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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

M.B. Johnsen † ‡ *, G.Å. Vie §, B.S. Winsvold † ||, J.H. Bjørngaard § ¶, B.O. Åsvold # ††, M.E. Gabrielsen #, L.M. Pedersen †, A.I. Hellevik ‡‡ §§, A. Langhammer §§, O. Furnes ||| ¶¶, G.B. Flugsrud ‡‡, F. Skorpen ##, P.R. Romundstad §, K. Storheim † ‡, L. Nordsletten ‡ ‡‡, J.A. Zwart † ‡

† *Communication and Research Unit for Musculoskeletal Disorders, Oslo University Hospital, Oslo, Norway*
‡ *Faculty of Medicine, University of Oslo, Oslo, Norway*
§ *Department of Public Health and General Practice, NTNU, Norwegian University of Science and Technology, Trondheim, Norway*
|| *Department of Neurology, Oslo University Hospital, Oslo, Norway*
¶ *Forensic Department and Research Centre Bröset, St. Olav's University Hospital, Trondheim, Norway*
# *K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health, NTNU, Norwegian University of Science and Technology, Trondheim, Norway*
†† *Department of Endocrinology, St. Olav's University Hospital, Trondheim, Norway*
‡‡ *Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway*
§§ *The HUNT Research Centre, NTNU, Faculty of Medicine, Levanger, Norway*
||| *The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway*
¶¶ *Department of Clinical Medicine, University of Bergen, Bergen, Norway*
Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

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SUMMARY

Objective: Smoking has been associated with a reduced risk of hip and knee osteoarthritis (OA) and subsequent joint replacement. The aim of the present study was to assess whether the observed association is likely to be causal.

Method: 55,745 participants of a population-based cohort were genotyped for the rs1051730 C > T single-nucleotide polymorphism (SNP), a proxy for smoking quantity among smokers. A Mendelian randomization analysis was performed using rs1051730 as an instrument to evaluate the causal role of smoking on the risk of hip or knee replacement (combined as total joint replacement (TJR)). Association between rs1051730 T alleles and TJR was estimated by hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were adjusted for age and sex.

Results: Smoking quantity (no. of cigarettes) was inversely associated with TJR (HR 0.97, 95% CI 0.97–0.98). In the Mendelian randomization analysis, rs1051730 T alleles were associated with reduced risk of TJR among current smokers (HR 0.84, 95% CI 0.76–0.98, per T allele), however we found no evidence of association among former (HR 0.97, 95% CI 0.88–1.07) and never smokers (HR 0.97, 95% CI 0.89–1.06). Neither adjusting for body mass index (BMI), cardiovascular disease (CVD) nor accounting for the competing risk of mortality substantially changed the results.

Conclusion: This study suggests that smoking may be causally associated with the reduced risk of TJR. Our findings add support to the inverse association found in previous observational studies. More research is needed to further elucidate the underlying mechanisms of this causal association.

* Address correspondence and reprint requests to: M.B. Johnsen, Communication and Research Unit for Musculoskeletal Disorders, Oslo University Hospital-Ullevål, Building 37B, PO Box 4956, Nydalen, N-0424, Norway. Fax: 47-23-01-61-50.

E-mail addresses: m.b.johnsen@medisin.uio.no (M.B. Johnsen), gunnhild.vie@ntnu.no (G.Å. Vie), bendik.s.winsvold@ntnu.no (B.S. Winsvold), johan.h.bjorngaard@ntnu.no (J.H. Bjørngaard), bjorn.o.asvold@ntnu.no (B.O. Åsvold), maikenbr@ntnu.no (M.E. Gabrielsen), limped@ous-hf.no (L.M. Pedersen), alf.hellevik@ntnu.no (A.I. Hellevik), arnulf.langhammer@ntnu.no (A. Langhammer), ove.furnes@helse-bergen.no (O. Furnes), GUNFLU@ous-hf.no (G.B. Flugsrud), frank.skorpen@ntnu.no (F. Skorpen), pal.romundstad@ntnu.no (P.R. Romundstad), kjersti.storheim@medisin.uio.no (K. Storheim), lars.nordsletten@medisin.uio.no (L. Nordsletten), j.a.zwart@medisin.uio.no (J.A. Zwart).

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Introduction

Hip and knee osteoarthritis (OA) are one of the leading causes of global disability and the burden of OA is anticipated to increase due to an ageing and more obese population[1]. No curative treatment for OA is available, which places emphasis on identifying modifiable risk factors for disease prevention and treatment of early OA[2]. The results of observational studies suggest that smoking could have a protective effect on the development of OA[3,4] and subsequent hip and knee replacement[5–7]. Although results from *in vitro* data have indicated a beneficial effect of nicotine on chondrocyte function, the mechanisms remain unclear[8,9]. The question remains; is there a causal effect of smoking on OA? Observational studies are prone to confounding and reverse causality; hence, it is difficult to infer causal links between smoking and OA or joint replacement using information from observational studies alone.

In Mendelian randomisation analysis, the causality of epidemiological relationships is investigated using genetic variants as proxies for the exposure of interest. Due to the random assortment of genetic variants at conception, genetic variants tend to be independent of potential confounders. Hence, genotypes associated with smoking are not likely to be associated with environmental factors that may confound conventional observational studies[10]. The C > T single-nucleotide polymorphism (SNP) rs1051730 in the CHRNA5–CHRNA3–CHRNB4 nicotinic acetylcholine receptor gene cluster on chromosome 15 is the strongest genetic contributor to smoking behaviour identified in genome-wide association studies to date[11–13]. Each additional T allele at the rs1051730 SNP is associated with an increase in the number of cigarettes smoked per day and increased cotinine levels, a metabolite of nicotine, among current smokers[14]. The rs1051730 SNP has been used as an instrument for smoking intensity in former Mendelian randomisation studies investigating the causal effect of cigarette smoking on body mass index (BMI), anxiety and depression and cardiovascular risk factors[15–19].

We are not aware of studies using the rs1051730 SNP to study the association between smoking and OA, or hip or knee replacement. Thus, the aim of the present study was to investigate whether the association observed between smoking and hip or knee replacement is likely to be causal by using the rs1051730 SNP as an instrumental variable in a Mendelian randomisation analysis.

Method

Study population

The Nord-Trøndelag Health Study (HUNT) is a population-based study with data collected through three cross-sectional surveys; HUNT1 (1984–1986), HUNT2 (1995–1997) and HUNT3 (2006–2008). The surveys comprise data from questionnaires, interviews, clinical examinations and blood sampling. All residents of Nord-Trøndelag County, Norway aged 20 years and older were invited to participate. The HUNT study has been described in detail elsewhere[20,21]. For the present study, we included participants from HUNT2; in which 65,232 (69.5% of those invited) participated. Of these, 56,625 participants were successfully genotyped for the rs1051730 SNP. A total of 880 participants were excluded because of hip or knee replacement prior to baseline in HUNT2 ($n = 503$), no date recorded for the primary hip or knee replacement ($n = 25$), missing information on age at participation ($n = 3$), or death/emigration before start of follow-up ($n = 2$). Current smokers of only pipes and cigars, but not cigarettes, were also excluded ($n = 347$). Our study sample therefore comprised 55,745 participants. The current study was approved by the Regional Committees for Medical and Health Research Ethics (REK), 2014/226/REK Central.

Genotyping

DNA was extracted from blood samples collected at baseline in HUNT2 and stored at the HUNT biobank. The rs1051730 SNP was genotyped at the HUNT biobank using a TaqMan assay (Assay ID: C_9510307_20, Applied Biosystems, USA) on an Applied Biosystems 7900HT Fast Real-Time PCR System, as described in former HUNT studies[15,16]. The call rate cut-off was set to 90%. The genotype was coded according to the number of T alleles (0 = no T allele, 1 = heterozygote for the T allele, 2 = homozygote for the T allele). The genotyping success rate was 99.3% and the quality score for each individual genotype was >90 (mean 99.6). There was no evidence of departure from the Hardy–Weinberg equilibrium (χ^2 test, $P = 0.26$). The minor allele frequency was in agreement with HapMap-CEU data (MAF = 0.335 and 0.389, respectively).

Smoking

Smoking status was self-reported in the HUNT2 questionnaire and categorised into never, former and current smokers. Current smokers were asked to report the average number of cigarettes smoked per day. Individuals, who reported being current smokers of pipes and cigars, but not cigarettes, were excluded from all analyses.

Covariates

Height and weight were measured by trained personnel. BMI is weight in kilograms divided by height in meters squared. Cardiovascular disease (CVD) was defined as a composite of myocardial infarction, angina or stroke[22].

Outcome

The outcome of interest was the first hip or knee replacement due to primary OA. To retain statistical power, hip and knee replacements were combined to one variable; total joint replacement (TJR). The unique 11-digit identity numbers of Norwegian citizens enabled us to link individuals' baseline data in HUNT2 with the corresponding prospective TJR data in the Norwegian Arthroplasty Register. The orthopaedic surgeon submits a standardized form to the register for each TJR performed, containing information about the diagnosis that lead to the TJR, any previous TJR or other operations performed in the joint, and the type of implant used. We censored TJRs secondary to injury (meniscal or ligamentous), rheumatoid arthritis, femoral neck fracture, congenital dysplasia, Perthes' disease, epiphysiolysis, ankylosing spondylitis and osteonecrosis of the femoral head, amongst others. The completeness of reporting hip and knee replacement in the register is high (>95%)[23,24].

Statistical analysis

Descriptive statistics according to the number of rs1051730 T alleles were compared using a χ^2 test for categorical variables and a linear regression for continuous variables. A Cox proportional hazards model was used both for the observational and Mendelian randomisation analyses. Estimates were given as hazard ratios (HRs) with 95% confidence intervals (CIs). Follow-up began on the day of inclusion in HUNT2 and ended at the date of TJR due to primary OA, date of TJR for conditions other than primary OA, date