Apold H, Meyer HE, et al. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. BMC Musculoskeletal Disorders 2014, 15:217.

Design: population based cohort study

Purpose of study: To estimate the association between possible risk factors for osteoarthritis (OA) of the knee and the development of clinical OA leading to knee replacements (KR)

Population/sample size/setting:

- 314,495 Norwegian citizens (153,795 men, 161,700 women) who were included in a National Health Screening between 1985 and 1994
    - Followup was initiated on January 1, 1994, after the period of screening but before the occurrence of knee operations, and was continued for 12 years
    - Mean age for both sexes at the time of screening was 43, 46.8 at the start if followup, and 58.8 at the end of followup
- National 11-digit personal identification codes were used to link data from the National Health Screening to the Norwegian Arthroplasty Register, which provided data on KR beginning in January of 1994, the date when the Register began to record KRs, and the end of followup was February 1, 2006
- Individuals younger than 16 at the time of screening (n=484) or older than 80 at the start of followup (n=50) were excluded from the study, as were had Arthroplasty Register information on revision surgery but no information on primary surgery (n=121), and individuals who died or emigrated before the start of followup

Assessment of risk factors/exposures:

- The median participation rate for the national health screenings, which were done in the setting of cardiovascular health studies in all of Norway's 19 counties, was 75%
- Participants in the screening program filled out questionnaires at home and brought them to screening appointments, where they had the opportunity to discuss the questions with study nurses and clarify misunderstandings
- All participants had measurements of height and weight, with calculations of BMI
- Smoking habits were classified as never smoker, former smoker, or current smoker
- Information on physical activity at work and during leisure was classified in four ways
    - Physical activity at work had four grades
        - Sedentary--predominantly sitting (desk worker, sitting assembly line worker handling light goods)

        - Moderate—sitting or standing with some walking (cashier, general office worker, light tool or machinery worker, foreman)
        - Intermediate—walking, some handling of material (mail delivery, restaurant server, construction worker, heavy tool and machinery worker)
        - Intensive—heavy manual labor (forestry, dock worker, farm worker, ditch digger)
    - Leisure activity also had four grades
        - Sedentary-- Reading, watching television or other sedentary activities
        - Moderate-- Walking, bicycling or moving around in other ways at least 4 hours per week (including walking or cycling to work, Sunday walks etc.)
        - Intermediate-- Participation in recreational athletics, heavy garden work etc. for at least 4 hours/week
        - Intensive—Participation in hard training or athletic competition regularly and several times/week

Outcome analysis :

- Cox proportional hazard regression was used for assessing the magnitude of the risk factors
    - This method essentially compares different levels of a risk factor with respect to "time to event" measurements; if a factor is present and the time to an event such as a KR is 2 years on average, and if time to the same kind of event in the absence of the factor is 4 years on average, then the factor on average cuts the time to the event by a factor of 2 and the hazard ratio is reported as 2.0, and this represents the relative risk of experiencing the event
    - The regression method means that for every factor in the Cox model, adjustments are made for all the other factors in the model, such that if smokers weigh less than nonsmokers and participate in fewer physical leisure activities, the effect of smoking can take those differences into account
- Each sex was analyzed separately, and the exposures were divided into quartiles, where the lowest quartile was the reference level for the three other quartiles
    - That is, the lowest quartile of BMI was used as the comparison category, so the risk of having a KR in the heaviest 25% of the population could be compared with the risk in the leanest 25%; the part of the population between the 50^{th} and 75^{th} percentile of BMI could be compared with the leanest 25%, and similarly the part of the population between the 25^{th} and 50^{th} percentile could be compared with the leanest 25%, but the absolute level of BMI was not part of the definition of the quartiles

- The cohort was also divided into three levels of absolute BMI, based on WHO definitions of normal weight (BMI less than 25), overweight (BMI between 25 and 30) and obese (BMI greater than 30)

Results:

- During 12 years of followup, 1323 individuals had KR in the Arthroplasty Register; there were 225 unicondylar and 1098 total knee replacements
    - 367 of these were censored (removed from the analysis) because they had KR for an indication other than OA, such as rheumatoid arthritis or because of meniscal injury caused by trauma
- 19,690 individuals from the initial 315,495 participants died or emigrated during followup and were also removed from the analysis
- Among men, about 38% had sedentary work, 28.5% had moderate work, 21% had intermediate work, and 12.5% had intensive work
    - Among women, the approximate corresponding percentages were 28.5%, 52%, 17%, and 2%
- The risk of KR increased with higher age at screening; for each 5 years of age, the relative risk was 1.5
- Women had a relative risk of 2.7 compared to men for having KR
- Men in the highest BMI quartile had 6.16 times the risk of the leanest quartile when all other factors were accounted for
    - For women, the same relative risk of KR was 11.06
- For men, moderate physical activity at work had a relative risk of 1.51 compared to sedentary work; intermediate activity had a RR of 1.64, and intensive activity had a RR of 2.41, constituting a dose-response relationship
    - For women, the corresponding RR for work activity compared to sedentary work were 1.18, 1.30, and 2.29
- For leisure physical activity, there was no relationship with the risk of KR, and no dose-response trend as was the case for work activity
- Men who smoked had a RR of 0.82 and women smokers had a RR of 0.66, indicating that smokers were less likely to have KR than nonsmokers
    - This is likely due to the fact that smokers have other medical problems and are poorer surgical risks than nonsmokers, accounting for their lower rates of surgery
- The statistical tests showed no interaction between BMI and work activity; the effect of work activity was the same in lean and in heavier participants in the study

Authors' conclusions:

- Both BMI and physical activity at work have been previously linked to symptomatic knee OA, and these risk factors were confirmed in this population-based study

- Joint replacement surgery was used as the marker of symptomatic OA; because severe obesity is a general contraindication to any kind of surgery, this definition of knee OA would underestimate the true effect of obesity on the development of disease in the knee joint
- The study involved a large unselected Norwegian cohort, making the results generalizable
- The funding of health care makes the operation free of charge to patients, and public sick leave is available for those not able to return to work; this makes socioeconomic factors an unlikely cause of confusion regarding the results of the study
- A small percentage (2.6% of men and 0.5% of women) had intensive leisure physical activity; the small numbers may account for the lack of finding an effect on KR
- The combination of high BMI and heavy physical labor leads to a 12-fold risk of KR in men and a 16 fold increase in women

Comments:

- The advantages of a large population registry, a centralized database for health care, and high participation in a health screening program are clearly illustrated in this study
- The screening was done prior to the period in which the first knee operation was done, meaning that the data on risk factors was collected before the period in which the events of interest, knee replacement operations, were entered in the Arthroplasty Register, removing one of the major threats to internal validity of observational studies
- The dose-response relationship between physical labor and KR also supports a causal relationship between the two
- The fact that a large number of events took place means that the statistical models are likely to have stable coefficients for each of the risk factors (sex, age, BMI, physical labor) which were entered for analysis
- As the authors note for both smoking and BMI, these factors can influence the treatment decisions made by the surgeons; this is known as “confounding by indication” and means that obese patients would have been likelier to have had a KR if obesity had not been a factor and that smokers also would have been likelier to have had an operation if they had been nonsmokers; smoking does not prevent OA of the knee, but does decrease the likelihood that an operation will be done when OA is present

Assessment: High quality large cohort study supporting good evidence that obesity in men increases the risk of symptomatic knee OA at least sixfold, and that it increases the risk in women at least elevenfold. There is good evidence that intensive physical work more than

doubles the risk of symptomatic knee OA, and that there is a dose-response relationship between work load and the development of knee OA