Do patients receiving Non-steroidal anti-inflammatory drugs have an increased risk of emergency presentation or death from COVID-19?

Study Protocol

Version: v2.0

Date: 1 July 2020

This is a collaboration between the following institutions as part of the OpenSAFELY EHR Research Platform:

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- Electronic Health Records Research Group, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine

Contents

Amendments

Date	Original Version	Resulting Version	Section	Summary of Change	Rationale
1 July 2020	v1.0	v2.0	Inclusion/ Exclusion Criteria	In both cohorts: - Change from ever receiving aspirin prior to 1st March to receiving aspirin within 10 years prior to 1st March in the main analysis	People with cardiovascular diseases prevention are unlikely to be prescribed aspirin 10 years before but not during the past 10 years before the cohort entry. We will add a sensitivity analysis to test the robustness of the results by excluding people ever prescribed aspirin before cohort entry.
1 July 2020	v1.0	v2.0	Inclusion/ Exclusion Criteria	In both cohorts: - Specify prescription for asthma to be SABA inhaler - Change the time frame to identify asthma prescription from within 3 months to within 4 months of 1st Mar 2020.	Specify asthma prescription to be SABA inhaler. The time frame to identify asthma prescription is now consistent with that for other medication covariates. Patients often have their prescription refill every four months.
1 July 2020	v1.0	v2.0	Figure	Add covariates and edit the exclusion criteria about time frame to identify aspirin prescription	Same as above for time frame to identify aspirin prescription and same as below for adding covariates.
1 July 2020	v1.0	v2.0	Follow-up and outcomes	Add death as one of the censoring events in the text.	In the original protocol, death was listed as one of the censoring events in Figure 1 but has not been incorporated in the text.
1 July 2020	v1.0	v2.0	Covariates	Further elaboration on immunosuppression: including organ transplant, sickle cell anaemia, and splenectomy, HIV, a condition inducing permanent immunodeficiency ever diagnosed, or aplastic anaemia or temporary immunodeficiency recorded within the last year	Elaborate what conditions to be included for the definition of immunosuppression
1 July 2020	v1.0	v2.0	Covariates	Add three more covariates for both cohorts: - Current oral prednisolone use, within 4 months of 1st Mar 2020 - Current hydroxychloroquine use, within 4 months of 1st Mar 2020 - Current other Disease-Modifying Antirheumatic Drug	Steroid and Disease-Modifying Antirheumatic Drug are commonly used in patients with rheumatoid arthritis. The use of these drugs might reflect the severity of the disease and thus the prescribing decision of NSAIDs. They are also

				use, within 4 months of 1st Mar 2020	recently suggested to have responses to COVID-19.
1 July 2020	v1.0	v2.0	Sensitivity analysis	Add a sensitivity analysis to exclude people ever prescribed aspirin before 1st Mar 2020	Same as above.
1 July 2020	v1.0	v2.0	Statistical analysis	Add adjusted survival curves for each exposure group	Hazard ratios are difficult to be interpreted for causal association analysis. Therefore, we will present adjusted survival curves to provide a comprehensive set of results.
1 July 2020	v1.0	v2.0	Statistical analysis	Specify the stratified Cox model (stratified by geographical regions) will only be conducted in fully adjusted models	Make clear which models will be conducted by stratifying by geographical regions.
1 July 2020	v1.0	v2.0	Statistical analysis	Add a statement about how to account for competing risk: We will account for competing risk by modelling the cause-specific hazard (i.e. censoring other deaths for COVID-19 death analysis, and censoring any death for A&E attendance due to COVID-19 analysis).	Add clarifications on how to account for competing risk.

Introduction

The coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), has been diagnosed in approximately 7 million patients with >400,000 deaths in more than 200 countries as of 9 June 2020.[1] While most infected people have mild symptoms, early descriptive studies suggested people aged ≥70, or those with cardiovascular disease, hypertension, diabetes, chronic respiratory disease and cancer are more likely to have poorer disease prognosis, leading to Intensive Treatment Units (ITU) admissions and death.[2-4]

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for relief of pain and inflammation in patients with acute migraine, osteoarthritis and rheumatoid arthritis. In the last 12 months, nearly 11 million NSAID prescriptions were dispensed from GP prescriptions in England.[5] Additionally some NSAIDs (ibuprofen, aspirin and naproxen) are available "over the counter" without a prescription, though it is anticipated very little naproxen is obtained in this way. In contrast, one brand of ibuprofen alone has sales of over £100million. Despite the widespread use of NSAIDs with tolerable safety profile, non-interventional studies have suggested that NSAIDs are associated with a complicated course in lower respiratory tract infections.[6-14] It was postulated that NSAIDs might delay diagnosis and thus clinical care, by masking the symptoms of a worsening infection.[6 10-13 15] In-vivo and in vitro cellular studies show that NSAIDs weaken the immune response to pathogens by limiting the local recruitment of innate immune cells and reducing antibody synthesis but the immunomodulatory effects of NSAIDs are not fully understood.[16 17] These led to a debate over whether NSAIDs would similarly worsen the prognosis of COVID-19. Recently, it has also been suggested that ibuprofen upregulates angiotensin-converting enzyme 2 (ACE2) which has a role in binding SARS-Cov-2 to target cells and could increase the risk of developing severe COVID-19 disease through this route.[18] Whilst most studies have focused on the potential for NSAIDs to worsen outcomes in patients with respiratory infections, many complex biological pathways are affected by NSAIDs, which are not identical in their actions. Indeed there is also evidence that indomethacin may have protective effects.[19]

Due to the lack of clear clinical evidence on the association between NSAIDs and disease prognosis for COVID-19, UK Medicines and Healthcare products Regulatory Agency, European Medicines Agency and US Food and Drug Administration recommended that individuals who currently use NSAIDs for the management of chronic diseases should continue the treatment. Importantly, clinical studies are urgently needed to elucidate the effects of NSAIDs on COVID-19 to better understand anecdotal reports and basic science findings.

We therefore set out to investigate the association between the use of NSAIDs and presentation to an emergency department with symptoms for COVID-19, and deaths from COVID-19 using linked data from over 17 million patients in England.

Objectives

The specific objectives of the study are:

Primary Objectives

1. Estimate the effect of NSAID use on the risk of death from COVID-19 among people receiving NSAIDs in the past 3 years and living in England.
2. Estimate the effect of NSAID use on the risk of death from COVID-19 among people with rheumatoid arthritis and osteoarthritis living in England.
3. Investigate whether the effect of NSAID use on the risk of death from COVID-19 varies by age and types of NSAIDs (Cox-2 specific and non-specific; ibuprofen and other NSAIDs).

Secondary Objectives

1. Estimate the effect of NSAID use on the risk of A&E attendance due to suspected/definite COVID-19 among people receiving NSAID in the past 3 years living in England.
2. Estimate the effect of NSAID use on the risk of A&E attendance due to suspected/definite COVID-19 among people with rheumatoid arthritis and osteoarthritis living in England.

Initially, results for the primary objective only will be presented. Further development work is ongoing to understand the data required to define the secondary outcome reliant on A&E attendance.

Exploratory Objectives

1. If either a positive or negative effect of NSAID use is found, use quantitative bias analysis to quantify the strength of unmeasured confounding that would need to be present for the association to have been solely explained by unmeasured confounding.
2. We may define NSAID exposures based on more detailed dosing instructions as well as estimated adherence.

Methods

Data Source

We will use data from general practice (GP) records, obtained from the GP software provider The Phoenix Partnership (TPP), linked to COVID-19 Office for National Statistics (ONS) death certifications. The data will be accessed, linked and analysed through OpenSAFELY.org - a new data analytics platform created to address urgent questions relating to the epidemiology and treatment of COVID-19 in England, hosted by TPP. OpenSAFELY provides a secure software interface that allows NHS records to be pseudonymised, linked and analysed in near real-time; the GP patient data held on OpenSAFELY never leaves TPP's secure environment; other datasets are linked to it.

The research dataset analysed through OpenSAFELY is based on GP records retrieved from the TPP SystmOne electronic health record system. These data include diagnoses, medicines, physiological parameters, such as body mass index and vital signs, prior investigations, such as blood test results, and basic sociodemographics for almost 24 million individuals – approximately 40% of the English population. Data extracted by TPP SystmOne have previously been used in medical research, as part of the ResearchOne dataset. These records were subsequently linked to data from a number of other organisations who were directed under the Health Service (Control of Patient Information) Regulations 2002 to make their data available for COVID-19 research with the OpenSAFELY initiative. Currently, linkage is possible to: (1) the NHSE/NHSX Emergency Care Data Set (ECDS), which contains data on emergency attendance at A&E clinics across England; (2) the NHSE/NHSX Second Generation Surveillance System (SGSS) data on SARS-COV-2 test results; (3) the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme, containing data on COVID-19 related ITU admissions; (4) the NHSE/NHSX COVID-19 Patient Notification System (CPNS) data on deaths among COVID-19 inpatients occurring in hospitals[20 21]; and (5) ONS death data, which includes information on all deaths, including those due to non-COVID-19 causes as well as those occurring outside the hospital setting.

All data is held in a secure research environment hosted by TPP, which is a Tier 3 data centre, accredited to NHS Digital standards for centrally hosted clinical systems (ISO 27001 standard and IG Toolkit version 2).

Study Design and Population

We will use a population-based cohort design. Patients will be followed from the 1st March 2020, considered the start of risk for experiencing the outcomes due to the dynamics of the coronavirus outbreak in the UK.

From the raw data, we will select two cohorts: 1) those prescribed NSAIDs in the past 3 years; and 2) patients with rheumatoid arthritis or osteoarthritis, as follows:

Cohort 1: NSAID Users in the past 3 years

This cohort aims to group together patients who have been prescribed an NSAID in general practice in recent years.

Individuals meeting the following criteria will be included:

Inclusion criteria:

1. At least one prescription for an oral NSAID within 3 years prior to 1st Mar 2020.
2. Recorded male or female gender in TPP primary care record at the 1st Mar 2020.

Exclusion criteria:

1. Less than 12 months of primary care records whilst registered in a TPP practice available at the 1st Mar 2020, which may preclude adequate characterisation of potentially important confounding variables.
2. <18 years of age or >110 years of age at 1st Mar 2020
3. Receiving aspirin within 10 years prior to 1st Mar 2020. Aspirin is used for cardiovascular outcome prevention and users constitute a different population from other NSAID users. This will be evaluated through prescribing and use of codes indicating over the counter aspirin use, or QoF code indicating current aspirin use.
4. A record of stroke or myocardial infarction prior to 1st Mar 2020. Most or many people with stroke or myocardial infarction are expected to be receiving aspirin.
5. A record of asthma diagnosis within 3 years of 1st Mar 2020 and a prescription for asthma (short-acting beta agonists (SABA) inhaler) within 4 months of 1st Mar 2020. NSAIDs are generally avoided in people with currently active asthma as they may cause bronchospasm.
6. A record of gastrointestinal bleed prior to 1st March 2020. Gastrointestinal bleeding is a contraindication to NSAID use.
7. A very small number of patients (<1%) are anticipated to have a missing Index of multiple deprivation (IMD) status and will be excluded from the analysis.

Cohort 2: Patients with Osteoarthritis or Rheumatoid Arthritis

This cohort attempts to group together potential NSAID users with similar underlying diseases.

Individuals meeting the following criteria will be included:

Inclusion criteria:

1. A diagnosis of osteoarthritis or rheumatoid arthritis prior to 1st Mar 2020.
2. Recorded male or female gender in TPP primary care record at the 1st Mar 2020.

Exclusion criteria:

1. Less than 12 months of primary care records whilst registered in a TPP practice available at the 1st Mar 2020, which may preclude adequate characterisation of potentially important confounding variables.
2. <18 years of age or >110 years of age at 1st Mar 2020
3. Receiving aspirin within 10 years prior to 1st Mar 2020. Aspirin is used for cardiovascular outcome prevention and users constitute a different population from other NSAID users. This will be evaluated through prescribing and use of codes indicating over the counter aspirin use, or QoF code indicating current aspirin use.
4. A record of stroke or myocardial infarction prior to 1st Mar 2020. Most or many people with stroke or myocardial infarction are expected to be receiving aspirin.
5. A record of asthma diagnosis within 3 years of 1st Mar 2020 and a prescription for asthma (SABA inhaler) within 4 months of 1st Mar 2020. NSAIDs are generally avoided in people with currently active asthma as they may cause bronchospasm.

6. A record of gastrointestinal bleed prior to 1st Mar 2020. Gastrointestinal bleeding is a contraindication to oral NSAID use.
7. A very small number of patients (<1%) are anticipated to have a missing IMD status and will be excluded from the analysis.

Study Measures

Discussions and decisions on every measure have been documented before implementing the final underlying code to complete the analysis. Detailed information on compilation and sources for every individual codelist is available at https://codelists.opensafely.org/ and the lists are available for inspection and re-use by the broader research community.

Exposures

In both cohorts, the exposure of interest is oral NSAID prescribed in the 4 months prior to 1st Mar 2020 to capture usage in pre-pandemic conditions within a reasonable timeframe (Table 1). This date was chosen due to reports of substantial early and over-ordering of medicines and appeals by the NHS not to extend prescription durations in March. Therefore, prescribing patterns from March may not represent usual usage e.g. with respect to levels of adherence. The non-current use of NSAID group will be people who do not have a record of an NSAID prescription in the 4 months prior to 1st Mar 2020.

Table 1. Operational Definition for oral NSAID

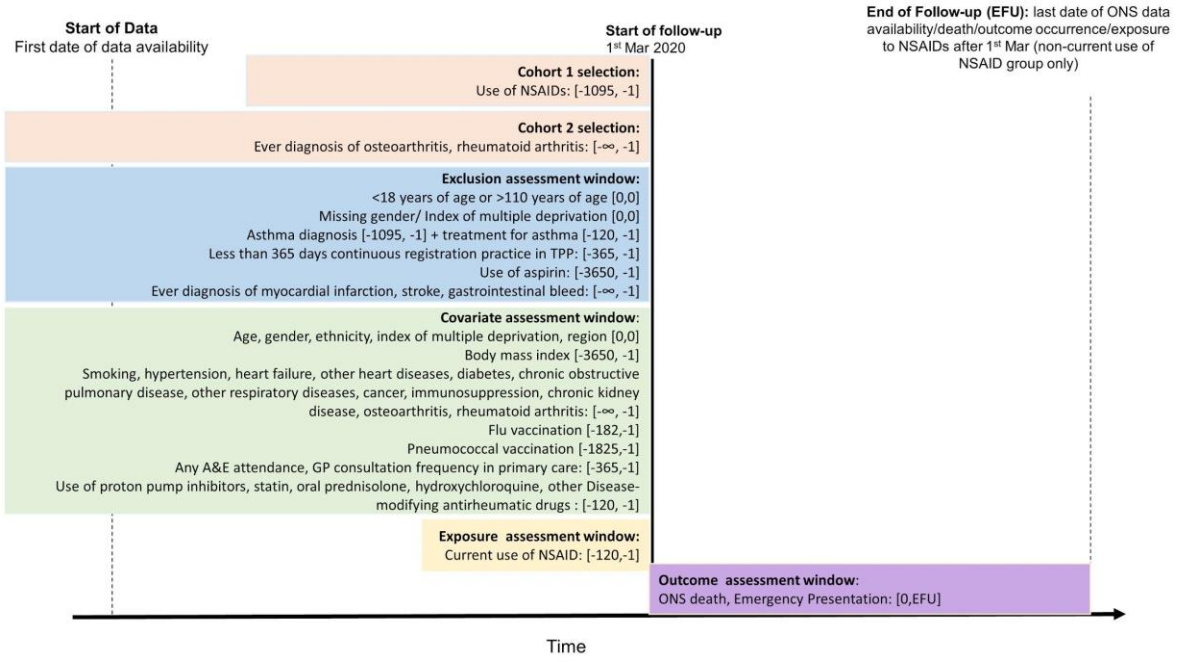
Variable	Variable level	Category	Definition	Timeframe
Drug Exposure	0	Non-current use of NSAID	No record of NSAID prescription	4 months prior to 1st Mar 2020
	1	Current use of NSAID	Meeting both criteria: 1. At least one NSAID prescription: https://github.com/opensafely/nsaids-research/issues/4 2. Oral route of administration	

Follow up and Outcomes

Follow up for each cohort will begin on 1st March 2020 and end at the latest of the outcome of interest in each analysis, death or last date of ONS data availability. If people in non-current use of NSAID group receive a NSAID prescription after 1st Mar, we will additionally censor their follow-up on the prescription start date (Figure 1).

The primary outcome is confirmed or probably death from COVID-19 in the ONS dataset. The secondary outcome is presenting at an emergency unit with suspected or confirmed COVID-19 using ECDS data.

Figure 1. Illustration of the Study Design



An operational definition for the primary outcome is provided in Table 2.

Table 2. Operational Definition for the Primary Outcome Variable

Variable	Definition	Timeframe
COVID-19 Death	Death information from ONS will be used to capture confirmed and probable deaths from COVID-19. The event date is defined as the death date. ICD-10 codes will be used to identify COVID-19 related outcomes in ONS: ● U071 COVID-19, virus identified ● U072 COVID-19, virus not identified	On or after the 1st March 2020 until the end of data availability

All code (including early versions) for identifying outcomes will be made public in the study github repository. SNOMED codes to identify confirmed, suspected and probably COVID-19 disease in ECDS are yet to be determined.

Covariates

The covariates of interest were chosen following discussion with practising clinicians to identify potential important determinants of NSAID prescribing and the outcomes of interest. The covariates which were pre-specified as potentially important confounding variables are listed below. Definitions and code lists are available at https://codelists.opensafely.org/ and are available for inspection and re-use by the broader research community.
Unless otherwise specified, variables were created using diagnostic codes present ever in a patients' medical record prior to 1st March.

- Age as of 1st March 2020
- Sex
- Ethnicity
- Body Mass Index, ascertained from weight measurements within the last 10 years, restricted to those taken when the patient was over 16 years old
- Smoking, most recent code prior to 1st March 2020
- Hypertension
- Heart failure
- Other heart diseases
- Diabetes, categorised as controlled (HbA1c <58 mmols/mol), uncontrolled (HbA1c ≥58 mmols/mol) or HbA1c not measured.
- Chronic obstructive pulmonary disease
- Other respiratory diseases (not including asthma)
- Cancer
- Immunosuppression, including organ transplant, sickle cell anaemia, splenectomy, HIV, a condition inducing permanent immunodeficiency ever diagnosed, or aplastic anaemia or temporary immunodeficiency recorded within the last year
- Chronic Kidney Disease, using creatinine measurements (within 1 year of 1st March 2020) OR having a code for renal dialysis ever prior to 1st March 2020

- Osteoarthritis (in *Cohort 1* only)
- Rheumatoid arthritis (in *Cohort 1* only)
- Osteoarthritis/rheumatoid arthritis/both, coded as 1 for osteoarthritis, 2 for rheumatoid arthritis, and 3 for both osteoarthritis and rheumatoid arthritis (in *Cohort 2* only)
- GP consultation rate in the year prior to 1st Mar 2020, dichotomised as 0 or ≥1
- A&E attendance rate in the year prior to 1st Mar 2020, dichotomised as 0 or ≥1
- Flu vaccination status, between 1st Sep 2019 and 29th Feb 2020
- Pneumococcal vaccination status, 5 years prior to 1st Mar 2020
- Current statin use, within 4 months of 1st Mar 2020
- Current proton pump inhibitor use, within 4 months of 1st Mar 2020
- Current oral prednisolone use, within 4 months of 1st Mar 2020
- Current hydroxychloroquine use, within 4 months of 1st Mar 2020
- Current other Disease-Modifying Antirheumatic Drug use, within 4 months of 1st Mar 2020
- Index of Multiple Deprivation (2019)

Missing Data

In the primary analysis, those with missing BMI will be assumed non-obese and those with missing smoking information will be assumed to be non-smokers on the assumption that both obesity and smoking would be more likely to be recorded if present. We anticipate ~25% missing data on ethnicity and will exclude this variable from the primary models. A sensitivity analysis will be done amongst people with recorded ethnicity, adjusting for this variable in addition to the others. We anticipate ~5% missing data on GP consultation rate and will add this variable into a sensitivity analysis amongst those with complete recording of this variable. Patients with missing data on eGFR measurements, who do not have a code for end-stage renal disease, will be assumed to not have chronic kidney disease.

Statistical Analysis

Primary Objectives

We will present the number of patients meeting each inclusion and exclusion criteria for the cohorts using flowcharts. The characteristics of patients in each cohort will be summarised using descriptive statistics, stratified by exposure status.

Time to the primary outcome, death due to COVID-19 as registered by the ONS, will be displayed in Kaplan-Meier plots with time in study as the timescale. We will present adjusted survival curves for each exposure group. Cox regression will be used to estimate hazard ratios and 95% confidence intervals for the association between the current NSAID use and the outcome. We will account for competing risk by modelling the cause-specific hazard (i.e. censoring other deaths for COVID-19 death analysis, and censoring any death for A&E attendance due to COVID-19 analysis). Univariable models, models adjusted for age and sex as well as fully adjusted models, including all of the confounders listed in the covariate section, will

be presented. In fully adjusted models, hazard ratios will be estimated, stratified by geographical regions. Graphical methods and tests based on Schoenfeld residuals will be used to explore violations of the proportional hazards assumption. *Post-hoc* models including other adjustments, or removing some adjustment variables may be fit. However, these will be clearly marked as *post-hoc* exploratory work in the presentation of any results.

A priori we will determine whether the association between current exposure to NSAID and death varies by age (<70 years, ≥70 years), and types of NSAIDs (Cox-2 specific and non-specific; ibuprofen separated from other NSAIDs). For pragmatic purposes, Cox-2 specific will be defined as celecoxib and etoricoxib, the two currently available oral NSAIDs with highest Cox-2 specificity whilst other NSAIDs are non-specific. Additionally, we will conduct a subgroup analysis according to dose of naproxen by defining NSAID exposure as none, high dose naproxen (500mg), low dose naproxen (250mg) or any other NSAID based on the strength of the formulation. Naproxen accounts for ~63% NSAID prescribing and has a ~60:40 split for high:low dose. If an effect is found, we will also explore whether this varies according to calendar time (pre and post lockdown in the UK, 23rd Mar 2020). This investigation would depend on having a sufficient number of cases in our study population pre-lockdown.

Secondary Objectives

The methodology for the secondary outcome (A&E attendance due to suspected/definite COVID-19) will be as described for the primary objectives above.

Exploratory Objectives

For any non-null association, with 95% confidence intervals wholly above or below 1 in the primary analysis, we will conduct a quantitative bias analysis. This will estimate how strong unmeasured confounding would need to be in order to explain the association. We will use Ding and Vanderweele's e-value formulae, alongside probabilistic bias analysis, to estimate how strongly associated one or more unmeasured confounders would need to be with exposure and outcome to fully explain the observed association.

A final exploratory objective relates to defining exposure variables based on more detailed dosing instructions as well as estimated adherence. In the subgroup analysis, we have grouped NSAID exposure into low dose naproxen, high dose naproxen and other NSAIDs, as a readily available dosing instruction decode facilitating assignment of low or high dose of other NSAIDs is not currently available. In future work, if/when this becomes available we aim to further separate low and high dose of other NSAIDs. Similarly, in later work a secondary definition of exposure categories, based around likely treatment adherence will be defined if possible. The rationale for this is that any signal regarding a causal protective effect should be stronger in a more adherent group, assuming adherence does not change during the pandemic. Preliminary exposure groups, based on adherence, are listed below:

- Non-current use of NSAID (reference group)

- Any NSAID prescribing with high adherence (≥70% by proportion of days covered in the previous 12 months)
- Any NSAID prescribing with low adherence (<70% by proportion of days covered in the previous 12 months)

Sensitivity Analyses

We will also conduct a sensitivity analysis to evaluate the robustness of our results. We will repeat the analysis by varying the definition of currently receiving an NSAID to within 2 months of 1st Mar 2020. As indomethacin was the only NSAID that was suggested to have antiviral activity against SARS virus[19], we will repeat the analysis but excluding indomethacin from all NSAIDs. We anticipated low usage of indomethacin and therefore insufficient power to conduct a subgroup analysis. Because of potential stockpiling after 1st Mar 2020, we will also conduct another sensitivity analysis by not censoring people who were prescribed NSAIDs after 1st Mar in the non-current NSAID use group. We will also exclude people ever prescribed aspirin before 1st Mar 2020 to test the robustness of the results.

It should be noted that more sensitivity analyses may be added based on the initial results of analyses. These will be clearly marked as *post-hoc* analyses in any reporting of the results.

Figures

Figure 1. Flowchart for inclusion

Figure 1a. Flowchart for inclusion in people receiving NSAIDs between 1st Mar 2017 and 29th Feb 2020 (Cohort 1).

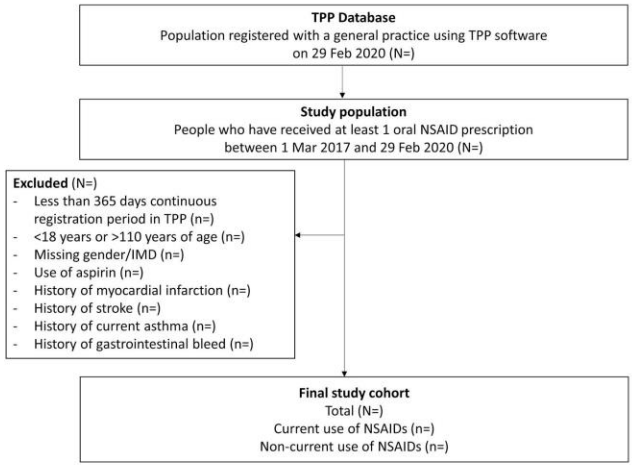


Figure 1b. Flowchart for inclusion in people with osteoarthritis or rheumatoid arthritis (Cohort 2).

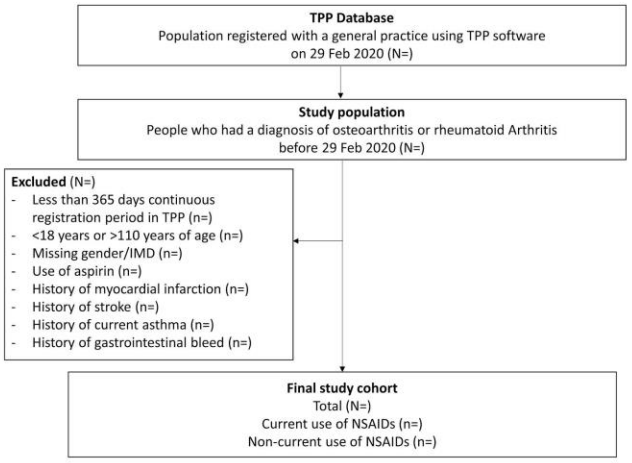


Figure 2. Kaplan-Meier Plot of Time to in-hospital COVID-19 death, stratified by current use of NSAID

[Note: Including number under follow-up at each time-point, with and without current use of NSAIDs]

Figure 3. Forest Plots of Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death

Tables

Note: Table shells are presented for the primary objectives only. The tables will be adapted and repeated for secondary objectives as required. Figures are not included as shells.

Table 1. Descriptive Characteristics

	Cohort 1: People receiving NSAIDs in past 3 years		Cohort 2: Patients with rheumatoid arthritis or osteoarthritis	
	Non-current use of NSAIDs	Current use of NSAIDS	Non-current use of NSAIDs	Current use of NSAIDS
Total				
Age as of 1st March 2020				
18-<40				
40-<50				
50-<60				
60-<70				
70-<80				
80+				
Sex				
Female				
Male				
Body mass index				
<18.5				
18.5-24.9				
25-29.9				
30-34.9				
35-39.9				
Missing				
Ethnicity				
White				
Mixed				
Asian or Asian British				
Black				
Other				
Missing				
Index of Multiple Deprivation				
1 (least deprived)				
2				
3				
4				
5 (most deprived)				
Smoking status				
Never				
Current				
Former				
Missing				
Comorbidities				
Hypertension				

Heart Failure				
Other Heart Disease				
Diabetes				
Controlled (HbA1c < 58 mmols/mol)				
Uncontrolled (HbA1c ≥ 58 mmols/mol)				
HbA1c not measured				
Chronic obstructive pulmonary disease				
Other respiratory diseases				
Cancer				
Immunosuppression				
Chronic kidney disease				
Osteoarthritis				
Rheumatoid arthritis				
GP consultations				
Median, IQR				
Min, Max				
A&E attendance				
Median, IQR				
Min, Max				
Vaccination				
Flu				
Pneumococcal				
Medications				
Statin				
Proton pump inhibitors				
Oral prednisolone				
Hydroxychloroquine				
Other Disease-modifying antirheumatic drugs				

Table 2. Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death

	Number of death (person-time)	Unadjusted	Age-Sex Adjusted	Fully Adjusted
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-current use of NSAID (reference)		1.00	1.00	1.00
Current use of NSAIDs				

Strengths and Limitations

The strengths of this study will include the size of the source population: OpenSAFELY represents one of the largest EHR databases in Europe. This will allow analyses to have as high power as is possible during this stage of the pandemic. The primary outcome, death as recorded in ONS, is also being recorded and analysed in near real-time, which will allow the number of outcome events to be maximised and, again, ensuring analyses are as well powered as possible. The richness of the EHR will allow us to characterise patients' medical history with a relatively high degree of accuracy, as we will not be relying on data being collected during the pandemic to characterise comorbidities. This should allow us to better control for confounding by indication compared to studies conducted solely in the hospital setting. Other strengths will include the pre-specified objectives and analysis plan, which will clearly allow readers to see which hypotheses and analyses were planned in advance. Finally, all source code that is used both to define the study population and run the analysis will be made publicly available for other researchers to both re-use and scrutinize.

However, there are also limitations which should be borne in mind when interpreting any results. Notably, these limitations would tend to apply to any study addressing this question using non-interventional data, and are not unique to this study. Firstly, although we will attempt to reduce confounding by adjusting for potentially important confounders, we cannot entirely remove residual confounding – either due to variables we have not measured, or those we have measured imperfectly. Confounding by indication is a particular concern in *Cohort 1* (users of NSAIDs regardless of indications). There might be systematic health differences between those recently prescribed NSAIDs compared to those who were not. However, we also choose a more restricted study cohort (i.e. *Cohort 2*: people with rheumatoid arthritis and osteoarthritis) to minimise confounding by indication. If any association between NSAIDs and COVID-19 outcomes is pharmacological and therefore causal, it is expected to be identifiable and similar in each cohort. Differences in findings between cohorts would point to possible non-causal associations in one or both populations. If our analyses are subject to confounding by indication (i.e. people who recently prescribed NSAIDs are generally sicker), we might expect to observe an increasing risk of death among patients recently prescribed NSAIDs compared to those who were not. Comparisons of baseline characteristics will help us explore this. To aid the interpretation of our results, for all detected associations we will quantify the strength an unmeasured confounder or group of unmeasured/imperfectly measured confounders would need to remove the observed association using quantitative bias analysis.

Any changes over time in the relationship between the exposures of interest and the outcomes will be evaluated as part of checking the assumption of proportional hazards in the Cox regression models. Deviations from proportional hazards will be considered and explored carefully, as we would not expect a true pharmacological association to vary over time, even as the pandemic progresses.

Our analyses are also subject to risk of exposure misclassification. First, we do not know whether or not patients were truly taking the medications as prescribed. Second, over-the-

counter medicine is unlikely to be captured in TPP and NSAIDs are available without prescription, therefore we might underestimate the use of NSAIDs in our cohorts. However, exposure misclassification due to over-the-counter NSAIDs is minimal in *Cohort 2* (i.e. people with rheumatoid arthritis and osteoarthritis) as these people receive prescriptions regularly to manage their medical condition. Third, people are more likely to purchase over-the-counter NSAIDs for acute use, for instance, treatment of pyrexia and pain relief. Therefore, our results will limit the generalisability of findings to long-term NSAID users only. We are also not able to capture any NSAID use during hospitalisation. However, due to the speculation of the effect of NSAIDs on COVID-19, they are unlikely to be prescribed over paracetamol for relieving symptoms of COVID-19 during hospitalisation.

Given the inherent limitations of the study design, our results should be taken as hypothesis exploring/generating. Multiple studies of different designs, in different populations, will be needed before a conclusive answer relating to the impact of NSAID exposure on COVID-19 infection risk and outcomes can be given.

References

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