Methods

Study Population

We drew on the UK Biobank study population of 502,494 study subjects who provided consent without withdrawing as assessed on May 1, 2020 to consider associations between analgesic medication use by medication category on development of chronic back pain. For the present analysis, to classify back pain inclusion and outcome status, we drew on touch screen questionnaire data from baseline (v0) and from the first two of subsequent visits (v1 and v2) as implemented on a subset of subjects. Subjects were selected into the study based on the question "In the last month have you experienced any of the following that interfered with your usual activities? (You can select more than one answer)" if back pain was selected at v0 (field 6159), amounting to 130,084 individuals. We excluded subjects who answered “Yes” to “Have you had back pain for more than 3 months (field 3571), leaving 40,531 subjects. We then only included subjects who answered the verbal interview question on number of medications entered (field 137), and who answered the field 3571 back pain question data at v1 or v2 (435 subjects were present for v1 and v2), leaving a final set for inclusion of 2,624 subjects. Family relatedness among the 2,624 subjects was considered and only two pairs of individuals were found to be related; one individual was selected at random for inclusion. The final set of controls who reported acute back pain at v0 but did not develop chronic back pain at v1 or v2 was 2,163 subjects (answering no to the back pain question (field 3517) and 461 cases developed chronic back pain at v1 or v2 (answering yes to the back pain question (field 3517)). The mean span between v0 and v1was 4.4 years (SD = 0.91) for cases and 4.4 years (SD =0.91) for controls, and between v0 and v2 was 7.7 years (SD = 1.4) for cases and 7.7 years (SD = 1.4) for controls.

Based on field 137 from the verbal interview at v0, we considered medications with known analgesic effects falling into categories NSAIDs, paracetamol, opioids, anti-depressants and pregabalin/gabapentin. We also considered corticosteroids -- after examination of individual entries falling under corticosteroids, we noted that for all but seven subjects who developed chronic pain at a subsequent visit, the type of corticosteroids reported were topical. Given the small sample size among cases of systemic corticosteroid use, this medication category was discarded from analyses. In order to classify individual mediation use, specific drug name reported for each individual (trade name or generic) as mentioned in DF:20003.0 (baseline, <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20003>) considered according to the code assigned for the particular drug in the UKB database. This code was used to match with the WHO ATC code (https://www.whocc.no/atc\_ddd\_index/) for each drug. The first three levels of the ATC code were used to assign class favoring analgesic medication classes in case of ambiguity. Drug taken by fewer than 10 individuals were not considered. Baseline differential leukocyte percentages were accessed from the fields 30220, 30210, 30180, 30190 and 30200 for basophils, eosinophils, lymphocytes, monocytes and neutrophils, respectively.

Statistical Methods

We fit logistic regression models to test for association between each of these categories and development of chronic back pain at v1 or v2. Preliminary data analysis identified potential confounders: age at baseline, sex and ethnicity – these variables were used as covariates in all logistic regression models. Models were fit one by one for each medication exposure variable. A full model was fit including all medication categories together. Logistic regression modeling was conducted in R v. 4.0.2 using the function glm with the binomial (logit) family specified for estimation of odds ratios and Wald tests were conducted and corresponding p-values computed for each explanatory variable.

Results

Odds ratio (OR) risk estimates and their 95% confidence intervals as well as Wald test p-values are presented in Table X across explanatory variables in a separate model for each of the medication categories (Models 1-5) and in the full model including all medication categories (Model 6) from multivariate logistic regression analyses. Elevated risk of back pain chronicization was identified for NSAIDs only (Model 1), and this was maintained in the full model, adjusting for use of all other medication categories. From Model 1, individuals with acute back pain were at 1.74 (1.34-2.25) times greater risk of developing chronic back pain if they reported NSAID usage (p = 0.00027) than if they were not taking NSAIDs, adjusting for age, sex and ethnicity. This estimate remained nearly unchanged at 1.74 (1.31-2.29) when additionally adjusting for usage of the other analgesics, paracetamol, opioids, anti-depressants and pregabalin/gabapentin (Model 6), (p = 0.000075). No other analgesic medication category showed statistically significant association with back pain chronicization, either across models with the corresponding medication class variable adjusted for demographic covariates alone (Models 2-5), or in the full model (Model 6).

Next, we looked at association of different leukocyte subset percentages with back pain chronicization by adding each cell subset, one at a time, to the full model (model 6). Odds ratio risk estimates and their 95% confidence intervals as well as Wald test p-values are presented in Table X (model 7) for neutrophils and Supplementary Table XX (models 1-4) for all other subsets. Only neutrophil and lymphocyte percentages were associated with back pain chronicization with OR of 0.98 (0.97-0.99) and 1.02 (1.00-1.04), respectively. The protective association of neutrophils with back pain chronicization was absent in individuals who consumed NSAIDs (Supplementary Table XX, model 7).

Table X. Adjusted Odds Ratios among xxx subjects from the UK Biobank reporting acute back pain at baseline for development of chronic back pain at subsequent visits depending on analgesic medication class

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Model 1** | | **Model 2** | | **Model 3** | |
|  | **OR (95% CI)** | | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| **NSAIDs** | 1.74 (1.34-2.25) | | 0.00027 |  |  |  |  |
| **Paracetamol** |  | |  | 1.18 (0.89-1.57) | 0.24 |  |  |
| **Opioids** |  | |  |  |  | 3.65 (0.72-16.68) | 0.09 |
| **Anti-depressants** |  | |  |  |  |  |  |
| **Pregabalin/**  **Gabapentin** |  | |  |  |  |  |  |
| **Age** | 0.99 (0.98-1.01) | | 0.38 | 0.99 (0.98-1.01) | 0.23 | 0.99 (0.98-1.00) | 0.17 |
| **Male** | 0.85 (0.69-1.04) | | 0.12 | 0.83 (0.68-1.02) | 0.08 | 0.82 (0.67-1.01) | 0.06 |
| **Ethnicity--Asian** | 0.83 (0.28-2.00) | | 0.71 | 0.80 (0.27-1.94) | 0.66 | 0.80 (0.72-1.94) | 0.66 |
| **Ethnicity--black** | 0.83 (0.19-2.54) | | 0.76 | 0.83 (0.19-2.53) | 0.77 | 0.84 (0.19-2.58) | 0.79 |
| **Ethnicity--mixed** | 1.39 (0.31-4.73) | | 0.63 | 1.47 (0.33-4.97) | 0.56 | 1.45 (0.32-4.91) | 0.58 |
| **Ethnicity--other** | 1.25 (0.35-3.48) | | 0.70 | 1.26 (0.36-3.50) | 0.68 | 1.26 (0.36-3.50) | 0.68 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Model 4** | | | **Model 5** | | | **Model 6** | |
|  | **OR (95% CI)** | | **p** | **OR (95% CI)** | | **p** | **OR (95% CI)** | | **p** |
| **NSAIDs** |  | |  |  | |  | 1.74 (1.31-2.29) | | 0.000075 |
| **Paracetamol** |  | |  |  | |  | 0.97 (0.71-1.31) | | 0.85 |
| **Opioids** |  | |  |  | |  | 2.56 (0.44-14.59) | | 0.27 |
| **Anti-depressants** | 1.41 (0.94-2.08) | | 0.09 |  | |  | 1.41 (0.92-2.09) | | 0.10 |
| **Pregabalin/**  **Gabapentin** |  | |  | 1.23 (0.06-8.33) | | 0.86 | 0.52 (0.02-4.37) | | 0.60 |
| **Age** | 0.99 (0.98-1.00) | | 0.18 | 0.99 (0.98-1.00) | | 0.18 | 0.99 (0.98-1.01) | | 0.36 |
| **Male** | 0.84 (0.68-1.03) | | 0.10 | 0.82 (0.67-1.01) | | 0.06 | 0.86 (0.70-1.06) | | 0.16 |
| **Ethnicity--Asian** | 1.82 (0.28-1.98) | | 0.69 | 0.80 (0.27-1.93) | | 0.66 | 0.85 (0.29-2.05) | | 0.74 |
| **Ethnicity--black** | 0.85 (0.20-2.59) | | 0.79 | 0.84 (0.19-2.57) | | 0.78 | 0.84 (0.19-2.57) | | 0.78 |
| **Ethnicity--mixed** | 1.49 (0.33-5.03) | | 0.55 | 1.45 (0.32-4.89) | | 0.58 | 1.42 (0.31-4.86) | | 0.60 |
| **Ethnicity--other** | 1.28 (0.36-3.56) | | 0.66 | 1.25 (0.36-3.48) | | 0.69 | 1.27 (0.36-3.56) | | 0.67 |

|  |  |  |
| --- | --- | --- |
|  | **Model 7** | |
|  | **OR (95% CI)** | **p** |
| **NSAIDs** | 1.68 (1.26-2.23) | 0.00037 |
| **Paracetamol** | 0.97 (0.71-1.31) | 0.83 |
| **Opioids** | 2.80 (0.48-16.73) | 0.23 |
| **Anti-depressants** | 1.49 (0.98-2.24) | 0.05 |
| **Pregabalin/Gabapentin** | 0.83 (0.03-7.27) | 0.88 |
| **Age** | 0.99 (0.98-1.00) | 0.52 |
| **Male** | 0.87 (0.71-1.08) | 0.22 |
| **Ethnicity--Asian** | 0.85 (0.28-2.06) | 0.74 |
| **Ethnicity--black** | 0.89 (0.20-2.81) | 0.85 |
| **Ethnicity--mixed** | 1.55 (0.34-5.45) | 0.52 |
| **Ethnicity--other** | 1.30 (0.36-3.68) | 0.65 |
| **Neutrophils %** | 0.98 (0.97-0.99) | 0.03 |

Supplementary Table XX.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|  | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| **NSAIDs** | 1.63 (1.21-2.18) | 0.001 | 1.71 (1.27-2.28) | 0.0003 | 1.69 (1.27-2.25) | 0.0003 | 1.65 (1.24-2.20) | 0.0006 |
| **Paracetamol** | 1.02 (0.74-1.40) | 0.88 | 0.95 (0.69-1.3) | 0.74 | 0.94 (0.68-1.27) | 0.67 | 0.98 (0.71-1.33) | 0.90 |
| **Opioids** | 2.27 (0.38-13.15) | 0.34 | 1.63 (0.2-10.5) | 0.61 | 2.75 (0.48-16.36) | 0.24 | 2.24 (0.37-12.98) | 0.35 |
| **Anti-depressants** | 1.49 (0.96-2.25) | 0.07 | 1.51 (0.98-2.27) | 0.06 | 1.57 (1.03-2.35) | 0.03 | 1.55 (1.01-2.32) | 0.04 |
| **Pregabalin/Gabapentin** | 0.72 (0.03-7.38) | 0.80 | 0.62 (0.03-5.21) | 0.69 | 0.85 (0.04-7.4) | 0.89 | 0.68 (0.03-7.08) | 0.77 |
| **Age** | 1.00 (0.98-1.01) | 0.66 | 1.00 (0.98-1.01) | 0.67 | 1.00 (0.98-1.01) | 0.59 | 1.00 (0.98-1.01) | 0.63 |
| **Male** | 0.86 (0.69-1.07) | 0.19 | 0.84 (0.68-1.04) | 0.12 | 0.90 (0.73-1.12) | 0.35 | 0.88 (0.71-1.10) | 0.26 |
| **Ethnicity--Asian** | 0.89 (0.30-2.15) | 0.81 | 0.98 (0.33-2.41) | 0.97 | 0.85 (0.29-2.07) | 0.75 | 0.90 (0.30-2.19) | 0.84 |
| **Ethnicity--black** | 0.84 (0.19-2.59) | 0.79 | 0.90 (0.21-2.81) | 0.87 | 0.96 (0.21-3.09) | 0.95 | 0.82 (0.19-2.54) | 0.76 |
| **Ethnicity--mixed** | 2.07 (0.43-7.99) | 0.31 | 1.25 (0.18-5.29) | 0.78 | 1.54 (0.33-5.42) | 0.53 | 1.59 (0.34-5.59) | 0.50 |
| **Ethnicity--other** | 1.20 (0.27-3.84) | 0.77 | 1.14 (0.26-3.66) | 0.84 | 1.31 (0.37-3.70) | 0.64 | 1.34 (0.38-3.77) | 0.61 |
| **Basophils %** | 1.05 (0.68-1.61) | 0.82 |  |  |  |  |  |  |
| **Eosinophils %** |  |  | 1.03 (0.95-1.12) | 0.49 |  |  |  |  |
| **Lymphocytes %** |  |  |  |  | 1.02 (1.00-1.04) | 0.02 |  |  |
| **Monocytes %** |  |  |  |  |  |  | 0.98 (0.93-1.04) | 0.52 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 5** | | **Model 6** | | **Model 7** | | **Model 8** | |
|  | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| **Age** | 1.00 (0.98-1.01) | 0.54 | 1.00 (0.98-1.01) | 0.62 | 1.00 (0.98-1.01) | 0.55 | 1.00 (0.98-1.01) | 0.57 |
| **Male** | 0.86 (0.69-1.04) | 0.15 | 0.88 (0.71-1.09) | 0.26 | 0.86 (0.70-1.06) | 0.16 | 0.88 (0.71-1.09) | 0.23 |
| **Ethnicity--Asian** | 0.82 (0.28-2.00) | 0.70 | 0.83 (0.28-2.00) | 0.70 | 0.82 (0.28-1.99) | 0.69 | 0.83 (0.28-2.00) | 0.70 |
| **Ethnicity--black** | 0.87 (0.19-2.54) | 0.83 | 0.91 (0.20-2.94) | 0.89 | 0.87 (0.20-2.75) | 0.83 | 0.91 (0.20-2.94) | 0.89 |
| **Ethnicity--mixed** | 1.50 (0.31-4.73) | 0.56 | 1.49 (0.32-5.25) | 0.56 | 1.50 (0.32-5.28) | 0.55 | 1.50 (0.32-5.26) | 0.55 |
| **Ethnicity--other** | 1.26 (0.31-4.73) | 0.69 | 1.27 (0.35-3.59) | 0.68 | 1.27 (0.36-3.60) | 0.68 | 1.25 (0.35-3.55) | 0.70 |
| **NSAIDs** | 1.68 | 0.0002 | 1.68 (1.28-2.19) | 0.0002 |  |  |  |  |
| **Neutrophil %** | 0.98 | 0.03 |  |  |  |  |  |  |
| **Lymphocyte %** |  |  | 1.02 (1.00-1.03) | 0.02 |  |  |  |  |
| **Neutrophil % : NSAIDs [No]** |  |  |  |  | 0.98 (0.97-1.00) | 0.01 |  |  |
| **Neutrophil % : NSAIDs [Yes]** |  |  |  |  | 0.99(0.98-1.01) | 0.23 |  |  |
| **Lymphocyte % : NSAIDs [No]** |  |  |  |  |  |  | 1.02 (1.00-1.03) | 0.0479 |
| **Lymphocyte % : NSAIDs [Yes]** |  |  |  |  |  |  | 1.03 (1.01-1.05) | 0.0004 |