ISO/EN 17025 accredited lab (Danish Technological Institute, Taastrup, Denmark).

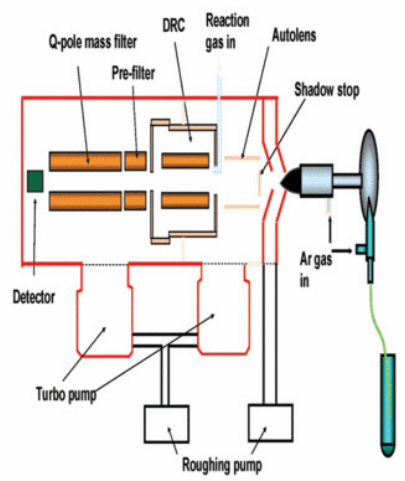


Fig. 14. Image used by permission by PerkinElmer Inc.

ICP Mass Spectrometry (ICP-MS) is the synergistic combination of an inductively coupled plasma (ICP) with a quadrupole mass spectrometer.
The ICP is heat source reported to reach temperatures as high as 10,000°K. The Plasma is created from an argon gas made conductive. Inside an induced magnetic field, these charged particles forced to flow in a closed annular path. As they meet resistance to their flow heating takes place. The sample is spray-injected through this hot loop, experiencing useful temperatures between 5,500 °K and 8,000 °K. These temperatures allow complete atomization of the sample elements, minimizing chemical interference effects.
The singly charged ions from the sample are then directed into a quadrupole mass spectrometer (MS) which quantitates the number of ions present.
Mass overlap can occur where the calcium ion from the serum sample binds to the argon and imitates the atomic weight of the chromium ion. To separate the chromium ammonia can be added to tie up the calcium using Dynamic Reaction Cell™ (DRC™) technology.
An ICP-MS performs analyses at the parts-per-trillion level and lower.
For the specific lab the serum Chromium detection limits (LOD) ranged from 0.04 to 0.08 ppb and 0.2 ppb for the Co.

Following the method study DTI experienced frequent breakdowns of the ICP-MS, and we had to find alternative analyzing facilities.
We found an ICP-SFMS Finnigan ELEMENT (Finnigan MAT, Bremen, Germany) in a ISO 17025/ISO 9001:2000 accredited lab (ALS Scandinavia's laboratories, Luleå, Sweden). Inductively coupled plasma Sector Field Magnet Spectrometry (ICP-SFMS), also called high resolution (HR-ICP-MS) can separate particles with a much smaller difference in mass. As a result it avoids both the interference issues with calcium and can be used on whole blood despite the proteins. It is a more refined analysis that can detect lover ion concentrations than ICP-MS and cost is the only disadvantage.
Both serum and whole blood Co and Cr concentrations are investigated in this study. When the project was started serum was recommended due to the relative ease of analysing (MacDonald et al., 2004), whole blood do give a better estimate of complete ion content, and with the improved availability of ICP-SFMS we were able to include this measure. The serum concentrations were slightly higher than the whole blood levels, but no significant difference in the interpretation of results from serum or whole blood. It is at times confusing with that many analyses, and in the

future whole blood will be the medium of choice, not least due to the initial ease of handling compared to serum.

Blood sampling.
The sampling and handling of the blood components is a source to possible contamination. Drawing the blood by needle has the benefits of a closed system, but the risk of adding Cr dust from the lumen of the needle. Inserting a plastic cannula and letting the blood drip into a container avoids the risk of metal dust, but is more troublesome for the investigator and uncomfortable for the patient, and has the theoretical disadvantage of the open system with exposure to whatever is in the air. At the start of the study we were unaware of the scale of the contamination, and initially sampled the patients in the randomized study using both methods (study 3).
The method study demonstrated that the use of a steel needle contaminated the serum with chromium in contrast to the plastic cannula. The contamination is most pronounced in the "first flush" of the needle, whereas the following sample only adds an average steel-needle contribution of 0.033 ppb. That is in the grey- area around the detection limit and when monitoring a MoM population this contamination is likely to be of little consequence. The metal levels in these patients have large variations and are manifold greater than the contribution from the needle from both first and following "flushes".
Despite adding slightly more Cr than the plastic cannula, we chose to continue with the more user friendly steel needle in the randomized population. Using the first flush sample would not have effected the results in this population, but as it was of no inconvenience we chose to discard it.
We used a specific brand of steel needles for this study and whether the results can be extrapolated to other steel needles cannot be concluded. We recommend testing other types of steel needle for contamination level prior to commencing a study.

3.13. Lymphocytes.
Initially a 7 mLVacuette® (456057) CPDA tube (BectonDickinson, NJ, USA) was used for the subpopulation analysis and a 4 mL Venosafe EDTA tube (Terumo, Europe) for the total lymphocyte count. From the beginning of 2010 the EDTA tube were used for both samples.
The department of immunology, Odense University Hospital handled all lymphocyte analysis. Lymphocyte subsets were determined according to their immuno phenotype. Until the beginning of 2010 the samples were analyzed on a Becton Dickinson FacsCalibur flow cytometer with three-color combinations of monoclonal antibodies (MAbs) obtained from DakoCytomation. The antibodies included CD3-FITC/CD4-RPE/CD45-RPE-Cy5, CD3-FITC/CD8-RPE/CD45-RPE-Cy5 and CD3-FITC/CD19-RPE/CD45-RPE-Cy5, and the isotype control tubes IgG1-FITC/IgG1-RPE/IgG1-RPE-Cy5.
Each subset of T lymphocytes ($CD3^+$) and B lymphocytes ($CD19^+$), the natural killer cells (NK) ($CD16/56^+$), and the major T lymphocyte subsets, T helper ($CD4^+$) and T cytotoxic ($CD8^+$) was expressed as percentage of lymphocytes and the absolute cell counts (numbers of cells per microliter) measured by a Model Xt-1800i (Sysmex Co. Ltd., Kobe Hyogo, Japan).
From 2010 the lab switched to use a Becton Dickinson FacsCanto II flow cytometer. Absolute counts of lymphocyte subpopulations were hereafter determined by a single-platform, lyse-no-wash procedure using the BD Multitest 6-Color TBNK reagent (TruCount tubes, BD Biosciences).
Before the FacsCanto II flow cytometer began operation, it was validated that there was no significant difference in either the measured percentage or absolute counts of the various sub-populations between the two cytometers or sample tubes.
Control of the instrument settings was done daily with CST (Cytometer Setup and Tracking) beads (BD Biosciences) and FACSDiva™ software according to the standard procedure.

3.14. Literature:

Using the PubMed and COCRANE databases, the following search criteria (both MeSH and free text) were used to find relevant background literature.
'resurfacing', 'RHA', 'SRA'; 'hip', 'THA', 'metal-on-metal', 'MoM', 'ROM', 'range of motion', 'rehabilitation', 'activity', 'UCLA', 'WOMAC', 'HHS', 'EQ-5d', 'quality of life', 'pedometer', 'steps', 'pain', 'metal ions', 'cobalt', 'chromium', 'BMD', 'DEXA', 'DXA', 'Dual X-ray Absorbtiometry', 'Radiostereometry', 'Radiostereometric analysis', 'Roentgen stereophotogrammetric analysis', 'RSA'.
The list was supplemented with relevant papers from the reference list of other papers.

3.15. Data collection and handling:

A key file linked CPR numbers to patient id. Each id had a paper file that was filled out at every follow up.
Epidata version 3.1 was used to build a database. All data, except for Cr/Co ion concentrations, lymphocyte counts and RSA data were entered using double entry mode for validation.
Cr/Co ion concentrations, lymphocyte counts and RSA data were reported in an excel data sheet, and were copy/pasted directly into a STATA data file.
Detailed data content and logs of notes/remarks on the data are available upon request, but not added to the index due to volume.

3.16. Statistics

When the project was planned, the scope was to compare the clinical function of the new resurfacing concept to the standard THA, and to investigate implant micro motion. At that time less focus was on potential harmful effects of the metal debris and metal ion analysis was planned as a control of the manufacturer's theory that a low clearance would minimize the wear. The RSA analysis requires only few patients, so range of motion was chosen as the clinical endpoint for sample size based on early short term resurfacing papers reporting favorably on increased range of motion with these implants (la Rosa et al., 2007; Vail et al., 2006; Burroughs et al., 2005) and the expectation that a larger ROM would facilitate a better function (Davis et al., 2007). The Davis paper reported 20 degrees difference, measured on flexion, external rotation and abduction, between high and average Harris hip score. We do currently not know how large the difference in *total* ROM has to be to be clinically relevant for the function, but as a large study with little ROM difference didn't find any function difference(Vail et al., 2006), we assumed it had to be higher. ROM measurements are difficult to assess accurately with a standard deviation of 42 degrees,(Holm et al., 2000) so we chose 45 degrees to represent a meaningful difference. Sample size was calculated to 15 patients in each group and we aimed to include 20. That number was also adequate for lymphocyte and DXA comparison. We were aware that a n=20 design would only allow us to demonstrate relatively large differences (e.g. 2 points out of 10 for UCLA) for the questionnaire based rehabilitation data (UCLA, WOMAC, EQ5D), but chose to include these endpoints regardless.

Considering the diversity of the data, a bio statician Lars Korsholm (former assistant professor, University of Southern Denmark) was employed to make sure the right statistical analyses were chosen and carried out.
The metal ion and Lymphocytes data were assumed non-parametric and analyzed within group with Wilcoxon signed-rank test. Between group used linear regression with robust variance estimation (Hubert White). Correlation analysis between metal ions and lymphocytes.

Clinical outcomes (study 1) between groups were compared by Analysis of variance (ANCOVA) adjusted for baseline values, and the actual days of sick leave by a stratified log -rank test, adjusted for centre effect. Group difference in being in or out of work was compared using Fishers exact test.

DXA: ANCOVA adjusted for baseline raw value were used to evaluate differences between the two groups as well as the trend over time.

RSA: Our focus was movement from baseline to 2 years and movement from 1 year onwards, where the implant must be assumed to be settled, and rather than analyzing all intermediate follow-up times we limited the statistical analysis to 2 paired t test (baseline to 2 years and 1 to 2 years)

The repeated measurement studies (DXA and RSA) evaluated the precision between repeated measurements by calculating confidence intervals for the SDdiff's (Gluer et al., 1995), and the rotational study compared the SDdiff's by the Variance ratio tests (F-test).

4. Summary of the papers

Study 1: Clinical outcome after resurfacing, large head or standard total hip arthroplasty in patients with osteoarthrosis. Two year results from a randomised clinical trial

Background: Large size hip articulations may improve Range of motion and function compared to a 28 mm THA, and the low risk of dislocation allows the patients more activity postoperatively. Adversely the larger surgery for resurfacing hip arthroplasty (RHA) could impair rehabilitation.
Purpose: To investigate the effect head size and surgical procedure on postoperative rehabilitation in a randomized clinical trial (RCT).
Methods: We followed randomized groups of RHA, large head THAs and standard THAs at 2 m, 6 m, 1 and 2 years postoperatively, recording clinical rehabilitation parameters.
Results: The 2 year total ROM (sd) for RHA, standard THA and large head THA was 221.1° (35.4), 231.6° (36.0) and 225.0° (29.8) respectively ($p=0.60$). We observed a tendency for the large articulations to improve an additional 15° in total range of motion during the first 6 postoperative months but the advantage was non significant and transient. The study did not find any group difference in the HHS, UCLA activity score, step rate, quality of life or sick leave.
Interpretation: In this study head size did not influence range of motion and the lack of restriction allowed for large articulations did not improve the clinical and patient perceived outcomes and the surgical procedure of RHA did not impair the rehabilitation.

Study 2: Metal ion levels and Lymphocyte subset counts. Randomised 2 year results for the ASR hip resurfacing prosthesis vs. a standard Bimetric THA.

Background and purpose: Wear particles from metal on metal arthroplasties are under suspicion for adverse effects locally in the joint as well as systemically. Design related features as well as implant size and position may affect the wear. The DePuy ASR™ Hip Resurfacing System has above average failure rates. The aim of the study was to compare lymphocyte counts following surgery with RHA or THA and to relate ASR™ Cr and Co ion concentrations to component size and position
Method: In a randomised controlled trail 19 total hip arthroplasty (THA) and 19 resurfacing hip arthroplasty (RHA) patients were followed for 2 years. Lymphocyte subsets, Cr and Co ion concentrations and clinical rehabilitation outcomes were measured at each follow-up point.
Results: The lymphocyte subsets $CD3^+$, $CD4^+$, $CD8^+$, $CD16/56^+$ or $CD19^+$ did not differ between RHA and THA patients. The median RHA Cr and Co concentrations were below 2 ppb, with higher concentrations characterized by small components above 45 deg inclination.. No difference was found in clinical outcomes.
Conclusion: The data did not support a previously reported association between high metal ions and low $CD8^+$ counts

Study 3: Serum chromium levels sampled with steel needle versus plastic IV cannula. Does method matter?

Modern Metal-on-metal (MoM) joint articulations releases metal ions to the body. Research tries to establish how much this elevates metal ion levels and whether it causes adverse effects. The steel needle that samples the blood may introduce additional chromium to the sample thereby causing bias. This study aimed to test that theory.
Method: We compared serum chromium values for two sampling methods, steel needle and IV plastic cannula, as well as sampling sequence in 16 healthy volunteers.

Results: We found statistically significant chromium contamination from the steel needle with mean differences between the two methods of 0.073 ng/mL, for the first sample, and 0.033 ng/mL for the second. No difference was found between the first and second plastic sample. The first steel needle sample contained an average of 0.047 ng/mL more than the second. This difference was only borderline significant.
Conclusion: The chromium contamination from the steel needle is low, and sampling method matters little in MoM populations. If using steel needles we suggest discarding the first sample.

Study 4: Changes in bone mineral density at the femoral neck, gruen zones and the acetabulum following total and resurfacing hip arthroplasty. Two year results from a randomized study.
Resurfacing Hip Arthroplasty (RHA) preserves the femoral bone mineral density (BMD) compared to total hip arthroplasty (THA), but no studies have investigated the acetabular side. Following randomization, 2 x 19 patients with either RHA or THA were followed for two years. RHA maintained proximal femoral BMD and, compared to THA, increased BMD in Gruen zones 2, 3, 6 and particularly zone 7 with a gain of 8% compared to a loss of 15%. RHA maintained medial femoral neck BMD and increased between 12 and 26% in the lateral zones. On the acetabular side BMD was similar at any zone at any point in time. The average BMD of all acetabular regions in the RHA group dropped to 96% and for the THA to a non-significant 98 %. Four and 5% were lost superior to the cup in W1, 10% and 9% just medial for the cup in W2 for RHA and THA respectively. RHA lost 7% in W3 and maintained BMD below the cup as did THA. In conclusion, in this study the bone preserving ability of the resurfacing concept only applies to the femoral side.

Study 5: Bone Mineral Density of the femoral neck in resurfacing hip arthroplasty. DXA precision biased by region of interest and rotation of the hip.
Background and purpose: Resurfacing Total Hip Arthroplasty (RTHA) may preserve the femoral neck bone-stock post-operatively. Bone Mineral Density (BMD), could be affected by the hip-position, and bias longitudinal studies. We investigated BMD precision dependency on type of ROI and position.
Method: We DXA scanned the femoral neck of 15 resurfacing patients twice with the hip in 3 different rotations; 15° internal, neutral, and 15° external. For each position BMD was analyzed with 3 surface area models. One model measured BMD in the total femoral neck, the second model divided the neck in two, and the third model had 6 divisions.
Results: When all hip positions were pooled an average Coefficient of variation (CV) of 3.1%, 3.6% and 4.6% was found in the 1, 2 and 6-region models. The external rotated hip position was less reproducible. When rotating in increments of 15° or 30°, the average CVs rose to 7.2%, 7.3% and 12% in the 3 models. Rotation affected the precision most in the model that divided the neck in 6 sub regions, predominantly in the lateral and distal regions. For larger-region models, some rotation could be allowed without compromising the precision.
Interpretation: If hip rotation is strictly controlled, DXA can reliably provide detailed topographical information about the BMD changes around a RTHA. As rotation strongly affects the precision of the BMD measurements in small regions, we suggest applying a less detailed analyzing model in studies where the leg position hasn't been firmly controlled.

Study 6: Early micro motion of the ASR^{TM} femoral component. 2 year radiostereometry (RSA) results
Radiostereometry (RSA) can detect the early micro motion in unstable implant designs likely to experience above average failure rates. In 2010, the ASR resurfacing implant was withdrawn from

the marked due to excess failure rates. A few RSA studies exist on competing femoral resurfacing components, and all have displayed initial implant stability. The mean (sd) micro motion over the first two years of nineteen femoral Articular Surface Replacement (ASR) components was a lateral movement of 0.107 (0.513) mm, distal migration of 0.055 (0.204) mm, and anterior movement of 0.150 (0.413) mm. The backward tilt around the x axis was -0.08°(1.088), there was 0.165°(0.924) internal rotation and 0.238° (0.420) varus tilt. The baseline to 2 year varus tilt was statistically significant from zero movement, but on a group level no significant movement was present from 1 year onwards. We conclude, that the ASR femoral implant achieves initial stability, and that early migration is not the mode of failure for the ASR implant.

5. Summary in Danish

Studie 1: Kliniske resultater efter resurfacing, stort hoved og total hoftealloplastik hos patienter med slidgigt. To års resultater fra en randomiseret klinisk undersøgelse.

Baggrund: En stor størrelse hofteartikulation kan muligvis forbedre bevægelighed og funktion sammenlignet med en 28 mm THA, og den lave risiko for hofteskred giver patienten mulighed for større aktivitet efter operationen. Omvendt kunne det større kirurgiske indgreb i forbindelse med resurfacing hofte alloplastik (RHA) forsinke rehabiliteringen.
Formål: At sammenligne effekten af hovedstørrelse og kirurgisk procedure på den postoperative rehabilitation i en randomiseret klinisk undersøgelse.
Metode: Vi fulgte randomiserede grupper af RHA, stort hoved THA og standard THA 2 mdr., 6 mdr. 1 og 2 år postoperativt, og opsamlede kliniske rehabiliterings parametre.
Resultater: To års total ROM (sd) for RHA, standard THA and large head THA var hhv. 221.1° (35.4), 231.6° (36.0) og 225.0° (29.8) (p=0.60). Vi observerede en tendens til at de store artikulationer forbedredes 15° ekstra i total bevægelighed i løbet af de første 6 postoperative måneder men fordelen var ikke statistisk signifikant og forsvandt igen. Studiet fandt ikke nogen gruppeforskel på HHS, UCLA activity score, antal skridt, livskvalitet eller sygefravær.
Tolkning: I dette studie påvirkede hovedstørrelsen ikke bevægeligheden og manglen på restriktioner for de store artikulationer forbedrede ikke de kliniske og patient oplevede resultater. Den kirurgiske procedure forbundet med RHA forsinkede ikke rehabilitationen.

Studie 2: Metal ion koncentrationer og lymfocyt subgruppe tællinger. Randomiserede 2 års resultater for ASR hofteprotesen sammenlignet med en standard Bimetric THA.

Baggrund og formål: Slidpartikler fra metal-metal alloplastikker er under mistanke for at forsage bivirkninger lokalt i leddet samt systemisk. Designmæssige forhold samt implantatets størrelse og position påvirker muligvis sliddet. DePuy's ASR™ Hip Resurfacing System har en reoperationsrate over gennemsnittet. Formålet med studiet var at sammenligne lymfocyttællingerne efter kirurgi med hhv. RHA og THA samt at relatere Cr og Co koncentrationerne i en ASR™ population til komponent størrelse og position.
Metode: I et randomised kontrolleret studie med 19 total hofte alloplastik (THA) og 19 resurfacing hofte alloplastik (RHA) blev patienterne fulgt gennem 2 år. Lymfocyt subpopulationer samt Cr og Co ion koncentrationer blev målt ved hver kontroltidspunkt.
Results: The lymphocyte subsets $CD3^+$, $CD4^+$, $CD8^+$, $CD16/56^+$ or $CD19^+$ did not differ between RHA and THA patients. The median RHA Cr and Co concentrations were below 2 ppb, with higher concentrations characterized by small components above 45 deg inclination.. No difference was found in clinical outcomes.
Resultater: Der var ingen forskel på lymfocyt subpopulationerne $CD3^+$, $CD4^+$, $CD8^+$, $CD16/56^+$ eller $CD19^+$ mellem RHA og THA patienterne. De mediane RHA Cr og Co koncentrationer var under 2 ppb, hvor de højere målinger var karakteriseret af små komponenter med over 45 graders inklinationsvinkel.
Konklusion: Resultaterne støttede ikke en tidligere rapporteret sammenhæng mellem høje metal ion koncentrationer og lave $CD8^+$ tællinger.

Studie 3: Serum chrom niveauer trukket med stål nål sammenlignet med plastik venflon. Har metoden betydning?

Moderne metal-metal led artikulationer frigører metal ioner til kroppen. Forskning prøver at etablere hvor meget dette metal ion niveauerne og hvorvidt det er skadeligt.

Stål nålen man trækker blodprøven med frigører muligvis yderligere chrom til blødprøven og giver dermed usikkerhed. Studiets formal var at teste denne teori.
Metode: Vi sammenlignede serum chrom værdierne for 2 målemetoder; stål nål og iv. Plastic venflon, såvel som blodprøve rækkefølge I 16 raske frivillige.
Resultater: Vi fandt statistisk significant chrom forurening fra stål nålen med en gennemsnitlig forskel på de to målemetoder på 0.073 ng/mL, for den først trukne prøve og 0.033 ng/mL for den næste. Der var ingen forskel mellem første og anden venflon prøve. Den første stål nål prøve indeholdt gennemsnitligt 0.047 ng/mL mere end den anden. Denne forskel var kun borderline signifikant.
Konklusion: Chrom forureningen fra stål nålen er lav og blodprøvetagningsmetoden betyder kun lidt i en metal-metal population. Hvis man vælger stål nålen anbefaler vi at man kasserer den første prøve.

Studie 4: Ændringer i knogle mineral densitet omkring femur halsen, Gruen zonerne og acetabulum efter total og resurfacing hofte alloplastik. To års resultater fra en randomiseret undersøgelse.

Resurfacing hofte alloplastik (RHA) bevarer den femorale knogle mineral densitet (BMD) sammenlignet med total hofte alloplastik (THA), men ingen studer har undersøgt den acetabulære side. Efter randomisering til enten RHA eller THA blev 2 x 19 patienter fulgt i to år. RHA bevarede proximal femoral BMD og, sammenlignet med THA, øgedes BMD I Gruen zones 2, 3, 6 og specielt i zone 7 med en vækst på 8% sammenholdt med et tab på 15%. RHA bevarede medial femur hals BMD og medførte en øgning mellem 12 and 26% i de laterale zoner. På den acetabulære side var BMD sammenlignelig i alle zoner til hvert kontroltidspunkt. Den gennemsnitlige BMD i alle de acetabulære regioner faldt til 96% i RHA gruppen og for THA til non-signifikante 98%. Fire og 5% blev tabt ovenfor skålen i W1, 10% og 9% lige medialt for skålen i W2 for hhv. RHA og THA. RHA mistede 7% i W3 og bevarede BMD neden for skålen, i lighed med THA. Det konkluderes at I dette studie demonstrerer RHA kun knoglebevarende egenskaber på den femorale side.

Studie 5: Knogle mineral densitet I femur halsen omkring en resurfacing hofte aloplastik. DXA præcision påvirket af skanningsregion og hoftens rotation.

Baggrund og formal: Resurfacing hofte alloplastik (RHA) bevarer muligvis den femoral knogle postoperativt. Knogle mineral densitet (BMD) kunne påvirkes af hoftens stilling og indføre fejlkilder i longitudinelle studier.
Vi undersøgte BMD præcisionens afhængighed af skanningsregionen og hoftens stilling.
Metode: Femten RHA patienter blev DXA skannet 2 gange med hoften i 3 forskellige stillinger; 15° internt, neutral, and 15° eksternt roteret. For hver stilling blev femur hals BMD analyseret med 3 forskellige modeller. En model målte BMD I den totale femur hals, den anden model delte halsen op i 2 og den tredje model havde 6 opdelinger.
Resultat: Når alle hoftestillinger blev lagt sammen blev der fundet en gennemsnitligt Coefficient of variation (CV) på 3.1%, 3.6% and 4.6% 1 hhv. 1, 2 og 6-regions modellerne. Den eksternt roterede hofte var mindre reproducérbar. Når rotationen belv øged i spring på 15° eller 30°, så steg det gennemsnitlige CVs til 7.2%, 7.3% and 12% in de 3 modeller. Rotationen påvirkede præcisionen mest i den analysemodel som delte halsen ind i 6 regioner, og især i de laterale og distale regioner. De modeller med store regioner kunne tillade nogen rotation uden at kompromittere præcisionen.
Tolkning: Hvis hoftens rotation kontrolleres kan DXA give pålidelig detaljeret topografisk information om BMD ændringerne omkring en RHA. Da rotationen påvirker præcisionen stærkest i analyser af små regioner, foreslår vi at man benytter en mindre detaljeret analyse model i studier hvor hoften stilling ikke er blevet kontrolleret.

Studie 6: Tidlig mikro bevægelse af den femorale ^{TM} komponent. 2 års radiostereometri (RSA) resultater.

Radiostereometri (RSA) kan opdage den tidlige mikro bevægelse I ustabile implantat designs, som har stor risiko for reoperationsrater over gennemsnittet. Resurfacing komponenten ASR blev trukket af markedet I 2010 grundet forhøjede reoperationsrater. Der eksisterer et par RSA studier på konkurrerende implantater som alle har vist tidlig stabil forankring. Den gennemsnitlige (sd) mikro bevægelse I løbet af de første 2 år I en gruppe af 19 ASR femorale komponenter var en lateral bevægelse på 0.107 (0.513) mm, distal migration på 0.055 (0.204) mm, og anterior bevægelse på 0.150 (0.413) mm. Bagudrotationen omkring x aksen var -0.08°(1.088), der var 0.165°(0.924) intern rotation og 0.238° (0.420) varus kip. Varus kippet fra baseline til 2 år var statistisk significant fra nul-bevægelse men som en gruppe sås der ingen signifikant bevægelse fra 1 år og fremad. Vi konkluderer at ASRs femorale component opnår tidlig stabil forankring , og at tidlig migration ikke er baggrunden for den større reoperationsrate.

6. Discussion of the results:

This thesis focuses on several aspects of resurfacing implants and the ASR (DePuy) resurfacing implant in particular.

Rehabilitation (Study 1):

ROM.

The first paper focuses on rehabilitation and in particular total range of motion, where we set out to demonstrate a 45° difference between concepts, but the maximum difference found was roughly 16° in favour of the large articulations, it was transient and statistically non significant and after 1 and 2 years (Table 6) the total ROM only differed by a few degrees. If the early difference in ROM is real (and n.s. due to sample size scaled to find 45 degrees difference) the later convergence of ROM makes head size an unlikely cause of the difference. The result is more likely biased by the restraints for the standard THAs, which may have limited the initial flexibility of the soft tissue or have held back the examiner in testing outer positions. Once the restrictions were lifted and time passed the patients became less aware of and used the hip more naturally causing the standard THA group to catch up with the larger articulations.

In hindsight 45 degrees difference may have been optimistic. The initial studies promoting RHA as beneficial indicated additional improvements reaching 20 degrees (Burroughs et al., 2005; la Rosa et al., 2007) and the De la Rosa paper may even be biased in the respect that the patients younger than ours and instructed to stretch from 6 weeks postoperatively,.

The total ROM from our RHAs match other early (within the first year) series (Hing et al., 2007; Dela Rosa et al., 2007; Hakkinen et al., 2010), but with variation similar to what we initially observe between our small and large articulation. Those studies are limited by the lack of a proper control group, but a RCTs by Howie et al did not observe any differences within the first year, and unlike the present study no difference was noted in abduction (Howie et al., 2005). The study is limited by a high failure rate in the RHA group resulting in very low numbers unlikely to detect a difference, but larger 2-3 year retrospective comparisons have, despite favouring either THA (Stulberg et al., 2009) or RHA.(Vail et al., 2006), only found a few degrees difference unlikely to be of clinical importance. In contrast to the theories of increased ROM with large heads and large head/neck ratios (Bader et al., 2004; Kluess et al., 2008), most clinical studies do not find a lasting difference between concepts, and our results supports a study of patients with RHA in one and THA in the other hip that suggests that all hips have a predetermined ROM that the hip reverts to following surgery (Le Duff et al., 2009).

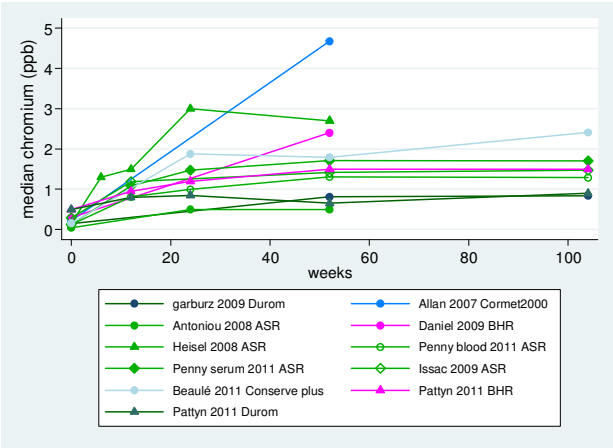
Table 6	n	ROM	ΔROM	HHS	UCLA	WOMAC	Steps	Eq-5d
RHA								
Bl	20	156 (31)		63 (10)	5.8 (2.2)	50 (21)	1.8 (0.9)	0.6 (0.3)
8 w	19	196 (40)	38(33)	87 (9)	6.7 (1.5)	9 (7)	2.0 (1.1)	0.8 (0.1)
6 m	17	237(52)	82 (50)	89 (13)	7.4 (1.5)	7 (8)	2.3 (0.9)	0.8 (0.3)
1 y	19	233 (36)	75 (42)	93 (9)	7.3 (1.6)	5 (5)	2.7 (1.1)	0.9 (0.3)
2 y	19	221 (35)	64 (40)	92 (9)	7.3 (1.8)	8 (13)	3.0(2.0)	0.8 (0.3)
THA								
Bl	19	167 (34)		57 (10)	6.2 (1.8)	53 (17)	2.3 (1.5)	0.6 (0.2)
8 w	19	202 (35)	35 (39)	88 (8)	6.8 (1.6)	14 (11)	2.5 (1.2)	0.8 (0.2)
6 m	18	230 (43)	54 (36)	90 (10)	8.0 (1.3)	11 (10)	3.0 (0.9)	0.8 (0.2)
1 y	19	231 (37)	64 (37)	90 (16)	7.4 (2.0)	12 (19)	3.0 (1.3)	0.8 (0.2)
2 y	19	226 (33)	59 (37)	91 (14)	7.2 (2.1)	13 (21)	3.2 (1.3)	0.9 (0.2)
P-value								
Bl								
8 w		0.91	0.91	0.37	0.94	0.11	0.51	0.37
6 m		0.17	0.17	0.35	0.28	0.29	0.56	0.76
1 y		0.61	0.61	0.76	0.97	0.10	0.70	0.64
2 y		0.90	0.90	0.33	0.58	0.48	0.72	0.82
Reported as mean (sd). t-tests adjusting for baseline values (ANOVA)								

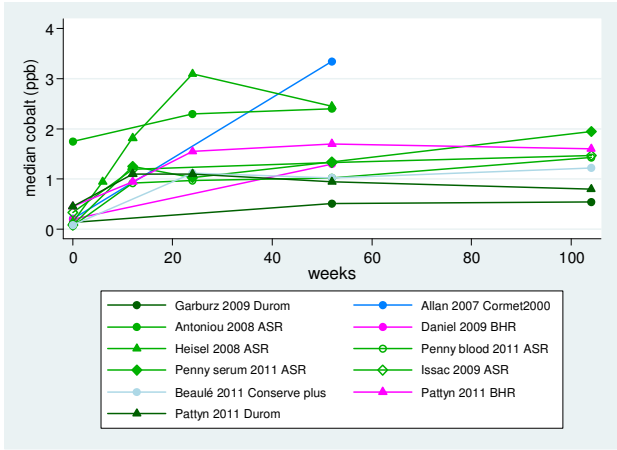
Secondary clinical outcomes.
The HHS, WOMAC, steps and EQ5d (Table 6) reflect the results of other early studies of both RHA, standard and large head THA (Vail et al., 2006; Stulberg et al., 2009; Zhou et al., 2009; Lavigne et al., 2009; Garbuz et al., 2009; vendittoli P, 2006; Daniel et al., 2009; Bohannon, 2007; van der et al., 2011; Garellick et al., 2011a), where little clinical difference was observed . Despite reporting low functional impairment on the WOMAC score and having minimal initial restrictions, the large articulation patients did not take advantage of the opportunity to engage in more activity in first months following surgery. UCLA activity did however come close to favouring the larger articulations at 2 years and other un-blinded activity studies have demonstrated better results for RHA (Vail et al., 2006; vendittoli P, 2006) than THA, but at present the only blinded studies compares RHA to large head THA (Lavigne et al., 2009; Garbuz et al., 2009) where no UCLA differences are noted between the large articulations. The apparent advantage of the large articulation may be caused by different information, where THA patients are recommended to refrain from certain activities (Berry, Bozic, 2010), due to both risk of dislocation and increased wear. Blinded UCLA studies including standard polyethylene lined THA are needed to provide a conclusive answer. The similarity of the clinical end points in the above mentioned studies do however suggest that the patients improve to the same degree regardless of the concept, and the advantage of the resurfacing concept lies in the proposed wear resistance and bone conservation. The relative low activity level in this randomized population indicates that the general ambition is modest, well within the allowance of a PE liner.

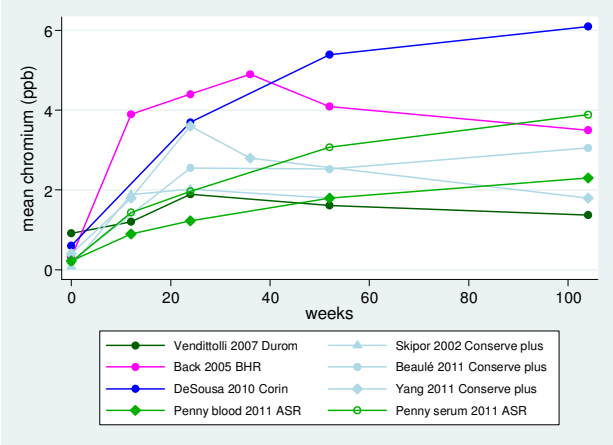
Metal ions and lymphocyte counts (Study 2):
Clinically there may not be a large difference between the RHA and standard THA, but the wear products set the concepts apart.

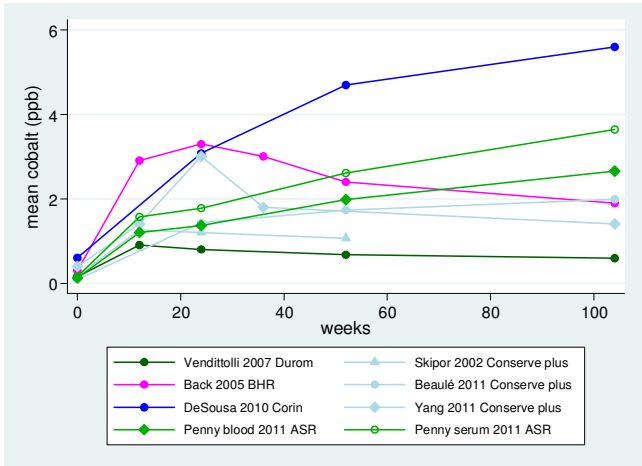
Clearance:

The simulation study by Dowson et Al. (Dowson et al., 2004b) suggested that a large head and a low clearance would promote a fluid film lubrication to diminish wear, but the results from the present study with a low clearance component produced very middle-of-the-road systemic metal ion concentrations. We've looked at metal ion levels from other prospective studies (Isaac et al., 2009; Heisel et al., 2008b; Antoniou et al., 2008; deSouza et al., 2010; Allan et al., 2007; Beaule et al., 2011; Daniel et al., 2009; Pattyn et al., 2011; Skipor et al., 2002; Yang et al., 2011) (Garbuz et al., 2009; Pattyn et al., 2011; Vendittoli et al., 2007), comparing them by their reporting method (mean/median) and blood component used (whole blood, serum, plasma) (Fig. 15).. The Durom, with its radial 68 µm reports consistently low ions, but we saw no evidence of a ranking by clerance size, suggesting that the fluid film theory is of limited importance for wear. The Dowson study compared a low clearance to a higher clearance component, but had filed off parts of the outer cup of the latter. The alterations may have destabilized the cup causing the higher wear pattern that does not reflect in vivo wear rates.









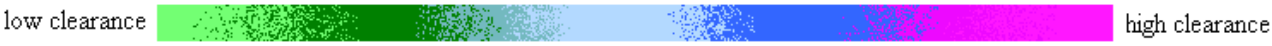


Fig. 15

Cup position.
During the last few years research points towards cup placement, as a more decisive factor for implant wear. Low or negative cup Anteversion may cause wear by impingement but an increased anteversion may also lead to a metal ion increase (Langton et al., 2008). The Anteversion is biased by being correlated to the inclination and more difficult to measure accurately than the inclination angle. Most studies focus on inclination (Hart et al., 2009a; Hart et al., 2008; Vendittoli et al., 2007; De Haan R. et al., 2008), where steeply inclined cups produce higher metal ion concentrations. A diminished design related arch of cover causes increased edge wear (De Haan R. et al., 2008), and with a relative smaller arch of cover in small ASR component, this design seems more sensitive to mal positioning in the small components (Langton et al., 2009; Langton et al., 2008).
The present study did not find a correlation between metal ions and cup anteversion (data not shown) and actually found higher ion concentrations in optimally placed cups (45 deg). The paradox is likely coincidental due to small numbers, where most of the small implants were placed around 45 deg inclination.

Head size.
Head however reproduce previous findings (De Haan R. et al., 2008; Vendittoli et al., 2007; Langton et al., 2009) where a decreasing head size correlated to increased metal ion concentrations, in accordance with both arch of cover and fluid film theory. Patients with the highest concentrations were characterized by smaller implants (one exception) and inclination angles above 45 degrees. The implant is no longer on the marked, but extra attention should be directed towards follow up of ASR patients with these characteristics (Medicines and Healthcare products Regulatory Agency, 2010).

Lymphocytes.
As for the possible adverse effects of raised metal ion levels, Adverse reaction to metal debris (ARMD) with pseudotumors and recurrent pain is the major focus point. Large studies or preferable registres are required for these kind of effects, but the present study also focused on the proposed adverse/depressive effect on the immune system, in particular the $CD8^+$ lymphocyte subset. Apart from the intermittent correlation, dismissed as mass significance, between metal ions and $CD4^+$ this study found nothing to support a link between a raised metal ion level and a depressive effect on the immune system (in terms of absolute numbers and not functionality). A single study of aseptically loose metal-on-polyethylene THA lends weak support to a damaging influence of metal ions on the $CD4^+$ subset (Savarino et al., 1999), but the find is isolated (Hart et al., 2006; Hart et al., 2009b; Granchi et al., 2003; Hailer et al., 2011).
This study failed to reproduce earlier findings of an association between raised Cr/Co ions and a decrease in absolute numbers of $CD8^+$ T cells (Hart et al., 2009b; Hart et al., 2006). Some of the studies without significant findings (Savarino et al., 1999; Granchi et al., 2003), may be criticised for having both small numbers and low ion levels in general. The present study is smaller scaled than those of Hart et al., but our randomized design with several follow up measurements should compensate for low numbers. In our case it was not just a question of lacking significance, but a lack of difference all together. A recent randomised Swedish study (without baseline) even found higher $CD8^+$ numbers in the MoM group, so at present the evidence points away from a systemic effect on the immune system. What may happen locally is beyond the scope of this thesis.

A drawback of our study design was leaving out the metal ion analysis in the large head THAs. This group had one failure, a female with a well placed cup size 56, with whole blood Cr of 4.6 and Co of 10.8 ppb and joint liquid concentrations of 37200 and 2040 ppb.

The discussion of the results from the **method study between blood sampled by steel needle or IV plastic cannula (study 3)** is part of the Metal ion chapter 3.12 under the Methodological Considerations section.

Prospective BMD (study 4):
The natural transferring of weight through the femoral neck preserves the calcar bone to a greater extent in RHA compared to THA. None of the RHA BMD studies have included the acetabulum(Hakkinen et al., 2011; Hayaishi et al., 2007; Smolders et al., 2010), but with revisions also affecting the cup, we found it important to investigate the issue.

The acetabulum.
The results showed that the resurfacing concept does not seem to affect the acetabular bone differently from a standard THA (Fig. 16). Our study was biased by the acetabular components not being from the same manufacturer and with uncoated THA cups opposed to hydroxyapatite (HA) coated RHA cups. But as studies of both different cup materials and coatings all have very similar BMD results to ours (Laursen et al., 2006; Baad-Hansen et al., 2011a), we do not believe that coating has played any role on the loss of bone in some of the Wilkinson zones. The different types of cup mainly loose BMD in W2, ie at the apex of the cup. It could possible reflect that the cups are inserted in press fit. We do not know the actual loading forces, but is seems reasonable to speculate that the maximum bone-implant stresses are near the egde of the cup. Loading would stimulate the bone relatively less away from the egdes leading to some stress shielding in W2, regardless of the femoral component. It is only speculation, as that kind of conclusions lies beyond the data in the present study.

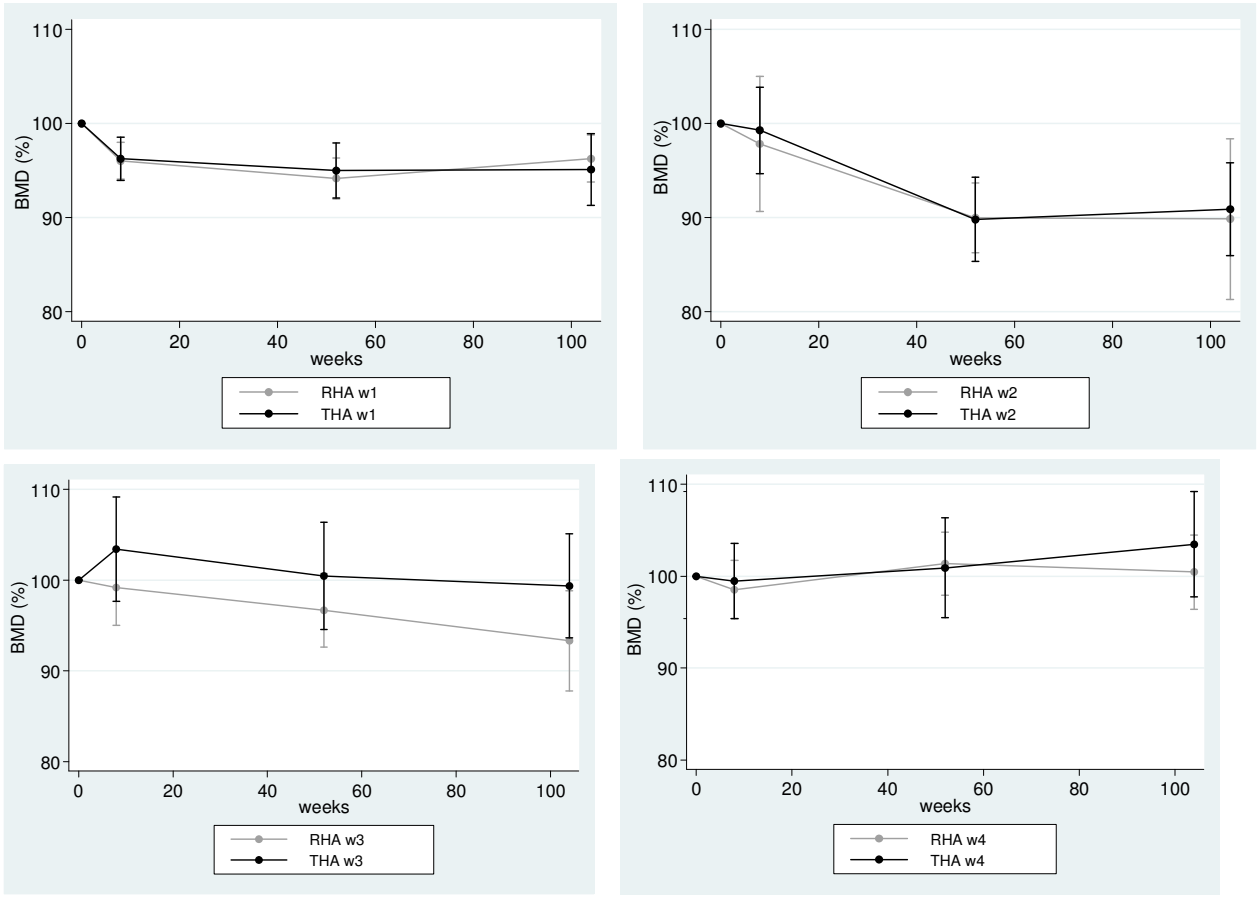


Fig. 16. The change in BMD in 4 Wilkinson/Laursen zones around the acetabular component.

Femoral neck BMD.
Increased primarily on the lateral side and primarily for men. With one exception using the Conserve plus (Smolders et al., 2010) all other resurfacing studies have used the BHR implant. A two year BHR study using the same neck region reported results similar to ours in all zones bar M2, where they found an increase, and in L2 where they did not find any change.(Kishida et al., 2004) In contrast, the remaining 1 and 2 year studies have found either none or smaller effect, with the increase predominantly on the medial side of the pin.(Hakkinen et al., 2011; Lian et al., 2008; Cooke et al., 2009; Smolders et al., 2010) A large prospective study of 423 BHR patients found no overall BMD change but measured only close to the implant rim and did not separate lateral from medial (Cordingley et al., 2010).
There are no comparable ASR studies available. Gupta *et al.* performed a finite element study of an ASR^{TM} implant (Gupta et al., 2006), where the simulation predicted a BMD loss in the proximal neck near the rim, unlike the results of this study. As the ASR no longer is available, we will not know if this pattern is specific for this implant, but more studies are needed on implants other than the BHR to establish whether there is a design or cementation related difference in loading stresses to the femoral neck.

The Gruen zones.
Finally our results from the proximal femur demonstrated that the ASR^{TM} RHA like other RHA maintained BMD laterally and increased it medially (Hakkinen et al., 2011; Hayaishi et al., 2007; Kishida et al., 2004; Smolders et al., 2010). The increase was especially pronounced in Gruen zone 7, where THA, our as well as other types of uncemented stems, decline following surgery (Smolders et al., 2010; Kishida et al., 2004; Sano et al., 2007; Tanzer et al., 2001; Wolf et al., 2010; Kim et al., 2007), most likely as a result of the more distal anchoring of the implant.

Gender.
The gender difference found in the femoral neck zones is debated (Cordingley et al., 2010; Hakkinen et al., 2011). By chance, despite randomization, the study bordered on having more women in the RHA group, but the gender had no effect in the Wilkinzon/Laursen and Gruen zones, so the skewness does not affect our conclusions there. As for the femoral neck, the skewed distribution only strengthens our conclusion, as the females did not increase in BMD, but the mean BMD still increased significantly despite the large proportion of females The study is limited by a small sample size where a larger study could have strengthened or perhaps dismissed the findings, and if supporting then allowed for more sub group analysis e.g. implant position.
In the short term RHA appears to preserve BMD compared to THA. Future studies are needed to establish whether the effect is permanent or if it has any clinical advantages.

The discussion of the results from the method study of the reproducibility of the femoral neck regions (study 5) is part of the DXA chapter 3.3 under the Methodological Considerations section.

RSA (study 6):
Migration.
The last paper deals with the initial stability if the ASR femoral component and is the first to show the early migration pattern of the withdrawn ASR RHA. The mean migration parameters of the ASR^{TM} implant are comparable to those of implants with better survival (Itayem et al., 2005; Gulati et al., 2009; Glyn-Jones et al., 2004) and this indicate that the high failure rates shown in registries in Denmark, the UK and Australia may not be explained by loosening problems of the femoral head

as a result of a unstable design. Despite resurfacing implant differences like cementation technique and inner surface design; how much left under the cap and how deep the interdigitation, the femoral component seems to be firmly attached to the bone thus achieving initial stability.
RSA has its limitations, and one cannot conclude that an initially stable implant is a guarantee for success. The conclusion is limited by only addressing the femoral component as the software was unable to distinguish head from cup.

No migration but an implant with above average failure rates.
Apart from the initial displaced cup, we did not have any failures in the RHA and standard THA groups, but generally the RHAs, as a group, revisions due to ARMD comprises less than 10% off all failures, the early failures are due to femoral neck fracture, and first after 6 years does the aseptic loosening take over as leading cause (Graves et al., 2011), so were unlikely to revise any patients with only two years of follow-up. National hip registres however clearly demonstrates a general problem with the ASR^{TM}(Graves et al., 2011; Johanson et al., 2010; Porter et al., 2012), but how the revision causes are distributed for the ASR implant is presently unknown. The present study identified a few patients with detectable migration following the first year. The most unstable, but not all, were characterized by small components and above average metal ion levels, and excess failure of the ASR implant is suspected to have some relation to metal debris, with higher edge load wear caused by reduced arch of cover in this particular implant (De Haan R. et al., 2008). They're presently not considered failures, but we will continue to follow our patients in search for an emerging pattern. Our early RSA results support that the femoral implant achieves initial stability, and that early femoral migration is not the mode of failure.

7. Conclusion:

Overall the conclusions of this study, with the limitations a small sample size imposes, is that in a osteoarthritis population selected primarily by age, the large head or the RHA concept does not provide any clinical advantage compared to a standard THA with regard to ROM, HHS, steps or quality of life. Nor did it – in the first two years – have any clear disadvantages. RSA found the femoral ASR^{TM} component stable. The metal wear products concentration encountered in this study was not raised compared to other brands of RHA and did not appear harmful to the immune system. Some RHA patients displayed a rise in metal ion concentrations following the running in period and a failure in the large head THA group had an Co ion concentration above 10 ppb, so long term concerns about possible adverse effects to ions and particles in MoM in general as well as the ASR^{TM} remain.
The one parameter in our study that would advocate the continued use of RHA was the clear preservation of the BMD demonstrated on the femoral side.

8. Future perspectives/studies:

BMD.

Little is known for certain about the clinical importance of preserved BMD, but hopes are that it will prolong the life of the primary implant, ease future revision technically and prolong the survival of the revision implant. Larger and longer studies in proportions that will encounter failures is needed to answer that question, and require only that DXA routinely is booked along with (or instead of) the conventional X-ray for standard follow up.
Our set-up with immobilising jigs to control the hip during DXA scans, required both custom made equipment, took time for the lab assistants and was slightly uncomfortable for the patients. Standard foot rests would enable DXA as routine follow up, and a study comparing the BMD variation between standard footrests and our rigid 15° inward or neutral rotation could provide an answer to whether a more comfortable restraining device is adequate for reproducibility in the small analyzing regions. If not, larger analyzing zones could be chosen.

Role of RSA and metal ion analysis?

Metal wear may very likely cause ARMD (Hart et al., 2009a; Kwon et al., 2010; Langton et al., 2010), but more RHAs are revised for loosening and not all have raised metal ion concentrations (Davda et al., 2011). Prolonged RSA follow up of both this and other studies could perhaps help answer whether failure by aseptic loosening is particle mediated. If the loosening came first it could easily lead to increased wear from micro collisions, with a pattern of rising ion concentrations and micro motion *coinciding* in time. A pattern with increased ion concentrations followed by *later* micro motion would support that the loosening was wear related. It would require closer follow up than the present 2 to 5 year gap to detect that relationship, and as most RSA studies are small with small risk of encountering failures, pooling of data from several studies would be advisable.

Training.

Following surgery the patients followed a home based hip exercise regime. Typical spontaneous physical activity in RHA patients does not restore hip function to normal levels following surgical detachment of the gluteus maximus (Hakkinen et al., 2010; Jensen et al., 2011), and wether specific hip training could maintain or increase the clinical endpoints could be a subject for further investigation. The option of larger heads in standard THA open up for blinded RCTs.

Candidates for RHA.

Despite being pain free, the relative low activity level in this randomized population indicates that the general ambition is modest, well within the allowance of a PE liner. The larger head sizes used in combination with newer harder PE liners will reduce risk of dislocation and allow a free range of motion, but whether they can cope with high activity, a risk of failure in older THAs (Kilgus et al., 1991), still remains to be seen. RHA may still have a role in patients that wish to continue high impact Where RHA in general has larger revision rates than THA the risk is less pronounced for younger men (Johanson et al., 2010), and the UK hip register find lower 5 year revision rates for the BHR implant than for the below 60 year olds with an uncemented THA (standard choice in DK). That could indicate that if optimising the design, getting past the learning curve and selecting the candidates carefully (mainly younger active men with large heads) the RHA concept could be superior to THA in a selected sub segment. RCTs with “high-impact” candidates would help answer the question, but considering the numbers needed and the limited candidates available, such a study would be most difficult to carry out in Denmark and would probably require multicenter studies.

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Clinical outcome after resurfacing, large head or standard total hip arthroplasty in patients with osteoarthrosis.

Two year results from a randomised clinical trial

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Abstract:

Background: Large size hip articulations may improve Range of motion and function compared to a 28 mm THA, and the low risk of dislocation allows the patients more activity postoperatively. Adversely the larger surgery for resurfacing hip arthroplasty (RHA) could impair rehabilitation.

Purpose: To investigate the effect head size and surgical procedure on postoperative rehabilitation in a randomized clinical trial (RCT).

Methods: We followed randomized groups of RHA, large head THAs and standard THAs at 2 m, 6 m, 1 and 2 years postoperatively, recording clinical rehabilitation parameters.

Results: The 2 year total ROM (sd) for RHA, standard THA and large head THA was 221.1° (35.4), 231.6° (36.0) and 225.0° (29.8) respectively (p=0.60). We observed a tendency for the large articulations to improve an additional 15° in total range of motion during the first 6 postoperative months but the advantage was non significant and transient. The study did not find any group difference in the HHS, UCLA activity score, step rate, quality of life or sick leave.

Interpretation: In this study head size did not influence range of motion and the lack of restriction allowed for large articulations did not improve the clinical and patient perceived outcomes and the surgical procedure of RHA did not impair the rehabilitation.

Registration: The project is registered on ClinicalTrails.gov under # NCT01113762

Introduction:

The traditional total hip arthroplasty (THA) with a cemented polyethylene (PE) cup or a cementless cup with a (PE) inlay against a metal head on a stemmed femoral component may have some disadvantages including postoperative restrictions due to the risk of dislocation and recommendations of a moderate activity level. Younger patients have a higher activity level (Bohannon, 2007), which leads to increased polyethylene wear (Schmalzried et al., 2000), a contributing factor to poor implant survival in this age group with a revision frequency of approximately 15-20% after 15 years (Overgaard et al., 2008,Karrholm et al., 2008).

Metal-on-Metal (MoM) articulations can limit the volumetric wear (Anissian et al., 1999) and has the advantage of a large head size either as large head THA or resurfacing hip arthroplasty (RHA). A large head may facilitate a better function by increasing the range of motion (ROM) (Davis et al., 2007,Bader et al., 2004) (la Rosa et al., 2007,Vail et al., 2006,Burroughs et al., 2005), particularly for the large head THA as apposed to the RHA(Bengs et al., 2008,Kluess et al., 2008). The reduced risk of dislocations (Beaule et al., 2002,Burroughs et al., 2005,Padgett et al., 2006), allows patients with large articulations an unrestricted movement regime postoperatively. It causes the patient less anxiety (Nissen et al., 2011) and permits more intensive training, which has lead to a faster recovery when using the anterolateral approach (Sharma et al., 2009,Kuijer et al., 2009). A RHA further offers the potential advantage of preserving bone for future revision surgery (McGrath et al., 2008) and a restoration of joint mechanics (Girard et al., 2006), but when using the postero-lateral approach it also requires a larger incision than THA (vendittoli P, 2006,Swank and Alkire, 2009). Mini vs. standard incisions have demonstrated a few immediate advantages but no lasting effect on function (Sharma et al., 2009), but the surgical detachment of the distal part of gluteus maximus to access the acetabulum is relatively larger, could affect muscular function, increase pain and blood loss, and could both delay the early as well as permanent function.

A fast and full recovery is not only important for the well-being of the patient, but the length of sick absence is highly associated to expulsion from the work force (The Danish ministry of Occupation, 2001) and as the majority of younger patients are still in employment, a speedy recovery becomes an important aspect of returning to the job..

The aim of this RCT was to compare Range of motion between RHA, large head or standard THA, for 2 years following surgery due to osteoarthrosis.
Our secondary endpoints were clinical function, measured by HHS, UCLA activity, WOMAC, EQ-5d and step rate during the first 2 years as well as the rate of return to work.

Materials and methods

Inclusion of the patients:
The sample size was based on range of motion. ROM measured by goniometer has some variation (Holm et al., 2000), and it was decided to look for a difference of 45 degrees to demonstrate a difference. Assuming a type I error of 5% and a type II error of 20%, and a minimal relevant difference, the sample size was calculated to 16 patients in each group.
Following ethical committee approval (project-ID: VF-20050133, Nov. 9th 2005, the ethical review board, Funen County, Denmark), oral and written patient information, all patients gave informed consent, and were included at two departments, where one (Hospital South, Naestved, Region Zealand, Denmark) randomized to standard THA and a large head THA whereas the other department (Odense University Hospital, Denmark) randomized to standard THA and RHA.
Sealed envelopes filled by nurse was used for the allocation. Odense had two surgeons and the envelopes were bloc randomized with half of each intervention for each (10+10), and in Naestved one surgeon operated all the patients. Upon inclusion the patient picked out an envelope and the intervention was known to the patient and staff before surgery which was necessary due to different instruments for each patients group.
Both departments followed identical inclusion/exclusion criteria, The inclusion criteria were; primary osteoarthritis, secondary osteoarthritis due to mild dysplasia and an age from 40 to 65 years, exclusion criteria: Dysplasia with CE angle < 25 degrees on the AP projection, severe femoral head deformation, reduced femoral neck length, leg length discrepancy more than 1 cm, need for restoration of offset, deformation after fractures or earlier osteotomies, a previous hip arthroplasty, inflammatory arthritis, endocrine disease with bone metabolic manifestations, renal disease, malignant disease, neuro-muscular or vascular diseases of the affected leg, osteoporosis (BMD <2.5 Sd), use of opioid pain killers due to other diseases, high dose corticosteroids, obese with BMI > 35, pregnant or planning to be, or presented problems that would prevent completing our follow-up program.
All authors participated in finding the patients and JOP finally included the patients which were operated from April 2007 to December 2009.

Prosthetic components.
The RHA group received an Articular Surface Replacement (ASR®, DePuy, Leeds, UK) made from a high-carbon cobalt-chromium-molybdenum alloy. Resurfacing median head size: 51 (47 to 57). The study only included head sized from 47 mm and up due to increased risk for fractures identified at time of study start. The large head THA group received an M2aMagnum/ReCap articulation made from cast, high carbon Cobalt-Chromium. Median head size 50 (range 44-56) in combination with a cementless forged titanium Bimetric stem.
The standard THAs received a titanium Mallory-Head acetabular shell with an arcom Ringlock polyethylene liner, and a 28 mm Biolox delta modular ceramic head, mounted on a titanium Bimetric stem (all Biomet, Brigde End, UK).
The standard metal-on-PE group received a standard CrCo head and a titanium *Trilogy CH* cup, in combination with a VerSys Fiber titanium metal taper stem. The first 9 patients had a Trilogy UHMWPE liner, and the last 6 a Longivity liner (Zimmer, Warsaw, IN, US).

Surgery:
The anesthetic procedure was spinal analgesia when possible. All patients were administered identical antibiotic, bleeding and antithrombotic prophylaxis.
The RHA was implanted according to the manufacture's instructions via a postero-lateral approach. The gluteus maximus muscle was divided, and the insertion was detached along with the external rotators. The cup was placed cementless in press-fit 1 mm under reamed and the femoral component was cemented with SmartSet™ GHV Bone Cement (DePuy, Leeds, UK). The other cups were inserted reamed size to size and the femoral stem using standard instruments all via the identical posterolateral approach but with smaller incision and without the gluteal muscle release.
We aimed for a cup inclination of 45° with a 20° anteversion.
Additional surgery time was added for RHA and large head THA, where tantalum markers was inserted around the acetabulum and the proximal femur for a Radiostereomety-study.

Rehabilitation program:
Postoperative rehabilitation included full weight-bearing in all patients. Apart from free range of motion (ROM) in the RHA and large head THA groups, the hospital physiotherapists gave identical instructions in a home based training program to all patients. If the patients asked for supervised training at the 8 week check-up we referred them to a council based training facility (similar hip program as they already followed just supervised). Some patients may have been referred via their GP. Patients were informed to expect an average sick leave of 2-3 months but told that they could start when ready.

Outcome instruments:
During hospitalization we recorded the surgery time (incision to close), blood loss, length of incision, intraoperative complications, the pre- and 2.nd day postoperative hemoglobin levels and the length of stay.
Clinical function was evaluated in the out patient clinic preoperatively, at 8 weeks, 6 months 1 and 2 years. ROM was evaluated by a single trainee orthopedic surgeon (JOP) aiming to control the pelvic tilt. A clear 18 cm plastic goniometer was used. Extension was tested in the prone position. Flexion, abduction, adduction, internal and external rotation in the supine position, the latter two with the hip and knee flexed in 90°. Function otherwise scored by the Harris hip score (HHS) (Harris, 1969) and the UCLA activity score (Zahiri et al., 1998), going from 1-10 where 10 is the best. As activity levels can be difficult to asses using a questionnaire (Stratford and Kennedy, 2004,Kennedy et al., 2006,Zahiri et al., 1998), we supplemented with walking activity measured with the Yamax (YX200) pedometer (Schneider et al., 2003) for a week prior to each follow-up visit. Self reported quality of life was rated using the EQ-5d (Wittrup-Jensen et al., 2009) with values from minus to plus one, where plus one is the optimum health state and the self reported function was rated by the WOMAC questionnaire (Bellamy et al., 1988), using a VAS scale, with values from 0-100 where 0 is the best result.
Patients available for the work force were asked their occupations and the date for returning to their job. The job classifications grouped them in 7 socio-economical groups (Spieker F and Plougsing J, 1997), but due to low numbers we analyzed "desk jobs" (SOCIO 11+ 131-133) and "manual labor" (SOCIO 134, 135 and 2) group based on the physical demands of the job (Fig.1).

Statistical analysis:
As a result of randomizing at two departments we had two standard THA groups. Despite different bearing materials they were merged to one larger standard THA group as we regarded them equal with respect to potential in the rehabilitation period.

The clinical data are presented as mean (sd), and were compared with ANCOVA analysis adjusted for the baseline measurement. Fisher's exact test was used to evaluate differences between the distributions of job classes.
A stratified log -rank test, adjusted for centre effect was used to compare the length of the sick leave. STATA 11.2 (StataCorp LP, College Station, Texas) software was used for all analyses, a Biostatistician supervised the data handling and a p-value below 0.05 was considered statistical significant.

Results:

Fig 2.depicts a Consort flow chart of the inclusion and follow-up, and there is a discrepancy between the number of assessments in each department as one of the departments screened the GP referrals prior to assignment to the project. If the referral mentioned one of the exclusion criteria they were never assessed.
The demographic data are presented in Table 1, where a borderline significant difference was noted for age.
Data related to surgery and blood loss are presented in Table 2. Despite the larger incision the RHA group did not bleed more, and we observed the lowest haemoglobin decrease in this group.
The RHA patients were on average hospitalized 3.6 (1.8) days, the large head THA 4.2 (1.5) days and the standard THA 3.7 (1.2), which was not statistically different ($p = 0.82$).
With regards to complication, the RHA group had one cup displacement the day after surgery. The patient had the cup repositioned and he was excluded from further follow up. One RHA patient was prescribed per oral antibiotics by the GP, suspecting infection around the skin clips. We were not involved and infection was not confirmed.
A large head THA patient suffered a pulmonary embolus following a deep vein thrombosis. She recovered but with a slightly reduced lung capacity. Another large head THA experienced pain and raised metal ions levels following the first year. She was revised and subsequently excluded. The THA group saw 3 dislocations, all occurring within the first 2 postoperative weeks. All were treated with closed reduction, none have had recurrences and none were excluded.

The ROM changes over time only differed statistically in the adduction movements at 8 weeks and 6 months, where the RHA and large head THA improved a little more than the standard THA ($p<0.01$ and $= 0.03$) (Table 3). After 6 months the large articulations appeared to improve the total ROM (by 16°) compared to standard THA but the difference was not statistically significant. During the following 1½ years RHA total ROM and, the standard THA continued to improve slightly and the large head THA remained status quo, resulting in all 2 year total ROM being within 10° of each other.

For all groups the secondary outcomes improved from baseline up to 6 months following surgery (Table 4). The Harris hip score reached steady state at 6 months for all articulations. UCLA activity peaked for RHA and 28 mm THA, but continued upwards for large head THA. The 28 mm THA group had a relative large baseline step rate, and reached steady state at months, where the large articulations improved their step rate up to 2 years. Despite slightly different patterns over time the unrestricted large articulations did not demonstrate statistical improvements on the Harris hip score or walked longer distances than the 28 mm THA, The UCLA activity score indicated larger improvement in/more strenuous activity for the large articulations by 0.7 to 1.3 points compared to standard THA but with a p value of 0.08 the difference was not statistically significant.
The patients reported outcomes also improved drastically following surgery. The WOMAC scores reported less than half of the original discomfort as early as 3 weeks post surgery, and only around a

fifth after 8 weeks. After that, the improvement slowed down and very little change in patient perceived function was seen following 6 months.
There was no group difference with regards to the quality of life.

The mean (sd) sick leave period for RHA, standard THA and large head THA respectively was 86.6 (54.4), 101.4 (79.9) and 140.7 (91.7) days. Despite a seemingly large difference favouring the RHA patients, we could not validate this statistically ($p = 0.82$)

Discussion:

The present study investigated in a RCT the outcome after insertion of a resurfacing, large head or standard total hip arthroplasty in patients with osteoarthrosis. The study showed no clinical relevant difference with regard to ROM, HHS, WOMAC, UCLA activity, EQ-5d, steps or sick leave.
The strength of this study is the randomized design, with standardized follow up and clearly defined in- and exclusion criteria.
The major limitation is the small numbers. We did not demonstrate the sought after 45 degree difference and more patients are needed in search of smaller differences. The study was sized to evaluate ROM and we are aware that more analyses are carried out. With more analyses comes a risk of false statistical significance and our few statistical significant findings must be interpreted cautiously. An example may be the significant differences in some sub movements of the total ROM both at baseline movements and at further follow-ups. Despite statististical significance the differences are small and of doubtful clinical importance. The data however adds information to the field so we choose to include it.
The unblinded design is another drawback that was chosen from fear of dislocations, of which we saw 3, in the standard THA group. It is a clear limitation of the study, not only for UCLA activity and ROM but also for WOMAC, where the fear for dislocations may have influenced the standard THA group negatively. The development in stronger polyethylene and subsequent use of larger standard heads should minimise the risk of dislocations and could allow for blinding in future studies. A final limitation of the study is the gluteal muscle detachment that was performed on all RHA to standardize the study. Experienced surgeons can avoid it in many cases so the data in the present study reflects a RHA group that, as a whole, have undergone more extensive surgery than the average RHA group. We were unable to demonstrate any negative effect of the larger muscle injury from RHA, but cannot know whether muscle sparing surgery would have improved the RHA outcomes.
Range of motion was our primary outcome and this study failed to demonstrate an advantage of the unrestricted regime allowed for the large articulations. During the first 6 months we observed a small (ns) difference favouring the large articulations, but the larger head size may not be the cause. The difference could partly be explained by improvement in adduction and improvement in internal rotation, i.e. the movements the standard THA group was prohibited from during the first 8 weeks. The pattern with very similar 2 year ROM changes indicates that the restraints could have limited the initial flexibility of the soft tissue. Once the restrictions were lifted and time passed the patients became less aware of and used the hip more naturally causing the standard THA group to catch up with the larger articulations.
Only few comparative studies of early ROM exists, and our early (within the first year) RHA results regarding ROM match those reported earlier (Hing et al., 2007,Dela Rosa et al., 2007,Hakkinen et al., 2010), but Howie et al randomized to RHA and standard THA and did not observe any differences within the first year. Unlike the present study no difference was noted in abduction (Howie et al., 2005), but the study is limited by a high failure rate in the RHA group resulting in very low numbers unlikely to detect a difference. Larger 2-3 year retrospective comparisons

between RHA and standard THA have favoured both THA.(Stulberg et al., 2009) and RHA.(Vail et al., 2006), but only with a few degrees and unlikely to be of clinical importance.
The non significant tendency to early ROM improvement for large articulations in the present study may be coincidental, or it may be real and the study under scaled to demonstrate statistical significance. If the difference is real, it seems to be of a more modest magnitude than we set out to find and also seems to be transient, as both the present as well as other studies find total ROM within a few degrees 1-2 years postoperatively. Head size does not seem to be the decisive ROM factor suggested by simulation studies (Kluess et al., 2008,Bengs et al., 2008,Davis et al., 2007) and our study support the suggestion that all hips, in time, return to a predestined ROM (Le Duff et al., 2009).

Despite a larger incision/surgical procedure for RHA our secondary outcome measures generally failed to demonstrate a clinical or patient perceived difference between the interventions, and apart from an overall unexplained lower step rate in all groups, our results reflect other early studies of both RHA, standard and large head THA (Vail et al., 2006,Stulberg et al., 2009,Zhou et al., 2009,Lavigne et al., 2009,Garbuz et al., 2009,vendittoli P, 2006,Daniel et al., 2009,Bohannon, 2007,van der et al., 2011,Garellick et al., 2011), where little clinical difference was observed .
Despite reporting low functional impairment on the WOMAC score and having minimal initial restrictions, the large articulation patients did not take advantage of the opportunity to engage in more activity in first months following surgery. UCLA activity came close to favouring the larger articulations by, but the improvement compared to standard THA, was observed at 2 years and not earlier on as might be expected. UCLA activity outcome can be biased by both patient selection and the surgeon asking the THA patients to refrain from certain activities due to both risk of dislocation and increased wear. Our randomized design should disperse with the selection bias, but the problem with patient information persists. A few un-blinded activity studies have demonstrated better results for RHA (Vail et al., 2006,vendittoli P, 2006), but at present the only blinded studies compare RHA to large head THA (Lavigne et al., 2009,Garbuz et al., 2009). In these, no UCLA differences are noted between the large articulations, which the results from the present study also support, but blinded UCLA studies including standard polyethylene lined THA are needed to provide a conclusive answer.
Our patients take longer mean sick leaves than those reported in the UK (Mobasheri et al., 2006), but the outcome is difficult to compare as those patients are slightly younger and our groups include some on sick leave prior to surgery. In contrast to a larger randomised study (vendittoli P, 2006), the present study failed to demonstrate a faster return to work for the large articulations and in opposition to our hypothesis of a quicker rehabilitation for restriction free implants, the large head THA demonstrated the longest sick leave (ns) despite reporting the lowest WOMAC scores.
Occupational medicine is a complex area with many confounders and one possible explanation for this conflicting result could be that the large head THA group tended to be a little older and more likely to have a manual job than other groups, so despite reporting low disability, the demands of the job may exceed the WOMAC tasks, and cause them to postpone the return.
The design of the study, with two centres in different parts of the country have introduced bias via an inhomogeneous distribution of age, level of education and job types, that the present study is too small to adjust for. Furthermore, the faster return to work was assumed to be based on a quicker rehabilitation and as the groups did not demonstrate a different rehabilitation it would be unreasonable to expect an effect.
The ASR™ RHA used in this study has been withdrawn from the marked due to above average failure rates. Our radiostereometry study (data not published yet) have found the femoral component stable, and apart from the initial cup dislocation, the RHA patients are all functioning

well with clinical outcome measures similar to other brands of RHA so it seems reasonable to draw conclusions on the RHA as a concept and not a specific type of RHA. Overall we found only little objective difference between the RHA, standard THA and large head THA during the first postoperative years and were unable to demonstrate any clear benefit from lack of postoperative restrictions. The very similar end stage functional level just above UCLA 7, both for both this and other RHA studies could indicate that the average patient just reach their desired level of activity at 6 months and have no interest in participating in more strenuous activities than bicycling despite having an implant that is supposed to cope with the strain. This calls for careful patient selection when choosing RHA or large head THA candidates as more short term complications are associated with this type of implant (Porter et al., 2010).

The present study cannot advocate for the use of RHA or large head MoM THA with regard to clinical outcome. These results in addition to results from national registries showing inferior survival of RHA (Graves et al., 2011,Johanson et al., 2010,Porter et al., 2012) and large-head MoM(Porter et al., 2012) question that any patient group can favor for these implants with regard to both clinical outcome and implant survival. More studies are needed.

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Contributions of the authors:

Designed the study: SO, OO, KB, JØP
Obtained and analyzed the data: JØP
Wrote the initial draft: JØP. SO, OO, JEV
Ensured the accuracy of the data and analysis: JØP (and Lars Korsholm)

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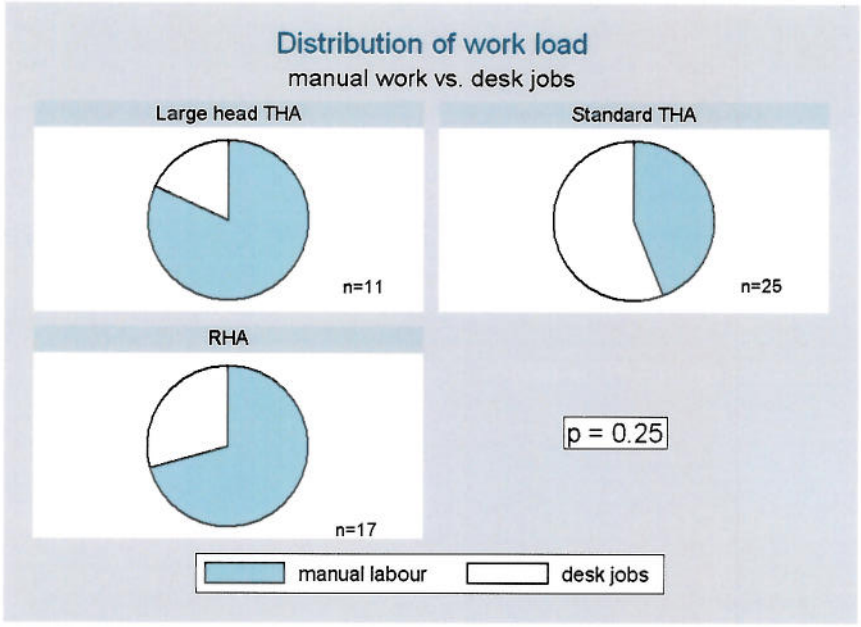
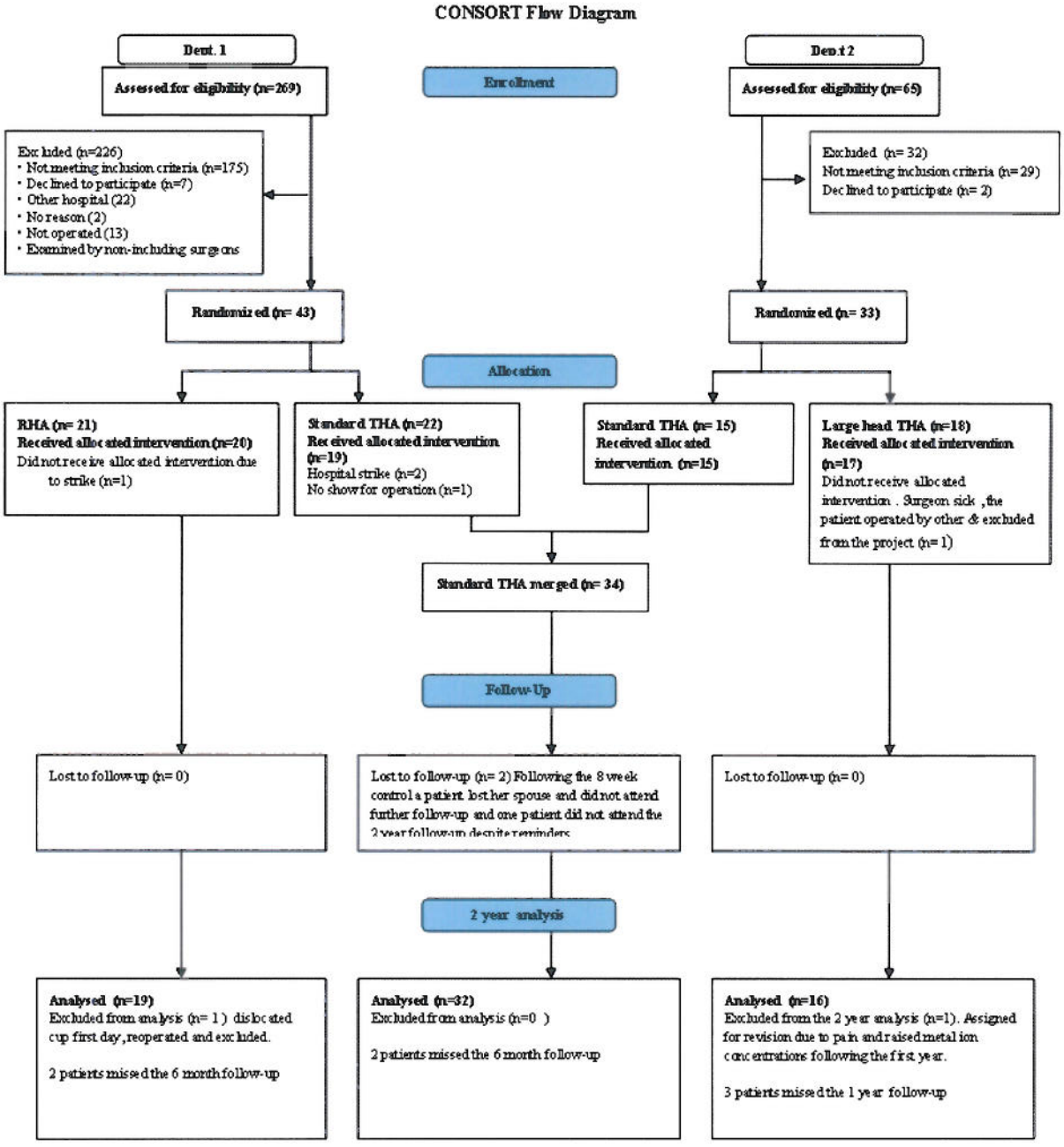

Distribution of work load
manual work vs. desk jobs
Large head THA
n=11
Standard THA
n=25
RHA
n=17
p = 0.25
manual labour
desk jobs

Fig 1.


CONSORT Flow Diagram
Dent. 1
Assessed for eligibility (n=269)
Enrollment
Dent 2
Assessed for eligibility (n=65)
Excluded (n=226)
• Not meeting inclusion criteria (n=175)
• Declined to participate (n=7)
• Other hospital (22)
• No reason (2)
• Not operated (13)
• Examined by non-including surgeons
Excluded (n= 32)
Not meeting inclusion criteria (n=29)
Declined to participate (n= 2)
Randomized (n= 43)
Randomized (n= 33)
Allocation
RHA (n= 21)
Received allocated intervention (n=20)
Did not receive allocated intervention due to strike (n=1)
Standard THA (n=22)
Received allocated intervention (n=19)
Hospital strike (n=2)
No show for operation (n=1)
Standard THA (n= 15)
Received allocated intervention. (n=15)
Large head THA (n=18)
Received allocated intervention (n=17)
Did not receive allocated intervention . Surgeon sick , the patient operated by other & excluded from the project (n= 1)
Standard THA merged (n= 34)
Follow-Up
Lost to follow-up (n= 0)
Lost to follow-up (n= 2) Following the 8 week control a patient lost her spouse and did not attend further follow-up and one patient did not attend the 2 year follow-up despite reminders
Lost to follow-up (n= 0)
2 year analysis
Analysed (n=19)
Excluded from analysis (n= 1) dislocated cup first day, reoperated and excluded.
2 patients missed the 6 month follow-up
Analysed (n=32)
Excluded from analysis (n=0)
2 patients missed the 6 month follow-up
Analysed (n=16)
Excluded from the 2 year analysis (n=1). Assigned for revision due to pain and raised metal ion concentrations following the first year.
3 patients missed the 1 year follow-up

501

502 Fig 2. Consort flow diagram

503

504

Table 1	RHA	Standard THA	Large head THA	p value
n	20	34	17	
Age (years)	57.0 (53.5- 61.1)	56.4 (52.1- 62.0)	62.6 (54.1- 64.0)	0.07
Females (%)	40	29	47	0.14
Charnley class I (%)	80	69	59	0.69
BMI (kg/m^2)	27.9 (24.0- 30.8)	27.3 (25.4- 29.2)	28.1 (25.7- 31.5)	0.94

505 Demographic data. Age and BMD presented as median (range)

506

507

Table 2	RHA	Standard THA	Large head THA	p value
n	20	34	17	
Surgery time (min)	113.3 (15.4)*	65.6 (10.8)	83.3 (11.6)*	<0.0001
Incision length (cm)	23.5 (2.8)	14.2 (2.8)	15.0 (2.6)	<0.0001
Blood loss (mL)	625.0 (467.2)	515.4 (215.5)	752.9 (315.3)	0.09
Haemoglobin decrease (mmol/L)	1.7 (0.7)	1.8 (0.5)	2.2 (0.6)	0.46
* 10 min surgery time is due to insertion of tantalum markers				

508 Surgery related outcomes. Presented as man (sd).

509

Table 3		n	Total ROM	delta ROM	Eksten-sion	Flexion	Abduction	Adduction	Internal rotaion	External rotation
RHA										
	Baseline	20	155.9 (30.6)		-0.5 (3.2)	90.3 (11.6)	26.0 (11.7)	14.0 (7.0)	4.7 (9.3)	21.5 (8.1)
	8 weeks	19	195.5 (39.7)	37.7 (32.6)	2.4 (5.1)	95.0 (11.3)	28.9 (10.1)	23.9 (7.0)	21.1 (9.7)	24.2 (8.0)
	6 months	17	236.5 (51.5)	81.6 (49.7)	4.7 (9.6)	100.9 (11.6)	36.5 (12.6)	29.7 (8.0)	32.6 (16.3)	32.1 (10.2)
	1 year	19	232.9 (36.1)	75.1 (41.8)	4.5 (5.0)	105.5 (9.0)	36.1 (8.6)	25.5 (7.1)	27.6 (12.2)	33.7 (6.8)
	2 years	19	221.1 (35.4)	64.0 (40.0)	6.7 (5.7)	103.3 (12.4)	31.4 (5.4)	24.2 (6.0)	25.3 (10.4)	30.3 (8.5)
Stand ard										
	Baseline	34	160.6 (43.9)		1.2 (3.7)	91.0 (12.5)	24.7 (11.1)	14.0 (8.9)	6.2 (14.1)	23.5 (11.5)
		34								
	8 weeks		193.5 (35.5)	32.9 (38.3)	4.4 (5.5)	93.1 (12.2)	31.3 (8.2)	18.1 (8.3)	20.1 (8.8)	26.5 (11.2)

	6 months	31	227.3 (35.5)	64.3 (40.5)	4.8 (6.5)	103.7 (10.4)	34.3 (8.2)	22.8 (9.1)	26.7 (10.9)	35.0 (10.8)
	1 year	33	228.2 (34.4)	66.9 (39.0)	4.4 (6.0)	105.6 (10.5)	34.7 (8.8)	22.1 (5.5)	25.3 (9.8)	37.2 (8.8)
	2 years	32	231.6 (36.0)	69.5 (37.8)	5.3 (5.7)	106.6 (14.2)	35.6 (9.8)	24.2 (7.3)	24.8 (9.4)	35.0 (7.9)
Large head										
	Baseline	17	144.6 (29.2)		1.5 (3.9)	85.0 (12.6)	21.5 (8.2)	13.2 (6.4)	1.6 (10.2)	21.8 (8.6)
	8 weeks	17	195.6 (25.4)	51.0 (33.7)	0.9 (5.1)	95.9 (10.2)	30.6 (6.1)	22.1 (4.4)	20.6 (9.3)	25.6 (9.2)
	6 months	17	224.7 (35.1)	80.1 (31.1)	3.5 (4.2)	103.7 (10.4)	34.4 (7.9)	24.7 (8.0)	26.8 (9.7)	33.2 (8.1)
	1 year	14	215.7 (36.0)	71.6 (38.8)	3.6 (4.6)	100.7 (10.4)	32.5 (7.8)	23.2 (7.2)	23.9 (11.5)	31.8 (8.5)
	2 years	16	225.0 (29.8)	80.4 (35.5)	2.5 (4.8)	103.1 (9.6)	36.3 (7.9)	24.1 (5.2)	24.4 (10.0)	34.7 (9.2)
P values										
	Baseline		0.16		<0.05	0.04	<0.05	0.27	0.96	0.62
	8 weeks		0.20	0.20	0.18	0.09	0.70	<0.01	0.48	0.60
	6 months		0.32	0.32	0.59	0.97	0.65	0.03	0.17	0.71
	1 year		0.77	0.77	0.94	0.89	0.27	0.11	0.80	0.19
	2 years		0.60	0.60	0.22	0.74	0.38	0.99	0.77	0.37

510 Primary outcome Range of Motion (TotalROM), including details of the movements adding up to the total. .

511

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513

514

Table 4	**n**	**Harris Hip Score (HHS)**	**UCLA activity**	**Steps (mill/y)**	**WOMAC**	**Eq-5d**
RHA						
Baseline	20	63.0 (10.1)	5.8 (2.2)	1.8 (0.9)	50 (21)	0.6 (0.3)
8 weeks	19	87 (9)	6.7 (1.5)	2.0 (1.1)	9 (7)	0.8 (0.1)
6 months	17	89 (13)	7.4 (1.5)	2.3 (0.9)	7 (8)	0.8 (0.3)
1 year	19	93.1 (9.1)	7.3 (1.6)	2.7 (1.1)	5 (4)	0.9 (0.3)
2 years	19	92.5 (9.6)	7.3 (1.8)	3.0(2.0)	8 (13)	0.8 (0.3)
Standart THA						
Baseline	34	55.8 (8.7)	6.3 (1.8)	2.3 (1.5)	55 (16)	0.6 (0.2)
8 weeks	34	86.5 (9.5)	6.4 (1.5)	2.3 (1.1)	12 (9)	0.8 (0.2)
6 months	31	90.0 (9.3)	7.5 (1.3)	2.7 (0.9)	10 (9)	0.8 (0.2)
1 year	33	90.9 (13.5)	7.3 (1.9)	2.8 (1.2)	9 (15)	0.9 (0.2)
2 years	32	91.4 (13.5)	7.0 (2.0)	2.8 (1.4)	10 (18)	0.9 (0.2)

Large head THA						
Baseline	17	57.8 (8.4)	5.8 (1.6)	1.6 (0.6)	49 (20)	0.6 (0.2)
8 weeks	17	84.4 (8.5)	5.9 (1.2)	1.8 (0.6)	9 (9)	0.8 (0.1)
6 months	17	93.1 (5.7)	6.9 (1.8)	2.0 (0.8)	4 (3)	0.9 (0.1)
1 year	14	92.6 (11.1)	7.6 (1.5)	2.2 (1.2)	5 (6)	0.9 (0.1)
2 years	16	94.9 (5.8)	7.8 (1.7)	2.5 (1.2)	5 (6)	1.0 (0.1)
P values						
Baseline		0.15	0.80	0.56	0.76	0.90
8 weeks		0.74	0.83	0.64	0.27	0.58
6 months		0.53	0.21	0.77	0.07	0.81
1 year		0.96	0.55	0.84	0.16	0.48
2 years		0.86	0.08	0.45	0.76	0.44

Clinical rehabilitation parameters.presented as mean (sd)

Title:

Metal ion levels and Lymphocyte counts. Randomised 2 year results for the ASR™ hip resurfacing prosthesis vs. a standard THA.

Running title: Two year randomized metal ion levels and lymphocyte counts

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Abstract:
Background and purpose: Wear particles from metal on metal (MoM) arthroplasties are under suspicion for adverse effects locally in the joint as well as systemically. Design related features as well as implant size and position may affect the wear. The DePuy ASR™ Hip Resurfacing System (RHA) has above average failure rates. The aim of the study was to compare lymphocyte counts in patients with RHA to THA and to correlate Cr and Co ion concentrations to component size and position in the resurfacing group.
Method: In a randomized controlled trail (RCT) 19 total hip arthroplasty (THA) and 19 resurfacing hip arthroplasty (RHA) patients were followed for 2 years. Lymphocyte subsets, Cr and Co ion concentrations and clinical rehabilitation outcomes were measured at each follow-up point.
Results: The absolute lymphocyte counts or the $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD16^+CD56^+$ or the $CD19^+$ subgroups did not differ between RHA and THA patients. The median RHA Cr and Co concentrations were below 2 ppb, with higher concentrations characterized by small components above 45 deg inclination.
Intepretation: The ASR™ RHA had Co and Cr ion concentration comparable to other types of RHA. No difference in lymphocyte subgroups were found between RHA and THA and these randomized data do not support a previously reported association between high metal ions and low $CD3^+CD8^+$ counts.

Level of Evidence: Unblinded randomized study level 1b

Introduction:
The increasing use of resurfacing metal-on-metal articulations (MoM) in young persons has raised concerns about the possible adverse effects of the cobalt and chromium (Co and Co) ions released to the body. A strong link between high wear rates, raised systemic ion levels and painful hips or pseudotumors, (Kwon et al., 2009,Hart et al., 2009a,Pandit et al., 2008) puts wear products under suspicion for inducing a local toxic or immunological reaction, but elevated blood ion concentrations has also been associated with systemic reduced in-vivo $CD3^+$ and $CD8^+$ T cell count (Hart et al., 2006,Hart et al., 2009b). These studies however, are biased by lacking a baseline value, and at present, there exists no clinical evidence of a detrimental effect of the proposed reduced lymphocyte count.
The DePuy ASR™ Hip Resurfacing System was recalled from the market in 2010 due to higher than average failure rates (Porter et al., 2010) . Revisions are most pronounced in women and by the use of small implants. It has been suggested that the ASR™ has increased risk of edge load wear in the small implants, particularly if the components are sub-optimally placed which might give rise to accelerated particle production and elevated ion concentrations (Langton et al., 2009,Langton et al., 2010,De Haan R. et al., 2008)

The aim of the present study was to compare the Co/Cr ion concentration and the absolute levels of lymphocytes and the subgroups $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cells, the $CD16^+CD56^+$ NK-cells and the $CD19^+$ B-cells in patients implanted with the ASR™ RHA to a ceramic on polyethylene THA and to correlate the absolute levels of these lymphocyte subgroups to the metal ion concentrations.

Secondly the association between metal ion levels and implant size and cup position was investigated.

PATIENTS AND METHODS:

Following approval by the Ethical Review Board, Funen County, Denmark (VF-20050133) , written and verbal informed consent, the patients were randomized, using sealed envelopes filled by nurse in blocs of 10, to RHA (n=19) or standard ceramic-on-polythylene THA (n=19). Upon inclusion the patient picked out an envelope and the intervention was known to the patient before surgery.
The inclusion criteria were; primary osteoarthritis or secondary osteoarthritis due to mild dysplasia and an age from 40 to 65 years. The flow-chart in Figure 1 depicts the inclusion/exclusion process. Sixty five percent of the patients assessed for participation in this study fell for the exclusion criteria. The relatively large number reflects exclusion of contra lateral hip implants as metal ion analysis was undertaken and exclusion of moderate and severe hip dysplasia as they were non eligible for RHA at our institution. The present study therefore investigates a selected sub segment of the osteoarthritis patients. The patients were operated from April 2007 to March 2009 at Odense University hospital and the demographic data are presented in table 1.
The RHA group received an Articular Surface Replacement (ASR™, DePuy, Leeds, UK) made from a high-carbon cobalt-chromium-molybdenum alloy. The 28 mm ceramic-on-Polethylen THAs were implanted with a titanium Mallory-Head acetabular shell, a 28 mm Biolox delta modular ceramic head, an Arcom Ringlock Polyethylene Liner and a titanium Bimetric stem (Biomet, Bridge End, UK).
All ASR patients underwent hip resurfacing through a standard posterior approach by two consultant surgeons (OO, SO). The distal gluteal insertion was detached along with the external rotators. The cup was placed cement less in press-fit and the femoral component was cemented with SmartSet™ GHV Bone Cement (DePuy, Leeds, UK).
The THAs were inserted cementless via a postero-lateral approach of shorter incision length without the distal muscle release. Apart from free range of motion in the RHA group they followed the same post-operative rehabilitation program including full weight bearing.
The patients were evaluated in the out-patient clinic preoperatively, at 8 weeks, 6 months, 1 and 2 years. Two THA patients had a contra lateral THA after 15 and 20 months. No RHA was bilateral within the study period.
Blood analysis: Whole blood was sampled in trace element 6/7 mL Plus K2EDTA tubes (368381) and serum in 6/7 mL Plus serum tubes (368380) (both Becton Dickinson, NJ, USA) . Sampling and handling described previously (Penny and Overgaard, 2010). The first sample was discarded. The serum tubes were centrifuged for 10 minutes at 1500 rpm, before pipetting of the serum. The whole blood was transferred to 3.8 mL acid washed Nunc tubes (Thermo Fisher Scientific, Denmark) and stored at minus 80 °C. The samples were analyzed for Co and Cr content on a ICP-SFMS Finnigan ELEMENT (Finnigan MAT, Bremen, Germany) in a independent ISO 17025/ISO 9001:2000 accredited lab (ALS Scandinavia's laboratories, Luleå, Sweden).
Lymphocyte analysis: Initially a 7 mLVacuette® (456057) CPDA tube was used for the subpopulation analysis and a 4 mL Venosafe EDTA tube (Terumo, Europe) for the total lymphocyte count. From the beginning of 2010 the EDTA tube were used for both samples. Subsets were determined according to their immuno phenotype ($CD3^+$, $CD3^+$, $CD4^+$, $CD3^+$, $CD8^+$, $CD19^+$, $CD16^+CD56^+$,). Until the beginning of 2010 the samples were analyzed on a Becton

Dickinson FacsCalibur flow cytometer with three-color combinations of monoclonal antibodies (MAbs) obtained from DakoCytomation. From 2010 the lab switched to use a Becton Dickinson FacsCanto II flow cytometer. Absolute counts of lymphocyte subpopulations were hereafter determined by a single-platform, lyse-no-wash procedure using the BD Multitest 6-Color TBNK reagent (TruCount tubes, BD Biosciences). Before switching systems, it was validated that there was no significant difference (data not shown).
The cup inclination, defined as the angle between the long axis of the ellipse formed by the cup and the horizontal line of the pelvis, was measured from supine standard AP pelvic radiographs.

Statistical methods:
Sample size calculations:
This RCT is initially sized to a rehabilitation study, with the aim of including 20 patients in each group.
In the present metal ion study the $CD3^+CD8^+$ data from Hart et al. was used to estimate the sample size. We looked for the same $CD8^+$ difference of 0.152 10^9/L between the groups using SDs of 0.166 (metal on polyethylene group) and 0.231 (metal on metal group) (Hart et al., 2006). For a two sample study with repeated measures, 1 baseline and 4 follow up samples, a correlation of 0.88 (data from own study) and a type two error of 0.05, 13 patients in each group was needed to reproduce previous $CD3^+CD8^+$ results with a power of 90%, but all RCT patients were sampled for maximum power and in anticipation of failed samples.

Ion concentrations below the detection limit were assigned a value of half the detection limit. Ion data were compared using Wilcoxon signed-rank test in STATA 11.2 (StataCorp LP, College Station, Texas). Lymphocytes analyzed by ANCOVA adjusted for baseline values. Correlation analysis used linear regression with robust variance estimation (Hubert White). Probability values below 0.05 indicated a significant difference.

RESULTS:

At all follow up times all metal ion levels were significantly higher in patients with a RHA as compared with THA. By the first year the median RHA whole blood ion concentrations had reached a steady state. Some individuals continued to increase their Co and Cr ion concentrations markedly following the first year, but the effect on the median was non significant (p=0.12 and 0.11) The serum Co and Cr concentrations followed the same pattern as whole blood, but with slightly raised concentrations throughout the study period. The serum ion concentrations continued to increase in both Co and Cr from the first to the second year (p=0.04 and p=0.004) (fig 2 and 3), 5 RHA patients had serum or whole blood levels above 7 ppb (table 2). The definition of 7 ppb as raised levels is based on whole blood (Medicines and Healthcare products Regulatory Agency, 2010b), but to be conservative, serum values are included in the table.
Details of the lymphocyte results for both RHA and THA are reported in table 3. Except for CD4+ (THA) and CD19+ cells (both groups) the lymphocyte counts displayed a declining tendency over the 2 year period. This decline is borderline significant for total lymphocytes (RHA) and significant for CD8+ for (RHA + THA). There was no group difference between RHA and THA in relation to total lymphocytes or any of the lymphocyte sub-groups during the 2 year study period.
Nor was there any significant correlation between the absolute Cr and Co concentrations and the absolute lymphocyte or lymphocyte subgroup counts. Of the total 96 correlations between the

changes in metal ion concentrations and lymphocyte counts, 14 were negatively correlated (table 4), but after correcting for multiple testing (Bonferroni) the correlations were non significant.
A small head size was correlated to higher levels of Cr and Co ($p<0.05$) (Fig 4), as was the inclination, where larger metal ion concentrations were associated with cups placed optimally around the 45 deg. angle. ($p<0.05$ apart from whole blood Cr with $p=0.051$) (Fig 5). The head size was not correlated to the inclination angle, but female gender was an independent risk factor for a higher Co level regardless of component size and cup placement ($p < 0.05$) but not for Cr.

DISCUSSION:

The present study is the first to present prospective lymphocyte data in a metal on metal (MoM) population, and it failed to reproduce earlier findings of an association between raised Cr/Co ions and a decrease in absolute numbers of $CD3^+CD8^+$ T cells. (Hart et al., 2009b,Hart et al., 2006) . Former studies failing to demonstrate significant associations (Savarino et al., 1999,Granchi et al., 2003), has low power due to both small numbers and general low ion levels. The present study is smaller scaled than those of Hart et Al. suggesting a depressive metal ion effect on the $CD8^+$ cells, but the present study is strengthened by the randomized design with several follow up measurements that compensate for the lower numbers.
When comparing the absolute number of $CD3^+CD8^+$ T-cells, it was not just a question of lacking statistical significance, but a lack of group difference all together. If only the absolute numbers (Table 3) at any follow-up period were compared, it appears as if the RHA patients had a depressed $CD3^+CD8^+$ count. However, in relation to the baseline values, it is apparent that the RHA group, purely by coincidence, had lower levels from the very beginning, and this illustrates the strength of randomized or prospective studies.
A recent randomised Swedish study (without baseline) (Hailer et al., 2011) even found higher $CD3^+CD8^+$ numbers in the MoM group, so at present, the evidence of a systemic effect on the $CD3^+CD8^+$ count must be considered questionable.
Apart from the intermittent correlation, between metal ions and $CD3^+CD4^+$ and, to some extent $CD3^+$, which encompasses the $CD3^+CD4^+$, this study found nothing to support a depressive effect on the immune system (in terms of absolute numbers and not functionality) of raised metal ion levels. The only study lending some support to a damaging influence of metal ions on $CD3^+CD4^+$ cells (Savarino et al., 1999) is biased by using a younger healthy control group, and as several other studies have failed to find an effect (Hart et al., 2006,Hart et al., 2009b,Granchi et al., 2003) we dismiss this non consistent correlation as mass significance,
Despite using an RHA implant later withdrawn from the marked due to excess failure rates and including a rather large proportion of females and heads below average, the median ion concentrations, measured in the present study, were comparable to other RHA studies
In accordance with previous findings (De Haan R. et al., 2008,Vendittoli et al., 2007), the present study found a correlation between wear and head size. Others have failed to demonstrate this connection (Beaule et al., 2011,Pattyn et al., 2011b), but the combination of registers reporting higher failures for small components(Graves et al., 2011a), and studies identifying failing, high-ion hips as small diameter(Langton et al., 2010,Langton et al., 2011), supports some relationship to size. Fluid film lubrication in large head/small gap components is one theory (Dowson et al., 2004), but prospective data from components classified as high,(Back et al., 2005,Daniel et al., 2009,Pattyn et al., 2011b) medium (deSouza et al., 2010,Allan et al., 2007,Beaule et al., 2011,Skipor et al., 2002,Yang et al., 2011) and low clearance (Garbuz et al., 2009,Pattyn et al., 2011a,Vendittoli et al., 2007,Isaac et al., 2009b,Heisel et al., 2008,Antoniou et al., 2008), including our own data, do not support that a small clearance minimises wear. The cup placement, in particular the inclination angle, seems to be a stronger candidate to explain increased wear in small

components, which however not could be demonstrated in the present study (De Haan R. et al., 2008,Hart et al., 2011). In relation to this, it is argued that the arc of cover diminishes with a steep cup position and may lead to increased edge wear. A 10 mm arc demands a flatter inclination the smaller the cup size and the problem may be particular accentuated by the sub-hemispheric design of and initial edge instep of the ASR™ cup.
Our protocol aimed for a 45 deg. inclination as the optimal cup position (Grammatopoulos et al., 2010), and contrary to expected, higher Cr and Co levels were found in patients implanted with cups in this position. Our study is limited by a small number and will be sensitive to coincidences and outliers. No correlation was seen between size and position, but most of the small components were placed just around/above the 45 deg. inclination, which could explain the conflicting result. Later reports (De Haan R. et al., 2008,Medicines and Healthcare products Regulatory Agency, 2010a) emerging after our patients were operated, stipulates that an inclination of 45 deg. is the *upper* limit for the ASR™ component, which our results support by the lack of elevated metal ion concentration found in cups ≤ 45 deg. The steepest cups would be expected to have high metal ion concentrations, but all cups placed above 50 deg. resulted in low ion concentrations. Coincidently these components were all characterized by large heads (55-57 mm), so our results, with the limitations of the small numbers, also support the theory that the ASR™ component is more forgiving to mal positioning in the large components (Langton et al., 2009).
Earlier associations between raised ion levels and female sex (Isaac et al., 2009a,Vendittoli et al., 2007) has disappeared following multivariate analysis, and is thought to reflect their smaller cup size in earlier studies. In contrast, the present study found female sex to be associated with high Co despite of head size and cup position and recently large register data supports female sex to be an independent risk factor for failure (Graves et al., 2011b) The actual wear must be assumed to be gender independent, but in depth knowledge about Co and Cr distribution and excretion in males and females is not available and theoretically they could differ. Due to the limited sample size, these results should be considered as preliminary and needs to be confirmed in larger independent studies.

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Contributions of the authors:
Designed the study: SO, OO, JEV, JØP
Obtained and analyzed the data: JØP, CN
Wrote the initial draft: JØP. CN, SO, OO, JEV
Ensured the accuracy of the data and analysis: JØP, CN.

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Table 1	RHA	THA	p value
n	19	19	
Age (years)	57.0 (45.8 to 64.3)	54.9 (44.1 to 64.4)	0.32
Females	8	3	0.07
BMI (kg/m^2)	27.9 (19.2 to 36.5)	27.5 (22.6 to 35.7)	0.58

Demographic data. By chance, despite randomization, the majority of patients included in the RHA group were women.

Table 2 Status at 2 years	Blood Co (ppb)	Blood Cr (ppb)	Serum Co (ppb)	Serum Cr (ppb)	Head size (mm)	Inclination. (deg)	Anteversion. (deg)	Pain 100 is max	HHS
Female (66y)	8.27	4.2	10.7	7.3	47	47	15	0	97
Female (59y)	5.8	5.6	6.7	9.3	49	48	20	58	79
Female (59y)	5.5	7.2	9.5	15.3	47	48	32	0	93
Female (56y)	5.3	3.4	7.8	7.0	53	46	23	1	100
Male (66y)	3.8	5.4	4.4	9.1	47	47	13	18	92

Patients with whole blood or serum ion concentrations above 7 ppb. Currently none of the hips are considered failures.The female patient with the high pain score was diagnosed with a systemic neuropathy. The male patient with the pain score of 18 was awaiting contra lateral hip replacement.

Details of the lymphocyte results reported as median (range) 10^9/L

Table 3	Baseline	8 weeks	6 months	1 year	2 years	Delta baseline to 2 years*	P-value bl to 2 y
RHA n	14	17	13	17	18	13	
Total lymphocytes	1.65 (0.84-2.34)	1.54 (0.91-2.77)	1.64 (0.76-2.21)	1.55 (0.98-3.14)	1.6 (0.73-3.01)	-0.21 (-1.01-0.60)	0.05
$CD3^+$	1.13 (0.66-1.85)	1.25 (0.63-2.08)	1.10 (0.57-1.58)	1.15 (0.71-2.32)	1.13 (0.53-2.37)	-0.14 (-0.54-0.19)	0.09
$CD3^+CD4^+$	0.74 (0.47-1.30)	0.73 (0.41-1.57	0.66 (0.40-1.18)	0.73 (0.50-1.83)	0.76 (0.38-1.80)	-0.08 (-0.56-0.19)	0.10
$CD3^+CD8^+$	0.32 (0.18-0-70)	0.31 (0.14-0.75)	0.33 (0.15-0-.65)	0.30 (0.16-0-63)	0.29 (0.12-0.69)	-0.06 (-0.40-0.17)	0.05
$CD19^+$	0.18 (0.08-0.41)	0.15 (0.09-0.31)	0.18 (0.12-0.40)	0.19 (0.14-0.39)	0.19 (0.10-0.40)	-0.01 (-0.14-0.11)	0.55
$CD16^+CD56^+$	0.19 (0.05-0.45)	0.17 (0.09-0.56)	0.20 (0.03-0.59)	0.19 (0.05-0.38)	0.17 (0.06-0.56)	-0.02 (-0.28-0.12)	0.31
THA n	17	19	14	15	19	17	
Total lymphocytes	1.66 (0.76-2.52)	1.70 (0.68-3.13)	1.74 (0.76-2.21)	1.67 (0.86-2.57)	1.55 (0.53-2.66)	-0.14 (-0.52-0.48)	0.42
$CD3^+$	1.39 (0.53-2.16)	1.24 (0.43-2.35)	1.33 (0.65-3.31)	1.22 (0.55-2.16)	1.15 (0.42-2.29)	-0.08 (-0.40-0.44)	0.79
$CD3^+CD4^+$	0.86(0.39-1.47)	0.75(0.31-1.87)	0.88 (0.40-2.36)	0.73 (0.37-1.43)	0.75 (0.37-1.43)	0.02 (-0.27-0.58)	0.43
$CD3^+CD8^+$	0.41 (0.11-1.27)	0.37 (0.09-0.89)	0.45 (0.13-1.50)	0.37 (0.11-1.16)	0.35 (0.08-0.97)	-0.05 (-0.30-0.11)	0.01
$CD19^+$	0.18 (0.04-0.56)	0.13 (0.03-0.38)	0.13 (0.04-0.61)	0.14 (0.03-0.44)	0.15 (0.03-0.55)	0.00 (-0.08-0.18)	0.79
$CD16^+CD56^+$	0.19 (0.05-0.53)	0.17 (0.09-0.52)	0.15 (0.08-0.27)	0.16 (0.06-0.33)	0.17 (0.06-0.34)	-0.04 (-0.19-0.06)	0.06
* some baseline values are missing and delta values cannot be calculated directly from the a bsolute medians.							

Table 4		8 weeks	6 months	1 year	2 years
Total lymphocytes	wb C0	ns	ns	ns	ns
	wb Cr	ns	ns	ns	ns
	se Co	ns	ns	ns	ns
	se Cr	ns	-0.45 (p=0.03)	ns	ns
$CD3^+$	wb C0	ns	ns	ns	ns
	wb Cr	ns	-0.55 (p=0.01)	ns	ns
	se Co	ns	-0.47 (p=0.02)	ns	-0.40 (p=0.03)
	se Cr	ns	-0.57 (p= 0.01)	ns	ns
$CD3^+CD4^+$	wb C0	ns	-0.44 (p<0.05)	ns	ns
	wb Cr	ns	-0.59 (p=0.01)	ns	-0.47 (p=0.01)
	se Co	ns	-0.52 (p=0.01)	ns	-0.49 (p=0.01)
	se Cr wb Cr	ns	-0.59 (p=0.003)	ns	-0.44 (p=0.02)
$CD3^+CD8^+$	wb C0	ns	ns	ns	ns
	wb Cr	ns	ns	ns	ns
	se Co	ns	ns	ns	ns
	se Cr wb Cr	ns	-0.53 (p=0.01)	ns	ns
$CD19^+$	wb C0	ns	ns	ns	ns
	wb Cr	ns	-0.49 (p=0.02)	ns	ns
	se Co	ns	ns	ns	ns
	se Cr wb Cr	ns	ns	ns	ns
$CD16^+CD56^+$	wb C0	ns	ns	ns	ns
	wb Cr	ns	ns	+0.56 (p=0.03)	ns
	se Co	ns	ns	+0.54 (p=0.01)	ns
	se Cr wb Cr	ns	ns	ns	ns

Correlations between change in metal ion concentration and change in lymphocyte counts. + (rho) equals positive correlation where an 1 ppb increase in metal ion concentration increases the lymphocyte count by X 10^9/L and – is a negative correlation.

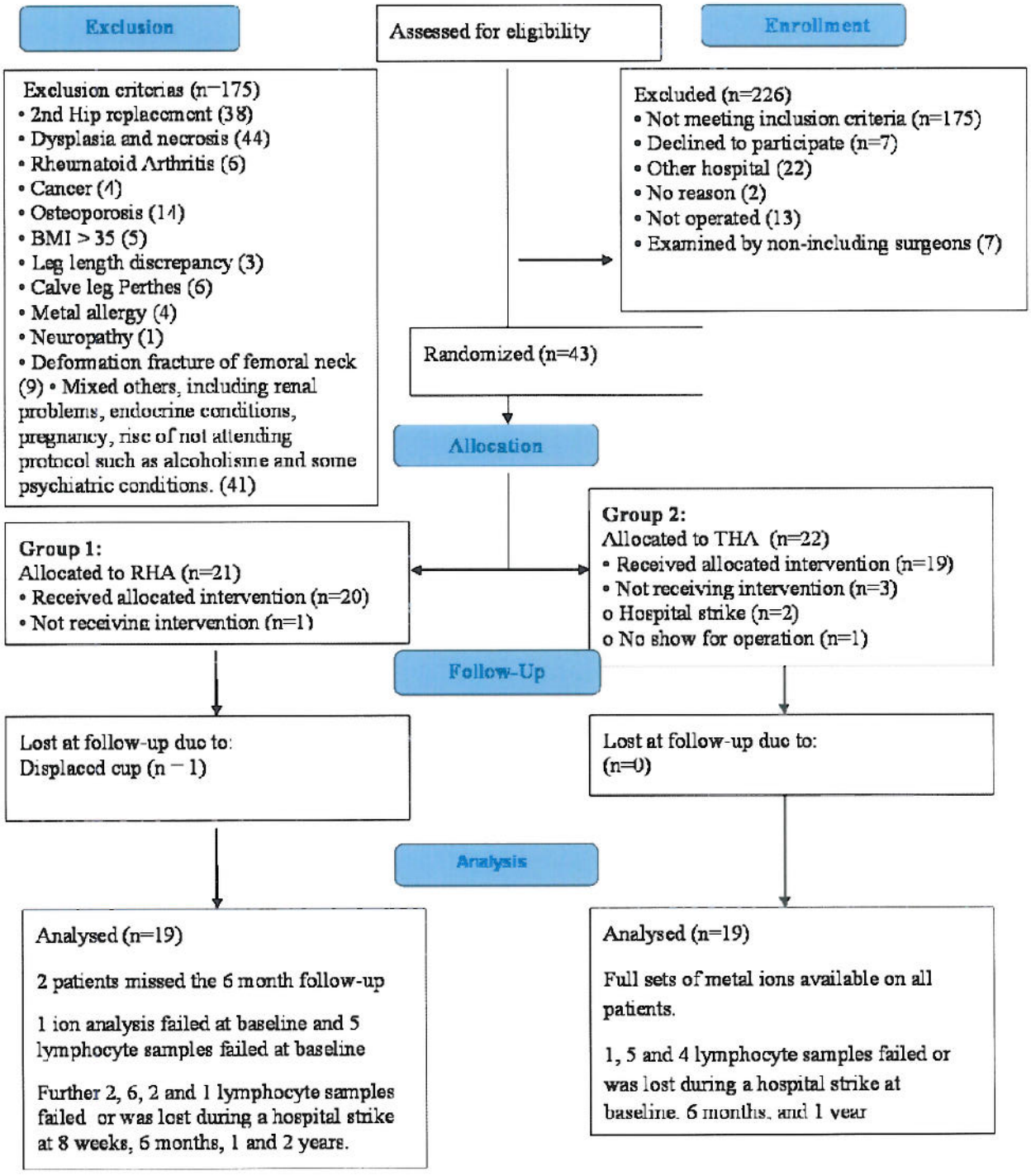
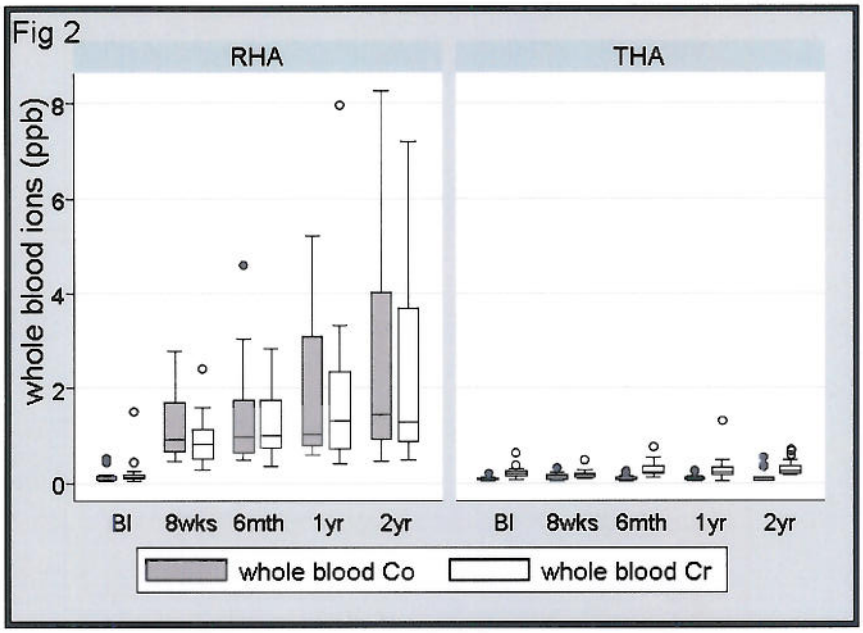


Fig 1. CONSORT Flow chart depicting the inclusion and analysis process of the RCT.



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394 Fig 2: Median whole blood Co and Cr ion concentrations for RHA and THA.

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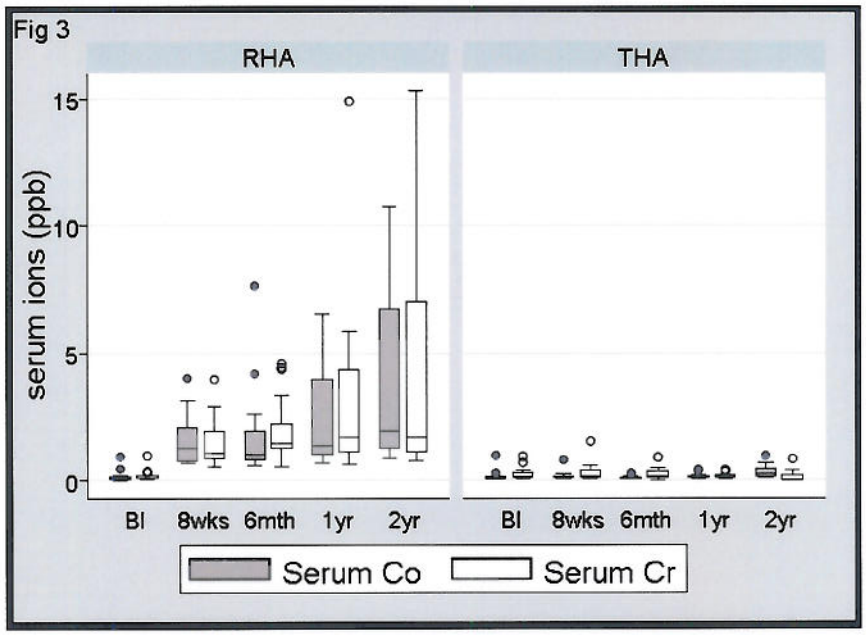

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397 Fig 3: Median serum Co and Cr ion concentrations for RHA and THA.

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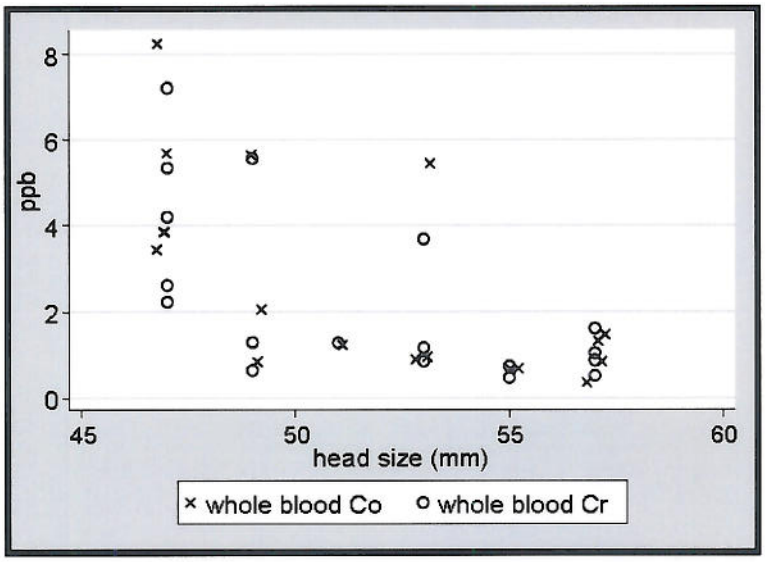

Fig 4: The correlation between whole blood Co/Cr concentrations and head size

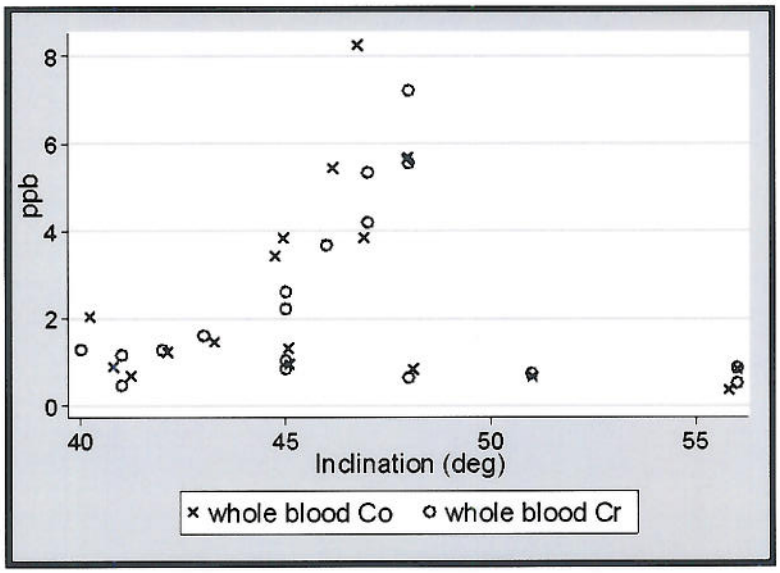

Fig 5: The correlation between whole blood Co/Cr concentrations and inclination angle of the cup

Serum Chromium Levels Sampled With Steel Needle Versus Plastic IV Cannula. Does Method Matter?

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Abstract: ***Purpose:*** **Modern metal-on-metal (MoM) joint articulations releases metal ions to the body. Research tries to establish how much this elevates metal ion levels and whether it causes adverse effects. The steel needle that samples the blood may introduce additional chromium to the sample thereby causing bias. This study aimed to test that theory.** ***Methods:*** **We compared serum chromium values for two sampling methods, steel needle and IV plastic cannula, as well as sampling sequence in 16 healthy volunteers.** ***Results:*** **We found statistically significant chromium contamination from the steel needle with mean differences between the two methods of 0.073 ng/mL, for the first sample, and 0.033 ng/mL for the second. No difference was found between the first and second plastic sample. The first steel needle sample contained an average of 0.047 ng/mL more than the second. This difference was only borderline significant.** ***Conclusion:*** **The chromium contamination from the steel needle is low, and sampling method matters little in MoM populations. If using steel needles we suggest discarding the first sample.** © 2009 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 92B: 1–4, 2010

Keywords: blood-material interaction; metal ions; stainless steel; measurement/assessment; cobalt-chromium (alloys)

INTRODUCTION

Metal-on-metal articulations (MoM) in total hip replacement have gained increasing popularity in recent years due to possible greater range of motion,[1,2] greater stability of the artificial joint and less linear wear as compared to the standard articulation of polyethylene cup/liner and a metal head.[3] However, MoM produces metal ions that can be measured both locally, in urine and in blood. This has raised concerns about local hypersensitivity reactions (ALVAL),[4] local toxic effects leading to tissue necrosis and formation of pseudo tumor,[5] and possible carcinogenetic effects.[4,6–8]

When measuring very low concentrations of metal ions, contamination could have a tremendous impact.

A possible source of contamination is the steel needle used to draw the sample. The concern is that chromium bound in the alloy as well as dust from the manufacturing process can be transferred to the blood sample. Flushing the steel needle for metal dust is recommended in order to avoid contamination, but to our knowledge not documented.[9] To completely avoid the chrome contact some recent publications have taken to using plastic IV cannulas instead.[10–14]

We have found the plastic IV cannula method more difficult to handle. Not all patients have veins suitable for placing the plastic cannula, and the lack of a vacuum means that the flow stalls in some patients before all tubes are filled. Many of our patients have also remarked that they find the method more uncomfortable than the steel needle, and given the choice we would prefer using steel needles.

Our aim with the study is to compare serum chromium levels sampled with steel needles to those from plastic IV cannulas, and to compare the metal levels from first to second flush within each method. The null-hypothesis being that there is no difference of either of the purposes.

PATIENTS AND METHODS

Eighteen healthy volunteers (9 men, 9 women) median age 41 yrs (24–58 yrs) from the staff at the orthopedic dept.

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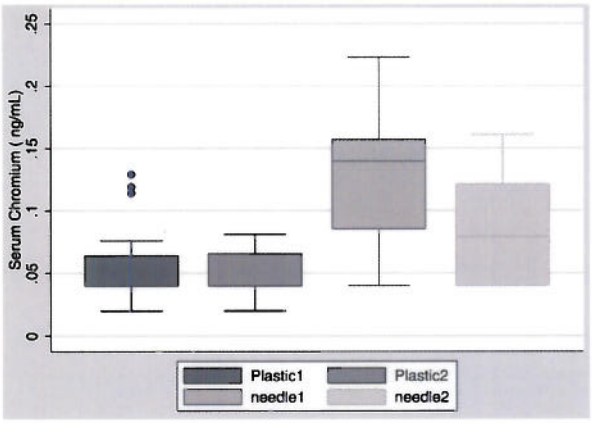

Figure 1. Median serum chromium levels with different sampling methods.

were included after informed consent. They had no occupational exposition to chrome and no metal implants. Two volunteers were excluded from the analyzes as the blood flow stopped while sampling using the plastic IV cannula. Institutional board review was obtained 26th of November 2007 (project-ID: S-20070118). Sample size was calculated to 16 based on a power of 90%, a delta SD of 0.03 ng/mL of a MIREDIF of 0.025 ng/mL and a 5% type-one error. Our chosen MIREDIF corresponds roughly to 10% of the serum chromium levels measured in pre 2008 studies of nonimplanted populations,[12,15–20] our rationale being that anything below 10% variability is a reliable result and hence that difference should be acceptable even in the lowest-chromium populations.

Design and Materials

With sealed envelopes we randomized to "plastic cannula first" or "steel needle first". Two blood samples were drawn from each arm. On one side through the steel needle, and on the other side through the plastic cannula. A cobalt-free steel needle (Nickel 9.2%, Chromium 18.4%, Manganese 1.8%, Iron 69.6%, and Mixed listing1%); Vacutainer® "Safety-Lok Blood collection set" (21 G 0.8 × 19 mm × 304.8 mm)(BectonDickinson, NJ) and a small plastic tube; Venflon Pro (18G-1, 3 × 32 mm) (BectonDickinson, NJ) were used. The blood was collected in 6 mL BD Vacutainer® plus serum plastic tubes (368380) (BectonDickinson, NJ) and allowed to coagulate. The first sample was labeled "Needle/Plastic 1" and the following sample was labeled "Needle/Plastic 2," depending on method. Powder free vinyl gloves, Sempercare Vinyl (Sempermed, FL) were used during sampling and handling and all pipettes and vials had been soaked for a week in 0.14 *M* HNO_3 and verified contamination free.

Analyzing Methods

Samples were initially handled in a ISO/EN 17025 accredited hospital based trace element lab. The tubes were centrifuged for 10 min at 1500 rpm, and the serum transferred to 3,8 mL acid washed Nunc tubes (Thermo Fisher Scientific, Denmark) and frozen at minus 80°C. The frozen serum samples were analyzed for chrome and chromium content on a Perkin–Elmer, Elan 6100 DRC FI-ICP-MS (Perkin–Elmer, MA) in a ISO/EN 17,025 accredited lab (Danish Technological Institute, Taastrup, Denmark). In order to avoid potential contamination from theoretically higher metal ion concentrations, we analyzed the samples in the following order; 0.14 *M* HNO_3, Plastic 2, Plastic 1, 0.14 *M* HNO_3, steel needle 2 and steel needle 1.

Chromium detection limits ranged from 0.04 to 0.08 ng/mL.To measure the chromium content we used a DCR technique with ammonia as the reactive gas, the detection limit was higher for cobalt due to calcium oxide interference, namely 0.2 ng/mL.

Statistical Methods

Serum levels below the detection limit were assigned a value of half the detection limit. Total serum values are presented as medians in box plots. Data were compared as means using 95% Limits of agreement (LOA).

Statistical difference was evaluated by using Wilcoxon signed-rank test in STATA 10.0 (StataCorp LP, College Station, Texas). Probability values below 0.05 were considered statistical significant.

RESULTS

All cobalt measurements were, as expected, below the detection limit. The chromium levels are presented in Figure 1, and the difference of the means with 95% LOA in Table I. For chromium, there were significant differences between plastic and steel for both the first ($p = 0.0006$), and the second sample ($p = 0.0322$). The difference between the first and second plastic samples was not statistically significant ($p = 0.585$). Although the mean Cr level of the second sample steel needle was 36% percentages lower than the first sample, the 0.047 ng/mL difference was not statistical significant, however, with $p = 0.059$ it was bordering.

DISCUSSION

To our knowledge no publication has compared a plastic versus steel cannula when measuring metal ions in serum.

TABLE I. Difference of the Mean (95%LOA) Serum Chromium Content

	Plastic 1	Needle 2
Needle 1	−0.073 (−0.188 to 0.042) ng/mL[a]	−0.047 (−0.220 to 0.127) ng/mL
Plastic 2	−0.007 (−0.063 to 0.048) ng/mL	−0.033 (−0.135 to 0.068) ng/mL[a]

[a]Indicates statistical significant difference.

The investigation is highly relevant for studies where low concentrations of metal ions are found. The study demonstrated that the use of a steel needle contaminated the serum with chromium in contrast to the plastic cannula.

The chromium contamination from the steel needle is statistical significant and there is a clear systematic difference between plastic and steel for the first sample in particular. For the second samples the average steel needle contribution of 0.033 ng/mL is in the gray-area around the detection limit.

When monitoring a MoM population this contamination is likely to be of little consequence. The metal levels in these patients have large variations and are manifold greater than the contribution from our needle with median serum levels ranging from 0.91 to 5.5 ng/mL.[15,19,21–24]

To compare results from different research groups, consensus in handling and analyzing the samples is suggested.[9]

There are several factors which might influence the measured value of metal-ion concentrations. The medium used (serum, whole blood or erythrocytes)[12,23,25–27] contributes significantly to the result, and as the analyzing machines themselves (ICP-MS, High Resolution ICP-MS or GAFFS) have different degrees of precision and detection limits some variability must be accounted for in this link as well.

Compared to that variation, the choice of steel needle versus IV plastic cannula seems of less consequence for the final ion level.

If there was a difference in serum Cobalt we did not demonstrate this due to the high detection limit for cobalt There was the option of running the tests again specifically for Cobalt, without using the ammonia gas, but as the steel needle used in the study is a cobalt-free alloy and previous testing of 10 steel needles all yielded cobalt levels below a detection limit of 0.03 ng/mL, we are satisfied that the needle does not add cobalt to the samples. We therefore refrained from running the tests again.

We were not able to reject our null-hypothesis for the "first flush" procedure. The first steel needle sample was only borderline significantly different from the second needle sample. We may have underpowered our study though. Our calculated sample size was based on a SD of 0.03 ng/mL. In reality it was double that, 0.06 ng/mL for the first steel needle sample. As our found difference of 0.047 ng/mL was twice the size of our designed MIREDIF of 0.025 ng/mL it seems fair to speculate that a larger sample size would have lead to a statistically significant difference.

That, combined with the slightly larger variation within the first steel needle sample, leads us to support the continued use of the "first flush" procedure for the steel needle.

One cannot help speculating if the trocar from the plastic cannula, like the steel needle, in some cases could leave behind some metal dust from the manufacturing process. The first plastic sample did display some outliers and had double the variation of the second sample, but overall there was very little chromium difference from the first to second sample and, although flushing the system with an extra blood sample imposes little inconvenience, we have not demonstrated a need when using the IV plastic cannula.

We used a specific brand of steel needles for this study and whether the results can be extrapolated to other steel needles cannot be concluded. Previous contamination testing of 10 needles using demineralised water and 0.14 *M* HNO_3 and a DL of 0.02 ng/mL found median chromium levels of 0.092 ng/mL, range 0.01–0.51. It seems reasonable to assume that other needles matching these levels can be used in the same way.

In conclusion, stainless steel needles, in contrast to IV plastic cannulas contaminated the serum samples. The importance of measuring the "true" chromium value must be weighed very high in scientific investigations and according to our study, we should chose the plastic cannula. However, in MoM- studies there are no clinical relevance of the difference we found and that has to be weighted against patient discomfort and the risk of not getting the sample at all or changing the sampling method in some patients. For metal-on-metal studies we suggest that the researcher should examine whether contamination is a problem if using a steel needle. If using a steel needle we suggest discarding the first flush. When measuring in low-chromium populations (e.g. occupational health testing) the steel needle could influence the "true" value, and in these cases we suggest using the IV plastic cannula as standard to minimize contamination.

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Changes in bone mineral density at the femoral neck, gruen zones and the acetabulum following total and resurfacing hip arthroplasty. Two year results from a randomized study.

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Abstract:
It is well-recognised that Resurfacing Hip Arthroplasty (RHA) preserves the femoral bone mineral density (BMD) compared to total hip arthroplasty (THA), but no studies have investigated the acetabular side. Following randomization, 2 x 19 patients with either RHA or THA were followed for two years. RHA maintained proximal femoral BMD and, compared to THA, increased BMD in Gruen zones 2, 3, 6 and particularly zone 7 with a gain of 8% compared to a loss of 15%. RHA maintained medial femoral neck BMD and increased between 12 and 26% in the lateral zones. On the acetabular side BMD was similar at any zone at any point in time. The average BMD of all acetabular regions in the RHA group dropped to 96% and for the THA to a non-significant 98 %. Four and 5% were lost superior to the cup in W1, 10% and 9% just medial for the cup in W2 for RHA and THA respectively. RHA lost 7% in W3 and maintained BMD below the cup as did THA. In conclusion, in this study the bone preserving ability of the resurfacing concept only applies to the femoral side.

Introduction:

The risk of revision of total hip arthroplasty (THA) is higher for the younger patients and the majority of the revisions are due to aseptic loosening (Karrholm et al., 2008; Overgaard, Pedersen, 2011). Aseptic loosening leads to bone loss in the proximal femur, compromising the survival of the revision components.
Bone is also lost as a consequence of the non-physiological loading produced by THA with stress shielding in parts of the proximal femur and acetabulum (Sabo et al., 1998; Kim et al., 2007; Laursen et al., 2006; Wilkinson et al., 2005). Such bone loss may be recovered (Karachalios et al., 2004; Thien et al., 2010) and a definite link to reduced survival of the THA has not been established. Loose stems, however, are found in association with reduced bone mineral density (BMD) (Boden et al., 2004; Venesmaa et al., 2000) suggesting that preservation of bone is desirable.
Resurfacing Hip Arthroplasty (RHA) reduces the volumetric wear, thought to play a prominent role in aseptic loosening/osteolysis (Hallan et al., 2006; Ingham, Fisher, 2000), and may maintain the natural load transfer to the proximal femur thought to prevent stress shielding, thereby maintaining bone stock and quality postoperatively. Several studies have demonstrated that the use of RHA preserves femoral bone mass (Hayaishi et al., 2007; Cordingley et al., 2010; Kishida et al., 2004; Smolders et al., 2010; Cooke et al., 2009), but, to the best of our knowledge, no studies have investigated bone loss at the acetabular side.
We hypothesized that there would be no change in BMD at the acetabulum, femoral neck and Gruen zones following RHA compared with THA.

Patients and methods
Design
The study was randomized and open-labelled.

Patients
Following approval by the Ethical Review Board, Funen County, Denmark (VF-20050133), written and verbal informed consent, the patients were randomised to RHA (n=20) or standard ceramic-on-polythylene THA (n=19). One patient in the RHA was excluded following failed surgery, leaving two groups of 19 patients.
Randomization was performed using sealed envelopes in blocs of 10.

The inclusion criteria were; primary osteoarthritis or secondary osteoarthritis due to mild dysplasia and an age from 40 to 65 years. The flow-chart in Figure 1 depicts the inclusion/exclusion process.

Surgery

The patients were operated from April 2007 to March 2009. Demographic data are presented in table 1. Despite the randomization process the gender distribution borders on being statistically skewed.

The RHA group received an Articular Surface Replacement (ASR™)(DePuy, Leeds, UK) made from a high-carbon cobalt-chromium-molybdenum alloy. The cup had an outer porous-bead coating "Porocoat®" coated with hydroxyapatite (HA) (low crystalline, high purity, thickness 30-50 microns). The implant was retracted from the marked in august 2010 due to above average failure rates in the UK and Australian hip registres.

The 28 mm ceramic-on-Polyethylen THAs were implanted with a titanium Mallory-Head acetabular shell, a 28 mm Biolox delta modular ceramic head, an Arcom Ringlock Polyethylene Liner and a titanium Bimetric stem (Biomet, Brigde End, UK). None of the Biomet components were HA coated.

All patients underwent RHA through a standard posterior approach by two consultant surgeons (OO, SO). The gluteal muscle was divided, and the distal insertion was detached along with the external rotators. The cup was placed cement-less in press-fit under reamed by 1 mm and the femoral component was cemented with SmartSet™ GHV Bone Cement (DePuy, Leeds, UK). No cement was applied around the central pin of the femoral component.

The THAs were inserted cement-less via the same approach of shorter incision length without the distal muscle release. Apart from free range of motion in the RHA group they followed the same post-operative rehabilitation program including full weight bearing.

Dual energy X-ray absorptiometry (DXA)

The patients were DXA scanned postoperatively (within a week of surgery), at 8 weeks, 1 and 2 years. At 1 year two sequential DXA examinations were taken on the same day with repositioning between each scan. We performed double measurements with up-and-go at 1 year.

BMD was measured using a Hologic 4500A (Waltham, MA, USA) DXA-scanner, applying the Hologic "metal-removal" software (version V8.26A/3). Scans were performed with a resolution of 0.5 line pair/mm and a speed of 2.5 mm/sec. Radiation dosage was 20 µSv per examination. Quality controls for the DXA equipment were undertaken daily, according to the manufacturer's guidelines, to verify the stability of the system.

The patients were placed in supine position, the hip was 15° internally rotated and controlled by strapping the leg in a suitable size hard plastic shell which has been validated earlier (Penny et al., 2010). Three patients (1 RHA) could not fit any shell and in these cases, the 15° inward foot-rest supplied by Hologic was used.

Regions of Interests (ROI)

We measured the acetabular BMD around the metal cup in 4 regions described by Wilkinson *et al.* and modified by Laursen *et al.* (Laursen et al., 2005; Wilkinson et al., 2001) (Fig. 2a).

BMD at the femoral neck was analyzed in a 6-ROI model as suggested by (Kishida et al., 2004) with 3 regions medial (M1-3) and 3 regions lateral (L1-3) to the pin and (Fig 2b). No specialized software was available for creating the acetabular or femoral neck regions. All regions were marked manually according to the protocol.

The proximal femur of the THA group was divided into 7 Gruen zones (Gruen et al., 1979) using the software supplied by Hologic.
As no stem existed for RHA, the Gruen zones were created manually for RHAs. Since a rough relationship was seen between stem size and height in THAs, the RHAs were divided into 4 stem groups according height. We then applied the Gruen template of corresponding stem size. Care was taken to move the regions away from the femoral canal out to the cortex, in order to imitate the regions used in THA (Fig.2c). An experienced technician marked all regions following the protocol.

The regions were defined on the baseline scan. Patient specific adaptations were saved and via "compare mode" used to analyze the subsequent scans in the longitudinal study. For the Gruen zones in the RHA, the inner borders had to be adjusted to the cortex if the image was not perfectly aligned with the baseline. To estimate the error on the manual adjustment, the first 1-year image of all the ASR patients was measured twice and limits of agreement (LOA) were calculated.
A total of 4 THA and 5 RHA had varying degrees of trochanteric heterotopic ossification. Such areas were removed manually from the ROI to avoid bias (Downing et al., 2008).

STATISTICS
The most proximal bone around a THA often looses 10-20 % BMD(Sabo et al., 1998; Sano et al., 2007; Wolf et al., 2010). When the study was designed, we only knew the SD of Gruen zones around regular THA. Based on data published by Sabo *et al.* regarding Gruen zone 1 (Sabo et al., 1998), the minimum number of participants needed in each group to obtain a power of 80% with a significance level of $p < 0.05$, was determined as 14, assuming a difference in BMD of 15% (SD 14) between the groups.
To evaluate the precision of the system, we calculated the 95% (LOA) as 1.96 times the standard deviation of the difference between two repeated measurements. The procedure was repeated on the difference between two different markings of the same RHA Gruen image to estimate the error on the manual adjustment.
The longitudinal and between-groups data was analysed using an ANCOVA model using Student's t-test adjusting for baseline values. STATA 11.2 (StataCorp LP, College Station, Texas) software was used for all analyses. A bio-statistician supervised the data handling.

Results:

Acetabulum. The Wilkinson/Laursen zones around the cup (Figure 3) displayed similar patterns as the femoral side for the two concepts with initial declines in W1 and W2 followed by a steady state from 1 year onwards and an initial slight dip in W4 followed by a weak increase. W3 differed initially with an insignificant rise at 8 weeks for the THA group, but after the first months both groups displayed a declining pattern. At no time during follow-up did the two groups differ significantly.

The decline in BMD for W1-3 was statistically significant ($p < 0.01$ to 0.03) for both concepts except from W3 in the THA group. The increase in W4 was statistically significant for THA ($p=0.05$) but not RHA. Overall the RHA group lost 4% ($p<0.01$) and the THA 2% (ns).

Femoral neck: In the RHA-group, a significant increase in femoral neck BMD during the two-year period was seen (Table 2). In the early postoperative period, BMD remained unchanged or displayed a declining tendency. During the next two years BMD in the medial regions M1-2 tended to increase. BMD at distal medial region M3 rose more markedly, but the lateral side of the pin (L1-3) increased most. There was a gender difference ($p=0.02$) as the overall increase was only seen in males with a two-year net BMD of 115 % (105-125) whereas in females the 102% (96-107) increase was insignificant.

Proximal femur: A larger increase in BMD was seen in the RHA group in Gruen zone 2, 3, 6 and 7 compared with the THA group, which in turn showed a larger increase in Gruen zone 1. The THA only changed from baseline in the proximal zones where as the RHA increased distally and medially but remained unchanged laterally (Fig 4).

Apart from the femoral neck, where men increased in BMD and women did not ($p=0.02$), no significant impact of gender was seen on BMD changes.

LOA. For the individual patient the 95% limits of agreement for a real change were widest around the acetabulum (table 3). The manual marking of the fictional Gruen was quite accurate with the highest LOA span of -4% to 5% in zone 2 and the lowest from -1% to1% in zone 1 and 4., indicating greater consistency in marking process but greater BMD variation due to a combination of errors of the metal removal program and shifts of position despite the positioning shell.

Discussion:

RHA vs. THA

To our knowledge this study is the first to report prospective acetabular BMD around a resurfacing implant. In THA, cups are revised more often than femoral components (Porter et al., 2010; Overgaard, Pedersen, 2011). For RHA the picture is reversed (Graves et al., 2011), but with 35% cup revisions, the issue still calls for investigation.

The RHA concept displayed a little more (2% non-significant) BMD loss than the THA, but by direct comparison of the groups at the different points in time, no statistical differences were revealed. Perhaps a larger sample size could have lead to statistical significance, but it is uncertain if 2% would have a clinical meaning so our interpretation of the results is that the resurfacing concept does not seem to affect the acetabular bone differently from a standard THA in the present design. The cup used is a particular brand now retracted from the marked due to above average failure rates. None of the implants displayed evidence of failing during the study period, leading us to infer that the BMD pattern we see is typical for the RHA concept, but prospective studies on different implant types are needed to fully establish that assumption.

In our study, femoral neck BMD increased primarily on the lateral side and primarily for men in RHA. With one exception, using the Conserve plus (Smolders et al., 2010), all other resurfacing studies have used the BHR implant. A single two year BHR study using the same neck region reported results similar to ours in all zones bar M2, where they found an increase, and in L2 where

they did not find any change.(Kishida et al., 2004) By contrast, the remaining 1 and 2 year studies have found either no or a smaller effects, with the increase predominantly on the medial side of the pin.(Hakkinen et al., 2011; Lian et al., 2008; Cooke et al., 2009; Smolders et al., 2010) A large prospective study of 423 BHR patients found no overall BMD change but measured only close to the implant rim and did not separate lateral from medial (Cordingley et al., 2010).
There are no comparable ASR studies available. Gupta *et al.* performed a finite element study of an ASR™ implant (Gupta et al., 2006), which predicted a BMD loss in the proximal neck near the implant rim, unlike the results of this study. As the ASR no longer is available, the results cannot be re-tested and we will not know if this pattern is specific for this implant, but more studies are needed on implants other than the BHR, to establish whether there is a design or cementation related difference in loading stresses to the femoral neck.

Further distally in the Gruen zones the RHA displayed an initial small BMD dip followed by either restoration to baseline laterally or an increase medially. Despite the implant brand that seems to be a common pattern following resurfacing.(Hakkinen et al., 2011; Hayaishi et al., 2007; Kishida et al., 2004; Smolders et al., 2010) The increase is especially pronounced in Gruen zone 7, where THA, ours as well as other types of uncemented stems, decline following surgery. (Smolders et al., 2010; Kishida et al., 2004; Sano et al., 2007; Tanzer et al., 2001; Wolf et al., 2010; Kim et al., 2007).
In the longer term run a 10 year study indicate that the low is at two years, and may recover,(Karachalios et al., 2004) so the clinical effect of the two year BMD loss remains disputed. A good calcar bone stock is desirable at the time of a future revision, but these results are from patients with well functioning hips, and so far there is no knowledge about BMD changes in failing RHAs.
Strengths and weaknesses;
Our study was biased by the acetabular components not being from the same manufacturer and with uncoated THA cups opposed to HA coated RHA cups. However we do not believe that this has played any role on the loss of bone in some of the Wilkinson zones in RHA, but more likely that any difference should be attributed to the different concepts of THA vs. RHA A randomised study of +/- HA coated cups found no BMD difference after 2 years (Laursen et al., 2006), the study investigated a fibre mesh cup, where our cups were porous plasma sprayed (THA) and bead sintered (RHA). Despite these differences the pattern of changes in BMD was remarkably similar in all Wilkinson zones. Further support to a notion that the bias from different cup materials and coatings is negligible, comes from an RCT between the fibre mesh cup and a fibrous tantalum monobloc cup, where again the pattern was very similar between the interventions and very similar to our results. (Baad-Hansen et al., 2011). A single THA study reports a deviation from this pattern with a 2-year decrease medial/inferior to a bead-sintered cup. (Kim et al., 2007). The loss did turn into a gain at 5 years, but as the regions of interest were non-comparable, we cannot be sure that this cup truly performs differently.
Pelvic tilt and precision;
This study did not control for pelvic tilt. Pelvic tilt above 20° may alter the measured BMD in W2 and W3, resulting in a lower BMD. (Laursen et al., 2005) If the patients were contracted in hip at the baseline scan and tilted the symphysis backwards to allow the leg to be stretched out on the table, the baseline BMD would be artificially low. At subsequent scans on a relaxed hip an unchanged BMD would be measured artificially high, and the observed loss in W2 and W3 would be underestimated. We assumed that the inflexible positioning shell stabilised the pelvis sufficiently and our technicians observed the pelvic position. But as our variation on W2 was higher (coefficient of variation of 7%) than that reported by Laursen *et al.* (3%, calculated from table 3) we cannot rule out some tilt between measurements. However, as Computer Tomography, that can

adjust for pelvic tilt, support our results with a 6% BMD loss above the cup and 15 to 20% around it (Mueller et al., 2006), the risk that positioning has biased our results seems small.
By chance, despite randomization, the study bordered on having more women in the RHA group. The gender had no effect in the Wilkinzon/Laursen and Gruen zones, so the skewness does not affect our conclusions there. As for the femoral neck, the skewed distribution only strengthens our conclusion, as the females did not increase in BMD, but the mean BMD still increased significantly despite the large proportion of females. The gender difference found in the femoral neck zones receives partial support (only men above 65) in one study (Cordingley et al., 2010) but is rejected in another (Hakkinen et al., 2011). Several confounders, amongst them femoral component position, may well affect BMD, but additional sub-analysis is limited by the small sample size, so the result should be considered preliminary and needs to be confirmed in larger independent studies.
Finally, 65% of the patients assessed for participation fell for the exclusion criteria. The relatively large number reflects exclusion of contra lateral hip implants as metal ion analysis was undertaken and exclusion of moderate and severe hip dysplasia as they were non eligible for RHA at our institution The interpretation of our results should therefore bear in mind that we're addressing a selected sub segment of the osteoarthritis patients and the results may not be extrapolated to all.

In conclusion, the ASR™ displayed increase in BMD on the superior femoral neck. Both RHA and THA experience a little stress shielding on the acetabular side and the load seems to be distributed in a similar pattern for the different concepts. The apparent advantage of RHA is seen on the femoral side, where it maintains and increases the femoral bone BMD especially in the calcar area.

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Table 1. Demographic baseline data. Data are presented as median (range).

Table 1	RHA	THA	p value
n	19	19	
Age (years)	57.0 (45.8-64.3)	54.9 (44.1-64.4)	0.32
Females (n)	8	3	0.07
BMI (kg/m^2)	27.9 (19.2-36.5)	27.5 (22.6-35.7)	0.58

Table 2. BMD of the femoral neck zones in 19 patients treated with RHA during follow-up. Data are shown as percent of baseline (immediately after surgery) (mean (95%CI)).

Table 2			RHA		
Femoral neck zone	Baseline	8 weeks	1 year	2 year	P value baseline vs. 2 y
n	19	19	19	17	
M1	100.0	98.4(95.2-101.5)	102.5(97.4-107.7)	101.5(96.6-106.5)	0.52
M2	100.0	98.5(96.5-100.5)	101.3(98.3-104.2)	101.7(97.3-106.1)	0.43
M3	100.0	99.0(96.5-101.5)	101.9(99.4-104.4)	104.6(100.9-108.4)	0.02
L1	100.0	100.1(96.5-103.7)	115.0(106.8-123.3)	125.9(107.1-144.6)	0.01
L2	100.0	96.2(93.3- 99.1)	110.8(102.3-119.2)	120.1(107.1-133.1)	<0.01
L3	100.0	95.4(91.1- 99.6)	107.4(100.5-114.2)	112.8(104.3-121.4)	<0.01
average	100.0	97.8(95.7- 99.8)	105.3(101.2-109.5)	109.6(103.0-116.2)	<0.01

Table 3. 95% Limits of agreement (LOA) on repeated scans, as well as manual remarking of the same Gruen zone image.

Table 3	THA (BMD %)	RHA (BMD %)	Remarking same image
Prox. Femur:Gruen			
G1	-5 to 3	-5 to 4	-1 to 1
G2	-8 to 8	-7 to 8	-4 to 5
G3	-8 to 8	-4 to 4	-1 to 1
G4	-6 to 6	-3 to 3	-3 to 2
G5	-5 to 5	-3 to 4	-2 to 2
G6	-7 to 5	-5 to 4	-2 to 2
G7	-14 to 15	-6 to 7	-2 to 3
G average	-3 to 2	-2 to 2	-2 to 2
Acetabulum:Wilkinson/Lauersen			
W1	-5 to 6	-3 to 3	
W2	-16 to 14	-13 to12	
W3	-15 to 16	-10 to 8	
W4	-5 to 5	-13 to 9	
W average	-3 to 4	-7 to 7	
Femoral neck: Kishida			
M1		-5 to 6	
M2		-8 to 8	
M3		-8 to 7	
L1		-7 to 6	
L2		-9 to 6	
L3		-7 to 5	
Femoral neck average		-4 to 3	

8
9

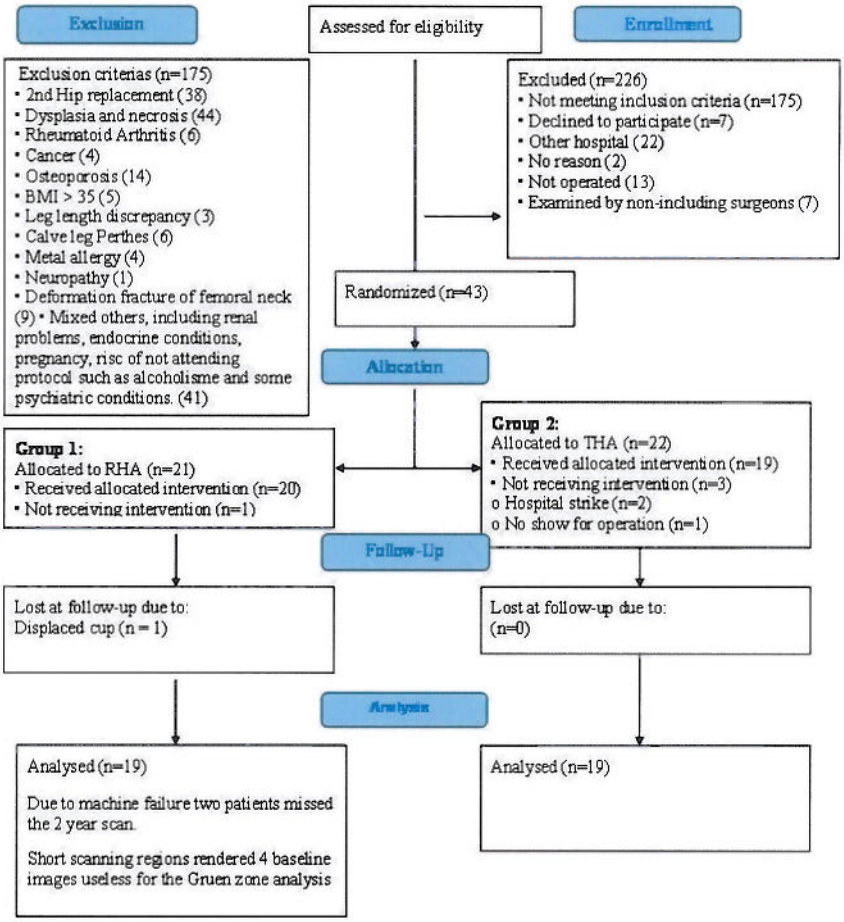


Fig 1

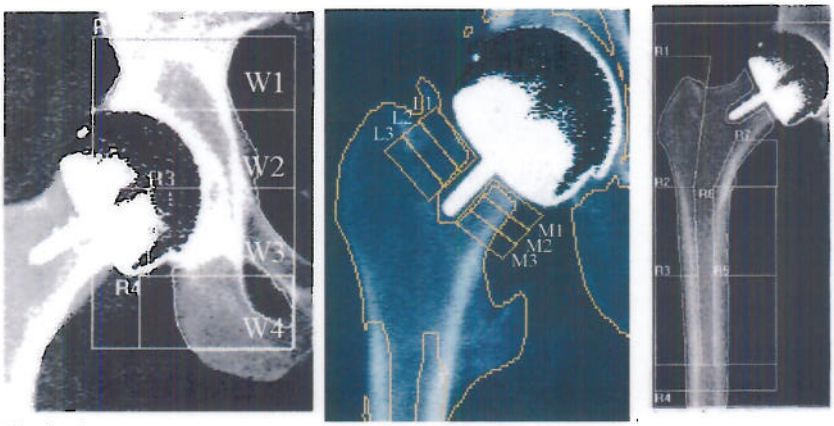
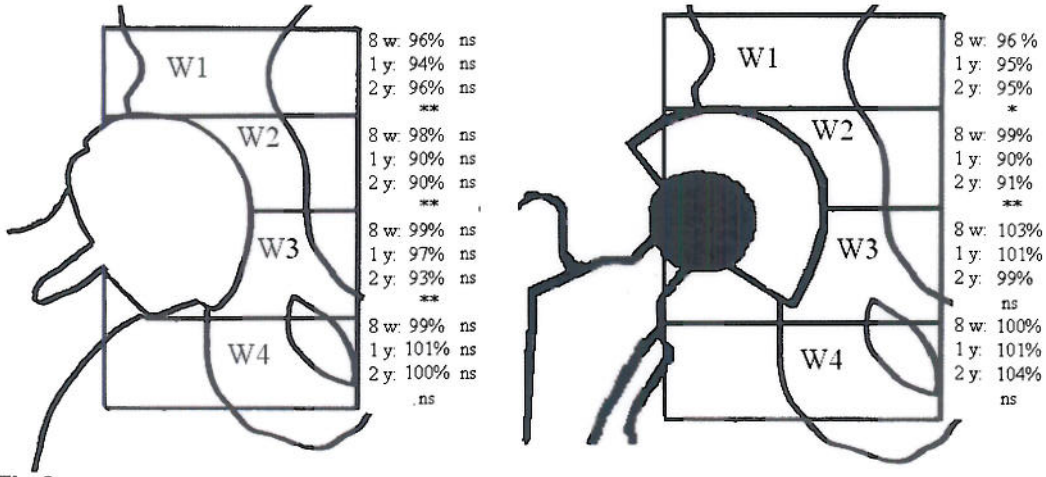


Fig 2a,b,c



17

Fig 3

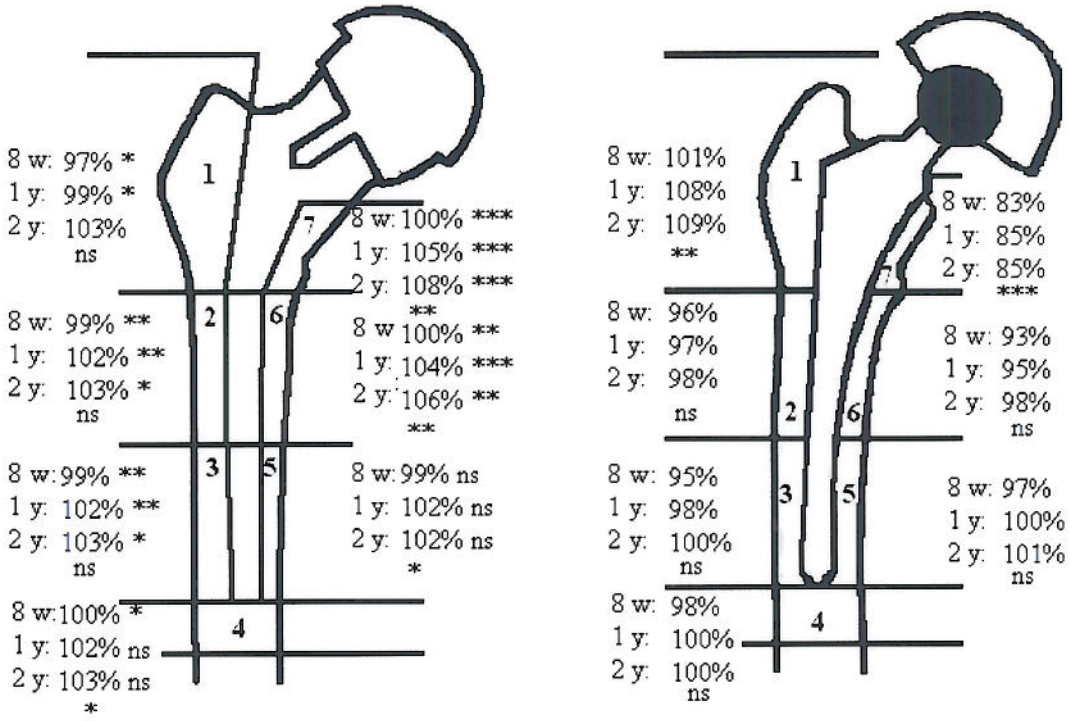


Fig 4.

Captions

Fig 1
Inclusion of participants.

Fig 2abc. (uploaded as 3,4 and 4)
Regions of interest used in DEXA-scan. Left panel shows the acetabular/Wilkinson/Laursen ROIs, the middle panel the femoral neck/Kishida ROIs and the right panel the Gruen ROIs.

Fig 3
BMD in the acetabular/Wilkinzon/Laursen zones: Changes from baseline at 8 weeks, 1 and 2 years. Horizontal asterisk or *ns* to the right of RHA percentages compares between THA and RHA. The asterisk below each column compares change within the group from baseline to 2 years. * $p<0.05$, ** $p<0.01$ ***, $p<0.001$

Fig 4
BMD in the Gruen zones: Changes from baseline at 8 weeks, 1 and 2 years.
Horizontal asterisk or *ns* to the right of RHA percentages compares between THA and RHA. The asterisk below each column compares change within the group from baseline to 2 years. * $p<0.05$, ** $p<0.01$ ***, $p<0.001$

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Bone mineral density of the femoral neck in resurfacing hip arthroplasty

Precision of DXA biased by region of interest and rotation of the hip

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Background and purpose **Resurfacing total hip arthroplasty (RTHA) may preserve the femoral neck bone stock postoperatively. Bone mineral density (BMD) may be affected by the hip position, which might bias longitudinal studies. We investigated the dependency of BMD precision on type of ROI and hip position.**

Method **We DXA-scanned the femoral neck of 15 resurfacing patients twice with the hip in 3 different rotations: 15° internal, neutral, and 15° external. For each position, BMD was analyzed with 3 surface area models. One model measured BMD in the total femoral neck, the second model divided the neck in two, and the third model had 6 divisions.**

Results **When all hip positions were pooled, average coefficients of variation (CVs) of 3.1%, 3.6%, and 4.6% were found in the 1-, 2-, and 6-region models, respectively. The externally rotated hip position was less reproducible. When rotating in increments of 15° or 30°, the average CVs rose to 7.2%, 7.3%, and 12% in the 3 models. Rotation affected the precision most in the model that divided the neck in 6 subregions, predominantly in the lateral and distal regions. For larger-region models, some rotation could be allowed without compromising the precision.**

Interpretation **If hip rotation is strictly controlled, DXA can reliably provide detailed topographical information about the BMD changes around an RTHA. As rotation strongly affects the precision of the BMD measurements in small regions, we suggest that a less detailed model should be used for analysis in studies where the leg position has not been firmly controlled.**

Aseptic loosening is the major cause of revision of total hip arthroplasty (THA), and data from the Nordic national hip registries have demonstrated higher revision rates, up to 20% after 10 years, for younger patients (Kärrholm et al. 2008, Overgaard et al. 2008). To improve longevity, the metal-on-metal resurfacing total hip arthroplasty (RTHA) is now widely used. RTHA reduces volumetric wear (Anissian et al. 1999, Fisher et al. 2006), thought to play a prominent role in osteolysis (Ingham and Fisher 2000, Hallan et al. 2006, Howie et al. 2007). In addition, the load is thought to be naturally transferred to the proximal femur, which may prevent stress shielding (Harty et al. 2005, Hayaishi et al. 2007, Little et al. 2007, Lian et al. 2008), thereby preserving bone stock postoperatively. This mechanism should also protect the femoral neck, but there have been few prospective bone mineral density (BMD) studies focusing on the femoral neck alone. There are, however, indications that bone strain in the femoral neck of a RTHA differs from normal strain near the rim of the implant (Gupta et al. 2006), and that the entire neck area can be influenced by implant position (Vail et al. 2008) and cementation (Radcliffe and Taylor 2007). Longitudinal in vivo studies on the femoral neck are needed to determine whether RTHA preserves the bone, and if not, whether change is correlated to failure. For these prospective studies, a precise method is needed.

Dual-energy X-ray absorptiometry (DXA) is used to study BMD around standard femoral stem designs using the Gruen zones, and reliability studies have shown good reproducibility (Yamaguchi et al. 2000). In RTHA, the bone of interest is the femoral neck, which allows only rather small regions of interest (ROIs) and may contribute to reduced precision when measuring BMD (Engelke et al. 1995, Gehrchen 1999). No consensus exists on which size of ROIs to use in the femoral neck. Several models have been used (Kishida et al. 2004, Murray et al. 2005, Lian et al. 2008), but only 1 publication has reported the reproducibility (Murray et al. 2005). If region size is a factor, then we must also consider the anatomy of the neck. The anteversion means that rotations of the hip will alter

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the neck length of the screen image and cause a change in region size that could affect the BMD results.

We evaluated the reproducibility of BMD in the femoral neck surrounding an RTHA under 2 different set-ups: (1) the effects of increasing subdivisions/numbers of ROIs in the neck area, and (2) the effects of hip rotation on the precision of BMD measurement.

Patients and methods

Patients

Our sample size of 16 was based on 5% type-one error, 20% type-two error, a minimal relevant difference (MEREDIF) of 0.02 g/cm^2, and a standard deviation (SD) of 0.02 g/cm^2. There have been no publications linking a specific BMD loss to failure. As the clinical MIREDIF is therefore unknown, we chose to dimension our study to be able to detect a difference of the same size as the SD found in rotation studies estimating reproducibility for the intact femoral neck (Goh et al. 1995, Rosenthall 2004).

15 patients with RTHA could be included in the study, leading to a power of 78%. Permission from the Regional Ethics Committee of Vejle and Funen Counties was obtained (issued November 21, 2006; ref no. VF-20060090), and an invitation to participate in the study was sent to all 68 previously operated RTHA patients resident in Funen County, Denmark. After obtaining verbal and written informed consent, 15 patients (11 male) with a self-rated well-functioning hip were included in the study. The patients had a median age of 62 (38–73) years at the time of surgery. They were operated at Odense University Hospital from October 2005 to October 2006. Median time from surgery to DXA scan was 11 (6–18) months.

Surgical technique and implants

The posterolateral approach was used and an ASR RTHA (DePuy, Warsaw, IN) was inserted following guidelines from the manufacturer. The components were made from a high-carbon cobalt-chromium-molybdenum alloy. The cup had an outer porous-bead coating ("Porocoat") of hydroxyapatite (low crystalline, high purity, thickness 30–50 μm), and was placed without cement (press-fit). The femoral component was fixed with SmartSet GHV bone cement (DePuy). We aimed for a cup inclination of 45° with 20° anteversion. The pin of the femoral head was intended to be parallel with the axis of the femoral neck in the axial view and parallel or in slight valgus in the AP view. Full weight bearing was allowed after surgery.

Scanning techniques

BMD was measured using a Hologic 4500A (Waltham, MA) DXA scanner and Hologic "metal-remove" software version 8.26A/3. Scans were performed with a resolution of 0.5 line pair/mm and a speed of 2.5 mm/sec. Radiation dosage was 0.20 mGy per examination.

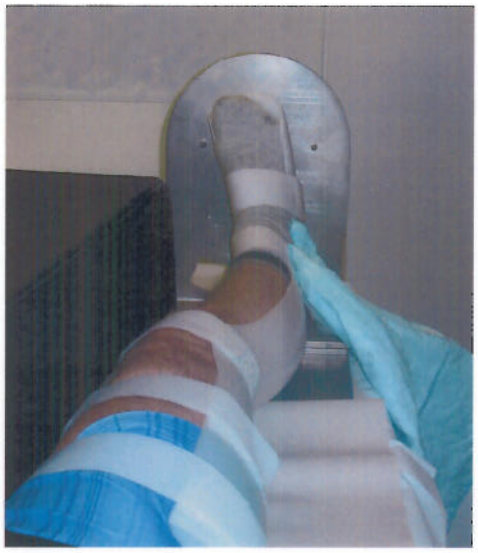

Figure 1. The leg strapped in the plastic shell and positioned in 15° internal rotation.

The patients were placed in supine position. The leg was strapped in a suitable-sized shell (Figure 1). The shells, custom-made from hard plastic by a prosthetic limb manufacturer (Sahva A/S, Odense, Denmark), were modeled on 4 different leg sizes (left and right leg). They went from the toes to the mid/upper thigh, with an anterior opening for entry, and were fitted with Velcro straps for circumference adjustments. The ankle and knee were reinforced for stability. The shells were designed to lock movements of the knee and foot/ankle joints, so that hip rotation could be controlled during scanning. A metal peg was mounted in the heel of the mold and fitted in an angle measurer. It could rotate the shell 45° in either direction, could be locked in any position, and was supplemented with holes and a peg for exact replication of the 15° internal, 0° neutral (toes up), and the 15° external positions. As the normal anteversion of the femoral neck ranges from 10° to 20° (Reikeras et al. 1983), we assumed that the optimal scan for a direct view of the neck would be in-between, i.e. 15° of internal rotation As this is also the standard position in most manufactured footplates, we chose to scan the femoral neck in that position. Postoperatively, however, the patients are often more comfortable with the hip in external rotation and will seek this position despite the footplate by flexing the ankle and knee. At later follow-ups, they are often able to rotate inwards. Consequently, rotation of more than 15° is likely to occur in a longitudinal study. We therefore investigated the effect of increments of rotation of 15°, from 15° of internal rotation to neutral and from neutral to 15° of external rotation, as well as the effect of a full 30° rotation from internal to external rotation.

For investigation of reproducibility, the patients were mobilized and walked around for a few minutes after the first scan-

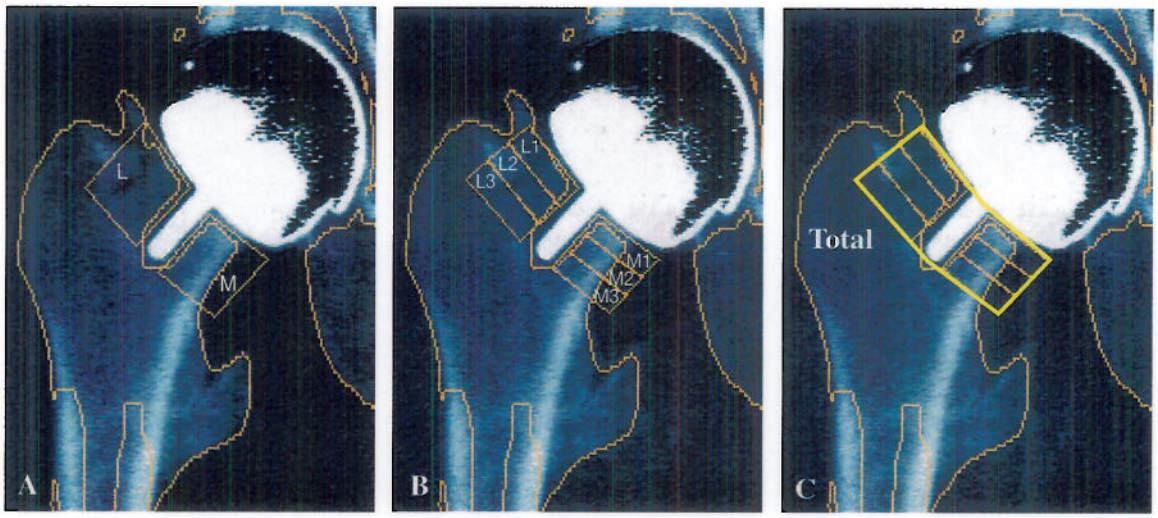

Figure 2. A. The 2-ROI model with a medial (M) and a lateral (L) region. The length of a region was equal to the pin length in the on-screen image. The width of the region corresponded to the distance from the pin to the rim of the femoral component. B. The 6-ROI model. The on-screen pin length was divided by 3 to create 6 subregions: 3 medial regions (M1-3) and 3 lateral regions (L1-3), again with width defined by pin and rim. C. All 6 subregions combine to make the 1-ROI (total) model.

ning before being strapped in the shell again for the second scanning. To imitate different scanning sessions, the shell and angle measurer were detached, moved, and reattached between the 2 scans.

Regions of interest

BMD (g/cm^2) was analyzed in 3 models: (A) in a 2-region of interest (ROI) model with a subregion medial (M) and lateral (L) to the femoral pin; (B) in a 6-ROI model as suggested by Kishida et al. (2004) with 3 regions medial (M1-3) and 3 regions lateral (L1-3) to the pin; and (C) in a model including the total femoral neck (total) (Figure 2). No software was available for computing the regions; a technician marked them following protocol. A new set of regions had to be marked for each position of the hip, as on-screen pin length and distance to the rim of the femoral component changed with rotation due to change in anteversion. The computer automatically summed up all the marked regions for a "total" femoral neck BMD.

Data acquisition

For calculation of reproducibility from first to second scan, the regions marked on the first scan were copied using the "compare" mode of the computer. Copying rather than marking the model up again may give a high reproducibility in 2 repeated scans, but it reflects reality. It is common to create a permanent analyzing model at baseline. When analyzing around a THA, the software provides a Gruen zone model that is adapted to the patient's THA. The patient-specific adaptation is saved and, via the "compare mode", is used to analyze the following scans in a longitudinal study.

For the rotation analyses, we used the first series of scans, where we compared BMD in corresponding regions but in different rotations.

All DXA measurements were performed and analyzed according to protocol by a single trained technician who was blinded regarding the endpoint results.

Statistics

The same bone, scanned twice a few minutes apart, should have the same BMD. If the results are close, the variation from scan to scan is little and the method is precise. As a measure of the precision of the DXA scans, standard deviations were calculated on the difference between 2 paired BMD measurements (SDdiff). To evaluate the precision between repeated measurements in the same position or different rotations, we calculated confidence intervals for the SDdiff values (Gluer et al. 1995) and compared the SDdiff values by the variance ratio tests (F-test). A 5% level of statistical significance was chosen. Thus, all statistical inference is based on the SDdiff values. To facilitate comparison with other studies, we also report coefficients of variation (CVs). The CV is a percentage-wise transformation for the precision of the BMD result. It is computed as CV = SDdiff × 100/mean BMD, and the lower the CV the more precise is the method. To give a conservative estimate of CV, the SDdiff of any rotation was compared to the higher of 2 possible SDdiff values from the repeated-measurement study.

Likewise, the rotational CVs were computed using the higher of 2 potential mean BMDs. STATA software version 9.2 (StataCorp LP, College Station, TX) was used for all analyses. A biostatistian supervised the data handling.

Table 1. BMD, SDdiff, and CV values in 3 hip positions (repeated measurements)

Regions	15° internal rotation Mean BMD (SD) g/cm²	SDdiff (95% CI)	CV%	neutral (0°) Mean BMD (SD) g/cm²	SDdiff (95% CI)	CV%	15° external rotation Mean BMD (SD) g/cm²	SDdiff (95% CI)	CV%
Total	0.94 (0.096)	0.028 (0.021–0.044)	3.0	0.95 (0.097)	0.024 (0.018–0.039)	2.5	0.99 (0.12)	0.037 (0.027–0.058)	3.7
2-ROI									
Medial	1.2 (0.10)	0.028 (0.021–0.045)	2.3	1.2 (0.12)	0.027 (0.020–0.042)	2.2	1.2 (0.13)	0.043 (0.031–0.067)	3.5
Lateral	0.73 (0.083)	0.029 (0.021–0.046)	4.0	0.75 (0.090)	0.025 (0.019–0.040)	3.3	0.80 (0.14)	0.048 (0.035–0.075) [a]	6.0
6-ROI									
M1	1.2 (0.095)	0.056 (0.041–0.089) [a]	4.6	1.2 (0.12)	0.028 (0.021–0.044)	2.3	1.2 (0.15)	0.054 (0.040–0.085) [a]	4.3
M2	1.2 (0.11)	0.034 (0.025–0.053)	2.8	1.2 (0.12)	0.036 (0.026–0.056)	3.0	1.2 (0.12)	0.052 (0.038–0.081)	4.2
M3	1.2 (0.211)	0.033 (0.024–0.052)	2.9	1.2 (0.14)	0.039 (0.029–0.061)	3.2	1.3 (0.15)	0.052 (0.038–0.082)	4.1
L1	0.73 (0.094)	0.037 (0.027–0.058)	5.1	0.72 (0.086)	0.035 (0.025–0.055)	4.8	0.75 (0.097)	0.054 (0.040–0.085)	7.2
L2	0.72 (0.10)	0.044 (0.032–0.069)	6.1	0.74 (0.11)	0.039 (0.028–0.061)	5.3	0.80 (0.16)	0.052 (0.038–0.081)	6.5
L3	0.82 (0.18)	0.038 (0.028–0.060)	4.6	0.79 (0.13)	0.027 (0.020–0.043)	3.4	0.86 (0.20)	0.074 (0.054–0.12) [b]	8.6

[a] statistically significantly different from neutral.
[b] statistically significantly different from both neutral and 15° internal rotation.

Results

All BMD values (with SD), SDdiff values (with 95% CI), and CV values for the repeated measurements in different hip positions are given in Table 1.

6-subregion (6-ROI) model

The repeated BMD measurements, with the hip held firmly in the same position, gave an average (all 3 rotations and all 6 subregions combined) SDdiff of 0.044 (0.028–0.074) g/cm², corresponding to an average CV of 4.6% (2.3–8.6). The CVs in the 6-ROI subregions tended to be higher with the hip scanned at 15° of external rotation. The SDdiff values for regions M1 and L3 in the 15° external position were larger than for the neutral position ($p = 0.02$ and $p < 0.001$, respectively); the remaining regions had p-values ranging from 0.1 to 0.3. The variance was larger in the internal position than in the neutral position for the M1 region ($p = 0.01$) but the variation in the other 5 regions was quite similar, with p-values ranging from 0.2 to 0.8. Compared to the internal position, the variation was larger for the external position in the L3 region ($p = 0.02$). The remaining 5 regions generally had low p-values, but not enough to demonstrate any statistically significant difference in favor of the internal position.

2-region (2-ROI) model

The average SDdiff of the 2 region model was 0.033 (0.025–0.048) g/cm², corresponding to a CV of 3.6% (2.2–6.0). Again, when the hip was scanned at 15° of external rotation, the lateral region had higher variation than the neutral position ($p = 0.02$), and was bordering on being statistically significant for the 15° internal position ($p = 0.07$). The medial region was unaffected by foot position.

1-region model (total)

When the femoral neck was analyzed as one region (total), the average SDdiff value was 0.030 (0.024–0.037) g/cm², corresponding to a CV of 3.1% (2.5–3.7), and the position of the leg did not affect the variation significantly.

We observed that when we increased the number of regions in the analysis model, we detected larger variability/declining precision, but this observation was not statistically significant.

Effects of hip rotation

Rotating the hip in increments of 15° or 30° adversely affected the variation reflected by an increasing SDdiff (Table 2), and thereby increased the CV compared to the repeated measurements.

6-region (6-ROI) model

In the 6-ROI model, the average SDdiff (based on all 3 rotation arches) more than doubled to 0.11 (0.034–0.31) g/cm², corresponding to an average CV of 12% (2.7–36). The BMD measurements changed mainly in the distal and lateral parts of the neck, where the variation, even for smalll rotations, was statistically significantly larger compared to repeated measurements in the same position.

2-region (2-ROI) model

During rotation in the 2-ROI model, the average SDdiff (all 3 rotation arches) rose to 0.065 (0.024–0.13) g/cm², corresponding to a CV of 7.4% (1.9–16), but only the lateral region was adversely affected to a statistically significant extent.

1-region model (total)

Compared to repeated measurements, the total femoral neck was significantly affected over a 30° rotation arch with SDdiff increasing to 0.071 g/cm2, corresponding to a CV of 7.2% ($p = 0.01$), but the increase in CV from 15° of internal rotation to neutral or from neutral to 15° of external rotation did not reach statistical significance.

Table 2. SDdiff and CV values in 3 rotational increments

Regions	15° internal rotation to 0° SDdiff (95% CI) g/cm^2	CV%	0° to 15° external rotation SDdiff (95% CI) g/cm^2	CV%	15° internal to 15° external rotation SDdiff (95% CI) g/cm^2	CV%
Total	0.033 (0.024–0.052)	3.5	0.054 (0.040– 0.086)	5.5	0.071 (0.052–0.112) [a]	7.2
2-ROI						
M	0.040 (0.029–0.062)	3.3	0.024 (0.017–0.037) [a]	1.9	0.055 (0.040–0.087)	4.5
L	0.053 (0.039–0.084) [a]	7.1	0.088 (0.065–0.14) [a]	11	0.131 (0.096–0.207) [a]	16
6-ROI						
M1	0.070 (0.051–0.11)	5.7	0.051 (0.037–0.081)	4.2	0.095 (0.070–0.15) [a]	7.8
M2	0.043 (0.031–0.068)	3.5	0.034 (0.025–0.053)	2.7	0.060 (0.044–0.094)	4.9
M3	0.17 (0.12–0.26) [a]	14	0.051 (0.037–0.080)	4.0	0.16 (0.12–0.25) [a]	12
L1	0.057 (0.04–0.089)	7.8	0.084 (0.062–0.13)	11	0.091 (0.067–0.14) [a]	12
L2	0.059 (0.043–0.093)	8.0	0.12 (0.085–0.18) [a]	15	0.16 (0.12–0.25) [a]	20
L3	0.23 (0.17–0.36) [a]	28	0.14 (0.10–0.21) [a]	16	0.31 (0.23–0.49) [a]	36

[a] statistically significantly different from largest of two SDdiff values of the repeated mesurements.

Again, we observed that when we increased the number of regions in the analysis model we observed greater variability and declining precision.

Discussion

We found that all models had low CVs when the hip was scanned in the same position. The 15° externally rotated position tended to be less reproducible than the others. One explanation could be that the area was slightly smaller (as seen from the higher BMD) in external rotation, leading to some difficulty in placing the ROIs.

As expected (Gehrchen 1999), we observed declining reproducibility with regions of smaller size. However, despite the fact that we subdivided the femoral neck into 6 small regions, a mean CV of 4.6% meant that DXA could detect a mean BMD change of 9% with 95% confidence in this population.

Because the CV is only slightly greater than CVs obtained from the Gruen zones around a standard THA (Cohen and Rushton 1995, Kroger et al. 1996, Sabo et al. 1998, Yamaguchi et al. 2000) and substantially better than in plain radiographs (Engh et al. 2000), it seems reasonable to use DXA in longitudinal evaluations of bone changes around an RTHA.

In contrast to the Gruen zones (Kroger et al. 1996, Mortimer et al. 1996), the femoral neck regions were highly sensitive to change in position. Rotation of the leg in increments of 15° and 30° increased the variability in all models, and had dramatic effects on the distal part of the 6-ROI model, where the CV was increased to unacceptable levels of up to 36%. Not all subregions showed statistically significant effects. It could be that there were none, but it could also be that our study was under-dimensioned, as we had a power of only 78% and those regions had change of variation below the set MIREDIF of 0.02 g/cm^2 that our study was dimensioned to detect. That the BMD of the distal part of the femoral neck was affected the most can be explained by the dependence of precision on variation in area (Engelke et al. 1995). Over a rotation arch, this part of the bone—being furthest away from the center of rotation—would experience the largest change of area.

Rotation also affects the intact femoral neck (Wilson et al. 1991, Goh et al. 1995, Rosenthall 2004) but contrary to our findings around a RTHA, the effect is less important with CVs below 3% for the rotations found in clinical settings. As the intact-neck studies have also used a model that includes the outer margins of the neck and where area depends on the rotation, the only explanation for the exaggerated response in our models must be an added variability from the metal or removal of the metal on the scan.

Our study might have been strengthened further if we had also measured the precision achievable with the standard footrests. A precision study by Murray et al. (2005) found an overall CV of 5% using inward-rotated standard footrests modified with an extra Velcro strap, which compares well with our rigid fixation. However, Murray's patients are well-functioning after 2-year follow-ups, presumably with no difficulty in maintaining the inward rotation. In a longitudinal study, postoperative pain and contractures could cause a resistance to the inward rotation at baseline and at the early follow-ups.

We tried to control the rotation better than with standard footrests, but we could not validate this. However, we would not have been able to do our rotation study with the standard footrest alone. To demonstrate that the femoral neck actually moves correspondingly with the shell, we could have used CT validation but refrained from that as the radiation from repeated scans could pose a risk to the patients. To support our assumption, the shells were meticulously designed to rotate in the hip alone. We asked the patients to try to move inside the shell; none could—and finally it was obvious from the appearance of the lesser trochanter on the scans that the hip joint moved with the shell. As immobilizing the knee and ankle is found to reduce the measuring error by almost half compared to standard footrests (Goh et al. 1995), we would not expect footrests to be adequate in a scanning model sensitive to rotation, but if useable, it would certainly be more comfortable for the patients and cause less effort for the staff.

The larger-region analysis models are the most precise, but they lack detail. If we had collected longitudinal scans without rigid control of the hip, we would have analyzed them using the 2-ROI model. With CVs under 5%, the medial region is robust during rotation, and would enable us to focus on the calcar bone stock in particular. The lateral region is sensitive to rotation and cannot be trusted to provide valid BMD measurements, but the computer can automatically create a "total" from the 2 regions and give us a valid overall femoral neck BMD that can allow smaller rotations. However, if planning a longitudinal RTHA trial, we suggest that the more detailed 6-ROI model should be used. It requires rigid fixation but provides regional detail, and future studies may tell us whether a particular anatomical localization of the femoral neck is crucial to the long-term survival of the prosthesis.

SO, OO, KB, and JØP designed the study. JØP obtained and analyzed the data. All authors wrote the initial draft of the manuscript. JEV ensured the accuracy of the data and of the analyses.

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Early micro motion of the ASR™ resurfacing femoral component. Two year radiostereometry (RSA) results.

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Abstract:
Radiostereometry (RSA) can detect the early micro motion in unstable implant designs likely to experience above average failure rates. In 2010, the ASR resurfacing implant was withdrawn from the marked due to excess failure rates. A few RSA studies exist on competing femoral resurfacing components, and all have displayed initial implant stability. The mean (sd) micro motion over the first two years of nineteen femoral Articular Surface Replacement (ASR) components was a lateral movement of 0.107 (0.513) mm, distal migration of 0.055 (0.204) mm, and anterior movement of 0.150 (0.413) mm. The backward tilt around the x axis was -0.08°(1.088), there was 0.165°(0.924) internal rotation and 0.238° (0.420) varus tilt. The baseline to 2 year varus tilt was statistically significant from zero movement, but on a group level no significant movement was present from 1 year onwards. We conclude, that the ASR femoral implant achieves initial stability, and that early migration is not the mode of failure for the ASR implant.

Introduction:
Resurfacing hip arthroplasty (RHA) has had a renewed interest during the past decade due to improved design materials and implant fixation. In recent years, however, it has transpired that compared to total hip arthroplasty (THA), RHA might have an increased incidence of failure (Johanson et al., 2010). This occurs most often on the basis of pain/aseptic loosening, but also due to early femoral neck fractures (Graves et al., 2009; van der et al., 2011). A strong link amongst high wear rates, raised systemic ion levels and painful hips, (Kwon et al., 2010; Hart et al., 2009; Langton et al., 2011) puts wear products under suspicion for inducing a local toxic or immunological reaction (adverse reaction to metal debris/ARMD or pseudotumor) causing failure. Few studies have looked at implant stability which might be a predictor for implant failure. Ideally, the principles about stepwise introduction would mean that all new resurfacing implants were studied by radiostereometry (RSA) (malchau H, 1995), where 1 to 2 year migration is an indicator for increased risk of early or intermediate term revisions (Karrholm et al., 1997), but only a few clinical studies have published RSA results on RHA. Two on the Birmingham hip resurfacing arthroplasty, (Glyn-Jones et al., 2004; Itayem et al., 2007; Itayem et al., 2005) one on the Conserve plus system (Gulati et al., 2009) and one on the ReCap (Baad-Hansen et al., 2011). These devices are RSA stable and based on registry data the implant survival is good for the first two. (Porter et al., 2009; Graves et al., 2011).
The DePuy ASR™ Hip Resurfacing System has had above average failure rates.(Porter et al., 2010) and was recalled from the marked in 2010 due to that reason. Presently no one has looked at the stability of the ASR implant in a RSA study.

The aim of this study was evaluate the implant stability of the femoral component of the DePuy ASR™ Hip Resurfacing System by use of RSA.

Patients and Methods:
Study design.
The RSA study is part of a randomised clinical trial aiming to investigate several outcomes regarding RHA vs. THA. It was block randomized and open-labelled and registered at clinicaltrials.gov as # NCT01113762. Despite the randomization process there was no intention of comparing RSA data between the intervention groups. RSA analysis was only planned for the RHA group.
Patients.

Patients eligible to participate had primary osteoarthritis, secondary osteoarthritis due to mild dysplasia and an age from 40 to 65 years. The CONSORT flow-chart is presented in Figure 1. Following IRB approval (project-ID: VF-20050133, 2005, the ethical review board Funen county, Denmark) and informed consent, the patients were randomised using sealed envelopes and operated with RHA (n=20) or a standard ceramic-on-polythylene THA (n=19). One RHA was excluded following cup displacement the day after surgery, leaving two groups of 19. Only the RHA group was RSA examined.

The patients were operated from April 2007 to March 2009 at the Department of Orthopaedics and Traumatology, Odense University Hospital, Denmark. Of the 19 patients 8 were female, the median (range) age was 57.0 (45.8 to 64.3) yrs. and the Body mass index 27.9 (19.2 to 36.5). The median head size was 51 mm (range 47 to 57 mm)

Surgery

The RHA group received an Articular Surface Replacement (ASR®, DePuy, Warsaw, IN, USA) made from a high-carbon cobalt-chromium-molybdenum alloy. The cup had an outer porous-bead coating "Porocoat®" coated with hydroxyapatite (low crystalline, high purity, thickness 30-50 microns). All patients underwent hip resurfacing through a standard posterior approach by two consultant surgeons (SO, OO) who both had performed more than 40 RHA procedures prior to including. The gluteus maximus muscle was divided, and the distal insertion was detached along with the external rotators. After dislocating the hip, the femoral head was temporarily prepared in order to get more space for the reaming of acetabulum. A guide-wire was inserted on top of the head and centrally into the femoral neck avoiding notching. A cup, two sizes above the corresponding templated size of the matching acetabulum, was selected, and placed cementless in press-fit under reamed by 1 mm.

After cup insertion the final head chamfer reamer prepared the head. Multiple anchorage-holes were prepared with a 3 mm drill. The bone surface was washed by using of high pressure lavage. The femoral component was cemented with SmartSet™ GHV Bone Cement (DePuy, Warsaw, IN, USA) mixed in the Semvac Vaccum mixing system (DePuy) according to the manufacturers manual. Cement was digitally pressured into the bone surface and drill holes but not into the central pin hole approximately 2 minutes after start of mixture, where after the femoral component was introduced over the head. The prosthetic concept leaves a thin cement layer. After 12 minutes the surfaces were washed by using of high pressure lavage and the hip was reduced. The patients were allowed full weight-bearing when able, postoperatively on the same day of surgery.

RSA

The femoral component had four 0.8 mm tantalum markers mounted on the peg of the femoral head component. A special cutting tool was designed to create a groove in the pin-hole. The markers were injected into the bone using the UmRSA® Injector™ (RSA Biomedical, Sweden). Five 0.8 mm tantalum beads were inserted into the greater and 3 into the lesser trochanter and one approximately 15 cm distal to the greater trochantor tip.

The patients were RSA X-rayed postoperatively (within 3 days of surgery following mobilisation), at 8 weeks, 6 months, 1 and 2 years. Thirteen double examinations were carried out to assess the precision of the RSA system and the radiographic tubes and the calibration box were repositioned between the two examinations.

The patients were placed in supine position over a uniplaner UmRSA® Calibration Cage™ , cage 43 (RSA Biomedical, Sweden) with ceiling mounted X-ray tubes at approximately 35 deg. angle to each other. The exposure was set to 130 kV and 20 mAs. All x-ray images were stored electronically in GE PACS (GE Healthcare, Waukesha,Wisconsin, USA)

The X-ray images were retrieved via the DICOM Link to the computer where the Digital Measure™ package from the UmRSA® Software 6.0 system (RSA Biomedical, Sweden) was used

to identify bone markers and reference points. The UmRSA® Analysis™ package was used to compute potential femoral implant migration and rotation.
For marker stability, an upper limit of 0.35 mm was selected for the mean error of rigid body fitting, and an upper conditioning number (CN) of 150 for distribution.
Following the guideline by Valstar et al. (Valstar et al., 2005), translations and rotation of the pin (centre of gravity) are presented as mean ± SD.
We report signed values of translations along and rotations around the X, Y and Z axis (Fig 2). The right-hand side of the body is used as anatomical reference point, with a positive X being a medial motion, positive Y being superior and positive Z being anterior movement. Left hip reverses the sign for the lateral-medial translation as well as the internal rotation and adduction to compare right and left hips.

Statistics

The RTC with both RHA and THA was dimensioned with Range of motion as primary outcome, and had a calculated sample size of 16 in each group. In order to allow for drop-outs we aimed for a sample size of 20 in each group. Sample size for the RSA study, based on a minimal relevant vertical migration of 0.4 mm (Kobayashi et al., 1997), and a SD of 0.17 mm (vertical translation, max values for both cup and femoral component) (Itayem et al., 2007), a type I error of 5% and a type II error of 20% needed only 12 patients to be included. As drops outs and poor images do occur, we chose to perform RSA on all RHA patients.

Probability plots did not indicate any relevant diversion from normality. Our focus was movement from baseline to 2 years and movement from 1 year onwards, where the implant must be assumed to be settled, and rather than analyzing all intermediate follow-up times we limited the statistical analysis to 2 paired t test (baseline to 2 years and 1 to 2 years) where $p<0.05$ (two tailed) was considered statistically significant.
To evaluate the precision of the system we calculated the 95% limits of agreement (LOA) as 1.96 times the standard deviation of the difference between two repeated measurements (Bland, Altman, 1986).
STATA 11 (StataCorp LP, College Station, Texas) software was used for all analyses, and a biostatiscian supervised the data handling.

Results:

No patients were excluded from analysis, but a few follow-up data are missing. Three 6 months RSA examinations were missed due to a hospital strike, and one patient forgot the 2 year examination. One 6 month image was excluded from analysis due to poor image quality, and one 2 year image due to poor visibility of the bone markers with a CN of 519, thus leaving 17 for the two year analysis of the femoral component.
The average condition number for the inserted bone markers was 40 and for the implant it was 135.

The mean migration in every direction was small (Table 1). Only a rotation of 0.24 degrees in the z-axis from baseline to 2 years constituted a movement statistically significant from zero ($p=0.03$). The rotation around the z axis was not statistically different from zero movement from one year onwards.
At 2 years, the greatest mean rotation was around the anterior-posterior (z) axis -0.238° (0.420) and the maximum translation also along the z axis, with 0.150 mm (0.413) in the anterior direction. The migration pattern over time is displayed in Fig. 3.

The precision analysis of 13 double examinations revealed 95% limits of agreement

of [-0.297 to 0.531] mm translation and [-0.927 to 0.801°] in rotation along the X axis, [-0.182 to 0.155] mm and [-0.947 to 0.936°] along the Y axis, and [-0.516 to 0.449] mm and [-0.433 to 0.370°] along the Z axis. 95% of individuals with zero movement will be within these limits. Outside these limits the implant is most likely moving. Eleven out of 17 patients displayed movement different from zero movement within the two year period, but only four implants continued migrating after the first year (Table 2).

Discussion:

The present paper is the first to show the early migration pattern of the withdrawn ASR RHA in a RSA study. The study showed that only little micro movement, and in particular subsidence, took place within the first two years of studying the ASR femoral component.

The study period identified statistically significant movement in the baseline to 2 year rotation around the Z axis of -0.238 °(0.420). A single patient, no. 91 (Table 2), displayed substantial movement and is statistically an outlier, and without this patient the two-year Z-rotation was only -0.168° (0.314) with a p value just below 0.05. Even being conservative and including this patient, these movements are still very small, and unlikely to be clinically significant as there is no measurable movement from 1 to two years. I.e. the implant seems to be stable.

Compared to other RHA such as ReCap (Baad-Hansen et al., 2011) and BHR (Itayem et al., 2005; Glyn-Jones et al., 2004), the 2 year ASR Z rotation was larger, but contrastingly the lateral- medial movement was smaller.

From 1 to two years, where the femoral implants must be assumed to be settled in their cement, none of the RHA studies detect mean movement different from zero movement. The micro movements are equally distributed above and below the values from the present study. The rotations of ASR and BHR implants stays within 0.2 deg, whereas the ReCap component displays slightly larger external rotational movement of 0.5 deg, but again, without any of these rotations being statistically different from zero. Translations in all studies, the present as well as a study of 20 Conserve plus implants reporting 3D migration included (Gulati et al., 2009), is below 0.2 mm in either direction. No translations are statistically significant from zero movement and especially the distal migration is small.

For THA it has been demonstrated that different implants seems to have different "safe" migration patterns. There can be large initial subsidence of 1 mm for uncemented implants,(Strom et al., 2007) but cemented total hip arthroplasties (THA) also differ in their migration. Some highly polished stems benefits from compressing in the cement (faro-Adrian et al., 2001) and the rougher surfaces are stable in their cement immediately (Strom et al., 2006) without this influencing the final stability and survival (Garellick et al., 2011; Overgaard, Pedersen, 2011). Despite RHA differences in cementation technique and inner surface design (tapered, chamfered, cylindrical) their migration patterns all seem to indicate initial stability.

The two year migration parameters in the present study are increased due to a single outlier, but even including this individual, the mean migration parameters of the ASR™ implant are comparable to those of an implant with better survival (Itayem et al., 2005; Glyn-Jones et al., 2004), as well as another implant with above average risk of failure (Graves et al., 2011; Baad-Hansen et al., 2011).

This indicate that the high failure rates shown in registries in UK, DK and Australia is not explained by general loosening problems of the femoral head.

The primary cause for resurfacing revision is loosening/lysis (35 %), closely followed by fracture (32 %)(Graves et al., 2011). The femoral neck fractures can not be ruled out as a contributing factor to implant specific failure, but the neck fracture is predominantly a risk within the first year, and as

the major differences in revision rate amongst the different implants become more apparent at a later stage, other causes are more likely. In case of ASR, the design of the cup seems to increase the risk of edge load wear in the small implants (De Haan R. et al., 2008; Langton et al., 2009). The metal particles may cause soft tissue reactions, and in time, maybe loosening. Finally, despite more revisions on the femoral side, the stability of the cup itself could also be a cause for higher revision rates. Currently cup micro motion data is only available for the BHR cup (Itayem et al., 2005), where the very small migrations measured by RSA analysis has indicated stable cup implantation.
Strengths and limitations.
This study would have been further strengthened by including cup measurements, but that has not been technically possible.
As part of a RCT it benefits from being selected with strictly defined in- and exclusion criteria, and is further strengthened by having both a larger proportion of women/smaller femoral components than the average resurfacing population(Graves et al., 2011)– if anything our migration data should be negatively biased by investigating a population with larger risk of failure.

The limitations of this, and other RSA studies, lies in the small number and short follow up where clinical failure is unlikely to occur and thus directly support the RSA data.
The components used in this study are modified by adding protruding pin-markers, and it has been suggested that RSA data from modified implants are flawed as the cement will flow into the pin canal and alter the natural behaviour of the implant.(Glyn-Jones et al., 2004) The ASR implant uses normal viscosity cement applied around the pin canal and will thereby avoid cementation of the pin. By altering the original implant by the addition of markers on the stem, we cannot guarantee that we have not introduced a possible bias, but as the unaltered BHRs report similar results to peg marked BHRs (Itayem et al., 2005) it does not seem to have any consequence.
The Gulati et al. study of the Conserve Plus RHA reported a single outlier with lateral movement above 4 mm. The patient was asymptomatic but failed during the following year (Gulati et al., 2009). A ReCap study reported an early failure due to femoral neck fracture. The patient had, prior to failure, a lateral translation of 0.7 mm at 3 months, ranking it the highest in the dataset, (Baad-Hansen et al., 2011) but none of the other RSA studies have reported failures or individual high migration. Itayem et al identified 6 components with 2 year posterior migration above the detection limit, and none had failed within 5 years.(Itayem et al., 2007)
Most of our patients had detectable movement in one direction within the study period, but only 4 from 1 year onwards. Two, including one patient with relatively large movement in all directions, are characterized by small implants and elevated/sub-elevated metal ion levels (Medicines and Healthcare products Regulatory Agency, 2010). The patients had few complaints from their operated hip and presently the implants are not considered failures, but are followed.

Our early RSA results support that the ASR femoral implant achieves initial stability with no continuous micro motion. Minimal micro motion measured by RSA may be taken as a seal of approval, but our results underline the limitations of RSA. A stable implant is not a guarantee for success, but a contributing factor. The surgical factor and patient selection also affects the implant survival and the patients in the present RSA study is operated by two experienced surgeons past their learning curve. Only 5.3% of the 132 ASR implants from our institution have been revised after an average follow up of 4.6 years, which is well below the rates reported from national registries.
The study questions that early aseptic loosening of the ASR femoral implant is the mode of failure. Subsequent failure, loosening or ARMD may likely be particle mediated, but further speculations are beyond the scope of this paper.

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Table 1. Translation and rotation (mean (sd)) at two months, six months, one and two years of the femoral ASR head

	Movement	2m	6m	1y	2 y	P value post op to 2 y		1 to 2 y	P post 1 year to 2 y
n		19	15	19	17			17	
Translation (mm)	Transverse (x)	0.128 (0.263)	-0.015 (0.344)	-0.033 (0.278)	-0.107 (0.513)	0.40		-0.039 (0.541)	0.77
	Vertical (y)	-0.042 (0.115)	-0.005 (0.232)	-0.004 (0.166)	-0.055 (0.204)	0.29		-0.041 (0.235)	0.48

	Anteriorposterior (z)	0.002 (0.300)	-0.088 (0.389)	-0.029 (0.272)	0.150 (0.413)	0.15		0.134 (0.418)	0.20
Rotation (°)	Transverse (x)	0.024 (0.723)	-0.155 (1.202)	-0.106 (0.925)	-0.08 (1.088)	0.77		-0.100 (0.648)	0.53
	Vertical (y)	0.096 (0.907)	0.216 (1.423)	0.179 (0.851)	0.165 (0.924)	0.47		-0.101 (0.611)	0.51
	Anteriorposterior (z)	-0.098 (0.259)	-0.054 (0.622)	-0.136 (0.309)	-0.238 (0.420)	0.03		-0.122 (0.386)	0.21

Table 2. Measurable migrators from 1 to 2 years.

1 to 2 years	**Xtrl (mm)**	**Ytrl (mm)**	**Ztrl (mm)**	**Xrot °**	**Yrot °**	**Zrot °**	**Gender**	**Head size (mm)**	**UCLA**	**HHS**	**Pain**	**Co (ppb)**	**Cr (ppb)**
9	0.653	0.118	0.191	-1.05	-0.46	0.06	m	51	6	92	4	1.3	1.3
11	-0.541	-0.001	0.117	-0.59	-1.42	0.09	f	47	5	93	1	5.5	7.2
82	-0.254	-0.049	-0.072	0.83	-0.01	-0.1	m	55	7	96	1	0.81	0.74
91	-1.834	-0.901	1.648	-1.69	-1.13	-1.44	m	47	10	92	18	3.76	5.35

The measurable migrations are marked highlighted in grey. Patient 11 had some lower back pain (known from before surgery), but no hip pain. Patient 91 had complaints from the contra lateral hip and was awaiting hip surgery.

UCLA= University California Los Angeles Activity Score, 1 to 10 with 10 as maximal activity, HHS= Harris Hip score 0 to 100 with 100 as max, Pain= WOMAC Osteoarthritis Index, pain score, VAS scale 0-100, where 0 is pain free.

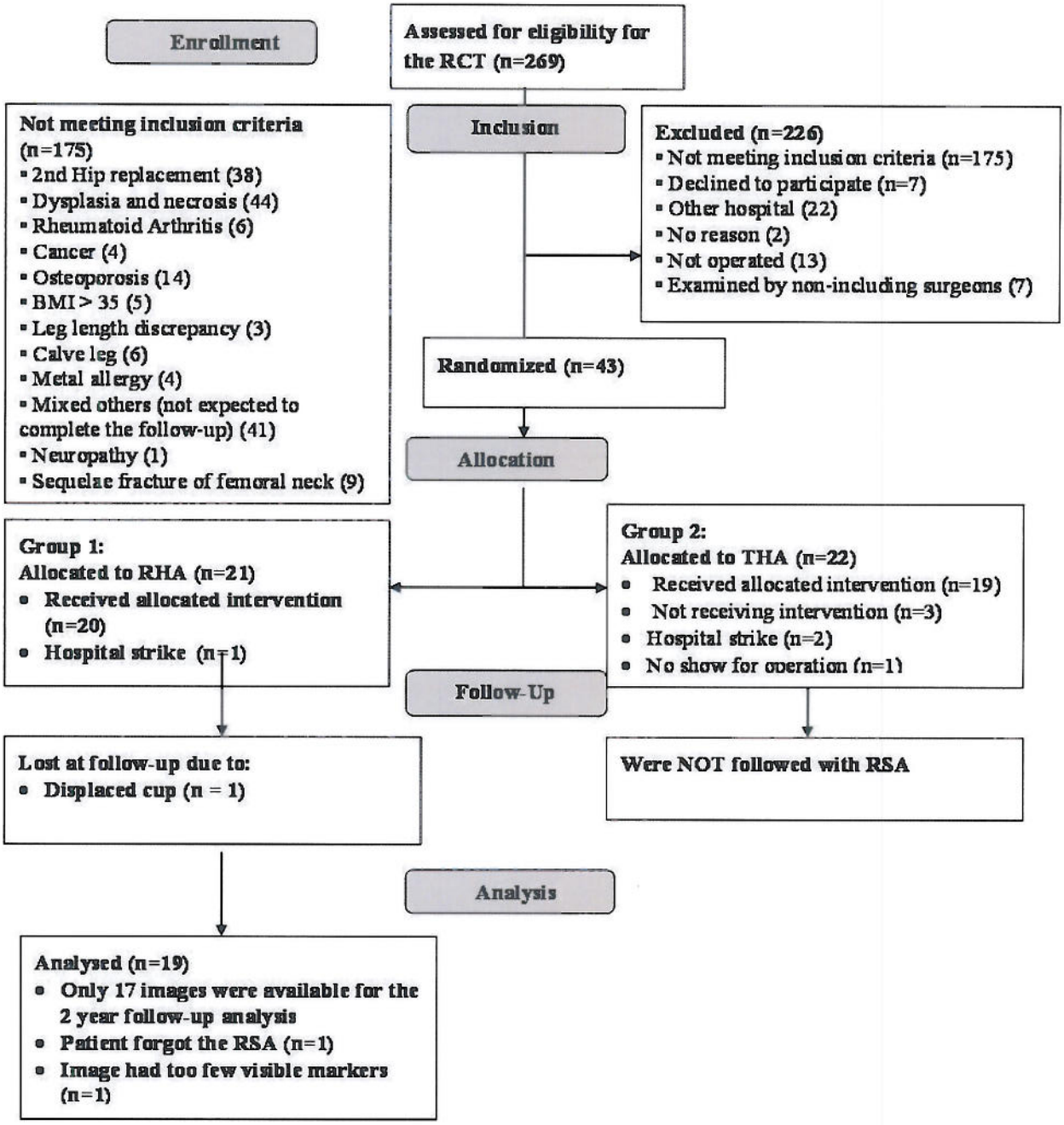
Enrollment
Assessed for eligibility for the RCT (n=269)
Not meeting inclusion criteria (n=175)
▪ 2nd Hip replacement (38)
▪ Dysplasia and necrosis (44)
▪ Rheumatoid Arthritis (6)
▪ Cancer (4)
▪ Osteoporosis (14)
▪ BMI > 35 (5)
▪ Leg length discrepancy (3)
▪ Calve leg (6)
▪ Metal allergy (4)
▪ Mixed others (not expected to complete the follow-up) (41)
▪ Neuropathy (1)
▪ Sequelae fracture of femoral neck (9)
Inclusion
Excluded (n=226)
▪ Not meeting inclusion criteria (n=175)
▪ Declined to participate (n=7)
▪ Other hospital (22)
▪ No reason (2)
▪ Not operated (13)
▪ Examined by non-including surgeons (7)
Randomized (n=43)
Allocation
Group 1:
Allocated to RHA (n=21)
• Received allocated intervention (n=20)
• Hospital strike (n=1)
Group 2:
Allocated to THA (n=22)
• Received allocated intervention (n=19)
• Not receiving intervention (n=3)
• Hospital strike (n=2)
• No show for operation (n=1)
Follow-Up
Lost at follow-up due to:
• Displaced cup (n = 1)
Were NOT followed with RSA
Analysis
Analysed (n=19)
• Only 17 images were available for the 2 year follow-up analysis
• Patient forgot the RSA (n=1)
• Image had too few visible markers (n=1)

Fig 1

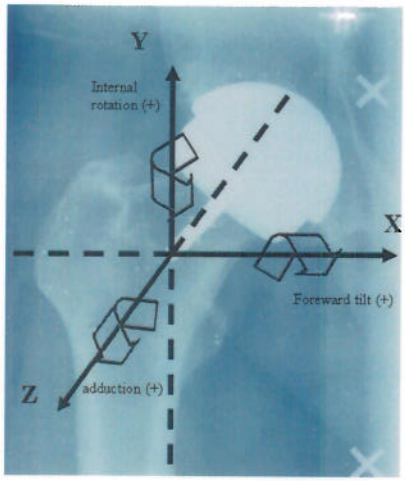

Fig 2

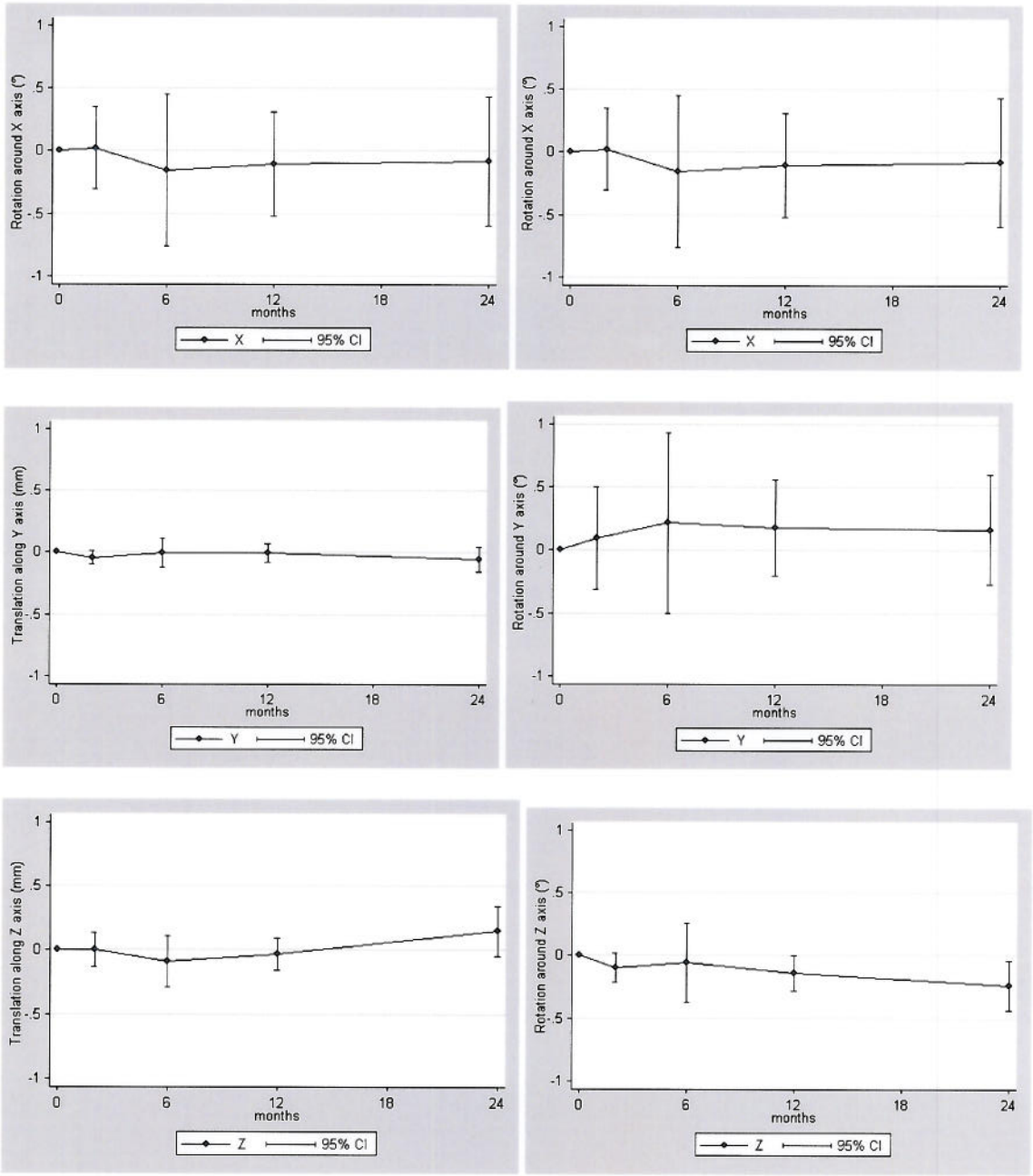

Fig 3

Acknowledgements
We wish to thank Project nurse Annie Gam-Pedersen, the technical staff at the RSA unit and statistician Lars Korsholm for their help.

Appendix 1

Abbreviation	Data categori	Details
Q	Questionnaires	EuroQol 5-d, UCLA activity score
W	WOMAC	VAS scales, 100 mm
C	Clinical data	Harris Hip Score and complications
P	Pedometer	Steps measured a week prior to the follow up visit
M	Metal ions	Serum and whole blood levels of chrom, cobolt
X	X-rays	AP and side view
B	Basic data	Height, weight, prior exposure to metals.
R	RSA	migrationsdata in the x,y og z axes
D	DXA	BMD in 6 regioner of the femoral neck on RHA (Kishida), 4 regions around the acetabulum (Wilkinson), and 7 regions around the proximal femur stem
I	In hospital	Intraoperative details, postoperative bleeding, mobilization, use of analgesics, daily pain score by pain component of WOMAC VAS scale

Appendix 2

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ Centre No ☐ Patient No ☐☐☐

SCREENING 1. BESØG I KLINIKKEN, ALLE 40-65 ÅR. SKEMAER FRA EKSKLUDEREDE/ØNSKER IKKE AT DELTAGE I ÆGGES TIL JEANNETTE Ø PENNY

INCLUSION CRITERIA (All must be "Yes")

○ Yes ○ No	Patients who are between 40 and 65 years.
○ Yes ○ No	Patients with primary idiopathic osteoarthrosis and minor dysplasia
○ Yes ○ No	Patients who understand the conditions of the study and are willing and able to comply with the post-operative scheduled clinical and radiographic evaluations and the prescribed rehabilitation
○ Yes ○ No	Patients who signed the Ethics Committee approved Informed Consent Form prior to surgery

EXCLUSION CRITERIA (All must be"No")

○ Yes ○ No	Patients with limb length discrepancies more then 1 cm.
○ Yes ○ No	Patients with dysplasia: Acetabulum on AP images with CE <25º
○ Yes ○ No	Patients with anteversion of the femoral neck more than 25 degrees
○ Yes ○ No	Patients with severe primary arthrosis with deformation of head, reduced femoral neck length and restoration of offset reduction
○ Yes ○ No	Patients with deformation after previous fracture / osteotomy or with previous hip arthroplasty
○ Yes ○ No	Patients with inflammatory joint disorder
○ Yes ○ No	osteoporosis: Earlier low energy fracture or diagnosed osteoporoses (BMD< 2.5 SD),
○ Yes ○ No	Patients with neuro-muscular or vascular disease in the affected limb
○ Yes ○ No	BMI >35
○ Yes ○ No	endocrinological disease with bone metabolic manifestations
○ Yes ○ No	renal disease
○ Yes ○ No	malignant disease
○ Yes ○ No	Patients needed fixed daily dosages of morphine for other reasons than the hip disease
○ Yes ○ No	High dose corticosteroids
○ Yes ○ No	Metal allergy
○ Yes ○ No	Other reasons (please specify below) _____

All Inclusion criteria must be answered with Yes and all Exclusion criteria must be answered with No in order to be able to include the patient in the study!

Investigators signature_____ Date ☐☐-☐☐-☐☐☐☐

Appendix 2

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ Centre No ☐ Patient No ☐☐☐

SCREENING 1. BESØG I KLINIKKEN, ALLE 40-65 ÅR. SKEMAER FRA EKSKLUDEREDE/ØNSKER IKKE AT DELTAGE I ÆGGES TIL JEANNETTE Ø PENNY

INCLUSION CRITERIA (All must be "Yes")

O Yes O No	Patients who are between 40 and 65 years.
O Yes O No	Patients with primary idiopathic osteoarthrosis and minor dysplasia
O Yes O No	Patients who understand the conditions of the study and are willing and able to comply with the post-operative scheduled clinical and radiographic evaluations and the prescribed rehabilitation
O Yes O No	Patients who signed the Ethics Committee approved Informed Consent Form prior to surgery

EXCLUSION CRITERIA (All must be"No")

O Yes O No	Patients with limb length discrepancies more then 1 cm.
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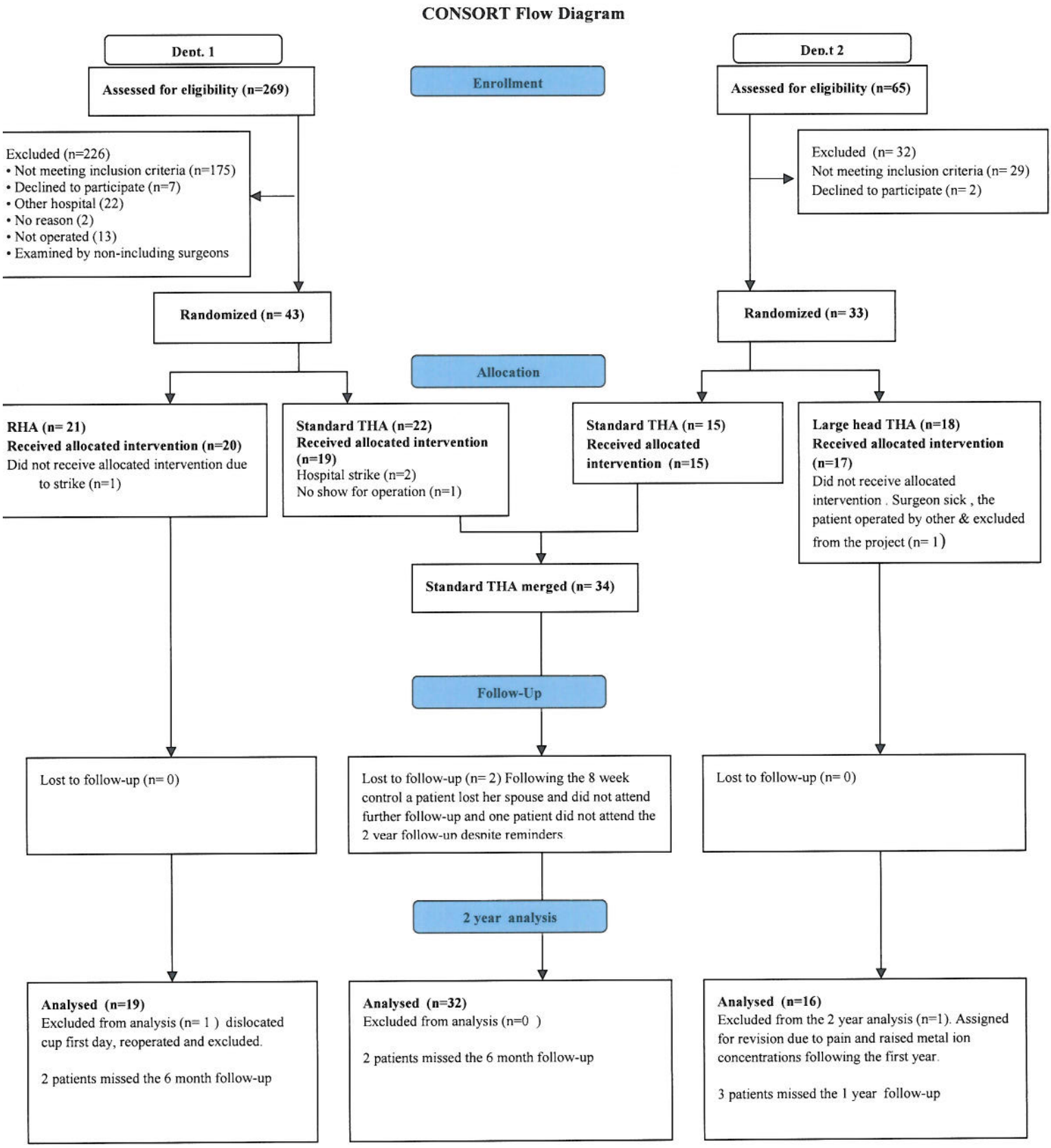
O Yes O No	osteoporosis: Earlier low energy fracture or diagnosed osteoporoses (BMD< 2.5 SD),
O Yes O No	Patients with neuro-muscular or vascular disease in the affected limb
O Yes O No	BMI >35
O Yes O No	endocrinological disease with bone metabolic manifestations
O Yes O No	renal disease
O Yes O No	malignant disease
O Yes O No	Patients needed fixed daily dosages of morphine for other reasons than the hip disease
O Yes O No	High dose corticosteroids
O Yes O No	Metal allergy
O Yes O No	Other reasons (please specify below)

_____

All Inclusion criteria must be answered with Yes and all Exclusion criteria must be answered with No in order to be able to include the patient in the study!

Investigators signature_____ Date ☐☐-☐☐-☐☐☐☐

Appendix 3


CONSORT Flow Diagram
Dept. 1
Assessed for eligibility (n=269)
Enrollment
Dep.t 2
Assessed for eligibility (n=65)
Excluded (n=226)
• Not meeting inclusion criteria (n=175)
• Declined to participate (n=7)
• Other hospital (22)
• No reason (2)
• Not operated (13)
• Examined by non-including surgeons
Excluded (n= 32)
Not meeting inclusion criteria (n= 29)
Declined to participate (n= 2)
Randomized (n= 43)
Randomized (n= 33)
Allocation
RHA (n= 21)
Received allocated intervention (n=20)
Did not receive allocated intervention due to strike (n=1)
Standard THA (n=22)
Received allocated intervention (n=19)
Hospital strike (n=2)
No show for operation (n=1)
Standard THA (n= 15)
Received allocated intervention (n=15)
Large head THA (n=18)
Received allocated intervention (n=17)
Did not receive allocated intervention . Surgeon sick , the patient operated by other & excluded from the project (n= 1)
Standard THA merged (n= 34)
Follow-Up
Lost to follow-up (n= 0)
Lost to follow-up (n= 2) Following the 8 week control a patient lost her spouse and did not attend further follow-up and one patient did not attend the 2 year follow-up despite reminders
Lost to follow-up (n= 0)
2 year analysis
Analysed (n=19)
Excluded from analysis (n= 1) dislocated cup first day, reoperated and excluded.
2 patients missed the 6 month follow-up
Analysed (n=32)
Excluded from analysis (n=0)
2 patients missed the 6 month follow-up
Analysed (n=16)
Excluded from the 2 year analysis (n=1). Assigned for revision due to pain and raised metal ion concentrations following the first year.
3 patients missed the 1 year follow-up

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ Centre No ☐ Patient No ☐☐☐

UCLA activity score Pre OP	Activity level
1: ☐	Wholly inactive: dependent on others: cannot leave residence
2: ☐	Mostly inactive: very restricted to minimum activities of daily living
3: ☐	Sometimes participates in mild activities such as walking, limited housework, and limited shopping
4: ☐	Regularly participates in mild activities
5: ☐	Sometimes participates in moderate activities such as swimming and can do unlimited housework or shopping
6: ☐	Regularly participates in moderate activities
7: ☐	Regularly participates in active events such as bicycling
8: ☐	Regularly participates in very active events such as bowling or golf
9: ☐	Sometimes participates in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor, or backpacking
10: ☐	Regularly participates in impact sports

Investigators signature_____ Date ☐☐-☐☐-☐☐☐☐ 11

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ Centre No ☐ Patient No ☐☐☐

PRE-OPERATIVE ASSESSMENT (3/3) (JØ kopieret fra Skema A/direkte fra A til database)

SMERTER I HOFTEN*:
- O 1 Ingen
- O 2 Lette, ingen aktivitetsbegrænsning
- O 3 Milde, ej aktivitet, kun svær anstrengelse
- O 4 Moderate, kun ved dagl. aktiviteter + arb og analgetica
- O 5 Sværere, stærk begrænsning I dagl. aktiviteter
- O 6 Invaliderende hvilesmerter

GANGAFVIKLING*:
- O 1 Ingen halten
- O 2 Let halten
- O 3 Tydelig halten
- O 4 Udtalt halten

GANGDISTANCE*:
- O 1 Ubegrænset
- O 2 1,5-2 km
- O 3 0,5-1 km
- O 4 kun indendørs
- O 5 Bunden til seng/kørestol

HJÆLPEMIDLER TIL GANGFUNKTION*:
- O 1 Ingen
- O 2 Én stok ved lange ture
- O 3 Næsten altid én stok
- O 4 Én albue/aksilkrykke
- O 5 To stokke
- O 6 To krykker eller rollator

TRAPPER*:
- O 1 Bruger ikke gelænderet
- O 2 Bruger gelænderet
- O 3 Yderst besværligt
- O 4 Kan ikke

SKO OG STRØMPER*:
- O 1 Uden besvær
- O 2 Med besvær
- O 3 kan ikke

SIDDEFUNKTION*:
- O 1 Bekvemt I lænestol
- O 2 På høj stol I ca. 30 min.
- O 3 Sidder aldrig bekvemt

OFFENTLIGE TRANSPORTMIDLER*:
- O 1 Kan bruge dette
- O 2 Kan ikke bruge dette

BENLÆNGDE
- O 1 Lige lange +/- 1 cm

Venstre længst	Højre længst
O 2. >1-2 cm	O 5. >1-2 cm
O 3. >2-3 cm	O 6. >2-3 cm
O 4. >3 cm	O 7. >3 cm

EKSTENSION (grader)	ADDUKTION (grader)
+	+
- _____	- _____
FLEKSION (grader)	**IDADROTATION (grader)**
+	+
- _____	- _____
ABDUKTION (grader)	**UDADROTATION (grader)**
+	+
- _____	- _____

Harris Hip Score* (HHS):_____

Investigators signature_____ **Date** ☐☐-☐☐-☐☐☐☐

5

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ **Centre No** ☐ **Patient No** ☐☐☐

PREOPERATIV WOMAC (1/3)

Afsnit A

SMERTER

Tænk på smerterne De har haft i hoften i de sidste 48 timer som følge af slidgigt. (Angiv svarene med et kryds "X".)

SPøRGSMÅL: Hvor mange smerter har De…..			Udfyldes af undersøgelseslederen
1. Når De spadserer på en vandret flade?			
Ingen smerter	_____	Stærke smerter	PAIN 1 _____
2. Når De går op eller ned ad trapper?			
Ingen smerter	_____	Stærke smerter	PAIN 2 _____
3. Om natten når De ligger i sengen?			
Ingen smerter	_____	Stærke smerter	PAIN 3 _____
4. Når De sidder eller ligger?			
Ingen smerter	_____	Stærke smerter	PAIN 4 _____
5. Når De står oprejst?			
Ingen smerter	_____	Stærke smerter	PAIN 5 _____

Afsnit B

STIVHEDEN

Tænk på stivheden (ikke smerterne), De har haft i hoften i de sidste 48 timer som følge af slidgigt.

Stivheden er fornemmelsen af at have nedsat **bevægelighed** i leddet. (Angiv svarene med et kryds "X".)

			Udfyldes af undersøgelseslederen
6. Hvor alvorlig er stivheden, når De først vågner om morgenen?			
Ingen stivhed	_____	Ekstrem stivhed	STIFF 6 _____
7. Hvor alvorlig er stivheden, når De har siddet, ligget eller hvilet Dem senere på dagen?			
Ingen stivhed	_____	Ekstrem stivhed	STIFF 7 _____

Investigators signature_____ **Date** ☐☐-☐☐-☐☐☐☐

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ **Centre No** ☐ **Patient No** ☐☐☐

PREOPERATIV WOMAC (2/3)

Afsnit C

VANSKELIGHEDER VED AT UDFøRE DAGLIGE AKTIVITETER

Tænk på, hvor vanskeligt det har været for Dem at udføre følgende daglige aktiviteter i de sidste 48 timer som følge af slidgigt i hoften. Med dette menes den måde hvorpå De er i stand at bevæge Dem og klare Dem selv. (Angiv svarene med et kryds "X".)

SPøRGSMÅL: Hvor vanskeligt er det for Dem at…..			Udfyldes af undersøgelseslederen
8. Gå ned ad trapper?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 8 _____
9. Gå op ad trapper?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 9 _____
10. Rejse dem op efter at have siddet?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 10 _____
11. Stå oprejst?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 11 _____
12. Bøje Dem ned til gulvet?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 12 _____
13. Spadsere på en vandret flade?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 13 _____
14. Stige ind/ud af en bil eller af/på en bus?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 14 _____
15. Gå på indkøb?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 15 _____

Investigators signature_____ **Date** ☐☐-☐☐-☐☐☐☐

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ **Centre No** ☐ **Patient No** ☐☐☐

PREOPERATIV WOMAC (3/3) VANSKELIGHEDER VED AT UDFØRE DAGLIGE AKTIVITETER, forts.

Tænk på, hvor vanskeligt det har været for Dem at udføre følgende daglige aktiviteter i de sidste 48 timer som følge af slidgigt i hoften. Med dette menes den måde hvorpå De er i stand at bevæge Dem og klare Dem selv. (Angiv svarene med et kryds "X".)

SPøRGSMÅL: Hvor vanskeligt er det for Dem at…..			Udfyldes af undersøgelseslederen
16. Tage sokker/strømper på?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 16 _____
17. Stå op af sengen?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 17 _____
18. Tage sokker/strømper af?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 18 _____
19. Ligge i sengen?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 19 _____
20. Stå ned i/op af badekarret?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 20 _____
21. Sidde?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 21 _____
22. Sætte Dem på/rejse Dem fra toilettet?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 22 _____
23. Udføre tungere husarbejde?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 23 _____
24. Udføre lettere husarbejde?			
Ikke vanskeligt	_____	Meget vanskeligt	PFTN 24 _____

WOMAC total _____**(mm)**

Investigators signature_____ **Date** ☐☐-☐☐-☐☐☐☐

Appendix 7

Metal-Metal STUDY

Multicentre Prospective Clinical Study

Date of Examination ☐☐-☐☐-☐☐☐☐ **Centre No** ☐ **Patient No** ☐☐☐

Pre OP EuroQol 5-d	
SKEMA OM DIT HELBRED IDAG	
Hvordan synes du dit helbred er alt i alt?	Fremragende.....1 Vældig godt.....2 Godt.....3 Mindre godt.....4 Dårligt.....5
Føler du dig frisk nok til at gennemføre det som du har lyst til at gøre?	Ja, for det meste.....1 Ja, af og til.....2 Nej, sjældent.....3
Hvert af de næste spørgsmål har tre mulige svar. Sæt kryds ud for det svar som passer bedst for i dag. Hvordan har du det mht....(det ord der står i hvert af spørgsmålene)....i dag?	
Bevægelighed	1 Jeg har ingen problemer med at gå omkring 2 Jeg har nogle problemer med at gå omkring 3 Jeg er bundet til sengen
Personlig pleje	1 Jeg har ingen problemer med min personlige pleje 2 Jeg har nogle problemer med at vaske mig eller klæde mig på 3 Jeg kan ikke vaske mig eller klæde mig på
Sædvanlige aktiviteter fx arbejde, studie, husarbejde, familie- eller fritidsaktiviteter	1 Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter 2 Jeg har nogle problemer med at udføre mine sædvanlige aktiviteter 3 Jeg kan ikke udføre mine sædvanlige aktiviteter
Smerter/ubehag	1 Jeg har ingen smerter eller ubehag 2 Jeg har moderate smerter eller ubehag 3 Jeg har ekstreme smerter eller ubehag
Angst/depression	1 Jeg er ikke ængstelig eller deprimeret 2 Jeg er moderat ængstelig eller deprimeret 3 Jeg er ekstremt ængstelig eller deprimeret
Særlige kommentarer vis du ønsker at uddybe svarene: _____ _____ _____ _____ _____	
Samlet EuroQol 5-d score:_____	

Investigators signature_____ **Date** ☐☐-☐☐-☐☐☐☐

Appendix 8

SOCIO grading:

11 Self-employed:
111 50 or more employees
112 10-49 employees
113 1-9 employees
114 no employees

12 Assisting Spouse

13 Employees:
131 Leading executives
132 Employees at the highest educational level (bachelor level+)
133 Employees at a medium educational level (lab assistant, pre school teacher etc.)
134 Employees at a low educational level (Plummer, office clerk etc.)
135 Employees without education

2 Unemployed