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# **MARKERS ASSOCIATED WITH SYNOVIAL INFLAMMATION CAN IDENTIFY WOMEN AT HIGH RISK OF DEVELOPING PAINFUL RADIOGRAPHIC KNEE OSTEOARTHRITIS: A PROSPECTIVE COMMUNITY BASED COHORT.**

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## **Abstract:**

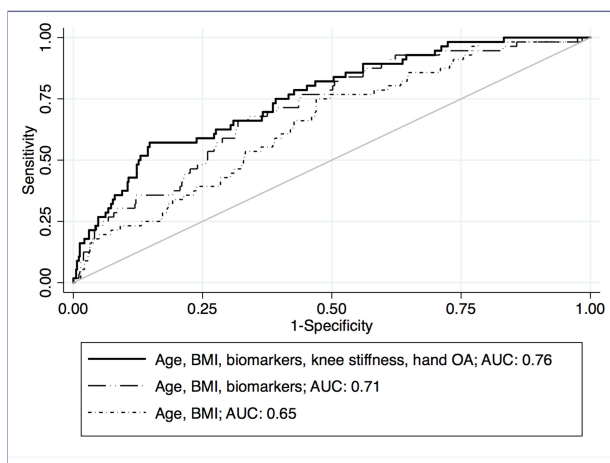
**Purpose:** Knee osteoarthritis (KOA) is commonly defined by radiographic changes and knee pain. KOA has a multifactorial aetiology, but there are several well-recognised strong risk factors for the incidence of KOA. These include age, sex, body mass index (BMI), previous injuries, bone density, smoking and pre-existing hand osteoarthritis (HOA). Factors associated with mild systemic and synovial inflammation are potential markers for KOA incidence.

The hypothesis for this research was that selected markers associated with synovial inflammation and/or variables linked with metabolic syndrome (MetS) are prognostic for KOA incidence. Self-reported knee stiffness, serum markers associated with knee synovitis, and variables associated with MetS were selected as potential risk factors for KOA incident.

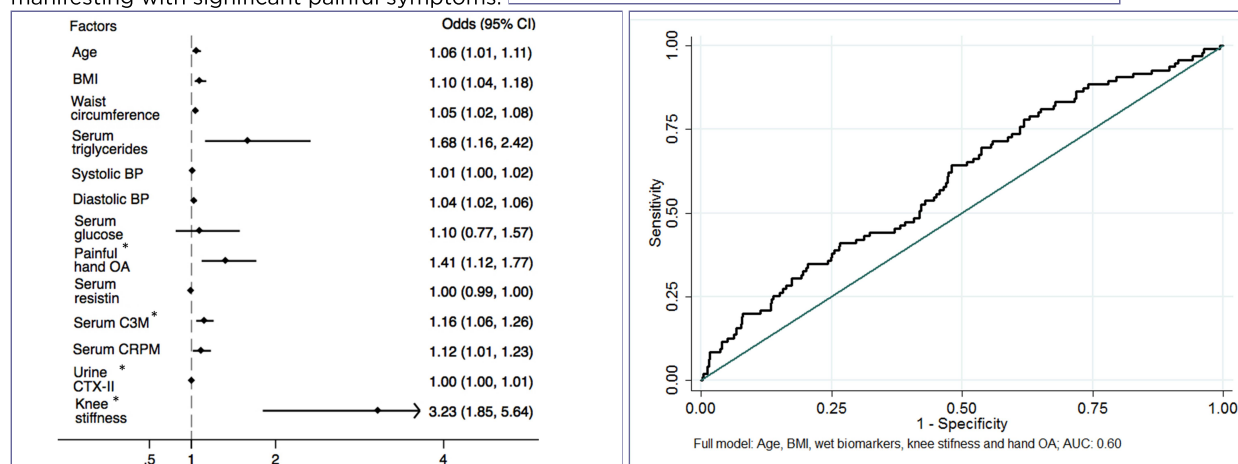
**Methods:** We included a subgroup of the Chingford Cohort, a prospective, population-based cohort study of representative for the UK group of middle-aged women, with no baseline RKOA (n=750) for analysis. 82% (Median age 52.9, mean BMI 24.2) of them were followed-up and had radiographic and knee pain data collected during a 10-year follow-up visit. Women were classified as having no RKOA if they had a Kellgren-Lawrence (K/L) grade of 0 in both knees at baseline. They were classified as having RKOA if they had a K/L grade of 2 or more in at least one knee at year 10 follow-up. Participants were asked if they had experienced any knee pain in the past month and the number of days this had occurred. Knee pain was classified as positive if 'yes' and 'more than 0 days' were reported. Painful RKOA was defined as RKOA and knee pain in the same side. 9% developed painful RKOA and 15% RKOA not associated with any knee pain. Systemic and knee specific factors linked with inflammation, were selected as potential risk factors for painful RKOA incidence in univariate logistic regression models. Potential risk factors included self-reported knee stiffness, three novel serum markers (Resistin, Matrix metalloproteinase (MMP)-generated collagen type III (C3M) and CRP (CRPM)) and variables associated with MetS components. Established risk factors were also included in the analyses: presence of HOA and urine concentration of CTX-II. Variables statistically significant in the univariate analysis were selected for inclusion in the multivariate models adjusted for baseline age and Body Mass Index (BMI). Those statistically significant after adjusting for baseline age and BMI were then tested together to estimate risks of either a) painful RKOA or b) non-painful RKOA incidence at 10-year follow-up. Model discrimination of the models were estimated using area under the curve (AUC) measurement.

**Results:** Only BMI and the waist circumstance were positively associated with incident of non-painful RKOA in univariate logistic regression models. Knee stiffness, serum C3M, urinary CTX-II and presence of HOA at baseline, were predictors of incident painful RKOA independently to age and BMI. Results of the final risk model based on those variables were significantly different for incidence of painful and non-painful RKOA, with discriminatory analysis showing an AUC of 0.76 (95% confidence interval: 0.70-0.82) and AUC 0.60(95% CI:0.51-0.63) respectively.

**Conclusions:** For the first time RKOA has been shown to have different risk factors, which vary according to the presence or absence of knee pain. This analysis supported the hypothesis that markers linked with either systemic or local inflammation can aid in identifying individuals at higher risk of developing painful RKOA. Furthermore, markers associated with synovial inflammation are good predictors for incidence of RKOA associated with pain. Ability to more accurately profile groups at risk of KOA will potentially make primary and secondary preventive intervention trials feasible. This also suggests that KOA is a heterogeneous disease, with a different pathogenesis of radiographic disease associated with pain to one which is not



manifesting with significant painful symptoms.



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