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BRIEF REPORT

The Maternal and Paternal Effects on Clinically and Surgically Defined Osteoarthritis

Eirik Weldingh,[1] Marianne Bakke Johnsen,[2] Kåre Birger Hagen,[3] Nina Østerås,[4] May Arna Risberg,[1] Bård Natvig,[1] Barbara Slatkowsky-Christensen,[4] Anne Marie Fenstad,[5] Ove Furnes,[6] Lars Nordsletten,[2] and Karin Magnusson[7]

Objective. It is currently unknown whether osteoarthritis (OA) is inherited mainly from the mother, father, or both. This study was undertaken to explore the effect of maternal and paternal factors on hip, knee, and hand OA in offspring.

Methods. Participants from the Musculoskeletal Pain in Ullensaker Study (MUST) (69% female; mean ± SD age 64 ± 9 years) and a Norwegian OA twin study (Nor-Twin) (56% female; 49 ± 11 years) reported whether their mother and/or father had OA. Using a recurrence risk estimation approach, we calculated whether maternal and paternal OA increased the risk of 1) surgically defined hip and knee OA (i.e., total joint replacement) and 2) clinically defined hip, knee, and hand OA (i.e., the American College of Rheumatology criteria) using logistic regression. Relative risks (RRs) with 95% confidence intervals (95% CIs) were calculated.

Results. Maternal OA consistently increased the risk of offspring OA across different OA locations and severities. Having a mother with OA increased the risk of any OA in daughters (RR 1.13 [95% CI 1.02–1.25] in the MUST cohort; RR 1.44 [95% CI 1.05–1.97] in the Nor-Twin cohort) but not (or with less certainty) in sons (RR 1.16 [95% CI 0.95–1.43] in the MUST cohort; RR 1.31 [95% CI 0.71–2.41] in the Nor-Twin cohort). Having a father with OA was less likely to increase the risk of any OA in daughters (RR 1.00 [95% CI 0.85–1.16] in the MUST cohort; RR 1.52 [95% CI 0.94–2.46] in the Nor-Twin cohort) and sons (RR 1.08 [95% CI 0.83–1.41] in the MUST cohort; RR 0.93 [95% CI 0.35–2.48] in the Nor-Twin cohort).

Conclusion. OA in the mother increased the risk of surgically and clinically defined hip, knee, and hand OA in offspring, particularly in daughters. Our findings imply that heredity of OA may be linked to maternal genes and/or maternal-specific factors such as the fetal environment.

INTRODUCTION

The etiology of hip, knee, and hand osteoarthritis (OA) is multifactorial, with familial factors playing a major role in disease development. Several studies have consistently demonstrated a strong genetic contribution to hip and hand OA (1–3). For the knee joint, familial OA in any joint, as well as other risk factors, predicts the future risk of having knee arthroplasty due to OA and a diagnostic code of knee OA (4).

Previous studies of familial aggregation have largely focused on the estimation of the broad-sense heritability using twin and sibling designs (1,3,5). However, this heritability alone may not be informative in the clinical setting as it cannot predict disease risk associated with the presence of OA in a family member, such as in the father or mother. The maternal versus paternal effects on the risk of mild-to-severe OA of the hip, knee, and hand joints are also unclear. To our knowledge, there are no studies exploring whether OA is mainly inherited from the mother or the father.

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[1]Eirik Weldingh, MD, May Arna Risberg, PT, PhD, Bård Natvig, MD, PhD: Oslo University Hospital, Oslo, Norway; [2]Marianne Bakke Johnsen, PT, PhD, Lars Nordsletten, MD, PhD: Oslo University Hospital and University of Oslo, Oslo, Norway; [3]Kåre Birger Hagen, PT, PhD: Norwegian Institute of Public Health and Diakonhjemmet Hospital, Oslo, Norway; [4]Nina Østerås, PT, PhD, Barbara Slatkowsky-Christensen, MD, PhD: Diakonhjemmet Hospital, Oslo, Norway; [5]Anne Marie Fenstad, MSc: Haukeland University Hospital, Bergen, Norway; [6]Ove Furnes, MD, PhD: Haukeland University Hospital and University of Bergen, Norway; [7]Karin Magnusson, PT, PhD: Diakonhjemmet Hospital, Oslo, Norway, and Lund University, Lund, Sweden.

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Address correspondence to Karin Magnusson, PT, PhD, Diakonhjemmet Hospital, National Advisory Unit on Rehabilitation in Rheumatology, PO Box 23, Vinderen, 0319 Oslo, Norway. E-mail: karin.magnusson@med.lu.se.

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A parent-of-origin approach in OA risk estimation may provide information on where to search for genetic or fetal environmental factors in future studies on the etiology of OA. Improved knowledge of familial risk (i.e., whether OA in the mother or father increases the risk of OA in male or female offspring) may also further improve total risk prediction in OA and facilitate disease prevention (4). We investigated maternal and paternal effects on moderate-to-severe definitions of hip, knee, and hand OA using a recurrence risk estimation approach. To allow interpretation of our findings in relation to the results of previous studies, these effects were compared to the sibling effect.

PATIENTS AND METHODS

Study subjects and data collection. Data were obtained from 2 population-based cohorts: 1) the Musculoskeletal Pain in Ullensaker Study (MUST), a cross-sectional study of 630 persons ages 40–79 years with self-reported OA who attended a clinical examination between 2010 and 2013 (6), and 2) the Norwegian OA twin study (Nor-Twin), a longitudinal study of a sub-cohort of 7,175 persons (of a total of 18,058) ages 30–75 years in 1990 who responded to questionnaires between 1990 and 1998 (1). Information on maternal, paternal, and sibling/twin OA was self-reported at baseline in both studies (a yes/no answer to the question, "Did your mother/father/sibling have OA?"). For the MUST cohort, data on clinically defined hip, knee, and hand OA and on total joint replacement (TJR) due to OA in offspring were obtained at a clinical joint examination by an experienced rheumatologist (BSC). For the Nor-Twin cohort, data on surgically treated OA of the hips and knees were obtained through linkage (in 2015) to the Norwegian Arthroplasty Register (7), which includes >95% of all prosthesis surgeries in Norway with information on reason and date of surgery (since 1987 and 1994 for hip and knee surgeries, respectively). Both the MUST and Nor-Twin studies were approved by the Regional Ethics Committee (Oslo, Norway).

Outcome measure definitions. Clinical OA of the hip, knee, and hand joints was defined according to the American College of Rheumatology (ACR) criteria (8–10) and based on a thorough examination of soft tissue swelling, bony enlargement, joint tenderness, and reduced joint mobility (6). Visible osteophyte presence on radiographs was also required for defining knee OA, whereas an erythrocyte sedimentation rate (ESR) of <20 mm/hour, joint space narrowing, and visible osteophyte presence on radiographs was required for defining hip OA (6). We defined surgical OA as an individual having had TJR due to primary OA in the left or right hip or knee (at any date until the examination date for the MUST cohort and until 2015 for the Nor-Twin cohort) (1,6). Full data on surgery of the hand joints were lacking and thus not analyzed in the current study.

Statistical analysis. We calculated the relative risk (RR) of recurrence (with 95% confidence intervals [95% CIs]), which is a prospective measure of risk used for counseling. RR can be estimated as the offspring's risk of disease with the presence of disease in a sibling/parent divided by the offspring's risk of disease without the presence of disease in a sibling/parent. We used logistic regression to estimate RR for the following OA outcomes: clinically defined hip, knee, and hand OA (MUST cohort only) and surgically defined hip and knee OA (MUST and Nor-Twin cohorts). We studied the 2 OA definitions as mutually exclusive groups to account for the fact that OA frequently presents as a generalized disease (11). Thus, as an example, people who had TJRs did not fulfill the ACR criteria for OA in other joints. Similarly, the control group without the OA definition in question was also free of any OA at any other site. In this manner, the control group was similar for all OA definitions in question, and thus similar for all analyses.

The relatives' disease status included OA present in mothers, fathers, and siblings. In the Nor-Twin study, offsprings' siblings were either identical twins or fraternal twins of the same sex. In stratified analyses, we explored whether OA was mainly transmitted from parent to daughter and/or from parent to son. Adjustment for confounding or mediation was not relevant because the effect estimate represents an indirect effect between individuals rather than a direct or total causal effect within the individual (12). All analyses were performed using Stata MP, version 14.0.

RESULTS

The MUST study cohort was generally older, included a higher proportion of women, had attained a higher level of education, had higher body mass index levels, and had a lower proportion of smokers than the Nor-Twin study cohort (Table 1). The prevalence

Table 1. Demographic and clinical characteristics of the study participants*

	MUST (n = 630)	Nor-Twin (n = 7,184)
Age, mean ± SD years	63.9 ± 8.8	49.1 ± 10.9
Sex, female	437 (69.4)	4,034 (56.2)
College/university education	178 (28.3)	1,316 (18.3)
Body mass index, mean ± SD kg/m^2	28.0 ± 4.8	22.6 ± 2.9
Current smoker	95 (15.2)	2,777 (38.7)
Offspring		
Hip OA, ACR†	103 (16.4)	–
Hip OA, surgery‡	60 (9.5)	255 (3.6)
Knee OA, ACR†	116 (18.4)	–
Knee OA, surgery‡	48 (7.6)	133 (1.9)
Hand OA, ACR†	328 (52.1)	–
Familial OA		
Mothers with OA	235 (37.3)	767 (10.7)
Fathers with OA	83 (13.2)	320 (4.5)
Siblings with OA	148 (23.5)	140 (2.0)

* Except where indicated otherwise, values are the number (%). MUST = Musculoskeletal Pain in Ullensaker Study; Nor-Twin = Norwegian Twin Osteoarthritis Study.
† As defined in the American College of Rheumatology (ACR) criteria for the classification of osteoarthritis (OA).
‡ Defined as a participant having had a total joint replacement due to primary OA in the left or right hip or knee.

Table 2. Familial recurrence of surgically defined OA in the MUST and the Nor-Twin cohorts*

	Hip OA				Knee OA			
	MUST		Nor-Twin		MUST		Nor-Twin	
Family relationship	Prevalence, no./total no. (%)	RR (95% CI)	Prevalence, no./total no. (%)	RR (95% CI)	Prevalence, no./total no. (%)	RR (95% CI)	Prevalence, no./total no. (%)	RR (95% CI)
Mother								
No OA	35/155 (22.6)	1.00 (referent)	221/6,062 (3.6)	1.00 (referent)	24/144 (16.7)	1.00 (referent)	113/5,954 (1.9)	1.00 (referent)
With OA	25/71 (35.2)	1.56 (1.02–2.40)	34/649 (5.2)	1.44 (1.02–2.04)	24/70 (34.3)	2.06 (1.26–3.35)	20/635 (3.2)	1.66 (1.04–2.65)
Father								
No OA	53/198 (26.8)	1.00 (referent)	245/6,448 (3.8)	1.00 (referent)	40/185 (21.6)	1.00 (referent)	122/6,235 (1.9)	1.00 (referent)
With OA	7/28 (25.0)	0.93 (0.47–1.84)	10/263 (3.8)	1.00 (0.54–1.86)	8/29 (27.5)	1.28 (0.67–2.44)	11/264 (4.2)	2.16 (1.18–3.95)
Siblings								
No OA	41/180 (22.8)	1.00 (referent)	245/6,645 (3.7)	1.00 (referent)	127/6,527 (2.0)	1.00 (referent)	33/172 (19.2)	1.00 (referent)
With OA	19/46 (41.3)	1.81 (1.17–2.81)	10/66 (15.2)	4.11 (2.29–7.37)	6/62 (9.7)	1.86 (1.12–3.10)	15/42 (35.7)	4.97 (2.28–10.85)

* RR = relative risk; 95% CI = 95% confidence interval (see Table 1 for other definitions).

of OA was higher in the MUST cohort, which was expected due to all participants having self-reported OA. However, upon clinical examination, 166 participants had no OA according to the ACR criteria or any OA-related surgery in any joint and were included in the disease-free control group. Disease-free controls in the Nor-Twin cohort had no self-reported OA (unspecified site) or surgery due to hip or knee OA (n = 6,456). To evaluate the impact of selection of all persons self-reporting OA in the MUST cohort, we studied whether familial OA was associated with self-reported OA among offspring (nonspecific site) in the Nor-Twin OA cohort. In these analyses, maternal OA (RR 3.10 [95% CI 2.54–3.79]), paternal OA (RR 3.29 [95% CI 2.55–4.25]), and sibling OA (RR 11.35 [95% CI 9.51–13.53]) increased the risk of self-reported OA by offspring.

Having a mother or a sibling with OA increased the risk of OA-related hip surgery by 44–56% in the MUST and Nor-Twin cohorts (Table 2). The most clearly elevated risk was observed for OA-related knee surgery in those with maternal OA, and for OA-related knee surgery, risk also increased (by 28–116%) in those with paternal OA (Table 2). However, for OA-related knee surgery, there was a difference in effect estimates as well as precision for the MUST cohort versus the Nor-Twin cohort reported in Table 2, potentially due to fewer observations in the MUST study than in the Nor-Twin study.

Paternal OA consistently did not increase the risk of OA-related hip surgery (Table 2), and it also did not increase the risk of clinically defined knee, hip, or hand OA in offspring (Table 3). In contrast, maternal OA increased the risk of offspring clinical hip and hand OA by 21–38%, and sibling/twin OA increased the risk of offspring knee and hand OA by 26–44% (Table 3). Due to a low number of subjects, we did not attempt to study identical and fraternal twins separately.

With the generally consistent findings for maternal and paternal OA and the specific OA definitions, we grouped all types of OA together when analyzing the parent–daughter and

Table 3. Familial recurrence of clinically defined OA in the MUST trial*

	Hip OA		Knee OA		Hand OA	
Family relationship	Prevalence, no./total no. (%)	RR (95% CI)	Prevalence, no./total no. (%)	RR (95% CI)	Prevalence, no./total no. (%)	RR (95% CI)
Mother						
No OA	62/182 (34.1)	1.00 (referent)	72/192 (37.5)	1.00 (referent)	192/312 (61.5)	1.00 (referent)
With OA	41/87 (47.1)	1.38 (1.02–1.87)	44/90 (48.8)	1.30 (0.98–1.72)	136/182 (70.1)	1.21 (1.07–1.37)
Father						
No OA	86/231 (37.2)	1.00 (referent)	98/243 (40.3)	1.00 (referent)	282/427 (66.0)	1.00 (referent)
With OA	17/38 (44.7)	1.20 (0.81–1.78)	18/39 (46.2)	1.14 (0.79–1.66)	46/67 (68.7)	1.04 (0.87–1.24)
Siblings						
No OA	81/220 (36.8)	1.00 (referent)	84/223 (37.7)	1.00 (referent)	230/369 (62.3)	1.00 (referent)
With OA	22/49 (44.8)	1.22 (0.86–1.74)	32/59 (54.2)	1.44 (1.08–1.92)	98/125 (78.4)	1.26 (1.11–1.42)

* RR = relative risk; 95% CI = 95% confidence interval (see Table 1 for other definitions).

parent–son associations (surgical and clinical OA in any joint for the MUST cohort; surgical OA in any joint for the Nor-Twin cohort). Having a mother with OA consistently increased the risk of any OA in daughters (RR 1.13 [95% CI 1.02–1.25] in the MUST cohort; RR 1.44 [95% CI 1.05–1.97] in the Nor-Twin cohort), and (though with less certainty) in sons (RR 1.16 [95% CI 0.95–1.43] in the MUST cohort; RR 1.31 [95% CI 0.71–2.41] in the Nor-Twin cohort) (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41023/abstract). In contrast, having a father with OA did not increase the risk of any OA in daughters (RR 1.00 [95% CI 0.85–1.16] in the MUST cohort; RR 1.52 [95% CI 0.94–2.46] in the Nor-Twin cohort) or in sons (RR 1.08 [95% CI 0.83–1.41] in the MUST cohort; RR 0.93 [95% CI 0.35–2.48] in the Nor-Twin cohort) (Supplementary Table 1 at http://onlinelibrary.wiley.com/doi/10.1002/art.41023/abstract). These findings were confirmed in the MUST cohort for clinical OA of the hand, which was the most prevalent OA location/definition in our study (Supplementary Table 2 at http://onlinelibrary.wiley.com/doi/10.1002/art.41023/abstract).

DISCUSSION

In our study of 2 population-based Norwegian cohorts, we found that moderate-to-severe OA at any site, as well as OA in the hip and hand joints in offspring, may be inherited from the mother rather than from the father. Maternal OA also consistently increased the risk of offspring knee OA, whereas risk estimates for knee OA in offspring with paternal OA were more inconclusive. Finally, we found that OA at any site may most likely be transmitted to offspring if the offspring is a daughter.

Our findings shed new light on previous studies of familial OA clustering. We showed for the first time that OA is more common in individuals with a mother affected with OA than in individuals with a father affected with OA. We also confirmed results of previous studies of sibling OA, showing that OA of the hips, OA of the knees, and OA of the hands are largely familial traits (3,13). These associations are likely due to common maternal influence (because there is no transfer of genes between siblings) rather than paternal influence. Similar to our findings, Jonsson et al reported a high relative risk of interphalangeal OA in the offspring of mothers with OA (13). We expanded on this knowledge by additionally studying paternal OA and including OA at other joint sites. However, we were unable to study different joint sites in hand OA because of challenges in finding a sufficiently large comparison group with no OA in the MUST cohort. Still, our analysis of offspring sex indicated that any OA and hand OA may be more likely to be inherited from the mother if the offspring is female, which suggests an important direction for future research.

Our findings imply that there may be differences in maternal and paternal inheritance depending on joint site and grade of OA severity. As an example, we could not conclude as to whether paternal OA increases offspring's knee OA risk. For OA-related knee surgery, the 95% CI of the risk associated with paternal OA in the Nor-Twin cohort was 18–395%, yet the 95% CI in the MUST cohort included a decreased risk of up to 33%. Further, effect estimates were also lower for clinical knee OA, in relation to both maternal and paternal OA. Our findings might be due to true diversity and/or the number of samples being too small to observe a sufficient number of fathers with OA. We believe future studies should further explore the role of paternal inheritance, particularly in knee OA, on daughters and sons.

In our study, the disease-free comparison group was selected to be as similar as possible across all OA sites, avoiding the possibility that persons with OA at sites other than the site in question would falsely deflate the RR of offspring OA. Hence, the disease-free comparison group was not allowed to have individuals with clinical or surgical OA at the site in question or at any other site. However, in accordance with existing knowledge that OA often presents as a generalized disease (11), we allowed the inclusion of offspring with OA who also had OA at other sites, but not with definitions other than the definition in question. Despite our attempt to minimize bias, we cannot exclude the possibility that the selection of persons who self-reported OA impacted our findings in the MUST cohort. However, because of the strong associations between maternal, paternal, and sibling OA and self-reported OA (nonspecific site) in the offspring in the Nor-Twin study (RR 3.10–11.35), we believe any selection bias in the MUST cohort has likely led to an underestimation, rather than overestimation, of familial effects.

The current findings have implications for future studies of risk counseling and the etiology of OA. First, our results suggest a stronger role of genetic inheritance from the mother than the father in OA etiology. Future research on OA etiology may therefore explore the role of maternal-specific factors, such as the intrauterine environment or mitochondrial DNA (14). Another possibility is the direct inheritance of OA genes or genotypes from the mother only (potentially related to female reproductive hormones) as we could confirm OA inheritance from mother to daughter but with less certainty from mother to son. We acknowledge, though, that the lower certainty for sons might be due to inclusion of fewer men with OA. Second, our findings may improve the prediction of future OA outcomes. In existing prediction models of knee OA, familial OA in general is included as a predictor (i.e., without specification of maternal, paternal, or sibling OA and without specification on offspring sex) (4). Future prediction studies may explore whether a more precise prediction can be made when familial OA is specified by family member for women versus men. Future studies may also further explore the maternal and paternal effects on early and mild OA disease stages, i.e., those involving structural joint features or joint pain only (15).

This study has some potential limitations. In the Nor-Twin cohort, clinical joint examination was not performed, and other

information not obtained, on nontwin siblings. Indeed, for surgical hip and knee OA, the RR of OA in subjects who had a twin with OA (Nor-Twin cohort) was higher than the RR of OA in subjects who had a sibling with OA (MUST cohort) (Table 2), which may be due to the stronger genetic and environmental link present between twins than between siblings. We included siblings/twins only to attenuate the comparison to existing studies on heritability and familial aggregation (1,3). Another limitation may be the stricter definition for clinical OA of the hip than for the knee, as we required more morphologic changes for the hip joint than for the knee joint; this may have led to the estimates for clinical hip OA yielding more severe OA whereas the estimates for clinical knee OA yielded milder OA. The last limitation is the inability to distinguish between different locations and severities of OA in family members. For example, it may be hypothesized that maternal hand OA increases the risk of offspring hand OA, but not of offspring hip or knee OA. However, we believe that such detailed parental data would be largely affected by recall bias if obtained from the offspring. A benefit of using the simple question on familial OA in the 2 cohorts studied is the ease of translation to the clinical setting.

In conclusion, we showed that there is a higher risk of moderate and severe OA in offspring when the mother had OA than when the father had OA and/or when no close family members had OA. Maternal inheritance may be of particular relevance if the offspring is a daughter. Future studies may reveal the mechanism for this heritability since a limited number of chromosomes and DNA are involved in OA etiology.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. 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.

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Acquisition of data. Hagen, Østerås, Risberg, Natvig, Slatkowsky-Christensen, Fenstad, Furnes, Nordsletten, Magnusson.

Analysis and interpretation of data. Magnusson.

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