

Supplementary appendix for the manuscript

Risk of COVID-19 diagnosis and hospitalization in patients with osteoarthritis or back pain treated with ibuprofen compared to other NSAIDs or paracetamol: a network cohort study

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Annex 1. Database information

- IQVIA Open Claims collected from office-based physicians and specialists covering over 300 million people (~80% of the US population)
- IQVIA PharMetrics Plus comprises adjudicated claims for more than 150 million unique commercially insured enrollees across the US

Annex 2. Concept IDs

The tables in this annex contain the concept codes used in this study. You can find more details regarding these codes in the Athena website (<https://athena.ohdsi.org/search-terms/terms>) hosted by OHDSI.

Supplementary table 1. Concepts related to osteoarthritis and back pain

Concept Id	Concept Name	Domain	Vocabulary	Descendants
80180	Osteoarthritis	Condition	SNOMED	YES
36516951	Back pain	Condition	MedDRA	YES

Supplementary table 2. Concepts related to ibuprofen

Concept Id	Concept Name	Domain	Vocabulary	Descendants
1177480	Ibuprofen	Drug	RxNorm	YES

Supplementary table 3. Concepts related to ns-NSAIDs

Concept ID	Concept Name	Domain	Vocabulary	Descendants
1139179	bromfenac	Drug	RxNorm	Yes
1124300	diclofenac	Drug	RxNorm	Yes
1195492	etodolac	Drug	RxNorm	Yes
1153928	fenoprofen	Drug	RxNorm	Yes
1156378	flurbiprofen	Drug	RxNorm	Yes
1178663	indomethacin	Drug	RxNorm	Yes
1185922	ketoprofen	Drug	RxNorm	Yes
1136980	ketorolac	Drug	RxNorm	Yes
1180182	meclofenamate	Drug	RxNorm	Yes
1197736	mefenamate	Drug	RxNorm	Yes
1150345	meloxicam	Drug	RxNorm	Yes
1113648	nabumetone	Drug	RxNorm	Yes
1115008	naproxen	Drug	RxNorm	Yes
1118045	oxaprozin	Drug	RxNorm	Yes
19025925	oxyphenbutazone	Drug	RxNorm	Yes
1135710	phenylbutazone	Drug	RxNorm	Yes
1146810	piroxicam	Drug	RxNorm	Yes
1236607	sulindac	Drug	RxNorm	Yes
1102917	tolmetin	Drug	RxNorm	Yes

Supplementary table 4. Concepts related to COX-2 inhibitors

Concept Id	Concept Name	Domain	Vocabulary	Descendants
21603991	Coxibs	Drug	ATC	YES

Supplementary table 5. Concepts related to paracetamol (acetaminophen)

Concept Id	Concept Name	Domain	Vocabulary	Descendants
1125315	acetaminophen	Drug	RxNorm	YES

Supplementary table 6. Concepts related to COVID-19 conditions

Concept Id	Concept Name	Domain	Vocabulary	Descendants
439676	Coronavirus infection	Condition	SNOMED	YES
4100065	Disease due to Coronaviridae	Condition	SNOMED	YES
37311060	Suspected disease caused by 2019-nCoV	Observation	SNOMED	YES
37311061	Disease caused by 2019-nCoV	Condition	SNOMED	YES

Supplementary table 7. Concepts related to SARS-COV-2 positive test; pre-coordinated

Concept Id	Concept Name	Domain	Vocabulary	Descendants
37310282	2019 novel coronavirus detected	Measurement	SNOMED	YES

Supplementary table 8. Concepts related to SARS-CoV-2 positive test

Concept Id	Concept Name	Domain	Vocabulary	Descendants
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Measurement	OMOP Extension	YES
4126681	Detected	Measurement value	SNOMED	NO
45877985	Detected	Measurement value	LOINC	NO
4181412	Present	Measurement value	SNOMED	NO
45879438	Present	Measurement value	LOINC	NO
9191	Positive	Measurement value	SNOMED	NO
45884084	Positive	Measurement value	LOINC	NO

Supplementary table 9. Inpatient visit

Concept Id	Concept Name	Domain	Vocabulary	Descendants
262	Emergency Room and Inpatient Visit	Visit	Visit	YES
9201	Inpatient Visit	Visit	Visit	YES

Supplementary table 10. Concept sets related to negative control outcomes

Concept ID	Concept Name	Domain	Vocabulary	Descendants
435574	Abnormal form of root of tooth	Condition	SNOMED	YES
4262562	Abnormal heart beat	Condition	SNOMED	YES
436409	Abnormal pupil	Condition	SNOMED	YES
378256	Abnormal reflex	Condition	SNOMED	YES
137989	Abnormal results of cardiovascular function studies	Condition	SNOMED	YES
4088290	Absence of breast	Condition	SNOMED	YES
4092879	Absent kidney	Condition	SNOMED	YES
4088768	Absent nipple	Condition	SNOMED	YES
435720	Adverse anesthesia outcome	Condition	SNOMED	YES
433753	Alcohol abuse	Condition	SNOMED	YES
4303805	Allergic reaction to bite and/or sting	Condition	SNOMED	YES
434916	Amphetamine or psychostimulant dependence, continuous	Condition	SNOMED	YES
4198962	Amputated thumb	Condition	SNOMED	YES
4103642	Amputated toe	Condition	SNOMED	YES
4060259	Antenatal amniocentesis - abnormal	Condition	SNOMED	YES
4061157	Antenatal ultrasound scan abnormal	Condition	SNOMED	YES
321689	Apnea	Condition	SNOMED	YES
443563	Arteriosclerosis of coronary artery bypass graft	Condition	SNOMED	YES
4151169	Baby birth weight less than 751gm	Condition	SNOMED	YES
4114976	Balanced rearrangement and structural marker	Condition	SNOMED	YES
78200	Benign mammary dysplasia	Condition	SNOMED	YES
4216219	Bizarre personal appearance	Condition	SNOMED	YES
4195873	Breath smells unpleasant	Condition	SNOMED	YES
74698	Breech presentation	Condition	SNOMED	YES
134765	Cachexia	Condition	SNOMED	YES
443792	Calculus of bile duct	Condition	SNOMED	YES
434327	Cannabis abuse	Condition	SNOMED	YES
4228429	Carnitine deficiency	Condition	SNOMED	YES
4213540	Cervical somatic dysfunction	Condition	SNOMED	YES
444064	Cholesteatoma of middle ear and mastoid structure	Condition	SNOMED	YES
197318	Cholesterolosis of gallbladder	Condition	SNOMED	YES
432303	Cocaine abuse	Condition	SNOMED	YES
196454	Colostomy and enterostomy malfunction	Condition	SNOMED	YES
4201390	Colostomy present	Condition	SNOMED	YES
439125	Complete trisomy 21 syndrome	Condition	SNOMED	YES
46269889	Complication due to Crohn's disease	Condition	SNOMED	YES
434675	Complication of gastrostomy	Condition	SNOMED	YES
438624	Complication of renal dialysis	Condition	SNOMED	YES

4309151	Complications of attempted introduction of embryo in embryo transfer	Condition	SNOMED	YES
373204	Conjunctival xerosis	Condition	SNOMED	YES
4022071	Convalescence	Condition	SNOMED	YES
433270	Cord entanglement without compression	Condition	SNOMED	YES
380724	Corneal ghost vessels	Condition	SNOMED	YES
4311591	Cramp in limb	Condition	SNOMED	YES
441267	Cystic fibrosis	Condition	SNOMED	YES
40486120	Delay in physiological development	Condition	SNOMED	YES
436233	Delayed milestone	Condition	SNOMED	YES
438183	Denture occlusion incorrect	Condition	SNOMED	YES
438759	Descemet's membrane fold	Condition	SNOMED	YES
4096201	Dietary calcium deficiency	Condition	SNOMED	YES
4101282	Dietary selenium deficiency	Condition	SNOMED	YES
4101283	Dietary zinc deficiency	Condition	SNOMED	YES
4115402	Difficulty sleeping	Condition	SNOMED	YES
4019971	Discord in school	Condition	SNOMED	YES
4022078	Discord with counselor	Condition	SNOMED	YES
201091	Disproportion - major pelvic abnormality	Condition	SNOMED	YES
372329	Dissociated deviation	Condition	SNOMED	YES
4155818	Does climb	Condition	SNOMED	YES
433111	Effects of hunger	Condition	SNOMED	YES
439791	Emotional upset	Condition	SNOMED	YES
4029271	Essential fatty acid deficiency	Condition	SNOMED	YES
437448	Exhaustion due to excessive exertion	Condition	SNOMED	YES
45757488	Eye and vision examination normal	Condition	SNOMED	YES
4059015	Falls	Condition	SNOMED	YES
4083100	Fasciitis with eosinophilia syndrome	Condition	SNOMED	YES
4182437	Female genital cutting	Condition	SNOMED	YES
4262519	Female sexual arousal disorder	Condition	SNOMED	YES
4118057	Fetal or neonatal effect of maternal oligohydramnios	Condition	SNOMED	YES
4229403	Flat anterior chamber of eye	Condition	SNOMED	YES
4264617	Foot-drop	Condition	SNOMED	YES
374801	Foreign body in ear	Condition	SNOMED	YES
259995	Foreign body in orifice	Condition	SNOMED	YES
4096540	Foreskin deficient	Condition	SNOMED	YES
4215117	Fructose metabolism disorder	Condition	SNOMED	YES
73564	Full thickness rotator cuff tear	Condition	SNOMED	YES
439788	Galactosemia	Condition	SNOMED	YES
196456	Gallstone	Condition	SNOMED	YES
4166231	Genetic predisposition	Condition	SNOMED	YES
437202	Giardiasis	Condition	SNOMED	YES
434164	Glycosuria	Condition	SNOMED	YES

4101199	Hearing problem	Condition	SNOMED	YES
440532	Heavy-for-dates at birth regardless of gestation period	Condition	SNOMED	YES
4163735	Hemochromatosis	Condition	SNOMED	YES
440329	Herpes zoster without complication	Condition	SNOMED	YES
195212	Hypercortisolism	Condition	SNOMED	YES
4284559	Hypermagnesemia	Condition	SNOMED	YES
133729	Hyperparathyroidism	Condition	SNOMED	YES
4287416	Hyperphenylalaninemia	Condition	SNOMED	YES
4058388	Hypertrophic scar	Condition	SNOMED	YES
4098611	Hyperuricemia without signs of inflammatory arthritis and tophaceous disease	Condition	SNOMED	YES
435522	Hypervitaminosis D	Condition	SNOMED	YES
443236	Hypnotic or anxiolytic dependence	Condition	SNOMED	YES
440072	Hypogammaglobulinemia	Condition	SNOMED	YES
4098604	Hypomagnesemia	Condition	SNOMED	YES
435515	Hypo-osmolality and or hyponatremia	Condition	SNOMED	YES
40481585	Hypoplasia of maxillary bone	Condition	SNOMED	YES
435371	Hypothermia	Condition	SNOMED	YES
437390	Hypoxemia	Condition	SNOMED	YES
443447	Iatrogenic hypotension	Condition	SNOMED	YES
4223399	Iliac crest spur	Condition	SNOMED	YES
433605	Ill-defined disease	Condition	SNOMED	YES
432596	Immune defect	Condition	SNOMED	YES
374375	Impacted cerumen	Condition	SNOMED	YES
4311629	Impaired glucose tolerance	Condition	SNOMED	YES
4344500	Impingement syndrome of shoulder region	Condition	SNOMED	YES
193020	Incomplete emptying of bladder	Condition	SNOMED	YES
441417	Incoordination	Condition	SNOMED	YES
434485	Increase in body fat	Condition	SNOMED	YES
4168222	Intra-abdominal and pelvic swelling, mass and lump	Condition	SNOMED	YES
440710	Intraretinal microvascular abnormality	Condition	SNOMED	YES
196168	Irregular periods	Condition	SNOMED	YES
4168681	Irritability and anger	Condition	SNOMED	YES
434063	Jaw to cranial base anomaly	Condition	SNOMED	YES
72404	Joint stiffness	Condition	SNOMED	YES
432593	Kwashiorkor	Condition	SNOMED	YES
437078	Large head	Condition	SNOMED	YES
133088	Late amputation stump complication	Condition	SNOMED	YES
440382	Learning difficulties	Condition	SNOMED	YES
436041	Leech infestation	Condition	SNOMED	YES
4228331	Leukokeratosis nicotina palati	Condition	SNOMED	YES
195873	Leukorrhea	Condition	SNOMED	YES
377873	Lid lag	Condition	SNOMED	YES

435516	Lipoprotein deficiency disorder	Condition	SNOMED	YES
4210746	Localized amyloidosis	Condition	SNOMED	YES
433997	Lymphangioma	Condition	SNOMED	YES
4083487	Macular drusen	Condition	SNOMED	YES
4051630	Malingering	Condition	SNOMED	YES
436426	Malleus mobility reduced	Condition	SNOMED	YES
438808	Mammary duct ectasia	Condition	SNOMED	YES
432798	Mechanical complication of internal orthopedic device, implant AND/OR graft	Condition	SNOMED	YES
439082	Menopausal syndrome	Condition	SNOMED	YES
45757258	Minimal keratinized residual ridge mucosa	Condition	SNOMED	YES
441536	Mixed acid-base balance disorder	Condition	SNOMED	YES
4298207	Mouth breathing	Condition	SNOMED	YES
4009035	Multifocal fibrosclerosis	Condition	SNOMED	YES
134315	Myelophthisis	Condition	SNOMED	YES
441553	Myoclonus	Condition	SNOMED	YES
375077	Neglect of one side of body	Condition	SNOMED	YES
4119307	Neurogenic claudication	Condition	SNOMED	YES
4209423	Nicotine dependence	Condition	SNOMED	YES
40304526	Nocturia	Condition	SNOMED	YES
4035269	Non-ketotic hyperglycinemia	Condition	SNOMED	YES
439907	Non-traumatic tendon rupture	Condition	SNOMED	YES
45770922	Open anterior occlusal relationship	Condition	SNOMED	YES
44789003	Open wound of thumb with damage to nail	Condition	SNOMED	YES
438130	Opioid abuse	Condition	SNOMED	YES
437359	Osteochondritis dissecans	Condition	SNOMED	YES
313601	Oxygen supply absent	Condition	SNOMED	YES
44782778	Pain disorder with psychological factor	Condition	SNOMED	YES
4091513	Passing flatus	Condition	SNOMED	YES
4022076	Patient dependence on care provider	Condition	SNOMED	YES
443788	Peritoneal adhesions with obstruction	Condition	SNOMED	YES
437092	Physiological development failure	Condition	SNOMED	YES
22856	Polyglandular dysfunction	Condition	SNOMED	YES
437369	Postmature infancy	Condition	SNOMED	YES
4094448	Pregnancy test negative	Condition	SNOMED	YES
4114585	Primary gonarthrosis, bilateral	Condition	SNOMED	YES
4080568	Problem behavior	Condition	SNOMED	YES
46286594	Problem related to lifestyle	Condition	SNOMED	YES
199876	Prolapse of female genital organs	Condition	SNOMED	YES
439790	Psychalgia	Condition	SNOMED	YES
4049367	Psychologic conversion disorder	Condition	SNOMED	YES
440068	Psychosexual dysfunction	Condition	SNOMED	YES
4245252	Raised prostate specific antigen	Condition	SNOMED	YES
436246	Reduced libido	Condition	SNOMED	YES

73754	Restless legs	Condition	SNOMED	YES
4168212	Restlessness and agitation	Condition	SNOMED	YES
45772079	Retinopathy of prematurity stage 0	Condition	SNOMED	YES
4013540	RhD negative	Condition	SNOMED	YES
444372	Rupture of tendon of biceps, long head	Condition	SNOMED	YES
436828	Saliva abnormal	Condition	SNOMED	YES
138821	Seborrhea	Condition	SNOMED	YES
4068847	Segmental and somatic dysfunction	Condition	SNOMED	YES
435088	Senility	Condition	SNOMED	YES
4049121	Separated epiphysis	Condition	SNOMED	YES
4052226	Sequelae of injuries of lower limb	Condition	SNOMED	YES
4198492	Shoulder joint unstable	Condition	SNOMED	YES
25518	Sickle cell trait	Condition	SNOMED	YES
137682	Skin sensation disturbance	Condition	SNOMED	YES
4305303	Sleep deprivation	Condition	SNOMED	YES
4125590	Slurred speech	Condition	SNOMED	YES
4176908	Snapping thumb syndrome	Condition	SNOMED	YES
4248728	Snoring	Condition	SNOMED	YES
4019836	Social exclusion	Condition	SNOMED	YES
36713918	Somatic dysfunction of lumbar region	Condition	SNOMED	YES
444127	Specimen satisfactory for evaluation but limited	Condition	SNOMED	YES
4079874	Sphingolipidosis	Condition	SNOMED	YES
200527	Splenomegaly	Condition	SNOMED	YES
443172	Splinter of face, without major open wound	Condition	SNOMED	YES
138278	Sprains and strains of joints and adjacent muscles	Condition	SNOMED	YES
443082	Starvation	Condition	SNOMED	YES
4008710	Stenosis due to any device, implant AND/OR graft	Condition	SNOMED	YES
40479573	Stimulant abuse	Condition	SNOMED	YES
40483172	Stimulant dependence	Condition	SNOMED	YES
440233	Strain of supraspinatus muscle AND/OR tendon	Condition	SNOMED	YES
72415	Synovial plica	Condition	SNOMED	YES
4194160	Thyroid function tests abnormal	Condition	SNOMED	YES
77081	Tibialis tendinitis	Condition	SNOMED	YES
4201387	Tracheostomy present	Condition	SNOMED	YES
4309320	Transplanted organ rejection	Condition	SNOMED	YES
4029731	Trimethylaminuria	Condition	SNOMED	YES
40482801	Type II diabetes mellitus uncontrolled	Condition	SNOMED	YES
4101289	Tyrosinemia	Condition	SNOMED	YES
4199550	Unable to mobilize	Condition	SNOMED	YES
4092743	Unsteady when standing	Condition	SNOMED	YES
196821	Urethral discharge	Condition	SNOMED	YES
4216708	Urgent desire for stool	Condition	SNOMED	YES

442282	Urinary casts	Condition	SNOMED	YES
79873	Urolith	Condition	SNOMED	YES
4088910	Uterine cervix absent	Condition	SNOMED	YES
4088920	Uterus absent	Condition	SNOMED	YES
4275889	Visual hallucinations	Condition	SNOMED	YES
4104132	Vomit contains feces	Condition	SNOMED	YES
439405	Walking disability	Condition	SNOMED	YES
4193634	Worried	Condition	SNOMED	YES
435723	Wound seroma	Condition	SNOMED	YES
440193	Wristdrop	Condition	SNOMED	YES

Annex 3. Propensity score model and balance

To build large-scale PS models, we systematically engineered and extracted a large, consistent set of baseline patient characteristics that included:

- Demographics (age in 5-year bands, gender, index month)
- Conditions (condition occurrence in lookback window, SNOMED level)
 - Any time prior to index date
 - 180 days prior to index date
 - 30 days prior to index date
- Drugs (drug exposure in lookback window; RxNorm ingredient level)
 - Any time prior to index date
 - 180 days prior to index date
 - 30 days prior to index date
- Procedures (procedure occurrence in lookback window)
 - Any time prior to index date
 - 180 days prior to index date
 - 30 days prior to index date
- Devices (device exposure in lookback window)
 - Any time prior to index date
 - 180 days prior to index date
 - 30 days prior to index date
- Measurement (measurement occurrence in lookback window)
 - Any time prior to index date
 - 180 days prior to index date
 - 30 days prior to index date
- Measurement values
 - 180 days prior to index date
- Clinical index scores
 - CHA₂DS₂VASc
 - Diabetes Complications Severity Index (DCSI)
 - Charlson comorbidity index – Romano adaption

Annex 4. Complete data and results for Ibuprofen comparisons

Supplementary table 11. Incidence of COVID-19 diagnosis in PS-matched Ibuprofen and comparator cohorts

Comparisons	Database	Persons each Cohort ¹	Cases		Follow up (years)		Incidence (%)		Incidence (per 1k person years)		
			Ibu	Comp	Ibu	Comp	Ibu	Comp	Ibu	Comp	
On treatment (Nov 2019- Jan 2020)											
Ibuprofen vs COX-2i	PharMetrics Plus	39,572	156	480	6,931	14,539	0.39	1.21	22.5	33.0	
Ibuprofen vs COX-2i	OpenClaims	272,097	1,407	3,432	62,849	138,466	0.52	1.26	22.4	24.8	
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	69,723	174	449	9,038	16,081	0.25	0.64	19.3	27.9	
Ibuprofen vs ns-NSAIDs	OpenClaims	563,839	1,885	4,100	98,946	168,055	0.33	0.73	19.1	24.4	
Ibuprofen vs Paracetamol	PharMetrics Plus	54,074	119	414	6,830	10,454	0.22	0.77	17.4	39.6	
Ibuprofen vs Paracetamol	OpenClaims	437,928	1,334	4,523	71,973	141,905	0.30	1.03	18.5	31.9	
On treatment (Feb 2020 - Oct 2020)											
Ibuprofen vs COX-2i	PharMetrics Plus	67,190	532	1,247	10,894	21,898	0.79	1.86	48.8	57.0	
Ibuprofen vs COX-2i	OpenClaims	457,280	3,551	7,370	92,004	193,931	0.78	1.61	38.6	38.0	
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	120,954	689	1,334	14,424	24,796	0.57	1.10	47.8	53.8	
Ibuprofen vs ns-NSAIDs	OpenClaims	943,006	5,382	9,682	143,309	241,999	0.57	1.03	37.6	40.0	
Ibuprofen vs Paracetamol	PharMetrics Plus	101,635	575	834	11,617	15,820	0.57	0.82	49.5	52.7	
Ibuprofen vs Paracetamol	OpenClaims	776,963	4,325	8,106	110,110	188,659	0.56	1.04	39.3	43.0	
ITT 6 months (Nov 2019- Jan 2020)											
Ibuprofen vs COX-2i	PharMetrics Plus	40,040	240	206	17,926	17,863	0.60	0.51	13.4	11.5	
Ibuprofen vs COX-2i	OpenClaims	276,702	2,102	1,796	134,908	135,196	0.76	0.65	15.6	13.3	
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	76,940	502	471	34,390	34,220	0.65	0.61	14.6	13.8	
Ibuprofen vs ns-NSAIDs	OpenClaims	598,264	5,192	5,241	289,125	289,699	0.87	0.88	18.0	18.1	
Ibuprofen vs Paracetamol	PharMetrics Plus	70,622	461	358	31,534	31,111	0.65	0.51	14.6	11.5	
Ibuprofen vs Paracetamol	OpenClaims	535,642	4,999	4,543	258,697	258,560	0.93	0.85	19.3	17.6	
ITT 6 months (Feb 2020 - Oct 2020)											
Ibuprofen vs COX-2i	PharMetrics Plus	68,118	2,031	1,875	30,782	30,946	2.98	2.75	66.0	60.6	
Ibuprofen vs COX-2i	OpenClaims	465,534	11,227	9,650	224,472	225,405	2.41	2.07	50.0	42.8	
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	136,417	4,214	4,328	61,266	61,417	3.09	3.17	68.8	70.5	
Ibuprofen vs ns-NSAIDs	OpenClaims	1,012,319	26,929	26,771	480,605	481,832	2.66	2.64	56.0	55.6	
Ibuprofen vs Paracetamol	PharMetrics Plus	136,221	4,408	4,386	61,007	61,139	3.24	3.22	72.3	71.7	
Ibuprofen vs Paracetamol	OpenClaims	991,235	27,457	27,707	470,064	469,717	2.77	2.80	58.4	59.0	

¹Ibuprofen and comparator cohorts are matched 1:1 on PS and are therefore the same size. Ibu – Ibuprofen, Comp - Comparator
Supplementary table 12 Incidence of hospitalization with COVID-19 in PS-matched Ibuprofen and comparator cohorts

Comparisons	Database	Persons each cohort ¹	Cases		Follow up (years)		Incidence (%)		Incidence (per 1k person years)	
			Ibu	Comp	Ibu	Comp	Ibu	Comp	Ibu	Comp
On treatment (Nov 2019- Jan 2020)										
Ibuprofen vs COX-2i	PharMetrics Plus	39,572	29	89	6,963	14,660	0.07	0.22	4.2	6.1
Ibuprofen vs COX-2i	OpenClaims	272,097	446	961	63,317	139,848	0.16	0.35	7.0	6.9
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	69,723	24	91	9,073	16,183	0.03	0.13	2.7	5.6
Ibuprofen vs ns-NSAIDs	OpenClaims	563,839	561	1,171	99,526	169,551	0.10	0.21	5.6	6.9
Ibuprofen vs Paracetamol	PharMetrics Plus	54,074	18	82	6,854	10,565	0.03	0.15	2.6	7.8
Ibuprofen vs Paracetamol	OpenClaims	437,928	386	1,274	72,392	143,803	0.09	0.29	5.3	8.9
On treatment (Feb 2020 - Oct 2020)										
Ibuprofen vs COX-2i	PharMetrics Plus	67,190	112	211	10,979	22,153	0.17	0.31	10.2	9.5
Ibuprofen vs COX-2i	OpenClaims	457,280	1,044	1,948	92,847	196,320	0.23	0.43	11.2	9.9
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	120,954	128	262	14,506	25,020	0.11	0.22	8.8	10.5
Ibuprofen vs ns-NSAIDs	OpenClaims	943,006	1,456	2,432	144,396	244,609	0.15	0.26	10.1	9.9
Ibuprofen vs Paracetamol	PharMetrics Plus	101,635	120	185	11,687	16,004	0.12	0.18	10.3	11.6
Ibuprofen vs Paracetamol	OpenClaims	776,963	1,143	2,228	110,941	191,379	0.15	0.29	10.3	11.6
ITT 6 months (Nov 2019- Jan 2020)										
Ibuprofen vs COX-2i	PharMetrics Plus	40,040	54	55	17,947	17,880	0.13	0.14	3.0	3.1
Ibuprofen vs COX-2i	OpenClaims	276,702	707	592	135,081	135,347	0.26	0.21	5.2	4.4
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	76,940	109	104	34,432	34,263	0.14	0.14	3.2	3.0
Ibuprofen vs ns-NSAIDs	OpenClaims	598,264	1,492	1,504	289,591	290,180	0.25	0.25	5.2	5.2
Ibuprofen vs Paracetamol	PharMetrics Plus	70,622	97	82	31,576	31,144	0.14	0.12	3.1	2.6
Ibuprofen vs Paracetamol	OpenClaims	535,642	1,421	1,382	259,150	258,952	0.27	0.26	5.5	5.3
ITT 6 months (Feb 2020 - Oct 2020)										
Ibuprofen vs COX-2i	PharMetrics Plus	68,118	382	280	31,108	31,248	0.56	0.41	12.3	9.0
Ibuprofen vs COX-2i	OpenClaims	465,534	2,969	2,385	226,202	226,903	0.64	0.51	13.1	10.5
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	136,417	633	670	61,979	62,136	0.46	0.49	10.2	10.8
Ibuprofen vs ns-NSAIDs	OpenClaims	1,012,319	5,868	5,902	485,097	486,264	0.58	0.58	12.1	12.1
Ibuprofen vs Paracetamol	PharMetrics Plus	136,221	684	632	61,741	61,853	0.50	0.46	11.1	10.2
Ibuprofen vs Paracetamol	OpenClaims	991,235	5,823	6,202	474,662	474,421	0.59	0.63	12.3	13.1

¹Ibuprofen and comparator cohorts are matched 1:1 on PS and are therefore the same size. Ibu – Ibuprofen, Comp - Comparator

Supplementary table 13. NCO effect estimate summary for Ibuprofen comparisons

Comparisons	Database	Total NCOs (n)	Significant NCOs (n)	Significant NCOs before calibration (%)	Significant NCOs after calibration (%)
On treatment (Nov 2019- Jan 2020)					
Ibuprofen vs COX-2i	OpenClaims	125	20	16	4.8
Ibuprofen vs COX-2i	PharMetrics Plus	95	9	9.5	3.2
Ibuprofen vs ns-NSAIDs	OpenClaims	133	17	12.8	2.3
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	97	9	9.3	6.2
Ibuprofen vs Paracetamol	OpenClaims	131	32	24.4	4.6
Ibuprofen vs Paracetamol	PharMetrics Plus	90	10	11.1	2.2
On treatment (Feb 2020 - Oct 2020)					
Ibuprofen vs COX-2i	OpenClaims	130	33	25.4	6.2
Ibuprofen vs COX-2i	PharMetrics Plus	103	18	17.5	4.9
Ibuprofen vs ns-NSAIDs	OpenClaims	140	21	15	5.0
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	110	14	12.7	3.6
Ibuprofen vs Paracetamol	OpenClaims	136	48	35.3	4.4
Ibuprofen vs Paracetamol	PharMetrics Plus	104	33	31.7	2.9
ITT 6 months (Nov 2019- Jan 2020)					
Ibuprofen vs COX-2i	OpenClaims	140	27	19.3	3.6
Ibuprofen vs COX-2i	PharMetrics Plus	117	9	7.7	1.7
Ibuprofen vs ns-NSAIDs	OpenClaims	145	26	17.9	7.6
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	124	11	8.9	4.8
Ibuprofen vs Paracetamol	OpenClaims	147	47	32	6.8
Ibuprofen vs Paracetamol	PharMetrics Plus	127	17	13.4	7.1
ITT 6 months (Feb 2020 - Oct 2020)					
Ibuprofen vs COX-2i	OpenClaims	141	43	30.5	7.8
Ibuprofen vs COX-2i	PharMetrics Plus	119	12	10.1	2.5
Ibuprofen vs ns-NSAIDs	OpenClaims	154	37	24	3.2
Ibuprofen vs ns-NSAIDs	PharMetrics Plus	134	8	6	5.2
Ibuprofen vs Paracetamol	OpenClaims	151	58	38.4	5.3
Ibuprofen vs Paracetamol	PharMetrics Plus	137	28	20.4	5.8

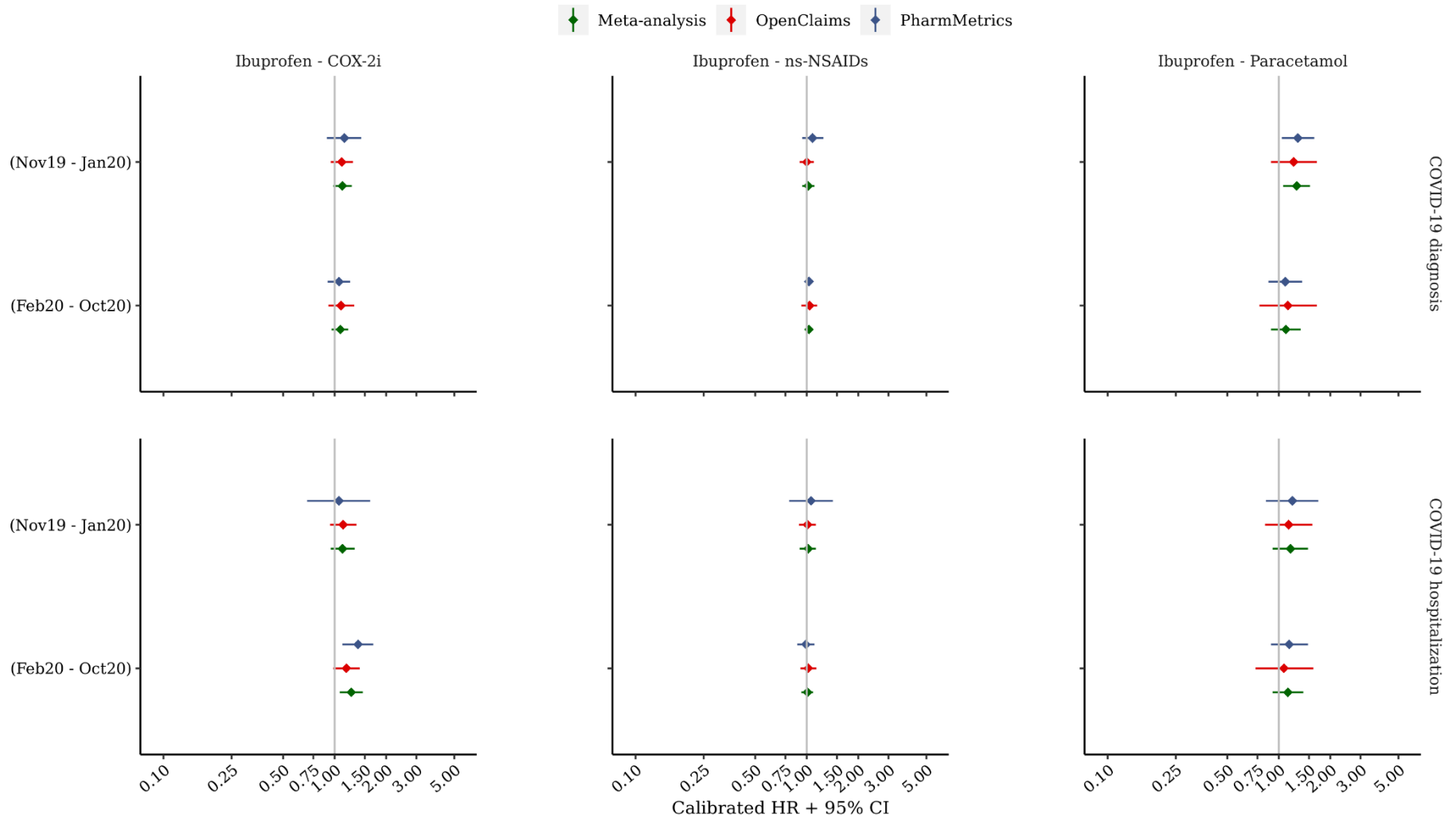
NCO – Negative control outcome.

Red - comparisons that were not completely calibrated (<5% NCOs)

Supplementary table 14. Calibrated HRs for COVID-19 outcomes in Ibuprofen users versus other analgesic users in ITT analysis

Comparisons	Database	<u>COVID-19 diagnosis HR (95% CI)</u>		<u>Hospitalization with COVID-19 HR (95% CI)</u>	
		Nov 2019 - Jan 2020	Feb 2020 - Oct 2020	Nov 2019 - Jan 2020	Feb 2020 - Oct 2020
ITT 6 months					
Ibuprofen - COX-2i	Open Claims	1.10 (0.95 - 1.28)	1.09 (0.92 - 1.30)	1.12 (0.94 - 1.34)	1.17 (0.98 - 1.40)
Ibuprofen - COX-2i	PharMetrics Plus	1.14 (0.90 - 1.43)	1.06 (0.91 - 1.23)	1.06 (0.69 - 1.61)	1.37 (1.11 - 1.68)
Ibuprofen - COX-2i	Meta-analysis	1.11 (0.98 - 1.26)	1.08 (0.96 - 1.20)	1.11 (0.95 - 1.31)	1.25 (1.07 - 1.46)
Ibuprofen - ns-NSAIDs	Open Claims	1.00 (0.91 - 1.10)	1.04 (0.93 - 1.15)	1.01 (0.90 - 1.13)	1.02 (0.92 - 1.14)
Ibuprofen - ns-NSAIDs	PharMetrics Plus	1.08 (0.94 - 1.25)	1.03 (0.98 - 1.08)	1.06 (0.79 - 1.42)	0.99 (0.88 - 1.11)
Ibuprofen - ns-NSAIDs	Meta-analysis	1.02 (0.94 - 1.11)	1.03 (0.99 - 1.08)	1.02 (0.91 - 1.13)	1.01 (0.93 - 1.09)
Ibuprofen - Paracetamol	Open Claims	1.22 (0.90 - 1.67)	1.13 (0.77 - 1.67)	1.14 (0.83 - 1.57)	1.07 (0.73 - 1.59)
Ibuprofen - Paracetamol	PharMetrics Plus	1.29 (1.04 - 1.61)	1.09 (0.87 - 1.37)	1.20 (0.84 - 1.70)	1.15 (0.90 - 1.48)
Ibuprofen - Paracetamol	Meta-analysis	1.27 (1.06 - 1.52)	1.10 (0.90 - 1.34)	1.17 (0.92 - 1.48)	1.13 (0.92 - 1.39)

Supplementary figure 1. Calibrated HRs for COVID-19 outcomes in Ibuprofen users versus other analgesic users in ITT analysis



Supplementary table 15. On-treatment time at risk of COVID-19 diagnosis in PS-matched cohorts

		Time at risk distribution (days)						
Cohort	Database	Min	P10	P25	Median	P75	P90	Max
(November 2019 – January 2020)								
Ibuprofen	OpenClaims	2	6	9	29	156	250	758
COX-2i	OpenClaims	2	29	29	89	486	607	762
Ibuprofen	PharMetrics Plus	2	6	9	29	106	181	541
COX-2i	PharMetrics Plus	2	22	29	58	353	429	587
Ibuprofen	OpenClaims	2	5	9	29	94	173	759
ns-NSAID	OpenClaims	2	9	19	29	231	362	762
Ibuprofen	PharMetrics Plus	2	4	9	21	82	112	589
ns-NSAID	PharMetrics Plus	2	7	14	29	181	289	600
Ibuprofen	OpenClaims	2	5	9	29	89	154	752
Paracetamol	OpenClaims	1	2	4	13	380	594	753
Ibuprofen	PharMetrics Plus	2	5	9	21	78	105	534
Paracetamol	PharMetrics Plus	2	2	3	6	185	353	590
(February 2020 – October 2020)								
Ibuprofen	OpenClaims	1	6	9	29	126	195	708
COX-2i	OpenClaims	1	29	29	86	365	488	723
Ibuprofen	PharMetrics Plus	1	6	9	29	108	166	506
COX-2i	PharMetrics Plus	1	29	29	71	266	333	513
Ibuprofen	OpenClaims	1	4	9	21	89	139	684
ns-NSAID	OpenClaims	1	6	14	29	180	280	702
Ibuprofen	PharMetrics Plus	1	4	9	19	81	107	509
ns-NSAID	PharMetrics Plus	1	6	14	29	160	223	515
Ibuprofen	OpenClaims	1	4	9	21	89	122	732
Paracetamol	OpenClaims	1	2	4	9	197	402	775
Ibuprofen	PharMetrics Plus	1	4	9	19	75	96	509
Paracetamol	PharMetrics Plus	1	2	3	6	124	243	515

Supplementary table 16. On-treatment time at risk of hospitalization with COVID-19 in PS-matched cohorts

		Time at risk distribution (days)						
Cohort	Database	Min	P10	P25	Median	P75	P90	Max
(November 2019 - January 2020)								
Ibuprofen	OpenClaims	2	6	9	29	157	253	758
COX-2i	OpenClaims	2	29	29	89	505	610	762
Ibuprofen	PharMetrics Plus	2	6	9	29	107	182	541
COX-2i	PharMetrics Plus	2	22	29	58	359	432	587
Ibuprofen	OpenClaims	2	5	9	29	94	174	759
ns-NSAIDs	OpenClaims	2	9	19	29	234	369	762
Ibuprofen	PharMetrics Plus	2	4	9	21	82	113	589
ns-NSAIDs	PharMetrics Plus	2	7	14	29	181	292	600
Ibuprofen	OpenClaims	2	5	9	29	89	154	752
Paracetamol	OpenClaims	2	2	4	13	398	596	753
Ibuprofen	PharMetrics Plus	2	5	9	21	78	105	534
Paracetamol	PharMetrics Plus	2	2	3	6	190	360	590
(February 2020 - October 2020)								
Ibuprofen	OpenClaims	1	6	9	29	127	197	708
COX-2i	OpenClaims	1	29	29	86	374	500	723
Ibuprofen	PharMetrics Plus	1	6	9	29	109	168	506
COX-2i	PharMetrics Plus	2	29	29	71	269	341	513
Ibuprofen	OpenClaims	1	4	9	21	89	140	684
ns-NSAIDs	OpenClaims	1	6	14	29	182	286	702
Ibuprofen	PharMetrics Plus	1	4	9	19	82	108	509
ns-NSAIDs	PharMetrics Plus	1	6	14	29	162	226	515
Ibuprofen	OpenClaims	1	4	9	21	89	123	732
Paracetamol	OpenClaims	1	2	4	9	203	421	775
Ibuprofen	PharMetrics Plus	1	4	9	19	76	97	509
Paracetamol	PharMetrics Plus	1	2	3	6	126	247	515