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Does arthritis in other joints and spine influence the 1-year outcome of total hip replacement? A prospective multicenter cohort study (EUROHIP) measuring the influence of musculoskeletal morbidity

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ABSTRACT

Background

Whilst arthritis in other affected joints and back pain is known to lead to worse outcomes following total hip replacement surgery, these risk factors have not previously been operationalized as a musculoskeletal morbidity profile. The aim of this study was to measure the influence of other joints and spine (as grades of musculoskeletal morbidity) on the 1-year outcome of primary total hip replacement.

Methods

The European Collaborative Database of Cost and Practice Patterns of Total Hip Replacement study consists of 1,327 patients receiving primary THR for osteoarthritis across 20 European orthopedic centers. The primary outcome was the responder rate for THR at 12-months as measured by the relative effect per patient (REPP score), calculated for each patient using the total WOMAC score. The primary predictor of interest was combinations of arthritis of large joints and spine grouped into four musculoskeletal morbidity (MSM) grades: 1 (single-joint), 2 (multi-joints), 3 (single-joint and spine), 4 (multi-joints and spine). Confounders adjusted for were: age, sex, body mass index, living alone, years of hip pain, ASA grade, anxiety/depression, pre-operative WOMAC subscales.

Results

845 patients were included for this analysis with complete 12-month follow-up WOMAC scores. The mean age was 65.7 years and 55.2% were female. Increasing MSM grade was associated with worse outcomes of surgery, where the **proportion of patients responding to** THR were: 254 (92.4%) MSM grade 1, 272 (87.2%) MSM grade 2, 46 (80.7%) MSM grade 3, 142 (74.4%) MSM grade 4. This was confirmed in adjusted logistic regression models: MSM grade 4 vs. 1 **relative risk ratio** (**RRR**) 0.**82** 95% confidence interval (CI) (0.**75**, 0.**90**); MSM grade 3 vs. 1 OR 0.**87** 95%CI (0.**77**, 0.**99**); MSM grade 2 vs. 1 OR 0.**95** 95%CI (0.**89**, 1.00).

Conclusions

Other joints and spine measured as musculoskeletal morbidity have a strong influence on the 1-year outcome after THR. The effect size was large in comparison to other risk factors. Even so, the majority of patients in MSM grade 4 can still profit from surgery (>75% **response to surgery**).

Level of evidence

Prognostic Study (Level II)

INTRODUCTION

Even if primary total hip replacement (THR) might be considered today as "standardized" surgery the outcome varies from patients with no more symptoms and/or disability after THR, to those with some symptoms/disability left, to those with even more symptoms and/or disability. This variation corresponds to the average WOMAC score in EUROHIP a year after THR not being zero but 15% or a responder rate not being 100% but 84.5%. Other studies confirm this variation with responder rates for primary THR from 84% to 93%[1-5]. Predictors for worse outcome are higher age, low symptom/disability score, high body mass index, number of general comorbidities, musculoskeletal morbidity and depression[3, 4, 6-17].

Although it is well known, that musculoskeletal comorbidity can have a negative impact on the overall outcome[6, 11, 14], it is still not clear how big its influence is. Hawker found a prevalence of troublesome other large joints (contralateral hip, knees) of 81.2% in a cohort with hip osteoarthritis coming for THR and only half of these patients achieved a good outcome[11]. Quintana described in a large multicenter study for THR a high prevalence of contralateral hip osteoarthritis (42.9%) and back pain (54.5%) separately with less improvement on some of the SF-36 and WOMAC domains 6 months after THR[14]. Ayers found coexisting pain in the lumbar spine and other nonoperatively treated joints to be an important confounder for outcome after joint replacement for the knee and described the need for a Musculoskeletal Comorbidity Index[18].

There is a limited number of possibilities to grade the severity of musculoskeletal comorbidities focusing on functional limitations as proposed by Charnley and Katz[19, 20]. Charnley differentiated the patients coming for THR in three groups depending on factors which limit the walking capacity (group A one hip involved, B both hips involved and C other factors). Katz et al. proposed a score of musculoskeletal functional limitations as the sum of limitations in 6 anatomic regions separately (knee, hip, back, hand/wrist/arm/shoulders, foot/ankle, neck). Both approaches to grade functional limitations and the status of affected joints were not included.

The objective of this study was to measure the influence of other joints and spine (as grade of musculoskeletal morbidity (MSM)) on the outcome 1 year after THR in a large European multicenter cohort (EUROHIP). The null hypothesis was that MSM does not influence THR outcome.

MATERIALS AND METHODS

STUDY DESIGN

Observational prospective cohort study

Level of Evidence: II (prospective outcome study)

SETTING AND SOURCE OF DATA
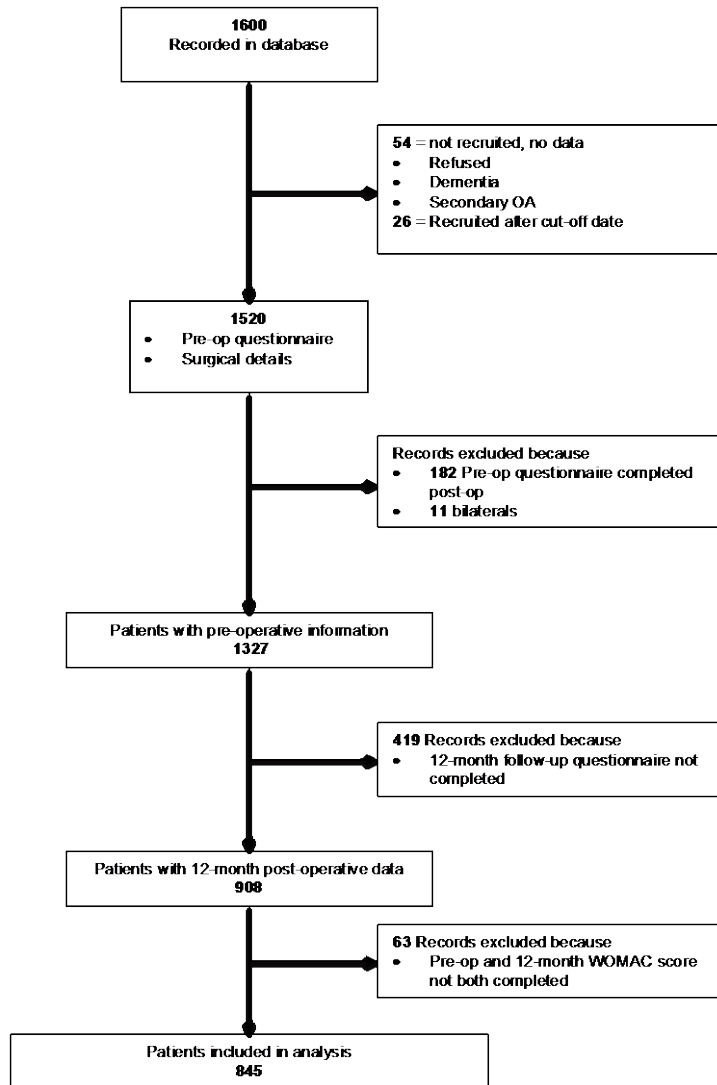
The EUROHIP study comprised of 1,327 patients receiving primary THR across 20 European orthopedic centers in 12 nations[21]. It began collecting data in January 2004 and concluded December 2006. Inclusion criteria were a diagnosis of **primary** hip osteoarthritis (OA), primary THR, and a signed informed consent. **Primary osteoarthritis of the hip was defined as symptomatic hip disease**

with radiographic evidence of osteoarthritis, and no obvious predisposing cause such as unequivocal dysplasia, congenital dislocation of the hip, Perthe's disease or osteonecrosis. Exclusion criteria comprised severe mental illness or dementia, and patient's unwillingness/inability to participate, **and unequivocal evidence for secondary osteoarthritis**. Each center was responsible for local ethical approval. The study protocol and data collection forms were designed in Bristol, UK and Ulm, Germany by the study principle investigators (PD and KD) and the study coordinator (SW). The patient questionnaire was reviewed for acceptability in Bristol and modified accordingly before being sent to Ulm for translation and distribution. Questionnaires were sent to each center for translation and returned for editing before printing and distribution with a set of instructions. 845 patients were included in this study with a complete follow up of **Patient Reported Outcome Measure**s (WOMAC) pre-THR and one year postoperatively (Figure 1).

Figure 1. Study flow chart (EUROHIP)

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                    ┌─────────────────────┐
                    │       1600          │
                    │ Recorded in database│
                    └─────────────────────┘
                              │
                              │──────────►  54 = not recruited, no data
                              │                 • Refused
                              │                 • Dementia
                              │                 • Secondary OA
                              │              26 = Recruited after cut-off date
                              ▼
                    ┌─────────────────────┐
                    │       1520          │
                    │ • Pre-op questionnaire
                    │ • Surgical details  │
                    └─────────────────────┘
                              │
                              │──────────►  Records excluded because
                              │                 • 182 Pre-op questionnaire completed
                              │                   post-op
                              │                 • 11 bilaterals
                              ▼
                    ┌─────────────────────────────┐
                    │ Patients with pre-operative  │
                    │ information                   │
                    │           1327               │
                    └─────────────────────────────┘
                              │
                              │──────────►  419 Records excluded because
                              │                 • 12-month follow-up questionnaire not
                              │                   completed
                              ▼
                    ┌─────────────────────────────┐
                    │ Patients with 12-month       │
                    │ post-operative data          │
                    │           908                │
                    └─────────────────────────────┘
                              │
                              │──────────►  63 Records excluded because
                              │                 • Pre-op and 12-month WOMAC score
                              │                   not both completed
                              ▼
                    ┌─────────────────────────────┐
                    │ Patients included in analysis│
                    │           845                │
                    └─────────────────────────────┘
```

OUTCOME

Patients completed a WOMAC questionnaire prior to surgery and at 12-months follow up[22]. This consists of 24 items in 3 subscales: pain (5), stiffness (2), and physical function (17). For each subscale a normalized score was created (0 indicating no symptoms, 100 extreme symptoms) by summing up the total score of each subscale, multiplying it by 100, and dividing by the maximum score. A total score out of 96 was created by combining the 3 subscales, then converted into a normalized score.

The relative effect per patient (REPP = (pretreatment score – post **treatment** score)/pre **treatment** score)[2, 23] was calculated for each patient using the total WOMAC score. A REPP of 1 (best score) corresponds to a patient without symptoms/disability after treatment, a REPP of 0.5 to 50% reduction, a negative REPP to more symptoms/disability in the follow up, -0.5 to an augmentation of 50%.

MAIN PREDICTOR

The primary predictor of interest was the influence of other joints and spine. Prior to surgery patients were asked whether they had arthritis in any other parts of their body including large joints (shoulder, elbow or hand; other hip; knee; ankle or foot) and spine (neck; lower back). All the patients can be differentiated into four grades of musculoskeletal morbidity (Table 1). *MSM grade 1:* single-joint (only index hip joint); *MSM grade 2:* multi-joints (index hip joint and one or more other

large joints); *MSM grade 3:* single-joint (index hip joint) and spine; *MSM grade 4:* multi-joints (index hip joint and one or more other large joints and spine).

Table 1. Description of Musculoskeletal morbidity (MSM) grades **and proportions**

	Without Spine	**With Spine**
Index Joint	**Grade 1**	**Grade 3**
	416 (32.1%)	112 (8.6%)
Index & Other large joints	**Grade 2**	**Grade 4**
	479 (36.9%)	291 (22.4%)

CONFOUNDERS

Prior to surgery patients completed questionnaires including a wide range of demographic information. Demographic information considered relevant in this study included: age, sex, body mass index (BMI), whether or not they live alone or with someone else, the number of years they have had hip pain. Surgical teams recorded information on patient's ASA grade (scored from 1 (normal, healthy) to 4 (life-threatening systemic disease). Information on Anxiety/Depression was taken from the EQ5D questionnaire subscale. Pre-operative WOMAC subscales of pain, stiffness and function were included as further potential confounders.

STATISTICAL METHODS

Descriptive statistics (mean, standard deviation for continuous variables and number, percentage for categorical) were used to describe the characteristics of patients within the four MSM groups. A Box-Whisker plot was used to graphically describe the overall REPP score within each of the four MSM groups.

Logistic regression modeling was used to describe the association of the main predictor (MSM groups) with the outcome of interest (responder according to REPP score), controlling for confounding variables. **Results of the regression model are presented as relative risk ratios by fitting a generalized linear model with a binomial error structure and a log link function (log-logistic model).** Fractional polynomial regression was used to assess evidence of linearity of continuous predictors with the outcome. Multiple imputation by chained equations was used to account for the cumulative effect of missing data in several of the variables[24]. Forty imputed datasets were generated using all potential factors (including the outcome) and estimated parameters were combined using Rubin's rules.

RESULTS

Table 2. Descriptive characteristics and comparison of patients with complete follow-up and baseline assessment

Variable	Missing	All patients (n=1327)	Complete follow-up (n=845)	Baseline (n=482)
MSM grades:	29 (2.2%)			

MSM grade 1		416 (32.1%)	275 (32.9%)	141 (30.5%)
MSM grade 2		479 (36.9%)	312 (37.4%)	167 (36.1%)
MSM grade 3		112 (8.6%)	57 (6.8%)	55 (11.9%)
MSM grade 4		291 (22.4%)	191 (22.9%)	100 (21.6%)
Age	29 (2.2%)	65.7 (10.9)	65.7 (10.6)	65.7 (11.3)
Sex	60 (4.5%)			
Male		559 (44.1%)	359 (44.8%)	200 (43.0%)
Female		708 (55.9%)	443 (55.2%)	265 (57.0%)
BMI	102 (7.7%)	27.5 (4.4)	27.8 (4.4)	27.0 (4.3)
Living alone	10 (0.8%)			
Alone		341 (25.9%)	207 (24.6%)	134 (28.3%)
Spouse/partner		900 (68.3%)	591 (70.1%)	309 (65.2%)
Somebody else		76 (5.8%)	45 (5.3%)	31 (6.5%)
Anxiety/Depression	76 (5.7%)			
None		698 (55.8%)	500 (59.9%)	198 (47.6%)
Moderate		496 (39.7%)	309 (37.0%)	187 (45.0%)
Extreme		57 (4.6%)	26 (3.1%)	31 (7.5%)
Years of hip pain	13 (1.0%)			
<1 year		141 (10.7%)	84 (10.0%)	57 (12.0%)
1-2 years		374 (28.5%)	242 (28.8%)	132 (27.9%)
3-5 years		403 (30.7%)	255 (30.4%)	148 (31.2%)
5+years		396 (30.1%)	259 (30.8%)	137 (28.9%)
ASA grade	152 (11.5%)			
1		209 (17.8%)	117 (15.8%)	92 (21.1%)
2		719 (61.2%)	469 (63.5%)	250 (57.3%)
3 or 4		247 (21.0%)	153 (20.7%)	94 (21.6%)
WOMAC Pain Pre-op	72 (5.4%)	55.4 (17.8)	54.2 (17.6)	57.9 (18.0)
WOMAC Stiffness Pre-op	61 (4.6%)	60.5 (20.7)	60.5 (20.1)	60.5 (22.0)
WOMAC Function Pre-op	74 (5.6%)	60.1 (16.7)	58.6 (16.5)	63.3 (16.8)

The characteristics of patients that completed the 12-month follow-up questionnaire (n=845) were similar to those of patients in the whole sample (n=1327) (Table 2). Patients with only baseline assessment (n=482) (lost to follow-up) were more likely to be living alone and had higher levels of anxiety and depression.

Of the 845 patients included for this analysis, the mean age was 65.7 years (range 26 to 92) and 55.2% were female. A quarter of patients lived alone and 59.9% reported no symptoms of anxiety or depression. The majority of patients (90%) had symptoms of hip pain for more than a year prior to surgery, with 30.8% of these patients having symptoms for more than 5-years. For the pattern of MSM, 32.9% had hip OA in the index joint only (grade 1), 37.4% OA in multiple joints (grade 2), 6.8% hip OA in the index joint with spine OA (grade 3), and 22.9% OA in multiple joints in addition to spine OA (grade 4).

Table 3. Characteristics of patient subgroups in the four MSM grades

	MSM grade 1	MSM grade 2	MSM grade 3	MSM grade 4
Age	64.9 (11.4)	64.9 (10.9)	66.8 (8.8)	67.6 (9.3)
Sex				
Male	127 (48.7%)	130 (43.6%)	25 (47.2%)	72 (40.0%)
Female	134 (51.3%)	168 (56.4%)	28 (52.8%)	108 (60.0%)
BMI	27.5 (4.5)	28.2 (4.6)	26.3 (3.3)	27.8 (4.3)

Living alone				
Alone	59 (21.5%)	74 (23.7%)	12 (21.1%)	59 (31.1%)
Spouse/partner	201 (73.4%)	222 (71.2%)	44 (77.2%)	118 (62.1%)
Somebody else	14 (5.1%)	16 (5.1%)	1 (1.8%)	13 (6.8%)
Anxiety/Depression				
None	171 (63.1%)	187 (60.9%)	31 (55.4%)	106 (55.5%)
Moderate	94 (34.7%)	108 (35.2%)	23 (41.1%)	79 (41.4%)
Extreme	6 (2.2%)	12 (3.9%)	2 (3.6%)	6 (3.1%)
Years of hip pain				
<1 year	36 (13.1%)	31 (9.9%)	6 (10.5%)	11 (5.8%)
1-2 years	81 (29.5%)	96 (30.8%)	18 (31.6%)	46 (24.3%)
3-5 years	79 (28.7%)	85 (27.2%)	21 (36.8%)	67 (35.5%)
5+years	79 (28.7%)	100 (32.1%)	12 (21.1%)	65 (34.4%)
ASA grade				
1	47 (19.4%)	46 (17.1%)	10 (19.2%)	14 (8.3%)
2	166 (68.6%)	162 (60.2%)	31 (59.6%)	104 (61.9%)
3 or 4	29 (12.0%)	61 (22.7%)	11 (21.2%)	50 (29.8%)
WOMAC Pain Pre-op	51.4 (18.2)	54.8 (17.3)	53.3 (16.0)	57.7 (17.3)
WOMAC Stiffness Pre-op	58.1 (19.9)	62.2 (19.5)	60.3 (19.8)	61.2 (20.9)
WOMAC Function Pre-op	55.6 (16.9)	59.2 (15.9)	59.2 (15.6)	62.1 (16.6)

The characteristics of patients within each of the four MSM groups is described in table 3. Patients with spinal pathology were slightly older compared to those with OA in other joints, but overall the distribution of age was very similar across all morbidity groups (Figure 2). Patients with OA in multiple joints (MSM grade 2 and 4) were more likely to be female, live alone and have suffered with hip pain for a greater number of years prior to surgery. Anxiety and depression was more common in those with spinal OA (MSM grades 3 and 4). There were fewer patients with ASA grade 3 or 4 in group MSM grade 1 with hip OA only (12%) compared to those with spine and hip OA in multiple joints (30%). No differences were observed in pre-operative WOMAC subscales across the morbidity groupings.

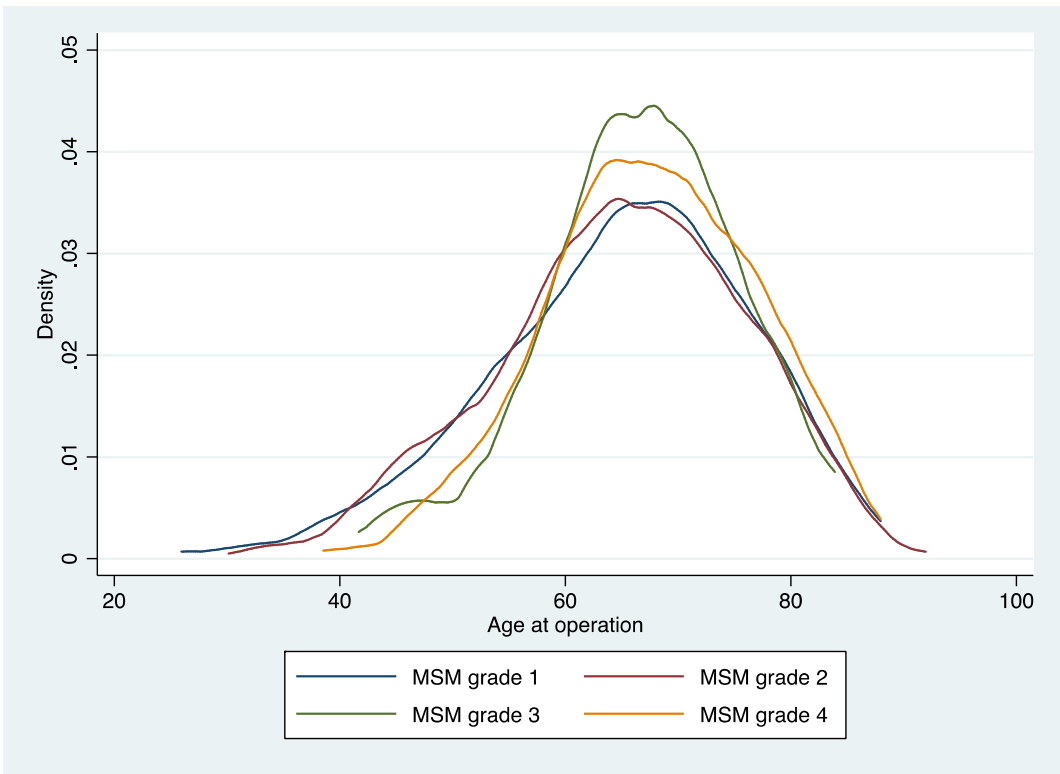**Figure 2.** Kernel density plot describing distribution of age within each MSM grade
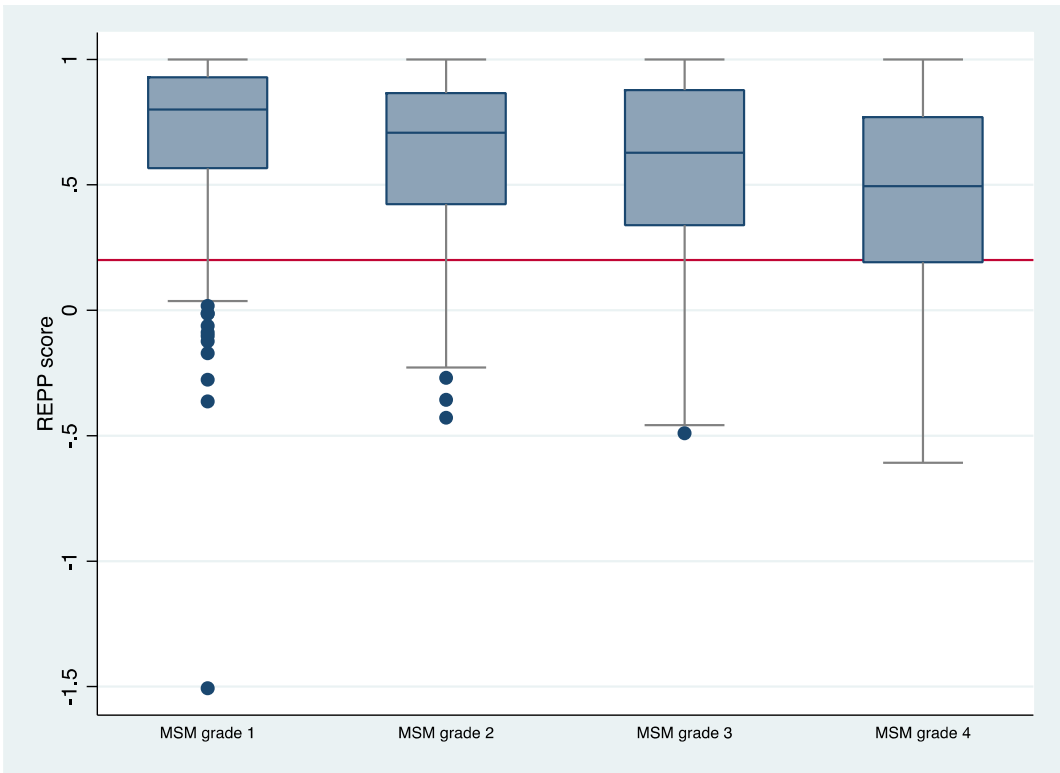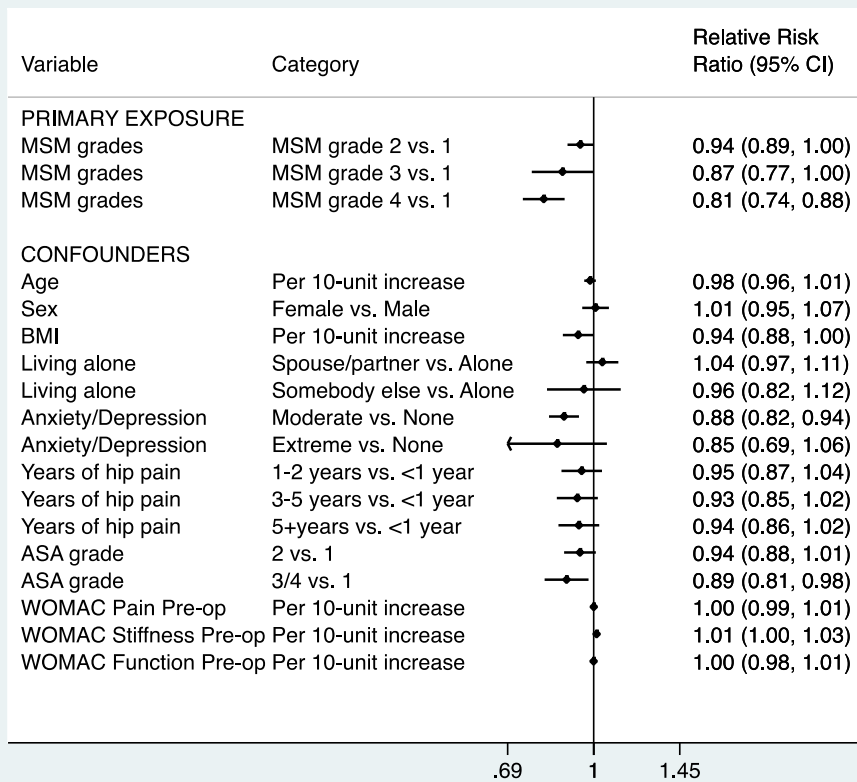
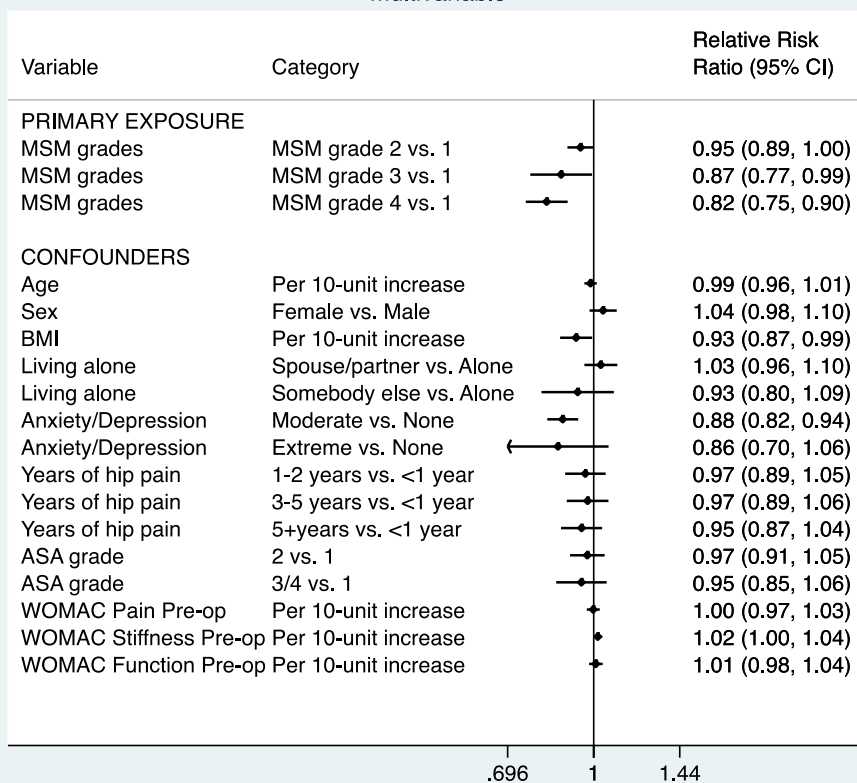**Figure 3.** Box-whisker plot describing REPP score with each MSM grade

As the grade of MSM increases the outcome according to the REPP score declined (Figure 3). Those in MSM grade 1 had the best outcome compared with those in grade 4, the worst.

Figure 4. Forest plot describing results of univariable and multivariable logistic regression models

Univariable

Variable	Category	Relative Risk Ratio (95% CI)
PRIMARY EXPOSURE		
MSM grades	MSM grade 2 vs. 1	0.94 (0.89, 1.00)
MSM grades	MSM grade 3 vs. 1	0.87 (0.77, 1.00)
MSM grades	MSM grade 4 vs. 1	0.81 (0.74, 0.88)
CONFOUNDERS		
Age	Per 10-unit increase	0.98 (0.96, 1.01)
Sex	Female vs. Male	1.01 (0.95, 1.07)
BMI	Per 10-unit increase	0.94 (0.88, 1.00)
Living alone	Spouse/partner vs. Alone	1.04 (0.97, 1.11)
Living alone	Somebody else vs. Alone	0.96 (0.82, 1.12)
Anxiety/Depression	Moderate vs. None	0.88 (0.82, 0.94)
Anxiety/Depression	Extreme vs. None	0.85 (0.69, 1.06)
Years of hip pain	1-2 years vs. <1 year	0.95 (0.87, 1.04)
Years of hip pain	3-5 years vs. <1 year	0.93 (0.85, 1.02)
Years of hip pain	5+years vs. <1 year	0.94 (0.86, 1.02)
ASA grade	2 vs. 1	0.94 (0.88, 1.01)
ASA grade	3/4 vs. 1	0.89 (0.81, 0.98)
WOMAC Pain Pre-op	Per 10-unit increase	1.00 (0.99, 1.01)
WOMAC Stiffness Pre-op	Per 10-unit increase	1.01 (1.00, 1.03)
WOMAC Function Pre-op	Per 10-unit increase	1.00 (0.98, 1.01)

.69   1   1.45

Multivariable

Variable	Category	Relative Risk Ratio (95% CI)
PRIMARY EXPOSURE		
MSM grades	MSM grade 2 vs. 1	0.95 (0.89, 1.00)
MSM grades	MSM grade 3 vs. 1	0.87 (0.77, 0.99)
MSM grades	MSM grade 4 vs. 1	0.82 (0.75, 0.90)
CONFOUNDERS		
Age	Per 10-unit increase	0.99 (0.96, 1.01)
Sex	Female vs. Male	1.04 (0.98, 1.10)
BMI	Per 10-unit increase	0.93 (0.87, 0.99)
Living alone	Spouse/partner vs. Alone	1.03 (0.96, 1.10)
Living alone	Somebody else vs. Alone	0.93 (0.80, 1.09)
Anxiety/Depression	Moderate vs. None	0.88 (0.82, 0.94)
Anxiety/Depression	Extreme vs. None	0.86 (0.70, 1.06)
Years of hip pain	1-2 years vs. <1 year	0.97 (0.89, 1.05)
Years of hip pain	3-5 years vs. <1 year	0.97 (0.89, 1.06)
Years of hip pain	5+years vs. <1 year	0.95 (0.87, 1.04)
ASA grade	2 vs. 1	0.97 (0.91, 1.05)
ASA grade	3/4 vs. 1	0.95 (0.85, 1.06)
WOMAC Pain Pre-op	Per 10-unit increase	1.00 (0.97, 1.03)
WOMAC Stiffness Pre-op	Per 10-unit increase	1.02 (1.00, 1.04)
WOMAC Function Pre-op	Per 10-unit increase	1.01 (0.98, 1.04)

.696   1   1.44

Findings of the logistic regression model confirmed an important significant association of grade of MSM on patient outcomes of THR surgery. As the grade of MSM increased, patients were less likely to achieve a response to THR surgery. **The proportion of patients responding to surgery was 75% in MSM grade 4 compared to 92% in MSM grade 1.** This remained after adjusting for a wide range of confounding factors, **where the risk of response was 18% lower in MSM grade 4 versus 1 (Relative Risk Ratio 0.82 95% CI (0.75 to 0.90) (Figure 4)**. Hence, the null hypothesis is rejected.

DISCUSSION

The grade of musculoskeletal morbidity influences the outcome of THR; in this study, it had the highest odd's ratios of all compared parameters. A strength of this study was the large number of participants, and generalizability with participants from 20 different centers across Europe, different cultural regions and eight languages.

The model of four grades of MSM allows separating the "heterogeneous" cohort **of patients with hip OA coming for THR** in four "homogenous" groups including the index joint, considering the other joints and spine respectively not as comorbidity but as morbidity of a system of **musculoskeletal system**. **This should allow the surgeon to better manage the patients' expectations especially in patients with higher grades of MSM. In these cases the patients can present in the follow up after THR with symptoms deriving from other joints and/or spine respectively. To the authors it seems important to focus not only on the affected hip joint but also on the other joints and spine which can influence the outcome; So the THR can be considered as a part of the treatment of the musculoskeletal system. A failure to provide this perception to the patient is likely a key source of patient dissatisfaction.**

This model covers all different situations of patients with hip OA coming for THR; from the "simple" case with only one hip affected to the complex case with multiple other large joints affected and spine pathology. This grading can also be applied for bilateral OA of the hip or other joints; for instance in bilateral hip osteoarthritis (MSM grade 2) or in patients with knee or shoulder osteoarthritis. **The MSM grading system can equally be applied to patients with knee OA coming for knee replacement, and shoulder arthritis for shoulder replacement. That would allow to separate these patient groups in 4 more homogeneous groups with respect to outcome. Especially in knee OA it is known and reported that it occurs most frequently bilateral (MSM grade 2) and rather rarely monolateral (MSM grade 1). Although this would need to be tested in other external cohorts of patients, as our data here is only for those receiving hip replacement surgery.**

An unexpected finding, was the high prevalence of patients with MSM grades 2,3 and 4 of 68%; in other words only a third of the patients had just osteoarthritis of the index joint. A second unexpected finding was that there were no differences in the gender and age distribution of patients in each of the 4 MSM grades. From literature we expected a higher average age in the patient groups higher MSM grade >1[11]. These findings need further research.

Using the 4 MSM grades in daily practice allows to counsel the patients better preoperatively and to manage their expectations of outcome with higher precision. Even patients with hip OA and MSM grade 4 still profit from surgery with a responder rate of 75%, but the score after THR remains higher compared to MSM grade 1. In difficult, unclear situations, a test infiltration with local anesthetics of the affected hip may illustrate the potential effect of THR for the patient.

Bellamy designed the WOMAC questionnaire to measure osteoarthritis of one hip or knee (MSM grade 1). One third of the patients fulfilled this criterion and were "properly" assessed[22]. Knowing this fact, we realized retrospectively that in two thirds of patients that the WOMAC is capturing additional symptoms/disability from other joints and/or spine. A basic difficulty might be the lack of localization of symptoms in the WOMAC. New patient questionnaires have integrated the localization of symptoms for the global patient as a whole e.g. Pationnaire, ICOAP (both mannequin based systems)[25-28].

In this study were different limitations: All participating centers had experience and interest in THR and so a positive selection bias of the included patients has to be supposed. This may lead to better

results and a higher responder rate than in daily routine. **A limitation of the study is that it is not possible to separate ipsilateral vs. contralateral pathologies. Another limitation is the problem of ipsilateral hip and knee arthritis, where the principal symptoms present in the thigh and it is a difficult situation to diagnose.** There was no information about complications during the study/after THR and the further management of these patients. So it may be, that one clinic excluded these patients with no further follow up in the study or that they still were included without knowing about reduction or revision surgery. This influence remains unknown. The grading of MSM depended on an additional question tested and validated locally in Bristol by one coauthor (PD). The distributions of the MSM grades showed no substantial differences across the participating centers.

CONCLUSIONS

Arthritis in other large joints and spine measured as musculoskeletal morbidity has a strong influence on the 1-year outcome after THR. In this study, compared to other risk factors (mental factors, low score, gender and age) it has the largest impact on outcome. The responder rates decline linearly with each MSM grade (MSM grade 1 (single-joint) > MSM grade 2 (multi-joints) > MSM grade 3 (single-joint and spine) > MSM grade 4 (multi-joints and spine). The prevalence of MSM grades 2, 3 and 4 in patients with osteoarthritis of one hip is higher than expected (68% of the cohort). Even patients in MSM grade 4 still profit from surgery (>75% responder rate).

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