Outcome of osteoarthritis and arthroplasty from patient perspective to molecular profiling.

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Waar in ’t bronsgroen eikenhout, ’t nachtegaaltje zingt.
Over 't malse korenveld, ’t lied des leeuweriks klinkt.

Limburgs volkslied.

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Introduction

Predictors of joint disease and outcome of arthroplasty from patient perspective to molecular profiling.

The average life expectancy is increasing, and it is predicted that by 2045 over 30% of the population in the Western World will be aged over 60 years of age. With older age, health deteriorates and the prevalence of most chronic diseases increases, however, the extend of these diseases varies between men and women.[1] Loss of independency at higher age is most often due to problems of the musculoskeletal system (MSK). Out of all rheumatic diseases, osteoarthritis (OA) is the most frequent cause of these MSK problems, which may cause severe disability of patients. OA is the most prevalent chronic joint disorder worldwide, affecting the joints of hip, knee, hands, spine and feet and is strongly influenced by metabolic health and age.[2-4]

In short, OA is characterized by deterioration of the cartilage of the joint and leads to narrowing of the joint space until the presence of bare bone on bone contact and the formation of osteophytes.[5] Of the 291 conditions studied in the Global Burden of Disease study, OA ranks as the 11th highest contributor to global disability and has been found to be the leading source of morbidity (i.e. pain and functional disability) in industrialized countries.[6,7] Incidence and prevalence vary widely depending upon the used definition and sampled population.[8,9] Knee OA is more prevalent than hip OA with an estimated global prevalence of radiographically confirmed knee OA of 3.8% (95%CI: 3.6-4.1), while for hip OA this was 0.85% (95%CI: 0.74-1.02%).[10,11] In the Netherlands, the average prevalence of osteoarthritis is 5.7% in males and 10.4% in females, affecting more often the knee than the hip.[12]

In 2007, the health care costs of joint related diseases in the Netherlands, including osteoarthritis, were estimated at 2.1 billion euro, 3.6% of the national medical costs.[13] By 2015, the total direct costs attributable to osteoarthritis alone were 1.3 billion euro, which was 1.6% of the total healthcare costs for the Netherlands in 2015.[14] Thus, adequate treatment and the adequate selection of patients to undergo treatment is paramount to keep public healthcare affordable in the near future.

Efficient treatment is hampered by the heterogeneity of this disease; the disassociation of radiographic and clinical symptoms makes the diagnosis a container of diverse pathological processes. Currently, no cure exists to halt the progression of osteoarthritis and treatment consists of pain relief and minimizing the impact on functioning in daily life.

Patients will start with pain medication such as analgesics, intra articular steroids and/or intra articular hyaluronic in order to relieve their symptoms.[15-18] As these medications only affect the symptoms of OA, they do not slow down the progression of the disease. When the symptoms have become too severe and pain medication is not sufficient anymore, arthroplasty will be performed. Arthroplasty is a major invasive surgery during which the joint is replaced by an implant.

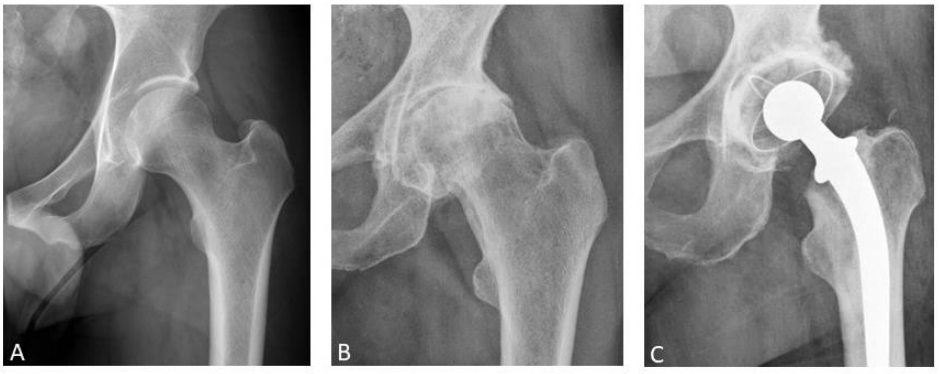

Figure 1 - Rontgen photos of (A) a healthy hip joint, (B) an osteoarthritic hip joint and (C) a hip joint after total joint replacement (arthroplasty) surgery.

In the Netherlands, 29,937 total hip arthroplasty (THA) and 29,221 total joint arthroplasty (TKA) surgeries were performed in 2017.[19] The procedure is very safe and effective with a mean survival rate of a hip or knee prosthesis of 95% at 15 years after surgery.[20-24] Despite these excellent results with respect to revision of the knee or hip prostheses, patients perceived satisfaction varies. While some patients are very satisfied (mean 83 points out of 100 on a visual analog scale), a large group (up to 20%) is not satisfied with their surgery.[25-28]

Postsurgery factors associated with outcome of joint arthroplasty: prosthesis and physical activity.

Reasons for this large portion of less favorable outcomes are multifactorial and can be related to surgical factors (i.e. surgical technique), joint status (i.e. deformity or degree of osteoarthritis) but also patient factors, like preoperative patient expectations, patient selection and baseline health status. The latter will also be associated with the metabolic state of the patient, thus determining recovery and rehabilitation after a surgical intervention, like a total joint arthroplasty, which has a tremendous impact on a patient. Next to this, other preoperative factors related to metabolic health, affecting muscle function (i.e. mitochondrial function) will also have an effect on postoperative recovery and thus rehabilitation after a major surgical procedure.

This is underscored even more, since the majority of the patients who have total joint arthroplasty at the age of about 70 years have one or more comorbidities, resulting in higher perioperative risks with concomitant less favourable outcome of TJA surgery. Finally, outcome after TJR can be affected by the total joint arthroplasty itself, which is related to foreign body reactions to wear debris produced by the artificial new joint. In this thesis, we assess three main factors that are related with the outcome; (I) the implant, (II) physical activity and (III) baseline health of the patient.

I Bearings of prostheses (implants).

Many designs and types of hip and knee prostheses are available, not only with different shapes but also with different types of bearings. One of these bearings is a metal-on-metal bearing used in total hip replacement, with the idea that it is more durable (i.e. less wear) than a metal on polyethylene bearing. Since metal-on-metal (MOM) bearings produce metal wear debris, causing both local and systemic adverse effects (e.g. nephrotoxicity or cardiotoxicity), these implants are no to be used.[29] However, since these MOM hip prostheses are still in place thousands of patients, a discussion on long-term effects of these implants on patients is important.

II Postoperative physical activity

One of the main hallmarks of successful total joint arthroplasty is its actual use, as is reflected by the level of physical activity (PA) of the patients. Postoperative rehabilitation is essential to have an optimal postoperative result since both muscle strength as well as range of motion of the joint after the arthroplasty will affect PA.[30] The literature on PA after arthroplasty up to now is conflicting and an age-matched comparison with the general population of postoperative PA is lacking.

III Baseline health of the patient

Since OA is prevalent especially among elderly patients, their preoperative baseline health varies considerably. The heterogeneity in baseline health status can be measured in many different ways.[31] Here we discuss to what extent the baseline frailty index, a standardized measurement of handgrip strength or molecular profiling associate with the outcome.

Baseline health factors associated with outcome of joint arthroplasty: frailty index, handgrip strength & molecular profiling.

III A Frailty

In the Netherlands, up to 83% of the THA patients and 79% of TKA patients are 60 years and older.[19] As frailty is highly prevalent in the elderly, with a prevalence of 10.7% in this age group, it is likely that a considerable proportion of patients undergoing THA or TKA are frail.[32] This may have an effect on recovery after a TJA and thus the functional outcome after such an intervention.

Although there is not one definition for frailty, the most often used definitions include a combination of decrease of independence, strength, cognition, activity, energy, weight and walking speed.[33-39] Considerable heterogeneity in the extent of frailty between individuals is present, with some persons accelerating fast while others are slowly progressing to more severe levels of frailty.[40] Between persons of the same age, the onset of frailty differs greatly per individual. The pooled prevalence rates for persons aged 65-69 is less than 5%, while for those aged 80-85 this is over 15% and even over 25% for persons aged ≥85.[41-44]

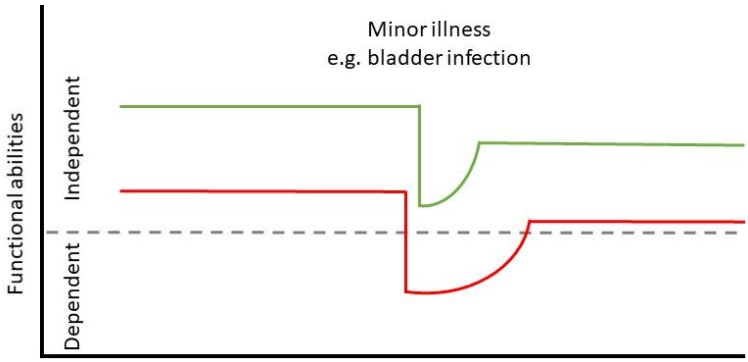

Figure 2 – Capability to resist stressors such as a minor illness. Certain persons can maintain a level of independence in their functional abilities whereas others are strongly affected by a minor illness and need a long recovery phase.

Frailty represents less resilience, with less capability to resist stressors, and thus reflects overall health and functional status of an individual, as simplified in figure 2. As such frailty might be associated with less favorable outcome after arthroplasty surgery (i.e. a cause for the 15-20% less favourable results after hip- and knee arthroplasty surgery).[41,45-47] Frailty can be assessed by means of a validated questionnaire, and in order to assess the role of frailty in the outcome of total joint surgery, we used the self-reported Groningen Frailty Indicator (GFI) questionnaire to classify patients as frail or non-frail.[48]

III B Handgrip strength

As the GFI is a self-reported questionnaire, one can also assess the prognostic value of a more objective measure, handgrip strength (HGS). HGS is a proxy for overall muscular strength and is associated with worse general health and all-cause mortality.[49-55] In various patient groups, HGS has been shown to be a predictor for disability, malnutrition and surgery complications.[56-65] Also, HGS may reflect a degree of sarcopenia, the loss of skeletal muscle. Sarcopenia is relatively common in eldely, with prevalence of up to 50% in those aged over 80.[66] The relation of preoperative HGS and changes of hip and knee function and quality of life after arthroplasty needs more investigation.

III C Metabolic Health

Variation in the baseline health status of elderly patients is strongly determined by their immune and metabolic health. With the increased lifespan of the world population, as well as increasing levels of metabolically compromised and obese individuals and sedentary lifestyles, the baseline health of elderly decreases and the incidence and the burden on society of OA will increase as a consequence. Years of biomedical ageing research, predominantly in animal models, has recently made progress into understanding how immune and metabolic health varies and influences the individual ageing and disease rates (e.g. by accumulation of senescent cells, blood born factors and damaged proteins). [40]

This research resulted in novel treatment strategies for OA, currently being testing in clinical trials. The field is, however, in need of new biomarkers that may classify which baseline risks would require such treatment. Defining biomarkers for ageing and how these affect the onset and progression of diseases and of outcome of interventions like THA or TKA, would enhance patient specific treatment option. Biomarker research may also increase knowledge on the primary physiological processes underlying OA. For personalized medicine, it is paramount to increase our understanding of osteoarthritis as well as to find proper markers of predictive and prognostic value.

Epidemiological studies have shown associations of OA with unfavorable metabolic parameters, such as high body mass index (BMI), waist hip ratio and proportion of fat mass, which are especially features of metabolic diseases, such as hypertension, obesity and diabetes mellitus.[68-75] In concordance with this, weight loss reduces the symptoms of OA, relieves the pain and increases the physical function of people with OA.[76-79]

For hip and knee OA, this association is partly explained by increased mechanical load; however, also an association of high BMI and hand OA, a non-weight bearing joint, has been found.[80,81] The latter suggests a connection between OA and obesity beyond axial loading.[82,83] Furthermore, the association of OA with classical markers

of poor metabolic health such as LDL-cholesterol indicates that the metabolic health of individuals affects susceptibility for OA.[84-86] Currently, more and more evidence is emerging linking OA to the metabolic syndrome.[87-91]

To increase our understanding of the relationship of OA with baseline metabolic health more intense analyses of metabolism are required, for example by measuring metabolites in the circulation. Metabolites, the intermediate end products of metabolism, represent the influence of genotype, phenotype and environment on cell, tissues and organ functions. Novel metabolomics assays may assist in estimating the metabolic health of individuals. Such assays, as for example the well-standardized ^{1}H-Nuclear Magnetic Resonance (NMR) based plasma metabolite assays, detect a fraction of the blood metabolome and can be applied to estimate the relation between baseline metabolic health and OA disease risk.

Thus, a metabolite profile which differs between OA patients and healthy persons may reflect the aetiology of OA, the metabolites may refer to pathways that causally contributed to the OA process. Alternatively, such differences may reflect (be a biomarker of) the baseline health status of patients indicative of the resilience to recover from arthroplasty and may be part of the puzzle to explain the 15-25% of adverse outcome after a total hip- or knee arthroplasty in these OA patients.

Outline of this thesis

This thesis addresses several characteristics (potential (bio)markers), tested for their association with outcome after a total hip or knee arthroplasty. Characteristics of different nature were included: material of prosthesis, physical activity, questionnaires, clinical measures and metabolomics. This thesis aims to evaluate some of these aspects related to outcome of arthroplasty, from patient perspectives to molecular profiling (e.g. metabolic health).

First, in **chapter 2**, a meta-analysis as well as a systematic review was performed in order to assess the mortality in patients with metal-on-metal total hip prostheses as compared to patients with non-metal-on-metal total hip prostheses. Following, in **chapter 3**, the level of physical activity in hip and knee prosthesis patients was compared to the general population in order to get an indication of the actual 'use' of the prosthesis.

We then focused on baseline health factors such as frailty index, handgrip strength and molecular profiling. In **chapter 4**, the Groningen Frailty Indicator (GFI) was validated for patients scheduled to undergo hip or knee arthroplasty. Subsequently, in **chapter 5**, the GFI was applied in order to assess whether it can be used as a prognostic factor for functional outcome after hip or knee arthroplasty. Since the GFI is a subjective questionnaire, a more objective measure such as handgrip strength was assessed in similar fashion in **chapter 6**.

Finally, in **chapter 7** metabolomics-profiling was used to identify possible biomarkers of OA and OA-progression. This type of biomarker may contribute to a prognostic tool to select patients who will benefit substantially from arthroplasty. Additionally such a biomarker may lead to a more profound understanding of the pathophysiology of OA.

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Increased mortality in metal-on-metal versus non-metal-on-metal primary total hip arthroplasty at 10 years and longer follow-up: a systematic review and meta-analysis

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Abstract

Importance: There are concerns about increased mortality in patients with metal-on-metal bearings in total hip arthroplasty.

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

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

Study selection: Two reviewers screened and identified randomised controlled trials and observational studies of primary total hip arthroplasty comparing MOM THA with non-MOM THA. Two reviewers independently extracted study data and assessed risk of bias. Risk differences (RD) were calculated with random effect models. Meta-regression was used to explore modifying factors.

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

Results: There were 47 studies included, comprising 4000 THA in randomised trials and over 500.000 THA in observational studies. For mortality, random effects analysis revealed a higher pooled RD of 0.7% (95%CI 0.0% to 2.3%); I-square 42%; the heterogeneity was explained by differences in follow-up. When restricted to studies with long-term follow-up (i.e. 10 years and more) the RD for mortality was 8.5% (95%CI 5.8% to 11.2%); number needed to treat was 12. Further subgroup analyses and meta-regression random effects model revealed no evidence for other moderator variables (study level covariates e.g. resurfacing vs non-resurfacing MOM) than follow-up duration. The quality of the evidence presented in this meta-analysis was characterized as moderate according to the CLEAR-NPT (for non-pharmacological trials) and Cochrane risk of bias table.

Conclusions and Relevance: Meta-analysis revealed an increased long-term risk of mortality and revision surgery for patients with MOM THA compared to patients with non-MOM THA. Results based on the meta-analysis have major implications on treatment decisions and may be used for future research directions.

Introduction

Metal-on-metal bearings have been used since the early years of total hip arthroplasty (THA) development, and are still used today with 2.000 procedures in 2014 in the National Joint Registry alone.[1] Early historical prostheses from the 1960's 1970's and 1980s include the McKee-Farrar hip and Ring hip prosthesis.[2] They can be considered the first generation of metal-on-metal THA (MOM-THA). However, a recent long-term follow-up study of first generation MOM-THA reported increased mortality in patients with metal-on-metal bearings in total hip arthroplasty compared to patients with non-metal-on-metal bearings.[3] While this is an isolated report, metal-on-metal bearings in THA are known to produce metallic particles due to wear and corrosion.[4]

These metallic particles may lead to local and systemic adverse effects (e.g. nephrotoxicity, cardiotoxicity, carcinogenicity, and structural changes in the visual pathways and basal ganglia), which in turn could lead to increased mortality.[5,6] These reports are in conflict with two recent registry-based studies of modern, second generation MOM-THA which do not report higher mortality associated with metal-on-metal hips.[7,8] However, there are concerns that registry-based studies in this setting may be subject to residual confounding.[9] The purpose of this systematic review and meta-analysis is therefore to determine the overall mortality and morbidity in randomised controlled trials and observational studies for first- and second-generation MOM bearings compared to non-MOM bearings after primary THA in patients with end-stage primary and secondary osteoarthritis.

Methods

The reporting of this systematic review is in accordance with the PRISMA statement and a protocol has been registered a priori at the Prospero registry (PROSPERO 2014: CRD42014007417).[10] After the PROSPERO protocol was registered, we also performed a systematic review of observational studies evaluating mortality and medical complications (i.e. cancer incidence, kidney failure or cardiomyopathy) for metal-on-metal bearings compared to non-metal-on-metal bearings in patients with total hip arthroplasty.

This would allow us to compare the results from randomised controlled trials (RCTs) to the results from observational studies. The population of interest consisted of patients treated with primary total hip arthroplasty due to endstage primary and secondary osteoarthritis of the hip after failed conservative treatment. The intervention group consisted of patients who received metal-on-metal bearings, including total hip resurfacing with metal bearings: MOM THA. The control group consisted of patients with primary total hip arthroplasty with non-metal-on-metal bearings (e.g. metal-on-polyethylene, metal-on-ceramic, ceramic-on-ceramic, ceramic-on-polyethylene): non-MOM THA. The primary outcome was mortality, expressed as the number of patients who died within the study period. The secondary outcome was morbidity, expressed as the number of surgical and medical complications experienced by the subjects within the study period.

Data Sources and Searches

The search strategy was composed in collaboration with a librarian experienced in the field of total hip arthroplasty, and included studies, abstracts, and trial registry records from the date of their their inception to the end of March 2015. The following databases were searched: PubMed, MEDLINE, EMBASE, Web of Science, Cochrane, CINAHL, Academic Search Premier. The following journal publisher databases were also searched: ScienceDirect and Wiley. References of included articles were screened for relevant studies. Finally, clinical trial registers (clinicaltrails.org; WHO InternationalClinicalTrialsRegistryPlatform; Multi-register; Dutch-TrialRegistry) were searched to identify any ongoing trials that were

completed but not yet published. Contact persons of eligible trial registry records were contacted by e-mail, and at least two reminders were sent in case of no response. The search strategy for the RCTs consisted of the following components, each defined by a combination of controlled vocabulary and free text terms:

1. implant type: metal-on-metal, resurfacing and brand names
2. total hip arthroplasty
3. randomised controlled trial.

Study Selection

Initially, the literature was screened on title and abstract. This screening was performed by two reviewers (BP and JM) independently. Both reviewers recorded their findings in a pre-designed electronic database. Both databases were then compared and any disagreements were resolved by consensus or by consulting a referee. When the information in the abstract did not suffice, or if any doubt remained, the studies remained eligible. The fulltext papers of eligible studies were independently evaluated by two reviewers (BP and JM). Both recorded their findings in a pre-designed electronic database. Any disagreements were resolved by consensus or by consulting a referee. All bibliographic records identified through the electronic searches were collected in an electronic reference database and subjected to the following inclusion and exclusion criteria:

Inclusion criteria:

1) primary total hip arthroplasty
2) comparison of metal-on-metal bearing with non-metal–on-metal bearing
3) randomised controlled trial or quasi-randomised controlled trial (for RCTs)
4) follow-up of at least 3 months.

Exclusion criteria:

1) only bilateral cases with metal-on-metal and non-metal-on-metal in the same patient (this would not allow us to determine mortality for the groups separately).
2) no reporting/evaluation of mortality or morbidity.

Data Extraction and Quality Assessment

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

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

Data Synthesis and Analysis

A random effects model was employed to pool the risk difference of individual studies in order to estimate an overall risk difference and its associated confidence interval. The inverse variance method, which gives more weight to larger studies, was used to pool outcomes for different studies.

The overall effects, corresponding to a random effects model, is reported in the forest plots along with its confidence intervals. The sizes of the square boxes on the forest plots are proportional to the total number of patients in the selected studies.

An overall test on heterogeneity between studies was performed. To estimate between-study variance, DerSimonian-Laird's method was employed.[12] In case moderators are incorporated in the model, the weighted estimation gives an estimate of the weighted least squares relationship between the moderator variables and the true effect. All analyses were performed using Metafor Package R statistics.[13]

The measure of interest chosen was risk difference (RD) to account for any "empty cells" for mortality or morbidity corresponding to a particular study. Randomised controlled trials of first and second generation MOM THA and observational studies of first generation MOM THA (evolution of prosthesis development) were eligible for meta-analysis. Observational studies of second generation MOM were considered subject to strong selection bias, so they were not eligible for meta-analysis.[7-9]

The amount of heterogeneity was assessed through visual inspection of forest plots and by calculating tau-squared statistics (which is the amount of heterogeneity in the true RDs) and I-squared statistics. The latter estimates how much of the total variability in the effect size estimates is due to heterogeneity among the true effects.

In the presence of heterogeneity, and if data allowed, random effects meta-regression on pre-defined factors (study level covariates) was employed. These factors were defined in the PROSPERO protocol: type of metal bearing (resurfacing vs. non-resurfacing), type of non-metal bearing, head size, fixation method (cemented vs. cementless), indication for THA (primary vs. secondary osteoarthritis), methodological items from CLEAR NPT and Cochrane risk of bias Table, duration of follow-up, mean age at operation, gender distribution (% of females and males), and pre-operative health (American Society of Anesthesiologist (ASA) scores).

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

Results

RCTs

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

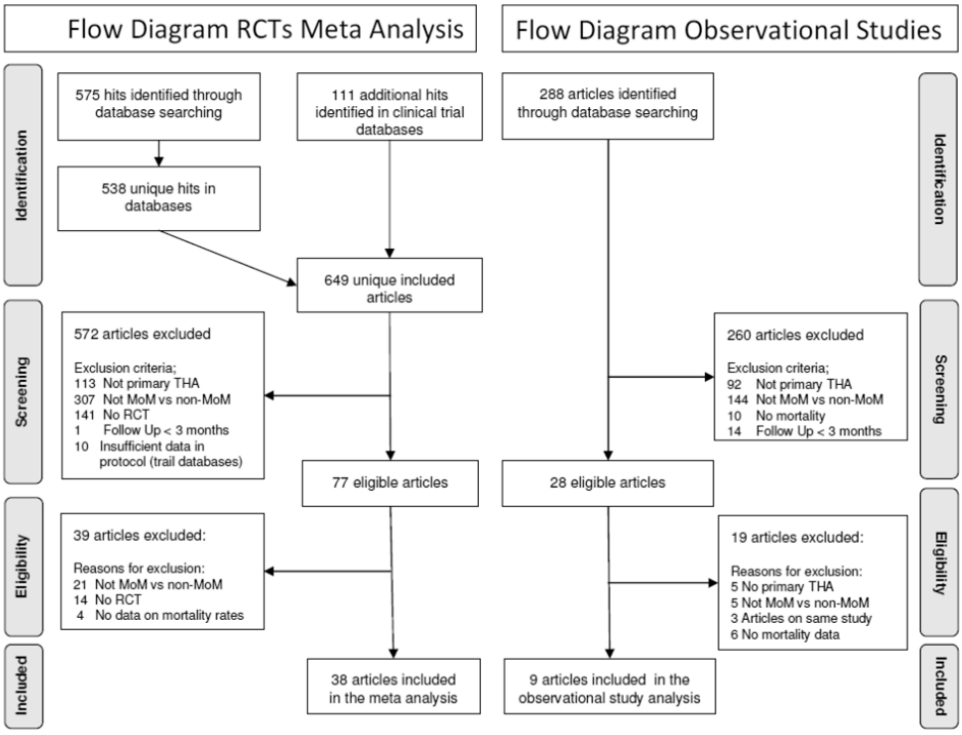

Fig 1. PRISMA flow chart

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

Observational studies

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

Mortality

There were 25 RCTs (31 papers) that reported mortality.[14,16–27,29,31–38,40–42] These RCTs comprised 1225 patients with MOM THA (71 mortalities) and 1486 patients with non-MOM THA (80 mortalities). There were five observational studies that reported mortality: one with first generation MOM THA and four with second generation MOM THA.[3,7,8,43,48] Meta-analysis of RCTs and first generation MOM observational studies showed a difference trend towards higher mortality for MOM THA: RD 0.7% (95%CI: 0.0% - 2.3%), I-square equal to 42%.

Figure 2 shows the results of three different meta-analyses, including the RD of the

MOM vs. non-MOM studies and the 95%CI associated to each individual study. The overall effect for each separate meta-analysis based on a random effects model is shown. This heterogeneity, I-square 42%, was explained by differences in follow-up, as shown in Figure 2.

After correction for follow-up with random effects meta-regression, there was no residual heterogeneity, and I-square was equal to 0%. When restricted to studies with long term follow-up (10 years or more)[3,35,36,38], the RD was 8.5%, (95%CI: 5.8% - 11.2%); number needed to treat was 12. This analysis used the unadjusted data from *Visuri et al*[3]. When using adjusted data from *Visuri et al*[3], the RD was equal to 4.4% (95%CI: 1.4% - 7.4%).

Table 1. Details of included RCTs

Author	Publication year	MOM						non MOM					Follow-up time
		Generation	N patients	N hips	N deaths	N revision	Resurfacing	N patients	N hips	N deaths	N revision	Type non-MOM	in year
Zagra	2013	2nd	20	20	0	0	no	40	40	0	0	Polyethylene - Ceramic	0.33
Grubl	2006	2nd	15	15	0	0	no	13	13	0	0	Ceramic - Ceramic	1
Schouten	2012	2nd	39	39	0	0	no	42	42	0	0	Ceramic-Metal	1
Jensen	2011	2nd	21	21	0	0	yes	22	22	0	0	Polyethylene - Ceramic	1
Zijlstra	2011	2nd	25	25	0	0	no	25	25	0	0	Polyethylene - Metal	1
Hanna	2012	2nd	28	28	0	0	no	23	23	0	0	Polyethylene - Metal	2
Weissinger	2011	2nd	42	42	0	.	no	38	38	0	.	Ceramic - Ceramic	2
Tiusanen	2013	2nd	46	46	0	2	no	46	46	0	1	Polyethylene - Metal	2
Penny	2012	2nd	21	21	0	0	yes	22	22	0	0	Polyethylene - Metal	2
NCT00208494		2nd	196	196	1	.	no	194	194	1	.	Ceramic - Metal	2
Gauthier	2013	2nd	25	25	0	1	no	25	25	2	0	Polyethylene - Metal	2
Malviya	2011	2nd	50	50	1	2	no	50	50	2	2	Polyethylene - Metal	4
Brodner	2003	2nd	50	50	1	1	no	50	50	2	1	Polyethylene - Ceramic	5
Gustafson	2014	2nd	26	26	0	1	yes	26	26	0	0	Polyethylene - Metal	5
Macdonald	2005	2nd	23	23	1	0	no	18	18	0	0	Polyethylene - Metal	5.1
Wang	2012	2nd	37	37	0	0	yes	40	40	0	0	Ceramic - Ceramic	6
Engh	2014	2nd	68	68	2	1	no	37	37	2	1	Polyethylene - Metal	6.5
Bjorgul	2013	2nd	123	129	6	8	no	251	268	16	4	Mixed	7
Zerahn	2011	2nd	74	74	6	.	no	225	225	14	.	Mixed	7.6
NCT01422564		2nd	12	12	2	.	no	12	12	0	.	Polyethylene - Metal	8
Hailer	2011	2nd	41	41	1	.	no	44	44	4	.	Polyethylene - Metal	8
Howie	2005	2nd	11	11	0	8	yes	13	13	0	2	Polyethylene - Metal	10
Desmarchelier	2013	2nd	111	125	19	3	no	116	125	13	1	Ceramic - Ceramic	10
Zijlstra	2010	2nd	101	102	30	4	no	97	98	23	2	Polyethylene - Metal	10.7
Pabinger	2003	2nd	31	32	1	1	no	28	29	1	0	Polyethylene - Ceramic	.

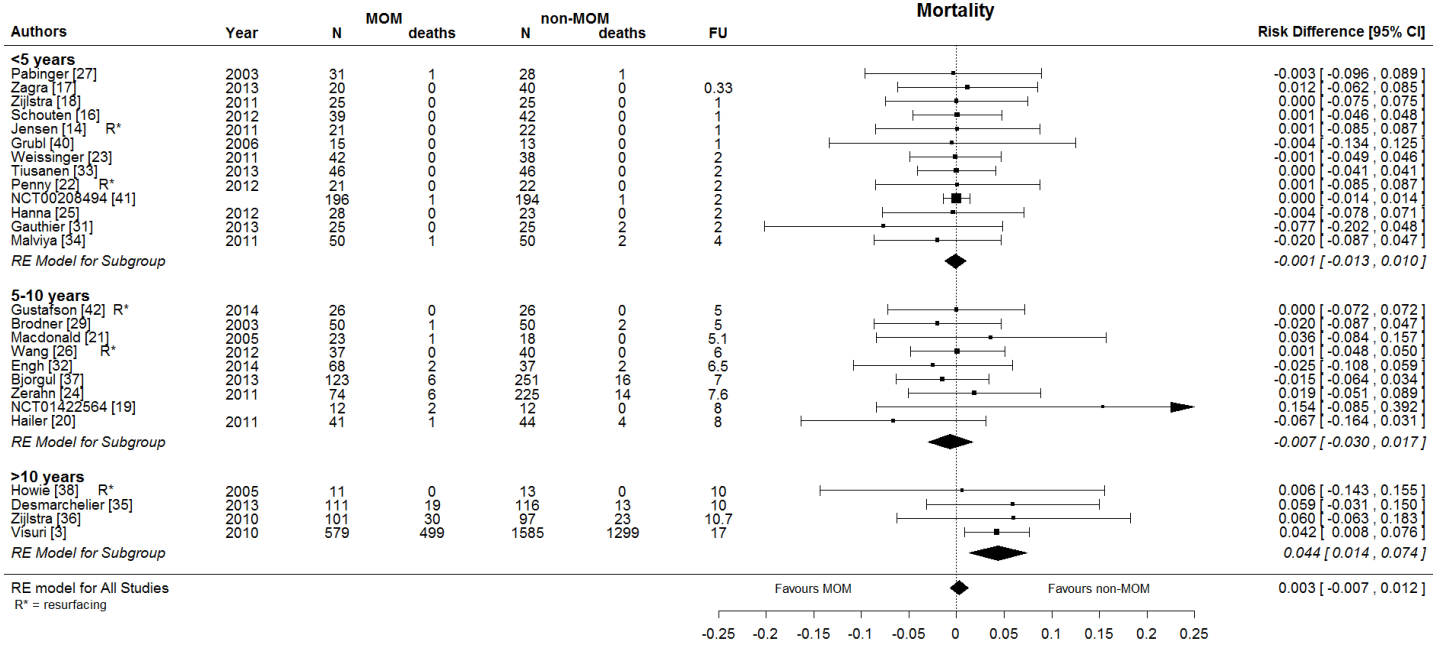

Fig. 2 – Forest Plot for rmortality in MOM as compared to non-MOM

Further subgroup analyses and meta-regression revealed no evidence for other modifying factors (e.g. resurfacing vs. non-resurfacing MOM). Sensitivity analyses with “leave one out” methodology indicated that the results were not significantly influenced by any single study.

Table 2 shows all-cause mortality and cause-specific mortality for first and second generation MOM observational studies. The first generation MOM observational study, which looked at non-resurfacing MOM in patients with primary osteoarthritis, showed a trend towards increased risk of mortality for patients with MOM compared to non-MOM THA, Incidence Rate Ratio 1.05, which is in line with the long term results from the RCTs.[3]

The second generation MOM observational studies showed decreased risk of mortality for patients with MOM compared to non-MOM-THA, Hazard Ratios ranging from 0.51 to 0.90.[7,8,43,48] This is in contrast with the long-term results from RCTs and first generation observational study.

Table 2 – Results from observational studies

Outcome	Study	Resurfacing	MOM generation	IRR	95%CI	FU	N MOM	N non-MOM
All cause mortality	Visuri 2010	No	1st	1.05	0.95-1.16	17	579	1 585
	Lubbeke 2014	No	2nd	0.90*	0.70-1.20	9.6	883	2 458
	Makela 2014	Mixed	2nd	0.78	0.69-0.88	4.6	10 728	18 235
	McMinn 2012a	Yes	2nd	0.61*	0.50-0.75	3.6	8 352	53 409
	McMinn 2012b	Yes	2nd	0.68*	0.55-0.84	3.6	8 352	50 529
	Kendal 2013a	Yes	2nd	0.51*	0.45-0.59	6	7 437	22 311
	Kendal 2013b	Yes	2nd	0.55*	0.47-0.65	5	8 101	24 303
Cancer Mortality	Visuri 2010	No	1st	1.27	0.98-1.63	17	579	1 585
	Makela 2014	Mixed	2nd	0.78	0.63-0.97	4.6	10 728	18 235
Cardiac Mortality	Visuri 2010	No	1st	1.07	0.93-1.22	17	579	1 585
	Makela 2014	Mixed	2nd	0.79	0.64-0.97	4.6	10 728	18 235
Cancer Incidence	Visuri 1996	No	1st	1.25	0.99-1.58	13.5	698	1 831
	Smith 2012	No	2nd	1.02*	0.93-1.12	3	21 264	248 995
	Lomohammed 2013	No	2nd	1.04*	0.70-1.56	3.2	988	9 714
	Makela 2012	Mixed	2nd	0.92	0.81-1.05	4	10 728	18 235
	Smith 2012	Yes	2nd	0.72*	0.61-0.86	3	19 312	248 995

IRR = Incidence rate ratio, * Hazard Ratio, FU = Follow Up in years
a = cemented, b= uncemented,.

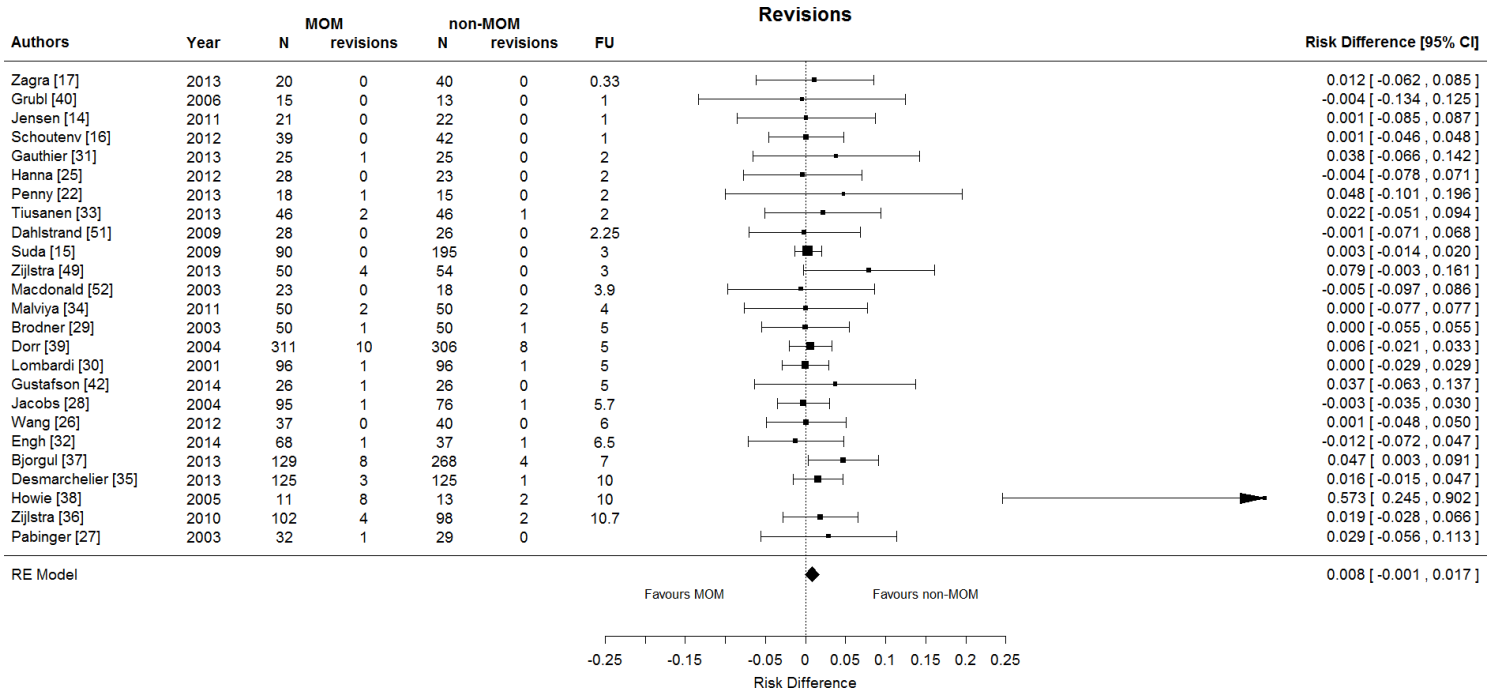

Fig. 3 – Forest Plot for revision surgery in MOM as compared to non-MOM

Morbidity: surgical complications

There were 26 RCTs (30 papers), all of second generation MOM THA, that reported revisions.[14–17, 25–40,42,49–52] These studies comprised 1546 MOM THA (49 revisions) and 1746 non-MOM THA (24 revisions). There were more revisions in MOM THA compared to non-MOM THA: RD 0.8% (95%CI: -0.1% - 1.7%); I-square 0%; random effects meta-analysis presented in Figure 3. This effect was stronger for cemented THA, with more revisions in MOM than non-MOM THA: RD 2.7% (95%CI: 0.1% - 5.3%); number needed to treat was 37. Regarding revision for aseptic loosening the RD was 0.6% (95%CI: -0.3% - 1.4%), and regarding revision for septic loosening the RD was 0.3% (95%CI: -0.3% - 0.9%). Sensitivity analyses with "leave one out" methodology indicated that the results were not significantly influenced by any single study.

Morbidity: medical complications

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

Table 3 – Medical complications for RCTs**.**

Author	Metal-on-Metal					Non Metal-on-Metal				
	N	N cancer	N nephro	N cardio	N any	N	N cancer	N nephro	N cardio	N any
NCT00208494	196	2	1	4	35	194	3	3	5	37
NCT01422564	12	1	.	1	.	12	0	.	0	.
Desmarchelier	111	.	.	.	2	116	.	.	.	5
Penny	18	.	.	.	1	15	.	.	.	0

Nephro = nephrotoxicity, cardio = cardiotoxicity.

There were four observational studies that reported cancer incidence: one with first generation MOM THA and three with second generation MOM THA, see Table 2.[44–47] The first generation MOM observational study showed increased risk of cancer for patients with MOM compared to non-MOM THA.[44] The second generation MOM observational studies showed no difference in risk of cancer for patients with MOM compared to non-MOM THA.[45–47]

Risk of bias

Risk of bias items from the CLEAR-NPT and Cochrane are presented in Figure 4. All studies suffered from problems with allocation concealment and blinding of patients, caregivers, and outcome assessors. The strong points of all studies were that compliance with the treatment was of course 100%, follow-up was similar for both MOM and non-MOM groups, and the skill/experience of the surgeons was similar for MOM and non-MOM THA (non-resurfacing).

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

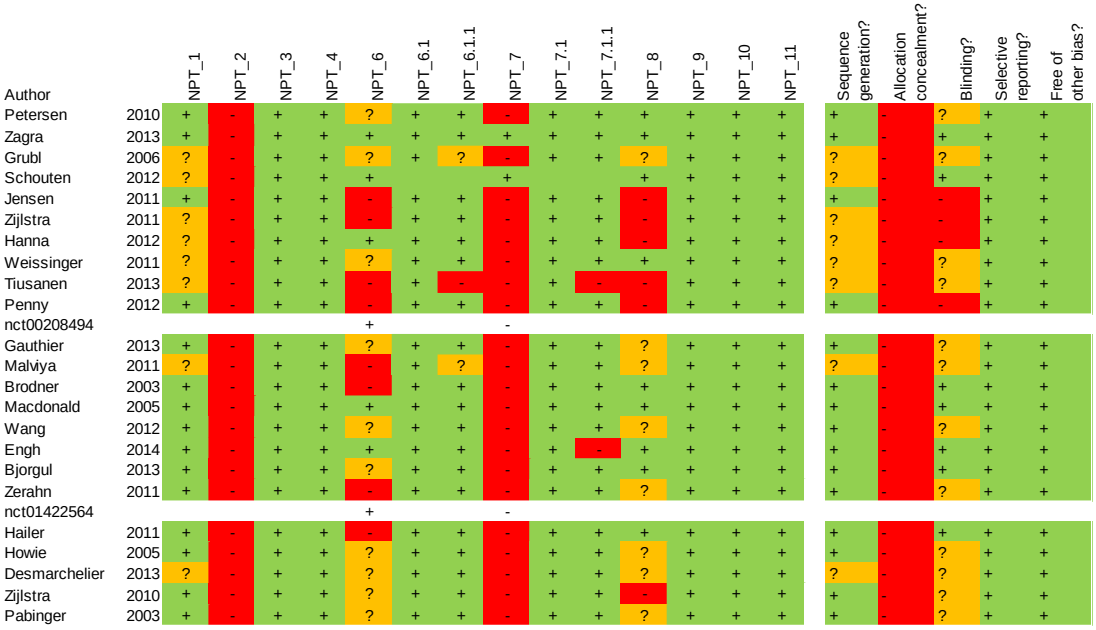

Fig. 4 - Risk of bias assessed by means of the Clear NPT and Cochraine scoring form.

NPT_1	Was the generation of allocation sequences adequate?
NPT_2	Was treatment allocation concealed?
NPT_3	Were details of the intervention administered to each group made available?
NPT_4	Were careproviders'experience or skill in each arm appropriate?
NPT_6	Were participants adequately blinded?
NPT_6.1	If participants were not adequately blinded; were all other treatments and care the same in each randomized group?
NPT_6.1.1	If participants were not adequately blinded; were withdrawals and lost to follow-up the same in each group?
NPT_7	Were care providers or persons caring for the participants adequately blinded?
NPT_7.1	If care providers were not adequately blinded; were all other treatments and care the same ine ach randomized group?
NPT_7.1.1	If care providers were not adequately blinded; weere withdrawels and lost to followup the same in each randomized group?
NPT_8	Were outcome assessors adequately blinded to assess the primary outcomes?
NPT_9	If outcome assessors were not adequately blinded, were specifi methods used to avoid ascertainment bias
NPT_10	Was the followup schedule the same in each group
NPT_11	Were the main outcomes analysed according to the intention-to-treat principe?

Publication bias

The potential influence of publication bias is small, as shown by a nearly symmetrical funnel plot in Figure 5. Also, the trim-and-fit method and the cumulative meta-analysis showed small potential influence of publication bias that would not influence the results. Furthermore, the results from the non-published RCTs (identified from the trial registries) were similar to those of published studies: RD for mortality in the non-published studies was -0.3% (95%CI: -1.8% - 1.1%), and in the published studies was 0.1% (95%CI: -1.3% - 1.5%).

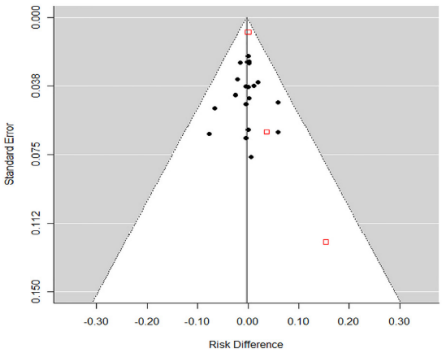

Fig 5. Funnel plots of RCTs. The red open boxes represent an abstract and two trial registry reports that have not been published.

Discussion

Principal findings

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

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

Since data on post-operative medical complications were reported in only a few studies, no valid meta-analysis could be done on differences between the two THA groups. Regarding the observational studies, one first generation MOM study showed an increased risk of cancer for MOM patients compared to non-MOM THA patients.[44] The second generation MOM observational studies showed no difference in overall cancer risk. However, risk of soft-tissue sarcoma and basalioma was higher for MOM THA patients.[48] The risk of mortality for MOM THA from observational studies of second generation MOM THA was different from those of first generation MOM THA and RCTs between (non) MoM THA, suggesting confounding by indication in studies of second generation MOM THA as previously reported by *Kandala et al.*[9] In a recent review, *Hartmann et al*[6] demonstrated that metal ion concentrations were persistently elevated after implantation of MOM bearings in whole blood, serum, plasma, erythrocytes and urine, irrespective of patient characteristics and study characteristics.

Of concern is that the same authors found very high serum cobalt concentrations in several of their included studies—above 50 µg/L, while the detection limit for serum cobalt is typically 0.3 µg/L. They found the highest metal ion concentrations in patients with a stemmed, large-head MOM implant and in patients with hip resurfacing arthroplasty. Our sensitivity analyses did not identify any association between MOM head size (either resurfacing or THA) and mortality or surgical complications. However, the number (25) and size (2700 pts) of our included RCTs may have been too small to detect a difference.

Toxic and carcinogenic effects

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

Furthermore, *Moulin et al*[57] have shown that metal workers exposed to cobalt have an increased mortality rate from lung cancer. Although most emphasis in literature is on cobalt toxicity (PHACT), the effects of chronic exposure to elevated chromium or nickel levels should not be dismissed. The International Agency for Research on Cancer (IARC) has classified chromium and nickel as group 1, "carcinogenic to humans".[56] Chromium (VI) in particular is carcinogenic through direct DNA damage after intra-cellular reduction to chromium (III), mutation, genomic instability, aneuploidy, and cell transformation.[56] Exposure to chromium by ingestion or inhalation is associated with increased risk of lung cancer, sinonasal cancer, and stomach cancer.[56 58-61]

The connection between chromium inhalation/ingestion and an increased risk of lung cancer, sinonasal cancer, stomach cancer, and possibly melanoma do not directly extrapolate to increased cancer risk due to increased plasma chromium levels in MOM THA. *Briggs et al*[62] have shown a strong relationship between whole blood levels of chromium and total chromosomal aberration indices in peripheral lymphocytes of MOM patients. *Ladon et al*[63] have shown an increase of both chromosome translocations and aneuploidy in peripheral blood lymphocytes at 6, 12, and 24 months after MOM-THA. Therefore, the association of increased chromium plasma levels and increased risk of mortality through cancer warrants further research. The arguments for this association are the carcinogenic effect of chromium through direct DNA-damage, strong relationship between whole blood levels of chromium and total chromosomal aberration indices in patients with MOM, chronically increased chromium plasma levels in patients with MOM, and increased long-term mortality in MOM patients as shown by the present systematic review.[6,56,62,63] Furthermore, patients with MOM THA are not only exposed to a single metal but to a "cocktail" of metal ions including chromium, cobalt, titanium, nickel, and molybdenum, of which at least two are potentially carcinogenic (chromium and nickel) and one is possibly carcinogenic (cobalt).[6,56]

Strengths and limitations

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

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

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

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

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

Comparison with other studies

Visuri et al[3,44] showed increased mortality and increased cancer incidence from MOM THA in an observational study of first generation MOM hip prostheses implanted between 1967 and 1973: the McKee-Farrar. This study is particularly interesting since the McKee-Farrar is part of the evolution of total hip prostheses and was not subject to modern marketing, nor was it labelled a "sports hip". The results from *Visuri et al*[3] are in accordance with the results of the RCTs of second generation (modern) MOM THA, therefore reinforcing our conclusion that MOM THA is associated with an increased risk of mortality in the long term. *Kendal et al*[7] found increased mortality in non-MOM THA in a registry based study of second generation

MOM THA using propensity score matching. Their results are in disagreement with the results of our meta-analysis, likely because registry-based studies are subject to residual confounding by indication. Indeed, *Kandala et al*[9] have shown that confounding by indication is likely for the Kendal study, since one-fifth of the metal-on-metal subjects are predicted to live beyond 100 years of age, making metal-on-metal total hip replacement more beneficial for longevity than any other known treatment. This latter finding is highly unlikely, and confounding by indication for the Kendal study is the most likely reason for this predicted longevity. *Mäkela et al*[48] found at short-term follow-up no difference in cancer incidence and cause-specific mortality in patients with second generation MOM THA compared to non-MOM THA. For the short-term follow-up, their results are in agreement with the results of our meta-analysis.

Conclusions and implications for clinicians and researchers

Studies with follow-up of greater than 10 years seem to suggest an increased risk of mortality in MOM THA compared to non-MOM THA. Additionally there is an increased risk of revision in MOM THA compared to non-MOM THA. In the light of these results, more long-term follow-up of RCTs reporting mortality is paramount. Also, future observational studies should address the dose-response association of person/hip years exposure to MOM THA and/or levels of metal ions to the risk of mortality and other medical complications e.g. cancer incidence, cardiomyopathy and renal failure. There is currently no case for the use of MOM THA giving the increased risk of long-term mortality and revision without any proven major advantage. Considering the results discussed above, it is prudent to closely follow the patients that have already received a MOM THA, especially in the long-term.

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Patients who underwent total hip or knee arthroplasty are more physically active than the general Dutch population.

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3

Abstract

Background: Total hip arthroplasty (THA) and total knee arthroplasty (TKA) bring relief of pain and functional disability to patients with end-stage osteoarthritis, however, the literature on their impact on patients' level of physical activity (PA) is scarce.

Methods: Cross-sectional study in patients who underwent THA/TKA surgery in the preceding 6–22 months and a random sample of persons aged >40 years from the Dutch general population, participating in a national survey. PA in minutes per week (min/week) and adherence to the Dutch recommendation for PA (NNGB yes/no) were measured by questionnaire to assess health-enhancing PA. Multivariable linear (total min/week) and logistic regression analyses (meeting recommendations PA), adjusting for confounders, were performed for THA and TKA separately.

Results: In total, 258 THA (62.3% female, aged 69.4 (9.1)) and 221 TKA (65.7% female, aged 69.5 (8.9)) patients and 4373 persons from the Dutch general population (51.4% female, aged 58.9 (11.6)) were included. The presence of THA was associated, after adjusting for age, sex, BMI education and musculoskeletal comorbidities, with more total min/week spent on PA (THA 13.8% increase, 95%CI 1.6–27.6%), whilst both TJA groups were associated with adhering to NNGB (THA: OR 1.79, 95%CI 1.26–2.56; TKA: OR 1.73, 95%CI 1.20–2.51).

Discussion: As this study used questionnaires to compare the PA of THA/TKA patients to the general population, some recall and selection bias might have been induced. After surgery, overall, TJA patients are more likely to adhere NNGB than a representative sample of persons >40 years from the Dutch general population.

Introduction

Worldwide, the numbers of patients undergoing total hip or total knee arthroplasty (THA or TKA) for hip or knee osteoarthritis (OA) are rapidly increasing. Overall, the outcomes are favourable, with a large majority of patients having less pain and improved physical functioning after surgery.[1–4]

Although the benefits of THA and TKA are well documented for pain and function, relatively little is known on their impact on one specific aspect of physical functioning, i.e. physical activity (PA). Just like for any other individual, achieving and maintaining a sufficient level of PA is important for patients with hip and knee OA with respect to their potential general health benefits.

Moreover, in patients who undergo THA or TKA, PA may have an additional beneficial effect on the quality of the bone, which in turn may prevent complications such as early loosening.[5–8] In addition, PA may have a positive effect on muscle strength and range of motion of the affected leg.[9]

With respect to the literature on PA after THA or TKA, de Groot et al. demonstrated in 84 THA and TKA patients that 6 months post-operatively PA levels as measured with an activity monitor did not significantly differ from the preoperative activity levels.[10] Harding *et al*[11] found similar results when measuring PA by means of an accelerometer in 63 American THA and TKA patients before surgery and 6 months post-operatively. Kahn and Schwartzkopf[12] found no difference in PA as measured with an accelerometer between those on the waiting list for TKA and those who had TKA 2 years earlier. By using the patient-reported University of California at Los Angeles (UCLA) activity questionnaire, Baumann *et al*[13] found that both THA and TKA patients were regularly active on moderate to high levels after on average 6–12 months after surgery. This finding is supported by Dahm *et al*[14], who reported that 5.7 years after surgery TKA patients had an average physical activity score of 7.1 out of 10, with 10 being highly active. In contrast to these findings, Kahn and

Schwartzkopf[12] observed, using an accelerometer, that adherence to health-enhancing PA guidelines was only 5% in persons with TKA.

In all of these studies, a comparison with the general population was lacking. Two Dutch studies compared patient-reported physical activity in THA[15] and TKA[16] patients at 1–5 years postoperatively to that of age and gender-matched controls. It was found that in THA the proportion of persons reaching the Dutch Public Health Physical Activity guideline (the "Nederlandse Norm Gezond Bewegen", NNGB) was similar to that of matched controls (51.2% (THA) vs 48.8% (controls))[15], whereas in TKA patients the proportion of patients adhering to the guideline (54.5%) was significantly lower than that of the matched control population (63.7%).[16] However, these studies did not take BMI into account, whilst BMI is one of the determinants of physical activity.[17]

Given the lack of knowledge on post-operative PA levels after total joint arthroplasty (TJA) compared to the general population, the aim of the present study was to compare the minutes of PA and proportion meeting the public health guidelines of THA and TKA patients to those of the general Dutch population. Moreover, factors other than TJA, possibly contributing to levels of physical activity, were also evaluated.

Methods

This cross-sectional, multicentre study concerned a comparison of PA levels of THA and TKA patients approximately one year after surgery with those of the general Dutch population. The data from the population of patients with THA and TKA were obtained from a study primarily aiming to make an inventory of the use of physical therapy and the presence of comorbidity[18], whereas the data from the general population were obtained from the Dutch National Bureau of Statistics (in Dutch: Centraal Bureau voor de Statistiek, CBS).

Since the survey had to be filled in only once by patients, it was judged to fall outside the remit of the law for Medical Research Involving Human Subjects Act; MO [in Dutch; Wet medisch wetenschappelijk onderzoek met mensen (WMO)]. An exemption for medical ethical review was therefore given by the Medical Ethical Committee of the Leiden University Medical Center. The health monitoring conducted by the CBS commissioned by the Dutch Government also falls outside the remit of the WMO. The study was conducted in accordance with the Handbook for Good Clinical Research Practice of the World Health Organization[19] and the Declaration of Helsinki principles.[20]

Patients with THA or TKA

The patient data were obtained from a cross-sectional study performed in 2012, including patients who underwent THA or TKA for hip or knee OA in 2011 in four different hospitals in the Leiden region (Leiden University Medical Center in Leiden, Rijnland Hospital in Leiderdorp, Groene Hart Hospital in Gouda and Reinier de Graaf Hospital in Delft, the Netherlands). Patients receiving THA or TKA for reasons other than end-stage OA (such as fracture or rheumatoid arthritis) were excluded from the study, as well as patients undergoing revision surgery. Between July 2012 and October 2012, all patients operated in 2011 were approached by mail by their orthopaedic surgeon, resulting in a range of post-surgery time of 7–22 months. The orthopaedic surgeon sent all eligible persons an invitation letter, information leaflet, informed consent form, survey and pre-stamped return envelope. Patients who returned the envelope with a completed survey and signed informed consent were included in the study.

Data general population

Data from the Dutch general population were provided by the CBS and were derived from a nationwide survey on general health (Gezondheids-enquête).[21] This questionnaire is annually administered to a representative sample of ±8.000 Dutch inhabitants and is the prime health monitor tool of the Dutch government.[22] The selection of participants is drawn from municipality registers. Persons living in institutionalized homes (e.g. nursing homes) are excluded. For the present study on physical activity, only data were selected from 2011, i.e. the same year as the data from patients with THA or TKA, and from respondents who were over 40 years of age, as none of the persons with arthroplasty was aged below 40.

Assessments

Included in both surveys were the following variables or questionnaires:

- Socio-demographic and basic health characteristics

Demographic variables included: age, gender and marital status (split into either married or not married). The height and weight of the patient were asked in order to calculate the body mass index (BMI). Smoking status (non-smoker, ex-smoker and smoker) and educational level (low (elementary school, lower secondary education), medium (secondary school or college) or high (higher secondary education or university)) were recorded.

- Physical activity (PA)

PA was assessed using the validated Dutch version of the short questionnaire to assess health (SQUASH).[23,24] The SQUASH records the total amount of minutes per week (min/week) spent on PA in an average week in the past 12 months regarding eight different domains of active life: commuting, work activities, walking, cycling, gardening, odd jobs, household and sports. With the aid of the compendium of Ainsworth[25], PA can subsequently be categorized into light, moderate or vigorous intensity. Using this information, it is possible to define whether an individual adhered

to the Dutch Public Health recommendation (NNGB) for PA (30 min of moderate intensity PA on at least 5 days per week).[26]

- Quality of life (QoL)

QoL of the persons with a THA/TKA was assessed with the Short Form 36 (SF36) questionnaire, whilst the QoL of the general Dutch population was assessed with the Short Form 12 (SF12).[27,28] The SF36 outcomes of the THA/TKA patients were transformed to SF12 outcomes.

From the SF12, two summary scales were derived: the physical component scale (PCS) and the mental component scale (MCS). The higher the score on these scales, the better the physical or mental functioning.

- Comorbidity

The presence of comorbidity was assessed by means of a self-reported questionnaire of the CBS which comprised 19 different comorbidities.[29] For every comorbidity, the participants of the survey were asked to respond with either yes or no to the question "*Have you received any treatment for [condition] in the past year*".

The included diseases were clustered into three groups:

- *Musculoskeletal comorbidities*: Severe back pain (including slipped disc), severe neck or shoulder pain, severe elbow wrist or hand pain, inflammatory arthritis or other joint conditions.
- *Non-musculoskeletal comorbidities*: Asthma or COPD (chronic obstructive pulmonary disease), (severe) cardiac disorder or coronary disease, arteriosclerosis (abdomen or legs), hypertension, (consequences of) stroke, severe bowel disorder, diabetes mellitus, migraine, psoriasis, chronic eczema, cancer and urine incontinence.
- *Sensory comorbidities*: Hearing impairments (group and face-to-face conversation), vision impairments (short and long distance) and dizziness in combination with falling.

Statistical analyses

The demographic and health characteristics of patients undergoing THA or TKA were each compared with those of the general Dutch population by means of two sample t-tests or Chi-square tests, where appropriate. Mann–Whitney tests were conducted to compare the min/week spent on PA for each of four different age groups (aged under 65, 65–69, 70–74 and 75+).

The min/week of PA was log-transformed to reach a normal distribution. Multivariable linear regression models were used to assess whether having had a joint replacement was associated with min/week spent on PA. Each analysis was done separately for THA versus the general Dutch population and TKA versus the general Dutch population. The antilog of the effect sizes (beta's) is reported for both the analyses with the 95% confidence interval (CI).

Multivariable logistic regression was used to assess the association between the presence of a joint replacement and adherence to the Dutch public health physical activity guideline. These results are presented as odds ratio (OR) with the 95% CI. The analyses were done separately for THA versus the general Dutch population and TKA and the general Dutch population.

All models (multivariable linear and multivariable logistic regression analyses) were constructed using a stepwise method. Potential confounders for the level of physical activity, i.e. sex, BMI, age and education level, were included in the models.

The determinants of minutes per week spent on activities categorized according to the three different levels of intensity of physical activity were determined for the arthroplasty groups and the Dutch population separately, by means of linear regression models including the variable of interest and correcting for age and sex. These analyses were performed including the variables age, sex, BMI, education, non-musculoskeletal comorbidities, musculoskeletal comorbidities, sensory comorbidities, MCS, PCS and time since surgery.

The level of statistical significance was set at $P< 0.05$, and analyses were performed using the SPSS statistical package (version 20.0, SPSS, Chicago, IL).

Results

Study population

Of the 545 THA and 465 TKA patients of the 4 hospitals who were invited to participate, 258 THA patients (response rate 47.3%) and 221 TKA patients (response rate 47.5%) completed the questionnaires. The selection of data from the general Dutch population from the year 2011 yielded 4373 surveys completed by people aged 40 years or older. Of those, 568 persons (13%) replied positively to the question *"Have you received any treatment for osteo- or rheumatic arthritis in the past year?".*

The arthroplasty groups comprised statistically significantly more females, and the patients had a higher mean age and higher BMI than the general Dutch population. The PCS and MCS were statistically significantly lower in both the THA and the TKA groups than in the general population. There was no difference in the presence of sensory comorbidities between the arthroplasty groups and the general population. However, both musculoskeletal and non-musculoskeletal comorbidity were more present in the arthroplasty patients as compared to the general population (see also Table 1).

Table 1 - Characteristics of patients with Total Joint Arthroplasty and the general Dutch population

		General Dutch Population	Total Hip Arthroplasty	P*	Total Knee Arthroplasty	P*
Total		4373	258		221	
Female		2248 (51.4%)	159 (62.3%)	0.01	144 (65.7%)	<0.01
Age (year)		59 ± 11.6	69 ± 9.1	<0.01	70 ± 8.9	<0.01
Body Mass Index		26 ± 5.0	27 ± 4.1	<0.01	29 ± 5.0	<0.01
Education level	Low	653 (15.6%)	75 (37.3%)	<0.01	72 (41.1%)	<0.01
	Medium	2391 (57.0%)	86 (42.8%)		81 (46.3%)	
	High	1150 (27.4%)	40 (19.9%)		23 (12.6%)	
SF-12	PCS	53.9 ± 9.4	47.6 ± 11.2	<0.01	46.6 ± 10.8	<0.01
	MCS	44.1 ± 5.0	39.8 ± 5.2	<0.01	40.6 ± 5.1	<0.01
Comorbidities	≥ 1 Non-MSK	2465 (57.4%)	142 (72.8%)	<0.01	138 (84.1%)	<0.01
	≥1 MSKI	1224 (27.9%)	93 (39.7%)	<0.01	84 (40.7%)	<0.01
	≥1 Sensory	400 (9.3%)	21 (8.4%)	0.736	21 (9.9%)	0.717

Variables reported as mean±SD or N(%).

*P - P-value for two sample T test or Chi^2 between hip/knee arthroplasty and the general population
MSK – Musculoskeletal comorbidities, PCS/MCS – Physical /Mental Component Score

Table 2 - Total minutes per week spent on physical activity by, age group for hip or knee arthroplasty or the general Dutch population

		General Dutch population		Total hip arthroplasty			Total knee arthroplasty		
Gender	Aged	N	Mean ± SD	N	Mean ± SD	P*	N	Mean ± SD	P*
Men	<65	2521	2846 ± 1543	32	2722 ± 1252	0,692	21	2924 ± 1468	0,959
	65-69	414	1976 ± 1474	23	2315 ± 1336	0,052	20	2079 ± 1316	0,640
	70-74	313	1784 ± 1330	20	2130 ± 843	0,003	12	1968 ± 1667	0,912
	≥75	372	1461 ± 1209	21	1443 ± 1065	0,840	22	2193 ± 1477	0,018
Female	<65	2761	2845 ± 1530	38	2745 ± 1148	0,857	46	2883 ± 1695	0,956
	65-69	401	2075 ± 1412	34	2480 ± 1908	0,364	25	2048 ± 1539	0,764
	70-74	286	1967 ± 1273	33	1867 ± 1071	0,888	28	1944 ± 2122	0,239
	≥75	525	1449 ± 1173	53	1703 ± 1453	0,350	45	1284 ± 912	0,577
		N	Count (%)	N	Count (%)	P*	N	Count (%)	P*
Adherence to NGBB		4373	2954 (67,6%)	258	195 (75,6%)	0,007	221	161 (72,9%)	0,105

* P-value for Mann-Whitney or Chi^2 as compared to the general population

Table 2 shows the crude number of minutes spent per week on PA, stratified for age and gender. As can be seen in Figure 1, male arthroplasty patients spend more minutes per week physically active in the higher age groups as compared to the general Dutch population. The proportion of persons adhering to the NNGB guideline is in the arthroplasty groups higher than in the general Dutch population (THA 76%, TKA 73% and general Dutch population 68%).

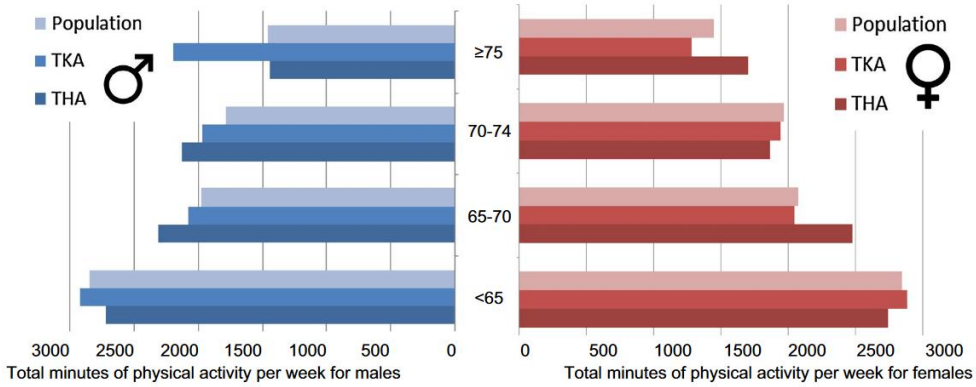

Fig. 1 - Stratified representation of total minutes per week physical activity per age group and gender

Association between TJA and minutes per week spent on total physical activity

Univariately, both THA and TKA were significantly associated with more minutes per week physical activity when compared to the general population. As there were major differences between the groups, it was needed to correct for potential confounders. When correcting for age, gender, BMI, education and musculoskeletal comorbidities a statistically significant association was for THA, not TKA. With the adjustments, persons with a THA spend 13.8% more minutes per week on physical activity compared to the general population (see Table 3).

Table 3 – Regression analyses of min/week physical activity and adherence to NNGB.

	Total min/week Physical Activity					
	Total Hip Arthroplasty			Total Knee Arthroplasty		
	Beta	95% CI	P*	Beta	95% CI	P*
Univariate[A]	1.229	1.099-1.352	<0.001	1.324	1.186-1.483	<0.001
Multivariate 1[B]	1.140	1.023-1.274	0.018	1.122	0.998-1.262	0.055
Multivariate 2[C]	1.138	1.016-1.276	0.024	1.112	0.986-1.256	0.084
	Adherence to NNGB					
	Total Hip Arthroplasty			Total Knee Arthroplasty		
	OR	95% CI	P*	OR	95% CI	P*
Univariate[A]	1.487	1.111-1.989	0.008	1.289	0.952-1.745	0.101
Multivariate 1[B]	1.750	1.243-2.465	0.001	1.750	1.219-2.512	0.002
Multivariate 2[C]	1.789	1.253-2.556	0.001	1.731	1.195-2.507	0.004

A – Univariate analysis
B – adjusted for age, sex, BMI and education
C – adjusted for age, sex, BMI, education and musculoskeletal comorbidities.

Association between TJA and meeting public health recommendation

The multivariable logistic regression models showed that, adjusted for age, gender, BMI, education and muscular comorbidities, both THA and TKA patients had a significantly higher likelihood of meeting public health recommendations for healthy PA as compared to the general population (THA: OR 1.79 (95%CI 1.25–2.55); TKA: OR 1.73 (95%CI 1.20–2.51)). See also Table 3.

Determinants of physical activity

Regarding the determinants of physical activity in the general population, age, sex, PCS and education were found to be statistically significantly associated with total minutes per week spent on PA and per category of intensity (see Table 4).

In the general population, BMI was associated with the number of min/week of moderate and vigorous intensity PA, but not with light intensity PA. Within both the arthroplasty groups, it was found that age was a significant determinant of total min/week of PA and the min/week of light intensity PA. Within the THA group, age was also a determinant for the min/week of moderately intensive PA. Sex was associated with the min/week of moderate and vigorous intensity PA in both arthroplasty groups and also with the min/week of light intensity PA in the THA group.

In the general population, comorbidities were only found to be a determinant of total minutes per week of PA, but not of the min/week in the three categories of PA intensity. In THA patients only the presence of sensory comorbidities was associated with the total min/week of PA, whereas in TKA the presence of comorbidities was not associated with PA.

Although the association of a number of potential determinants with PA in the TKA and TJA groups did not reach statistical significance, overall the directions of the associations were similar to those within the general population (results not shown).

Table 4 – Variables statistically significantly associated with min/week physical activity after adjusting for age and sex.

		General Dutch population		Total hip arthroplasty		Total knee arthroplasty	
		Beta	P*	Beta	P*	Beta	P*
Total Physical Activity	Age	0.973	<0.001	0.966	<0.001	0.966	<0.001
	Sex[A]	0.953	0.037				
	BMI	0.995	0.022	0.960	0.005		
	Physical Component Score	1.016	<0.001				
	Low education[B]	0.774	<0.001				
	Non-musculoskeletal comorbidities[C]	1.076	0.002				
	MusculoskeletalS comorbidities[C]	1.052	0.046				
	Sensory comorbidities[C]	1.202	<0.001	1.517	0.028		
Light Physical Activity	Age	0.966	<0.001	0.604	<0.001	0.973	<0.001
	Sex[A]	0.748	<0.001	0.604	<0.001		
	BMI					0.759	0.044
	Physical Component Score	1.007	<0.001				
	Low education [B]	0.809	<0.001				
	Medium education [B]	0.834	<0.001				
Moderate Physical Activity	Age	0.991	<0.001	0.984	0.031		
	Sex[A]	1.084	0.020	1.596	0.01	1.538	0.009
	BMI	0.912	0.022			0.964	0.027
	Physical Component Score	1.016	<0.001				
	Mental Component Score	0.989	0.001				
	Low education [B]	1.180	0.006				
	Medium education [B]	1.384	<0.001				
Vigourus Physical Activity	Age	1.026	<0.001				
	Sex[A]	1.189	<0.001	1.489	0.005	1.432	0.022
	BMI	0.986	0.003				
	Physical Component Score	1.014	<0.001			1.021	0.027
	Mental Component Score					0.957	0.008
	Medium education [B]	1.151	0.002				

A – Females were reference
B – High education as reference
C - Affected as reference

Discussion

This study demonstrated that the presence of a THA was associated with more min/week spent on PA as well as better adherence to public health recommendations for PA (NNGB) when compared to the general population. TKA was found to only be associated with adhering to the NNGB when compared to the general Dutch population.

Overall, it seems the Dutch population spends more minutes per week on physical activity, but since the patient group differs from the general population the comparison between these groups should be adjusted. When adjusting for age, sex, BMI and education it is found that persons with THA do spend more minutes per week on physical activity and that persons with a THA and TKA are more likely to adhere to the Dutch guideline on physical activity, NNGB.

That TKA is associated with the NNGB but not to the minutes per week activity can be explained by the level of intensity of the physical activity performed. In the general population, more associations between potential determinants of physical activity and the actual numbers of PA reached statistical significance than in the arthroplasty groups. The lack of significance is probably due to the relatively small sample sizes in the arthroplasty groups, limiting the statistical power.

Our groups spent more min/week on PA than reported by two other Dutch studies (for THA in this study 2183 min/week PA, THA in Wagenmakers *et al*[15] 1601 min/week, for TKA in this study 2153 min/week PA, TKA in Kersten *et al*[16] 1347 min/week PA). In parallel, regarding the proportion of patients adhering to the Dutch recommendation for physical activity, the outcomes were more favourable in the present study (THA in this study 75.6% and THA in Wagenmakers *et al*[15] 51.2%; TKA in this study 72.8% and TKA in Kersten *et al*[16] 55%).

Both these latter two studies were done at 1–5 years post-surgery, and our study included patients within the first 22 months after surgery. As reported earlier by our group (Peter *et al*[30]), 43.5% of the THA patients and 50.5% of the TKA patients had post-operative physiotherapy for more than 3 months. This implies that a vast

amount of our patients might still have intense training with aid of physiotherapists, motivating patients to adhere to the PA. As for the other two studies (Kersten, Wagenmakers), no data on prolonged post-operative physiotherapy are present, and thus, these patients might resume easier into their old, less active activity level.

A recent systematic review on physical activity after THA or TKA measured with accelerometers showed that the post-operative PA levels were lower in the arthroplasty groups as compared to healthy control participants.[31] The differences in outcome could be because our sample of the general population might not be totally healthy and be less active than selected healthy persons. Also, as this study used a questionnaire whilst the systematic review concerned objective measures, participants might have caused some recall bias.

The general population in our study had an adherence rate to the Dutch PA of 67.5% which is comparable to reports from CBS published (Dutch adult population, 66% adhered to the Dutch public health physical activity guideline in 2012).[32] The minutes per week spent on PA in our study was also consistent with the numbers reported by CBS (2589 min per week in 2012 and 2525 min per week in our study for overall physical activity for the Dutch population).[33]

Factors we identified as influencing the level of PA of persons with hip or knee arthroplasty (BMI, increased age, physical component score) are in line with the findings in a systematic review by Stubbs *et al*[34] regarding PA in patients with hip or knee OA. The inverse association of BMI on the level of PA shows that it is an important factor, as well as age and gender, to include in any case–control study.[17] Low-impact activities like walking or cycling seem to protect against function loss and experienced pain from OA, in contrast heavy load activities might be a risk factor for the development of osteoarthritis, but also early implant failure although debate exists on the latter.[35-38] Since contradictory evidence exists on this topic, research into this field is necessary.

Current post-operative rehabilitation after a hip or knee arthroplasty is focussed at independent ambulation and regaining a normal walking pattern, which was deteriorated in the years before surgery due to the slowly progressing osteoarthritis. Secondary to this it aims at getting the patient physically active. As mentioned before, about half of our patients reported to receive physiotherapy for more than 3 months after surgery.[30] This might imply that these patients are more motivated to be active than the general population.

Another reason for the higher levels of PA in the arthroplasty groups might be the fact that PA is a risk factor for TJA.[39] As shown by de Groot *et al*[10], the post-operative levels of PA did not significantly differ from preoperative levels, suggesting that PA levels of TJA were probably higher than those of the general population before surgery as well. Finally, the patients filling in the questionnaire knew that the subject of the study was PA, whilst the Dutch general population had to fill in an elaborate list of questions including all aspects of life, with only a subset on PA. Thus, the patients in our study might have overestimated their PA.

The limitations of this study are potential overestimation of outcome measures and recall bias, due to using the SQUASH questionnaire, more objective measures like accelerometers should be used in future studies. Furthermore, the preoperative levels of PA should be taken into account as an important confounder for outcome as well. Thus, more valid comparisons with the general population are possible.
Also, patients in our study who refused to fill in the questionnaires were not asked about their reasons as to why they declined to participate, and therefore, we have no information about any possible self-selection bias. In addition, the comorbidities of participants were all self-reported and we were unable to confirm the presence of comorbidities both in the general Dutch population and the arthroplasty groups.

The findings of this study give insights into the movement patterns of arthroplasty patients compared to the general Dutch population. Findings show that although a part of the arthroplasty patients adhere to the Dutch public health guideline, there is still a considerable group who should increase their PA levels.

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Frailty in end-stage hip or knee osteoarthritis: Validation of the Groningen Frailty Indicator (GFI) questionnaire

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Abstract

Background/Objective: Frailty is highly prevalent in the elderly, increasing the risk of poor health outcomes. The Groningen Frailty Indicator (GFI) is a 15-item validated questionnaire for the elderly. Its value in patients with end-stage hip or knee osteoarthritis (OA) has not yet been determined. This study assesses the validity of the GFI in this patient-group.

Methods: End-stage hip or knee OA patients completed the GFI (range 0-15, ≥4 is frail) before arthroplasty surgery. Convergent validity was determined by Spearman-rank correlation between the SF12 physical (PCS) and mental (MCS) component scores and the physical and mental GFI-domains, respectively. Discriminant validity was assessed by means of overall GFI-score and the pain-domain of the Hip/Knee Osteoarthritis Outcome Score (HOOS/KOOS).

Results: 3275 patients were included of whom 2957 (90.3%) completed the GFI. Mean GFI-scores were 2.78(2.41) and 2.28(1.99) in hip and knee OA-patients, respectively, with 570(35.9%) of hip and 344(24.1%) of knee patients considered frail. The convergent validity was moderate to strong (physical domain R=-0.4, mental domain R=-0.6) and discriminant validity low (R HOOS/KOOS-pain domain=-0.2), confirming the validity of the GFI-questionnaire in this population.

Conclusion: With 90% of participants completing the GFI, it is a feasible and valid questionnaire to assess frailty in end-stage hip and knee OA-patients. One-third (33.3%) of the patients undergoing hip arthroplasty and a quarter (24.1%) of those undergoing knee arthroplasty are frail. Whether this is associated with worse outcomes and can thus be used as a pre-operative predictor needs to be explored.

Introduction

Osteoarthritis (OA) is a degenerative joint disease which often leads to disability and pain. A highly effective treatment for end stage OA is arthroplasty surgery.[1,2] Over 202,500 total hip and 402,100 total knee arthroplasties (THA and TKA) are performed annually in the United States of America alone, with the volume expected to increase up to 6-fold by 2030.[3]

At present, 83% of the patients receiving THA and 79% of patients receiving TKA are older than 60 years of age.[4] As frailty is highly prevalent in the elderly, it is likely that a considerable proportion of patients undergoing THA or TKA are frail.[5] Although there is not one definition for frailty, the most often used definitions include a combination of decrease of independence, strength, cognition, activity, energy, weight and walking speed.[6-12] Literature shows that there is considerable heterogeneity in the extent of frailty individuals may experience, with some persons accelerating fast while others are slowly progressing to higher levels of frailty.[13] Within persons of the same age, also the onset of frailty differs per individual.[14-17]

It is generally acknowledged that frailty hampers the ability to resist stressors, leading to vulnerability for adverse outcomes after surgery.[6, 16-19] As such, it is of importance to have more insight into frailty in the group of patients undergoing THA or TKA. As a first step into the exploration of the role of frailty in the outcomes of total joint surgery, an appropriate instrument for frailty is needed

The Groningen Frailty Indicator (GFI) is a frequently used questionnaire in the elderly to assess frailty. The advantage of the GFI is that it is a self-reported score, furthermore, this questionnaire has been validated specifically for elderly (mean age 81 years). In these elderly (both community dwelling and institutionalized), it was found that the GFI is feasible, reliable and valid.[20] However, it is not known yet how feasible the GFI is in a clinical setting as well as the validity of the GFI amongst the somewhat younger patients with end stage hip or knee OA waiting for arthroplasty surgery. Therefore, in this study we aimed to assess the feasibility and validity of the GFI as a tool to measure frailty in end stage hip or knee osteoarthritis patients scheduled to undergo arthroplasty surgery.

Methods

Study design

This study is part of the Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis study (LOAS). The LOAS study is an ongoing, multi-center, longitudinal prospective cohort study including patients undergoing primary total hip or knee arthroplasty (THA or TKA). Participants are recruited in 7 participating hospitals (the Leiden University Medical Center, Leiden; Alrijne Hospital, Leiden/Leiderdorp (former Diaconessenhuis and Rijnland Hospital); Groene Hart Hospital, Gouda; LangeLand Hospital, Zoetermeer; Reinier de Graaf Gasthuis, Delft; Albert Schweitzer Hospital, Dordrecht; Waterland Hospital, Purmerend). The LOAS study (Trial ID NTR3348) started in June 2012. The present study is only concerned with data gathered preoperatively from June 2012 – June 2016.[21]

Patients

All patients who were able to complete questionnaires in Dutch and who were 18 years or older were eligible for participation. Excluded were patients who did not provide informed consent, had insufficient Dutch language skills or of whom the physical or mental status did not allow participation. Eligible patients were informed about the study through written and oral information by their treating surgeon at the outpatient clinic. Only patients who agreed to be approached by the researcher received additional written information about the study by regular mail or e-mail, as well as a questionnaire, a stamped return envelope and a consent form.

Patients were included in the study once written informed consent was obtained according to the Declaration of Helsinki.[22] For the purpose of the present analysis only data from patients who returned the preoperative questionnaire between the start of the study in June 2012 until June 2016 were included. Ethical approval was obtained by the Medial Ethics Committee of the Leiden University Medical Center (registration number P12.047) and funding was received from the Dutch Arthritis Foundation (LLP13).

The questionnaires were incorporated in current clinical setting of the included hospitals which all participate in the collection of patient reported outcome measures (PROMs) for the national Dutch Arthroplasty Register (LROI).

Assessments

Frailty: Frailty was assessed by the Groningen Frailty Indicator (GFI). This questionnaire consists of 15 questions covering several aspects of life, such as independence in daily tasks, involuntary weight loss, medication use, mental state, vision and hearing. Together these questions lead to a score between 0 and 15, a score of ≥4 is considered to be frail. The GFI is specifically directed to elderly persons both living at home as well as in institutions.[20,23,24]

Overall health: Quality of life was measured using the validated Dutch version of the Short Form (SF)-12.[25] The SF-12 comprises 12 items on generic measurement of the overall health-related-quality of life. Scores range from 0 to 100, with 0 being lowest possible score and 100 the highest. From the SF12, 2 subscales can be calculated, the physical component score (PCS) and mental component score (MCS). These subdomains were assessed separately in the analyses.[26]

Hip / Knee Symptoms: The Hip disability/Knee injury Osteoarthritis Outcome Score (HOOS/KOOS) questionnaires are validated questionnaires to measure the function of patients with end-stage osteoarthritis for hip or knee respectively.[27,28] These questionnaires comprise five domains (activities of daily living, quality of life, sports, symptoms and pain). For the current study the validated Dutch version was used.[29,30]

Statistical Analyses

Patient characteristics were analysed using descriptive statistics. Rates of patients who did not, partially or completely filled out the GFI were computed. Comparisons between patients who filled in the GFI completely and those who did not or partially were done by means of either Chi-Square tests for categorical variables and t-tests for continuous variables. In addition, for each GFI item the proportion of missing values was determined.

To explore determinants for completing the questionnaire a binary variable “completion of questionnaire” was constructed. This variable was used in a logistic

regression analysis to see if age, sex, BMI and comorbidities are of significant influence on the completion of the questionnaire.

The internal consistency of the GFI in this patient population was assessed by means of Cronbach's alpha, with an alpha of >0.7 being considered as good consistency [31]. Convergent validity of the GFI was determined by computing correlations between the physical domain of GFI (questions 1-9) and the PCS of the SF-12. The mental domain of the GFI (question 14 and 15) was correlated with the MCS of the SF-12. Correlations were computed using a Spearman rank correlation coefficients. As the corresponding subscales of the GFI and SF12 aim to measure similar constructs it was hypothesized that the correlation between the subscales of the GFI and SF12 will be high.

Discriminant validity of the questionnaire was assessed by correlating the physical domain of the GFI to the MCS and the mental domain of the GFI to the PCS. Also, a Spearman rank correlation analysis including the total GFI-score and pain as measured by the HOOS/KOOS questionnaire was performed. As the correlated constructs are conceptually different, we hypothesized the correlation between these domains would be low.

For those THA and TKA patients who completed the GFI the prevalence of frailty was calculated, based on the cut-off score of four.[24] The demographic variables of those assigned frail and those not designated as frail were compared by means of a t-test or Chi-square test, whichever was appropriate.

All analyses were performed with IBM SPSS statistics software version 23.

Results

Within the time frame of the present analysis 3275 patients with end-stage hip OA (N=1691) and knee OA (N=1584) were included in the cohort study. For both end stage hip and knee OA, 90.3% of the participants completed the questionnaire. In Table 1 the socio-demographic variables of patients returning the questionnaire that did and did not complete it fully were compared. In hip OA, those who did not fully complete the questionnaire were significantly older, whereas in knee OA those who did not complete the questionnaire fully were more often female and had a lower score on the HOOS/KOOS-activities of daily life domain. In both end stage hip and knee OA those who did not complete the questionnaire had a significantly lower score on the MCS.

Table 1 – Characteristics of patients with end stage OA who did and did not complete the Groningen Frailty Indicator questionnaire.

		End stage Hip OA			End stage Knee OA		
		GFI completed N=1527	GFI incomplete N=164	P*	GFI completed N=1430	GFI incomplete N=154	P*
Female		925 (61.5%)	107 (67.3%)	0.155	911 (64.2%)	119 (77.3%)	0.001
Age		67.8 ± 9.8	70.9 ± 9.4	<0.001	67.4 ± 8.9	67.6 ± 9.1	0.818
BMI		27.2 ± 4.3	27.0 ± 5.4	0.529	29.4 ± 4.7	29.0 ± 4.4	0.373
Not living alone		1187 (77.7%)	118 (71.9%)	0.097	1095 (76.5%)	115 (75.7%)	0.598
Musculoskeletal Comorbidities		259 (17.8%)	29 (20.9%)	0.370	326 (24.1%)	39 (26.5%)	0.522
Other Comorbidities		942 (70.7%)	80 (69.0%)	0.692	900 (74.7%)	85 (73.9%)	0.855
SF12	Physical	32.2 ± 9.4	32.4 ± 9.2	0.821	32.3 ± 9.1	32.4 ± 9.7	0.918
	Mental	54.8 ± 9.9	52.9 ± 10.4	0.046	55.6 ± 9.4	54.0 ± 9.0	0.009
HOOS / KOOS	Pain	37.9 ± 18.6	39.8 ± 20.0	0.244	38.9 ± 17.6	36.4 ± 18.8	0.124
	Symptoms	39.8 ± 18.5	41.9 ± 20.6	0.252	43.7 ± 13.5	42.0 ± 12.4	0.178
	Activities of daily life	39.9 ± 19.2	41.8 ± 21.6	0.324	45.0 ± 18.2	40.8 ± 20.9	0.026
	Sport	18.1 ± 18.4	21.6 ± 21.7	0.200	10.7 ± 14.3	11.2 ± 15.5	0.852
	Quality of Life	33.4 ± 10.8	35.2 ± 12.1	0.083	33.6 ± 10.4	34.6 ± 11.8	0.327

* Charcteristics of patients who completed and did not complete the GFI were tested by means of a T-test (normal distribution), Mann-Whitney test (not normal distribution) or Chi-square test (discrete variables).

On a total of 15 items, the median number of missing items for both joint locations was 0 (range 0 to 15), whereas the mean (SD) was 0.4 (1.9) (hip OA: 0.4 (2.0), knee OA: 0.3 (1.8)). Of the 164 patients with hip OA who did not complete all questions, 29 did not fill in any question whereas 99 missed only one question. Of the 154 patients with knee OA who did not complete all questions, 21 did not fill in any question and 102 persons had only one missing question.

Table 2 shows the percentage of missing values per question. Most frequently missed was question 15 "*How would you rate your physical fitness on a scale of 1 to 10?*" for both hip and knee (hip 4.4% missing, knee 4.2% missing). This was the only question with no predefined answering options; instead patients had to write down the number themselves. In addition, in patients with hip OA question 2 *"Are you able to walk independently outside?"* (2.8% missing) and question 3 *"Are you able to (un)dress yourself?"* (2.7% missing) were relatively often missing, while in knee OA patients question 6 *"Do you encounter problems in daily life because of impaired hearing?"* (2.6% missing) and question 2 *"Are you able to walk independently outside?"* (2.3% missing) were relatively often missing.

	Table 2 – Percentage of missing per question for the Groningen Frailty Indicator	Hip	Knee
1	Are you able to do groceries by yourself?	2.5%	1.9%
2	Are you able to walk independently outside?	2.8%	2.3%
3	Are you able to (un)dress yourself?	2.7%	2.2%
4	Are you able to use the bathroom by yourself?	2.7%	2.0%
5	Do you encounter problems in daily life because of impaired vision?	2.5%	2.6%
6	Do you encounter problems in daily life because of impaired hearing?	2.4%	1.8%
7	Did you unintentionally lose weight over the past 6 months?	2.4%	1.8%
8	Do you use 4 or more types of medication	2.7%	1.8%
9	Do you have any complaints of your memory?	2.1%	1.8%
10	Do you experience emptiness around you?	2.2%	1.8%
11	Do you miss the presence of other people around you?	2.4%	2.0%
12	Do you feel left alone?	2.7%	1.8%
13	Have you felt down or depressed lately?	2.5%	2.0%
14	Have you felt nervous or anxious lately?	2.5%	2.0%
15	How would you rate your physical fitness on a scale of 1-10 ?	4.4%	4.2%

To assess determinants for completing the GFI questionnaire a logistic regression model was build including age, sex, BMI, musculoskeletal and other comorbidities. Table 3 shows the odds ratio's associated to this model. It was found that age and sex are statistically significant determinants for completing the questionnaire in persons with end-stage OA of the lower limb corrected for BMI and comorbidities.

Table 3 – Odds ratio's for demographic characteristics associated with completing the GFI.

	Odds Ratio	95% CI	P-value
Age	0.981	0.966-0.997	0.020
Sex	1.497	1.100-2.038	0.010
BMI	1.006	0.974-1.039	0.714
Musculoskeletal comorbidities	0.946	0.661-1.354	0.762
Other comorbidities	0.890	0.644-1.230	0.481

Characteristics were included in logistic regression analysis to assess their association with completing the GFI questionnaire (yes/no).

Older age is, independent of gender, BMI and comorbidities, associated to lower odds for completing the questionnaire (OR: 0.98, P-value 0.020) while for gender it was found that, when correcting for age, BMI, musculoskeletal and other comorbidities, females have higher odds for completing the questionnaire as compared to males (OR: 1.50, P-value; 0.010). BMI and having musculoskeletal or other comorbidities were not statistically significant associated to the completing of the GFI questionnaire for persons with end-stage hip or knee OA.

The internal consistency of the GFI in patients scheduled to undergo arthroplasty was 0.69, just below the threshold of 0.7 of good internal consistency [31]. Regarding the validity of the GFI questionnaire the mental and physical domains of GFI were strongly to moderately correlated with the MCS of the SF12 ($R = -0.59$, $P<0.001$) and the PCS ($R = -0.39$, $P<0.001$), respectively, confirming the validity of the questionnaire. When performing cross-over analysis by correlating the mental domain of the GFI to the PCS of the SF-12 discriminatory validity was confirmed with a very weak correlation ($R= -0.08$; $P<0.001$).

In addition, the correlation of the physical domain of the GFI and MCS had a low correlation of R= -0.28 (P<0.001). The correlation of the GFI with the HOOS/KOOS-pain score was, as hypothesized, low and also confirmed its discriminatory value to distinguish between pain and frailty (R = -0.23, P<0.001).

Of the 2957 patients with end stage hip or knee OA who did complete the questionnaire, 853 (28.8%) were considered frail (a score of ≥4 on GFI). Patients with hip OA scored on average higher on the GFI (mean (SD) score: 2.78 (2.41) versus 2.28 (1.99)) and were more often considered frail as compared to persons with knee OA (33.3% versus 24.1%). Table 4 shows that frail persons were statistically significantly more often female, older and had a higher BMI as compared to those who are not frail. Also, frail persons scored statistically significantly lower on all scales of physical functioning of the HOOS/KOOS as well as on the physical and mental component scale of the SF-12 before arthroplasty surgery.

Table 4 – Comparison of demographic characteristics of frail and non-frail end stage OA patients

		Frailty as measured by GFI		
		Non frail N=2104	Frail N=853	P-value*
Joint	End stage hip OA	1018 (66.7%)	509 (33.3%)	< 0.001
	End stage knee OA	1086 (75.9%)	344 (24.1%)	
Female		1216 (58.4%)	620 (73.6%)	< 0.001
Age		67.07 ± 9.02	68.99 ± 9.97	< 0.001
BMI		28.07 ± 4.41	28.69 ± 5.14	0.002
Musculoskeletal comorbidities		351 (17.5%)	234 (29.4%)	< 0.001
Other comorbidities		1248 (68.1%)	594 (84.4%)	< 0.001
SF12	Physical	33.38 ± 9.52	29.33 ± 7.80	< 0.001
	Mental	58.33 ± 6.79	47.01 ± 11.06	< 0.001
HOOS / KOOS	Pain	40.56 ± 17.53	32.96 ± 18.45	< 0.001
	Symptoms	43.05 ± 16.25	38.19 ± 16.34	< 0.001
	Activities of daily life	45.36 ± 18.22	34.97 ± 18.51	< 0.001
	Sport	16.07 ± 17.54	10.64 ± 14.57	< 0.001
	Quality of Life	34.49 ± 10.79	31.06 ± 9.75	< 0.001

* Charcteristics frail and non-frail patients were tested by means of a T-test (normal distribution), Mann-Whitney test (not normal distribution) or Chi-square test (discrete variables). A score of ≥4 was considered as frail.

Discussion

The GFI is a valid questionnaire to assess frailty in end stage hip or knee OA patients by means of a self-reported postal questionnaire. According to the GFI, using the cut-off of 4, about one-third of the patients undergoing THA and a quarter of the persons undergoing TKA are frail.

The feasibility of the use of the GFI within the current clinical setting for patients with end stage hip or knee OA is good, as 90% of the participants completed the questionnaire. In a study by Metzelthin et al. in older community dwelling persons showed that 77.4% of the persons completed the questionnaire.[32]

Those who did not complete the questionnaire were more often male and older. The open question (question 15) was most often left empty, indicating that it is probably easier for patients to have closed questions with predefined answer options. Further research is needed to reconsider the format of this question aiming to obtain higher response rates.

Although the Cronbach's alpha of 0.69 is just below the threshold of good internal consistency of 0.7, it does indicate that the internal consistency of the GFI in our patient group is satisfactory and it is comparable to the alpha of 0.68 as found by Peters et al in home dwelling elderly in the Netherlands.[20,31]

With respect to the convergent and discriminatory validity of the GFI for this specific patient group, the magnitude of the observed associations was in line with our hypotheses. Our convergent validity (range -0.6 –0.4) was comparable to the findings of Peters et al (range 0.4-0.61) [20]. The discriminatory validity in our patient group (range -0.08 - -0.3) was even stronger as compared to the elderly of Peters et al (range 0.08 - 0.5).[20]

Significantly more patients with end stage hip OA were considered to be frail as compared to end stage knee OA (hip; 33%, knee; 24%, P<0.001). However, both these numbers are lower as compared to the study of Peters *et al*[20] who found 60% of the independent living elderly in their study to be frail as measured by the GFI, but the average age in that study was 81 years, much higher than in the present study

(mean age 68 years). In a study among Romanian home-dwelling elderly (mean age 75), 75% of the participants were considered frail by the GFI.[33] These studies show that the presence of frailty shows wide variability depending on country, social status, diagnosis and age. The median and mean scores of the GFI in our patient group (2.00 and 2.54, respectively) were lower than the averages in independent living old persons found by Peters *et al*[20] (median 3) or reported by Metzelhin *et al*[32] and Drubbel *et al*[34] (means 3.8 and 3.2, respectively).

In both the latter studies the mean age was higher than in our study (77 and 73 years respectively). The lower frailty score in our patient groups can, apart from age, be explained by the fact that all patients were selected by an orthopaedic surgeon to receive arthroplasty surgery and were thus considered to be fit enough for major surgery.

The rates of persons with OA classified as being frail in our study are not easy to compare with other studies, as different methods to ascertain frailty were employed. Using Fried's Frailty Phenotype, Mandl *et al*[35] found that 8% of persons scheduled for knee arthroplasty were considered frail (although 17% reported difficulty with activities of daily life) with a similar rate found in men with hip osteoarthritis (8%) and in a study of persons with knee, hip or hand OA from 6 different European cohorts (10.2% considered frail). [6,36,37]
A larger proportion, i.e. 22.4% of persons with hip or knee OA, was considered frail using Fried's Frailty Phenotype in a Brazilian study.[38] With the interpretation of these proportions it must be taken into account that the criteria of Fried's Frailty Phenotype are to be ascertained by a physician and do not include activities of daily life. [6]

Dent *et al*[39] have published an overview of the most commonly used frailty-questionnaires including, besides the GFI, three other self-reported frailty assessments: the Tilburg Frailty Index, the PRISMA-7 and the SPQ. However, none of these other three self-reported questionnaires have to our knowledge been used to assess the occurrence of frailty in persons with osteoarthritis.

Since a large proportion, about one third, of the patients scheduled to undergo major implant surgery are considered frail as scored by the self-reported GFI, the effects of frailty on their postoperative outcome should be assessed in future studies. This study has shown that the use of the GFI to discriminate between frail and non-frail total joint arthroplasty patients is appropriate.

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Frailty questionnaire is no predictor for functional outcomes in hip or knee arthroplasty patients

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Abstract

Introduction: Up to 33% and 25% of end-stage hip and knee osteoarthritis (OA) patients are considered frail by the Groningen Frailty Indicator (GFI).[1] This study aims to assess whether frail patients have lower functional gains after arthroplasty and to assess GFI as a tool to discriminate between good or adverse change-score.

Materials and Methods: End-stage hip/knee OA patients scheduled for arthroplasty were recruited from the LOAS-study. Functional outcome was measured as change-score on the Hip/Knee Osteoarthritis Outcome Score (HOOS/KOOS), by subtracting pre-operative score from 1-year post-surgery score and then dichotomised based on a cut-off of 20 points. For each HOOS/KOOS-subscale 3 models were estimated: GFI univariate (model 1), GFI and baseline-score (model 2) and baseline-score univariate (model 3). A ROC-analysis was performed to assess the discriminative ability of each model.

Results: 805 end-stage hip (31.4% frail) and 640 end-stage knee OA patients (25.4% frail) were included. Frail patients were older, had a higher BMI, more comorbidities and lived more often alone. Persons considered frail by GFI had significant lower baseline-score; however, except for “function in sports & recreation” and “quality of life” change-scores were similar in frail and non-frail persons. The discriminatory value of GFI was negligible for all HOOS/KOOS-subscales. Baseline score, however, was adequate to discriminate between TKA patients with more or less than twice the minimal clinical important difference (MCID) on KOOS-symptoms-subscale (AUC=0.802)

Conclusion: Although frail OA patients have lower functioning scores at baseline, the change-scores on HOOS/KOOS-subscales are similar for both frail and non-frail patients.

Introduction

Osteoarthritis (OA) is a common, degenerative, disabling joint disease, affecting up to 23.1% of persons aged over 70 years.[2] These numbers are likely to increase due to population ageing and the epidemic proportions of obesity in the general population.[3,4] Thus far no cure for OA has been found; instead when pain relief is not sufficient anymore, the final treatment option is Total Joint Arthroplasty (TJA) in hip (THA) or knee (TKA). In the Netherlands, 28,798 THAs and 24,107 TKAs were performed in 2015 with up to 50% of the THA and 42% of TKA in persons aged ≥70.[5]

Despite these large numbers, about 10-20% of all THA and TKA patients are not satisfied with their post-operative results.[6,7] One of the reasons might be pre-operative state of the patient, reflected by frailty.

Frailty is a common syndrome in the elderly, with an overall prevalence of frailty amongst people aged ≥65 of 10.7%.[8,9] Frailty, as a representative of health and functional status, hampers the capacity to resist stressors, which in turn leads to increased susceptibility for adverse outcomes after surgery.[9-13] Reported levels of frailty vary greatly amongst age groups, with the pooled prevalence rates for persons aged between 65-69 being below 5% while for those aged 80-85 this is over 15% and even over 25% for persons aged ≥85.[8] Within persons of the same age group, substantial heterogeneity is present to the levels of frailty an individual might experience.[10,11,14-16]

Previously we have shown that the Groningen Frailty Indicator (GFI) is a feasible and validated questionnaire in persons with end stage hip or knee OA.[1] Using the GFI with a cut-off value of 4, we demonstrated that up to one third of the end stage OA-patients scheduled to undergo THA and a quarter of those scheduled for TKA are considered to be frail.[1]

Mandl *et al*[17] have addressed adverse events after TJA in 241 frail and non-frail patients and found that there was only an association between activities of daily life and adverse events after TJA. However, this study had a follow-up period of only 30 days and is not representative for the long-term functional outcome of TJA in patients

with end stage hip or knee OA. A study by McIsaac *et al*[18] (follow-up 1 year) in 125163 TJA-patients studied healthcare resource usage but not functional outcomes. They found frail patients to have increased mortality, increased length of stay in hospital, higher chance of re-admission and higher rates of discharge to institutional care after TJA as compared to non-frail TJA patients. A study on the impact of frailty on the long-term postoperative function has, to our knowledge, not yet been performed.

In this study, we aim to assess whether frail persons (cut-off value GFI≥4) have lower gain in post-operative function and quality of life. We also assess by means of ROC-curves whether the pre-operative GFI is valuable tool to discriminate between THA and TKA with high (good) and low (adverse) gain in function at one-year post-operative.

Methods

This analysis was performed in the longitudinal prospective cohort study *"Longitudinal Leiden Orthopaedics Outcomes of Osteo-Arthritis Study (LOAS, Trial ID NTR3348)"* which consists of patients undergoing total hip or knee arthroplasty for primary osteoarthritis. Participants were selected from 7 participating hospitals (the Leiden University Medical Center, Leiden; Alrijne Hospital, Leiden/Leiderdorp (former Diaconessenhuis and Rijnland Hospital); Groene Hart Hospital, Gouda; LangeLand Hospital, Zoetermeer; Reinier de Graaf Gasthuis, Delft; Albert Schweitzer Hospital, Dordrecht; Waterland Hospital, Purmerend).

Patients

All TJA patients aged over 18 years able to complete questionnaires in Dutch were eligible for participation. Patients were excluded if the physical or mental status did not allow participation or in case they did not sign the informed consent. Written and oral information about the study was given by the treating medical specialist at the outpatient clinic. Patients willing to be approached by the researcher received additional written information about the study by regular mail or e-mail, as well as a questionnaire, a stamped return envelope and a consent form. Patients were included once written informed consent was obtained according to the Declaration of Helsinki.[19]

For the purpose of the present analysis only data from patients who returned both the preoperative and the 12 month follow-up questionnaires was included. Ethical approval was obtained from the Medial Ethics Committee of the Leiden University Medical Center (registration number P12.047) and funding was received from the Dutch Arthritis Foundation (LLP13).

Assessments

Demographic variables: The collected socio- and demographic characteristics of the patients included: age (years); sex and length (cm) and weight (kg) to calculate the Body Mass Index (BMI). Living situation was also collected and divided in 'living alone' or 'living together', the latter category included persons living with family members as well as persons living in community housing.

Comorbidities: The presence of comorbidities was assessed by means of a self-reported questionnaire comprised of 19 different comorbidities. Patients were asked to respond with either yes or no to the question “Have you received any treatment for [disease] in the past year”. The included diseases were then clustered in two groups: musculoskeletal comorbidities (severe back pain, severe neck or shoulder pain, severe elbow wrist or hand pain, inflammatory arthritis or other joint conditions) or other comorbidities (asthma or COPD, cardiac disorder or coronary disease, arteriosclerosis, hypertension, stroke, severe bowel disorder, diabetes mellitus, migraine, psoriasis, chronic eczema, cancer and urine incontinence, hearing or visual impairments and dizziness in combination with falling).

Groningen Frailty Indicator: The presence of frailty was analysed by means of the Groningen Frailty Indicator (GFI). The GFI is a 15 item validated questionnaire based on many aspects of life: activities of daily life, medication use, mental state, vision and hearing. Each item can give one point, resulting in a maximum score of 15. A patient with a score of ≥4 was considered frail.[20-23] The GFI has been validated to be used in patients with end-stage OA scheduled to undergo arthroplasty surgery.[1]

Functional outcome (HOOS/KOOS): Patient function was assessed by the validated Hip disability/Knee injury Osteoarthritis Outcome Score (HOOS/KOOS) questionnaires for hip and knee patients respectively. Both questionnaires comprise five domains: activities of daily living (ADL), quality of life (QoL), sports (SP), symptoms (SYM) and pain (P).[24,25] For the current study the validated Dutch versions of the HOOS/KOOS were used.[26,27]

Statistical analyses

Demographic characteristics of frail and non-frail patients were compared for hip and knee arthroplasty separately by means of Student's T-test (continue, normally distributed variables), Mann-Whitney U-test (continue, not normally distributed variables) or Chi-square (categorical variables), whichever was appropriate; per joint site.

Functional outcomes were assessed by means of the 5 subscales of the HOOS/KOOS questionnaire (pain (P), symptoms (S), activity limitations of daily living (A), sport and recreation functioning (SP) and joint related quality of life (QoL)). Scores were compared between frail and non-frail patients by means of Mann-Whitney U-test for each time point (baseline and 12 months) separately. In addition, for each of these scores a change-score was calculated by subtracting pre-surgery score from the 1-year follow-up scores. These were compared between frail and non-frail patients (cut-off value GFI≥4) by means of Mann-Whitney U-test.

Adverse outcome was defined as improving less than twice the Minimal Clinically Important Difference (MCID), meaning an improvement of less than 20 points on the HOOS/KOOS in the year after surgery.[24] This binary score (more or less than twice MCID) was calculated for each subscale of the HOOS/KOOS. For each subscale a logistic regression model was estimated with the binary outcome score and GFI as continue independent risk factor (Model1). Then a multivariable logistic regression model with GFI and baseline HOOS/KOOS score as prognostic factor was estimated (Model 2). Finally, a univariate logistic regression model was estimated to assess the association of baseline HOOS/KOOS score on GFI (Model 3). AUC was estimated to assess the discriminatory ability of the logistic regression models.[28]

All analyses were performed separately for THA and TKA patients. Data were analysed using the SPSS statistical package (version 20.0, SPSS, Chicago, Illinois). The level of statistical significance was set at $P \leq 0.05$ for all analyses.

Results

Among the 3,190 patients that were included in the LOAS-cohort, 1,570 (873 THA and 697 TKA) completed the HOOS/KOOS questionnaires at baseline and at 12 months follow-up. Of these, 92% also completed the GFI, resulting in 1445 persons in our analyses (805 THA and 640 TKA), see also Figure 1. Patients who did not complete the GFI were significantly older than those who did (mean (SD) age in years completed 66 (9.1), mean (SD) age not completed 69 (8.6), P=0.008) and female (72.8% female not completed, 63.5% female completed, P=0.04). No significant differences for BMI, musculoskeletal or other comorbidities were observed.

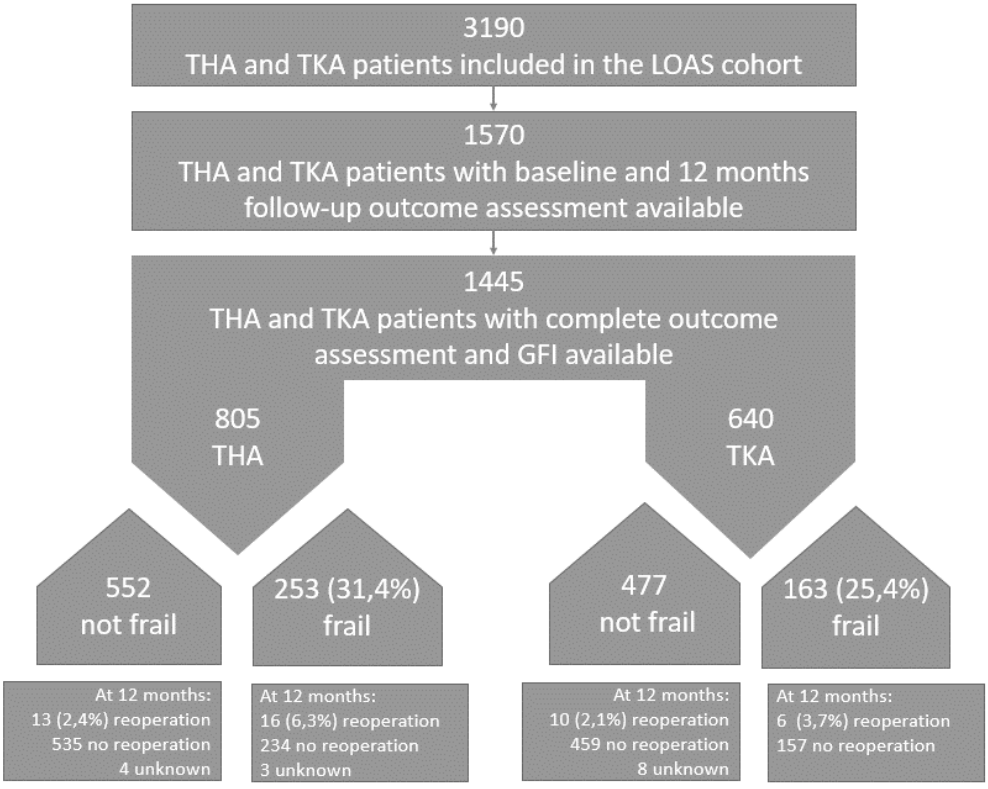

Figure 1 – Flowchart of patients included in the study and their final outcome.

Upon comparing frail patients to non-frail patients, significant differences were found for almost all the socio-demographic characteristics included in the analyses. Frail persons were more often female, older, had more comorbidities, a higher BMI and were more often living alone as compared to non-frail end-stage hip or knee OA patients (see also Table 1). Within the group of frail patients, frail patients with knee OA had significant higher BMI as compared to frail hip OA patients (results not shown).

Table 2 shows the crude baseline and the 12-month follow-up scores on each of the HOOS/KOOS subscales as well as the change score. Except for the KOOS-symptoms subscale, all baseline and 12 months scores of the HOOS/KOOS subscales were statistically significantly different in the frail persons as compared to non-frail patients. However, the significant difference between frail and non-frail is only clinically relevant at baseline in the subscale pain for hip and subscale ADL for both hip and knee. At 12 months the MCID-threshold of 10 is only reached in ADL for hip patients and in the subscale sports for hip and knee patients.[24]

Table 1 - Demographic characteristics of frail and non-frail (as defined by the Groningen Frailty Indicator (GFI)) end-stage osteoarthritis patients.

	Hip					Knee				
	Non-Frail		Frail (GFI≥4)			Non-Frail		Frail (GFI≥4)		
	N=552		N=253		P*	N=477		N=163		P*
Female N(%)	312	56.5%	187	74.2%	<0.001	291	61.5%	125	76.7%	<0.001
Age mean (SD)	66.2	9.1	68.3	10.3	0.004	66.1	8.6	68.2	8.7	0.010
BMI mean (SD)	26.6	3.8	28.1	5.3	<0.001	28.9	4.4	30.0	5.2	0.022
MSK comorb[A] N(%)	64	12.0%	60	25.0%	<0.001	98	21.6%	44	29.3%	0.054
Other comorb[B] N(%)	321	65.0%	185	84.1%	<0.001	294	70.5%	117	84.2%	0.001
Living alone N(%)	66	12.0%	88	34.8%	<0.001	78	16.4%	66	40.5%	<0.001

*P-value corresponding to Chi-square (discrete variables) or t-test (normally distributed continue variables) for differences between frail and non-frail persons within joint-specific group.

A MSK cormob. - Musculoskeletal comorbidities include severe back pain, severe neck or shoulder pain, severe elbow wrist or hand pain, inflammatory arthritis or other joint conditions.

B Other comorb _ Other comorbidities include asthma or COPD, cardiac disorder or coronary disease, arteriosclerosis, hypertension, stroke, severe bowel disorder, diabetes mellitus, migraine, psoriasis, chronic eczema, cancer and urine incontinence, hearing or visual impairments and dizziness in combination with falling.

Table 2 - Baseline and change scores of the HOOS/KOOS subscales at 12 months.

		Hip					Knee				
		Non-Frail		Frail (GFI≥4)		P-value*	Non-Frail		Frail (GFI≥4)		P-value*
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Pain	Baseline Score	40.9	17.9	30.9	17.8	<0.001	41.0	17.1	33.6	17.5	<0.001
	12 month Score	89.8	15.4	82.3	20.9	<0.001	87.5	17.3	81.1	19.0	<0.001
	Change Score	48.8	20.6	51.6	24.1	0.068	46.7	21.6	47.6	23.3	0.713
Symptoms	Baseline Score	41.4	18.5	35.2	17.3	<0.001	44.3	12.9	41.9	13.6	0.058
	12 month Score	82.7	18.6	73.0	20.5	<0.001	57.1	12.6	55.5	13.6	0.257
	Change Score	41.3	23.1	37.8	24.5	0.057	12.9	16.1	13.6	16.3	0.768
ADL^	Baseline Score	43.8	18.7	31.3	17.9	<0.001	48.8	17.0	37.8	17.8	<0.001
	12 month Score	87.5	15.7	76.7	22.0	<0.001	85.9	16.4	77.7	19.3	<0.001
	Change Score	43.7	20.5	45.4	24.5	0.261	37.1	19.9	39.9	22.6	0.136
Sports	Baseline Score	21.1	19.6	11.6	14.7	<0.001	11.3	14.2	7.4	12.5	<0.001
	12 month Score	70.5	25.0	54.3	29.0	<0.001	47.7	27.9	35.3	29.0	<0.001
	Change Score	49.4	27.9	42.6	29.9	0.002	36.4	26.7	27.9	27.7	<0.001
QoL$	Baseline Score	34.2	10.5	31.7	9.6	0.003	35.3	10.5	32.4	9.7	0.001
	12 month Score	60.5	15.7	56.1	18.3	0.003	54.4	16.3	48.5	15.4	<0.001
	Change Score	26.3	16.6	24.5	19.7	0.188	19.1	17.8	16.1	15.5	0.020

Scores of the HOOS/KOOS subscales at baseline and at 12 months. Included are also the change scores.

* Differences between frail and non-frail patients assessed by means of Mann-Whitley's test for non-parametric distributions.

^ ADL - Activities of Daily Life subscale of the HOOS/KOOS questionnaire

$ QoL - Quality of Life subscale of the HOOS/KOOS questionniare

The change-score for the Sports subscale was lower in frail as compared to non-frail in both hip (P=0.002) and knee (P<0.001). Also for the Quality of Life-subscale in knee a lower outcome change-score was found for frail persons (P=0.02). This suggests that the development over time, i.e. the change-score, in most subscales is similar in frail and non-frail persons. Only in Sports and QoL, non-frail persons have a more rapid increase in functioning after arthroplasty.

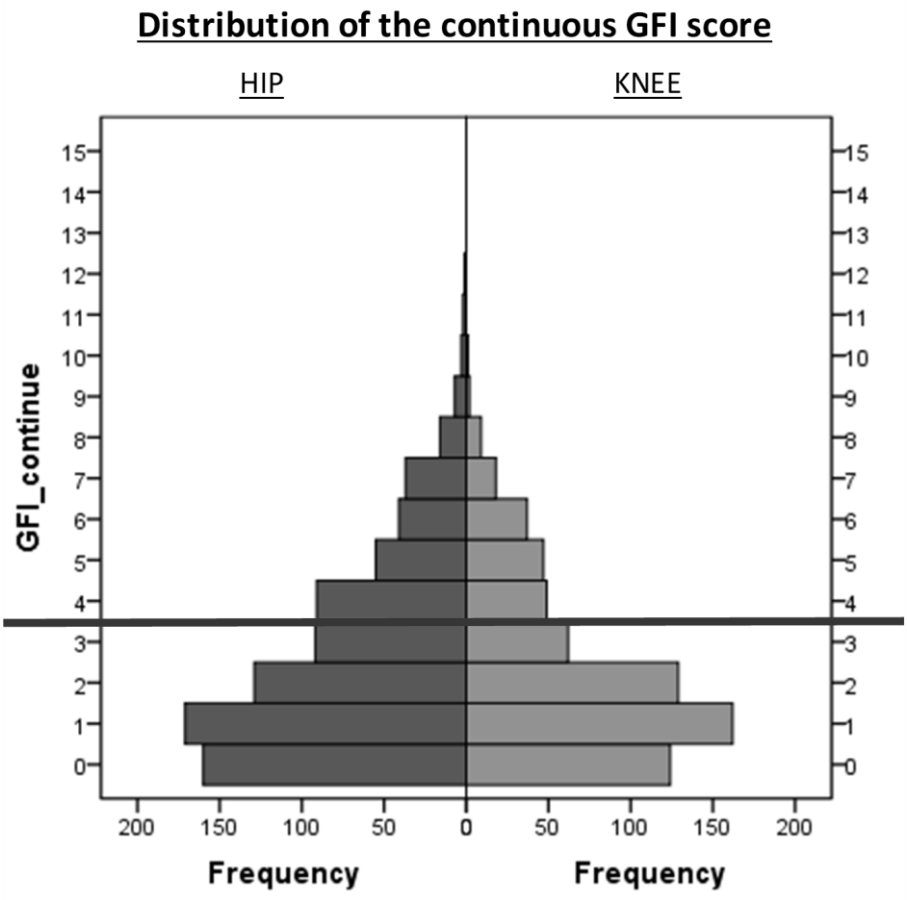

Figure 2 - Distribution of the Groningen Frailty Indicator (GFI) scores (range 0-15) stratified for affected joint.

Using the continuous scores of GFI (range 0-15, Figure 2); the potential of the GFI to discriminate between outcomes was assessed by constructing three models and the AUC for each model was estimated (Table 3). The model that included only GFI had poor discriminatory value (maximum AUC was 0.643 for Sports subscale in THA). The AUC for the model with GFI and baseline score as risk factors was equal to 0.804 for Symptoms in TKA while the model with only baseline score as risk factor had an AUC equal to 0.802 for Symptoms in TKA (Table 3).

Finally, we assessed the number of reoperations that were performed in the first 12 months post primary hip or knee arthroplasty and compared the rates of frail to the rate in the non-frail patients (Figure 1). Of the 163 frail patients with a knee replacement, 6 (3.7%) had to be re-operated on the same knee within 12 months, this rate was lower in the non-frail knee patients (2.1%, P=0.278). For persons with a hip replacement we did see a significant lower rate of re-operations in the non-frail patients (2.4%) as compared to the frail patients (6.4% P=0.005).

Table 3 – Discriminatory power between more or less than twice the MCID increase for various models in- and excluding Groningen Frailty Indicator (GFI).

	Hip			Knee		
	Model 1[A]	Model 2[B]	Model 3[C]	Model 1[A]	Model 2[B]	Model 3[C]
Pain	0.498	0.712	0.697	0.543	0.730	0.705
Symptoms	0.549	0.797	0.767	0.510	0.804	0.802
Activities of Daily Life	0.532	0.795	0.753	0.539	0.734	0.708
Sport	0.643	0.705	0.573	0.588	0.597	0.557
Quality of Life	0.575	0.623	0.623	0.561	0.611	0.582

Area under the estimated ROC curve corresponding to different models.
A - Model 1: Univariate analysis with Groningen Frailty Indicator (GFI) score as prognostic factor.
B - Model 2: Multivariate analysis with GFI and baseline score as prognostic factor.
C - Model 3: Univariate analysis with baseline score as prognostic factor.

Discussion

Although obvious preoperative (i.e. baseline) differences in values for the HOOS/KOOS subscales existed between frail and non-frail patients who undergo TJA, frailty did not discriminate between good or adverse outcome.

A model for TKA including GFI and pre-operative Symptoms-baseline score has an AUC equal to 80.4% for distinguishing between patients with a twofold MCID change on the symptoms subscale of the HOOS/KOOS. When only the pre-operative score was used, a similar AUC was found (80.2%), indicating that frailty has only a marginal additional value to increase this discriminatory value of post-surgery outcome in THA and TKA patients.

One reason might be the presence of selection bias, since only persons who are scheduled to undergo arthroplasty were included. This also explains skewed distribution of the continuous GFI scores. These persons have all undergone selection by the orthopaedic surgeon and those not considered fit to have surgery were excluded. The levels of frailty in this rejected group were unknown. However, amongst those undergoing surgery still 31.4% in hip and 25.4% in knee are considered frail by GFI (cut-off value of 4). Another problem may be the selection bias which is induced by excluding patients who, based on their mental or physical status, could not complete the questionnaires. Exactly these patients may be those who are most frail. Unfortunately, we did not have data to assess exactly how many patients were not capable to complete the questionnaires.

A study by O'Neill *et al*[29] demonstrated that the initial clinical impression by a physician of a patient is a useful screening tool to predict for mortality in patients undergoing major surgery. Also, a study conducted by Gerdhem *et al*[30] has demonstrated the subjective estimate of physicians of biological age is appropriate. Our results support these studies in the sense that improving outcome within the current selection of the physician, who apparently allowed GFI-indicated frail patients, is not possible by GFI since both frail and non-frail profited almost equally from the operation.

In our study we did find that persons who are considered frail by GFI have more often comorbidities and higher BMI, however, this is not a strong prognostic factor for postoperative functional outcomes. This might be due to selection bias by the treating orthopaedic surgeon (i.e. more severe comorbid patients or patients with even higher BMI were not selected). However, our results are in line with a study in head and neck cancer patients, showing that frailty as measured by the GFI is not predictive for postoperative complications after surgery.[31] In contrast, a study by Baitar *et al*[32] found that GFI is able to separate patients with cancer with normal and abnormal Comprehensive Geriatric Assessment.

We did find a higher reoperation rate in the frail patients as compared to the non-frail patients, confirming previous studies that found that frailty is a predictor for adverse events such as complications, readmission and reoperation.[33-35] This could be related to the increased number of comorbidities as we saw in our frail population; however, this should be further assessed in future studies.

For functional recovery after arthroplasty surgery, we have now shown that GFI is not a strong prognostic factor. We found that the functional baseline score is a strong prognostic score which can fairly well discriminate between good and adverse functional outcomes. In addition, we found that frail persons have significant lower functional baseline scores than non-frail persons. Therefore, baseline score seems a better measurement to give any indication about the to-be-expected outcome of surgery over frailty score when focusing on functionality, not necessarily when focusing on QoL or health care use. Jiang *et al*[33] have also identified that worse baseline scores of OKS are associated with worse post-surgery OKS up to 10 years after TKA. Exploring what other health assessments apart from functional parameters would predict post-surgery functionality, such as metabolic and inflammatory conditions at baseline, might improve patient-specific outcome prediction.

The cut-off of more or less than twice the MCID to assess the effect of GFI was arbitrarily, however, if we set the threshold at once the MCID (i.e. 10-point increase) similar results were found.

A limitation of this study is the aforementioned selection bias, as we only assessed persons selected by their treating surgeon to undergo surgery and did not have information of patients who were not selected to undergo surgery. These latter patients are most likely to be frail. Nevertheless, up to one-third of the patients who do undergo surgery are considered frail as measured by the GFI.

Among the patients selected for THA and TKA, baseline frailty assessed by the GFI did not provide added value in distinguishing between patients with more or less than twice the MCID change on functional outcome score by the HOOS/KOOS index, one year post-operative. Theoretically, it may be possible that more frail patients, currently not admitted to surgery, would profit functionally from THA/TKA surgery. However, as we do see higher reoperation rates in the frail patients, further research is needed before broadening the indication for arthroplasty surgery.

We conclude that although frail OA patients have lower functioning scores at baseline, the change-scores on HOOS/KOOS-subscales are similar for both frail and non-frail patients.

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Association of hand grip strength with patient reported outcome measures after total hip and knee arthroplasty

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Submitted

Abstract

***Background*:** About 33% of the osteoarthritis patients undergoing total hip/knee arthroplasty are not satisfied with the outcome, warranting the need to improve patient selection and to improve management of patient expectations. Previous research has found that quadriceps strength is related to outcome of arthroplasty and handgrip strength has been suggested as a proxy for overall muscle strength. This study aims to assess whether preoperative handgrip strength is associated with gain in hip/knee function and quality of life in arthroplasty patients.

Materials & Methods: 226 hip and 246 knee arthroplasty-patients were selected from a prospective cohort study, including patients from October 2010 to September 2012. Preoperative handgrip strength was assessed with a dynamometer and the HOOS/KOOS and SF-36 questionnaires were collected before arthroplasty and one year thereafter. The association of handgrip strength with the outcome change was assessed by linear regression models, including age, sex, body mass index and baseline score.

Results: Handgrip strength was strongly associated with change score on “sport & recreation”-domain in hip and moderately to “sport & recreation”-domain in knee and “symptoms”-domain in hip.

Conclusions*:* Handgrip strength can be used as a tool to provide patients with information about gains to be expected on certain aspects of life after arthroplasty.

Introduction

Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) are effective procedures to improve pain and functioning in osteoarthritis (OA) patients.[1,2] Despite high success rates, up to one-third of persons undergoing arthroplasty are not satisfied with the outcome of surgery, warranting the need to improve the selection of patients who may and may not benefit and manage expectations in this patient group. [3-5]

Besides age, gender, physical and mental status, poor quadriceps strength was associated with worse outcomes of knee arthroplasty.[6-8] Handgrip strength (HGS) is a proxy for overall muscular strength, with only a small number of measurements with a handgrip dynamometer considered necessary to characterize an individual's overall strength status.[9-11]

HGS has been demonstrated to associate with worse general health in the elderly as well as being a predictor for all-cause mortality in elderly.[12-18] In various patient groups, HGS has been shown to be predictor for disability, malnutrition and surgery complications.[19-29] To our knowledge, only one study focused on HGS in hip and knee arthroplasty patients, showing that a lower HGS is associated with increased length of hospital stay after hip or knee replacement while correcting for age.[30] Hence, the value of HGS as a predictor for long-term outcomes after lower limb arthroplasty surgery is currently unknown.

The purpose of this study is to assess the association of preoperative HGS with postoperative changes of hip and knee function and quality of life one year after total hip or knee arthroplasty as measured on the various subscales of the Hip disability and Osteoarthritis Outcome Score (HOOS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) and Short Form-36 Health Survey (SF-36) questionnaires.

Materials & Methods

This study on HGS as an indicator for THA and TKA outcome was part of a prospective observational cohort study on the outcomes of THA and TKA performed at the Department of Orthopedics of the Alrijne Hospital, Leiderdorp, the Netherlands, from October 2010 to September 2013 (inclusion of patients until September 2012).
The study protocol was in concordance with the Declaration of Helsinki[31] and was reviewed and approved by the local hospital Review Board of the Alrijne Hospital (registration number 11/02), which is supervised by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, the Netherlands.

This prospective cohort study aimed to include all consecutive patients undergoing a primary THA or TKA because of OA, aged 18 years or older, able to read and understand Dutch and being mentally and physically able to complete questionnaires.
Excluded were patients with revision of a THA or TKA, undergoing a hemi-arthroplasty of the hip and undergoing a THA or TKA because of a tumor or rheumatoid arthritis. All assessments were done preoperatively and 12 months thereafter and consisted of HGS measurement at the hospital and the collection of questionnaires, administered personally (preoperative assessment) and by regular mail (follow-up).

One day preoperatively, before being admitted to the hospital, information about the study was provided to all eligible patients. Patients received a response form as well as a set of questionnaires. The response form comprised statements for both patients who wished to participate (including signature) and those who did not want to participate. Each patient was asked to return the questionnaires and informed consent form and perform the HGS-test on the day of surgery, when admitted to the hospital.

Socio-demographic characteristics were recorded preoperative and included: age (years); gender and length (cm) and weight (kg) to calculate the Body Mass Index (BMI). Age was categorized into three groups; <60 years, 60-70 years and aged >70.

Isometric HGS was measured before arthroplasty using the JAMAR® hydraulic hand dynamometer (Patterson medical, Mississauga, Canada).[32] Results were expressed in kilograms. Patients were shown the correct operation of the dynamometer prior to measurements. They were instructed to keep their shoulders adducted and neutrally rotated, their forearm in a vertical position, and wrist in a neutral position and to squeeze the grip with maximal strength. The highest result of two grip strength trials with the dominant hand in a seated or semi-seated position was used.

Patient reported outcome scores were collected before arthroplasty surgery and at one year follow-up. The SF-36 questionnaire was used to assess overall quality of life and the HOOS/KOOS for joint specific PROMS measurements. The SF-36 is composed of 36 questions and standardized response choices. Summary component scores for physical health (PCS) and mental health (MCS) can be calculated from this questionnaire. In this study, scores of the Dutch general population were used to standardize our scores in order to apply norm-based scoring.[33]

In patients undergoing THA, the HOOS was used to assess functioning. This questionnaire consists of 40 items divided over 5 dimensions: pain (P); symptoms (S); activity limitations-daily living (ADL); function in sport and recreation (SP) and hip related quality of life (QoL). Persons with end stage knee OA received the similar KOOS questionnaire which comprises 42 items and uses the same 5 subscales as the HOOS. For the present study, validated Dutch versions of the HOOS and KOOS were used.[34,35]

Statistical Analyses:

Patients' socio-demographic characteristics were compared between those who did and did not complete the one year follow-up assessment by using unpaired Student's t-test (for continue variables) or Chi Square test (for categorical variables).

The SF-36 PCS and MCS subscales were included as outcome score as well as the five subscales from the HOOS/KOOS questionnaire: pain (P), symptoms (S), activity limitations of daily living (ADL), function in sport and recreation (SP) and quality of life (QoL). For each of these subscales a change score was calculated by subtracting the pre-surgery scores from the 1-year follow-up score.

Normality of the change scores was assessed by means of histograms, Q-Q-plot and Kolmogorov-Smirnov test. Multiple regression models for hip and knee patients were used to study the association between HGS and change scores adjusted for age group, gender, BMI and preoperative values of outcome measures. An interaction term between gender and age group was incorporated in the model to investigate possible additional different effects between males and females. These analyses were performed for THA and TKA separately.

The strength of the association of HGS to the outcome change score was quantified by assigning the unstandardized effect sizes to one of the categories: 0-0.19 very weak, 0.2-0.39 weak, 0.4-0.59 moderate, 0.6-0.79 strong, 0.8-1.00 very strong.[36]

All data was analyzed using the SPSS statistical package (version 20.0, SPSS, Chicago, Illinois). The level of statistical significance was set at $P \leq 0.05$ for all analyses.

Results

341 persons undergoing THA surgery completed the preoperative assessment of which 226 (66.3%) persons completed the one year follow-up. Among the 315 TKA patients, 246 (78.1%) completed the one year follow-up.

Demographic characteristics of patients with end stage OA, scheduled for either total hip or total knee arthroplasty are shown in Table 1. There were no statistically significant differences in age, gender and BMI between those who did and did not complete follow-up. Among those who completed the questionnaire, TKA patients were significantly more often female than those who underwent THA (P=0.001) and had a higher BMI (P<0.001), there was no significant difference in age between THA or TKA patients (P=0.605).

Table 1 - Demographic characteristics of patients with end stage OA, scheduled for either total hip or total knee arthroplasty.

	Total Hip Arthroplasty			**Total Knee Arthroplasty**		
	Completed N=226	Incomplete N=115	P*	Completed N=246	Incomplete N=69	P*
Sex %Female	127 (56.1%)	75 (65.2%)	0.109	176 (71.5%)	52 (75.3%)	0.531
Age (Years)	66.4 (9.5)	67.8 (10.8)	0.243	66.9 (9.2)	68.1 (11.5)	0.359
BMI	26.9 (4.4)	27.8 (4.8)	0.082	29.4 (4.5)	29.7 (4.7)	0.675

* P-value for differences between patients with end stage hip or knee OA who did and did not complete follow-up. Difference was calculated by means of Chi-Square or unpaired Student's T-test, where was appropriate.

Mean HGS was 26 kg for end stage hip OA and 24 kg (SD=10) in end stage knee OA patients, with males having higher scores than females in both hip (mean (SD) HGS males: 34(10) kg, females: 21(6) kg) and knee (mean(SD) HGS males: 34(10) kg, females 19(7) kg).

As can be seen in Table 2, for each outcome score except MCS a significant difference in pre- and post-surgery outcome score was found. In both hip and knee the change in outcome for PCS was higher than the minimal clinically important difference (MCID) of 10 points. However, for MCS the change scores were not significant, neither clinically relevant.[37,38] The smallest change score on the HOOS/KOOS subscales was 10.8, (KOOS-S) which is just above the MCID cut-off of 10.[39,40] Interestingly, the final scores on the "Function in sport and recreation" and "Symptoms" subscales of the HOOS/KOOS were significantly (both P<0.001) higher in the THA groups than the TKA group.

Table 2 – Outcome score at baseline and one year follow-up.

		Total Hip Arthroplasty N= 226			Total Knee Arthroplasty N=246		
		Baseline Mean (SD)	1 year FU Mean (SD)	P*	Baseline Mean (SD)	1 year FU Mean (SD)	P*
SF-36[a]	PCS [b]	40.2 (7.5)	53.3 (7.7)	<0,001	40.6 (7.3)	52.1 (8.9)	<0,001
	MCS [c]	52.1 (10.5)	53.4 (8.4)	0,096	52.8 (10.1)	52.0 (9.35)	0,115
HOOS KOOS [d]	ADL[e]	45.2 (17.8)	84.8 (16.9)	<0,001	50.1 (18.1)	84.2 (16.4)	<0,001
	Pain	43.2 (18.5)	88.2 (14.7)	<0,001	43.0 (16.5)	85.0 (17.0)	<0,001
	QoL[f]	35.7 (10.3)	54.8 (17.1)	<0,001	35.2 (9.9)	54.2 (17.1)	<0,001
	SP[g]	21.6 (19.3)	63.8 (26.6)	<0,001	14.0 (16.0)	47.1 (28.8)	<0,001
	Symptoms	38.2 (18.9)	80.5 (19.8)	<0,001	45.0 (13.5)	55.8 (12.0)	<0,001

* P-value for Wilcoxon test assessing outcome score at baseline and one year follow-up.
a SF-36: Short Form 36 Questionnaire.
b PCS: Physical Component Score of the SF-36 questionnaire
c MCS: Mental Component Score of the SF-36 questionnaire
d HOOS/KOOS: Hip disability / Knee injury Osteoarthritis Outcome Score.
e ADL: Activities of Daily Life – domain of the HOOS/KOOS Questionnaire
f QoL: Quality of Life – domain of the HOOS/KOOS Questionnaire
g SP – Function in sport and recreation – domain of the HOOS/KOOS Questionnaire

The unstandardized adjusted coefficients, showing the effect of preoperative HGS and the change on the postoperative PROMS outcome-variable, are shown in table 3 where the effect is quantified by the coefficient (coef). In both arthroplasty groups a significant effect of HGS on "function in sport and recreation"-scale of the HOOS/KOOS (THA: coef=0.68, P=0.005; TKA coef =0.52, P=0.049) was found. Some evidence for an effect of HGS on the "symptoms" subscale was seen in THA (coef=0.56, P=0.001), but not in the TKA group (coef=0.16, P=0.146). A small effect of HGS to "quality of life" as measured by HOOS/KOOS was seen on THA (coef=0.32, P=0.047) and TKA (coef=0.33, P=0.033). A significant effect of HGS was found on PCS for TKA (coef=0.31, P=0.001) but not in THA (coef=0.14, P=0.052). No evidence of effect of HGS on the MCS of the SF-36 on both THA and TKA group was found.

All observed statistically significant effects were positive, indicating that with increasing handgrip strength a positive change in the outcome measures occurs after arthroplasty surgery.

Table 3 – Outcome of multiple regression models for HGS and change score.

		Total Hip Arthroplasty N= 226			**Total Knee Arthroplasty** N=246		
		Coef (SE)	95% CI	P*	Coef (SE)	95% CI	P*
SF-36[a]	PCS[b]	0,136 (0,07)	[-0,001 - 0,273]	0,052	0,305 (0,09)	[0,135-0,476]	0,001
	MCS[c]	0,074 (0,07)	[-0,054 - 0,202]	0,257	-0,022(0,09)	[-0,192-0,148]	0,802
HOOS KOOS[d]	ADL[e]	0,253 (0,15)	[-0,037 - 0,543]	0,087	0,308 (0,15)	[0,012-0,604]	0,042
	Pain	0,270 (0,13)	[0,015 - 0,524]	0,038	0,188 (0,16)	[-0,119-0,496]	0,229
	QoL[f]	0,317 (0,16)	[0,005-0,630]	0,047	0,327 (0,15)	[0,026-0,628]	0,033
	SP[g]	0,681 (0,24)	[0,209-1,153]	0,005	0,520 (0,26)	[0,001-1,039]	0,049
	Sym[h]	0,564 (0,17)	[0,228-0,900]	0,001	0,159 (0,11)	[-0,056-0,373]	0,146

* P-value; potential confounder age group, sex, BMI and baseline-outcome.
a SF-36: Short Form 36 Questionnaire
b PCS: Physical Component Score of the SF-36 questionnaire
c MCS: Mental Component Score of the SF-36 questionnaire
d HOOS/KOOS: Hip disability / Knee injury Osteoarthritis Outcome Score
e ADL: Activities of Daily Life domain of the HOOS/KOOS
f QoL: Quality of Life domain of the HOOS/KOOS
g SP: Function in sport and recreation domain of the HOOS/KOOS
h Sym: Symptoms domain of the HOOS/KOOS

Discussion

This study shows that preoperative hand grip strength of total hip or knee arthroplasty patients is strongly associated to the change in outcome on the "*function in sport & recreation*"-subscale of the HOOS/KOOS in both the THA and TKA groups, a strong positive association was also found on the "*symptoms*"-subscale and some evidence for a smaller effect on "quality of life" of the HOOS in THA patients.

Our findings are in agreement with current research where low HGS before surgery is associated to adverse outcome scores. The associations of HGS with the increase in score for physical measures (reflected in "function in sports and recreation", "symptoms" and PCS) post-surgery is also discussed in Savino et al., the authors show that HGS is associated to walking recovery after hip fracture surgery.[41] In the same type of patients, Visser *et al*[42] have shown that a decline in HGS post-surgery is associated to less recovery of mobility and Beloosesky[43] has demonstrated that HGS can be used to predict motor functioning at 6 months post-surgery. Although we measure a more generic outcome measure in a different patient group with a longer follow-up, these findings are in line with published literature.

The association of HGS with "*function in sport and recreation*" was more pronounced in THA patients than TKA patients and the "*symptoms*"-subscale was only associated with HGS in THA patients, not in TKA patients. A systematic review by Skoffer *et al*[44] found that muscle strength training in THA is effective to improve QoL after surgery, whereas for TKA this is not demonstrated.

These outcomes, together with the present study, suggest that the association of muscle strength with surgery outcome is dependent on the joint site, however, the mechanism has yet to be elucidated. TKA patients were, at baseline, more overweight than THA patients, which may play a role. Indeed, it has been reported that obesity is negatively associated with functional score and quality of life after TKA but not in THA.[45] However, our results were corrected for BMI, nevertheless, we do find different results for both joints.

The mean HGS values found in our study (THA: males: 34, females: 21; TKA: males: 34, females 19) were lower than the reference values as reported by Leong *et al*[46] for males (HGS=42) and females (HGS=26) aged 61-70 from North America and Europe. These lower values are explained by the fact that our patients all have end-stage osteoarthritis, while the reference values were obtained in healthy adults.

This study suffers from a high rate of loss to follow-up (THA: 33.7% and TKA: 21.9%), although we did not find any statistically significant differences in age, sex or BMI distribution, those who did not complete follow-up tend to be older and have a higher BMI. As increased age and BMI are associated with worse outcomes, this is a major limitation to our study.

Since the guidelines on indication for hip and knee arthroplasty are based on limited evidence, the application of HGS as a tool to identify patients who may experience lower outcome changes may contribute to optimize patient specific care.[47,48] HGS could be applied to manage patients expectations and include patients in the shared decision making process.

In conclusion, a rather easily applicable clinical measurement such as HGS could contribute to the assessment of the postoperative outcome of THA and TKA, providing the orthopedic surgeon as well as patients an easy preoperative tool on certain aspects of the postoperative outcome of THA and TKA.

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The BBMRI metabolomic consortium: histidine, glutamine and fatty acid make-up associate with the prevalence and progression of hip and knee osteoarthritis.

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Abstract

Objective: Higher body mass index (BMI) is associated with osteoarthritis (OA) in both weight-bearing and non-weight-bearing joints, suggesting a link between OA and poor metabolic health beyond mechanical loading. This risk may be influenced by systemic factors accompanying BMI. We hypothesize that differences in metabolic state contribute to development of OA. This study explores the association of metabolites with radiographic knee/hip OA (HOA/KOA) prevalence and progression.

Methods: A ^{1}H-NMR-metabolomics assay was performed on plasma samples of 1564 cases for prevalent OA and 2125 controls collected from the Rotterdam Study, CHECK, GARP/NORREF and LUMC-arthroplasty cohorts. HOA/KOA was assessed by means of Kellgren-Lawrence (KL) score and the OARSI-atlas. End-stage knee/hip OA was defined as indication for arthroplasty surgery (TKA/THA). OA-progression was defined as an increase in KL-score, to at least ≥2. Controls did not have KOA/HOA at baseline or follow-up. Principal component analysis of 227 metabolites demonstrated 23 factors, of which 19 remained interpretable after quality-control. Associations of factor scores with OA definitions were investigated with logistic regression resulting in odds ratio's (OR) per SD.

Results: Two factors showed consistent associations with prevalence and progression of KOA/HOA and TKA/THA. The "Glutamine and Histidine" factor showed negative associations (HOA: OR=0.7,P<0.001; THA: OR=0.7,P<0.001; KOA: OR=0.8,P=0.004; KOA progression: OR=0.8,P=0.020). The "Fatty-acids make-up" factor, representing chain length, ratio of saturated fatty acids and degree of unsaturation, showed positive associations (THA: OR=1.4,P<0.001; TKA: OR=1.6,P<0.001; HOA-progression: OR=1.2,P=0.047).

Conclusion: Fatty acid-make-up, histidine and glutamine serum levels associate with both prevalence and progression of OA, independent of BMI.

Introduction

Osteoarthritis (OA) is a common, age-related, progressive degenerative disease of articular joints and one of the leading causes of disability and pain worldwide. Due to ageing, increased longevity, and increasing obesity of the population, the OA incidence is expected to rise in the near future.[1-3] Epidemiological studies have shown systemic effects including associations of OA with unfavourable metabolic parameters, such as high body mass index (BMI), waist hip ratio and proportion of fat mass with metabolic diseases, such as hypertension, obesity and diabetes mellitus[4-10] Conversely, weight loss reduces the risk, as well as, relieve the pain and increase the physical function of people with OA.[11-14]

Associations with BMI have been found for OA in both weight-bearing and non-weight bearing joints, suggesting a connection between OA and obesity beyond axial loading.[15-17] In line with this view, OA associates with classical markers of poor metabolic health such as increased circulating levels of (LDL) cholesterol.[18,19] Together these data indicate that the metabolic health of individuals likely affects susceptibility to OA.[16,20-25]

In addition to classical metabolic parameters, such as cholesterol and glucose levels, metabolic health can be assessed by a range of serum metabolites. In the current study we investigated whether prevalence and progression of radiographic knee and hip OA is associated with ^{1}H-NMR based plasma metabolite levels. A well standardized and affordable is that of Nightingale^{Ltd} Finland. The Nightingale platform provides data on 231 metabolites, representing a comprehensive and highly correlated spectrum of amino acids, keton-bodies, lipids, lipoproteins and composite scores such as fatty acid chain length and previously reported to be associated with metabolic syndrome, diabetes and cardiovascular disease.[26,27]

In the current study, we have analysed associations of the Nightingale ^{1}H-NMR based metabolites with prevalent radiographic hip and knee OA, and progression of radiographic knee and hip OA in multiple cohorts participating in the Biobanking and BioMolecular resources Research Infrastructure consortium (BBMRI metabolomics consortium).[28] Identifying an OA-specific metabolite profile independent of BMI would provide further insight into the characteristics of the link between poor metabolism and OA and may eventually help clinicians to better identify those knee and hip OA patients who may benefit most from a lifestyle intervention.

Methods

Study populations

CHECK study: CHECK *(Cohort Hip & Cohort Knee) is a prospective, 10-year follow-up, observational cohort study* of 1002 people aged between 45 and 65 years at the time of inclusion, with pain in their knee(s) and/or hip(s), who had never or not longer than 6 months ago visited a general physician for these complaints.[29] Blood samples were taken non-fasted. Hip and knee radiographs were scored pairwise according to the Kellgren & Lawrence (KL) scoring system. *When scored pairwise, t*hese people did not have obvious radiographic knee or hip OA at baseline (i.e. KL=0 or 1)*. As such, these persons were considered controls for the cross-sectional analyses on OA prevalence at baseline. Those who did not develop OA during follow-up were included as controls in the progression analyses.*

GARP study: The GARP cohort (N=217) consists of patients with advanced radiographic OA at two or more joint sites of hand, spine, knee or hip. Follow-up was performed at 5 years, at which radiographs for hip, knee and hand were scored pairwise using the OARSI Atlas and the KL scoring system. Matched to the GARP study, a normal reference control group (NORREF) was collected using the same protocol and included in this study as controls.[30-32] *Blood was collected non-fasted.*

LUMC Arthroplasty studies: The LUMC arthroplasty studies (N=462) consist of participants of the RAAK, TacTics (NTR309) and TOMaat (NTR303) studies.[33,34] These cross-sectional studies included OA patients who received THA or TKA. Since all participants underwent THA/TKA, all patients are considered as end-stage OA and included in the cross-sectional OA prevalence analysis. Blood samples were collected during surgery while patients were fasted.

Rotterdam Study: The Rotterdam Study (RS) is a large prospective population-based cohort study of men and women aged 55 years and older in the municipality of Rotterdam, the Netherlands. The study design and rationale are described elsewhere in detail.35 In summary, the objective of the study is to investigate the determinants, incidence and progression of chronic disabling diseases in the elderly. Baseline measurements were obtained through a home interview and visits to the

research centre for physical examinations and imaging and laboratory assessments, blood samples were taken while patient was fasted. The present study includes 2802 participants from RS-I (Ergo 4) who were followed for 7 years. *The study included both individuals* with and without OA at baseline with mean follow-up time of 6.51 (0.41) year.

Informed consent was obtained from all included participants according to the Declaration of Helsinki (WHO) and good clinical practise.[36] In addition, approval by the local Medical Ethics Committee was obtained.

Definitions of OA

Prevalent radiographic OA was defined as either having a KL score of ≥2 in hip and/or knee at baseline or having THA or TKA for primary OA.[37] THA/TKA patients were also assessed separately. Controls (N=2125) had no radiographic hip and knee OA (KL<2) and were selected from the Rotterdam Study, CHECK and NORREF as described above.

Data on radiographic OA progression were available for GARP, CHECK, and the Rotterdam Study. For GARP, progression of radiographic OA was defined as progression of joint space narrowing (JSN) and/or osteophyte size above the smallest detectable change.[32] For CHECK and the Rotterdam Study, this was defined as an increase in KL-score, resulting in a KL score of ≥2 at follow-up. Thus, both incidence (KL score of 0 or 1 at baseline and ≥2 at follow-up) and progression (increase at KL score with a baseline of ≥2) were defined as progression in our analyses.

Controls were selected from CHECK and the Rotterdam Study and had neither radiographic OA at baseline, nor developed radiographic OA during follow-up.

Metabolite measurement

EDTA plasma samples were taken either at the time of TKA/THA in the LUMC-arthroplasty-studies or at baseline for the cohort studies. Samples were shipped to Nightingale to perform standardized metabolomics analyses on a high throughput platform (Nightingale Ltd, Helsinki, Finland). The ^{1}H-NMR technique used by Nightingale provides simultaneous quantification of routine lipids, lipoprotein subclass profiling with lipid concentration units, resulting in 231 measurements. Details of the techniques have been described before.[38-40]

Statistical Analyses

Analyses were performed per joint (hip or knee) and are also depicted in a flowchart (Figure 1). Since most distributions of metabolites were skewed, metabolite levels were LN-transformed to obtain normal distribution. Metabolite levels below the detection limit were considered missing. Metabolites with more than 5% missing were removed from analysis. Principal component analysis (PCA) was applied to reduce the data dimension of correlated metabolites. Factors were examined by means of scree plots and factors with an eigenvalue above 1 after Varimax rotation with Kaiser Normalization were included in analyses. A metabolite was said to load on a given factor if its factor loading was >0.4 or <-0.4. For each subject, a score was computed for the measures loaded on the factor, representing the linear relationship (Pearson correlation under Varimax rotation) between a factor and variable.

Since some of the used cohorts consist of only controls (NORREF and CHECK at baseline) the presence of cohort effects among controls was assessed by relating each factor to cohort while adjusting for age, sex, BMI and fasting status. Factors with significant cohort effects were removed from the analyses.

The remaining factors were included in logistic regression analyses to assess their association with OA, adjusting for age, sex, BMI and fasting status. Results are expressed as odds ratios per standard deviation and were corrected for multiple testing according to Bonferroni. To assess the modifying role of BMI and fasting, analyses were also performed without an adjustment for BMI or fasting.

Since follow-up was performed at different time points, the progression analyses were done by means of meta-analysis. To increase power by reaching substantial

cases and controls in the analysis, CHECK and GARP were combined. The summary statistics (regression coefficients and standard errors) of GARP+CHECK were then combined with the summary statistics of the Rotterdam Study in a random effects meta-analysis using the “meta package” for R. The individual metabolitesof factors who associate to both cross-sectional OA and progression of OA were LN-transformed and Z-standardized before being included in regression analyses for their association with any OA or any arthroplasty.

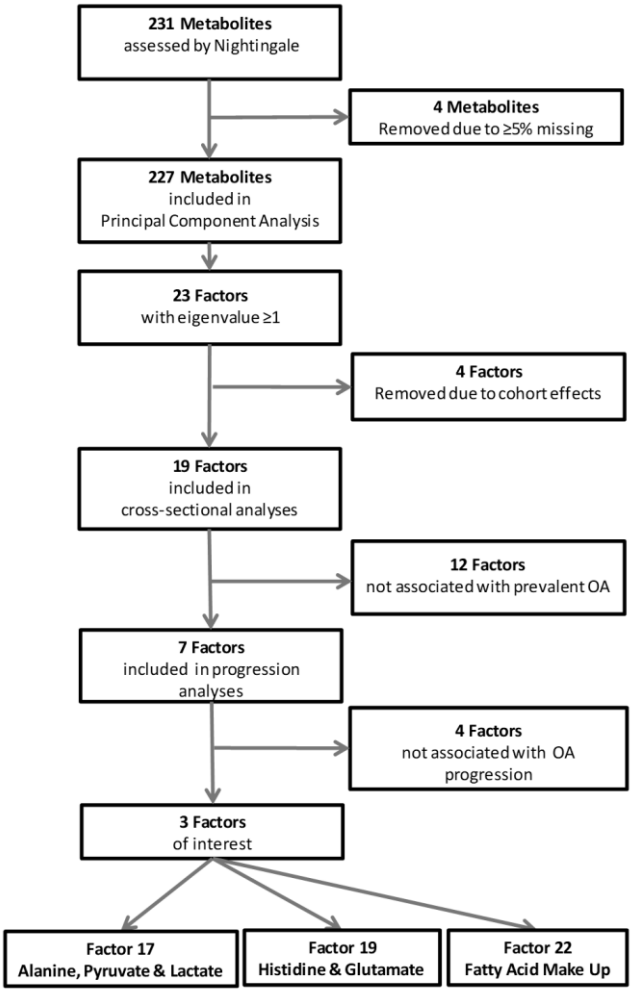

Figure 1 – Flowchart of analyses

Results

Of the 231 metabolites measured on the Nightingale platform, 4 metabolites had more than 5% of the measurements below the detection limit and were removed from analysis. These were conjugated linoleic acid (CLA), the ratio of CLA to total fatty acids (CLAFA), diglycerids (DAG) and ratio DAG to triglycerids (DAG/TG). See Supplementary Table 1 for complete list of assessed metabolites.

Principal component analysis

As shown in Supplementary Table 2, PCA revealed 23 factors with an eigenvalue of ≥1, accounting for 91,4% of the total variance. Notably, the first 2 components explained 56.4% of the variance. Based on the characteristics of the metabolites loading on each of the factors, we distinguished groups of metabolites representing low density lipids (LDL), very low density lipids (VLDL), high density lipids (HDL), fatty acids, and amino acids, se Supplementary Table 1.

Prior to analyses, quality control was performed within the control group with respect to cohort effects and led to removal of factor 2 (representing mostly VLDL-related metabolites), factor 10 and 13 (both representing HDL-related metabolites), and factor 16 (representing triglycerides in large HDL particles), accounting for 28.06% of the variance in the original dataset (see Supplementary Table 3).

Table 1 - Baseline characteristics of subjects in the cross-sectional analyses.

		HOA	THA	KOA	TKA	Controls
Age,	mean (SD)	69,6 (11,9)	68,0 (13,13)	72,5 (8,63)	71,0 (9,26)	66,1 (10,13)
Female,	N (%)	482 (65,6%)	313 (70,2%)	700 (70,8%)	142 (71,7%)	1301 (61,4%)
BMI,	mean (SD)	27,5 (4,4)	27,6 (4,6)	28,7 (4,53)	29,8 (4,1)	26,5 (3,9)
CHECK,	N	0	0	0	0	864
GARP/NORREF,	N	108	34	150	7	34
LUMC-cohorts,	N	302	302	153	153	0
Rotterdam Study,	N	326	111	687	39	1227
Total,	N	736	447	990	199	2125

HOA - Prevalent Radiographic Hip Osteoarthritis
THA – Total Hip Arthroplasty
KOA – Prevalent Radiographic Knee Osteoarthritis
TKA – Total Knee Arthroplasty

Cross-sectional analyses of factors 1, 3-9, 11, 12, 14, 15 and 17-23.

As depicted in Table 1, 736 cases with radiographic hip OA, 990 cases with radiographic knee OA, and 2125 controls without radiographic knee or hip OA at baseline were included in the cross-sectional analysis. These subpopulations differed with regard to age, gender and BMI. Therefore, all analyses were adjusted for age, sex and BMI.

As shown in Table 2, cross-sectional analyses with the remaining 19 factors (explaining 64.1% of variance) showed 3 factors that were positively associated with total joint arthroplasty of both the hip (THA) and knee (TKA) as compared to controls; factor 17 (THA: OR=1.38, 95%CI=1.20-1.59, P=0.002; TKA: OR=1.49, 95%CI=1.21-1.83, P=0.003), factor 22 (THA: OR=1.41, 95%CI=1.23-1.63, P=1.90E-5; TKA: OR=1.61, 95%CI=1.33-1.95, P=1.73E-5) and factor 23 (THA: OR=1.31, 95%CI=1.13-1.51, P=0.005; TKA: OR=1.71, 95%CI=1.40-2.09, P=2.66E-6).

Factor 1 showed a statistically significant association with TKA (OR=0.70, 95%CI=0.58-0.85, P=0.005), but, despite the similar effect size, did not reach statistical significance after correcting for multiple testing for THA (OR=0.85, 95%CI=0.74-0.99, P=0.646).

Three additional factors showed associations with THA, as well as, radiographic hip OA being; factor 4 (HOA: OR=1.37, 95%CI=1.23-1.53, P=4.17E-7; THA: OR=1.33, 95%CI=1.14-1.55, P=0.005), factor 11 (HOA: OR=0.82, 95%CI=0.74-0.91, P=0.002; THA: OR=0.77, 95%CI=0.67-0.88, P=2.00E-4) and factor 19 (HOA: OR=0.68, 95%CI=0.60-0.76, P=3.69E-10; THA: OR=0.65, 95%CI=0.55-0.75, P=5.93E-7).

Concurrent to factor 1, effect sizes of these factors in the association with OA in the knee were similar in direction but did not reach significance.

Table 2 - Outcomes of adjusted cross-sectional analyses

		Factor 1			Factor 17			Factor 22			Factor 23		
		Odds ratio	95% CI	P-value*	Odds ratio	95% CI	P-value*	Odds ratio	95% CI	P-value*	Odds ratio	95% CI	P-value*
Hip	HOA[A]	0,943	0,849-1,048	>1	1,147	1,036-1,270	0,171	1,127	1,015-1,252	0,494	1,088	0,982-1,206	>1
	THA[B]	0,854	0,739-0,988	0,646	1,381	1,198-1,591	0,002	1,414	1,228-1,627	1,90E-05	1,305	1,132-1,505	0,005
Knee	KOA[A]	0,982	0,897-1,075	>1	0,975	0,891-1,067	>1	1,055	0,964-1,155	>1	0,967	0,883-1,059	>1
	TKA[B]	0,703	0,583-0,849	0,005	1,491	1,213-1,834	0,003	1,613	1,333-1,952	1,73E-05	1,708	1,399-2,085	2,66E-06

		Factor 4			Factor 11			Factor 19		
		Odds ratio	95% CI	P-value*	Odds ratio	95% CI	P-value*	Odds ratio	95% CI	P-value*
Hip	HOA[A]	1,368	1,226-1,527	4,17E-07	0,82	0,741-0,906	0,002	0,675	0,601-0,757	3,69E-10
	THA[B]	1,328	1,141-1,546	0,005	0,765	0,665-0,881	0,004	0,645	0,553-0,754	5,93E-07
Knee	KOA[A]	1,18	1,071-1,300	0,019	0,891	0,816-0,973	0,19	0,825	0,745-0,914	0,004
	TKA[B]	1,329	1,059-1,668	0,266	0,809	0,655-0,998	0,912	0,791	0,630-0,993	0,817

Logistic regression analysis relating factor score to OA-phenotype corrected for age, sex, BMI and fasting status.

* P value Bonferroni corrected

A - Radiographic hip or knee OA, defined as Kellgrenn Lawrence score ≥2

B - Total hip or knee arthroplasty for primary OA

Factors 1, 4, 11, 17, 19, 22 & 23 and progression of radiographic hip and knee OA.
Subsequently, we investigated whether the observed associations of factors 1, 4, 11, 17, 19, 22, 23 with prevalent hip and/or knee OA also contributed to OA progression. Progression data were available for the participants of the CHECK, GARP and Rotterdam Study. In total, 282 individuals experienced progression of OA in hip and 463 persons experienced progression of OA in knee and 1244 persons did not have any incidence of OA after 5 to 7 years of follow-up, see Table 3.

Table 3 – Baseline characteristics of subjects in progression analyses.

		Hip Progression	**Knee Progression**	**Progression controls**
CHECK/GARP	N	125	292	523
Age	mean (SD)	58.9 (5.5)	57.4 (5.7)	55.4 (5.2)
Female	N (%)	89 (71.2%)	241 (82.5%)	410 (78.4%)
Body mass index	mean (SD)	26.0 (3.7)	28.0 (5.0)	25.7 (3.8)
Rotterdam Study	N	157	171	721
Age	mean (SD)	72.8 (5.0)	73.13 (5.1)	71.99 (4.6)
Female	N (%)	60.5%	66.1%	53.8%
Body mass index	mean (SD)	27.8 (4.4)	29.09 (4.3)	26.74 (3.5)
Total	N	282	463	1244

Baseline characteristics of persons with radiographic hip and knee progression as well as the controls for the progression analyses. Data are presented per cohort as included in meta-analysis.

A meta-analysis was performed to combine the results of the Rotterdam Study and CHECK and GARP cohorts (see also Table 4, corresponding forrestplots are depicted in Figure 2). Factor 19 associates to lower odds for knee OA (OR=0.84, 95%CI=0.73-0.97, P=0.020). Factor 22, as in the cross-sectional analyses, associates with increased odds for progression of hip OA (OR=1.16, 95%CI=1.00-1.34, P=0.047).

Notably, factor 17 had an inverse effect on progression of hip OA as compared to the cross-sectional analyses (hip progression: OR=0.87, 95%CI=0.75-1.00, P=0.047; cross-sectional hip OA: OR=1.38, 95%CI=1.20-1.59, P=0.002).

Table 4 - Results of meta-analysis for the progression of radiographic hip/knee OA.

		OR	95% CI	P-Value
Factor 1 (LDL)	hip	0,878	0,757-1,017	0,083
	knee	0,910	0,805-1,029	0,134
Factor 4 (LDL)	hip	1,064	0,872-1,298	0,541
	knee	0,963	0,849-1,093	0,560
Factor 11 (Fatty Acids)	hip	0,948	0,818-1,098	0,476
	knee	1,042	0,917-1,184	0,527
Factor 17 (Amino Acids)	**hip**	**0,855**	**0,749-0,998**	**0,047**
	knee	0,870	0,694-1,091	0,228
Factor 19 (Amino Acids)	hip	0,916	0,653-1,286	0,614
	knee	**0,844**	**0,732-0,973**	**0,020**
Factor 22 (Fatty Acids)	**hip**	**1,156**	**1,002-1,334**	**0,047**
	knee	1,045	0,925-1,180	0,483
Factor 23 (Amino Acids)	hip	0,962	0,828-1,119	0,617
	knee	0,918	0,806-1,046	0,201

Meta-analysis combining the results for the relation of factor to progression of hip/ knee OA from the Rotterdam Study and CHECK+GARP cohorts. Factors were studied when they had significant associations with prevalent radiographic hip or knee osteoarthritis. OR= odds ratio, 95%CI=95% confidence interval.

Assessment of individual metabolites of factors 17, 19 and 22.

Successively, we explored whether individual metabolites of the factors which go both with cross-sectional OA and progression of OA, drive any of the found associations. As shown in Supplementary Table 3, for Factor 17 the strongest effect was found in Pyruvate in any OA, whereas this effect got even stronger in arthroplasty (OR=1.21, 95%CI= 1.12-1.30, P=<0.001 and OR=1.93, 95%CI=1.72-2.16, P<0.001, respectively). Factor 19 appears to be mainly driven by Glutamine, which was negatively associated with both OA and TJA (OR=0.70, 95%CI=0.64-0.76, P<0.001 and OR=0.65, 95%CI=0.58-0.74, P<0.001, respectively). Of factor 22 was FALen consequently associated with both OA and arthroplasty (OR=1.26, 95%CI=1.16-1.36, P<0.001 and OR=1.83, 95%CI=1.64-2.05, P<0.001, respectively).

Assessment of individual metabolites of factors 17, 19 and 22 with OA-progression did not result in an obvious independent effect of any of the metabolites, nonetheless again the effect size of FALen was relatively large, albeit not statistically significant (Supplementary Table 4).

The effects of BMI and statins for factor 17, 19 & 22

To explore possible confounding effects of BMI in the associations observed, we performed analyses with and without adjustment for BMI. As shown in Supplementary Table 5, the effect sizes got slightly larger when omitting an adjustment for BMI.

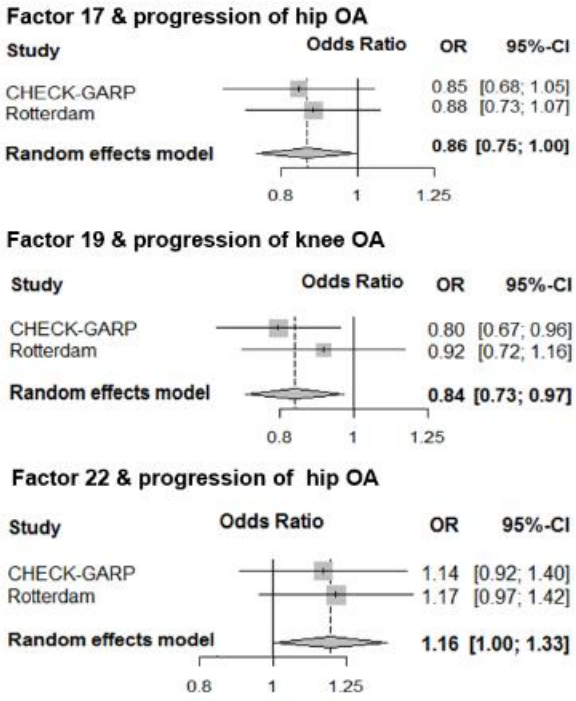

Figure 2 – Forrest plots from meta-analysis combining the results for the factors of interest with the progression of hip or knee OA from the Rotterdam Study and CHECK+GARP cohorts.

Moreover, as statins might affect the concentrations of metabolites, we performed sensitivity analyses to assess their influence on our outcomes.[41] The use of statins was known for all included studies except CHECK. Sensitivity analysis with subjects that did not use statins revealed only minor changes in the effect sizes (results not shown).

The modifying effect of fasting on associations of factor 17, 19 and 22 with OA

As some cohorts were fasted and others were unfasted, we also assessed in similar fashion the effects of fasting on the outcomes. Supplementary Table 6 shows the outcomes for the cross-sectional analyses for factors 17, 19 and 22 with and without the addition of fasting to the analysis. Although fasting had a strong significant effect in the analyses, the odds ratio's for factor and OA-phenotype were only marginally altered between the analyses.

Discussion

Serum metabolomics assay of hip and knee OA cases and controls were assessed by means of the Nightingale ^{1}H-NMR platform, resulting in 227 different metabolite measurements. These metabolites were included in PCA-analyses which identified 19 factors explaining 71.9% of variance eligible for further regression analyses. Of these, seven factors (1, 4, 11, 17, 19, 22 and 23) were associated with cross-sectional OA and three factors (17, 19 and 22) were found to be associated with cross-sectional hip or knee OA, as well as its progression. All associations were assessed independent of age, sex, fasting and BMI. As such, this study places composite scores of fatty acid-make-up, energy balance, histidine and glutamine at the heart of the link of osteoarthritis and metabolites.

Factor 19, composed of 2 amino acids: glutamine and histidine showed a consistent association with a decreased risk for hip and knee OA in the cross-sectional analysis (radiographic hip OA: OR=0.68, 95%CI=0.60-0.76, radiographic knee OA: OR=0.83, 95%CI=0.75-0.91 and THA OR=0.65, 95%CI=0.55-0.75) as well as for the knee progression analyses (OR=0.84, 95%CI=0.73-0.97). These findings are consistent with a previously performed NMR-based urine metabolomics study which found that low levels of histidine are associated to OA.[42] Another study by *Loeser et al*[43] *identified that histidine (as well as alanine) measured in urine is an important metabolite to discriminate between persons with knee OA progression as compared to BMI matched controls.* However, the exact nature of the underlying pathophysiological mechanism of the association between OA and histidine and glutamine remains to be elucidated.

Factor 22 represents measures of the make-up of fatty acids: fatty acid chain length, saturated fatty acids to total fatty acids ratio and the level of unsaturation. The latter 2 measures contributed in opposite fashion to the factor score. Factor 22 was associated with a higher risk for end stage hip (OR=1.41, 95%CI=1.23-1.63) and knee OA (OR=1.61, 95%CI=1.33-1.95), as well as a higher risk for hip OA progression (OR=1.16, 95%CI=1.00-1.34). Notably, fatty acid chain length is, in the analysis of individual metabolites, independent and strongly associated to the prevalent cross-sectional OA-phenotypes and seems to drive factor 22.

Nevertheless, in the OA-progression analyses this was less clear. A recent study has shown that longer-chain dietary fatty acids in rats induce both metabolic syndrome and OA like knee changes.[44] Fatty acids are known to play a role in a broad range of cardiovascular diseases as well as to the immune system, which might hint that there is a more generic pathway underlying the association of OA and fatty acid make up.[45,46]

Open for discussion is factor 17, representing alanine, lactate and pyruvate, which are produced during glycolysis in cells in aerobic and anaerobic conditions.[47-49] Factor 17 is associated with a higher risk for cross sectional hip OA (OR=1.38, 95%CI=1.20-1.59), knee OA (OR=1.49, 95%CI=1.21-1.83) and arthroplasty but with a decreased risk for hip OA progression (OR=0.86, 95%CI=0.75-0.99). This association of factor 17 with OA may be a reflection of different types of energy consumption in play as chondrocytes in OA switch from oxidative phosphorylation to glycolysis as their main source of energy metabolism.[50] Nevertheless, the opposite relation in the cross sectional and progression analyses is a result that we currently cannot explain. The association of factor 17 could therefore also be spurious and needs confirmation in additional cohorts.

In this study we choose to differentiate between patients who underwent total hip or knee arthroplasty from patients with radiographic signs of OA. This because THA and TKA patients are essentially in a different stage of the disease, their OA-symptoms were clinically assessed and severe enough to undergo arthroplasty surgery. In contrast, patients with radiological OA represent a range of patients who may not (yet) be severe enough for an indication for arthroplasty. The fact that we observed more consistent associations with arthroplasty patients justifies this approach. Although we found significant associations between some factors and knee or hip OA progression, none of the individual metabolites reached a statistically significant level for progression. This indicates that the baseline level of individual metabolites might be less informative then a complete metabolite profile.
A strength of our study was that this study comprises a large sample size of which a subset was followed overtime, enabling us to follow progression over time. The combination of different studies to reach more power also meant that we

incorporated some studies with only cases or controls, raising the chance of cohort effects. However, we did assess the presence of cohort effects within the control phenotype, where no differences should be present between the cohorts as all samples are the exact same phenotype. The factors which were free of cohort effects were included in our analyses.

We adjusted our analyses for BMI measured at baseline, however we cannot exclude the bias in our findings due to the effect of weight loss or gain right before blood collection. To obtain more insight in the modifying / confounding role of BMI in our analyses, we compared analyses with and without adjustment for BMI (Supplementary Table 5). The odds ratios between these analyses were only marginally altered, with the biggest change found for TKA in factor 19, where the odds ratio went from 0.791 (adjusted for age, sex, fasting and BMI) to 0.565 (adjusted for age, sex and fasting). As such we concluded that the observed metabolite associations with OA were independent or only slightly modified by BMI.

Moreover, the fact that our study included both fasted and nonfasted samples and metabolites are very sensitive to fasting status, the adjustment for fasting status may not have been sufficient to properly correct for dietary influences. To obtain more insight in the modifying role of fasting status, our metabolite factors and OA, we performed analyses with and without fasting adjustment. As shown in Supplementary Table 6, the odds ratios for OA in the two analyses showed only marginally changes i.e. effect sizes were very similar. Analyses were stratified by fasting status for HOA and factor 19, we found that the effect size was larger in the non-fasted samples as compared to the fasted samples (fasted samples: HOA OR=0.77, 95%CI=0.68-0.88, P=0.003; non-fasted samples: HOA OR=0.49, 95%CI=0.37-0.63, P<0.001).

The current paper is to our knowledge the first large scale hypothesis free approach in search for metabolites that associate to OA in a cross-sectional as well as a follow-up design. Future research should particularly focus on replication of the found results and, if this succeeds, further elucidate the mechanisms behind the association of the identified metabolites and OA should be performed.

Eventually, these studies could lead up to the identification of lifestyle changes which might alter the predisposition for OA. Identifying lifestyle changes such as different levels of fatty acid intake or physical training to improve the switch between aerobe/anaerobe metabolism may lessen the burden of OA. In conclusion, the current study identified a number of metabolic factors associated with OA, independent of BMI. This indicates that there is an altered metabolic state in patients with OA as compared to controls without OA. This is another token that OA should be seen as a component of poor metabolic health.

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Supplementary Table 1

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
AcetoAcetate	AcAce																							0,63
Acetate	Ace																							0,77
Alanine	Ala																	0,62						
Albumine	Alb																		0,69					
3-hydroxybutyrate	bOHBut																				0,59			0,41
Citrate	Cit																				0,60			
Creatinine	Crea																							
Glucose	Glc																							
Glutamine	Gln																			0,77				
Glycoprotein	Gp		0,58																					
Histidine	His																			0,67				
Isoleucine	Ile		0,50						0,73															
Lactate	Lac																	0,82						
Leucine	Leu								0,86															
Phenylalanine	Phe								0,70															
Pyruvate	Pyr																	0,81						
Tyrosine	Tyr								0,71															
Valine	Val								0,83															

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Esterified Cholesterol	EstC	0,91																						
Free Cholesterol	FreeC	0,89																						
HDL2-C hdl2 cholesterol particle density	HDL2C		-0,43	0,80																				
HDL3-C hdl3 cholesterol particle density	HDL3C	0,73																						
HDL-C hdl cholesterol	HDLC			0,79																				
Rem t-C non-hdl / ldl cholesterol	RemtC	0,79	0,58																					
Serum-C cholesterol	SerumC	0,91																						
Triglycerides	SerumTG		0,90																					

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Apolipoprotein A-I	ApoA1			0,80		0,41																		
Apolipoprotein B	ApoB	0,77	0,60																					
ApoB / ApoA1	ApoB/ApoA1	0,56	0,62	-0,48																				
Docosahexaenoic acid 22:6	DHA							0,86																
DHA / total fatty acids	DHA FA							0,94																
Estimated fatty chain length	Falen	-0,52																					0,46	
omega 3 fatty acid	FAw3							0,81																
FAw3 / total fatty acids	FAw3 fa							0,94																
omega 6 fatty acid	FAw6	0,74										0,46												
FAw6 / total fatty acids	FAw6 FA		-0,59									0,61												
Linoleic acid 18:2	LA	0,69										0,55												
LA / total fatty acids	LA FA		-0,42									0,67												
Monounsaturated fatty acids 16:1 18:1	MUFA		0,80																					
MUFA / total fatty acids	MUFAFA		0,60									-0,58												
Phosphatidycholine and other cholines	PC	0,52		0,59																				
polyunsaturated fatty acids	PUFA	0,74										0,42												
PUFA / total fatty acids	PUFA FA		-0,62									0,58												
Saturated fatty acids	SFA	0,48	0,70																					
SFA / total fatty acids	SFA FA																						-0,83	
sphingomyelines	SM	0,71																						
triglycerides / phosphoglycerides	TG PG		0,81	-0,40																				
cholines	TotCho	0,63		0,58																				
total fatty acids	TotFA	0,56	0,69																					
phosphoglycerides	TotPG	0,55		0,56																				
estimated degree of unsaturaization	UnsatDeg		-0,54					0,45															0,44	

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
HDL mean diameter hdl particle	HDL-D		-0,43	0,87																				
HDL Triglycerides	HDL-TG		0,74		0,42																			
XL-HDL Total Cholesterol	XL HDL C			0,81																				
XL-HDL Total Choleseterol to total Lipids	XL HDL C %			-0,67												0,43								
XL-HDL Cholesterol Esters	XL HDL CE			0,78																				
XL-HDL CholesterolEsters to total Lipids	XL HDL CE %			-0,72																				
XL-HDL Free Cholesterol	XL HDL FC			0,85																				
XL-HDL Free Cholesterol to total lipids	XL HDL FC %										-0,58													
XL-HDL Total lipids	XL HDLL			0,89																				
XL-HDL Particle concent n	XL HDL P			0,89																				
XL-HDL Phospholipids	XL HDL PL		-0,44	0,85																				
XL-HDL Phospholipids to total Lipids	XL HDL PL %		-0,47	0,64																				

XL-HDL Triglycerids	XL HDL TG		0,57	0,50																				
XL-HDL TriGlycerides to total Lipids	XL HDL TG %		0,78																					
L-HDL Total Cholesterol	L HDL C		-0,49	0,80																				
L-HDL Total Choleseterol to total Lipids	L HDL C %		-0,42							0,78														
L-HDL Cholesterol Esters	L HDL CE		-0,48	0,79																				
L-HDL CholesterolEsters to total Lipids	L HDL CE %									0,81														
L-HDL Free Cholesterol	L HDL FC		-0,49	0,78																				
L-HDL Free Cholesterol to total lipids	L HDL FC %		-0,45	0,50						0,48														
L-HDL Total lipids	L HDLL		-0,46	0,83																				
L-HDL Particle concent n	L HDL P		-0,45	0,83																				
L-HDL Phospholipids	L HDL PL		-0,44	0,81																				
L-HDL Phospholipids to total Lipids	L HDL PL %									-0,70														
L-HDL Triglycerids	L HDL TG			0,58														0,42						
L-HDL TriGlycerides to total Lipids	L HDL TG %		0,59																					
M-HDL Total Cholesterol	M HDL C			0,60		0,75																		
M-HDL Total Choleseterol to total Lipids	M HDL C %		-0,52											-0,72										
M-HDL Cholesterol Esters	M HDL CE			0,57		0,75																		
M-HDL CholesterolEsters to total Lipids	M HDL CE %		-0,45		-0,42									-0,65										
M-HDL Free Cholesterol	M HDL FC			0,59		0,64																		
M-HDL Free Cholesterol to total lipids	M HDL FC %	0,41																						
M-HDL Total lipids	M HDLL			0,58		0,79																		
M-HDL Particle concent n mol / L	M HDL P			0,57		0,79																		
M-HDL Phospholipids	M HDL PL			0,58		0,77																		
M-HDL Phospholipids to total Lipids	M HDL PL %													0,91										
M-HDLTriglycerids	M HDL TG		0,76																					
M-HDLTriGlycerides to total Lipids	M HDL TG %		0,77																					
S-HDL Total Cholesterol	S HDL C	0,62				0,44																		
S-HDL Total Choleseterol to total Lipids	S HDL C %	0,68																						
S-HDL Cholesterol Esters	S HDL CE	0,68																						
S-HDL CholesterolEsters to total Lipids	S HDL CE %	0,69																						
S-HDL Free Cholesterol	S HDL FC					0,80																		
S-HDL Free Cholesterol to total lipids	S HDL FC %																0,50							
S-HDL Total lipids	S HDLL					0,91																		
S-HDL Particle concent n mol / L	S HDL P					0,89																		
S-HDL Phospholipids	S HDL PL	-0,43				0,78																		
S-HDL Phospholipids to total Lipids	S HDL PL %	-0,69																						
S-HDL Triglycerids	S HDL TG		0,73		0,49																			
S-HDL TriGlycerides to total Lipids	S HDL TG %		0,70		0,46																			

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
LDL cholestrol	LDL C	0,99																						
LDL mean diameter ldl particle	LDL D										0,63													
LDL triglycerides	LDL TG	0,48			0,77																			
L-LDL Total Cholesterol	LLDL C	0,98																						
L-LDL Total Choleseterol to total Lipids	LLDL C %	0,79			-0,55																			
L-LDL Cholesterol Esters	LLDL CE	0,98																						
L-LDL CholesterolEsters to total Lipids	LLDL CE %	0,87																						

L-LDLFree Cholesterol	LLDL FC	0,97																						
L-LDL Free Cholesterol to total lipids	LLDL FC %		-0,73		-0,47																			
L-LDL Total lipids	LLDLL	0,98																						
L-LDL Particle concent n mol / L	LLDL P	0,97																						
L-LDL Phospholipids	LLDL PL	0,97																						
L-LDL Phospholipids to total Lipids	LLDL PL %	-0,95																						
L-LDL Triglycerids	LLDL TG	0,52			0,77																			
L-LDL TriGlycerides to total Lipids	LLDL TG %	-0,41			0,86																			
M-LDL Total Cholesterol	MLDL C	0,99																						
M-LDL Total Choleseterol to total Lipids	MLDL C %	0,83																						
M-LDL Cholesterol Esters	MLDL CE	0,99																						
M-LDL CholesterolEsters to total Lipids	MLDL CE %	0,90																						
M-LDL Free Cholesterol	MLDL FC	0,95																						
M-LDL Free Cholesterol to total lipids	MLDL FC %	-0,85																						
M-LDL Total lipids	MLDLL	0,97																						
M-LDL Particle concent n mol / L	MLDL P	0,97																						
M-LDL Phospholipids	MLDL PL	0,89																						
M-LDL Phospholipids to total Lipids	MLDL PL %	-0,92																						
M-LDL Triglycerids	MLDL TG	0,47			0,79																			
M-LDL TriGlycerides to total Lipids	MLDL TG %				0,89																			
S-LDL Total Cholesterol	SLDL C	0,98																						
S-LDL Total Choleseterol to total Lipids	SLDL C %	0,84																						
S-LDL Cholesterol Esters	SLDL CE	0,99																						
S-LDL CholesterolEsters to total Lipids	SLDL CE %	0,90																						
S-LDL Free Cholesterol	SLDL FC	0,90																						
S-LDL Free Cholesterol to total lipids	SLDL FC %	-0,78																						
S-LDL Total lipids	SLDLL	0,95																						
S-LDL Particle concent n mol / L	SLDL P	0,94																						
S-LDL Phospholipids	SLDL PL	0,82																						
S-LDL Phospholipids to total Lipids	SLDL PL %	-0,94																						
S-LDL Triglycerids	SLDL TG		0,57		0,69																			
S-LDL TriGlycerides to total Lipids	SLDL TG %		0,49		0,76																			

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
IDL Total Cholesterol	IDL C	0,96																						
IDL Total Choleseterol to total Lipids	IDL C %	0,45			-0,83																			
IDL Cholesterol Esters	IDL CE	0,94																						
IDL CholesterolEsters to total Lipids	IDL CE %				-0,81																			
IDL Free Cholesterol	IDL FC	0,96																						
IDL Free Cholesterol to total lipids	IDL FC %	0,56	-0,54																					
IDL Total lipids	IDLL	0,96																						
IDL Particle concent n mol / L	IDL P	0,96																						
IDL Phospholipids	IDL PL	0,98																						
IDL Phospholipids to total Lipids	IDL PL %		-0,78																					
IDL Triglycerids	IDL TG	0,44	0,43		0,76																			
IDL TriGlycerides to total Lipids	IDL TG %	-0,41			0,81																			

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
VLDLCholesterol	VLDL C	0,55	0,80																					
VLDL mean diameter vldl particles	VLDL D		0,90																					
VLDLTriglycerides	VLDL TG		0,91																					
XXL-VLDL Total Cholesterol	XXLVLDL C		0,93																					
XXL-VLDL Total Choleseterol to total Lipids	XXLVLDL C %						0,54						0,68											
XXL-VLDL Cholesterol Esters	XXLVLDL CE		0,87																					
XXL-VLDL CholesterolEsters to total Lipids	XXLVLDL CE %						0,62						0,44											
XXL-VLDL Free Cholesterol	XXLVLDL FC		0,95																					
XXL-VLDL Free Cholesterol to total lipids	XXLVLDL FC %												0,68											
XXL-VLDL Total lipids	XXLVLDLL		0,93																					
XXL-VLDL Particle concent n mol / L	XXLVLDL P		0,93																					
XXL-VLDL Phospholipids	XXLVLDL PL		0,92																					
XXL-VLDL Phospholipids to total Lipids	XXLVLDL PL %												0,44											
XXL-VLDL Triglycerids	XXLVLDL TG		0,92																					
XXL-VLDL TriGlycerides to total Lipids	XXLVLDL TG %												-0,81											
XL-VLDL Total Cholesterol	XLVLDL C		0,96																					
XL-VLDL Total Choleseterol to total Lipids	XLVLDL C %		-0,54				0,73																	
XL-VLDL Cholesterol Esters	XLVLDL CE		0,95																					
XL-VLDL CholesterolEsters to total Lipids	XLVLDL CE %		-0,46				0,71																	
XL-VLDL Free Cholesterol	XLVLDL FC		0,94																					
XL-VLDL Free Cholesterol to total lipids	XLVLDL FC %		-0,46				0,61																	
XL-VLDL Total lipids	XLVLDLL		0,96																					
XL-VLDL Particle concent n mol / L	XLVLDL P		0,96																					
XL-VLDL Phospholipids	XLVLDL PL		0,93																					
XL-VLDL Phospholipids to total Lipids	XLVLDL PL %														0,46									
XL-VLDL Triglycerids	XLVLDL TG		0,93																					
XL VLDL TG %	XLVLDL TG %						-0,68																	
L-VLDL Total Cholesterol	LVLDL C		0,96																					
L-VLDL Total Choleseterol to total Lipids	LVLDL C %						0,69																	
L-VLDL Cholesterol Esters	LVLDL CE		0,95																					
L-VLDL CholesterolEsters to total Lipids	LVLDL CE %						0,72																	
L-VLDL Free Cholesterol	LVLDL FC		0,94																					
L-VLDL Free Cholesterol to total lipids	LVLDL FC %														0,69									
L-VLDL Total lipids	LVLDLL		0,94																					
L-VLDL Particle concent n mol / L	LVLDL P		0,93																					
L-VLDL Phospholipids	LVLDL PL		0,92																					
L-VLDL Phospholipids to total Lipids	LVLDL PL %		0,41																			0,63		
L-VLDL Triglycerids	LVLDL TG		0,91																					
L-VLDL TriGlycerides to total Lipids	LVLDL TG %						-0,52								-0,47									

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
M-VLDL Total Cholesterol	MVLDL C		0,91																					
M-VLDL Total Choleseterol to total Lipids	MVLDL C %	0,49				0,55																		
M-VLDL Cholesterol Esters	MVLDL CE	0,43	0,86																					
M-VLDL CholesterolEsters to total Lipids	MVLDL CE %	0,48	-0,41			0,55																		
M-VLDL Free Cholesterol	MVLDL FC		0,92																					
M-VLDL Free Cholesterol to total lipids	MVLDL FC %														0,45									
M-VLDL Total lipids	MVLDLL		0,93																					
M-VLDL Particle concent n mol / L	MVLDL P		0,92																					
M-VLDL Phospholipids	MVLDL PL		0,92																					
M-VLDL Phospholipids to total Lipids	MVLDL PL %																					0,75		
M-VLDL Triglycerids	MVLDL TG		0,89																					
M-VLDL TriGlycerides to total Lipids	MVLDL TG %	-0,44				-0,54																		

Metabolite		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
S-VLDL Total Cholesterol	SVLDL C	0,69	0,65																					
S-VLDL Total Choleseterol to total Lipids	SVLDL C %	0,51	-0,58																					
S-VLDL Cholesterol Esters	SVLDL CE	0,78	0,52																					
S-VLDL Cholesterol Esters to total Lipids	SVLDL CE %	0,50	-0,56																					
S-VLDL Free Cholesterol	SVLDL FC	0,48	0,77																					
S-VLDL Free Cholesterol to total lipids	SVLDL FC %		-0,50																					
S-VLDL Total lipids	SVLDLL		0,83																					
S-VLDL Particle concent n mol / L	SVLDL P		0,84																					
S-VLDL Phospholipids	SVLDL PL		0,80																					
S-VLDL Phospholipids to total Lipids	SVLDL PL %					0,45																0,41		
S-VLDL Triglycerids	SVLDL TG		0,85																					
S-VLDL TriGlycerides to total Lipids	SVLDL TG %	-0,41	0,63																					
XS-VLDL Total Cholesterol	XSVLDL C	0,89																						
XS-VLDL Total Choleseterol to total Lipids	XSVLDL C %		-0,60		-0,62																			
XS-VLDL Cholesterol Esters	XSVLDL CE	0,85																						
XS-VLDL CholesterolEsters to total Lipids	XSVLDL CE %		-0,50		-0,61																			
XS-VLDL Free Cholesterol	XSVLDL FC	0,89																						
XS-VLDL Free Cholesterol to total lipids	XSVLDL FC %		-0,48																					
XS-VLDL Total lipids	XSVLDLL	0,84	0,42																					
XS-VLDL Particle concent n mol / L	XSVLDL P	0,81	0,47																					
XS-VLDL Phospholipids	XSVLDL PL	0,93																						
XS-VLDL Phospholipids to total Lipids	XSVLDL PL %	0,79																						
XS-VLDL Triglycerids	XSVLDL TG		0,74		0,50																			
XS-VLDL TriGlycerides to total Lipids	XSVLDL TG %		0,62		0,53																			

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. a Rotation converged in 18 iterations.

Supplementary Table 2 – Variance explained by factors.

Factor	Eigenvalue	% of Variance Explained
1	70.95	31.26
2	57.17	25.19
3	19.79	8.71
4	11.08	4.88
5	8.55	3.77
6	4.75	2.09
7	4.08	1.80
8	3.67	1.62
9	3.04	1.34
10	2.85	1.25
11	2.72	1.20
12	2.50	1.10
13	2.05	0.90
14	1.87	0.82
15	1.85	0.81
16	1.63	0.72
17	1.60	0.70
18	1.48	0.65
19	1.38	0.61
20	1.25	0.55
21	1.16	0.51
22	1.11	0.49
23	1.00	0.44

Eigenvalues and percentage of variance explained by the factors identified by principal component analysis on the included metabolites. The total variance explained by the 23 factors with an eigenvalue of >1 was 91,4%.

Supplementary Table 3 – Assessment of cohort effects in controls**.**

Factor	Effect size	95% CI	P-value*
1	-0,453	-0,846 - -0.060	0,552
2	**0,607**	**0,220 – 0.994**	**0,046**
3	0,382	0,025 – 0.740	0,828
4	0,113	-0,262 – 0.489	>1
5	0,328	-0,059 – 0.715	>1
6	-0,094	-0,484 – 0.296	>1
7	-0,418	-0,827 - -0.009	>1
8	0,139	-0,230 – 0.507	>1
9	0,157	-0,208 – 0.523	>1
10	**-0,796**	**-1,177 - -0.415**	**0,001**
11	-0,200	-0,589 – 0.189	0,314
12	0,075	-0,292 – 0.441	>1
13	**-0,649**	**-1,034 - -0.265**	**0,023**
14	0,106	-0,304 – 0.517	>1
15	-0,530	-0,917 - -0.143	0,161
16	**1,225**	**0,858 – 1.592**	**$1{,}64 \times 10^{-9}$**
17	0,249	-0,141 – 0.639	>1
18	-0,474	-0,831 - -0.117	0,207
19	-0,371	-0,708 - -0.033	0,713
20	-0,255	-0,626 – 0.116	>1
21	-0,560	-0,934 - -0.187	0,069
22	-0,236	-0,619 – 0.147	>1
23	-0,111	-0,489 – 0.268	>1

Association of cohort with the factor within controls. After adjusting for age, sex, BMI and fasting, four factors had a significant cohort effect and were removed from further analyses.
* Pvalue Bonferroni corrected

Supplementary Table 4: Individual metabolites and cross-sectional outcomes

Factor	Metabolite	Hip or knee OA			Hip or Knee arthroplasty		
		OR	95%CI	P*	OR	95%CI	P*
17	Alanine	0.91	0.84-0.98	0.088	0.82	0.72-0.93	0.008
	Lactate	1.00	0.92-1.08	>1	1.47	1.31-1.65	$7.0x10^{-10}$
	Pyruvate	1.21	1.12-1.30	$5.1x10^{-6}$	1.93	1.72-2.16	$8.0x10^{-20}$
19	Glutamine	0.70	0.64-0.76	$8.8x10^{-15}$	0.65	0.58-0.74	$2.0x10^{-11}$
	Histidine	0.91	0.84-0.98	0.120	0.92	0.81-1.04	>1
22	Fatty Acid Chain Length	1.26	1.16-1.36	$4.8x10^{-8}$	1.83	1.64-2.05	$8.0x10^{-20}$
	Saturated Fatty Acids Ratio	1.01	0.93-1.08	>1	0.95	0.84-1.07	>1
	Degree of Unsaturation	1.05	0.97-1.14	>1	1.12	0.99-1.28	0.560

* Pvalue Bonferroni corrected

Supplementary Table 5 – Individual metabolites and progression

Factor	Metabolite	Hip Progression			Knee Progression		
		Beta	SE	P*	Beta	SE	P*
17	Alanine	-0,126	0,334	>1	-0,609	0,27	0,192
	Lactate	-0,605	0,247	0,120	-0,569	0,448	>1
	Pyruvate	-0,518	0,393	>1	-0,307	0,168	0,544
19	Glutamine	-0,452	0,991	>1	-0,488	0,798	>1
	Histidine	-0,411	0,339	>1	-0,295	0,29	>1
22	Fatty Acid Chain Length	7,97	3,742	0,264	4,123	4,309	>1
	Saturated Fatty Acids Ratio	-1,907	1,593	>1	-0,102	1,377	>1
	Degree of Unsaturation	-0,028	1,432	>1	1,047	1,314	>1

* Pvalue Bonferroni corrected

Supplementary Table 6 – with and without adjustment for BMI or fasting

	Factor 17								
	OA ~ Factor + age + sex + fasting + BMI			***Excluding BMI***			***Excluding fasting***		
	OR	95%CI	P-value*	OR	95%CI	P-value*	OR	95%CI	P-value*
HOA	1,15	1,04-1,27	0.171	1.25	1.14-1.37	0.008	1,14	1,03 - 1,26	0.228
THA	1,38	1,20-1,59	1.5x10-4	1.52	1.35-1.72	2.28x10-10	1,34	1,17 - 1,55	7.4x10-4
KOA	0,98	0,89-1,07	>1	1.04	0.96-1.14	>1	0,97	0,89 - 1,06	>1
TKA	1,49	1,21-1,83	0.003	1.56	1.31-1.85	9.69x10-6	1,42	1,16 - 1,74	0.019
	Factor 19								
	OA ~ Factor + age + sex + fasting + BMI			***Excluding BMI***			***Excluding fasting***		
	OR	95%CI	P-value*	OR	95%CI	P-value*	OR	95%CI	P-value*
HOA	0,68	0,60-0,76	3.6x10-10	0,59	0,53-0,65	2.30x10-24	0,67	0,60 - 0,75	1.0x10-10
THA	0,65	0,55-0,75	5.9x10-7	0,52	0,46-0,59	6.8x10-24	0,62	0,53 - 0,72	5.6x10-9
KOA	0,83	0,75-0,91	0.004	0,71	0,65-0,78	1.7x10-11	0,82	0,74 - 0,91	0.003
TKA	0,79	0,63-0,99	0.817	0,57	0,48-0,67	3.2x10-10	0,76	0,61 - 0,95	0.266
	Factor 22								
	OA ~ Factor + age + sex + fasting + BMI			***Excluding BMI***			***Excluding fasting***		
	OR	95%CI	P-value*	OR	95%CI	P-value*	OR	95%CI	P-value*
HOA	1,13	1,02-1,25	0.494	1,20	1,09-1,32	0.004	1.13	1.02-1.26	0.380
THA	1,41	1,23-1,63	1.9x10-5	1,45	1,29-1,63	3.1x10-8	1.44	1.25-1.65	7.0x10-6
KOA	1,06	0,96-1,16	>1	1,06	0,97-1,16	>1	1.06	0.97-1.16	>1
TKA	1,61	1,33-1,95	1.7x10-5	1,46	1,24-1,72	7.6x10-5	1.67	1.38-2.02	1.8x10-6

Analyses performed with logistic regression analyse relating factor-score to the OA-phenotype. Standard analyse was adjusted for age, sex, fasting and BMI, whereas the extra analyse was adjusted for age, sex either BMI or fasting.

* Pvalue Bonferroni corrected.

HOA - Radiographic Hip OA; THA - Total Hip Arthroplasty for primary hip OA; KOA - radiographic Knee OA; TKA - Total Knee Arthroplasty for primary knee OA

Summary & General Discussion

With increasing life expectancy, the incidence and burden of osteoarthritis on society will increase. Currently, no treatment of end-stage symptomatic osteoarthritis is available and when symptoms become too severe a total joint arthroplasty (TJA) will be performed, replacing the affected joint with a prosthesis. Although replacement surgery of the hip (THA) or knee (TKA) is safe and commonly performed, up to 20% of the patients are unsatisfied with the outcome.[1-3] The exact reasons for this dissatisfaction are unknown but may vary from the type of surgical procedure itself, expectancy of the outcome of arthroplasty surgery to the patient's preoperative state of overall metabolic health.

This thesis aimed to evaluate some of these aspects related to outcome of TJA, from patient perspectives to molecular profiling (e.g. metabolic health). Characteristics of different nature were included: material of prosthesis, physical activity, questionnaires, clinical measures and metabolomics. This holistic approach enables the assessment of more patient specific targets such as advices on treatment modalities. Ultimately, selection of patients, both from a patient's as well as orthopaedic surgeon's perspective, will be optimised for the best intervention (either conservative or surgical) for a specific patient. Since osteoarthritis is currently the major driver for performing TJA, the conclusion of this thesis will spark future studies into OA and its overall effect on disability.

Post-surgery factors associated with outcome of joint arthroplasty: prosthesis and physical activity.

I Bearings of prostheses

Arthroplasty surgery with an implant aims to create a functional painless joint which has been destructed by a degenerative disease or even trauma. The overall success rate at 10 year follow-up show a mean hip or knee implant survival of 95%, resulting in the classification of total hip prosthesis as the operation of century.[4] There are many types of implants and within each type a multitude on designs of implants or prostheses are on the market. Each design claims to have their own specific benefits. One such type of hip-prosthesis is the metal-on-metal bearing total hip prosthesis (MoM THA), as with any artificial joint replacement, wear is present upon moving the

joint. The wear particles of the MoM THA are submicron metal debris particles (mostly chromium and cobalt particles), causing not only local, but also systematic reactions. For those reasons, the Netherlands Orthopaedic Association advised against its use since 2012, whilst further research was done.

The overall systematic effect, defined as mortality, of these metal particles was assessed by means of a meta-analysis of articles on metal-on-metal total hip prostheses, including 47 papers. The overall methodological quality of these papers was moderate. All studies suffered from allocation concealment problems and often patients, caregivers and outcome assessors were not blinded to the treatment. In addition, the observational studies clearly suffered from confounding by indication. However, all studies had a 100% compliance with the treatment as is inevitable with any implanted joint, as well as high levels of skills and experience by the surgeons. As shown in **Chapter 2,** at 10 year follow-up, there is an increased risk of mortality in patients with MoM THA as compared to patients with non-MoM THA: 8.5% risk difference (95%CI: 5.8% - 11.2%). The fact that for patients with less than 10-year follow-up we did not observe this mortality difference indicates a probable dose-response association for exposure to metal particles. This dose-response association is supported by a meta-regression analysis showing that the duration of follow-up was the only effect modifier.

This severe adverse effect of metal-on-metal prostheses has been demonstrated by studies describing cobalt-poisoning in patients with MOM prostheses, of whom the symptoms were relieved upon removal of the prosthesis.[5-7] On top of this, the International Agency for Research on Cancer (IARC) classified chromium as “carcinogenic to humans” and cobalt as “possibly-carcinogenic to humans”.[8] Surely, exposure to chromium has been demonstrated to elevate the risk to develop lung, sinonasal and stomach cancer.[9-11] Unfortunately, we did not have any information on the cause of death of patients with MOM prosthesis in our systematic review.

The exact effects of the exposure to the metal-ions-cocktail of chromium and cobalt for MOM patients are not clear yet, warranting further research into the dose-

response association of person/hip years exposure to MOM THA.[12] In addition, close monitoring of patients with a MOM THA prosthesis implanted is paramount.

II Postoperative physical activity

A successful total joint arthroplasty indicates that patients experience an extensive reduction in pain, have a better mobility of the joint and consequently experience more functionality (e.g. improved daily activities). How this relates to their peers in the general population was evaluated in **Chapter 3**. The functionality of THA and TKA patients was compared with the general population, using the level of physical activity (PA), as a measure of functionality.

We assessed both the minutes per week spent on a particular type of physical activity as well as the overall adherence to the Dutch guideline for physical activity (NNGB, 5 days per week more than 30 minutes of moderate intensity physical activity) between both groups.

Interestingly, THA and TKA patients adhere more often to the NNGB than the general Dutch population, when correcting for age, sex, BMI and education level (THA: OR 1.79, 95%CI: 1.26-2.56; TKA: OR 1.73, 95%CI: 1.20-2.51). Even more, patients who had a hip arthroplasty in the preceding 6-22 months spent more minutes on overall physical activity as compared to the general Dutch population (13.8% increase, 95%CI: 1.60-27.6%, P=0.024). For TKA, also an increase in the min/week on physical activity was observed, however this did not reach statistical significance (11.2% increase, 95%CI: -1.4 – 25.6%, P=0.084).

The increased level of PA in THA and TKA patients may be explained by postoperative physiotherapy, making them more prone to adhere to a more active lifestyle or may be to the memory of lost mobility in the preoperative state, thus underscoring the importance of maintaining mobility for overall functionality. Low-impact sports such as hiking or cycling are protective against function loss and pain associated with OA whereas heavy loading sports may be risk factors for developing OA as well as early implant failure.[13-17] More studies into the impact of physical activity on the development and prevention of OA as well as the recovery of joint replacement surgery are necessary to optimize patient care.

The level of physical activity in this study was based on validated self-reported questionnaires. As is known from several studies, a discrepancy exists between outcomes of questionnaires and more objective measures such as accelerometers. Indeed a systematic review on physical activity after THA or TKA measured by accelerometers found that arthroplasty patients were less physically active than our findings which were assessed by questionnaires.[18]

A study by Sabia *et al.*[19] found that this discrepancy between self-reported activity and accelerometer registered activity is dependent on socio-economic status (SES), with persons with a higher SES having a greater correlation between self-reported and accelerometer measured level of physical activity. Budget constrains science to rely on self-reported physical activity, however with increasing technological progress, data on physical activity may in the near future be collected by means of apps at the patient's mobile devices.

III Baseline health of the patient

As the life expectancy is increasing, the prevalence of OA will increase and subsequently also the number of performed total joint arthroplasties will increase. In the Netherlands, total hip arthroplasty has increased from 23.000 in 2010 to almost 30.000 primary hips in 2017 and primary total knee arthroplasty has increased from 20.000 to almost 30.000 implants in 7 years. These numbers underscore the importance of discriminating preoperatively which patients will benefit and who will not benefit from TJA. The latter improves not only patient care (i.e. optimise non-surgical treatment) but also reduces unnecessary surgery with subsequent unsatisfied patients and health care costs.

Baseline health factors associated with outcome of joint arthroplasty or OA disease status: frailty index, handgrip strength and molecular profiling.

Since the musculoskeletal system is a high energy-consuming organ, analysis into metabolic health of patients is important. We have assessed baseline health status in three different ways: first, by a questionnaire focussed on frailty (**Chapter 4** and **Chapter 5**), second by means of a physiological measure of muscle quality (**Chapter 6**) and third by evaluating blood metabolites in patients (**Chapter 7**).

III A Frailty

The Groningen Frailty Indicator (GFI) was developed for elderly (aged ≥ 65 years) to assess the level of frailty based on the following characteristics; mobility, cognition, perception, nutrition, poly-pharma, social status and depression. A first step to use it in end stage hip or knee OA patients was to assess the validity and feasibility in a population of over 3000 end stage OA patients on a waiting list for arthroplasty surgery. The GFI convergent and discriminatory validity in these patients was comparable to that in elderly. Using the GFI in our population showed in **Chapter 4** that about one-third of the patients undergoing THA (33%) and a quarter of the persons undergoing TKA (24%) are frail (GFI score ≥ 4).

Using the Frieds Frailty Phenotype (FFP) scoring system, Mandl *et al*[20], found that 8% of the end-stage knee OA patients experienced frailty. However, this scoring system does not include a domain on activities of daily life, which the GFI does include. Mandl *et al* did record the number of patients who report difficulties with activity of daily life, this was an additional 17%. Combining these percentages give comparable numbers of persons who experience frailty as found by our study using the GFI.

Chapter 5 demonstrated that GFI-determined frail patients scored preoperatively lower on each domain of the HOOS/KOOS as compared to the non-frail patients. However, both frail and non-frail patients improved similarly after surgery. Therefore, not the GFI but the functional level of the patient before surgery was the best predictor of functional outcomes after surgery.

Although the GFI does not preoperatively distinguish between the to be expected functional outcomes, frail THA patients did have a significantly higher reoperation rate in the year following their primary operation (6.4% in frail THA patients and 2.1% in non-frail patients, P=0.005). In TKA the reoperation rate in frail patients was also higher, albeit not statistically significant (3.7% in frail patients vs 2.1% in non-frail patients, P=0.278). The GFI may not predict functionality after surgery, it does give an indication of the success of surgery.

The importance of the pre-operative functional score as predictor for postoperative outcome raises new questions, such as 'what is the optimal timing to perform arthroplasty surgery'? The longer arthroplasty is postponed by means of pain-(pain)medication; the functional status of the patient will further decline. Currently there are no succinct guidelines for the timing of arthroplasty.[21] Optimisation of timing of surgery with respect to preoperative health status may improve outcomes.

Preoperative physiotherapy may boost the functional scores before undergoing arthroplasty surgery. Moreover, physiotherapy may change the patient's lifestyle and making him/her more prone to pursue a more active lifestyle after surgery. Although preoperative pain levels may prevent physical activity or physiotherapy, it is important to assess the patients' functional state before surgery, and prime patients to have an optimal musculoskeletal status before undergoing arthroplasty.

The fact that the GFI was not predictive for the postoperative outcome score may be due to selection bias by the orthopaedic surgeon during the preoperative period. Patients who at face value were deemed too frail by the surgeon are most probably not selected for TJA surgery and thus not included in this study. Though a surgeon does not use a frailty questionnaire, studies have shown that the 'initial clinical impression' of a physician gives a fair indication to assess the risk of mortality as well as of patient's biological age.[22,23]

III B Handgrip Strength

Although the GFI distinguished to some extend preoperatively between patients with good and less favourable outcome after TJA, a more objective clinical measure, such as handgrip strength (HGS) may be of better use (**Chapter 6**). HGS has been associated with adverse surgery outcomes and represents overall patient's strength and as such it may be a proxy for frailty.[24-26]

The HGS in end stage hip or knee OA patients (i.e. patients indicated for TJA surgery) was 34 kg for males and 20 kg for females, which is lower than the reference values of 42 kg for healthy males and 26 kg for healthy females of similar age.[27] Preoperative HGS was associated with the majority of the included outcome scores. The largest effect was seen for both THA and TKA patients for the domain '*function*

in sport and recreation' of the HOOS/KOOS questionnaire into functional outcomes, independent of gender, age, BMI and preoperative score (THA: 0.681, P=0.005; TKA: 0.520, P=0.049). For the THA patients, also a moderate effect was found for the domain "*symptoms*" (coefficient 0.564, P=0.001) of these scores.

This study had only one pre-operative HGS measurement, no measurements were made over time in the preoperative period nor post-surgery. However, although only one measurement was available, we did find that the pre-operative HGS was associated with some specific domains of functional outcome scores. This predictive power of HGS for postoperative outcome may improve if multiple preoperative measures were available. For that matter, a decline of the HGS, determined by multiple measurements, may be a stronger predictor of frailty compared to just one measurement. Nevertheless, also one time measurements of HGS, readily applicable in clinic, will provide the orthopaedic surgeon as well as the patient information on the to be expected outcome of THA and TKA. More accurate measurements into muscle mass and muscle quality may lead to better predictions of surgery outcomes, however, the measurement of HGS is fairly simple and feasible within the current clinical practise.

III C Metabolites

Recovering after major surgery like TJA, requires a strong ability to resist stressors. A lower ability to resist stressors, i.e. frailty, is reflected by poor metabolic health. There may be metabolic profiles that may reflect the susceptibility of a person to develop OA, their progression rate and may be key in their response to joint replacement surgery. To assess whether specific baseline metabolic profiles associate to prevalent OA and may eventually predict patients' outcome in terms of progression of disease, we performed a metabolomics analysis among OA patients in both a cross-sectional and a follow-up design. Over 200 different metabolites were assessed in 1564 OA cases of whom half had radiographic progression of OA over time. Many of the metabolomics parameters are correlated, therefore a principal component analysis was used to combine the metabolites into 23 different composite scores (i.e. groups of highly correlated metabolites). These composite scores were

linked to the different OA-phenotypes (hip OA, end-stage hip OA, hip OA progression, knee OA, end stage knee OA and knee OA progression), independent of age, sex, fasting status and BMI.

Three composite scores were found to be associated with both cross-sectional OA and OA progression. First, a lower level of a composite score of Histidine and Glutamine was associated with both prevalence of hip OA, end-stage hip OA and knee OA as well as with OA progression in the knee. This association has not been reported earlier.

Secondly, a composite score of fatty acid make-up was associated with end stage hip and knee OA and with progression of hip OA. This composite score consists of the fatty acid chain length, the saturated fatty acids ratio and the level of unsaturation of fatty acids. This finding is in line with observations in rats showing that long chain fatty acids induce both a metabolic syndrome as well as knee OA.[28-30]

Finally, we found a composite score of alanine, pyruvate and lactate, markers of energy metabolism, to be associated with end stage hip and knee OA and progression of hip OA. However, this association was positive in the cross-sectional analysis, but was inversely associated with progression of OA. The mechanisms of these associations are most probably driven through the energy consumption of chondrocytes, which are known to switch from oxidative phosphorylation to glycolysis in OA, provided that such a switch is in some way reflected by the metabolite profile in the circulation.[31] The inverse association for progression of hip OA, however, warrants further investigation.

This metabolomics study places composite scores of fatty acid make-up and energy balance, histidine and glutamine at the heart of the link of osteoarthritis and the metabolic syndrome. Future research should be aimed at replicating our findings, comparing them to OA markers currently used in the clinic and epidemiological studies and subsequently further elucidate the mechanisms behind these associations. Evidence for a causal link between the observed metabolites and OA may be explored by Mendelian Randomization studies in which genetic variants associated to the metabolites are tested for association with OA related endpoints.

Alternatively, metabolite levels and their relation to OA progression may be explored by intervention studies focused on histidine, fatty acid chain length and saturation. Physical exercise has well known effects on metabolic switches in the muscle and other basic aspects of ageing relevant for OA, such as cellular senescence. Such intervention studies may include also OA measures and cartilage tissue which is not regularly done.

The metabolites which were identified in **Chapter 7** may not be specific risk factors for developing OA, rather they may be markers of an overall state of vulnerability of the whole system. This vulnerable state may allow for the development of progression in chronic diseases such as OA.

The analyses presented in this thesis were all performed on previously collected data, either by performing a meta-analysis on available literature or by combining collected data from different prospective cohorts. Thus these “old” data gave a new impulse to research. The latter also stress the importance of making data collected for specific research questions available for new research questions. And to combine data from different groups to fill in the bigger picture on health related problems as well as principles on vitality.

This thesis stressed the importance of an overall integrated longitudinal study on patients, including repeated blood samples as well as patient reported outcome questionnaires, HGS and accelerometer measures as well as clinical measures at the start of the diagnosis of OA until years after their arthroplasty surgery. Such a study may identify markers that can help to distinguish patients with good and less favorable outcome and even the likelihood of adverse events after either conservative or surgical interventions, but will also give clues on preventive measures.

Conclusions

The current study is an exhaustive effort to elucidate predictors of outcome measures in surgically treated patients with end-stage osteoarthritis, ranging from patient reported outcome measures to molecular profiling. Some conclusions can be drawn:

- Metal-on-metal prostheses have an increased long-term risk of mortality (**Chapter 2**) and require close monitoring.

- Patients with hip or knee prostheses in situ adhere more often to the Dutch guideline for physical activity as compared to the general Dutch population (**Chapter 3**).

- The self-reported frailty as measured by Groningen Frailty Indicator is a valid questionnaire for end stage hip and knee osteoarthritis patients (**Chapter 4**), however, it does not have value in predicting the functional outcome of arthroplasty (**Chapter 5**).

- Frail patients have lower functional scores before arthroplasty, which may influence their functional outcome score after arthroplasty (**Chapter 5**).

- Handgrip strength is of value in predicting the outcome score on certain scales of the functional assessment questionnaire (**Chapter 6**).

- Osteoarthritis prevalence and progression is associated with certain composite scores of blood metabolites emphasizing the metabolic component in osteoarthritis (**Chapter 7**).

The future from a patients' perspective

As patients are becoming increasingly more interested in participating in the medical decision making process, the orthopedic surgeon needs tools to accurately inform patients on what to expect from surgery. The tools presented in this thesis (frailty questionnaire, handgrip strength and metabolic profiling) may give a patient and the treating orthopedic surgeon more specific individualized data which are associated with outcome. These data can be used in the complex process of pre-intervention (both conservative as well as surgical) counseling between patient and his/her orthopedic surgeon. It will improve the shared-decision-making-process, deciding whether it is best to opt for a surgical intervention or first do a serious effort for a conservative (physiotherapy / lifestyle interventions) approach to the treatment of osteoarthritis.

In the future evermore measures of the patients' general wellbeing and daily activities can be, and will be, collected; more wearables and apps are designed to monitor the patient's health, but also its shift from normality (which has to be defined).[32-34] Also, specific questionnaires which are part of cohort studies can be admitted to patients by means of apps, leading to a reduction of questions, thus saving time and costs and increase efficiency.[35]

Virtually every smartphone includes an accelerometer (e.g. pedometer), which keeps track of the number of steps, but also quality of walking (e.g. fast, slow or uphill) and heartbeat in relation to the activity. Currently, a systematic review is conducted on the use of apps in mobile devices as a measure to assess physical activity and sedentary behavior.[36] Besides monitoring, apps have also potential as motivating tools to coach individuals into a more active lifestyle. A good example of the potential of stimulating physical activity was the Pokémon-GO rage which urged sedentary people to use their musculoskeletal system.[37] The SMART-MOVE study demonstrated that besides increasing the physical activity levels of the participant, also their peers may get involved in using apps and increasing their physical activity levels.[38]

Skrepnik *et al*[39] report that the use of a smartphone app (OA GO) which is focused on increasing mobility in knee OA patients actually lead to more steps per day. Patients who were randomized to follow the application performed better on the six-minute walking test. With up to 80.2% of the patients following the program for 180 days and 67.3% of the physicians reporting to be likely or very likely to recommend the use of this application, it is a very feasible method to motivate patients with knee OA.

Besides motivating patients during the course of their disease to be physically active, prevention is an even more important issue to be addressed in earlier stages of health decline. By collecting handgrip strength measurements during lifetime, assess frailty every once in a while by means of validated assessments and check the metabolic profile of elderly regularly, the patients might be motivated to action themselves if data are presented in an accessible, understandable and comprehensive way, such as a personal story-board within an app, seems to have positive results.[40] The person, not-patient-yet, may take action and/or preventative measures when a gradual increase of vulnerability is detected, before a person gets actually sick. However, any action on presented data should be taken by persons themselves and not by an overall controlling system, human integrity of taking actions should be safeguarded.

Such long-term monitoring may prevent disease, lead to earlier detection of disease and prevent severe outcomes. Also, by having a clear overview of the patient's basic levels of resistance and vulnerability over time, the final outcomes of an intervention such as arthroplasty may be more predictable. Long term monitoring may improve health and prevent disability from chronic diseases.

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Appendix

Nederlandse Samenvatting
Riassunto Italiano
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Nederlandse Samenvatting

Artrose is een progressieve ziekte die de gewrichten aantast. Door artrose slijt het kraakbeen in het gewricht waardoor uiteindelijk bot-op-bot contact ontstaat. Bewegen wordt steeds pijnlijker en de patiënt functioneert steeds minder goed in het dagelijks leven. De diagnose 'artrose' is lastig te stellen omdat er weinig samenhang zit tussen de radiologische en de klinische symptomen. Er zijn patiënten met veel radiologische schade die weinig pijn ervaren, terwijl er ook patiënten zijn met heel veel pijn maar die erg weinig radiologische schade hebben. Op het moment is er nog geen genezing mogelijk voor artrose. Medicatie is gericht op symptoombestrijding terwijl de ziekte progressief doorgaat met het aantasten van de gewrichten. Uiteindelijk zal, als de pijn te erg wordt, een gewrichtsvervangende operatie worden uitgevoerd. Deze operaties (totale heup arthroplastiek (THA) voor de heup en totale knie arthroplastiek (TKA) voor de knie) worden erg vaak uitgevoerd en 95% van de geplaatste protheses blijven tot 15 jaar na de operatie goed zitten.

Ondanks deze goede prognoses, is toch 15 tot 20% van de mensen die een gewrichtsvervangende operatie ondergaan, na afloop niet tevreden. Er zijn vele verklaringen te bedenken voor deze slechte uitkomsten zoals operatieve factoren (bijv. chirurgische technieken), gewrichtsstatus (bijv. mate van artrose) maar ook patiënt gerelateerde factoren zoals verwachtingen, patiënt selectie en preoperatieve functionele status. De preoperatieve functionele status van de patiënt is gelinkt aan de metabole staat van de patiënt, welke ook invloed heeft op de mate waarop een patiënt kan herstellen en revalideren na een operatie. Daarnaast kan de uitkomst van een gewrichtsvervangende operatie worden beïnvloed door de prothese zelf, waarbij bijvoorbeeld deeltjes, die uit het gewrichtsvlak van de twee delen van de prothese slijten, kunnen lijden tot lichamelijke reacties.

De invloed van de deeltjes die vrijkomen bij een metaal-op-metaal (MOM) heupprothese vergeleken met een niet-metal-op-metaal (non-MOM, bijvoorbeeld polyethyleen, keramiek of carbon) prothese op mortaliteit is bestudeerd in **hoofdstuk 2** met behulp van een meta-analyse en systematische review.

Zevenenveertig artikelen met 4.000 patiënten uit gerandomiseerde studies en 500.000 patiënten uit observationele studies werden samengevoegd. Bij een follow-up van 10 jaar bestond er 8.5% risico verschil ten nadele van de mensen met een MOM-heupprothese vergeleken met mensen met een non-MOM heupprothese.

Bij mensen die de prothese minder dan 10 jaar geleden hadden gekregen vonden we dit risico verschil niet. Dit suggereert dat er een dosis-effect relatie is tussen de Chroom-Kobalt deeltjes, die vrijkomen bij de MOM-protheses, en de uiteindelijke mortaliteit. Er is meer onderzoek nodig naar de exacte mechanismen, daarnaast is het belangrijk om de patiënten met een MOM-prosthese van dichtbij te volgen en indien nodig hun prothese te vervangen.

Een goed functionerende prothese betekent dat je deze goed kunt gebruiken in het dagelijks leven. Om te kijken in hoeverre mensen met een nieuwe heup of knie bewegen in het dagelijks leven hebben we in **hoofdstuk 3** de mate van fysieke activiteit van patiënten vergeleken met die van de algemene Nederlandse bevolking. De waardes van de Nederlandse bevolking worden door het CBS bijgehouden, de waardes van de mensen die een gewrichtsvervangende operatie hebben ondergaan werden verzameld middels een vragenlijst 6-22 maanden na operatie.

Wanneer we tijd en intensiteit van beweging per week tussen de groepen vergeleken en corrigeerden voor verschil in leeftijd, geslacht, BMI en opleidingsniveau zagen we dat mensen met een nieuwe heup of knie vaker voldoen aan de Nederlandse Norm Gezond Bewegen (5 dagen per week 30 minuten matig bewegen). Daarnaast bewogen mensen met een nieuwe heup zelfs 13.8% meer als we beweging in absolute minuten uitdrukten.

Er zijn verschillende verklaringen te bedenken voor deze vindingen. Zo krijgen mensen met een nieuwe heup of knie fysiotherapie tijdens hun revalidatie, wat kan leiden tot een verandering van leefstijl. Daarnaast zijn deze mensen meer gefocust op de mate waarin zij bewegen, waardoor er een (te) optimistische inschatting gemaakt kan worden van de mate van bewegen.

Ongeveer 80% van de mensen die een gewrichtsvervangende operatie ondergaan zijn ouder dan 60 jaar. Het verouderingsproces binnen deze leeftijdsgroep verloopt

heel verschillend. De ene persoon veroudert sneller dan de ander, een proces dat gereflecteerd wordt in het concept van “frailty”, oftewel “kwetsbaarheid”.

Kwetsbaarheid behelst een lagere weerstand tegen ziektes, en weerspiegelt de reserves die een patiënt heeft om stressors, zoals een gewrichtsvervangende operatie, op te vangen. Zou het zo kunnen zijn dat de mensen met een slechte uitkomst een lagere weerstand hebben?

Om de weerbaarheid van ouderen te meten zijn er verschillende vragenlijsten ontworpen. Een van deze vragenlijsten, de Groningen Frailty Indicator (GFI), hebben we in **hoofdstuk 4** gevalideerd voor artrose patiënten die op de wachtlijst staan om een gewricht vervangende operatie te ondergaan. Nadat we hadden aangetoond dat de GFI gebruikt kan worden in onze populatie, vonden we dat 33% van de heup- en 24% van de knie artrose patiënten die binnenkort een gewrichtsvervanging ondergaan kwetsbaar zijn.

In **hoofdstuk 5** hebben we gekeken of de uitkomst van een gewrichtsvervangende operatie voor deze kwetsbare patiënten verschilt van de niet-kwetsbare patiënten. De functionele uitkomsten verbeterden met een vergelijkbare maat in de kwetsbare en niet-kwetsbare patiënten, maar omdat de kwetsbare patiënten een slechtere functionele score hadden voor de operatie was hun uiteindelijke functionaliteit een jaar na de operatie slechter vergeleken met niet-kwetsbare patiënten.

Het kan dus zo zijn dat het, in het belang van de patiënt, belangrijk is om voorafgaand aan de operatie de functionele score te verbeteren door middel van bijvoorbeeld pre-operatieve fysiotherapie. Of dat er niet te lang gewacht moet worden met het uitvoeren van een gewrichtsvervangende operatie, zodat de patiënt niet teveel van zijn/haar functionaliteit verliest. Op dit moment zijn er nog geen vaste richtlijnen wanneer een patiënt onder het mes gaat, mede doordat artrose zo’n heterogeen ziekte beeld heeft. Meer onderzoek naar het optimale moment voor het uitvoeren van een gewrichtsvervangende operatie is nodig.

Omdat een vragenlijst misschien geen goede reflectie is van kwetsbaarheid, hebben we in **hoofdstuk 6** gekeken naar een meer objectieve maat: handknijpkracht. Het is aangetoond dat handknijpkracht gerelateerd is aan de algemene spierkracht,

gezondheid en mortaliteit. Toegepast in patiënten die een gewrichtsvervangende operatie ondergaan, voorspelt handknijpkracht de uitkomst op enkele onderdelen van functionele vragenlijsten, namelijk ‘sport & recreatie’ en, voor heup patiënten, ‘symptomen’ .

Doordat handknijpkracht een makkelijk te meten maat is, en het iets kan zeggen over de te verwachten effecten van de gewrichtsvervangende operatie, kan het geïmplementeerd worden in het “shared decision making proces” voorafgaand aan de operatie.

Epidemiologische studies hebben aangetoond dat er een verband is tussen artrose en ongezonde metabole parameters zoals hoog BMI, een hoge heup-taille ratio en een hoge proportie van vetmassa. Daarnaast is aangetoond dat wanneer een artrose patiënt gewicht verliest hij/zij minder last heeft van de symptomen van artrose. Dit verband lijkt verklaart te kunnen worden door de mechanische belasting van het lichaam op de heup en knie, maar het feit dat dit verband ook is aangetoond voor hand-artrose betekent dat er misschien meer aan de hand is. Studies hebben aangetoond dat ook klassieke markers voor een slechte metabole status, zoals lage-dischtheid cholesterol (LDL-cholesterol), gelinkt zijn aan artrose. Zo worden er steeds meer aanwijzingen gevonden dat artrose een onderdeel is van het metabool syndroom.

Metabolieten zijn de producten van verschillende lichamelijke processen die plaatsvinden op het snijvlak van het genoom en de omgeving. Een metabool profiel van een persoon kan een indicatie geven van de metabole status van een patiënt, waarbij een slechte metabole staat kan betekenen dat een patiënt meer vatbaar is voor de ontwikkeling van allerlei zieken zoals artrose. Daarnaast zou dit metabool profiel misschien op de lange termijn een indruk kunnen geven van de ‘kwetsbaarheid’ van een patiënt en op die manier patiënten met slechte uitkomsten pre-operatief onderscheiden van patiënten met een goeie uitkomst.

Daarom hebben we in **hoofdstuk 7** gekeken of er bepaalde metabolieten zijn die gerelateerd zijn aan artrose en aan de progressie van artrose. Uiteindelijk hebben

we 231 verschillende metabolieten gemeten en deze teruggebracht naar 23 samengestelde scores van groepjes gecorreleerde metabolieten. Van deze metabolieten-groepen lieten er drie interessante associaties zien met zowel prevalente artrose als de progressie van artrose.

Allereerst was er de score die bestond uit histidine en glutamine, welke een negatieve associatie liet zien met prevalente heup en knie artrose en met de progressie van knie artrose. Daarnaast was een score van de opbouw van vetzuren positief geassocieerd met prevalente heup en knie artrose en met progressie van heup artrose. Deze score bestond uit de lengte van het vetzuur en de mate waarin deze vetzuren verzadigd zijn. Langere verzadigde ketens zijn geassocieerd met artrose, daarnaast is al bekend dat deze ook geassocieerd zijn met het metabole syndroom. Ten slotte vonden we ook een associatie met een score die bestond uit alanine, lactaat en pyruvaat. Alle drie deze metabolieten zijn gelinkt aan de energiehuishouding. Deze ‘energie’-score had een positieve associatie met prevalente heup en knie artrose en een negatieve associatie met de progressie van artrose. Het zou kunnen zijn dat we dit op het oog tegenstrijdige resultaat vinden doordat de verbranding van de cel kan omslaan van aëroob naar anaëroob.

Deze drie scores zullen verder moeten onderzocht om duidelijk te maken hoe deze mechanismes werken en hoe ze verband houden met artrose. Desondanks is het een aanwijzing dat artrose waarschijnlijk een onderdeel is van het metabole syndroom. Misschien zal het hebben van hoge waardes voor deze metabolieten niet direct leiden tot de ontwikkeling van artrose, maar waarschijnlijk wel tot meer kans op het ontwikkelen van een (ouderdoms)ziekte zoals artrose.

Riassunto in italiano

L'osteoartrosi è una malattia progressiva che colpisce le articolazioni. Essa causa l'usura della cartilagine nell'articolazione, con il conseguente contatto osso-osseo. L'esercizio fisico diventa sempre più doloroso con crescente disabilità per il paziente. La diagnosi di osteoartrosi è difficile da stabilire perché c'è poca correlazione tra sintomi radiologici e clinici. Ci sono pazienti con molti danni radiologici e deformità ossee che sperimentano poco dolore, mentre ci sono anche pazienti con molto dolore ma che hanno pochissimi danni radiologici.

Al momento non esiste una cura per l'osteoartrosi. I farmaci sono mirati al controllo dei sintomi mentre la malattia progredisce progressivamente con l'affezione delle articolazioni. Se il dolore è troppo grave, viene eseguita un'operazione di sostituzione dell'articolazione. Queste operazioni vengono eseguite molto spesso e il 95% delle protesi posizionate rimane in sede per più di 15 anni dopo l'operazione.

Ciò nonostante, il 15-20% delle persone che si sottopongono a un intervento di sostituzione dell'anca o ginocchio non sono soddisfatte. I motivi degli esiti avversi sono molteplici: fattori chirurgici (ad es. le tecniche chirurgiche), lo stato comune (o deformazione grado di osteoartrosi), come fattori correlati al paziente (quali le aspettative, la selezione dei pazienti) e lo stato funzionale preoperatorio. Lo stato preoperatorio del paziente è legato allo stato metabolico del paziente, che ha anche un'influenza sulla misura in cui un paziente può recuperare e riabilitarsi dopo un'operazione. Inoltre, il risultato della protesi articolare chirurgico è influenzato dalla protesi stessa. Per esempio, le particelle del materiale in cui le due parti della protesi è fatta, possono usurarsi e portare a reazioni fisiche.

L'influenza delle particelle che vengono rilasciati dalle protesi dell'anca metal-on-metal (MOM) sulla mortalità rispetto a un non-metal-on-metal (non-MOM, ad esempio, polietilene, ceramica, o fibra di carbonio) è stato studiato nel ***Capitolo 2*** usando una meta-analysis e systematic review. Sono stati combinati un totale di 47 articoli con 4000 pazienti in studi randomizzati e 500.000 pazienti in studi osservazionali. Abbiamo scoperto che con al meno 10 anni di follow-up, c'è una differenza di rischio dell'8,5% a scapito delle persone con una sostituzione dell'anca

MOM rispetto a persone con un diverso tipo di protesi d'anca. Nelle persone che avevano ricevuto la protesi meno di 10 anni fa, non abbiamo riscontrato questa differenza di rischio. Ciò suggerisce che esiste una relazione dose-effetto tra le particelle di cromo-cobalto, rilasciata dalle protesi della MOM, e la mortalità finale. Sono necessari ulteriori studi sui meccanismi esatti, inoltre è importante seguire da vicino i pazienti che hanno impiantato una protesi MOM e, se necessario, sostituire le loro protesi.

Una protesi correttamente funzionante significa che può essere usata nella vita quotidiana. Per vedere fino a che punto le persone con una nuova anca o ginocchio si muovono nella vita quotidiana, nel ***Capitolo 3*** abbiamo confrontato il grado di attività fisica dei pazienti con quello della popolazione generale olandese. I valori della popolazione olandese sono gestiti dalla CBS. I valori delle persone che hanno subito un'operazione di sostituzione dell'articolazione sono stati raccolti per mezzo di un questionario 6-22 mesi dopo l'intervento chirurgico. I minuti di esercizio a settimana sono stati corretti per le differenze di età, sesso, BMI e livello d'istruzione e abbiamo osservato che le persone con una protesi dell'anca o del ginocchio hanno un livello di attività fisica maggiore rispetto alla popolazione olandese.

Ci sono diverse spiegazioni per questi risultati. Ad esempio, le persone con una nuova anca o ginocchio sono sottoposti a fisioterapia durante la riabilitazione, che può portare a un cambiamento dello stile di vita. Inoltre, queste persone sono più focalizzate sulla importanza dell'attività fisica e quindi tendono a fare una valutazione (troppo) ottimistica del grado di esercizio.

Circa l'80% delle persone che si sottopongono a un intervento di sostituzione dell'articolazione ha più di 60 anni. Il processo di invecchiamento all'interno di questo gruppo di età è molto diverso. Una persona invecchia più velocemente dell'altra, un processo che si riflette nel concetto di "frailty" o "vulnerabilità". La vulnerabilità comporta una minore resistenza alle malattie e riflette le riserve che un paziente ha per affrontare i fattori stressanti, come la chirurgia sostitutiva delle articolazioni. Potrebbe essere che le persone con esiti avversi abbiano una resistenza inferiore?

Per misurare la resistenza degli anziani, sono stati progettati diversi questionari. Uno di questi questionari, Groningen Frailty Indicator (GFI), è stato convalidato nel ***Capitolo 4*** per i pazienti con osteoartrite in attesa di un intervento di sostituzione dell'articolazione. Dopo aver dimostrato che la GFI può essere utilizzata nella nostra popolazione, abbiamo scoperto che il 33% dei pazienti dell'anca e il 24% dei pazienti del ginocchio che presto subiranno una sostituzione dell'articolazione sono vulnerabili.

Nel ***Capitolo 5*** abbiamo esaminato se l'esito di un'operazione di sostituzione articolare per questi pazienti vulnerabili differisce dai pazienti non vulnerabili. I risultati funzionali sono migliorati in misura simile nei pazienti vulnerabili e non vulnerabili, ma poiché i pazienti vulnerabili avevano un punteggio funzionale peggiore prima dell'operazione, il loro punteggio finale rimane peggiore rispetto ai pazienti non vulnerabili.

È quindi possibile che sia nell'interesse del paziente migliorare il punteggio di base prima dell'intervento mediante, ad esempio, la terapia fisica preoperatoria. Oppure che l'attesa non dovrebbe essere troppo lunga per eseguire un'operazione di sostituzione dell'articolazione, in modo che il paziente non perda troppo della sua funzionalità. Al momento non ci sono linee guida fisse riguardo a quando un paziente si sottopone ad un intervento, in parte perché l'osteoartrosi ha un quadro di malattia così eterogeneo. Sono necessarie ulteriori ricerche sul momento ottimale per eseguire un'operazione di sostituzione dell'articolazione.

Poiché un questionario potrebbe non essere un buon riflesso della vulnerabilità, abbiamo esaminato una misura più obiettiva nel ***Capitolo 6***: forza di presa della mano (FPM). È stato dimostrato che la FPM è correlata alla forza muscolare generale, alla salute generale e alla mortalità. Applicato in pazienti sottoposti a sostituzioni articolari, la FPM predice il risultato su alcune componenti degli esiti funzionali: "Sport e Ricreazione" e, per i pazienti con anca, anche la parte "Sintomi". Poiché la forza manuale è una misura facile da misurare e può dire qualcosa sugli effetti attesi dell'operazione di sostituzione dell'articolazione, può essere implementata nel "processo decisionale condiviso" prima dell'operazione.

Studi epidemiologici hanno dimostrato che esiste un legame tra l'osteoartrite e parametri metabolici malsani come un alto indice di massa corporea, un alto rapporto vita-fianchi e un'alta percentuale di massa grassa. Inoltre, è stato dimostrato che quando un paziente affetto da osteoartrite perde peso, soffre meno dei sintomi dell'osteoartrosi. Questa connessione sembra essere spiegata dall peso fisico che poggia sull'anca e ginocchio, ma il fatto che questa connessione sia stata dimostrata anche per l'osteoartrite della mano significa che potrebbe esserci di più. Gli studi hanno dimostrato che i marcatori classici per uno scarso status metabolico, come il colesterolo a bassa densità (colesterolo LDL), sono collegati all'osteoartrosi. Sono presenti in letteratura sempre più evidenze che indicano che l'osteoartrosi è parte della sindrome metabolica.

I metaboliti sono i prodotti di vari processi fisici che avvengono all'intersezione tra il genoma e l'ambiente. Un profilo metabolico di una persona può dare un'indicazione dello stato metabolico di un paziente: uno scarso stato metabolico può significare che un paziente è più suscettibile allo sviluppo di alcuni i tipi di malattie, come l'osteoartrosi. Inoltre, questo profilo metabolico potrebbe dare un'indicazione a lungo termine della "vulnerabilità" di un paziente e in questo modo distinguere i pazienti con esiti negativi prima dell'intervento da pazienti con un buon esito.

Ecco perché abbiamo esaminato nel ***Capitolo 7*** se ci sono alcuni metaboliti correlati all'osteoartrosi e alla progressione dell'osteoartrosi. Infine, abbiamo misurato 231 diversi metaboliti e li abbiamo ridotti a 23 diversi punteggi compositi di metaboliti correlati. Di questi 23 gruppi di metaboliti, tre hanno mostrato interessanti associazioni con l'osteoartrosi prevalente e la progressione dell'osteoartrosi.

Il punteggio costituito da istidina e glutammina mostra un'associazione negativa con l'osteoartrosi prevalente dell'anca e del ginocchio e con la progressione dell'osteoartrosi del ginocchio. Inoltre, un punteggio composito di accumulo di acidi grassi è positivamente associato all'osteoartrosi dell'anca e del ginocchio prevalente e alla progressione dell'osteoartrosi dell'anca. Questo punteggio consiste nella lunghezza dell'acido grasso e nella misura in cui questi acidi grassi sono saturi. Catene saturate più lunghe portano più osteoartrite, è già dimostrato che queste

sono anche associate alla sindrome metabolica. Infine, abbiamo anche trovato un'associazione con un punteggio costituito da alanina, lattato e piruvato.

Tutti e tre i punteggi compositi dovranno essere ulteriormente studiati per chiarire come funzionano questi meccanismi, ma è chiaramente un suggerimento che l'osteoartrosi sia parte della sindrome metabolica. Forse avere valori elevati per questi metaboliti non porterà direttamente allo sviluppo dell'osteoartrosi, ma verosimilmente è più probabile che sviluppi una malattia di invecchiamento come l'osteoartrosi.

Curriculum Vitae

Jennifer Marie Theresia Anna Meessen was born on July 26th 1989 in Heerlen, Limburg, the Netherlands. She grew up with her parents Peter and Marie-Paule, sister Valerie and brother Max in Amstenrade and graduated from the Athenaeum of the Sint Janscollege in Hoensbroek, Heerlen in the summer of 2007.

In the same year, she moved to Amsterdam to study “Biomedical Sciences” at the Vrije Universiteit of Amsterdam. During her internship at the Institute for Cardiovascular Research at the VUMC she wrote her bachelor thesis on hypertrophied heart.

After obtaining her degree in 2010, she spent the summer volunteering in Perm, Russia, with the Memorial Organization (Международный Мемориал) to promote civil rights and preserve the Gulag Museum “Perm-36” in Kuchino, Russia.

Upon her return, Jennifer started the Research Master “Lifestyle and Chronic Disorders” at the Vrije Universiteit. By the end of the first year, she was invited to join the board of the Amsterdam section of the Erasmus Student Network as Treasurer. In that role she was voted to be the National Dutch Delegate to the European department of Erasmus Student Network.

In 2012, Jennifer resumed her Master studies and performed her internships at the “Azienda Sanitaria Locale – Osservatorio Epidemiologico” in Varese, Italy, studying mortality after proximal femoral fracture and the efficacy of the Italian colorectal cancer screening program.

After graduating in 2013, she moved back to the Netherlands and started her PhD at the Leiden Universitair Medisch Centrum under the supervision of Prof. P. E. Slagboom and Prof. R.G.H.H. Nelissen. The results of this PhD are presented in this thesis.

In 2018, Jennifer emigrated to Italy and started her work as a post-doc at the department of Cardiovascular Research at the Mario Negri Institute for Pharmacological Research, a non-profit organization dedicated to clinical and biomedical research. In addition to her job as post-doc, as of 2019 she works as epidemiologic and statistical consulent for the Fondazione per il tuo Cuore and the department of neonatal care at the Del Ponte Hospital in Varese.

In her free time she works as a member of the local political party “Malnate Sostenibile”, for which she participated in the local municipal elections of 2019 as candidate.

List of Publications

A Aimo, JL Januzzi, G Vergaro, A Clerico, R Latini, **JMTA Meessen**, IS Anand, JN Cohn, J Gravning, T Ueland, SH Nymo, HP Brunner-La Rocca, A Bayes-Genis, J Lupón, RA de Boer, A Yoshihisa, Y Takeishi, M Egstrup, I Gustafsson, HK Gaggin, KM Eggers, K Huber, I Tentzeris, C Passino, M Emdin. Revisiting the Obesity Paradox in Heart Failure: Percent Body Fat as Predictor of Biomarkers and Outcome. *Accepted for publication in European Journal of Preventive Cardiology.*

L Gattinoni, F Vasquez, L Camporota, **JMTA Meessen**, F Romitti, I Pasticci, E Duscio, F Vassalli, LG Forni, D Payen, M Cressoni, A Zanella, R Latini, M Quintel, JJ Marini. Understanding lactatemia in human sepsis: potential impact for initial management. *Accepted for publication in American Journal of Respiratory and Critical Care Medicine.*

BG Pijls, **JMTA Meessen**, K Tucker, S Stea, L Steenberge, AM Fenstad, K Makela, IC Stoica, M Goncharov, J Arias de la Torre, RGHH Nelissen. (2019). MoM total hip replacements in Europe: a NORE report. *EFORT Open Reviews 4 (6): 423-430.*

A Aimo, JL Januzzi, G Vergaro, A Ripoli, R Latini, **JMTA Meessen**, IS Anand, JN Cohn, J Gravning, T Ueland, SH Nymo, HP Brunner-La Rocca, A Bayes-Genis, J Lupon, RA de Boer, A Yoshihisa, Y Takeishi, M Engstrup, I Gustafsson, HK Gaggin, KM Eggers, K Huber, I Tentzeris, C Passino, M Emdin. (2019). Sex differences in plasma concentrations and prognostic value of NT-proBNP in chronic heart failure. *Journal of the American College of Cardiology 73 (9):1.*

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JMTA Meessen, CS Leichtenberg, C Tilbury, BL Kaptein, LA Koster, PE Slagboom, SHM Verdegaal, R Onstenk, HMJ van der Linden, H Kaptijn, SBW Vehmeijer, WJC Marijnissen, PJ Damen, RGHH Nelissen, TPM Vliet Vlieland. (2018). Frailty in end-stage hip or knee osteoarthritis: validation of the Groningen Frailty Indicator (GFI) questionnaire. *Rheumatology International 38 (5): 917-924.*

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K Panoutsopoulou, S Thiagarajah, E Zengini, AG Day-Williams, YF Ramos, **JMTA Meessen**, K Huetink, RGHH Nelissen, L Southam, NQ Rayner, M Doherty, I Meulenbelt, E Zeggini, JM Wilkinson (2017). Radiographic endophenotyping in hip osteoarthritis improves the precision of genetic association analysis. *Annals of Rheumatic Diseases 76 (7): 1199-1206.*

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Submitted work

JMTA Meessen, D Cardinale, F Ciceri, MT Sandri, M Civelli, B Bottazzi, GF Cucchi, E Menatti, M Mangiavacchi, GL Condorelli, E Barbieri, S Gori, A Colombo, G Curigliano, M Salvatici, P Pastori, F Ghisoni, A Bianchi, C Falci, M Aquilina, A Farolfi, A Monopoli, C Milandri, M Bregni, M Sicuro, A Malossi, D Nassiacos, C Verusio, LI Staszewsky, R Leone, D Novelli, G Balconi, EB Nicolis, S Masson, C Garlanda, A Mantovani, CM Cipolla, R Latini. *Circulating biomarkers and cardiac function in patients undergoing cancer chemotherapy with anthracyclines; the ICOS-ONE trial.*

S Lanfranconi, E Scola, G Bertani, B Zarino, R Pallini, G D'Alessandris, E Mazzon, S Marino, MR Carriero, E Scelzo, G Faragò, M Castori, C Fusco, A Petracca, L Dagruma, L Tassi, P D'Orio, MG Lampugnani, EB Nicolis, A Vasamì, D Novelli, V Torri, **JMTA Meessen**, R. Al-Shahi Salman, E Dejana, R Latini. *TREAT-CCM: A multicentre randomized clinical trial on propranolol in familial Cerebral Cavernous Malformation.*

S Gandolfi, A Luciani, **JMTA Meessen,** G Ristagno, F Semeraro, A Scapigliati, N Grieco. *A cross-sectional study to evaluate the high-quality of cardiopulmonary resuscitation manoeuvres: a new era in education is calling.*

JMTA Meessen F Saberi-Hosnijeh, N Bomer, W den Hollander, JG van der Bom, JA van Hilten, WE van Spil, C So-Osman, AG Uitterlinden, M Kloppenburg, RGHH Nelissen, CM van Duijn, PE Slagboom, JBJ van Meurs, I Meulenbelt. *Serum fatty acid make-up and energy cycle associated metabolites associate with prevalent and progressive osteoarthritis independent of BMI.*

T Pelle, AAOM Claassen, **JMTA Meessen**, WF Peter, TPM Vliet Vlieland, K Bevers, J van der Palen, FHJ van den Hoogen, CHM van den Ende. *Comparison of physical activity between patients with different stages of hip or knee osteoarthritis and the general population: a cross-sectional study.*

L de Luca, F Colivicchi, **JMTA Meessen**, M Uguccioni, F Piscione, P Bernabò, G Lardieri, A Granatelli, D Gabrielli MM Gulizia. *How do Cardiologists Select Patients for Dual Antiplatelet Therapy Continuation Beyond 1 Year after a Myocardial Infarction? Insights from the EYESHOT Post-MI Study .*

JMTA Meessen, M Fiocco, RL Tordoir, A Sjer, SHM Verdegaal, PE Slagboom, TPM Vliet Vlieland, RGHH Nelissen. *Association of hand grip strength with patient reported outcome measures after total hip and knee arthroplasty.*

F Carbone, A Bonaventura, A Vecchiè, **JMTA Meessen**, S Minetti, E Elia, D Ferrara, AM Ansaldo, G Tulli, V Mangani, N Rossi, M Ferrari, F Bona, P Caironi, R Latini, F Montecucco. *Early osteopontin levels predict mortality in patients with septic shock: a sub-study of the ALBIOS trial.*

R Coutinho de Alameida, A Mahfouz, H Mei, E Houtman, W den Hollander, J Soul, TE Hardingham, E Suchiman, N Lakenberg, **JMTA Meessen,** K Huentink, YFM Ramos, M Reinders, I Meulenbelt. *Identification and characterization of two consistent osteoarthritis subtypes by transcriptome and clinical data integration.*

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