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SINGLE-PAYER HEALTH INSURANCE MAY NOT MITIGATE INCOME-BASED DIFFERENCES IN TOTAL HIP ARTHROPLASTY UTILIZATION: A TRANSNATIONAL ANALYSIS

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Purpose (the aim of the study): Access to care varies across health systems. Countries with universal health insurance are thought to have less wealth-based health disparities, but it is unclear if this applies to total hip arthroplasty (THA) utilization and outcomes. The purpose of this study was to determine whether a single-payer healthcare system would mitigate income-based disparities in THA utilization and outcomes.

Methods: We retrospectively compared all patients undergoing THA from 1/2012 to 9/2018 in Ontario (ON), Canada and Pennsylvania (PA), United States. We obtained PA patient data from Pennsylvania Health Care Cost Containment Council and ON patient data from Ontario's Institute for Clinical Evaluative Sciences. Patient-level data were linked to Census data of median household income of the ZIP code or postal code of patients' residence. We then analyzed whether community income-based differences in THA utilization were reduced in Ontario compared to Pennsylvania due to Canada's single-payer healthcare system. We used logistic regression to examine the relative risks for lowest community income of outcomes such as rates of 1-year revision, 90-day mortality, and 90-day readmission in the two regions.

Results: Among all THAs, 13,280 patients (15.8%) and 16,850 patients (16.0%) lived in communities within the lowest income quintile in Ontario and Pennsylvania, respectively **(Table 1).** Overall THA utilization was lower in Ontario compared to Pennsylvania across income groups **(Figure 1)**. In Ontario, patients in the highest income quintile utilized THA 43.2% more than those in the lowest income quintile (12.6 vs 8.8); this difference in utilization was slightly greater than the difference in Pennsylvania, where patients in the highest income quintile utilized THA 41.7% more than patients in the lowest income quintile (21.4 vs. 15.1) ($p < 0.001$). Patients in the lowest community income quintile in Pennsylvania had a greater rate of 1-year revision, 90-day mortality, and 90-day readmission compared to patients in the lowest income quintile of Ontario. However, after adjusting for age, sex, hospital volume, and rural vs. urban hospital, the odds for patients in the lower-income group compared to the higher-income group of 1-year revision (ON: OR 1.70, 95% CI: [1.34, 2.15]. PA: 1.30 [1.12, 1.52]), 90-day mortality (ON: 1.92 [1.24, 2.98]. PA: 1.66 [1.18, 2.33]), and 90-day readmission (ON: 1.48 [1.34, 1.62]. PA: 1.43 [1.34, 1.54] were greater in Ontario compared to Pennsylvania **(Figure 2)**.

Conclusions: Income-based differences in THA utilization were greater in Ontario than in Pennsylvania. Additionally, patients in low-income communities in Ontario were at greater risk relative to higher community income patients for adverse outcomes. These findings suggest that a single-payer insurance system may not be sufficient to eliminate income-based differences in utilization and complications of THA.

Table 1: Characteristics of patients who underwent Total Hip Arthroplasty in Ontario or Pennsylvania

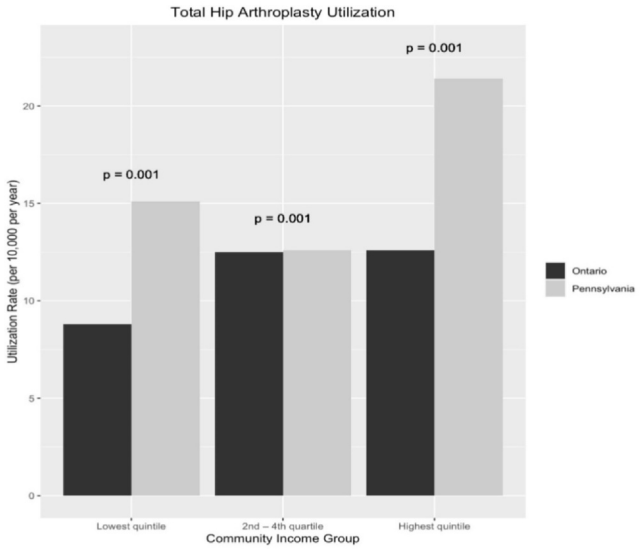

Figure 1: Utilization rate of total hip arthroplasty for patients in Ontario and Pennsylvania by community income level

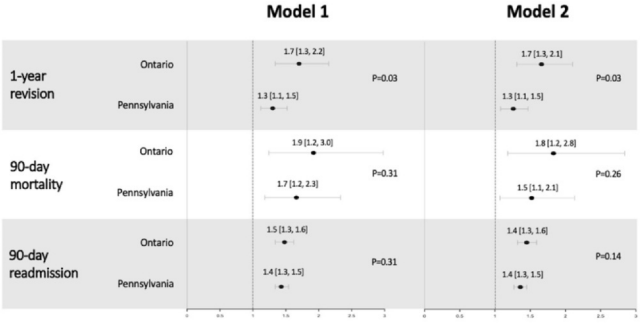

Figure 2: Adjusted odds ratios and 95% confidence intervals for risk of adverse outcomes in lowest community income group compared to highest community income group.Note: Model 1 adjusts for income group, age, sex, hospital volume, rural / urban hospital. Model 2 adjusts for income group, age, sex, hospital volume, rural / urban hospital, and Elixhauser index.

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EPIGENOMIC LANDSCAPE ACROSS HUMAN ARTICULAR CARTILAGE DEVELOPMENT

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Purpose (the aim of the study): The articulating human knee joint develops from a homogenous condensation of mesenchymal stem cells. This process requires the orchestrated expression of a multitude of genes. The transcriptome is primarily regulated through the spatiotemporal expression of transcription factors, yet epigenetic processes, including DNA methylation (DNAm) both underlie and reinforce developmental plasticity.

Genetic risk factors contribute ~30% to the lifetime risk of developing knee OA. Previous studies have identified methylation quantitative trait loci co-localising with OA risk SNVs (OA-mQTLs). This interplay between DNA sequence and methylation status has further been shown to underpin tissue-specific mechanisms of cartilage gene expression.

Developmental factors also play a role in the risk of OA. Our recent, targeted study investigated the presence of OA-mQTLs in developing human limbs, at 7 well-characterised loci, comprising 39 CpGs. At this small number of loci, we identified that 85% of the OA mQTLs also operated in foetal tissues.

Here, we examined the methylome of developing distal femoral cartilage. We sought to identify the presence of differentially methylated regions (DMRs) across a broad developmental window. Furthermore, we investigated the overlap between mQTLs within developing cartilage and OA risk SNVs.

Methods: Human foetal tissues (n=72, F=35, M=37) were obtained with informed consent from the Human Developmental Biology Resource (HDBR), Newcastle and London, UK. Samples ranged from 7-21 post-conception weeks (pcw; mean=13.3). The articular surface of the developing cartilage was micro-dissected and homogenised for nucleic acid extraction. DNA was used directly for genotyping (Infinium Global Screening Array, Illumina) or bisulphite converted (EZ DNA Methylation Kit, Zymo Research) for methylation analysis (Human MethylationEPIC, Illumina). Genotype imputation was performed via the Michigan Imputation Server (EUR) using the haplotype reference consortium (HRC) as reference population. The R package minfi was used to process DNAm data. Following QC, 677,677 CpGs were retained for analysis. Principal component analysis was performed on M-values using factoExtra. Differential methylated (DMR) analysis was performed using dmrff. QTL analysis was performed using the matrixEQTL R package, including batch, sex and developmental stage as covariates and testing for *cis*-associations within 500kb.

Results: Principal component analysis revealed developmental stage to have the largest influence upon global DNAm (accounting for 17.3% of the observed changes), with 47% of CpGs becoming *hypo*methylated over time. We identified 9912 developmental DMRs (dDMRs; n=2-58 CpGs) (FDR < 0.001, log2fc > 0.1). This highlighted genes and their regulatory elements essential for cartilage development, including *HOXA3* (n=58 CpGs; $3.5x10^{-122}$), *HOXD3* (39; $7.5x10^{-146}$), *SPON2* (25; $3.9x10^{-115}$), and *TBX3* (24; $1.1x10^{-08}$). GO analysis identified significant enrichment of biological processes including regulation of anatomical structure morphogenesis (FDR=$3.7x10^{-21}$), tissue morphogenesis ($9.2x10^{-21}$), and skeletal system development ($3.4x10^{-20}$). Intersection of these regions with open chromatin peaks from foetal knee cartilage (12pcw) identified overlap with 1996 dDMRs (20%).

Epigenome-wide mQTL analysis revealed 537,391 significant correlations between SNV genotype and DNAm at proximal CpGs (Bonferroni adjusted P-value (P.adj) < 0.05), consisting of 15,331 individual CpGs. Within this analysis, significant mQTLs (P.adj=0.03-$1.5x10^{-26}$) overlapped with 33 reported OA risk variants, correlating with DNAm at 40 CpGs across 20 risk loci, including those harbouring the genes *COLGALT2*, *ALDH1A2*, and *RUNX2*. Of the 40 CpGs, only 8 (20%) had previously been identified as co-localising with OA risk SNVs in previous studies of aged cartilage.

Conclusions: Here, we have investigated the epigenomic trajectory across development of the human knee, representing the first insight into methylomic plasticity across a large window of human skeletal development. We identified that developmental stage is the predominant determinant of methylation status within our samples, with ~12% of CpGs significantly changing across the captured period. Many dDMRs mapped to known drivers of limb development, including the *HOX* gene family, ECM proteins, and transcriptional regulators, highlighting the essential role of the DNA methylome in underlying and/or reinforcing such transcriptional changes.

mQTL analysis revealed overlap between mQTLs and known OA risk SNVs, confirming that the genetic and epigenetic interplay underlying OA risk can operate within chondrocytes from the start of life. Future studies including both aged and developmental samples will serve to identify potential subsets of genetic risk loci which are active across the human lifecourse, requiring earlier interventions to prevent the onset and progression of disease.

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EARLY-STAGE VS ESTABLISHED KNEE OSTEOARTHRITIS: A COMPARATIVE STUDY ON THE PREVALENCE, CHARACTERISTICS, AND OUTCOMES OF SUPERVISED EXERCISE AND EDUCATION AMONG 10, 365 PATIENTS

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Purpose (the aim of the study): It is hypothesized that an early-stage knee osteoarthritis (KOA) diagnosis allows for risk reduction and disease control earlier after symptom onset. However, early diagnosis is challenging. Radiography is unsuitable for early detection, and clinical criteria such as EULAR (European Alliance of Associations for Rheumatology) and ACR (American College of Rheumatology) may be biased towards advanced OA.

The 2021 Criteria for the Early Diagnosis of knee Osteoarthritis (CREDO) uses 7 clinical baseline factors to predict KOA diagnosis by 5 to 10-years follow-up. In a validation study investigating Osteoarthritis Initiative (OAI) participants at elevated risk of KOA, those diagnosed by CREDO showed significantly worse knee structure and symptom deterioration over 9 years compared to those undiagnosed. This shows a potential to identify individuals who might benefit from preventive strategies early in the disease process.

The Good Life with osteoArthritis in Denmark (GLA:D) program recruits patients with OA-related symptoms seen in primary care. It combines supervised exercise therapy and education to improve pain, function and quality of life. This study investigated GLA:D knee patients in fulfillment of 'early-stage' (CREDO) and 'established' (ACR/EULAR) KOA criteria, and compared changes in pain, function, and quality of life.

Methods: Data from patients with KOA-related complaints who started the GLA:D program in Denmark between May 2018 and May 2020 was analyzed. The program comprises 2 educational and 12 supervised neuromuscular exercise sessions, facilitated by trained physiotherapists. Patient groups were delineated based on the fulfillment of clinical criteria for 'established' and 'early-stage' KOA. The latter was diagnosed as previously reported, using model equations for probability estimates, which were categorized by higher 'CREDO 1' (≥ 70%) and lower 'CREDO 2' (> 30%) thresholds. The proportions of complete cases meeting a minimal clinically important improvement (MCII) was assessed for the primary outcome (pain intensity using the Visual Analogue Scale (VAS) 0-100 mm, MCII: -11) and KOOS QOL (0-100 points, MCII: 10) at 3 months (directly after the program) and 12 months, and for the 40-m walk test (MCII: 0.095 m/s) and 30-s chair stand test (MCII: 2 rises) at 3 months. Also, baseline values and changes in outcomes were analysed using mixed models with all available datapoints, adjusted for age, sex, BMI, and education.

Results: At baseline, the patients (n = 10,365) had a mean age of 65.4 years (SD 9.6), 68.8% (n = 7,135) were female, and mean BMI was 29.1 kg/m^2 (SD: 5.6). Figure 1 shows the overlap in fulfillment of criteria. The CREDO1 threshold was exclusively met by 27% of patients (CREDO1-only). Meanwhile, 62% of patients met at least one of the 'established KOA' criteria (ACR/EULAR). This group showed marked differences with patients who exclusively met the (lower) CREDO2 threshold (CREDO2-only; 10%), including higher analgesics usage (70% vs 40% of patients) and VAS pain intensity (mean (SE) mm, 51 (0.3) vs 34 (0.6)) at baseline, and larger improvements in pain (-15 (0.4) vs -10 (0.9); Table 1) at 12 months. However, the groups were similar in the proportion of patients who achieved a MCII in pain intensity (CREDO1-only: 53%, 'established KOA': 54% and CREDO2-only: 44%). At 12 months, improvement in KOOS QOL (mean (SE) points) was 10 (0.6) in the CREDO2-only group to 11 (0.4) in the CREDO1-only group, and 48 to 49% respectively, achieved a MCII. In the 40-m walk test and 30-s chair tests at 3 months, 50% and 53% in the CREDO2-only group to 56% and 59% in the 'established KOA' group, respectively, achieved a MCII.

Conclusions: Most GLA:D knee patients (82 and 98%) met the CREDO I and II criteria for 'early-stage' KOA. A third of these patients did not meet 'established KOA' criteria yet achieved similar improvements at 3 and 12 months as those who did. These findings support GLA:D as a viable management strategy for 'early-stage' KOA.