

Epidemiology Publish Ahead of Print

DOI: 10.1097/EDE.0000000000000806

Is the association between obesity and hip osteoarthritis surgery explained by familial confounding?

Karin Magnusson^{1,2}, Katrina J. Scurrah³, Ragnhild Elise Ørstavik⁴, Thomas Sevenius Nilsen⁴,
Ove Furnes^{5,6}, Kåre Birger Hagen¹

¹ National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, ² Clinical Epidemiology Unit, Orthopaedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, ³ Australian Centre of Excellence in Twin Research, Centre for Epidemiology & Biostatistics, University of Melbourne, Melbourne, Australia, ⁴ Norwegian Institute of Public Health, Oslo, Norway, ⁵ Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway, ⁶ Department of Clinical Medicine, Institute of Medicine and Dentistry, University of Bergen, Norway

Corresponding author and requests for reprints: Karin Magnusson, National Advisory Unit on Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Post box 23, Vinderen, 0319 Oslo, Norway, Telephone: +47 991 16 463, Telefax: +47 22 45 48 50, e-mail:

karin.magnusson@med.lu.se, www.nkrr.no

Type of manuscript: Original Research Article

Source of funding: The Norwegian Fund for Post-Graduate Training in Physiotherapy

Conflicts of interest: None declared.

Running head: Obesity, hip osteoarthritis and familial confounding

Word count: 4000

Acknowledgements: Data were obtained from the Norwegian Twin Registry, Norwegian Institute of Public Health and the Norwegian Arthroplasty Registry, Dept. of Orthopaedic

Sugery, Haukeland University Hospital. Data are not available because of privacy issues.

Computing codes are available by request to the corresponding author.

Data: Data are not available because of privacy issues. Computing codes are available by request to the corresponding author.

Abstract

Objective: Familial confounding is confounding due to genetics or environmental exposures shared by family members. We aimed to study whether familial confounding explains the association between body mass index (BMI) and severe hip osteoarthritis (OA).

Design: We linked data from the Norwegian Arthroplasty Registry with the Norwegian Twin Registry on the National ID-number in 2014, generating a population-based prospective cohort study of same-sex twins born 1915-60 (53.4% females). BMI was calculated from self-reported height/weight. The outcome was incident hip arthroplasty due to OA (follow-up time: 1987-2014, 424 914 person-years). We performed sex-specific co-twin control analyses of dizygotic (DZ, N=5226) and monozygotic (MZ, N=3803) twin pairs using Cox regression models and explored reasons for any familial confounding using bivariate twin models.

Results: The mean (SD) BMI was 22.6 (2.96), peak lifetime BMI 25.6 (2.61) and N=614 had hip surgery due to OA. In cohort analyses, BMI was associated with hip OA for women and men (Hazard Ratio, HR=1.09, 95% confidence intervals, CI=1.06-1.11 and HR=1.08, 95% CI=1.04-1.12, respectively). When adjusting for familial confounding within MZ twins, the association got stronger for women (HR=1.19, 95% CI=1.05-1.36) but weaker for men (HR=0.93, 95% CI=0.75-1.16). There was no genetic overlap between BMI and hip OA, yet the familial confounding in men provides suggestive evidence that the association could be explained by shared environmental factors.

Conclusion: The association between BMI and hip OA may be explained by familial confounding for men. For women, there was no evidence for familial confounding, consistent with a causal association.

Key words: Osteoarthritis, confounding, familial factors, sibling comparison

Background

Joint arthroplasty is the end-stage treatment of osteoarthritis (OA) and is a marker of severe pain and functional disability representing a major public health challenge. Strong and dose-dependent associations between obesity and severe hip OA have been found in several studies. Two large prospective cohort studies of >1 million participants reported consistent associations between obesity and hip OA as defined by diagnostic codes from primary care and as defined by hip arthroplasty.¹⁻³ These findings have been confirmed in a systematic review and meta-analysis (relative risk for joint surgery=1.16, 95% confidence intervals (CI) 1.11 to 1.22).⁴

Recent twin studies have estimated that genetic factors account for as much as 47%-73% of variation in disease risk for hip OA.⁵⁻⁷ A similar high heritability has been found for BMI. In a systematic review, the genetic contribution to BMI was found to vary between 47% and 90% and to decrease by age.⁸ A study of Norwegian twins further showed a slightly lower heritability among men (71%) than among women (78%).⁹

In a recent exploratory twin registry study, we found a more robust association for genetic factors than for BMI when studying time between hip prosthesis surgeries due to OA within twin pairs.⁵ However, BMI was also independently associated with shorter time between surgeries when adjusting for the genetic factors, implying environmental factors play a role.¹⁰ Hence, the association might just as well be dependent on early life exposures or lifestyle factors such as smoking, diet and physical activity level, as well as age and sex.¹¹⁻¹³ Whether the previously observed strong association between lifetime BMI and risk of hip OA leading to arthroplasty is a causal association or a result of familial confounding due to genetics or environmental factors is therefore unknown.

Twin studies are valuable for their ability to adjust for unmeasured confounding by familial factors and their ability to decompose the variation in a trait into genetic and environmental

factors, since monozygotic (MZ) and dizygotic (DZ) twins share 100% and on average 50% of their segregating genes respectively.¹⁴ Our aim was to study whether the association between BMI and hip OA leading to arthroplasty is causal or can be explained by familial confounding due to genetic and/or environmental factors for men and women. We expected the familial factors to explain the association.

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 Nor-Twin OA study), including in total N=20926 twins. The Norwegian Twin Registry was established in 2009 at the Norwegian Institute of Public Health.¹⁵ We included complete same-sex MZ and DZ twin pairs born 1915-1960 who were reared together. 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 at baseline in 1978-1982 (Q1) and 1990-1998 (Q2).¹⁵

The Norwegian Arthroplasty Registry was established in 1987 as a national hip arthroplasty registry.¹⁶ 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 OA are registered yearly.

In the current study, we started follow-up for all participants in January 1987 (baseline) and ended it when a person got hip OA surgery, was censored due to death or was censored due to end of follow-up in December 2014. Because of the young age, and surgery being rare prior to the initiation of the arthroplasty register, we assumed no participants had hip OA surgery prior to baseline. The exposure and covariate data were reported at varying time points around

baseline (1987), with the majority being reported prior to baseline (Q1, N=12721). We used data reported after baseline only when data was not available for Q1 (Q2 only, N=616).

The study was approved by the Regional Ethical Committee in Oslo, Norway.

Explanatory and outcome variables

Body height (cm) and weight (kg) were reported and body mass index (BMI, kg/m²) was calculated for baseline (i.e. at the time of questionnaire response). Peak lifetime BMI was calculated based on the highest recalled body weight except during pregnancy using the baseline heights. Prevalent and incident arthroplasty due to primary OA in the left or right hip joint were our main outcome variables. Arthroplasty due to other causes than OA (i.e. fractures, inflammatory rheumatic diseases etc.) were excluded.

Potential confounders

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. Smoking was categorized as never, former, and current smoking. Physical activity during leisure time was self-reported as “How much physical activity do you have during your leisure time?” with responses none, a little, moderate and a lot. The age at reporting was taken into account in statistical analyses.

Statistical analysis

Multiple imputation of missing data was indicated, which is described in detail elsewhere.⁵ Our statistical approach was divided in three main parts, including a cohort analysis, co-twin control analysis and twin correlational analyses. First, in brief, using a cohort and co-twin control design, we studied the sample as genetically unrelated (cohort analysis) and checked whether any association held within DZ pairs that share 50% of their genes and within MZ

pairs that share 100% of their genes (DZ and MZ co-twin control analyses, respectively). A strong within-pair association for MZ pairs strengthens the support for a causal association due to the adjustment for familial factors (including 100% of genes, and shared environmental factors).¹⁴ The correlational models determined the source of any familial confounding.¹⁷

1. Cohort analyses:

To explore a potential causal association between higher BMI and hip arthroplasty due to OA in cohort analyses, we first examined the presence of a dose-dependent association between baseline BMI and peak lifetime BMI using tertiles of BMI as exposure variables and incident hip arthroplasty due to OA as outcome variables in a Cox regression analysis of the entire cohort (using robust standard errors to account for clustering in twin pairs) (eFigure 1A; <http://links.lww.com/EDE/B316>). The cohort analyses were repeated for baseline and peak lifetime BMI as continuous exposure variables.

2. Co-twin control analyses:

Second, we took advantage of the paired twin structure of the data in co-twin control analyses, and additionally adjusted for both the observed and unobserved familial confounding through including a random effect at pair level, i.e. shared frailty in co-twin control analyses for MZ and DZ twins (eFigure 1B; <http://links.lww.com/EDE/B316>). Hence, using Cox shared frailty models, we examined the association between BMI and incident hip arthroplasty due to OA with a decomposition of covariates into within- and between-pair variables. The within-/between-pair parameter separation using random effect models has been described by several authors and is a frequently used approach since it distinguishes between twin-individual and pair-level effects of explanatory factors and confounders.¹⁸ Its application to censored survival outcomes is relatively novel.¹⁹ In the within- and between-model, the within-pair parameter represents the risk for hip OA for the twin with the higher BMI compared to the twin with the lower BMI (i.e. the average causal effect for the individual), whereas the

between-pair parameter represents the shared BMI in a pair, i.e. the familial effects parameterized as the mean BMI of the pair. The within- and between-model should be adjusted for both shared (age, sex and twin pair means) and non-shared confounders.^{18, 19}

Results from these analyses were compared to the cohort analyses.

3. Correlational analyses:

We finally validated our findings and explored the content of any familial confounding (genetic vs. environmental) in a binary twin correlational model for combined continuous and categorical variables (eFigure 1C; <http://links.lww.com/EDE/B316>). In this model, we studied the pattern of intra-pair correlations for baseline and peak lifetime BMI and the presence/absence of hip arthroplasty due to OA for twin 1 and twin 2 (i.e. overall phenotypic correlations, the trait-specific correlations and the cross-twin cross-trait association).¹⁷ The statistical significance and ratio of the cross-twin cross-trait associations between MZ and DZ pairs ($r_{MZ}:r_{DZ}$) are used to make inference on whether a potential common familial etiology of BMI and hip OA is due to common genetic influence, or influence by environmental factors shared vs. non-shared between twins in a pair.¹⁷

All analyses were performed in R (The R Project for Statistical Computing), v. 1.0.44 using the `coxph` functions and the `OpenMx` package.^{20,21} For the cohort analyses, we performed crude analysis, analyses adjusted for age and sex, and analyses additionally adjusted for education level, smoking, and physical activity level. In co-twin control analyses, we explored sex-specific associations for men and women separately, adjusted for the same covariates (with within- and between separation for each). The correlational models were adjusted for age and stratified by sex. Hence, through a systematic adjustment for observed confounding (cohort analyses) and unobserved familial confounding (co-twin control analyses), as well as a decomposition of any familial confounding, we could make inference regarding the strength

of causal pathways as presented in the conceptual model in eFigure 1A;

<http://links.lww.com/EDE/B316> for women and men.

Results

In total, N=18058 twins in N=9029 complete pairs (N=3803 MZ and N=5226 DZ pairs) were included in the analyses after exclusion of N=2868 lone twins who were not willing to participate or who had a co-twin who died early. Questionnaire data was available for N=13337 (73.8%) participants (28% missing for BMI, 27% for education level, 29% for smoking, and 28% physical activity). The participants with missing questionnaire data were more often males (N=2378 (50.3%), $p<0.001$), more often MZ twins (N=2980 (61.1%), $p<0.001$) and significantly older (mean (SD) age in 2014 was 74.5 (0.19)). Hence, since missingness depended on measured covariates, the data can be assumed to be missing at random and we performed multiple imputation to account for this skewness.⁵

The included participants' characteristics are presented in Table 1. The total follow-up time for hip arthroplasty for OA was 27 years (1987-2014), representing 424 914 person-years. The incidence rate and prevalence were similar across zygosity (i.e. 1.40 (95% CI =1.30-1.52) per 1000 person-years and 614/18058 (3.6%), respectively).

Cohort analysis overall and by sex

In the cohort analysis including both women and men treating the twins as individuals, there was a clear trend for a dose-dependent association between being in the 2nd and 3rd tertile of baseline and peak lifetime BMI and risk of hip arthroplasty due to OA compared to the lowest tertile (Table 2). Similar dose-dependent associations could be observed in complete case analyses (eTable 1; <http://links.lww.com/EDE/B316>). When treating baseline BMI and peak lifetime BMI as continuous variables in the cohort analyses stratified by sex, we similarly observed strong associations since 1 unit increase in BMI would give a 6%-9% higher risk of

hip OA surgery for both men and women (multiply imputed data in Table 3 and complete case data in eTable 2; <http://links.lww.com/EDE/B316>).

Co-twin control analysis by sex

In sex-stratified analysis additionally adjusted for familial factors (i.e. genetic and/or shared environmental confounding), age, sex and education level in co-twin control analyses, we observed that higher baseline BMI was associated with increased risk of hip arthroplasty within MZ twin pairs in women (HR=1.19, 95% CI=1.05-1.36) (Table 3). This is consistent with a causal effect implying higher BMI in a woman leads to higher risk of hip OA. A similar trend was observed for peak lifetime BMI in women (Table 3). For MZ men, there was no individual effect of BMI on hip OA (Table 3), but the between-pair baseline and peak lifetime BMIs were associated with risk of hip OA (HR=1.41, 95% CI=1.03-1.91 and HR=1.38, 95% CI=1.08-1.74, respectively), consistent with familial effects (genetic and/or shared environmental factors) on the BMI – hip OA association for men (Table 3).¹⁸ When baseline BMI analyses were additionally adjusted for smoking and physical activity level, similar estimates were found (within-pair for MZ women: HR=1.21, 95% CI=1.06-1.3, between-pair for MZ women: HR=1.05, 95% CI=0.89-1.25), within-pair for MZ men: HR=0.93, 95% CI=0.74-1.17), between-pair for MZ men: HR=1.47, 95% CI=1.06-2.02), implying no confounding effect by these covariates. No associations were observed for male or female DZ pairs. In general, we observed a similar pattern in complete case analyses. The magnitude and direction of change in effect estimates depended on which estimate was studied (within- or between-pair) for which strata (MZ or DZ twins among women or men) (eTable 2; <http://links.lww.com/EDE/B316>).

Correlational analysis and age effects

The familial effects were decomposed in analysis of phenotypic correlation and the patterns observed in co-twin control analyses for men and women were repeated and explored. The

overall phenotypic correlations between baseline BMI and hip OA were low (crude $r=0.13$, 95% CI=0.10-0.16). Further, increasing age explained a large part of the co-occurrence of high BMI and hip OA (overall phenotypic age-adjusted $r=0.06$, 95% CI=0.02-0.09).

We henceforth only present age-adjusted correlations. The intra-pair correlations specific for the two traits were high both for baseline BMI ($r_{DZ}=0.31$, 95% CI=0.29-0.34, $r_{MZ}=0.52$, 95% CI=0.50-0.54) and for hip OA ($r_{DZ}=0.39$, 95% CI=0.28-0.49, $r_{MZ}=0.71$, 95% CI=0.63-0.78). The patterns observed suggest that different, trait-specific genetic factors rather than common genetic factors account for most of the variation in BMI vs. the variation in hip OA.¹⁷

Last, we explored the source of the low phenotypic overlap for women and men through studying the association between baseline BMI of twin 1 and hip OA of twin 2. Only if this $r_{MZ}:r_{DZ}$ cross-twin cross-trait association was 2:1 and different from 0 would there be genetic overlap between BMI and hip OA.¹⁷

However, for women, we observed correlations overlapping 0 ($r_{DZ}=0.05$, 95% CI=-0.01-0.10, $r_{MZ}=0.06$, 95% CI=-0.00-0.11) which is indicative of environmental factors unique to the twin accounting for the co-variation in current BMI and hip OA.¹⁷ For men, there was stronger evidence for shared environmental factors, i.e. no causal association determining the phenotypic overlap since r_{MZ} was higher than 0 and the CI overlapped with that of r_{DZ} ($r_{DZ}=0.05$, 95% CI=-0.03-0.12, $r_{MZ}=0.09$, 95% CI=0.01-0.15). For all analyses of phenotypic correlations, similar patterns were observed for peak lifetime BMI. We present data based on multiply imputed data only because of model convergence issues in complete case analyses.

Discussion

We found a strong dose-dependent association between BMI and hip OA in cohort analyses. Using two different analytic approaches to explore familial confounding, we found that the

association between BMI and hip OA may be explained by shared environmental factors for men. In contrast, the association was not explained by any familial confounding in women.

There was no evidence for common genetic factors accounting for both higher BMI and higher risk of hip OA, neither for women nor for men.

Strengths of the current study were the population-based inclusion of twins, the long follow-up time and the nation-wide coverage of >95% of hip surgeries. To our knowledge, the present study is the first to examine the degrees of familial confounding and causes of co-variation in both the risk factor BMI and the outcome hip OA. Since the replication of these findings in controlled randomized intervention studies is challenging due to the required population size and follow-up time, our study provides clinically relevant information as to whether preventive strategies for a reduced BMI are likely to reduce surgery rates in a lifetime perspective. Our findings indicate that particularly women may benefit from preventive strategies targeted at reducing BMI, whereas there may be limited effect for men.

The non-causal association for men is remarkable and contradicts the common belief that obesity increases the risk of hip OA. However, similar trends have been observed in large prospective cohort studies. Flugsrud et al. found a stronger dose-dependent association between BMI and hip OA risk for women than for men in a cohort of 1.2 million Norwegians, with particularly strong associations observed for BMI in young adulthood.² However, there were no sex differences and strong associations were observed for both sexes in a systematic overview and meta-analysis of a range of different definitions of obesity and hip OA.⁴ We also found strong associations in our cohort analyses for men when not taking familial confounding into account. However, the association got weaker when the familial factors were adjusted for. According to our findings, previous studies may have been biased due to lack of adjustment for familial confounding at least for men. Hence, our findings partly

contradict and add nuance to previous studies of BMI and risk of hip OA leading to arthroplasty.

The association between BMI and risk of hip arthroplasty due to OA was consistent across BMI definitions for men, since only weak within-pair associations, but stronger between-pair associations, could be observed for both baseline and for peak lifetime BMI in co-twin control analyses. This consistency may confirm the relevance of familial factors rather than individual factors impacting on hip OA risk for men. Our bivariate twin correlation analyses further indicated this familial confounding was due to shared environmental factors in a pair rather than shared genetics. The shared environmental factors typically represent early life exposures, since twins are most likely to share their environment early in life when they e.g. are raised by the same parents. This interpretation is in accordance with findings of early life BMI being associated with hip arthroplasty due to OA in previous studies², yet it is unclear which early life exposures may contribute to both the elevated overweight/obesity risk and the elevated hip OA risk. As an example, we found no confounding effect of smoking or physical activity level in pooled analyses (Table 3, <10% change in HR). Since lifestyle behaviours are typically constant traits from adolescence to adulthood,²² our findings may indicate other unmeasured early life exposures play a role. Future research should further explore any early life exposure impact on both BMI and risk of hip OA in men.

We could find no previous study for comparison of our findings with regard to familial confounding and the current study raises several new research questions. For women, the BMI-hip OA association was independent of both genetic and shared environmental factors, education level, smoking, and physical activity level, increasing the probability of a causal effect of BMI. We believe the risk of residual twin-individual confounding was reduced by our analytic approach,²³ yet we cannot rule out an impact of e.g. nutrition on both BMI and hip OA risk. This impact might further have accounted for the minor differences in

association depending on whether baseline BMI or peak lifetime BMI was studied. In contrast to baseline BMI, peak lifetime BMI was weakly associated with hip OA risk for women within the pair. If a causal association was present, a stronger association also between peak lifetime BMI would be expected. The differences in findings might depend on a difference in information bias for peak lifetime body weight vs. baseline body weight for women. The addition of self-report bias and recall bias might have led to an underestimation of the true effect of peak lifetime BMI on hip OA. Indeed, we previously found a greater underreporting of body weight in heavier persons and in persons with clinical OA compared to lean and persons without OA²⁴, which might also have impacted on our estimates for baseline BMI in the current study. We included the peak lifetime BMI in the current study despite the additional risk of recall bias since the population mean baseline BMI was low, i.e. only 22.6 kg/m² at the measurement time and perhaps not giving elevated risk of hip OA. The mean peak lifetime BMI was 25.0 kg/m², potentially giving a more correct proportion of subjects at risk.

Our findings may imply that different approaches for men and women are needed to study and to improve preventive strategies for hip OA. If our findings are true, reducing body weight alone may be sufficient to reduce the risk of hip arthroplasty due to OA. A reduced body weight can be achieved by diet, exercise, and/or bariatric surgery, implying further twin studies should explore the association between weight reduction efforts and hip OA in a lifetime perspective for women. For men, more research on the early familial factors increasing both BMI and hip arthroplasty risk is required. Yet for both men and women the association between BMI and hip OA may be more complex than revealed in the current study. Both traits had a high independent genetic contribution.⁵ The high heritability of hip OA may imply either a fully genetically determined occurrence, or a gene–environment interaction between radiographic progression and/or pain and BMI. More specifically, the

association between BMI and OA may vary for radiographic OA as opposed to OA pain since there is a poor correlation between the two.²⁵ Radiographic OA and OA pain could not be separated in the current study due to lack of measurements and should be subject for further investigation.

Our study had some weaknesses. First, joint arthroplasty is a treatment decision and not the OA disease itself. No estimates for the positive predictive value (PPV) exist in the Norwegian Hip Arthroplasty Registry. However, the PPV of osteoarthritis based on medical records and radiographs was 85% (95% CI=75-92%) in a comparable arthroplasty registry.²⁶ However, for twins, the PPV might be different than for genetically unrelated individuals since twins to a larger extent may discuss whether to have OA surgery. These effects are called carryover effects and might have influenced our findings, not only through impacting on outcome data, but also on exposure data.^{27,28} As an example, the lifestyle and weight of twin 1 might impact on the lifestyle and weight of twin 2. However, these effects are likely symmetrical in twins and is taken account of through the inclusion of a between-pair effect in statistical analyses.

A second potential weakness of our study is that we may have violated the assumption of equal environments for MZ and DZ twins when making inference from the rMZ:rDZ ratio.¹⁷ However, the overall phenotypic correlations both for current and peak lifetime BMI were low and a potential violation has minor consequences for the major findings of this study. A third limitation of our study is the large amount of missing data for BMI and the covariates. We performed analyses on multiply imputed data, since the within- and between-pair analyses with estimation of many parameters required a high sample size in order to maintain statistical power. Any complete case analyses would imply an even larger loss of data than our approximately 27% since not only the twin individual with missing data would need to be excluded. We would also need to exclude his or her co-twin since a lone twin is not informative in co-twin control studies, leading to an additional and severe risk of bias in

complete case analyses.²³ Indeed, we observed less precision or non-convergence of models in complete case analyses, implying statistical power might be an issue in our study. It should be noted that analyses on multiply imputed data are a more appropriate approach when data are found to be missing at random, since the imputation can correct for the skewness induced by the missingness.²⁹ A final limitation of our study is that the binary correlation model did not take censoring into account and that we could not include potential competing risk of death when using the Cox shared frailty models as well as binary twin correlation models. In a previous study of the genetic contribution to hip and knee OA, our findings were not affected by competing risk of death.⁵

In conclusion, we found a dose-dependent association between BMI and hip OA surgery. This association was not explained by familial confounding due to shared genetics or environmental factors in women. For men, it could be explained by familial factors. Hence, the association between BMI and hip OA surgery may be non-causal for men. There was no evidence for genetic overlap between a higher BMI and hip OA surgery, meaning that the genetic contribution to BMI vs. hip arthroplasty due to OA is likely trait-specific.

References

1. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. *Arthritis Rheumatol* 2016;68:1869-75.
2. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Engeland A, Meyer HE. The impact of body mass index on later total hip arthroplasty for primary osteoarthritis: a cohort study in 1.2 million persons. *Arthritis Rheum* 2006;54:802-7.
3. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Meyer HE. Risk factors for total hip replacement due to primary osteoarthritis: a cohort study in 50,034 persons. *Arthritis Rheum* 2002;46:675-82.
4. Jiang L, Rong J, Wang Y, et al. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. *Joint Bone Spine* 2011;78:150-5.
5. Magnusson K, Scurrah K, Ystrom E, et al. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. *Osteoarthritis Cartilage* 2016. doi: 10.1016/j.joca.2016.
6. MacGregor AJ, Antoniadou L, Matson M, Andrew T, Spector TD. The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. *Arthritis Rheum* 2000;43:2410-6.
7. Skousgaard SG, Hjelmberg J, Skytthe A, Brandt LP, Moller S, Overgaard S. Probability and heritability estimates on primary osteoarthritis of the hip leading to total hip arthroplasty: a nationwide population based follow-up study in Danish twins. *Arthritis Res Ther* 2015;17:336.
8. Elks CE, den HM, Zhao JH, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. *Front Endocrinol (Lausanne)* 2012;3:29.

9. Harris JR, Tambs K, Magnus P. Sex-specific effects for body mass index in the new Norwegian twin panel. *Genet Epidemiol* 1995;12:251-65.
10. Harrap SB, Stebbing M, Hopper JL, Hoang HN, Giles GG. Familial patterns of covariation for cardiovascular risk factors in adults: The Victorian Family Heart Study. *Am J Epidemiol* 2000;152:704-15.
11. Johnsen MB, Hellevik AI, Baste V, et al. Leisure time physical activity and the risk of hip or knee replacement due to primary osteoarthritis: a population based cohort study (The HUNT Study). *BMC Musculoskelet Disord* 2016;17:86.
12. Lahti-Koski M, Pietinen P, Heliövaara M, Vartiainen E. Associations of body mass index and obesity with physical activity, food choices, alcohol intake, and smoking in the 1982-1997 FINRISK Studies. *Am J Clin Nutr* 2002;75:809-17.
13. Johnsen MB, Vie GA, Winsvold BS, et al. The causal role of smoking on the risk of hip or knee replacement due to primary osteoarthritis: a Mendelian randomisation analysis of the HUNT study. *Osteoarthritis Cartilage* 2017. doi: 10.1016/j.joca.2016.12.021
14. McGue M, Osler M, Christensen K. Causal Inference and Observational Research: The Utility of Twins. *Perspect Psychol Sci* 2010;5:546-56.
15. Nilsen TS, Brandt I, Magnus P, Harris JR. The Norwegian Twin Registry. *Twin Res Hum Genet* 2012;15:775-80.
16. Havelin LI, Engesaeter LB, Espehaug B, Furnes O, Lie SA, Vollset SE. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. *Acta Orthop Scand* 2000;71:337-53.
17. Rijdsdijk FV, Sham PC. Analytic approaches to twin data using structural equation models. *Brief Bioinform* 2002;3:119-33.

18. Begg MD, Parides MK. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Stat Med* 2003;22:2591-602.
19. Sjolander A, Lichtenstein P, Larsson H, Pawitan Y. Between-within models for survival analysis. *Stat Med* 2013;32:3067-76.
20. Neale MC, Hunter MD, Pritikin JN, et al. OpenMx 2.0: Extended Structural Equation and Statistical Modeling. *Psychometrika* 2016;81:535-49.
21. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer, New York . 2000.
22. Paavola M, Vartiainen E, Haukkala A. Smoking, alcohol use, and physical activity: a 13-year longitudinal study ranging from adolescence into adulthood. *J Adolesc Health* 2004;35:238-44.
23. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* 2012;23:713-20.
24. Magnusson K, Haugen IK, Osteras N, Nordsletten L, Natvig B, Hagen KB. The validity of self-reported body mass index in a population-based osteoarthritis study. *BMC Musculoskelet Disord* 2014;15:442.
25. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? *Ann Rheum Dis* 2015;74:682-8.
26. Pedersen A, Johnsen S, Overgaard S, Søballe K, Sørensen H, Lucht U. Registration in the Danish Hip Arthroplasty Registry Completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. *Acta Orthopaedica Scandinavica*, 75:4, 434-441, DOI: 10.1080/00016470410001213-1
27. Espehaug B, Furnes O, Engesaeter LB, Havelin LI. Hip arthroplasty in Norway 1989-2008. *Tidsskr Nor Laegeforen* 2011;131:1543-8.

28. Sjolander A, Frisell T, Kuja-Halkola R, Oberg S, Zetterqvist J. Carryover Effects in Sibling Comparison Designs. *Epidemiology* 2016;27:852-8.
29. Klebanoff MA, Cole SR. Use of multiple imputation in the epidemiologic literature. *Am J Epidemiol* 2008;168:355-7.

Table 1. Participants' characteristics.

	Complete case data N=13337	Multiply imputed data N=18058
Sociodemographics		
Sex, female, n (%)	7307 (54.8)	
Age at questionnaire response, mean (SD)	37.9 (12.3)	
Death, n (%)	5159 (28.6)	
Death age, mean (SD)	72.5 (13.4)	
Basic school (0-7 years), n (%)	5390 (40.6)	5673 (31.4)
Primary school (8-9 years), n (%)	1603 (12.1)	4629 (25.6)
Upper sec. school (10-12 years), n (%)	3156 (23.8)	4642 (25.7)
College/university (>12 years), n (%)	3114 (23.5)	3114 (17.2)
Lifestyle		
Current smoker, n (%)	5612 (43.5)	5633 (31.2)
Moderate/high physical activity level, n (%)	7529 (58.0)	11811 (65.4)
Anthropometrics		
BMI (kg/m ²), mean (SD)	22.6 (2.96)	22.7 (2.61)
Overweight (≥ 25 kg/m ²), n (%)	2016 (15.5)	2354 (13.0)
Obese (≥ 30 kg/m ²), n (%)	206 (1.6)	206 (1.1)
Peak lifetime BMI (kg/m ²), mean (SD)	25.0 (3.6)	25.1 (3.1)
Lowest lifetime BMI (kg/m ²), mean (SD)	20.3 (2.3)	20.4 (2.1)

BMI: body mass index, SD: standard deviation.

Table 2. The association between body mass index (BMI) and hip osteoarthritis (OA) leading to arthroplasty in Norwegian twins born 1915-60.

	N affected with hip OA/ total N in tertile	Crude	Age and sex adjusted	Age, sex and education adjusted	Age, sex, education, smoking and physical activity adjusted
	N/N	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Baseline BMI					
1st tertile (ref. category)	117/6032	1	1	1	1
2nd tertile (\geq 21.5 kg/m ²)	187/6026	1.75 (1.37-2.22)	1.50 (1.15-1.94)	1.49 (1.15-1.94)	1.51 (1.15-1.97)
3rd tertile (\geq 23.4 kg/m ²)	310/6000	3.43 (2.73-4.32)	2.66 (2.03-3.49)	2.69 (2.05-3.52)	2.86 (2.17-3.77)
Peak lifetime BMI					
1st tertile (ref. category)	121/6020	1	1	1	1
2nd tertile (\geq 23.9 kg/m ²)	170/6021	1.49 (1.17-1.90)	1.28 (1.00-2.91)	1.28 (0.99-1.65)	1.28 (0.99-1.66)
3rd tertile (\geq 25.9 kg/m ²)	323/6017	3.41 (2.73-4.26)	2.29 (1.79-2.91)	2.30 (1.80-2.92)	2.40 (1.88-3.06)

Cox regression analyses of multiply imputed data. CI: confidence interval, HR: Hazard Ratio.

Table 3. The within- and between-pair associations between Body Mass Index (BMI) and hip osteoarthritis (OA) leading to arthroplasty within sex-strata of Norwegian twins born 1915 and 1960.

	Women (N=4825 pairs)			Men (N=4202 pairs)		
	N affected with hip OA/ total N in strata	Within-pair HR (95% CI)	Between-pair HR (95% CI)	N affected with hip OA/ total N in strata	Within-pair HR (95% CI)	Between-pair HR (95% CI)
Baseline BMI						
Cohort ^a	432/9650		1.09 (1.06-1.11)	182/8408		1.08 (1.04-1.12)
Co-twin control (DZ) ^b	254/5508	1.04 (0.96-1.13)	1.04 (0.93-1.17)	100/4944	1.08 (0.95-1.24)	1.08 (0.87-1.29)
Co-twin control (MZ) ^b	178/4142	1.19 (1.05-1.36)	1.04 (0.88-1.23)	82/3464	0.93 (0.75-1.16)	1.41 (1.03-1.91)
Peak lifetime BMI						
Cohort ^a	432/9650		1.07 (1.05-1.10)	182/8408		1.06 (1.02-1.10)
Co-twin control (DZ) ^b	254/5508	1.01 (0.96-1.08)	1.08 (0.99-1.18)	100/4944	1.03 (0.93-1.15)	1.06 (0.91-1.24)
Co-twin control (MZ) ^b	178/4142	1.10 (0.99-1.22)	1.07 (0.94-1.22)	82/3464	0.90 (0.76-1.07)	1.38 (1.08-1.74)

a) Regular Cox regression analysis for the cohort (N=18058, i.e. parameters not decomposed into within- and between-pair parameters) and b) Cox regression analyses with shared frailty on twin pair level, i.e. decomposed parameters within and between DZ=dizygotic pairs (N=5226) and within and between MZ=monozygotic twin pairs (N=3803) on multiply imputed data stratified by sex, adjusted for age and education level, treating the exposure BMI as a continuous variable. CI: confidence interval, HR: Hazard Ratio.