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Nature vs nurture in knee osteoarthritis – the importance of age, sex and body mass index

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SUMMARY

Objective: (1) To estimate the life-time genetic contribution for knee osteoarthritis (OA) surgery and (2) to explore any differences in the genetic contribution across age, sex and body mass index (BMI).
Methods: We studied the sex-specific genetic contribution to knee OA surgery in a prospective cohort study of 62,490 twins aged 35 years or older with a follow-up period of up to 47 years (10,092 identical and 21,153 non-identical twin pairs, 54% women). To study interactions with age, we graphed the heritabilities over the lifespan for men and women. We also studied the sex-specific heritability across strata of the median BMI to explore any interactions with BMI.
Results: The overall heritability of knee OA surgery was 0.53 (95% confidence intervals [CI] = 0.31–0.75), with higher heritability among women (H^2 = 0.80 (95% CI = 0.73–0.87)) than men (H^2 = 0.39 (95% CI = 0.10–0.69)). For men, the heritability started to rise after age 68. The genetic contribution was particularly low in men above median BMI ($H^2_{\geq 23.7\ kg/m2}$ = 0.08, 95% CI = −0.32–0.48). For women, the heritability was consistently high from age 50 to death, independently of BMI ($H^2_{\geq 22.5\ kg/m2}$ = 0.77, 95% CI = 0.66–0.87).
Conclusion: There is a higher and more consistent genetic contribution for knee OA surgery in women than men. In men the genetic contribution was relatively low and varied with age and BMI.

Background

Knee osteoarthritis (OA) typically occurs in middle-aged and elderly. Women are more frequently affected and the disease is to a large extent associated with the modifiable risk factors obesity, joint injury and high occupational load[1]. The contribution of non-modifiable factors like familial factors including genetics and early life exposure is less well known. OA in the closest family members has been reported to increase the risk of future knee OA[2]. However, the relative importance of genetics vs other familial factors is still poorly understood.

Twin studies allow for the quantification of genetic vs environmental contribution to disease through the estimation of variance components[3]. In previous twin research of knee OA there was a wide distribution of the estimates of the genetic contribution, ranging from 6% to 84%[4–8]. Zhai *et al.* reported in studies of 128 and 618 twins that the genetic contribution to radiographic knee OA, cartilage volume and osteophytes were 65–84%[5,6]. In contrast, in a twin study of 250 women, a heritability for knee joint osteophytes of only 39% (95% confidence intervals [CI] = 26–52%) was reported[7]. Even lower heritabilities have been observed for a more clinically relevant OA definition; knee OA surgery was for 6% (95% CI = 0–56%) heritable in Denmark and 45% (95% CI = 30–58%) heritable in Norway[4,8].

The reasons for these varying estimates of genetic contribution may for instance be due to lack of precision, interactions with age and sex or the various OA definitions studied. As an example, a study of offspring of parents with and without knee OA surgery concluded that genetic factors were involved in the pathogenesis of knee pain but not of structural factors[9]. However, the study was much debated for not controlling for age and body mass index (BMI)[10,11]. Along this line, the genetic contribution to painful knee OA may also be hypothesized to interact with age, sex and BMI. Previous twin studies have indeed reported contrasting findings of

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the sex-specific heritability, which may be due to a low number of pairs concordant for knee OA[4,8], but also due to potential interaction with age and BMI. In a meta-analysis BMI was reported to be highly heritable (45–90%)[12]. Thus, BMI can be hypothesized to impact on heritability estimates of OA to a similar extent as age and sex do because BMI is often similar in twins.

Determining the genetic contribution to OA depending on BMI, age and sex is highly relevant as it may provide new and important insights into the potential for OA prevention. Thus, our aims were (1) to estimate the life-time genetic contribution for having knee OA surgery in men and women, respectively, and (2) to explore any differences in the genetic contribution across age, sex and BMI. To achieve our goals, we used the twin registry from Sweden, which is the world's oldest and largest of its kind.

Methods

Using a population-based prospective cohort design, we studied 80,740 twins born 1911 to 1980 included in the Swedish Twin Registry (STR). The STR was linked to the National Patient Register (NPR) to identify persons that had severe knee OA requiring surgery. Participants in the STR responded to postal questionnaire at the typical age of 20–50 years in the years 1961, 1963, 1967, 1970, 1973 and 1998–2002[13]. The NPR contains diagnostic codes of musculoskeletal disease obtained in specialist care from 1969 and onwards, including data on every hospitalization (from 1969 to 2016), 1-day surgery (from 1997 to 2016) and specialist outpatient care visits (from 2001 to 2016). Most of Sweden was covered by the NPR from 1969 to 1986 and full coverage was obtained from 1987.

In the current study, we included twins (reared together) aged 35 years or older with a minimum follow-up time of 1 year. For the same-sex twins, zygosity was determined based on questions about intra-pair physical similarities in childhood. Both twins in a pair were required to be alive in the year their county started to be covered by the NPR. If the twins were living in different counties, we started the follow-up in the earliest year from which they were both covered, ensuring that any left truncation was similar for both twins in the pair. Also, for inclusion in the study, the pairs were required to have complete data on BMI for both twins. BMI was calculated as kg/m^2 from the earliest adult reported height and weight in postal questionnaires. The study was approved by the Ethical Review Board at Lund University, Sweden.

Outcome – knee OA surgery

Incident knee OA surgery was defined from surgical codes with a corresponding diagnostic code for knee OA as a main diagnosis according to ICD-10, ICD-9 and ICD-8 system (i.e., codes M17, 715 and 713) from 1969 to 2016. We included the two typical surgical procedures that were performed for severe knee OA: osteotomy and primary total knee replacement. OA surgery may be used as a proxy for severe end stage OA as it has been shown that OA patients referred to surgery by orthopaedic surgeons have worse pain, worse physical function and worse radiographic OA than OA patients not referred to surgery[14]. Joint replacement surgery is also an established outcome in OA research, which is not prone to misclassification. We treated knee OA surgery as a time-to-event variable. A twin exited the study at the date of first knee OA surgery or when he or she died. Twins who did not have knee OA surgery or did not die prior to study end were censored at December 31st, 2016.

Statistical analyses

To determine the lifetime genetic contribution for knee OA surgery, we estimated the heritability from the classical ACE/ADE twin model with liability threshold as previously described[15]. In an ACE/ADE-model, "A" represents additive genetics, "C" represents environmental factors shared between twins in a pair, "D" represents dominant genetics and "E" represents environmental factors unique to the twins in a pair[3]. To account for the right censored data due to study end at different ages, and to allow for a time-independent estimation of the different variance components, we used inverse probability weighting[15]. In doing so, we used a competing risk approach and classified knee OA surgery and death as different types of failures to ensure same censoring (study end) for both twins[16]. We compared the different models (ACE, ADE and AE models) using the Akaike Information Criteria (AIC), variance components estimates and intra-pair correlations. Heritability estimates might be inflated by factors shared by twins in a pair, like BMI, which is genetically and environmentally determined. BMI was adjusted for in a separate analysis.

To provide more detail and validate our findings without the modeling assumptions required for estimating the heritability, we estimated the cumulative casewise concordance as well as intra-pair correlations for monozygotic (MZ) and dizygotic (DZ) twins using a biprobit model as previously described[16]. The casewise concordance is the probability that the second twin has knee OA surgery given that the first twin has knee OA surgery and that the second twin is alive. The cumulative casewise concordance is this probability at a given age. Since MZ twins share 100% of genes and DZ twins 50%, any differences in dependence measures between MZ and DZ twins may provide information on the contribution of genetic factors and/or the type of contribution (additive genetics vs dominant genetics). Thus, we also studied patterns of intra-pair correlations (rMZ:rDZ ratio) using the biprobit model for inference on the type of genetic contribution.

To infer whether the genetic contribution to knee OA surgery interacted with age and sex, we graphed the heritability and cumulative casewise concordance over the lifespan for MZ and DZ men and women separately. To study whether any sex differences were quantitative or qualitative, we graphed the cumulative casewise concordance for opposite-sex vs same-sex DZ twins. Finally, to explore interactions with BMI, we studied the sex-specific heritability in different BMI strata (below and above the sex-specific median of the pair mean BMI, i.e., both twins in a pair were in the *same* BMI strata). All analyses were performed using the METS package in R (The R Project for Statistical Computing), v. 3.4.1.

In a sensitivity analysis, we repeated the analyses with an alternative outcome definition, i.e., having a diagnostic code of knee OA (codes M17, 715 and 713) without requiring surgery.

Results

In total 80,740 twins were in the eligible age, of which 69,930 in complete pairs (Fig. 1). Of these, 62,490 twins (31,245 pairs) were in pairs with both twins alive at start of follow-up and had complete pair-level data on BMI (Fig. 1). Of the included twins, 1892 (3%) had knee OA surgery and 18,110 (29%) died during follow-up. The incidence rates of knee OA surgery per 1000 person-years were 1.15 (95% CI = 1.10–1.20) for the cohort and 1.11 (95% CI = 1.03–1.18) and 1.18 (95% CI = 1.11–1.26) for men and women, respectively, with similar rates for MZ and DZ twins. The incidence rates rose with increasing age for both men and women (eTable 1). Twins with knee OA surgery had a higher BMI and the concordance for MZ pairs was higher than for DZ pairs (Table I).

Heritability

The overall heritability of knee OA surgery was 0.53 (95% CI = 0.31–0.75), with a higher heritability for women (H^2 = 0.80

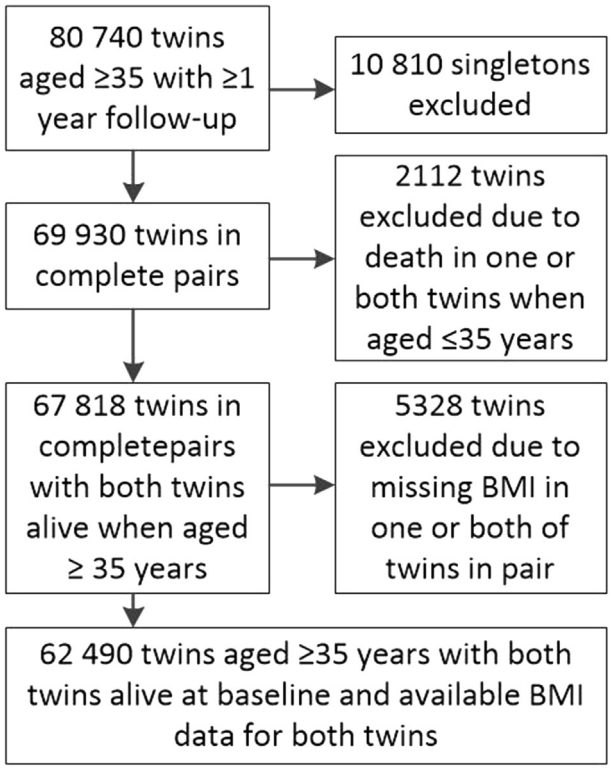

Fig. 1. Flowchart showing the numbers of included and excluded twins.

[95% CI = 0.73–0.87]) than for men (H^2 = 0.39 [95% CI = 0.10–0.69]). For men, the heritability (estimated from ACE model) was low until age 68, from which it started to rise (Fig. 2). For women, the heritability (estimated from AE model) was consistently high from age 50 to death (Fig. 3). The intra-pair correlations indicated additive genetics for men (rMZ:rDZ ratio = 2:1, i.e., rMZ = 0.66, 95% CI = 0.58–0.74 vs rDZ = 0.31, 95% CI = 0.18–0.42), and more dominant genetics for women (rMZ:rDZ ratio = 3:1, i.e., rMZ = 0.64, 95% CI = 0.55–0.71 vs rDZ = 0.20, 95% CI = 0.09–0.31)). For men, additive genetics were confirmed when comparing AIC for the additive (ACE) vs dominant genetic models (ADE) (eTable 1). For women, there were only minor differences in model fit and we chose the AE/ADE model (having similar estimates), because dominant genetic variation ("D") might often be masked by shared environment ("C) in twin and family studies, as well as inflate the "A" component in AE models (eTable 2)[17]. Findings were similar when the analyses were repeated for having a diagnostic code of knee OA (n = 2827, eFig. 1, eFig. 2), with the overall heritability of having a diagnostic code being slightly lower (overall: H^2 = 0.59 [95% CI = 0.40–0.78] (ACE-model), men; H^2 = 0.59 [95% CI = 0.28–0.91] (ACE-model), women; H^2 = 0.66 [95% CI = 0.58–0.74] (AE-model).

Impact of BMI

Similar Results were also observed when adjusting the heritability analyses of knee OA surgery for BMI (H^2_{women} = 0.80, 95% CI = 0.73–0.87, H^2_{men} = 0.38, 95% CI = 0.09–0.68). Thus, suggesting no or very limited bias introduced by confounding by BMI or due to conditioning on BMI as a collider[18]. To study interactions, men and women were divided into below and above sex-specific median BMI 23.7 kg/m^2 and 22.5 kg/m^2, respectively. For women, the heritability was consistently high both below and above median BMI (Table II). For men, the stratum specific heritability could not be precisely estimated as the CI overlapped 0 and/or 1 (Table II). This is likely due to the similar intra-pair correlations for MZ and DZ twins (Table II), which is consistent with no or only a low genetic contribution. Inconclusive results for men but not for women could also be seen in analyses using a diagnostic code of knee OA as outcome (eTable 3).

Sex-differences in cumulative casewise concordance

The sex-differences in heritability with increasing age were reflected in the MZ and DZ cumulative casewise concordance graphs,

Table I
Participants' characteristics

	All	Men		Women	
		No knee OA surgery	Knee OA surgery	No knee OA surgery	Knee OA surgery
Twin individual level	**n = 62,490**	**n = 27,941**	**n = 834**	**n = 32,657**	**n = 1058**
Age at start of follow-up, median (IQR)	35 (35–45)	35 (35–45)	37 (35–46)	35 (35–45)	41 (35–49)
Age at BMI reporting, median (IQR)	39 (29–47)	39 (29–47)	41 (31–53)	39 (29–46)	42 (33–52)
Primary school (≤9 years), n (%)	21,676 (34.7)	9958 (35.6)	370 (44.4)	10,901 (33.4)	447 (42.3)
Upper secondary school (1–4 years), n (%)	23,903 (38.3)	10,792 (38.6)	326 (39.1)	12,354 (37.8)	431 (40.7)
College/university (>1 years), n (%)	16,911 (27.1)	7191 (25.7)	138 (16.6)	9402 (28.8)	180 (17.0)
Length, cm, mean (SD)	170.6 (0.9)	178 (0.8)	178 (0.7)	165 (0.6)	165 (0.6)
Weight, kg, mean (SD)	68.1 (13.6)	75 (12.8)	79 (11.3)	61 (10.4)	67 (11.8)
BMI, kg/m^2, mean (SD)	23.3 (3.5)	24 (3.2)	25 (3.2)	23 (3.6)	25 (4.1)
Overweight (25–29.9 kg/m^2), n (%)	16,948 (27.1)	88,139 (29.1)	339 (40.7)	5515 (16.9)	368 (34.8)
Obesity (≥30 kg/m^2), n (%)	2587 (4.1)	1131 (4.1)	63 (7.6)	1290 (4.0)	103 (9.7)
Pair level, MZ pairs	**N = 10,092**	**N = 4210**	**N = 214**	**N = 5406**	**N = 262**
MZ pairs discordant for surgery, N (%)			174 (81.1)		221 (84.4)
MZ pairs concordant for surgery, N (%)			40 (18.7)		41 (15.6)
Pair level, same-sex DZ pairs	**N = 13,661**	**N = 5897**	**N = 321**	**N = 6978**	**N = 465**
DZ pairs discordant for surgery, N (%)			304 (94.7)		446 (95.9)
DZ pairs concordant for surgery, N (%)			17 (5.3)		19 (4.1)
Pair level, opposite-sex DZ pairs	**N = 7492***	**N = 7004***	**N = 488***	**N = 7004***	**N = 488***
DZ pairs discordant for surgery, N (%)			463 (94.9)		463 (94.9)
DZ pairs concordant for surgery, N (%)			25 (5.1)		25 (5.1)

MZ; monozygotic, DZ; dizygotic, BMI; body mass index. Lower case n represents individuals, upper case N represents pairs.
* Pairs consisting of male and female twins, i.e., similar N (%) presented for men and women.

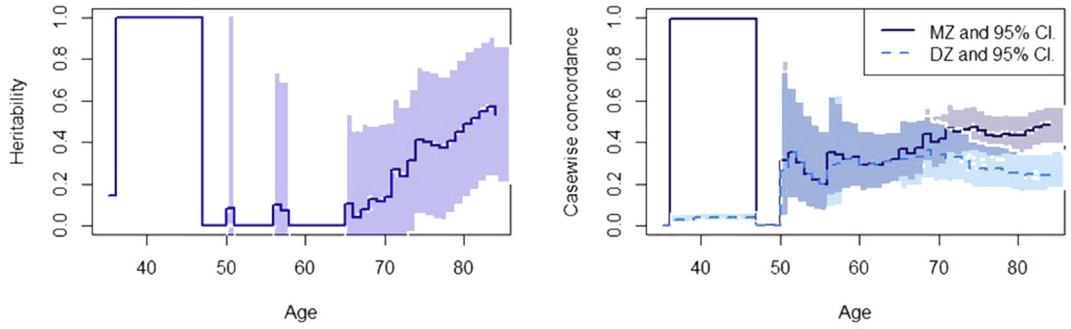

Fig. 2. For men: The heritability and cumulative casewise concordance graphs for monozygotic (MZ) and dizygotic (DZ) twins from age 35 to knee osteoarthritis surgery with 95% confidence intervals (CI). The largely varying estimates and lack of confidence intervals [CI] until age 50 reflects that very few pairs could be observed that were concordant for knee OA surgery.

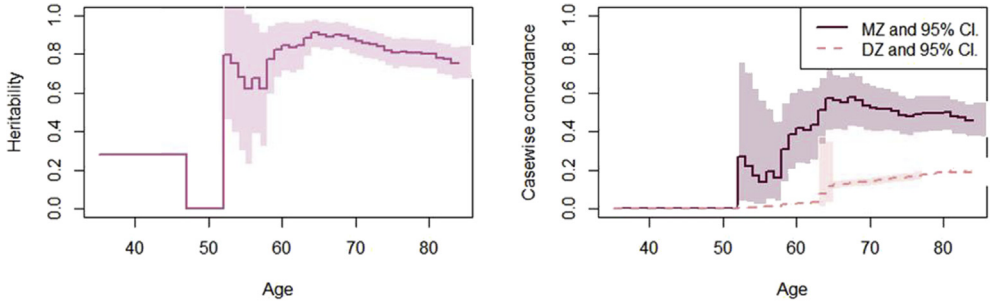

Fig. 3. For women: The heritability and cumulative casewise concordance graphs for monozygotic (MZ) and dizygotic (DZ) twins from age 35 to knee osteoarthritis surgery with 95% CI. The varying estimates and lack of CI until age 50 reflects that very few pairs could be observed that were concordant for knee OA surgery.

Table II
Intra-pair correlations and heritability for having knee OA surgery within different strata of sex and body mass index (BMI)

	Men		Women	
	N concordant pairs/total N of pairs	Estimate (95% CI)	N concordant pairs/total N of pairs	Estimate (95% CI)
Below median BMI*				
MZ	19/2511	$r = 0.91$ (0.76–0.97)	12/3251	$r = 0.88$ (0.70–0.96)
DZ	8/3579	$r = 0.61$ (0.25–0.82)	2/3985	$r = 0.44$ (0.38–0.50)
Heritability		$H^2 = 0.59$ (−0.00–1.19)		$H^2 = 0.88$ (0.77–0.99)
Above median BMI*				
MZr	21/1913	$r = 0.72$ (0.58–0.83)	29/2417	$r = 0.77$ (0.64–0.85)
DZr	9/2639	$r = 0.68$ (0.49–0.81)	17/3458	$r = 0.38$ (0.33–0.43)
Heritability		$H^2 = 0.08$ (−0.32–0.48)		$H^2 = 0.77$ (0.66–0.87)

* BMI as a shared factor: Sex-specific median of pair mean BMI, i.e., 23.7 kg/m^2 for men and 22.5 kg/m^2 for women. For men, we fitted ACE models and for women we fitted AE models according to the observed correlational ratio between MZ and DZ twins as well as the Akaike Information Criteria. MZ; monozygotic, DZ; dizygotic, r; correlation coefficient, BMI; body mass index, CI; confidence intervals.

i.e., when the twin model assumptions were relaxed and we applied the biprobit model (Figs. 2 and 3). Opposite-sex DZ twins had a similar cumulative casewise concordance as same-sex DZ twins, indicating no qualitative sex-differences. Hence, there was no evidence that differences in characteristics that are unique to each gender (such as e.g., hormonal factors) contribute to knee OA surgery (Fig. 4). This is consistent with only quantitative sex differences being of relevance, implying that the *same* genetic and environmental factors impact on the risk of knee OA surgery in men and women. A similar pattern could be observed when applying having a diagnostic code of knee OA as outcome (eFig. 3).

Discussion

In the current study we used the world's largest twin registry in order to estimate the genetic contribution to knee OA surgery. We found an overall heritability of 53% but with important interactions with sex, age and BMI. For men, there was little evidence of any genetic contribution to knee OA surgery until age 68, from when it started to rise. The genetic contribution seemed particularly low in men having higher BMI. Interestingly, for women, the genetic contribution was consistently high from age 50 independently of BMI.

Our study of more than 60,000 twins followed up to 47 years from age 35 is the first study to estimate the genetic contribution to a clinically-relevant definition of knee OA across age, sex and BMI. Our study thus sheds new light on the reported age- and sex-differences in the Danish and Norwegian Twin Registries. Similar as to our study, the genetic contribution to knee OA surgery in men was lower than that for knee OA surgery in women in Denmark[4]. However, only one MZ male pair was observed that was concordant for knee OA surgery in the Danish study, yielding very high uncertainty[4]. Similarly, Norwegian studies reported a higher heritability of knee OA surgery in young than elderly, yet the differences

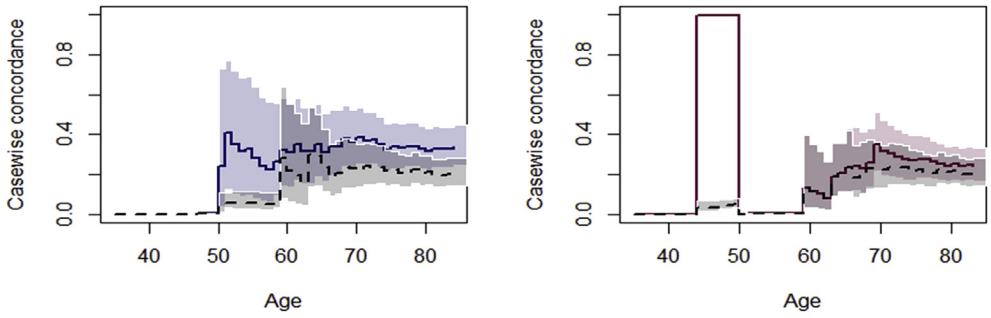

Fig. 4. The cumulative casewise concordance graphs for same-sex dizygotic (SS DZ) male twins (blue solid line), SS DZ female twins (red solid line) and opposite-sex dizygotic (OS DS) twins (black dashed line) from age 35 to knee osteoarthritis surgery with 95% CI. The varying estimates and lack of CI until age 50 reflects that very few pairs could be observed that were concordant for knee OA surgery.

in age could not be studied in sex-specific analyses due to the small sample size[8]. Importantly, using a longer follow-up time and a higher number of twins, we could nuance previous findings. Additionally, we could also adjust for one of the most important risk factors for knee OA, namely BMI.

The differences in genetic contribution across age for men and women provide new insights into the etiology of severe end-stage knee OA. It can be hypothesized from Fig. 2 that mainly non-shared, individual factors account for knee OA surgery in men up to age 68, with examples of causes being knee injury and/or individual adult lifestyle or occupational factors not shared by the twins. In the current study, adjustment for BMI, i.e., reducing the amount of unobserved variance and accounting for an inflated heritability by more similarly shared BMI in MZ than DZ twins did not essentially alter the heritability estimate. However, when BMI was treated as a *shared* factor, i.e., the heritability was studied separately for pairs with high vs low BMI, the heritability could not be precisely estimated although there were indications for a higher heritability in the low BMI group than the high BMI group. This pattern may be due to potential qualitative differences between men with low and high BMI, because those with high BMI may have different causal mechanisms explaining knee OA surgery than those with low BMI[3]. Examples may be the potential excess risk due to interaction with malalignment of the knee and BMI[19] in the high BMI group and potentially more isolated effects of knee injury, caused by heritable factors or sports, in the low BMI group.

The heritability for knee OA surgery was consistently high across age and BMI in women. However, this does not exclude any impact of modifiable environmental factors. In a cross-sectional study of 785 British female twins the authors reported that the strong association between BMI and radiographic knee OA was not mediated by genetic factors[20]. Our study sheds new light on these findings by proposing no or very limited interaction between heritability and BMI in women. Along this line, studying the impact of familial confounding as previously done for radiographic knee OA, as well as OA surgery of the hip may provide deeper insights into the prevention potential of knee OA progressing to a need for OA surgery by reducing BMI[20,21]. We recently reported that the effect of BMI on OA surgery of the hip in women could not be explained by familial confounding due to shared genetics or shared environmental factors; hence we concluded the association was likely causal[21].

Our analyses of same-sex and opposite-sex DZ pairs indicated no qualitative sex differences, i.e., there was no evidence that knee OA surgery was explained by characteristics unique to each gender such as hormonal factors. This is in line with the largest genome-wide association study performed in OA to date[22]. However, since our Results revealed a much higher genetic contribution to knee OA than observed in most previous studies particularly for women[4–8], qualitative sex differences in the etiology of severe end-stage OA or behavioral differences towards the decision to have surgery cannot be excluded. When we repeated the analyses using a diagnostic code of knee OA as outcome, we observed a slight attenuation of heritability estimates. In that regard, our findings among women may indeed be due to a true high direct genetic contribution to knee OA surgery, but may also be explained by other factors that are differently shared by female MZ and DZ twins such as menopausal age or more communication within a female than male MZ twin pair. It may be hypothesized that familial factors determine the menopausal age and/or amount of communication regarding health decisions particularly for women, i.e., causing a particularly high concordance for knee OA surgery among female MZ twins. Unfortunately, we had no data allowing for adjustment for female hormonal levels, behavioral or pain-related traits nor any potentially more shared communication on treatment decisions in women.

Some important limitations should be mentioned. First, we studied relatively late-stage OA in specialist care, which may be affected by people's hesitance to undergo surgery. Hence, we cannot infer whether our findings also apply to early knee OA. Second, knee OA surgery involves an important treatment decision and has in Sweden been reported to be associated with socioeconomic factors[23]. Due to the known differences in shared behavior of MZ vs DZ twins, also the decision to have surgery may more often be made in common by MZ than DZ twins (depending or not depending on socioeconomic status), leading to a violation of the equal environment assumption[17]. In general, the ACE/ADE twin model has low power to distinguish between the genetic contribution and the shared environmental contribution and we cannot exclude that shared decision making has inflated our heritability estimates for knee OA surgery. When repeating the analyses for having a diagnostic code of knee OA, a slight attenuation of the heritability estimates could be observed particularly for women. However, we believe that diagnostic codes are less well-defined outcomes that are more prone to misclassification than surgery codes. Any misclassification may have an additional impact in twin designs due to two individuals rather than one being misclassified[24]. In our study, misclassification may also have affected our BMI measures as they were self-reported, potentially leading to a risk of underestimation of body weight[25]. We included BMI for early adult ages and cannot exclude that the BMI at higher ages is of greater importance than the BMI at young age in the interaction with genetics. A final limitation we would like to bring to attention is the left truncated data, i.e., we could not observe all twins from age 35 years. This was though taken into account by including both twins from the same year they were both covered by the NPR, hence we do not expect this limitation to have impacted on our estimates.

In conclusion, we found a much higher and more consistent genetic contribution to knee OA surgery in women than men. Knee OA surgery in women had a strong genetic component already from age 50, independently of BMI. In men, knee OA surgery seemed to a larger extent to be determined by environmental factors like BMI at least until about age 70 when heritability started to rise.

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. Karin Magnusson performed statistical analyses and drafted the manuscript. Aleksandra Turkiewicz and Martin Englund contributed with acquisition of data, conception design, analyses and interpretation of data. 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.

Conflict of interest

We declare no conflict of interest, except for Dr. Englund reporting grants from The Swedish Research Council, grants from Österlund Foundation, grants from Governmental Funding of Clinical Research within National Health Service (ALF), grants from Greta and Johan Kock Foundations, grants from The Swedish Rheumatism Association, during the conduct of the study.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2018.12.018.

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