EXTENDED REPORTS

Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy

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Abstract

***Objectives*—The aim was to examine the relation between osteoarthrosis of the knee leading to prosthetic surgery among men and women and overweight, smoking, and hormone therapy.**

***Methods*—A case-referent study was performed with a study base of all men and women, born 1921–1938, living in 14 counties in Sweden during 1991–95. The cases (n=625) were identified through the Swedish Knee Arthroplasty Register. The referents (n=548) were randomly selected through the central population register from the same counties. Detailed information on general health status, height, weight, smoking habits, medication, use of hormones, specific physical loads from occupation and housework, and sports activities was collected by a telephone interview and a postal questionnaire. The cases were classified in terms of high, medium or low/non-exposure to the factors studied, according to the distribution of variables among the referents.**

***Results*—Women with high body mass index (BMI) at the age of 40 had a relative risk of 9.2 (95%CI 5.3, 16.0) of developing severe knee osteoarthrosis later in life, and for men at the same age the relative risk was 3.9 (95%CI 2.3, 6.4). Smokers were less likely to develop severe knee osteoarthrosis compared with non-smokers. Oestrogen therapy for women over 50 showed an increased relative risk of 1.8 (95%CI 1.2, 2.6), while use of oral contraceptives did not influence the risk .**

***Conclusion*—Overweight is a risk factor for knee osteoarthrosis leading to prosthetic surgery in men and women, with the strongest relation for women. Oestrogen therapy after 50 increased the relative risk, while smoking decreased it.**

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The results of different studies on the impact of constitutional and lifestyle factors for the development of knee osteoarthrosis have partially been inconsistent.[1–12] Overweight is the most consistent risk factor identified, and the effect seems to be strongest in women.[2 3 5–7 11] Smoking has in certain studies shown a negative association with knee osteoarthrosis,[1–3] and in others no association.[4] There are some clinical, laboratory, and epidemiological studies suggesting that there is a relation between sex hormones and the development of osteoarthrosis.[8–10] However, some epidemiological investigations have concluded that oestrogen use is not associated with knee osteoarthrosis.[3 12]

The aim of this study was to examine the relation between osteoarthrosis of the knee leading to prosthetic surgery among men and women, and overweight, smoking, and hormone therapy.

Methods

STUDY POPULATION AND DESIGN

The study base comprised all men and women born 1921 to 1938, and living in 14 counties in Sweden during 1991–95. The relation between constitutional and lifestyle factors and the development of severe knee osteoarthrosis in men and women was studied using the case-referent method in the study base.

The cases had undergone prosthetic knee replacement during 1991–93 because of clinically significant primary tibiofemoral osteoarthrosis. We included cases who were of ages 55–70 at the time of the sugery. They were identified through the Swedish Knee Arthroplasty Register, which is a national register system of knee arthroplasties performed at orthopaedic units in Swedish hospitals.[13] The register is annually updated by reports from the units. We confirmed the status of primary osteoarthrosis in an interview and in a postal questionnaire, and through checking the radiographic records from a random sample of the cases.

During the study period there were 72 units in Sweden where knee prosthetic replacement was carried out, and 67 of them reported regularly to the record. The aggregated information in the record has continuously been reported and evaluated using the hospital discharge register and found to be in agreement.[13]

The referents were men and women of the study base, randomly selected from the central population register in Sweden.

The referents were excluded if they reported osteoarthrosis of the knee or had experienced severe pain or dysfunction in the knees. Of

Table 1 Participation in the study

	Men		*Women*	
	Cases	*Referents*	*Cases*	*Referents*
Invited subjects	369	330	380	370
Only telephone interview	33	40	58	25
Refusals	8	20	10	51
Too ill to answer questions	3	6	12	10
Participation in the whole study	325 (88%)	264 (80%)	300 (79%)	284 (77%)

Table 2 Relative risks (95% CI) for men and women at different ages, with medium and high BMI compared with those with low BMI, to develop knee osteoarthrosis. The relative risks are controlled for potential confounding from age, smoking, physical load, sports and hormone substitution

	*30 years**	*40 years†*	*50 years‡*
Men			
medium exposure	2.0 (CI 1.2, 3.2)	2.2 (CI 1.4, 3.7)	3.4 (CI 1.8, 6.3)
% exposed cases	35	36	33
high exposure	3.9 (CI 2.4, 6.3)	3.9 (CI 2.3, 6.4)	5.9 (CI 3.1, 11.1)
% exposed cases	46	44	45
Women			
medium exposure	1.9 (CI 1.1, 3.1)	3.0 (CI 1.7, 5.3)	2.8 (CI 17, 4.8)
% exposed cases	28	22	40
high exposure	5.8 (CI 3.5, 9.7)	9.2 (CI 5.3, 16.0)	7.8 (CI 4.6, 13.3)
% exposed cases	51	57	54

*BMI men low –21, medium 22–23, high 24– women low –20, medium 21–22, high 23–. †BMI men low–22, medium 23–24, high 25– women low–21, medium 22–23, high 24–. ‡BMI men low–23, medium 24–25, high 26– women low–22, medium 23–25, high 26–.

course we cannot conclude they did not have symptomless radiographic knee osteoarthrosis, but the aim of this study was to focus on severe, clinically significant knee osteoarthrosis, with symptoms that required knee prosthetic surgery.

Both cases and controls were excluded if they reported earlier trauma or surgery to the knee or the surrounding tissues, rheumatoid arthritis or systemic disease involving the joints such as poliomyelitis or rachitis or had any musculoskeletal malformation.

In all 369 male cases and 380 female cases were invited to the study. The participation rate was 88% and 79%, respectively. The numbers among the referents were 330 male and 370 female contacted and 80% and 77% respectively participated in the whole study (table 1)

PROCEDURE

The subjects were invited to participate in the study through an introduction letter, and shortly after they were contacted by professional interviewers for a brief telephone interview with questions on occupational history, if they had ever damaged a knee joint or surrounding tissues. The cases were also asked about time of diagnosis and surgery, and the status of the other knee.

After the interview a postal questionnaire was sent to the subjects for further, more detailed information on general health status, height, weight at different ages in adult life, smoking habits, medication, use of hormones, specific physical loads from occupation and housework, and sports activities. All information was obtained after the surgery and the time course between the knee prosthetic surgery and the interview varied between one and four years. The subjects were of ages 56–74 at the time of the survey.

EXPOSURE CLASSIFICATION

Body mass index (BMI), an indicator of overweight, was calculated as weight (kg) divided by height (m^2). The referent's BMI was the basis for the classification of BMI in three groups. The 25% lowest values were considered as low, and the 25% highest values as high BMI. The 50% in between were the medium BMI values. This classification was made at 30, 40, and 50 years of age. The limits for low, medium, and high BMI, respectively, varied over time because the subject average weight increased, and there were differences between men and women (table 2).

Cigarette smoking habits were calculated as pack years. One pack year is the equivalent to 20 cigarettes/day during one year. The subjects were divided into three groups: never smokers, light smokers, and smokers. Light smokers were those with 1–14 pack years and smokers those with ≥15 pack years.

Women who had used oestrogen for one year or more after 50, were considered exposed, and the relative risk was estimated in relation to women who had never had oestrogen therapy. The total time of oestrogen use after 50 was included in the analysis, that is for the cases that medication both before and after the surgery could be included. We did not analyse the use of oestrogen before the age of 50 because there were only 14 women who had had oestrogen substitution at an earlier age. They were excluded, however, from the 50+ analysis.

The use of oral contraceptives was divided into an exposed group where the subjects had taken pills for one year or more and an unexposed group where the subjects had taken pills less than one year or not at all.

STATISTICAL ANALYSIS

The rate ratios for high and medium exposure compared with low or non-exposure were calculated for body mass, cigarette smoking, oestrogen therapy, and use of contraceptive pills.

The rate ratios were interpreted as estimates of the incidence rate ratios because the design was that of a population-based case-referent study.[14] The effect on the rate ratios from potential confounding factors was considered by stratified analysis and calculating the rate ratios according to the Mantel-Haenszel method.[15]

When body mass, cigarette smoking, and hormone therapy were analysed, each variable studied was controlled for confounding from the other two. Control of potential confounding from exposure to physical load and sports up to 50 years of age was also performed. The physical work load was classified in non/low, medium or high exposure according to the exposure in the referent group. For men, total hours in any sports were aggregated and divided in three classes, and for women it was dichotomised into ever or never being active in sports activities. However, no confounding was found.

The results of the impact on knee osteoarthrosis from physical load from occupation, housework, leisure time activities and sports are extensive, and will be reported later.

Table 3 Attributable proportion (AP) for cases with medium and high BMI respectively, and for all cases at the age of 40

	Women	*Men*
AP for cases with medium BMI	15%	20%
number of exposed cases	64 (22%)	27 (36%)
AP for cases with high BMI	50%	33%
number of exposed cases	82 (57%)	38 (22%)
AP for all cases	32%	21%
number of cases	288	313

The attributable proportion (AP), that is the proportion of knee osteoarthrosis that would be eliminated if the exposure of the exposed subjects was reduced to the level of the subjects with low or no exposure, was calculated when the observed association was strong.[16]

Results

The frequencies of female and male cases with a medium and high BMI at different ages are displayed in table 2. Obesity was associated with knee osteoarthrosis after 50, at the ages of 30, 40, and 50. At the age of 40, women with high BMI had a relative risk of 9.2 (95%CI 5.3, 16.0) of developing knee osteoarthrosis, and men had a relative risk of 3.9 (95%CI 2.3, 6.4) at this age. At 50, the relative risk for women was 7.8 (95%CI 4.6, 13.3), and for men 5.9 (95%CI 3.1, 11.1) (table 2). The attributable proportion was 50% for women with a high BMI at the age of 40, and 33% for men (table 3).

Both female and male smokers were less likely to develop knee osteoarthrosis leading to prosthetic surgery compared with non-smokers. There was a dose response association, as smokers had a stronger inverse relation than light smokers (table 4).

Thirty three per cent of the female cases and 22% of the referents had oestrogen substitution after the age of 50, and the mean value of the duration of this therapy was nine years among the cases, and also nine years among the referents. The relative risk for prosthetic surgery was 1.8 (95%CI 1.2, 2.6) for those who had had this substitution (table 4).

In table 4 a relative risk of 0.9 (95%CI 0.6, 1.4) is shown for women to develop severe knee osteoarthrosis leading to surgery in relation to the use of contraceptive pills—that is, the risk of knee osteoarthrosis does not seem to be influenced by the use of oral contraceptives for one year or more.

Table 4 Relative risks (95% CI) for smokers with a life long consumption of 20 cigarettes/day <15 years (light smokers) and >15 years (smokers) respectively, users of oral contraceptives and oestrogen to develop knee osteoarthrosis, and freqency of exposed cases and referents. The smokers are compared with those who have never smoked, and oestrogen and oral contraceptive users with those who have never been users or were users for less than one year. The relative risks are controlled for potential confounding from age, body weight, physical load, and sports

	Men		*Women*	
	Cases	*Referents*	*Cases*	*Referents*
Light smokers				
relative risk (CI)	0.9 (0.6, 1.4)		0.9 (0.6, 1.5)	
number	71 (25%)	56 (23%)	50 (16%)	46 (17%)
Smokers				
relative risks (CI)	0.6 (0.4, 1.0)		0.4 (0.2, 0.8)	
number	87 (30%)	98 (40%)	21 (7%)	98 (40%)
Oestrogen users				
relative risk (CI)			1.8 (1.2, 2.6)	
number			93 (33%)	60 (22%)
Oral contraceptive users				
relative risk (CI)			0.9 (0.6, 1.4)	
number			47 (15%)	50 (17%)

Discussion

The study strengthens the association between overweight at different ages and an increased risk of knee osteoarthrosis in men and women. The results demonstrate an exposure relation and the most overweight subjects had the highest risks. The relative risk is most pronounced for overweight women at the ages of 40 and 50. For women who had oestrogen therapy after the age of 50, we found an increased relative risk compared with those without such substitution. There was a negative association between cigarette smoking and severe knee osteoarthrosis in both men and women.

We shall discuss some methodological considerations and the consistency of the findings with other studies.

POTENTIAL MISCLASSIFICATION, SELECTION BIAS, AND CONFOUNDING

Potential selection for surgery could appear if subjects with other diseases, including extreme obesity, or diseases connected with heavy smoking hindered them from having surgery. Such bias would decrease the relative risk.

We analysed reported physical activity up to 50 years of age, before the onset of symptoms. Cases who had symptoms before the age of 50 were excluded from the study, which means that the included case's overweight was not caused by a more sedentary level of activity because of knee pain.

It has been shown that people with a high body weight tend to underestimate, and lightweight people to overestimate, self reported weight.[17] This could lead to less pronounced differences in the reported weight compared with the real weight, and a relative risk closer to unity.

Cases and referents would probably not remember smoking, oestrogen therapy or oral contraceptives differently, as these factors do not seem to be closely associated with the disease studied.

As there are few years between the postmenopausal oestrogen therapy (ORT) and the time of prosthetic surgery for these women there is reason to question the association between oestrogen replacement and knee osteoarthrosis that we found. We investigated subjects with severe osteoarthrosis and they could possibly, as a result of contact with physicians because of their symptomatic knee osteoarthrosis, to a greater extent also be provided with ORT compared with the referents. Also, as ORT prescribed in Sweden includes a gestagen component, we cannot exclude a possible effect from this.

COMPARISONS WITH OTHER STUDIES

The stress and amount of force on the weight bearing joints are increased in overweight subjects. This additional physical load could cause cartilage breakdown leading to osteoarthrosis.[18] It has also been proposed that overweight

persons have a higher bone density, which could be a risk factor.[18]

In this study the association between overweight and severe knee osteoarthrosis was stronger in women than in men, in agreement with the Framingham study[7] as well as studies of Cooper and coworkers[5] and Manninen and coworkers.[21] The sex difference indicates that other factors associated with an increased BMI but solely mechanical might affect the development of knee osteoarthrosis. In fact some studies have shown that obesity is associated with osteoarthrosis in non-weight bearing joints such as the small joints of the hand, which might indicate metabolic effects of overweight involved in the arthrotic process.[19 20] However, Davies and coworkers[22] and the Baltimore Longitudinal study[23] did not find any association between metabolic factors such as serum cholesterol, blood pressure or diabetes, and the development of knee osteoarthrosis.

Our study showed an increased relative risk among those women who had had postmenopausal ORT. Other investigations of ORT and the development of knee osteoarthrosis have shown inconsistent results.[24] There are four studies indicating a possible inverse relation between oestrogen intake and knee osteoarthrosis, but in all four studies the confidence intervals include unity.[3 12 25 26] Spector and coworkers recently published results from the Chingford Study where it was found that current use of oestrogen has a protective effect on knee OA.[27] In a study of Oliveria and Felson a tendency of a possible inverse relation was found for past use, but new or current use in women over the age of 55 was not associated with knee osteoarthrosis.[28] In a study of hip osteoarthrosis and the relation to oestrogen therapy by Vingård *et al*, a moderate protective effect was found.[29] This study had a similar design as the present investigation, but in the analysis also oestrogen medication before 50 was considered.

As knee osteoarthrosis in women increases considerably around the menopause there is reason to believe that the decrease in endogenous oestrogen possibly could effect the disease. The effect in women from ORT on the development of osteoarthrosis is in all probability dependent on the reason why ORT is prescribed and what group of women investigated. This might explain the inconsistency in different studies of ORT and the effect on osteoarthrosis. Oestrogen replacement has an effect on bone metabolism, which results in a higher bone mass and a reduction of bone loss after the menopause.[10 30] Higher bone mass because of oestrogen therapy can cause increased mechanical stress on cartilage during joint loading,[31] which might be connected with the development of osteoarthrosis.[32] Animal studies and laboratory trials have indicated an association between oestrogen and osteoarthrosis, although the results are inconclusive and need to be further investigated.[33 34]

We found that smokers had a lower risk of severe knee osteoarthrosis compared with nonsmokers, which is in agreement with some other studies.[1 4 6] As in the Framingham study[1] the association showed a dose response relation, and smokers were more protected than light smokers. In the cross sectional Chingford study a protective effect of smoking for radiological osteoarthritis in the hand and knee could not be seen, but for subjects with generalised osteoarthritis a possible inverse association was found.[4] In the NHANES survey the rate ratios for smoking demonstrated a protective effect in men and women, and heavy smokers were more protected than light smokers.[1]

The mechanism of a negative association between smoking and severe osteoarthrosis in the knee could either be explained by a physiological effect of smoking, or by not controlling for unidentified confounding factors. We had, however, controlled for physical work load, sports and BMI in our study. Smoking could of course not be recommended for prevention of knee osteoarthrosis, as other, harmful effects are overwhelming, but the aetiology of the potential association would be worth studying in the search for mechanisms of osteoarthrosis.

The results of this study confirm the association between overweight and knee osteoarthrosis for both men and women, with the strongest relation for women. Furthermore postmenopausal oestrogen therapy for women after the age of 50 increased the relative risk, while smoking decreased it in both men and women. Avoiding overweight could be an efficient preventive measure, while the potential effect of metabolic syndromes or factors and hormones needs to be studied further before discussing preventive measurements.

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Historical images

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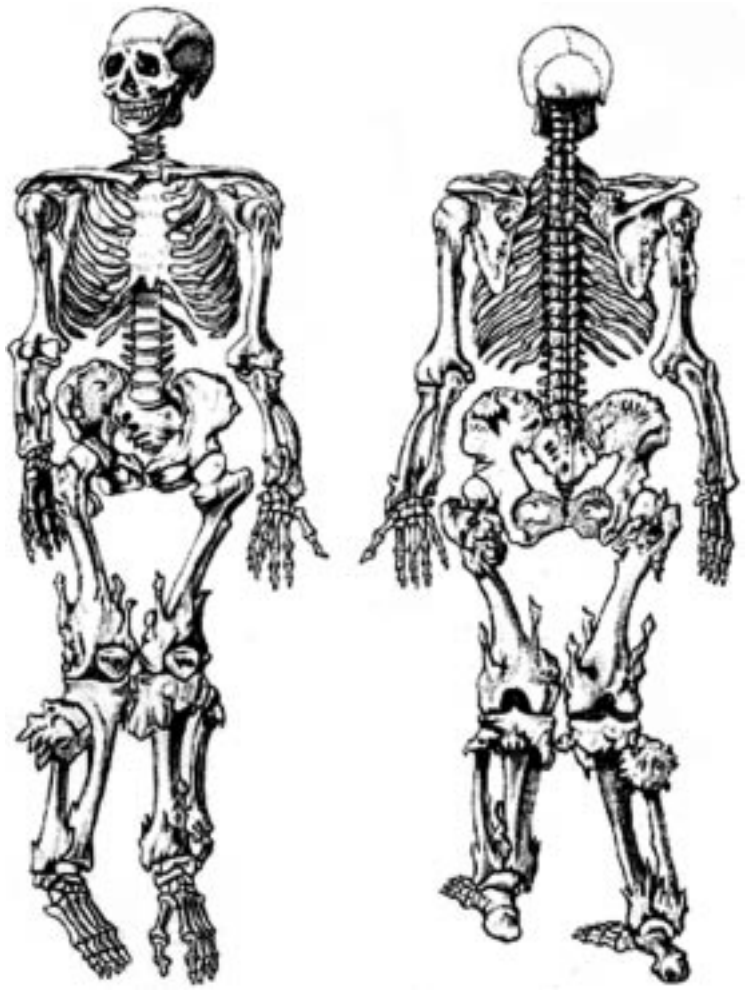

Figure 13 Osteogenic exostosis. Bernard L.
Dystrophies osseuses acquises d'origine obscure. In: Marfan A-B, Apert, Aviragnet, Bernard L, Garnier M, Hallé J, Milian. Maladies des os. Paris: Librairie J-B Baillière et fils, 1912.