Background: Overweight and obesity are associated with greater incidence and progression of the structural defects of knee osteoarthritis, but it is unknown if weight loss is of benefit.

Objectives: To describe the association between change in body mass index (BMI) and the incidence and progression of structural defects of knee osteoarthritis.

Methods: Scores from radiographic analyses of knees at baseline and at 4 to 5 years’ follow up were obtained from three independent data sets (the OA Initiative, MOST data sets from the United States from America, and the CHECK data set from the Netherlands). The exposure of interest was change in BMI from baseline to 4 to 5 years’ follow up. To investigate the incidence of structural defects of knee osteoarthritis, we selected a total of 9732 knees (from 5802 participants) that had a Kellgren-Lawrence (KL) grade of knee osteoarthritis at baseline of ‘none’ (0) or ‘doubtful’ (1) (the ‘incidence cohort’), and determined the odds of having a KL grade at follow-up of ‘minimal’ (2), ‘moderate’ (3), or ‘severe’ (4) (the ‘incidence cohort’). To investigate progression, we selected a total of 6084 knees (from 3996 participants) that had a KL grade at baseline of ‘minimal’ (2), ‘moderate’ (3), or ‘severe’ (4) (the ‘progression cohort’), and determined the odds of increasing by 1 or more KL grades by follow up. The degeneration of three individual structural features of knee osteoarthritis (i.e., joint space narrowing, osteophytes on the femoral surface, and osteophytes on the tibial surface), on both the medial and lateral sides of the knee, were also investigated in both the incidence and progression cohorts. Here, degradation was defined as an increase by 1 or more Osteoarthritis Research Society International (OARSI) grades.

Results: Change in BMI was positively associated with both the incidence and progression of knee osteoarthritis, as defined by KL grade. Specifically, for each one-unit change in BMI, the adjusted odds ratio for incidence was 1.05 (95% confidence interval [CI] 1.02 to 1.09), and for progression, the same adjusted odds ratio and 95% CI was also observed. Change in BMI was also positively associated with degradation (i.e., narrowing) of joint space on the medial but not the lateral side of the knee, with an adjusted odds ratio of 1.08 (95% CI 1.04 to 1.12) in the ‘incidence cohort’ and 1.08 (95% CI 1.03 to 1.12) in the ‘progression cohort’. Degradation of the tibial and femoral surfaces (i.e., osteophytes) was also seen on the medial but not the lateral side of the knee, but only in one of the two cohorts investigated (the ‘incidence cohort’), with an adjusted odds ratio of 1.07 (95% CI 1.03 to 1.12) for osteophytes on the femoral surface, and 1.05 (95% CI 1.01 to 1.09) for osteophytes on the tibial surface.

Conclusion: Each one-unit reduction in BMI was associated with a 5 to 8% decrease in the odds of the incidence and progression of the structural defects of knee osteoarthritis, with lower odds of structural degradation specific to the medial – not lateral – side of the knee.

Acknowledgements: We acknowledge the provision of datasets and/or research tools from three studies: the Osteoarthritis Initiative (OAI) Study; the Multicenter Osteoarthritis Study (MOST); and the Cohort Hip and Cohort Knee (CHECK) Study. The OAI is a collaborative informatics system created by the National Institute of Mental Health and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) to provide a worldwide resource to quicken the pace of biomarker identification, scientific investigation and OA drug development. The OAI data repository is housed within the National Institute of Mental Health (NIMH) Data Archive (NDA). For the MOST data set, we wish to acknowledge the contributions of the study participants, investigators and research staff involved. MOST is comprised of four (4) cooperative grants: U01 AG18820 David T.elson (Boston University); U01 AG18822 James Torner (University of Iowa); U01 AG18847 Cora E. Lewis (University of Alabama at Birmingham); U01 AG19069 Michael C. Nevitt (University of California, San Francisco), funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by MOST investigators. This manuscript was prepared using MOST data and does not claim, infer, or imply endorsement by MOST, by the MOST investigators and their respective institutions or by the University of California of the Data Recipients’ use of the Data, or the entity or personnel conducting the research, or of any results of the research.

The CHECK study is funded by the Dutch Arthritis Foundation. Involved are: Erasmus Medical Center Rotterdam; Kennemer Gasthuis Haarlem; Leiden University Medical Center; Maastricht University Medical Center; Martini Hospital Groningen /Affiliated Health Care Center for Rheumatology and Rehabilitation Groningen; Medical Spectrum Twente Enschede /Ziekenhuisgroep Twente Almelo; Reade Center for Rehabilitation and Rheumatology; St.Maartens-kliniek Nijmegen; University Medical Center Utrecht and Wilhelmina Hospital Assen.

Disclosure of Interests: Zubeyr Salis: None declared, Helen Keen: None declared, Blanca Gallego: None declared, Tuan van Nguyen: None declared, Amanda Sainsbury Speakers bureau: ZS and AS own 50% each of the shares in Zuman International, which receives royalties for books AS has written and payments for presentations, and provides paid training for higher degree students. AS additionally reports receiving presentation fees and travel reimbursements from Eli Lilly and Co, the Pharmacy Guild of Australia, Novo Nordisk, the Dieticians Association of Australia, Shoulhaven Family Medical Centres, the Pharmaceutical Society of Australia, and Metagenics, and serving on the Nestle Health Science Optifast VLCD advisory board from 2016 to 2018. Consultant of: ZS and AS own 50% each of the shares in Zuman International, which receives royalties for books AS has written and payments for presentations, and provides paid training for higher degree students. AS additionally reports receiving presentation fees and travel reimbursements from Eli Lilly and Co, the Pharmacy Guild of Australia, Novo Nordisk, the Dieticians Association of Australia, Shoulhaven Family Medical Centres, the Pharmaceutical Society of Australia, and Metagenics, and serving on the Nestle Health Science Optifast VLCD advisory board from 2016 to 2018.


OP0228

USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND RISK OF COMORBIDITIES IN PEOPLE WITH AND WITHOUT OSTEOARTHRITIS - A UK PRIMARY CARE DATABASE COHORT STUDY

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Background: People with osteoarthritis (OA) are at higher risk of developing a wide array of comorbidities. Whether the use of non-steroidal anti-inflammatory drugs (NSAIDs) contributes to the increased risk of some incident comorbidities remains unknown.

Objectives: To examine the contribution of NSAIDs in the development of a wide range of comorbidities in people with and without OA.

Methods: This observational cohort study used the UK primary care Clinical Practice Research Datalink (CPRD) GOLD containing data on 20+ million people covering 937 practices. We identified 259,000 people with incident OA and 259,000 people covering 937 practices. We identified 259,000 people with incident OA and 259,000 people at age ≥2 years, sex, and practice matched controls at 1:1 ratio. Controls were assigned the same index date (the date of first diagnosis of OA) as cases for the start of follow-up. Both cases and controls were further divided into two groups according to NSAID prescriptions at any time after the index date. This allowed us to examine both the main effect of each exposure and interaction between OA and NSAID exposure after the index date. People with an NSAID prescription before the index date were excluded from the study. NSAID exposure was defined as at least two prescriptions within 90 days. Exposure status of each participant was assessed every six months as yes (yes to the end of the study outcome of interest), no (no evidence of exposure to this drug available, whichever came first. Comorbidities were grouped into 9 categories as cancer, cardiovascular disease (CVD), endocrine, psychological, renal, gastrointestinal (GI), genitourinary, hepatic, and neurological conditions. Propensity scores for the prescription of NSAIDs were calculated using a logistic regression model including age, sex, body mass index (BMI), musculoskeletal and pain related conditions covariates. The propensity score adjusted time varying exposure analysis was undertaken using a multivariate COX model and hazard ratio (HR) and 95% confidence intervals were calculated. Proportional hazard assumption was tested using Schoenfeld test. Smoking, alcohol, the use of proton pump inhibitors (PPIs) and other comorbidities were included in the adjusted model. The additional contribution of NSAIDs
and OA towards the incident comorbidity was estimated using additive interaction methods. We also investigated the individual risk across non-selective, and COX-2 selective NSAIDs.

Results: The mean age was 59.4±12.8 years in people with OA and 60.2±12.8 years for controls with 57.7% being female. Nearly two thirds of people with OA were prescribed NSAIDs as defined, compared to one third in the control population. People with OA and exposed to NSAIDs had highest risk of developing psychological (1.51: 1.43, 1.60), CVD (1.38: 1.33, 1.43), cancer (1.94: 1.25, 1.44), GI (1.25: 1.16, 1.34) and renal (1.17: 1.11, 1.24) comorbidities after adjusting for all the covariates and PPI drugs, compared to the non-OA and non-NSAID group. (Figure 1) Interaction between OA and NSAID was significant for cancer, GI, renal, hepatic, and neurological outcomes. Within people with OA, non-selective NSAIDs increased the risk of CVD (1.25: 1.20, 1.30), cancer (1.11: 1.04, 1.19), endocrine (1.15: 1.10, 1.19), renal (1.19: 1.13, 1.26) and psychological (1.21: 1.15, 1.28) comorbidities, whereas COX-2 selective NSAIDs increased risk of incident CVD (1.34: 1.25, 1.44), endocrine (1.13: 1.04, 1.12), renal (1.25: 1.14, 1.37), and psychological (1.21: 1.09, 1.34) comorbidities.

Conclusion: Use of NSAIDs among people with OA is associated with increased risk of a wide variety of comorbidities. Non-selective and COX-2 selective NSAIDs are both associated with increased risk of cardiovascular, renal, and psychological comorbidities.

Acknowledgements: We thank the Patient Research Participants (PRP) members Jenny Cockshull, Stevie Vanhegan, and Irene Pitsillidou for their involvement since the beginning of the project. We would like to thank the FOREUM for financially supporting the research.

Disclosure of Interests: Subhashia Swain: None declared, Anne Kamps: None declared, Jos Runhaar: None declared, Andrea Dell’Isola: None declared, Michael Doherty Consultant of: Consultant of: Advisory boards on gout for Grunenthal and Mallinckrodt, Grant/research support from: Michael Doherty Grant/research support from: AstraZeneca funded the Nottingham Sons of Gout study, Aliya Sarmanova: None declared, Daniel Prieto-Alhambra Speakers bureau: paid speaker services from Amgen and UCB Biopharma., Consultant of: His department has received advisory or consultancy fees from Amgen, AstraZeneca, Johnson, and Johnson, and UCB Biopharma, Grant/research support from: Prof. Prieto-Alhambra’s research group has received grant support from Amgen, Chesi-Taylor, Novartis, and UCB Biopharma., Martin Englund: None declared, S.M.A. Bierma-Zeinstra: None declared, Weiya Zhang Speakers bureau: Bioiberica as an invited speaker for EULAR 2016 satellite symposium, Consultant of: Consultant of: Grunenthal for advice on gout management,


Figure 1. Hazard ratio of developing different comorbidities (reference group: no OA and no NSAIDs) OA: Osteoarthritis; NSAIDs: Non-steroidal anti-inflammatory drugs.

Scientific Abstracts

OP0229

OSTEOARTHRITIS OF THE KNEE, INFLAMMATION, AND THE EFFECT OF ADALIMUMAB (OKINADA): A RANDOMIZED PLACEBO-CONTROLLED TRIAL

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Background: Cytokines such as tumor necrosis factor (TNFα) have been shown to elicit inflammatory and catabolic events in the joints of patients with osteoarthritis. Recent RCTs demonstrated that TNFα inhibition has no effect on pain and MRI-detected synovitis or bone marrow lesions in patients with erosive hand OA1,2. However, the progression of bone erosions was reduced in a subgroup of patients with more clinically swollen distal interphalangeal joints in one RCT1. Consequently, it remains possible that TNFα inhibition may have beneficial effects in specific subgroups of patients with a high inflammatory component.

Objectives: We aimed to evaluate the efficacy and safety of a TNFα inhibitor, adalimumab (ADA), in a proof-of-concept study in patients with inflammatory OA of the knee.

Methods: OKINADA was a 52-week, randomized, double-blind, placebo-controlled, parallel-group study done at 11 sites in Canada (NCT02471118). Eligible participants were adults (aged ≥18 years) with a diagnosis of OA of the index knee and classified according to American College of Rheumatology criteria, including radiological evidence of OA (Kellgren-Lawrence grades 2 or 3) with clinical signs of knee effusion. Subjects had persistent knee pain of ≥1 month duration with a pain score of ≥4 (0-10 NRS) in the index knee at screening and baseline despite conventional treatment with maximum tolerated acetaminophen and/or non-steroidal anti-inflammatory drug. Patients were randomly assigned (1:1) to receive subcutaneous 40 mg ADA every 2 weeks or placebo (PBO). Primary endpoint was the Outcome Measures in Rheumatology and Osteoarthritis Research Society International set of responder criteria (OMERACT-OARSI) at week 16 defined as: (1) improvement in pain or function ≥50% and an absolute change ≥20 mm; or (2) improvement of ≥20% with an absolute change ≥10 mm in at least two of the following three categories: pain, function, and patient’s global assessment. Secondary endpoints included: the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the domains of pain, activities of daily living (ADL), OA symptoms, sport and recreation function (SRF), and knee-related quality of life (QoL), patient’s global assessment of disease status (PGAD), investigator global assessment of disease status (IGAD), and expanded Target Joint Assessment (TJA) score.

Results: A total of 59 patients were randomized (29 to PBO, 30 to ADA). The primary endpoint was not met: OMERACT-OARSI combined (ADA: 9 [30.0%] vs PBO: 7 [24.1%], p=0.62). For KOOS pain, ≥20% improvement was noted in 11 (36.7%) ADA vs 7 (24.1%) PBO patients (p=0.30), and ≥50% improvement in 5 (16.7%) ADA vs 6 (20.7%) PBO patients (p=0.69). There were no significant treatment-group differences in baseline to 16-week change in continuous secondary endpoints (ADA vs PBO: KOOS ADL 6.5 vs 8.4 (p=0.71), KOOS QoL 10.1 vs 7.4 (p=0.66), KOOS symptoms 78 vs 115 (p=0.42), KOOS SRF 5.8 vs 7.7 (p=0.76), PGAD -1.0 vs 0.1 (p=0.10), IGAD -1.5 vs -2.1 (p=0.30), TJA -2.4 vs -2.2 (p=0.87) or in lab markers (ESR, CRP). There were 11 withdrawals (4 ADA, 7 PBO) of which 2 were for adverse events (1 ADA, 1 PBO) and 2 for increasing knee pain (1 ADA, 1 PBO). No new safety signals were identified and there were no serious adverse events.