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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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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.

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 failed[3].

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 model[10]. 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 joints[13].

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 NorTwin OA study). The Norwegian Twin Registry was established in 2009 at the Norwegian Institute of Public Health[24]. 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 1994[25]. 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 yearly[26].

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/m^2) 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