

Osteoarthritis and Cartilage



Genetic factors contribute more to hip than knee surgery due to osteoarthritis – a population-based twin registry study of joint arthroplasty

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ARTICLE INFO

Article history:

Received 15 August 2016

Accepted 7 December 2016

Keywords:

Heritability

Twins

Osteoarthritis

Arthroplasty

SUMMARY

Objective: To explore and quantify the relative strengths of the genetic contribution vs the contribution of modifiable environmental factors to severe osteoarthritis (OA) having progressed to total joint arthroplasty.

Design: Incident data from the Norwegian Arthroplasty Registry were linked with the Norwegian Twin Registry on the National ID-number in 2014 in a population-based prospective cohort study of same-sex twins born 1915–60 (53.4% females). Education level and height/weight were self-reported and Body Mass Index (BMI) calculated. The total follow-up time was 27 years for hip arthroplasty (1987–2014, 424,914 person-years) and 20 years for knee arthroplasty (1994–2014, 306,207 person-years). We estimated concordances and the genetic contribution to arthroplasty due to OA in separate analyses for the hip and knee joint.

Results: The population comprised $N = 9058$ twin pairs ($N = 3803$ monozygotic (MZ), $N = 5226$ dizygotic (DZ)). In total, 73% (95% confidence intervals (CI) = 66–78%) and 45% (95% CI = 30–58%) of the respective variation in hip and knee arthroplasty could be explained by genetic factors. Zygosity (as a proxy for genetic factors) was associated with hip arthroplasty concordance over time when adjusted for sex, age, education and BMI (HR = 2.98, 95% CI = 1.90–4.67 for MZ compared to DZ twins). Knee arthroplasty was to a greater extent dependent on BMI when adjusted for zygosity and the other covariates (HR = 1.15, 95% CI = 1.02–1.29).

Conclusion: Hip arthroplasty was strongly influenced by genetic factors whereas knee arthroplasty to a greater extent depended on a high BMI. The study may imply there is a greater potential for preventing progression of knee OA to arthroplasty in comparison with hip OA.

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Introduction

Osteoarthritis (OA) is a highly prevalent musculoskeletal disease that may lead to considerable pain and reduced quality of life^{1,2}.

Total joint arthroplasty is indicated when both radiographic changes, severe joint pain and disability are present and other treatment modalities have failed³.

There exists no medical cure for OA and knowledge of potential causes is lacking. A higher age, female sex, and obesity are among known potential risk factors for hip and knee arthroplasty due to OA^{4–9}. A limited number of studies indicate genetic factors may contribute to OA. The genetic contribution to the disease may be studied in twins since identical twins share 100% of their genes and non-identical twins share 50%. The percentage of the total variance

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in a trait that is explained by genetic factors (“heritability”) can be calculated from intra twin pair correlations under the classical twin model¹⁰. In a smaller British twin cohort, the genetic contribution to radiographically defined hip and knee OA was estimated to 39–65% in women^{11–13}. A large degree of genetic overlap in prevalent radiographic OA was found in the finger joints whereas a lesser degree of genetic overlap was observed in the weightbearing joints¹³.

Although OA is assumed to be highly heritable, very little is known about the genetic contribution to a symptomatic and clinically relevant OA definition. Several studies indicate that joint pain may be a phenotype with its own causes that are independent of the structural damage to the joint^{14–16}. However, existing twin studies have until present not studied symptomatic and disabling OA diagnoses that are relevant to patients and accordingly may have impact for the subsequent development of preventive strategies. In fact, we are aware of only two studies of the genetic influence on symptomatic OA. Recent Danish twin studies found genetic factors to contribute to 47% of the variance in hip arthroplasty due to OA and only 18% for knee arthroplasty due to OA^{17,18}. This deviates from the estimates from studies using radiographic definitions^{11–13}.

Age and sex differences might also affect the association between genetic factors and OA^{17,18}. Furthermore, whether genetic factors or more modifiable environmental factors like a high Body Mass Index (BMI) and markers for health inequality such as a shorter education contribute the most to twin pairs becoming concordant over time is unknown. Previous studies have revealed both consistent and varying associations between obesity, level of education and joint arthroplasty but these are seldom adjusted for potential genetic confounding^{19–23}. Similarly, previous OA studies in twins have not adjusted for BMI^{17,18}.

There is a need for studies comparing the contribution of unmeasured genetic factors to clinically relevant OA of the hip and knee joints, taking the main risk factor obesity and markers of health inequalities into account. Using linked registry data from the Norwegian Twin Registry and the Norwegian Arthroplasty Registry, our main aim was to explore whether evidence exists for a genetic contribution, and to quantify the relative strengths of the genetic contribution vs the contribution of modifiable environmental factors to severe OA progressing to a need for arthroplasty.

Methods

The study is a prospective cohort study based on a linkage of the Norwegian Twin Registry and the Norwegian Arthroplasty Registry on the National ID number in December 2014 (the Norwegian Twin OA study). The Norwegian Twin Registry was established in 2009 at the Norwegian Institute of Public Health²⁴. We included complete same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs born 1915–1960. Twins with no co-twin registered due to early death or not being willing to participate were excluded. Zygosity, sociodemographic factors and height and weight were obtained from postal questionnaires in 1978–1982 (Q1) and 1990–1998 (Q2)²⁴.

The Norwegian Arthroplasty Registry was established in 1987 as a national hip arthroplasty registry and was extended to include all arthroplasty of artificial joints including knee joints in 1994²⁵. All orthopedic surgeons at all the Norwegian hospitals participate and are instructed to report the cause and date of all primary operations on a one-page form. In total, 95% of all prosthesis operations due to OA are reported and approximately 8000 surgeries of hip and 5500 of knee OA are registered yearly²⁶.

The study was approved by the Regional Ethical Committee in Oslo, Norway.

Outcome variables

Prevalent and incident arthroplasty due to primary OA in the left or right hip or knee joint were our main outcome variables. Arthroplasty due to other causes than OA (i.e., fractures, inflammatory rheumatic diseases etc.) were excluded.

Covariates

Education was reported in years and level (primary school to college/university). Participants were categorized into having primary school (0–7 years), lower secondary school (8–9 years), upper secondary school (10–12 years) and college/university (>12 years), with the number of years corresponding to the Norwegian education system at the time the data were collected. Body height and weight were reported and BMI (kg/m²) was calculated (continuous variable). For all covariates, the value reported in Q1 was used if available. If not available, data from Q2 was merged to the data of Q1 (age at reporting was taken into account).

Statistical analyses

All analyses were performed separately for the hip and knee joint. Multiple imputations of education level and BMI data were indicated, which are described in detail in the Online-Only material together with model specifications for all statistical models presented (eMethods). In brief, we initially performed Cox regression analyses for OA progression to arthroplasty (using the outcome age at arthroplasty), and subsequently fitted classical variance components models (using the binary outcome presence/absence of arthroplasty).

The age- and sex-stratified casewise concordances and intra-pair correlations for arthroplasty were calculated with 95% confidence intervals (CI)^{27,28}. Concordant twin pairs were pairs in which both twins had undergone joint arthroplasty due to OA. Discordant pairs were pairs in which only one twin had. To explore the rate at which MZ and DZ pairs became concordant over time, we inspected the cumulative incidence curves for time to hip or knee arthroplasty for the second twin.

If genetic effects are important, we would expect MZ twins to be more concordant and correlated for time to arthroplasty than DZ twins. To assess this, we fitted Cox regression models for time between the first twin's arthroplasty due to OA (index twin) till the second twin's arthroplasty due to OA (co-twin) or censoring taking competing risk of death into account. In an exploratory/descriptive regression analyses of whether genetic factors or modifiable environmental factors contributed the most to OA, we included zygosity (DZ = 0 and MZ = 1) as the independent variable (i.e., a proxy for genetic factors) and time to hip and knee arthroplasty due to OA of the co-twin as dependent variables. We also included sex, twin pair age at the index twin's surgery, education level and BMI of the co-twin as independent variables (both complete case (CC) and multiply imputed (MI) data analyses) in a multivariate analysis. The two latter covariates were included as proxies for modifiable, environmental factors. For statistical reasons we explored both a 4-category and a dichotomous operationalization of education level (short: ≤12 years, long >12 years), and treated BMI as a continuous variable. Further, we ran sensitivity analyses using intra-pair difference variables for education level and BMI (this was avoided in the main analyses due to missing data and risk of deleting whole pairs in CC analyses leading to more uncertain estimates). Results were presented as Hazard Ratios (HR) with 95% CI.

We finally obtained estimates of the percentage of the total variance in arthroplasty due to severe OA (with 95% CI) that can be ascribed to genetic factors (A), common (C) and unique

environmental (E) factors by fitting classical twin models¹⁰ (ACE, AC, AE and E variance components models were initially compared for model fit, see eMethods in the Supplement). We explored age/sex differences by performing analyses stratified by age (below and above median age at prosthesis surgery of 68 years) and sex (male/female). We also excluded pairs with one or more dead twin in sensitivity analyses. The statistical analyses were carried out using STATA MP v. 14 and R with the OpenMX v.2.3.1 package.

Results

In total, $N = 2868$ were excluded due to no information from the co-twin (early death or not willing to participate), leaving $N = 18,058$ twins in $N = 9029$ complete pairs ($N = 3803$ MZ and $N = 5226$ DZ pairs) for the analyses. Excluded participants were more often males ($N = 1817$ (63.3%), $P < 0.001$) and more often DZ twins ($N = 1935$ (67.5%), $P < 0.001$) than participants included (characteristics presented in Table I). Questionnaire data was available for $N = 13,337$ (73.8%) participants ($N = 6164$ for Q1 only, $N = 6557$ for both Q1 and Q2 and $N = 616$ for Q2 only). The participants with missing questionnaire data were more often males ($N = 2378$ (50.3%), $P < 0.001$), more often MZ twins ($N = 2980$ (61.1%), $P < 0.001$) and significantly older (mean (SD) age in 2014 74.5 (0.19)). Hence, we performed multiple imputations²⁹ (see eMethods in the Supplement). The included participants' characteristics are presented in Table I. The total follow-up times were 27 and 20 years for hip and knee arthroplasty, respectively (i.e., 424,914 and 306,207 person-years).

Prevalence, incidence and concordance

The prevalence of hip and knee arthroplasties in 2014 were 3.6% (614/18,058) and 1.8% (317/18,058), respectively (similar across zygosity for both joint sites). Incidence rates per 1000 person-years were 1.40 (95% CI = 1.30–1.52) for hip arthroplasty and 0.99 (95% CI = 0.89–1.11) for knee arthroplasty. Overall, the concordance and intra-pair correlations were higher for hip arthroplasty than knee

arthroplasty (Table II). For the hip joint, the MZ concordance was significantly higher than the DZ concordance ($P < 0.01$ in all strata). For the knee joint no differences were observed for any strata ($0.05 < P < 0.21$), which is consistent with a greater genetic contribution to hip OA than knee OA progressing to arthroplasty.

Cox regression model

We identified $N = 468$ and $N = 262$ pairs with both twins alive when the first twin (index twin) received hip or knee surgery due to OA, and recorded the time until the second twin's (co-twin) surgery. More pairs became concordant for hip arthroplasty than for knee arthroplasty over time (Fig. 1), and MZ pairs were more likely to become concordant.

There was a difference between joint sites in the exploratory Cox regression analyses. For the hip joint, the significant crude association between zygosity and a shorter time to arthroplasty of the co-twin remained statistically significant in all multivariable analyses (Table III). Education level was not associated with shorter time to hip arthroplasty (Table III). However, a high BMI was borderline significantly associated with hip arthroplasty both in CC and MI data (Table III). No association for BMI could be observed in analyses treating education level as binary (BMI: $HR_{CC} = 1.07$, 95% CI = 0.99–1.14, $HR_{MI} = 1.07$, 95% CI = 0.97–1.14). In these models (with fewer estimated parameters implying a gain in statistical power but a loss of information detail), all other results were similar (zygosity: $HR_{CC} = 2.72$, 95% CI = 1.57–4.71, $HR_{MI} = 3.00$, 95% CI = 1.93–4.69, education level (with ≤ 12 years as ref.cat.): $HR_{CC} = 1.69$, 95% CI = 0.93–1.06, $HR_{MI} = 1.48$, 95% CI = 0.84–2.61) as in analyses treating education level as a 4-category variable (Table III). Hence, these findings may be consistent with a genetic influence on hip arthroplasty. Similar results were obtained in analyses of within-pair differences of BMI and education level (data not shown).

In contrast, no significant crude association could be observed between zygosity and knee arthroplasty due to OA. However, there was a significant association in age/sex-adjusted as well as

Table I
Participants characteristics

	All	Hip arthroplasty due to OA	Knee arthroplasty due to OA
Individual level	$N = 18,058$	$N = 614$	$N = 317$
Sex, F, n (%)	9650 (53.4)	432 (70.4)	214 (67.5)
Age at questionnaire response, mean (SD)	37.9 (12.3)	45.0 (11.1)	40.8 (11.0)
Death, n (%)	5159 (28.6)	175 (28.9)	46 (14.5)
Death age, mean (SD)	72.5 (13.4)	82.2 (7.6)	83.1 (7.3)
Primary school (0–7 years), n (%)	5390 (40.6)	222 (50.2)	108 (46.8)
Lower sec. school (8–9 years), n (%)	1603 (12.1)	54 (12.2)	35 (15.2)
Upper sec. school (10–12 years), n (%)	3156 (23.8)	82 (18.6)	54 (23.4)
College/university (>12 years), n (%)	3114 (23.5)	84 (19.0)	34 (14.7)
BMI (kg/m ²), mean (SD)	22.6 (2.96)	23.4 (2.9)	23.8 (3.0)
Overweight (≥ 25 kg/m ²), n (%)	2221 (17.1)	107 (24.5)	74 (32.5)
Zygosity, MZ, n (%)	7606 (42.1)	260 (42.4)	141 (44.5)
Pair level: MZ death rates and intrapair correlation for covariates	$N = 3803$	$N = 210$	$N = 131$
Both twins dead by 2014, n (%)	721 (18.9)	40 (19.0)	10 (7.6)
Age at death, r	0.56	0.43	0.13
Age at questionnaire response, r	0.96	0.96	0.93
Education level, tetrachoric r	0.87	0.86	0.84
BMI (kg/m ²), r	0.65	0.74	0.70
Pair level: DZ death rates and intrapair correlation for covariates	$N = 5226$	$N = 324$	$N = 171$
Both twins dead by 2014, n (%)	968 (18.5)	74 (22.8)	18 (10.5)
Age at death, r	0.42	0.28	–0.33
Age at questionnaire response, r	0.94	0.94	0.97
Education level, tetrachoric r	0.63	0.48	0.78
BMI (kg/m ²), r	0.40	0.42	0.30

Abbreviation: SD: standard deviation. r = Pearson correlation coefficient.

Table II
Concordances and correlations for arthroplasty due to hip and knee OA

	No. of pairs with no TJR due to OA	No. of disc./conc. pairs for MZ twins	No. of disc./conc. pairs for DZ twins	Casewise concordance for MZ pairs (95% CI)	Casewise concordance for DZ pairs (95% CI)	MZ correlation (95% CI)	DZ correlation (95% CI)
Hip							
All	8495	160/50	294/30	0.38 (0.31–0.46)	0.17 (0.12–0.22)	0.71 (0.64–0.77)	0.45 (0.33–0.52)
Women	4449	112/33	208/23	0.37 (0.28–0.46)	0.18 (0.12–0.24)	0.67 (0.60–0.75)	0.40 (0.28–0.52)
Men	4046	48/17	86/7	0.41 (0.28–0.54)	0.14 (0.05–0.23)	0.77 (0.66–0.86)	0.47 (0.26–0.63)
Age <68 years	4164	35/10	51/3	0.36 (0.20–0.53)	0.11 (0.00–0.21)	0.72 (0.55–0.83)	0.45 (0.16–0.67)
Age ≥68 years	4331	125/40	243/27	0.39 (0.31–0.47)	0.18 (0.12–0.24)	0.69 (0.60–0.76)	0.38 (0.26–0.49)
Knee							
All	8727	121/10	166/5	0.14 (0.06–0.22)	0.06 (0.00–0.10)	0.45 (0.29–0.59)	0.23 (0.03–0.40)
Women	4622	81/7	111/4	0.15 (0.05–0.24)	0.07 (0.00–0.13)	0.44 (0.23–0.62)	0.21 (–0.02 to 0.42)
Men	4105	40/3	55/1	0.13 (0.00–0.26)	0.04 (–0.03 to 0.10)	0.45 (0.17–0.67)	0.22 (–0.17 to 0.54)
Age <68 years	4174	31/5	51/2	0.24 (0.07–0.42)	0.07 (–0.02 to 0.17)	0.66 (0.42–0.82)	0.34 (0.03–0.59)
Age ≥68 years	4553	90/5	115/3	0.10 (0.02–0.18)	0.05 (–0.00 to 0.10)	0.33 (0.11–0.52)	0.15 (–0.09 to 0.37)

Age = median age of arthroplasty due to OA. Disc.: discordant for the outcome (i.e., pairs in which only 1 twin has arthroplasty due to OA), Conc.: concordant for the outcome (i.e., pairs in which both twins have arthroplasty due to OA), Casewise concordance: the probability that an affected twin has a co-twin who is also affected.

multivariable analyses of MI data but not in CC data, indicating a potentially less robust association between zygoty and knee OA (Table III). Having a high BMI was significantly associated with a pair becoming concordant for knee OA when adjusted for zygoty in MI data (Table III). Education level was not associated with knee arthroplasty due to OA in any analyses. Results remained similar both in CC and MI data when treating education level as binary below and above 12 years, except for the association between BMI

and knee arthroplasty becoming statistically significant in CC data and stronger in MI data (BMI: $HR_{CC} = 1.10$, 95% CI = 1.00–1.21, $HR_{MI} = 1.14$, 95% CI = 1.04–1.25, zygoty: $HR_{CC} = 3.14$, 95% CI = 0.96–10.26, $HR_{MI} = 3.35$, 95% CI = 1.13–9.99, Education level (≤ 12 years was ref.cat.): $HR_{CC} = 1.95$, 95% CI = 0.67–5.70, $HR_{MI} = 1.71$, 95% CI = 0.58–5.03 adjusted for age and sex). Similar results were obtained in analyses of within-pair differences of BMI and education level (data not shown).

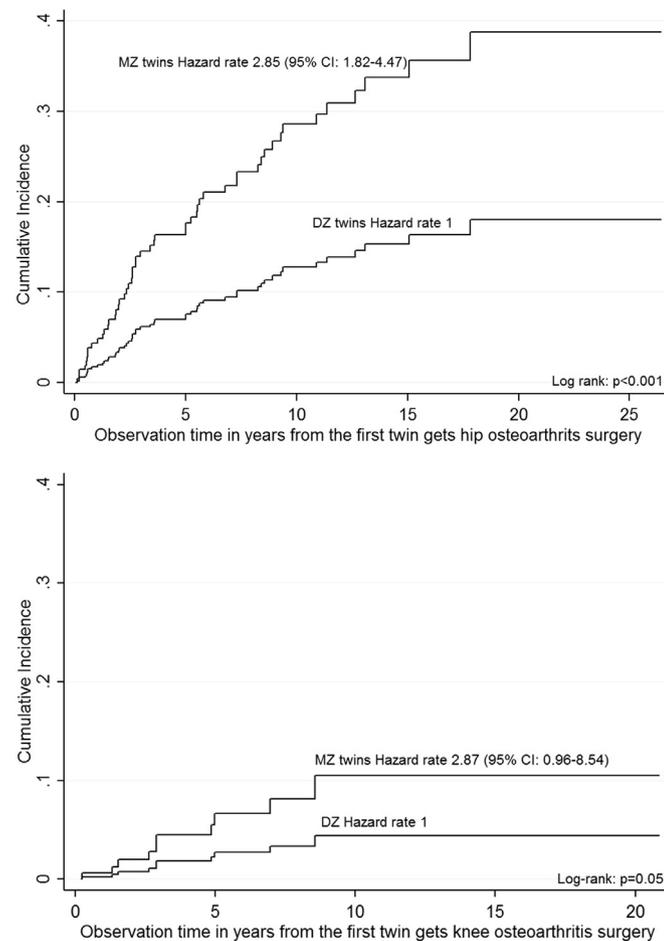


Fig. 1. Plot of cumulative incidence of hip arthroplasty due to OA (upper graph) and knee arthroplasty due to OA (lower graph) showing the hazard rate of MZ and DZ twins becoming concordant over time taking censoring due to end of observation time and competing risk of co-twin's death into account.

The classical twin model

For both hip and knee arthroplasty due to OA, a classical twin model including only genetic (A) and unique environmental factors (E) fitted the data best (i.e., environmental factors common to two twins in a pair [C] excluded, see eTable 1 and 2 in the Supplement). In total 73% (95% CI = 66–78%) of the variance in hip arthroplasty could be explained by genetic factors and 27% (95% CI = 22–34%) by unique environmental factors. There were no age or sex differences (eTable 1). In contrast, knee arthroplasty was to a greater extent determined by unique environmental factors (55%, 95% CI = 42–70%) than genetic factors (45%, 95% CI = 30–58%). Genetic factors contributed more to knee OA arthroplasty in persons <68 years (66%, 95% CI = 49–82%) than above (33%, 95% CI = 16–50%) although CI overlapped. No sex differences were observed for the knee joint (eTable 2).

For both hip and knee arthroplasty, the models did not converge when including age, sex, BMI and/or education level as fixed effect covariates. We repeated the analyses for living pairs only, with more or less similar results in an AE-model (A for hip OA progressing to need for joint surgery = 80%, 95% CI = 73–85% and A for knee OA progressing to need for joint surgery = 50%, 95% CI = 33–65%).

Discussion

This national twin registry study showed a high and consistent concordance for hip arthroplasty due to OA among identical twins, which was significantly higher than for non-identical twins when adjusted for sex, BMI and a low education level. Concordance for knee arthroplasty due to OA was to a greater extent dependent on modifiable factors like a high BMI. Our findings may indicate that the genetic contribution to incident, severe OA differs between the hip and knee joint.

Strengths of the current study were the population-based inclusion of twins, a long follow-up time and the high coverage of >95% of hip and knee arthroplasties being reported across the entire country. The present study is the first to explore the genetic contribution to hip and knee OA taking age, sex, educational level

Table III

Associations between zygoty and hip and knee arthroplasty due to OA in Norwegian twins born 1915–1960

	Univariate model HR (95% CI)	Sex adjusted model HR (95% CI)	Complete case analyses	
			Multivariate model HR (95% CI)	Multiple imputation Multivariate model HR (95% CI)
Hip joint				
Zygoty, MZ	2.85 (1.82–4.47)	3.03 (1.94–4.73)	2.59 (1.48–4.54)	2.98 (1.90–4.67)
Sex, F		1.08 (0.68–1.72)	1.63 (0.87–3.05)	1.24 (0.76–2.01)
Age		0.95 (0.93–0.97)	0.96 (0.94–0.99)	0.95 (0.93–0.97)
Lower sec. school (8–9 years)			1.50 (0.62–3.63)	1.28 (0.74–2.21)
Upper sec. school (10–12 years)			1.05 (0.47–2.35)	1.31 (0.68–2.53)
College/university (>12 years)			1.84 (0.97–3.50)	1.73 (0.92–3.25)
BMI (kg/m ²)			1.07 (0.99–1.15)	1.07 (1.00–1.15)
Knee joint				
Zygoty, MZ	2.87 (0.96–8.54)	3.14 (1.02–9.70)	2.88 (0.86–9.62)	3.32 (1.09–10.12)
Sex, F		1.09 (0.36)	2.10 (0.47–9.33)	1.29 (0.45–3.74)
Age		0.95 (0.89–1.01)	0.94 (0.87–1.01)	0.95 (0.88–1.01)
Lower sec. school (8–9 years)			0.56 (0.05–5.83)	1.06 (0.21–5.36)
Upper sec. school (10–12 years)			0.82 (0.14–4.95)	1.55 (0.34–7.13)
College/university (>12 years)			1.82 (0.53–6.25)	1.98 (0.54–7.21)
BMI (kg/m ²)			1.09 (0.98–1.21)	1.15 (1.02–1.29)

Cox regression analyses with zygoty and co-twins' value for sex, age at index twin's surgery, education level and BMI as independent variables taking competing risk of death into account. Ref.cat. for education level was primary school (0–7 years). Complete case analyses performed on $N = 312$ and $N = 196$ pairs with complete BMI and education data for hip and knee arthroplasty, respectively. In total $N = 468$ pairs for the hip joint and $N = 262$ pairs for the knee joint included in analyses based on multiple imputations of $N = 50$ datasets (ref.cat. is DZ twins).

and obesity as the main risk factors of hip and knee OA as well as time to prosthesis surgery into account.

Our main findings are both supportive and contradictory to those of previous studies and extend existing knowledge on potential causes for severe OA. The marked difference in genetic contribution depending on OA site previously observed was supported in the current study^{13,17,18}. For the hip joint, genetic factors comprised 73% of the variance, which is comparable to, or slightly higher than those of previous studies^{11,18}. However, in contrast to a Danish study¹⁸, we found no differences in this contribution across age or sex for hip arthroplasty. Our analyses for the hip joint were based on a higher total number of concordant/discordant pairs than in Danish analyses.

There were greater differences between current and previous findings for the genetic contribution to knee OA. According to the current study, genetic factors accounted for 45% of the variance in knee arthroplasty due to OA. In the Danish twin registry, genetic and unique environmental factors contributed to 18% and 82% of the variance, respectively¹⁷. The true contribution of genetic factors might have been underestimated in both studies due to a low knee OA incidence. However, similar trends across differences in follow-up time and sample size, which were high in both studies, strengthen our findings. Hence, the low concordances in relation to discordances and sample sizes in both studies may reflect a true low genetic contribution to severe knee OA (i.e., 15 concordant and 287 discordant pairs in 9058 pairs during 20 years in the present study vs 30 concordant and 273 discordant pairs in 24,961 pairs over 13 years in the Danish study)¹⁷. Age and/or sex differences were found in both studies of the knee joint, but should be further explored due to small strata.

Progression of OA to joint arthroplasties as studied in the current study showed a slightly higher heritability than isolated radiographic OA in previous studies (45% vs 37–44% for the knee joint and 73% vs 60% for the hip joint)^{11,12}. The differences in findings might be due to differences in OA definition, since a requirement for having joint arthroplasty is not only radiographic changes but also pain and disability. However, a study of British twins indicated that genetic factors explained only 28% (95% CI = 19–37%) of the variance in knee pain when not taking structural OA features into account¹⁴. The reasons for these discrepancies are unknown. We could find no heritability estimates for hip pain independent of radiographic hip OA.

In line with the high genetic contribution to hip OA, we observed a significant association between zygoty and OA progressing to arthroplasty of the hip joint, which was robust to the inclusion of sex, BMI and educational level in a Cox regression model. In contrast, no significant association could be observed for zygoty and knee arthroplasty except in imputed data. The differences in statistical significance from regression models for the two joint sites and the varying HR for knee arthroplasty are likely due to few concordant pairs for this joint site, leading to uncertainty. Indeed, the lower bound of the CI of the HR for zygoty was 1.90 for hip arthroplasty and 1.09 for knee arthroplasty in MI data. For risk of concordance for knee arthroplasty, we also found high and significant estimated HR for a high BMI. Since these analyses were adjusted for differences in genetics (by including zygoty), our findings may imply modifiable, environmental factors leading to a high BMI contribute more to knee OA than to hip OA. To our knowledge, no previous study has explored twin zygoty and concordance for OA taking the main modifiable risk factors into account.

The current findings may imply there is a greater potential for preventing severe knee OA than hip OA through maintaining a healthy BMI, shedding new light on the most powerful GWAS study performed in OA³⁰. In the arcOGEN study, one of the signals close to genome-wide significance was within the FTO gene, which is involved in the regulation of bodyweight. This GWAS study further found OA risk to differ between the hip and knee joint: a polymorphism can be associated with disease at the hip without showing any evidence of association at the knee³⁰. Hence, our epidemiological study may confirm and add nuance and context to results from genetic and molecular studies. The current study was of an exploratory nature, and future epidemiological family design studies should therefore further attempt to disentangle the causal association between genetics, OA, body weight, socioeconomic status, related lifestyle and lifestyle diseases.

Our findings with regard to education level and the need for joint arthroplasty confirm previous findings in genetically unrelated Nordic samples^{22,23}. However, previous studies not taking familial factors into account have shown obesity is associated both with hip and knee arthroplasty^{9,19}. Since BMI is a heritable trait³¹, the current study may imply that previous studies of BMI and arthroplasty of the hip joint to a greater extent have been confounded by unobserved common genetic factors than previous studies of arthroplasty of the knee¹⁹. Consistent with this theory,

we observed a higher MZ than DZ intra-pair correlation for BMI and education level (Table 1). This observation may further indicate that the central assumption of equal environments for MZ and DZ twins underlying the classical twin model is violated.

Due to the potential violation of the equal environment assumption, our results obtained from the classical twin model should be interpreted with caution. The study of genetic variance in categorical or time to event traits may also be criticized for depending on a range of other assumptions that are unverifiable, leading to high uncertainty of the estimates of genetic influence^{32–34}. We therefore believe the observable intra-pair differences and results from the Cox regression analyses should be weighted higher than those from the classical twin model in the current study. We included the classical twin model to allow for comparison to previous twin studies.

The main challenge in our study was the few pairs concordant for knee arthroplasty. A potential explanation may be the shorter observation time of 20 years compared to 27 years for the hip joints as well as the lower cumulative incidence for knee surgery than for hip surgery overall. There has also been an increase in the number of knee OA surgeries from the registry initiation till 2014, which may have contributed to a low knee OA concordance at the beginning of the observation time. However, the low concordance may also be due to a true lower heritability for knee OA than for hip OA¹⁷. We cannot rule out that other weaknesses of our study may have influenced the results. Inequalities may exist in the requirements for having OA surgery in different regions in Norway³⁵. MZ twins may to a lesser extent have moved apart and to a greater extent belong to the same operating hospital than DZ twins, potentially leading to an overestimated concordance among MZ twins in the present study. Similarly, joint arthroplasty is not OA itself, but a treatment decision, which may be more frequently simultaneously made by MZ than DZ twins. The decision to have joint arthroplasty may depend on differences in socioeconomic status and/or health inequalities and subsequent differences in demands to the joints that were not captured by our measure of education level²³. Our lack of work task data, activities performed in leisure time and willingness to undergo surgery is a limitation of our study. A final limitation of our study is the lack of inclusion of other risk factors for OA as well as the amount of missing data for BMI and education level. We indeed observed some minor differences in analyses on CC vs MI data.

In conclusion, we found differences in the genetic contribution to hip and knee arthroplasty due to OA. A higher MZ correlation is consistent with a contribution of genetic effects for hip OA. MZ and DZ differences in knee OA may be explained by more modifiable factors like a higher BMI.

Contributions

Karin Magnusson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Katrina Scurrah, Paulo Ferreira, Kåre Birger Hagen and Eivind Ystrøm contributed with conception and design, analyses and interpretation of data. Ragnhild Elise Ørstavik, Ólöf Anna Steingrimsdóttir, Thomas Nilsen and Anne Marie Fenstad, Ove Furnes contributed with acquisition of data and contributed in interpretation. All authors contributed in drafting the article or critically revising it for important intellectual content. All authors gave final approval for the version to be submitted.

Role of the funding source

The Norwegian Fund for Post-Graduate Training in Physiotherapy supported the work. The funder had no influence on the design or conduct of the study; collection, management, analysis, nor the interpretation of the data; preparation, review, or approval of the

manuscript; nor the decision to submit the manuscript for publication.

Competing interests

We declare no conflicts of interests, except for Dr. Scurrah reporting grants from the National Health and Medical Research Council (Australia), during the conduct of the study.

Acknowledgements

Standard acknowledgement to NTR and NAR: data were obtained from the Norwegian Twin Registry, Norwegian Institute of Public Health and the Norwegian Arthroplasty Registry, Dept. of Orthopaedic Surgery, Haukeland University Hospital.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.joca.2016.12.015>.

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