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Cyclooxygenase selectivity and chemical groups of non-steroidal anti-inflammatory drugs and the frequency of reporting hypersensitivity reactions: a case/non-case study in VigiBase

Running Title: Cyclooxygenase selectivity and chemical groups of NSAIDs on hypersensitivity reactions

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ABSTRACT

The reporting of hypersensitivity reactions (HSRs) among non-steroidal anti-inflammatory drugs (NSAIDs) according to cyclooxygenase (COX) selectivity and chemical groups has not been published yet in one study. This study assessed the reporting frequency of HSRs for NSAIDs based on their relative inhibitory potency towards COX enzymes and chemical groups, including the presence/absence of a functional sulfonamide group, in strata of 5 years after market authorization. A case/non-case study was performed among Individual Case Safety Reports (ICSRs) with NSAIDs as suspected drugs in Vigibase, the WHO spontaneous reporting database. Cases were ICSRs mentioning angioedema and anaphylactic/anaphylactoid shock conditions, while non-cases were ICSRs without HSRs. NSAIDs were categorized into (i) NSAIDs with highly COX-2 selectivity (coxibs), (ii) Non-coxib NSAIDs with COX-2 preference, (iii) NSAIDs with poor selectivity, or (iv) NSAIDs with unknown selectivity. Chemical groups were defined based on the Anatomical Therapeutic Chemical classification system and the presence/absence of a functional sulfonamide group. Reporting odds ratios (RORs) and 95% confidence intervals (95% CIs) were calculated using logistic regression analysis. We identified 13,229 cases and 106,444 non-cases. In the first 5 years after marketing, poor selectivity NSAIDs and acetic acid derivatives were associated with the highest ROR of HSRs (age- and sex-adjusted ROR 2.12, 95%CI: 1.98-2.28 and ROR 2.21, 95%CI: 1.83-2.66, respectively), all compared to coxibs, and also sulfonamide NSAIDs compared to non-sulfonamide NSAIDs (age- and sex-adjusted ROR 1.38, 95%CI: 1.29-1.47). After the first 5 years of marketing, most of the RORs returned to approximately 1.

Key words: Non-steroidal anti-inflammatory drugs, cyclooxygenase selectivity, chemical groups, a sulfonamide functional group, hypersensitivity reactions, spontaneous reporting.

ABBREVIATIONS

AADs	: Acetic Acid Derivatives
ADRs	: Adverse Drug Reactions
ATC	: Anatomical Therapeutic Chemical
CIs	: Confidence Intervals
COX	: Cyclooxygenase
EMA	: European Medicines Agency
FDA	: Food and Drug Association
HSRs	: Hypersensitivity Reactions
ICSRs	: Individual Case Safety Reports
MedDRA	: Medical Dictionary for Regulatory Authorities
NSAIDs	: Non-steroidal Anti-Inflammatory Drugs
PADs	: Propionic Acid Derivatives
PMDA	: Pharmaceutical and Medical Devices Agency
PTs	: Preferred Terms
RORs	: Reporting Odds Ratios
SMQs	: Standardized MedDRA Queries
UMC	: Uppsala Monitoring Center
UK	: United Kingdom

US : United State

WHO : World Health Organization

WHO-ART : WHO Adverse Reaction Terminology

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most often reported drugs associated with adverse drug reactions (ADRs) [1, 2]. This group of drugs might cause various type of hypersensitivity reactions (HSRs) and be classified into either allergic reactions or non-allergic reactions with similar symptoms, i.e., pseudoallergic (anaphylactoid reactions) [3, 4].

Both clinical trials and observational studies have shown that cyclooxygenase (COX) selectivity and chemical groups of NSAIDs were associated with differences in sensitizing capacities and hypersensitivity risks. Selective COX-2 inhibitors were associated with a lower hospitalization risk for angioedema compared to non-selective NSAIDs [5] and well tolerable for patients with angioedema and urticaria attributable to non-selective NSAIDs [6-10]. A pharmacovigilance study in the Netherlands showed that among all chemical groups of NSAIDs, propionic acid derivatives (PADs) and acetic acid derivatives (AADs) were associated with a higher risk of anaphylaxis compared to non-use [11]. The presence of a sulfonamide functional group in the chemical structure of NSAIDs is also suspected to affect the risk of HSRs [12].

Many studies have investigated the association between NSAIDs and risk of HSRs. These studies differed in study design and exposure definitions, and none of them evaluated the above-mentioned exposure classifications in one study. Therefore, our study was aimed to evaluate the association between NSAIDs, classified by their COX selectivity and chemical groups including the presence of a sulfonamide functional group, and HSRs as reported in Vigibase using one study design.

MATERIALS AND METHODS

Setting

For our study, we used coded fields from the WHO global individual case safety report (ICSR) database, VigiBase which holds reports on suspected ADRs submitted since 1968. In 1978, VigiBase was transferred from the WHO to the Uppsala Monitoring Center (UMC) in Sweden. Recently, >150 countries are members of the WHO Program for International Drug Monitoring and contribute reports from their respective national ADR reporting system.

Information from contributing countries is heterogeneous, but several items are obligatory to include, i.e., patient demographics (age, sex, and reporting countries), ADRs (onset, duration, and causality assessment), suspected drugs (route of administration, dates of first intake and discontinuation, dosing regimen, and co-medications), and administrative data (type of report, reporters, and source). Often, there is missing information. Duplication is detected by checking of case identifiers, manual inspection of case series, and specific statistical algorithms. The reported drugs are encoded using the WHO Drug Dictionary Enhanced, which uses the WHO Anatomical Therapeutic Chemical (ATC) Classification. ADRs are encoded in the WHO Adverse Reaction Terminology (WHO-ART) and the Medical Dictionary for Regulatory Authorities (MedDRA) in parallel. The MedDRA is used to assess medical issues involving a system, organ, or etiology using its hierarchical structure or through the distinctive feature of Standardized MedDRA Queries (SMQs) [13, 14]. By June 2016, >13 million ICSRs were recorded.

Design

We performed a case/non-case study using data from 1978 until June 2016. We nested our study among ICSRs with an NSAID as a suspected drug. Only individual NSAIDs with first market approval after 1977 were included. Information on the date of market approval for an individual NSAID was obtained from the US Food and Drugs Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceutical and Medical Devices Agency (PMDA) Japan. ICSRs with missing information on age, sex, or date of ADR occurrence were excluded.

Definitions of cases and non-cases

HSR cases were defined as ICSRs for angioedema and anaphylactic/anaphylactoid shock conditions using relevant SMQ codes, including 40 and 9 narrow scopes of preferred terms (PTs) MedDRA, respectively (**Table S1**). The narrow scope refers to most likely HSRs that give a high specificity. Non-cases were ICSRs without HSRs with an NSAID as a suspected drug. Since each NSAID-associated ICSR only contributed once, a single ICSR with multiple ADRs was considered as a case if one of these ADRs was a HSR, but as a non-case, if none of these was a HSR.

Drugs of Interest

NSAIDs were categorized based on both COX selectivity and chemical groups. The COX selectivity was defined based on their relative inhibitory potency towards COX enzymes as the ratios of inhibitory concentration 80% (IC_{80}) against COX-2 and COX-1 enzymes [15-21]. Inhibitory concentration 50% (IC_{50}) values are often used when comparing the potencies of NSAIDs against COX-1 and COX-2 with the following assumptions. The inhibitory curves should be preferably parallel, and NSAIDs produce a 50% or less reduction in prostanoid formation at therapeutic doses. However, since IC_{50} does not

meet these assumptions, IC_{80} is a more valid approach to be used to compare the potency of NSAIDs [15]. It includes (i) coxibs, i.e., NSAIDs based on the Anatomical Therapeutic Chemical (ATC) Classification system that inhibit both COX-2 and COX-1 with high selectivity towards COX-2 by 5 times or more, (ii) non-coxib NSAIDs based on ATC classification that inhibit COX-2 and COX-1 with high selectivity towards COX-2 by 5 times or more (iii) NSAIDs that inhibit both COX-2 and COX-1 with selectivity towards COX-2 enzyme <5 times (poor selectivity), and (iv) NSAIDs without available information on COX inhibitory potency. Individual NSAIDs under each category were shown in **Table S2**. Chemical groups of NSAIDs were categorized based on the ATC classification, i.e., butylpyrazolidines, AADs, oxicams, PADs, fenamates, coxibs, and other NSAIDs, i.e., NSAIDs that are not classified elsewhere. Based on the presence of a sulfonamide functional group, NSAIDs were categorized into (i) sulfonamide NSAIDs, i.e., oxicam group, celecoxib, valdecoxib, polmacoxib, parecoxib, and nimesulide, and (ii) non-sulfonamide NSAIDs, i.e., acetic acid and propionic acid derivatives, butylpyrazolidine and fenamate groups, rofecoxib, etoricoxib, lumiracoxib, nabumetone, niflumic acid, azapropazone, and proquazone. Concomitant use of two or more NSAIDs was excluded.

Data-analyses

We calculated reporting odds ratios (RORs) as a measure of disproportionality. Analogous to a case-control study, a ROR was calculated by dividing the exposure odds among cases divided by the exposure odds in non-cases [22]. To minimize the effect of under-reporting of ADRs, we considered time after market approval of a NSAID into the analyses. Even though the Weber effect is described as ADR reports that peak at the 2nd year after drug approval, other studies showed that ADR reports still increase until 5 years [23, 24]. We calculated RORs in 3 strata of 5 years after market approval to ensure that time after market approval indeed contributes to ROR differences. NSAID-associated ICSRs that were reported after this period were excluded. We stratified our analyses to the most

reported HSRs (urticaria, angioedema, and anaphylactic shock), age, sex, and reporting countries. Reports from the US were analyzed separately because these reports 1) were submitted by healthcare professionals (such as physicians, pharmacists, nurses, and others) as well as consumers (such as patients, family members, lawyers, and others), while from non-US countries reports were submitted mostly by healthcare professionals, 2) also come from other countries because of industry reports with head offices located in the US, and 3) contributed to the highest proportion of reports in Vigibase. Coxibs were the reference group in the analyses based on COX selectivity and chemical groups, and non-sulfonamide NSAIDs were the reference group for sulfonamide NSAIDs. If the proportion of individual NSAIDs that caused HSRs was >2%, these NSAIDs were further analyzed. Rofecoxib was used as the reference group because of having the most favorable tolerability for patients intolerant to NSAIDs [25, 26]. Since rofecoxib was approved in 1999 and then withdrawn in 2004, RORs for individual NSAIDs were calculated only for 5 years after marketing. Crude and age- and sex-adjusted RORs and 95% confidence intervals (95% CIs) were determined using logistic regression analysis. The statistical package SPSS version 24 was used to perform data analyses and p-values <0.05 were considered statistically significant.

Sensitivity Analysis

In sensitivity analyses, to test the robustness of our main findings, a broad scope of PT SMQs of HSRs was used to calculate the RORs. The broad scope includes terms that are often less likely to represent the outcome of interest but gives high sensitivity including 52 and 21 broad scopes for angioedema and anaphylactic/anaphylactoid shock conditions, respectively (**Table S2**).

RESULTS

By June 2016, VigiBase contained 394,957 ICSRs where an NSAID was a suspected drug. After excluding ICSRs reported before 1978, those without information on sex, age, or onset date, NSAIDs without information on the market authorization, NSAIDs with >15 years after market approval, and concomitant use of two or more NSAIDs, 119,673 ICSRs remained, including 13,229 HSR cases and 106,444 non-HSR cases. The inclusion flow diagram is presented in **Figure 1**. The mean age for the cases was lower than the non-cases (47.8 years vs. 57.8 years). Most of the cases and non-cases were <60 years old (75% vs. 52.2%) and female (69.4% vs. 64%). The most significant number of NSAID-associated ICSRs originated from the United States (US) (29.2%), followed by the United Kingdom (UK) (12.2%), Thailand (7.6%), South Korea (5.9%), and Singapore (4.9%). Among these countries, a NSAID as a suspected drug associated with HSRs was mostly found in Thailand. When ignoring the date of market authorization, NSAIDs with poor selectivity were more likely to be a suspected drug among cases (58.3%), while coxibs were more likely to be suspected drugs among non-cases (47.5%). According to chemical groups, coxibs were more likely to be suspected drugs among both cases and non-cases (27.9% and 47.5%, respectively). Also, non-sulfonamide NSAIDs were more likely to be suspected drugs among both cases and non-cases (61.4% and 62.4%, respectively). Heterogeneity in the proportion of cases and non-cases for the reporting countries and NSAIDs either according to COX selectivity and chemical groups was found ($p < 0.05$). The characteristics of ICSRs are shown in **Table 1**.

Within 5 years after market approval, NSAIDs with poor COX selectivity as suspected drugs were associated with the highest ROR of HSRs (age- and sex-adjusted ROR 2.12, 95%CI; 1.98-2.28) compared to coxibs. Of NSAIDs with unknown selectivity, no ICSRs were reported within 10 years after market approval (**Figure 2a and Table S3a**). As suspected drugs, of all chemical groups of NSAIDs, AADs, fenamates, and PADs were associated with the highest RORs (age- and sex-adjusted ROR 3.07, 95%CI; 2.83-3.33, ROR 2.21, 95%CI; 1.83-2.66, and ROR 1.93, 95%CI; 1.69-2.19,

respectively) compared to coxibs (**Figure 2b and Table S3b**), and sulfonamide NSAIDs were associated with a higher ROR (age- and sex-adjusted ROR 1.38, 95%CI; 1.29-1.47) compared to non-sulfonamide NSAIDs (**Figure 2c and Table S3c**). After the first 5 years of marketing, most of the RORs returned to approximately 1. Among individual NSAIDs, tolmetin, zomepirac, and loxoprofen as suspected drugs were associated with the highest RORs (age- and sex-adjusted ROR 12.83, 95%CI; 10.53-15.64, ROR 11.26, 95%CI; 9.89-12.81, and ROR 5.73, 95%CI; 4.64-7.09, respectively) compared to rofecoxib (**Table S3d**).

RORs stratified by individual HSRs, reporting countries, sex, and age

The RORs of most frequently reported HSRs (urticaria, angioedema, and anaphylactic shock) were similar to the composite of all HSRs for NSAIDs either based on COX-2 selectivity, chemical groups, and individual NSAIDs, except for ROR of anaphylactic shock for sulfonamide NSAIDs. Within 5 years after marketing, sulfonamide NSAIDs were associated with a similar ROR of anaphylactic shock compared to non-sulfonamide NSAIDs (**Table S4a-d, Table S5a-d, and Table S6a-d**). Different reporting countries were associated with different RORs for NSAID use based on both COX selectivity and the presence or absence of a sulfonamide group, but not on chemical groups nor individual NSAIDs. For non-US reports, non-coxib NSAIDs with COX-2 preference and NSAIDs with poor selectivity were associated with similar RORs, but for US reports, these groups were associated with higher RORs compared to coxibs. For non-US reports, sulfonamide NSAIDs were associated with a higher ROR, but for US reports, this group was associated with a similar ROR compared to non-sulfonamide NSAIDs (**Table S7a-d**). Finally, differences in age and sex generally were not associated with differences in the RORs (**Table S8a-d and Table S9a-d**).

Sensitivity analyses

By using a broad scope of HSRs to assess the RORs for NSAIDs, similar results were shown as the main findings (**Table S10a-d**).

DISCUSSION

Our results show that COX selectivity and chemical groups of NSAIDs, as well as time after market authorization, contribute to the differences in the reporting of HSRs for NSAID use. In the first 5 years after marketing, as suspected drugs, NSAIDs with poor COX selectivity were associated with the highest ROR compared to coxibs. This group was also associated with the highest ROR of urticaria and angioedema compared to coxibs. As suspected drugs, of all chemical groups, AADs, fenamates, and PADs compared to coxibs and sulfonamide NSAIDs compared to non-sulfonamide NSAIDs were associated with higher RORs. Among individual NSAIDs, tolmetin and zomepirac that belong to AADs, and loxoprofen that belongs to PADs were associated with the highest RORs compared to rofecoxib. Our sensitivity analyses supported these findings.

Our findings are in line with previous studies. Risk of hospitalization for angioedema was higher for non-selective NSAIDs compared to selective COX-2 inhibitors [5]. Celecoxib (a sulfonamide NSAID) had a higher risk of urticaria compared to rofecoxib (a non-sulfonamide NSAID), although both drugs belong to coxibs [12]. Also, zomepirac was associated with a high risk of allergy and anaphylaxis compared to other NSAIDs [27, 28].

Both non-allergic and allergic mechanisms might trigger NSAID-associated HSRs. The inhibition of COX-1 enzyme alters eicosanoid biosynthesis that leads to a disruption of the arachidonic acid pathway. It induces an imbalance of prostaglandins and cysteinyl leukotriene that are responsible for the clinical features of HSRs [29, 30]. The presence of an N1 heterocyclic ring and an arylamine group at the N4 position in a sulfonamide group is expected to be responsible for HSRs of sulfonamide

chemotherapeutics. This structure triggers mast cells to release IgE [31, 32]. However, since most sulfonamide NSAIDs do not contain this structure, the risk of HSRs probably involves other factors such as the effect of other chemical structures in sulfonamide group and the involvement of non-type I immune responses. Parent sulfonamide or its reactive metabolite can cause tissue damage or stimulate cellular or humoral immunity such as T cells to initiate an immune response towards haptenation or antigen. HSRs might also more likely occur among those with atopy [31, 33].

Several factors might also influence the reporting of ADRs next to time after marketing. First, mild ADRs such as urticaria and ADRs that are already included in the summary of product characteristics (SmPC) are less likely to be reported [34]. Second, several NSAIDs have been withdrawn from the market during observation time. Within 1982-2004, benoxaprofen, oxyphenbutazone, indoprofen, suprofen, piroprofen, fenclofenac, zomepirac, isoxicam, and rofecoxib were withdrawn due to various serious ADRs [28]. Moreover, an individual NSAID is often not marketed in the same year between countries. For example, celecoxib was approved in 1998 for the US market and in 2000 for the Dutch market. Third, when the WHO International Drug Monitoring Program was launched in 1968, only 10 countries participated, but currently, Vigibase contains data from >150 countries [13, 14]. Finally, an alert from regulatory authorities or media attention on safety issues might have a direct and substantial impact on reporting and clinical practice, such as a decrease in drug prescription or utilization [35-37].

For US reports, we found differences in RORs of HSRs for sulfonamide NSAIDs compared to our primary analyses. Differences in reporting habits and ethnicity [38, 39] might explain these differences as well as NSAID sales and consumptions between countries. For example, only celecoxib among coxibs is still available in the US market [40, 41].

Strengths and Limitations

The strengths of this study are that, first, Vigibase contains a large number of spontaneous reporting data collected from national pharmacovigilance centers worldwide, representing >90% of the global population. Second, Vigibase enables to study ADRs in a realistic setting [42], such as the use of over-the-counter medications that often are not recorded in electronic health record databases. Finally, this system can detect reporting ADRs immediately following market launch [43].

Nonetheless, we need to mention several limitations. First, pharmacovigilance data represents <10% of the actual events leading to problems in selective and under-reporting, and external validity [39, 44]. Second, we cannot completely neglect that within 5 years after market authorization, ADR reports are still possibly affected by factors like new drug policies from regulatory bodies or safety issues from media. Third, the quality of reports is variable causing misclassification of exposure and outcomes such as mild ADRs are less likely to be reported as mentioned above. Finally, information on COX selectivity was not available for several NSAIDs. However, the proportion of ICSRs for this group was small for both cases and non-cases.

Due to the heterogeneity of reports and the limited clinical data associated with HSRs, especially medical history, we cannot reach definite conclusions. Nonetheless, based on the strength of the associations, supported by the consistency of the findings in our sensitivity analyses, and mechanistic considerations, we detected a possible association between either COX selectivity and chemical groups of NSAIDs, including the presence of a sulfonamide functional group and HSRs. Further pharmacoepidemiological studies are needed to confirm these potential associations by using conventional electronic health databases and considering several important potential risk factors. These include allergic-associated factors such as atopy, genetic profiles, positive HSRs from re-challenging NSAIDs, and familial history, as well as co-medication use such as corticosteroids and antihistamines and comorbidities such as auto-immune disorders (e.g., rheumatoid arthritis and systemic lupus erythematosus).

It remains important to be vigilant during the initial marketing phase of a drug for all stakeholders. Health care professionals should stay aware of the benefits and risks when prescribing NSAIDs for those who are in need mainly during the first 5 years after market approval. Market authorization holders should report periodic safety up-date profiles of their products. Likewise, regulatory bodies should be reactive when a new signal pops-up, and pro-active to monitor for specific and unexpected signals or to follow the initial users of a drug.

CONCLUSION

COX selectivity and chemical groups of NSAIDs affect the risk of HSRs, including angioedema and urticaria according to spontaneous reporting data. As suspected drugs, NSAIDs with poor COX selectivity were associated with highest RORs of HSRs, as well as AADs all compared to coxibs, and sulfonamide NSAIDs compared to non-sulfonamide NSAIDs.

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CAVEAT STATEMENT

Even though the data provided by the UMC, the findings and conclusions are from the authors. The information comes from various sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The findings of this study do not represent the opinion of either the UMC, National Pharmacovigilance Centers, or WHO.

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REFERENCES

1. Blanca-Lopez N., et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin. Exp. Allergy* (2013) **43** 85-91.
2. Petrisor C. et al. Epidemiology of self-reported drug-induced immediate-type hypersensitivity reactions in the surgical population: a 5-year single-center survey in a Romanian allergeo-anaesthesia center. *Clujul. Med.* (2013) **86** 321-326.
3. Brockow K. Time for more clinical research on non-steroidal anti-inflammatory drug-induced urticaria/angioedema and anaphylaxis. *Clin. Exp. Allergy* (2013) **43** 5-7.
4. Giavina-Bianchi, P. et al. Angioedema associated with nonsteroidal anti-inflammatory drugs. *Curr. Opin. Allergy Clin. Immunol.* (2016) **16** 323-332.
5. Downing A. et al. Risk of hospitalization for angioedema among users of newer COX-2 selective inhibitors and other nonsteroidal anti-inflammatory drugs. *Br. J. Clin. Pharmacol.* (2006) **62** 496-501.
6. Borges M.S. et al. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann. Allergy Asthma Immunol.* (2001) **87** 201-204.
7. Goksel Ö. et al. Safety of meloxicam in patients with aspirin/non-steroidal anti-inflammatory drug-induced urticaria and angioedema. *J. Dermatol.* (2010) **37** 973-979.
8. Valero A. et al. NSAID-sensitive patients tolerate rofecoxib. *Allergy* (2002) **57** 1214-1215.

9. Colanardi M.C. et al. Safety of parecoxib in patients with nonsteroidal anti-inflammatory drug-induced urticaria or angioedema. *Ann. Allergy Asthma Immunol.* (2008) **100** 82-85.
10. Garcia-Rodriguez R.M. et al. Celecoxib, safe in NSAID intolerance. *Allergy* (2002) **57** 1085-1086.
11. van Puijenbroek E.P. et al. Different risks for NSAID-induced anaphylaxis. *Ann. Pharmacother.* (2002) **36** 24-29.
12. Wiholm B.E. Identification of sulfonamide-like adverse drug reactions to celecoxib in the World Health Organization database. *Curr. Med. Res. Opin.* (2001) **17** 210-216.
13. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. *Drug Inf. J.* (2008) **42** 409-419.
14. Uppsala_Monitoring_Centre. WHO Programme Members. 2016 12 April [cited 2016 May 9, 2016]; Available from: <http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442>.
15. Warner T.D. et al. Nonsteroid drug selectivities for cyclooxygenase-1 rather than cyclooxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc. Natl Acad. Sci.* (1999) **96** 7563-7568.
16. Cryer, B. and M. Feldman, Cyclooxygenase-1 and Cyclooxygenase-2 Selectivity of Widely Used Nonsteroidal Anti-Inflammatory Drugs. *Am J Med*, 1998. **104**(5): p. 413-421.
17. Grossman, C., et al., Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and Cox 2 inhibitors. *Inflamm Res*, 1995. **44**(6): p. 253-257.
18. Kawai, S., Cyclooxygenase selectivity and the risk of gastrointestinal complications of various non-steroidal anti-inflammatory drugs: a clinical consideration. *Inflamm Res*, 1998. **47**(2): p. 102-106.
19. Carbone, L.D., et al., Association Between Bone Mineral Density and the Use of Nonsteroidal Anti-Inflammatory Drugs and Aspirin: Impact of Cyclooxygenase Selectivity. *J Bone Miner Res*, 2003. **18**(10): p. 1795-1802.

20. Abraham, N.S., et al., Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. *Aliment Pharmacol Ther*, 2007. **25**(8): p. 913-924.
21. Danelich, I.M., et al., Safety of nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease. *Pharmacother*, 2015. **35**(5): p. 520-35.
22. De Bruin, M., et al., Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. *Eur Heart J*, 2005. **26**(6): p. 590-597.
23. Hoffman, K.B., et al., The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs Approved from 2006 to 2010. *Drug Saf*, 2014. **37**(4): p. 283-294.
24. Thiessard, F., et al., Trends in Spontaneous Adverse Drug Reaction Reports to the French Pharmacovigilance System (1986—2001). *Drug Saf*, 2005. **28**(8): p. 731-740.
25. Bavbek, S., et al., Rofecoxib, as a safe alternative for acetylsalicylic acid/nonsteroidal anti-inflammatory drug-intolerant patients. *J Investig Allergol Clin Immunol*, 2006. **16**(1): p. 57-62.
26. Bavbek, S., et al., Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: comparison of nimesulide, meloxicam, and rofecoxib. *J Asthma*, 2004. **41**(1): p. 67-75.
27. Strom, B.L., et al., The effect of indication on hypersensitivity reactions associated with zomepirac sodium and other nonsteroidal anti-inflammatory drugs. *Arthritis Rheum*, 1987. **30**(10): p. 1142-8.
28. Onakpoya, I.J., C.J. Heneghan, and J.K. Aronson, Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis. *Crit Rev Toxicol*, 2016: p. 1-13.
29. Cho, S.H., et al., NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy Asthma Immunol Res*, 2014. **69**(4): p. 438-44.
30. Hermans, M., et al., Nonsteroidal anti-inflammatory drug hypersensitivity: not always an allergy! A young farmer with dyspnoea; what is your diagnosis? 2018: p. 52.

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31. Brackett, C.C., Sulfonamide allergy, and cross-reactivity. *Curr Allergy Asthma Rep*, 2007. **7**(1): p. 41-48.
 32. Wulf, N.R. and K.A. Matuszewski, Sulfonamide cross-reactivity: is there evidence to support broad cross-allergenicity? *Am J Health-Syst Pharm*, 2013. **70**(17): p. 1483-1494.
 33. Strom, B.L., et al., Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med*, 2003. **349**(17): p. 1628-35.
 34. Weber, J., Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. *Adv Inflamm Res*. 1984.
 35. Dusetzina, S.B., et al., Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. *Med Care*, 2012. **50**(6): p. 466.
 36. Sessler, N.E., et al., Disproportionality analysis of buprenorphine transdermal system and cardiac arrhythmia using FDA and WHO postmarketing reporting system data. *Postgrad Med*, 2017.
 37. Piening, S., et al., Impact of safety-related regulatory action on clinical practice. *Drug Saf*, 2012. **35**(5): p. 373-385.
 38. Fournier, J.P., et al., Drug interactions between antihypertensive drugs and non-steroidal anti-inflammatory agents: a descriptive study using the French Pharmacovigilance database. *Fundam Clin Pharmacol*, 2014. **28**(2): p. 230-5.
 39. Alharbi, F.F., et al., The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in Vigibase. *Fundam Clin Pharmacol*, 2017.
 40. La Rochelle, P., J. Lexchin, and D. Simonyan, Analysis of the drugs withdrawn from the US market from 1976 to 2010 for safety reasons. *Pharmaceutical Med*, 2016. **30**(5): p. 277-289.
 41. U.S._Food_&_Drug_Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. 2017 25 April 2017 [cited 2017 April 26]; Available from: <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

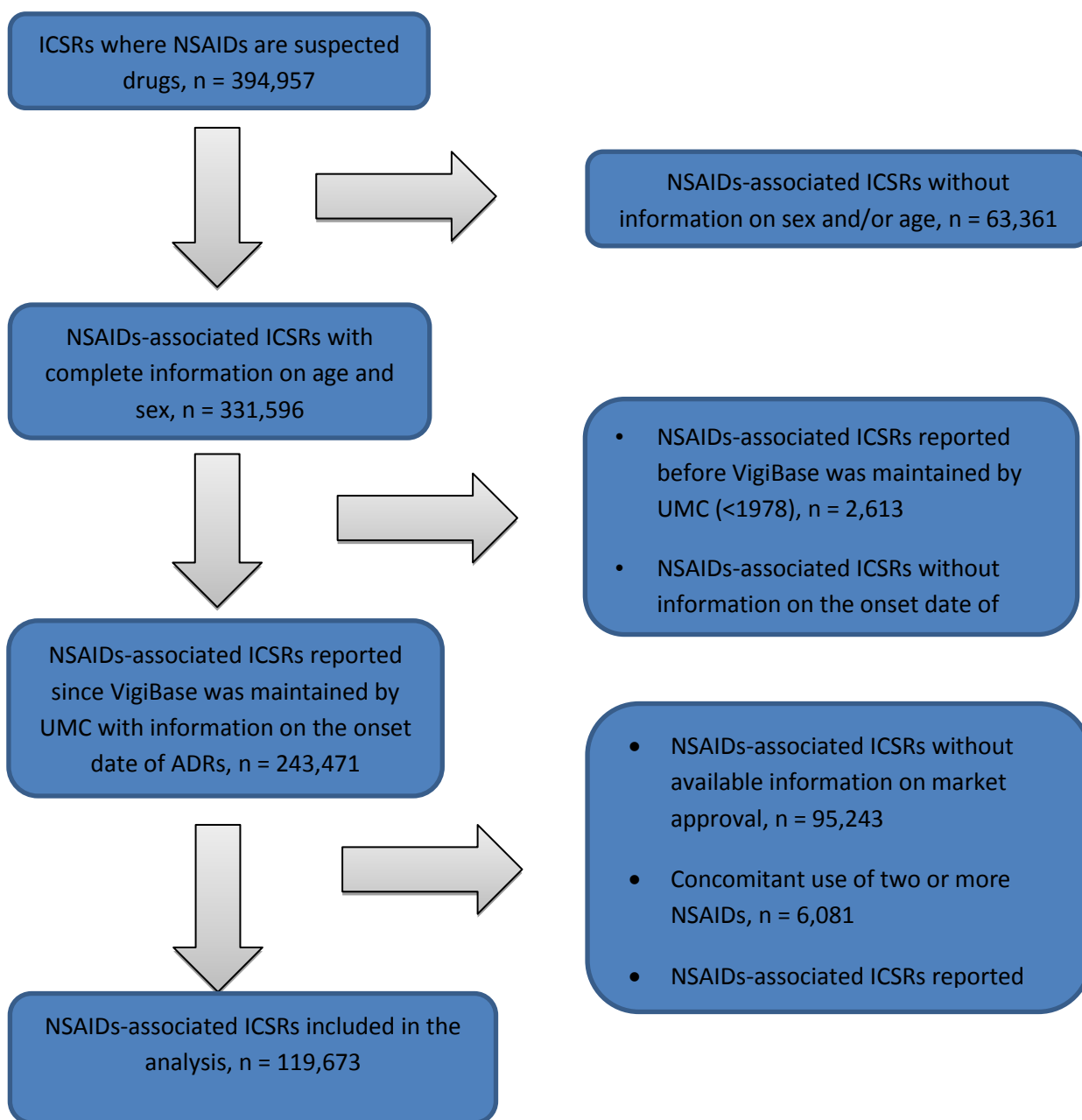
- Accepted Article
42. Willemen, M.J., et al., Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization Vigibase. *Diabetes care*, 2011. **34**(2): p. 369-374.
 43. Bate, A., M. Lindquist, and I. Edwards, The application of knowledge discovery in databases to post-marketing drug safety: example of the WHO database. *Fund Clin Pharmacol*, 2008. **22**(2): p. 127-140.
 44. Lumley, C., et al., The under-reporting of adverse drug reactions seen in general practice. *Pharmaceutical Med*, 1986. **1**(3): p. 205-212.

Table 1 Characteristics of ICSRs where NSAIDs are a suspected drug with hypersensitivity reactions (cases) and without hypersensitivity reactions (non-cases)

	Cases (n=13,229)	Non-cases (n=106,444)	p-value
Age, mean (year $\pm$ sd)	47.8 $\pm$ 17.6	57.8 $\pm$ 18.2	0.000*
Adults (<60 years old), n (%)	9,926 (75.0)	55,544 (52.2)	0.000*
Elderly ($\geq$ 60 years old), n (%)	3,303 (25.0)	50,900 (47.8)	
Sex			
Females, n (%)	9,180 (69.4)	68,149 (64.0)	0.000*
Males, n (%)	4,049 (30.6)	38,295 (36.0)	
Reporting NSAID use according to COX selectivity			
Coxibs, n (%)	3,689 (27.9)	50,596 (47.5)	0.000*
NSAIDs with poor selectivity, n (%)	7,706 (58.3)	41,123 (38.6)	
Non-coxib NSAIDs with COX-2 preference, n (%)	1,741 (13.2)	13,680 (12.9)	
Unknown potency, n (%)	93 (0.7)	1,045 (1.0)	
Reporting NSAID use according to chemical groups			
Coxibs, n (%)	3,689 (27.9)	50,596 (47.5)	0.000*
Oxicams, n (%)	3,006 (22.7)	20,290 (19.1)	
Acetic acid derivatives and related-substances, n (%)	2,754 (20.8)	16,389 (15.4)	
Fenamates, n (%)	2,427 (18.3)	6,820 (6.4)	
Propionic acid derivatives, n (%)	669 (5.1)	5,405 (5.1)	
Butylpyrazolidines, n (%)	132 (1.0)	1,096 (1.0)	
Other NSAIDs, n (%)	552 (4.2)	5,848 (5.5)	
Reporting NSAID use according to the presence/absence of sulfonamide group			
Non-sulfonamide NSAIDs, n (%)	8,124 (61.4)	66,380 (62.4)	0.033*
Sulfonamide NSAIDs, n (%)	5,105 (38.6)	40,064 (37.6)	
Reporting countries			
Thailand, n (%)	3,268 (24.7)	5,812 (5.5)	0.000*
United States, n (%)	2,210 (16.7)	32,779 (30.8)	
Singapore, n (%)	1,496 (11.3)	4,388 (4.1)	
Great Britain, n (%)	971 (7.3)	13,634 (12.8)	
South Korea, n (%)	905 (6.8)	6,176 (5.8)	
Other countries, n (%)	4,379 (33.1)	43,655 (41.0)	

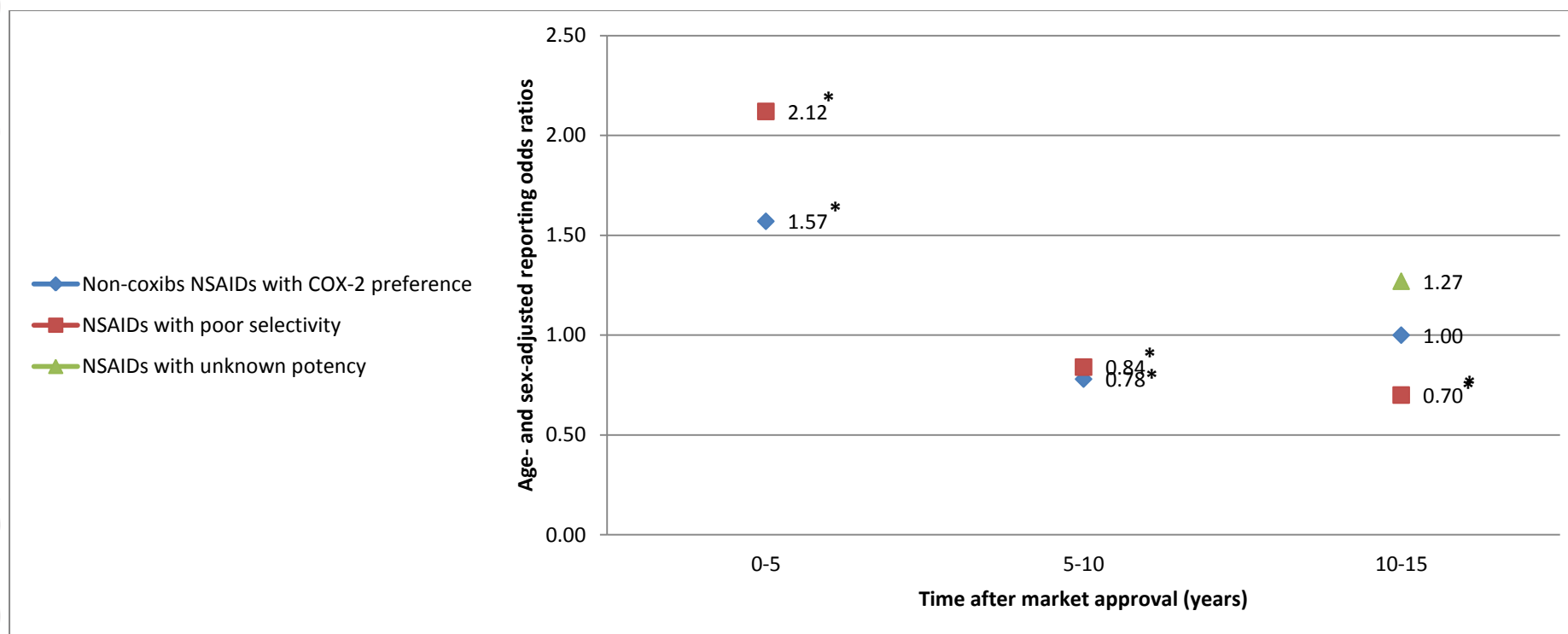
Abbreviations: COX = cyclooxygenase; ICSRs = individual case safety reports; NSAIDs = non-steroidal anti-inflammatory drugs

*statistically significant (p<0.05)



Abbreviations: ADRs = adverse drug reactions; ICSRs = individual case safety reports; NSAIDs = non-steroidal anti-inflammatory drugs; UMC = Uppsala Monitoring Center

Figure 1 Flowchart describing the inclusion of ICSRs



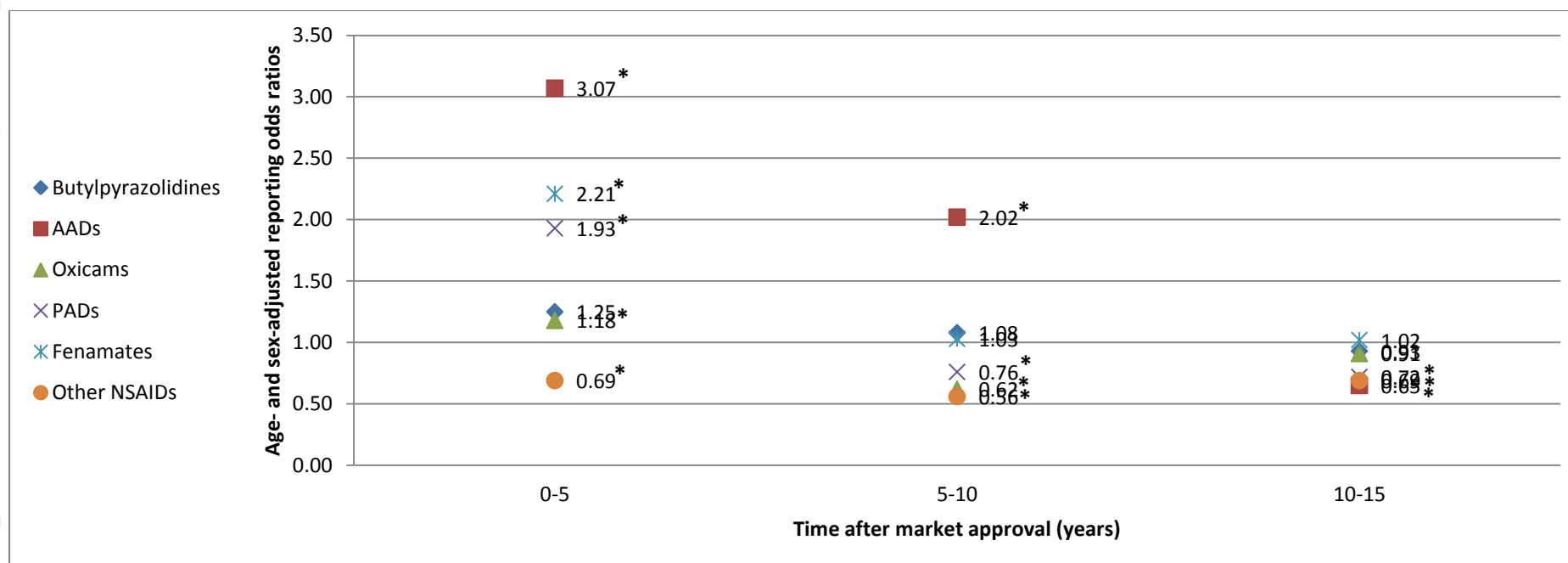
	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-Cases (n=56,477)	Cases (n=1,706)	Non-Cases (n=13,013)	Cases (n=1,804)	Non-Cases (n=12,854)
Coxibs						
Cases/non-cases, n (%)	2,226 (53.1)	40,743 (72.1)	629 (36.9)	4,257 (32.7)	715 (39.6)	4,565 (35.5)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1
NSAIDs with poor selectivity						
Cases/non-cases, n (%)	1,524 (36.3)	11,147 (19.7)	680 (39.9)	5,467 (42.0)	716 (39.7)	6,074 (47.3)
Crude RORs/Age- and sex-adjusted RORs	2.50 (2.34-2.68)*	2.12 (1.98-2.28)*	0.84 (0.75-0.95)*	0.84 (0.74-0.94)*	0.75 (0.67-0.84)*	0.70 (0.63-0.78)*
Non-coxib NSAIDs with COX-2 preference						

Cases/non-cases, n (%)	446 (10.6)	4,587 (8.1)	397 (23.3)	3,285 (25.2)	358 (19.8)	2,142 (16.7)
Crude RORs/Age- and sex-adjusted RORs	1.78 (1.60-1.98)*	1.57 (1.41-1.75)*	0.82 (0.72-0.94)*	0.78 (0.68-0.90)*	1.07 (0.93-1.22)	1.00 (0.87-1.15)
NSAIDs with unknown potency						
Cases/non-cases, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.0)	15 (0.8)	73 (0.6)
Crude RORs/Age- and sex-adjusted RORs	NA	NA	NA	NA	1.31 (0.75-2.30)	1.27 (0.72-2.24)

Abbreviations: COX-2 = cyclooxygenase-2; NA = not applicable; NSAIDs = non-steroidal anti-inflammatory drugs; RORs = reporting odds ratios

*statistically significant (p<0.05)

Figure 2a Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to cyclooxygenase selectivity with coxibs as a reference group



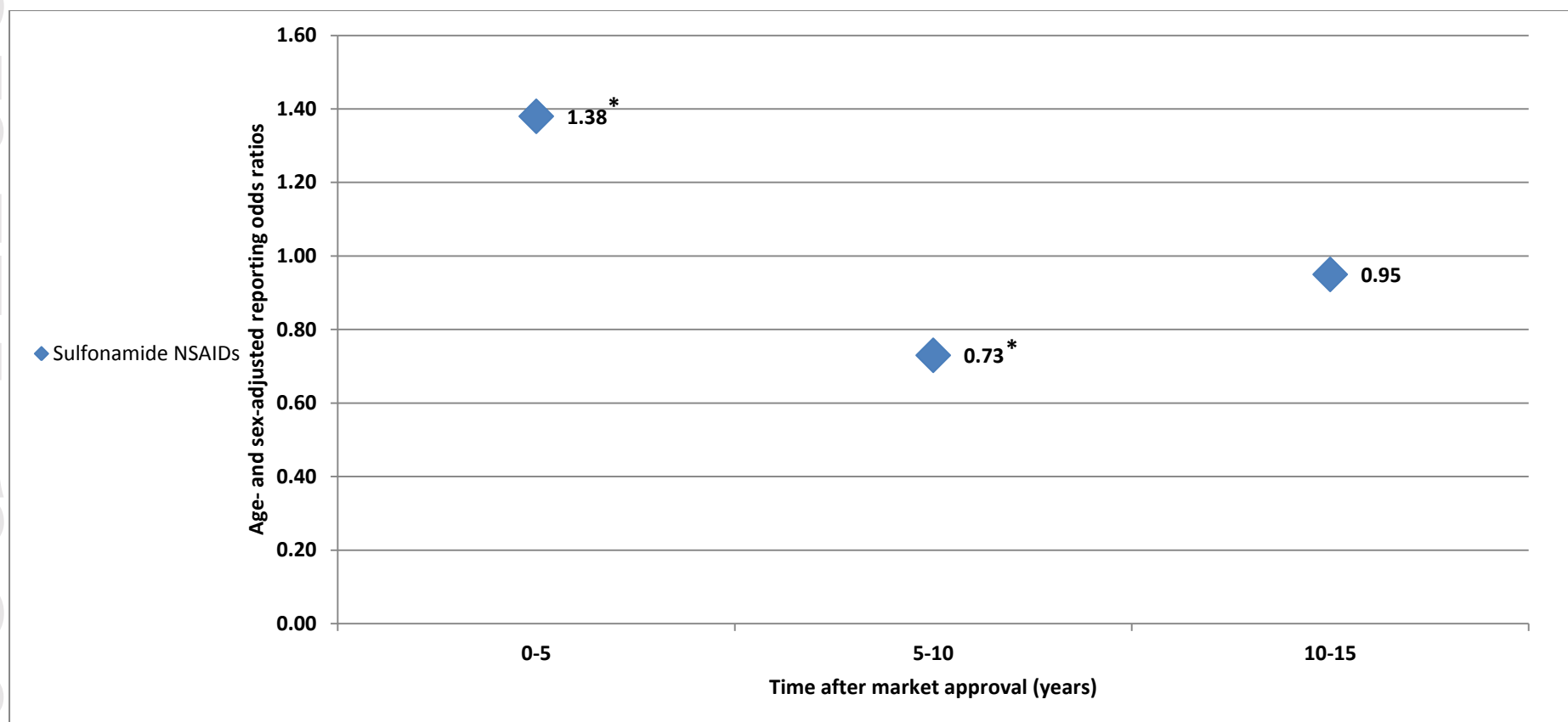
	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-cases (n=56,477)	Cases (n=1,706)	Non-cases (n=13,013)	Cases (n=1,804)	Non-cases (n=12,854)
Coxibs						
Cases/non-cases, n (%)	2,226 (53.1)	40,743 (72.1)	629 (36.9)	4,257 (32.7)	715 (39.6)	4,565 (35.5)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1
Oxicams						
Cases/non-cases, n (%)	371 (8.8)	5,270 (9.3)	347 (20.3)	4,009 (30.8)	424 (23.5)	2,983 (23.2)
Crude RORs/Age- and sex-adjusted RORs	1.29 (1.15-1.44)*	1.18 (1.05-1.32)*	0.59 (0.51-0.67)*	0.62 (0.54-0.71)*	0.91 (0.80-1.03)	0.91 (0.80-1.04)
Acetic acid derivatives and related substances						

Cases/non-cases, n (%)	1,047 (25.0)	5,299 (9.4)	236 (13.8)	852 (6.5)	333 (18.5)	3,059 (23.8)
Crude RORs/Age- and sex-adjusted RORs	3.62 (3.34-3.91)*	3.07 (2.83-3.33)*	1.88 (1.59-2.22)*	2.02 (1.70-2.39)*	0.70 (0.61-0.80)*	0.65 (0.57-0.75)*
Fenamates						
Cases/non-cases, n (%)	142 (3.4)	899 (1.6)	121 (7.1)	548 (4.2)	135 (7.5)	554 (4.3)
Crude RORs/Age- and sex-adjusted RORs	2.89 (2.41-3.47)*	2.21 (1.83-2.66)*	1.49 (1.21-1.85)*	1.03 (0.83-1.29)	1.56 (1.27-1.91)*	1.02 (0.83-1.27)
Propionic acid derivatives						
Cases/non-cases, n (%)	307 (7.3)	2,443 (4.3)	271 (15.9)	2,215 (17.0)	79 (4.4)	625 (4.9)
Crude RORs/Age- and sex-adjusted RORs	2.30 (2.03-2.61)*	1.93 (1.69-2.19)*	0.83 (0.71-0.96)*	0.76 (0.65-0.89)*	0.81 (0.63-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines						
Cases/non-cases, n (%)	56 (1.3)	698 (1.2)	21 (1.2)	114 (0.9)	10 (0.6)	58 (0.5)
Crude RORs/Age- and sex-adjusted RORs	1.47 (1.12-1.93)*	1.25 (0.95-1.65)	1.25 (0.78-2.00)	1.08 (0.67-1.75)	1.10 (0.56-2.16)	0.93 (0.47-1.83)
Others						
Cases/non-cases, n (%)	47 (1.1)	1,125 (2.0)	81 (4.7)	1,018 (7.8)	108 (6.0)	1,010 (7.9)
Crude RORs/Age- and sex-adjusted RORs	0.77 (0.57-1.03)	0.69 (0.51-0.92)*	0.54 (0.42-0.69)*	0.56 (0.44-0.71)*	0.68 (0.55-0.85)*	0.69 (0.56-0.86)*

Abbreviation: AADs = acetic acid derivatives and related substances; NSAIDs = non-steroidal anti-inflammatory drugs; PADs = propionic acid derivatives; RORs = reporting odds ratios

*statistically significant (p<0.05)

Figure 2b Reporting odds ratios of hypersensitivity reactions of any NSAIDs according to chemical groups with coxibs as a reference group



	0-5 years		5-10 years		10-15 years	
	Cases (n=4,196)	Non-cases (n=56,477)	Cases (n=1,706)	Non-cases (n=13,013)	Cases (n=1,804)	Non-cases (n=12,854)
Non-sulfonamide NSAIDs						
Cases/non-cases, n (%)	2,614 (62.3)	38,860 (68.8)	1,106 (64.8)	7,145 (54.9)	1,118 (62.0)	7,422 (57.7)
Crude RORs/Age- and sex-adjusted RORs	1	1	1	1	1	1
Sulfonamide NSAIDs						

Cases/non-cases, n (%)	1,582 (37.7)	17,617 (31.2)	600 (35.2)	5,868 (45.1)	686 (38.0)	5,432 (42.3)
Crude RORs/Age- and sex-adjusted RORs	1.34 (1.25-1.43)*	1.38 (1.29-1.47)*	0.66 (0.60-0.73)*	0.73 (0.66-0.82)*	0.84 (0.76-0.93)*	0.95 (0.86-1.06)

Abbreviation: NSAIDs = non-steroidal anti-inflammatory drugs; RORs = reporting odds ratios

*statistically significant (p<0.05)

Figure 2c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide groups with non-sulfonamide NSAIDs as a reference group

FIGURE LEGENDS

Figure 1 Flowchart describing the inclusion of ICSRs

Figure 2a Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to cyclooxygenase selectivity with coxibs as a reference group

Figure 2b Reporting odds ratios of hypersensitivity reactions of any NSAIDs according to chemical groups with coxibs as a reference group

Figure 2c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide groups with non-sulfonamide NSAIDs as a reference group

SUPPLEMENTARY

Table S1. Diagnoses of hypersensitivity reactions in MedDRA browser

1. Angioedema (SMQs code 20000024)			
Narrow scope	Preferred Term (PT) Codes	Broad scope	Preferred Term (PT) Codes
1. Allergic edema	10060934	1. Auricular swelling	10003800
2. Angioedema	10002424	2. Breast edema	10006294
3. Circumoral edema	10052250	3. Breast swelling	10006312
4. Conjunctival edema	10010726	4. Choking	10008589
5. Corneal edema	10011033	5. Choking sensation	10008590
6. Epiglottis edema	10015029	6. Drug cross-reactivity	10076743
7. Eye edema	10052139	7. Drug hypersensitivity	10058061
8. Eye swelling	10015967	8. Ear swelling	10018092
9. Eyelid edema	10015993	9. Endotracheal intubation	10067639
10. Face edema	10016029	10. Gastrointestinal edema	10058061
11. Gingival edema	10049305	11. Generalized edema	10018092
12. Gingival swelling	10018291	12. Genital swelling	10067639
13. Gleich's syndrome	10066837	13. Hypersensitivity	10020751
14. Hereditary angioedema	10019860	14. Laryngeal dyspnea	10052390
15. Idiopathic angioedema	10073257	15. Laryngeal obstruction	10059639
16. Idiopathic urticaria	10021247	16. Local swelling	10024770
17. Intestinal angioedema	10076229	17. Localized edema	10048961
18. Laryngeal angioedema	10023845	18. Nasal obstruction	10028748
19. Laryngotracheal angioedema	10023893	19. Nasal edema	10028750
20. Limbal swelling	10070492	20. Nipple edema	10059012
21. Lipedema	10024558	21. Nipple swelling	10058680
22. Lip swelling	10024570	22. Obstructive airways disorder	10061877
23. Mouth swelling	10075203	23. Edema	10030095
24. Oculo-respiratory syndrome	10067317	24. Edema genital	10030104
25. Edema mouth	10030110	25. Edema mucosal	10030111
26. Oropharyngeal edema	10078783	26. Edema neonatal	10061317
27. Oropharyngeal swelling	10031118	27. Edema peripheral	10030124
28. Palatal edema	10056998	28. Orbital edema	10031051
29. Palatal swelling	10074403	29. Penile edema	10066774
30. Periorbital edema	10034545	30. Penile swelling	10034319
31. Pharyngeal edema	10034829	31. Perinephric edema	10078818
32. Scleral edema	10057431	32. Peripheral edema neonatal	10049779
33. Swelling face	10042682	33. Peripheral swelling	10048959
34. Swollen tongue	10042727	34. Reversible airway obstruction	10062109
35. Tongue edema	10043967	35. Scrotal edema	10039755
36. Tracheal edema	10044296	36. Scrotal swelling	10039759
37. Urticaria	10046735	37. Skin edema	10058679
38. Urticaria cholinergic	10046740	38. Skin swelling	10053262
39. Urticarial chronic	10052568	39. Soft tissue swelling	10076991
40. Urticarial popular	10046750	40. Stridor	10042241
		41. Suffocation feeling	10042444
		42. Swelling	10042674
		43. Throat tightness	10043528
		44. Tracheal obstruction	10044291

		45. Tracheostomy 46. Type I hypersensitivity 47. Upper airway obstruction 48. Vaginal edema 49. Visceral edema 50. Vulval edema 51. Vulvovaginal swelling 52. Wheezing	10044320 10045240 10067775 10063818 10065768 10047763 10071211 10047924
2. Anaphylactic/anaphylactoid shock conditions (SMQ code 20000071)			
Narrow scope	Preferred Term (PT) Codes	Broad scope	Preferred Term (PT) Codes
1. Anaphylactic reaction	10002198	1. Acute kidney injury	10002198
2. Anaphylactic shock	10002199	2. Acute pre-renal failure	10002199
3. Anaphylactic transfusion reaction	10067113	3. Acute respiratory failure	10067113
4. Anaphylactoid reaction	10002216	4. Anuria	10002216
5. Anaphylactoid shock	10063119	5. Blood pressure immeasurable	10063119
6. Circulatory collapse	10009192	6. Cerebral hypo-perfusion	10009192
7. Distributive shock	10070559	7. Grey syndrome neonatal	10070559
8. Shock	10040560	8. Hepatic congestion	10040560
9. Shock symptom	10040581	9. Hepatojugular reflux	10040581
		10. Hepatorenal failure	10002198
		11. Hypo-perfusion	10002199
		12. Jugular vein distension	10067113
		13. Myocardial depression	10002216
		14. Neonatal anuria	10063119
		15. Neonatal multi-organ failure	10009192
		16. Organ failure	10070559
		17. Pre renal failure	10040560
		18. Propofol infusion syndrome	10040581
		19. Renal failure	10002198
		20. Renal failure neonatal	10002199
		21. Respiratory failure	10067113

Table S2. Categorization of NSAIDs based on COX selectivity as the ratios of inhibitory concentration 80% (IC₈₀) against COX-2 and COX-1 enzymes

No	Categories	Individual drugs
1.	Coxibs	celecoxib, rofecoxib, valdecoxib, polmacoxib, parecoxib, etoricoxib, and lumiracoxib
2.	Non-coxib NSAIDs	etodolac, meloxicam, nimesulide, loxoprofen, and zaltoprofen
3.	NSAIDs with poor selectivity	phenylbutazone, indomethacin, tolmetin, zomepirac, diclofenac, ketorolac, piroxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, suprofen, flurbiprofen, oxaprozin, carprofen, mefenamic acid, tolfenamic acid, flufenamate, niflumic acid, tenidap, nabumetone, and sulindac
4.	NSAIDs without available information on COX inhibitory potency	mofebutazone, oxyphenbutazone, clofezone, kebuzone, alclofenac, bumadizone, lonazolac, fentiazac, acetaminic, difenpiramide, oxametacin, proglumetacin, ketorolac, aceclofenac, bufexamac, droxicam, lornoxicam, fenbufen, benoxaprofen, pirprofen, indoprofen, tiaprofenic acid, ibuproxam, dexibuprofen, flunoxaprofen, alminoprofen, dexketoprofen, and naproxinod

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs

Table S3a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	2,226 (53.1)	40,743 (72.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,524 (36.3)	11,147 (19.7)	2.50 (2.34-2.68)*	2.12 (1.98-2.28)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	446 (10.6)	4,587 (8.1)	1.78 (1.60-1.98)*	1.57 (1.41-1.75)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	629 (36.9)	4,257 (32.7)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	680 (39.9)	5,467 (42.0)	0.84 (0.75-0.95)*	0.84 (0.74-0.94)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	397 (23.3)	3,285 (25.2)	0.82 (0.72-0.94)*	0.78 (0.68-0.90)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	715 (39.6)	4,565 (35.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	716 (39.7)	6,074 (47.3)	0.75 (0.67-0.84)*	0.70 (0.63-0.78)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	358 (19.8)	2,142 (16.7)	1.07 (0.93-1.22)	1.00 (0.87-1.15)
Unknown potency, n (%)	15 (0.8)	73 (0.6)	1.31 (0.75-2.30)	1.27 (0.72-2.24)

Abbreviations: COX = cyclooxygenase; NA = not applicable ; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S3b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	2,226 (53.1)	40,743 (72.1)	1 (reference)	1 (reference)
Oxicams, n (%)	371 (8.8)	5,270 (9.3)	1.29 (1.15-1.44)*	1.18 (1.05-1.32)*
Acetic acid derivatives and related substances, n (%)	1,047 (25.0)	5,299 (9.4)	3.62 (3.34-3.91)*	3.07 (2.83-3.33)*
Fenamates, n (%)	142 (3.4)	899 (1.6)	2.89 (2.41-3.47)*	2.21 (1.83-2.66)*
Propionic acid derivatives, n (%)	307 (7.3)	2,443 (4.3)	2.30 (2.03-2.61)*	1.93 (1.69-2.19)*
Butylpyrazolidines, n (%)	56 (1.3)	698 (1.2)	1.47 (1.12-1.93)*	1.25 (0.95-1.65)
Others, n (%)	47 (1.1)	1,125 (2.0)	0.77 (0.57-1.03)	0.69 (0.51-0.92)*
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	629 (36.9)	4,257 (32.7)	1 (reference)	1 (reference)
Oxicams, n (%)	347 (20.3)	4,009 (30.8)	0.59 (0.51-0.67)*	0.62 (0.54-0.71)*
Acetic acid derivatives and related substances, n (%)	236 (13.8)	852 (6.5)	1.88 (1.59-2.22)*	2.02 (1.70-2.39)*
Fenamates, n (%)	121 (7.1)	548 (4.2)	1.49 (1.21-1.85)*	1.03 (0.83-1.29)
Propionic acid derivatives, n (%)	271 (15.9)	2,215 (17.0)	0.83 (0.71-0.96)*	0.76 (0.65-0.89)*
Butylpyrazolidines, n (%)	21 (1.2)	114 (0.9)	1.25 (0.78-2.00)	1.08 (0.67-1.75)
Others, n (%)	81 (4.7)	1,018 (7.8)	0.54 (0.42-0.69)*	0.56 (0.44-0.71)*
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	715 (39.6)	4,565 (35.5)	1 (reference)	1 (reference)
Oxicams, n (%)	424 (23.5)	2,983 (23.2)	0.91 (0.80-1.03)	0.91 (0.80-1.04)
Acetic acid derivatives and related substances, n (%)	333 (18.5)	3,059 (23.8)	0.70 (0.61-0.80)*	0.65 (0.57-0.75)*
Fenamates, n (%)	135 (7.5)	554 (4.3)	1.56 (1.27-1.91)*	1.02 (0.83-1.27)
Propionic acid derivatives, n (%)	79 (4.4)	625 (4.9)	0.81 (0.63-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines, n (%)	10 (0.6)	58 (0.5)	1.10 (0.56-2.16)	0.93 (0.47-1.83)
Others, n (%)	108 (6.0)	1,010 (7.9)	0.68 (0.55-0.85)*	0.69 (0.56-0.86)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S3c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=4,196)	Non-cases (n=56,477)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	2,614 (62.3)	38,860 (68.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,582 (37.7)	17,617 (31.2)	1.34 (1.25-1.43)*	1.38 (1.29-1.47)*
5-10 years	Cases (n=1,706)	Non-cases (n=13,013)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,106 (64.8)	7,145 (54.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	600 (35.2)	5,868 (45.1)	0.66 (0.60-0.73)*	0.73 (0.66-0.82)*
10-15 years	Cases (n=1,804)	Non-cases (n=12,854)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,118 (62.0)	7,422 (57.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	686 (38.0)	5,432 (42.3)	0.84 (0.76-0.93)*	0.95 (0.86-1.06)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S3d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=4,195)	Non-cases (n=56,455)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	839 (20.0)	26,250 (46.5)	1 (reference)	1 (reference)
Celecoxib, n (%)	1,070 (25.5)	11,405 (20.2)	2.94 (2.68-3.22)*	2.93 (2.67-3.22)*
Zomepirac, n (%)	520 (12.4)	1,102 (2.0)	14.76 (13.03-16.73)*	11.26 (9.89-12.81)*
Tolmetin, n (%)	175 (4.2)	348 (0.6)	15.73 (12.96-19.11)*	12.83 (10.53-15.64)*
Sulindac, n (%)	166 (4.0)	1,969 (3.5)	2.64 (2.22-3.14)*	2.43 (2.04-2.89)*
Piroxicam, n (%)	164 (3.9)	2,488 (4.4)	2.06 (1.74-2.45)*	1.93 (1.62-2.29)*
Mefenamic acid, n (%)	136 (3.2)	777 (1.4)	5.48 (4.51-6.65)*	4.23 (1.92-2.81)*
Meloxicam, n (%)	133 (3.2)	1,998 (3.5)	2.08 (1.73-2.52)*	1.87 (1.55-2.26)*
Etoricoxib, n (%)	132 (3.1)	1,653 (2.9)	2.50 (2.07-3.02)*	2.32 (1.92-2.81)*
Loxoprofen, n (%)	120 (2.9)	565 (1.0)	6.65 (5.39-8.19)*	5.73 (4.64-7.09)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S4a Reporting odds ratios of urticaria for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	680 (52.2)	42,289 (71.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	470 (36.1)	12,201 (0.0)	2.40 (2.13-2.70)*	2.12 (1.88-2.40)*
Non-coxib NSAIDs with COX-2 preference, n (%)	153 (11.7)	4,880 (8.2)	1.95 (1.63-2.33)*	1.78 (1.49-2.13)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	139 (31.0)	4,747 (33.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	208 (46.4)	5,939 (41.6)	1.20 (0.96-1.49)	1.19 (0.95-1.48)
Non-coxib NSAIDs with COX-2 preference, n (%)	101 (22.5)	3,531 (25.1)	0.96 (0.74-1.25)	0.91 (0.70-1.19)
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	187 (40.8)	5,093 (35.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	182 (39.7)	6,608 (46.5)	0.75 (0.61-0.92)*	0.69 (0.56-0.85)*
Non-coxib NSAIDs with COX-2 preference, n (%)	81 (17.7)	2,419 (17.0)	0.91 (0.70-1.19)	0.85 (0.65-1.11)
Unknown potency, n (%)	8 (1.7)	80 (0.6)	2.72 (1.30-5.72)*	2.64 (1.25-5.56)*

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S4b Reporting odds ratios of urticaria for any NSAIDs based on chemical group

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	680 (52.2)	42,289 (71.2)	1 (reference)	1 (reference)
Oxicams, n (%)	150 (11.5)	5,491 (9.2)	1.70 (1.42-2.03)*	1.59 (1.33-1.90)*
Acetic acid derivatives and related substances, n (%)	283 (21.7)	6,063 (10.2)	2.90 (2.52-3.34)*	2.56 (2.21-2.95)*
Fenamates, n (%)	68 (5.2)	973 (1.6)	4.35 (3.36-5.62)*	3.57 (2.75-4.64)*
Propionic acid derivatives, n (%)	76 (5.8)	2,674 (4.5)	1.77 (1.39-2.25)*	1.56 (1.22-1.99)*
Butylpyrazolidines, n (%)	22 (1.7)	732 (1.2)	1.87 (1.22-2.88)*	1.67 *1.09-2.58)*
Others, n (%)	24 (1.8)	1,148(1.9)	1.30 (0.86-1.96)	1.21 (0.80-1.82)
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	139 (31.0)	4,747 (33.3)	1 (reference)	1 (reference)
Oxicams, n (%)	109 (24.3)	4,247 (29.8)	0.88 (0.68-1.13)	0.92 (0.71-1.19)
Acetic acid derivatives and related substances, n (%)	49 (10.9)	1,039 (7.3)	1.61 (1.16-2.25)*	1.67 (1.20-2.34)
Fenamates, n (%)	46 (10.3)	623 (4.4)	2.52 (1.79-3.56)*	1.78 (1.25-2.53)*
Propionic acid derivatives, n (%)	66 (14.7)	2,420 (17.0)	0.93 (0.69-1.25)	0.85 (0.63-1.14)
Butylpyrazolidines, n (%)	4 (0.9)	131 (0.9)	1.04 (0.38-2.86)	0.87 (0.31-2.38)
Others, n (%)	35 (7.8)	1,064 (7.5)	1.12 (0.77-1.64)	1.18 (0.81-1.72)
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	187 (40.8)	5,093 (35.9)	1 (reference)	1 (reference)
Oxicams, n (%)	113 (24.7)	3,294 (23.2)	0.93 (0.74-1.19)	0.93 (0.74-1.19)
Acetic acid derivatives and related substances, n (%)	64 (14.0)	3,328 (23.4)	0.52 (0.39-0.70)*	0.49 (0.36-0.65)*
Fenamates, n (%)	46 (10.0)	643 (4.5)	1.95 (1.40-2.72)*	1.29 (0.91-1.82)
Propionic acid derivatives, n (%)	14 (3.1)	690 (4.9)	0.55 (0.32-0.96)*	0.49 (0.28-0.84)*
Butylpyrazolidines, n (%)	1 (0.2)	67 (0.5)	0.41 (0.06-2.94)	0.33 (0.05-2.41)
Others, n (%)	33 (7.2)	1,085 (7.6)	0.83 (0.57-1.21)	0.84 (0.58-1.23)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S4c Reporting odds ratios of urticaria for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=1,303)	Non-cases (n=59,370)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	684 (52.5)	40,790 (68.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	619 (47.5)	18,580 (31.3)	1.99 (1.78-2.22)*	2.03 (1.82-2.27)*
5-10 years	Cases (n=448)	Non-cases (n=14,271)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	258 (57.6)	7,993 (56.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	190 (42.4)	6,278 (44.0)	0.94 (0.76-1.13)	1.05 (0.87-1.28)
10-15 years	Cases (n=458)	Non-cases (n=14,200)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	267 (58.3)	8,273 (58.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	191 (41.7)	5,927 (41.7)	1.00 (0.83-1.21)	1.15 (0.95-1.40)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S4d Reporting odds ratios of urticaria for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=1,302)	Non-cases (n=59,348)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	192 (14.7)	26,897 (45.3)	1 (reference)	1 (reference)
Celecoxib, n (%)	428 (32.9)	12,047 (20.3)	4.98 (4.19-5.91)*	4.95 (4.17-5.88)*
Zomepirac, n (%)	98 (7.5)	1,524 (2.6)	9.01 (7.03-11.55)*	7.13 (5.52-9.20)*
Tolmetin, n (%)	39 (3.0)	484 (0.8)	11.29 (7.91-16.11)*	9.41 (6.57-13.48)*
Sulindac, n (%)	61 (4.7)	2,074 (3.5)	4.12 (2.08-5.52)*	3.86 (2.88-5.16)*
Piroxicam, n (%)	73 (5.6)	2,579 (4.3)	3.97 (3.02-5.21)*	3.76 (2.86-4.94)*
Mefenamic acid, n (%)	65 (5.0)	848 (1.4)	10.74 (8.04-14.34)*	8.74 (6.51-11.72)*
Meloxicam, n (%)	47 (3.6)	2,084 (3.5)	3.16 (2.29-4.36)*	2.91 (2.10-4.01)*
Etoricoxib, n (%)	16 (1.2)	1,769 (3.0)	1.27 (0.76-2.12)	1.19 (0.71-1.99)
Loxoprofen, n (%)	17 (1.3)	668 (1.1)	3.57 (2.16-5.89)*	3.14 (1.90-5.19)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S5a Reporting odds ratios of angiodema for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=3,708)	Non-cases (n=59,965)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	2,013 (54.3)	40,956 (71.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,301 (35.1)	11,370 (20.0)	2.33 (2.17-2.50)*	2.00 (1.85-2.15)*
Non-coxib NSAIDs with COX-2 preference, n (%)	394 (10.6)	6,639 (8.1)	1.73 (1.55-1.93)*	1.54 (1.37-1.72)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	566 (39.4)	4,320 (32.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	531 (37.0)	5,616 (42.3)	0.72 (0.64-0.82)*	0.72 (0.63-0.81)*
Non-coxib NSAIDs with COX-2 preference, n (%)	339 (23.6)	3,343 (25.2)	0.77 (0.67-0.89)*	0.74 (0.64-0.85)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	678 (42.6)	4,602 (35.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	568 (35.7)	6,222 (47.6)	0.62 (0.55-0.70)*	0.58 (0.1-0.65)*
Non-coxib NSAIDs with COX-2 preference, n (%)	329 (20.7)	2,171 (16.6)	1.03 (0.89-1.19)	0.97 (0.84-1.12)
Unknown potency, n (%)	15 (0.9)	73 (0.6)	1.40 (0.80-2.45)	1.36 (0.77-2.40)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S5b Reporting odds ratios of angioedema for any NSAIDs based on chemical group

0-5 years	Cases (n=3,708)	Non-cases (n=59,956)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	2,013 (54.3)	40,956 (71.9)	1 (reference)	1 (reference)
Oxicams, n (%)	354 (9.5)	5,287 (9.3)	1.36 (1.21-1.53)*	1.25 (1.11-1.41)*
Acetic acid derivatives and related substances, n (%)	859 (23.2)	5,487 (9.6)	3.19 (2.93-3.47)*	2.72 (2.49-2.97)*
Fenamates, n (%)	131 (3.5)	910 (1.6)	2.93 (2.43-3.57)*	2.27 (1.87-2.75)*
Propionic acid derivatives, n (%)	255 (6.9)	2,495 (4.4)	2.08 (1.81-2.38)*	1.77 (1.54-2.03)*
Butylpyrazolidines, n (%)	49 (1.3)	705 (1.2)	1.41 (1.06-1.90)*	1.22 (0.91-1.64)
Others, n (%)	47 (1.3)	1,125 (2.0)	0.85 (0.63-1.14)	0.77 (0.57-1.03)
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	566 (39.4)	4,320 (32.5)	1 (reference)	1 (reference)
Oxicams, n (%)	328 (22.8)	4,028 (30.3)	0.62 (0.54-0.72)*	0.66 (0.57-0.76)*
Acetic acid derivatives and related substances, n (%)	137 (9.5)	951 (7.2)	1.10 (0.90-1.34)	1.16 (0.95-1.42)
Fenamates, n (%)	101 (7.0)	568 (4.3)	1.36 (1.08-1.71)*	0.93 (0.73-1.18)
Propionic acid derivatives, n (%)	212 (14.8)	2,274 (17.1)	0.71 (0.60-0.80)*	0.65 (0.55-0.77)*
Butylpyrazolidines, n (%)	18 (1.3)	117 (0.9)	1.17 (0.71-1.94)	1.04 (0.62-1.73)
Others, n (%)	74 (5.2)	1,025 (7.7)	0.55 (0.43-0.71)*	0.57 (0.44-0.73)*
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	678 (42.6)	4,602 (35.2)	1 (reference)	1 (reference)
Oxicams, n (%)	398 (25.0)	2,009 (23.0)	0.90 (0.79-1.03)	0.90 (0.79-1.03)
Acetic acid derivatives and related substances, n (%)	239 (15.0)	3,153 (24.1)	0.52 (0.44-0.60)*	0.48 (0.41-0.56)*
Fenamates, n (%)	115 (7.2)	574 (4.4)	1.36 (1.10-1.69)*	0.88 (0.70-1.10)
Propionic acid derivatives, n (%)	54 (3.4)	650 (5.0)	0.56 (0.42-0.75)*	0.50 (0.37-0.67)*
Butylpyrazolidines, n (%)	9 (0.6)	59 (0.5)	1.04 (0.51-2.10)	0.88 (0.43-1.78)
Others, n (%)	97 (6.1)	1,021 (7.8)	0.65 (0.52-0.81)*	0.65 (0.52-0.82)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S5c Reporting odds ratios of angioedema for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=3,708)	Non-cases (n=59,956)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	2,241 (60.4)	39,233 (68.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,467 (39.6)	17,732 (31.1)	1.45 (1.35-1.55)*	1.49 (1.39-1.59)*
5-10 years	Cases (n=1,436)	Non-cases (n=13,283)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	902 (62.8)	7,349 (55.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	534 (37.2)	5,934 (44.7)	0.73 (0.66-0.82)*	0.82 (0.73-0.92)*
10-15 years	Cases (n=1,590)	Non-cases (n=13,068)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	954 (60.0)	7,568 (58.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	636 (40.0)	5,482 (41.9)	0.92 (0.83-1.03)	1.05 (0.94-1.17)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S5d Reporting odds ratios of angioedema for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=3,707)	Non-cases (n=56,943)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	753 (20.3)	26,336 (46.2)	1 (reference)	1 (reference)
Celecoxib, n (%)	985 (26.6)	11,490 (20.2)	3.00 (2.72-3.31)*	2.98 (2.71-3.29)*
Zomepirac, n (%)	419 (11.3)	1,203 (2.1)	12.18 (10.67-13.91)*	9.36 (8.16-10.74)*
Tolmetin, n (%)	117 (3.2)	406 (0.7)	10.08 (8.10-12.54)*	8.22 (6.59-10.26)*
Sulindac, n (%)	148 (4.0)	1,987 (3.5)	2.61 (2.17-3.13)*	2.40 (2.00-2.88)*
Piroxicam, n (%)	162 (4.4)	2,490 (4.4)	2.76 (1.91-2.71)*	2.13 (1.79-2.54)*
Mefenamic acid, n (%)	125 (3.4)	788 (1.4)	5.55 (4.53-6.79)*	4.32 (3.52-5.31)*
Meloxicam, n (%)	121 (3.3)	2,010 (3.5)	2.11 (1.73-2.57)*	1.90 (1.56-2.31)*
Etoricoxib, n (%)	118 (3.2)	1,667 (2.9)	2.48 (2.03-3.03)*	2.31 (1.89-2.82)*
Loxoprofen, n (%)	91 (2.5)	594 (1.0)	5.36 (4.25-6.76)*	4.64 (3.67-5.87)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S6a Reporting odds ratios of anaphylactic shock for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	55 (45.1)	42,914 (70.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	51 (41.8)	12,620 (20.8)	3.15 (2.15-4.62)*	2.38 (1.61-3.53)*
Non-coxib NSAIDs with COX-2 preference, n (%)	16 (13.1)	5, 017 (8.3)	2.49 (1.43-4.35)*	2.06 (1.18-3.62)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	30 (30.3)	4,856 (33.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	36 (36.4)	6,111 (41.8)	0.95 (0.59-1.55)	0.94 (0.58-1.53)
Non-coxib NSAIDs with COX-2 preference, n (%)	33 (33.3)	3,649 (25.0)	1.46 (0.89-2.41)	1.40 (0.85-2.31)
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	20 (25.6)	5,260 (36.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	47 (60.3)	6,743 (46.2)	1.83 (1.09-3.10)*	1.73 (1.02-2.93)*
Non-coxib NSAIDs with COX-2 preference, n (%)	11 (14.1)	2,489 (17.1)	1.16 (0.56-2.43)	1.10 (0.53-2.32)
Unknown potency, n (%)	0 (0.0)	88 (0.6)	NA	NA

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S6b Reporting odds ratios of anaphylactic shock for any NSAIDs based on chemical group

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	55 (45.1)	42,914 (70.9)	1 (reference)	1 (reference)
Oxicams, n (%)	4 (3.3)	5,637 (9.3)	0.55 (0.20-1.53)	0.49 (0.18-1.35)
Acetic acid derivatives and related substances, n (%)	26 (21.3)	6,320 (10.4)	3.21 (2.02-5.12)*	2.50 (1.55-4.03)*
Fenamates, n (%)	10 (8.2)	1,031 (1.7)	7.56 (3.85-14.89)*	5.11 (2.55-10.26)*
Propionic acid derivatives, n (%)	22 (18.0)	2,728 (4.5)	6.29 (3.83-10.33)*	4.65 (2.79-7.75)*
Butylpyrazolidines, n (%)	5 (4.1)	749 (1.2)	5.21 (2.08-13.05)*	4.01 (1.59-10.10)*
Others, n (%)	0 (0.0)	1,172 (1.9)	NA	NA
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	30 (30.3)	4,856 (33.2)	1 (reference)	1 (reference)
Oxicams, n (%)	12 (12.1)	4,344 (29.7)	0.45 (0.23-0.87)*	0.46 (0.23-0.90)*
Acetic acid derivatives and related substances, n (%)	6 (6.1)	1,082 (7.4)	0.90 (0.37-2.16)	0.91 (0.38-2.20)
Fenamates, n (%)	12 (13.1)	656 (4.5)	3.21 (1.67-6.18)*	2.69 (1.37-5.28)*
Propionic acid derivatives, n (%)	34 (34.3)	2,452 (16.8)	2.24 (1.37-3.68)*	2.12 (1.29-3.48)*
Butylpyrazolidines, n (%)	3 (3.0)	132 (0.9)	3.68 (1.11-12.21)*	3.20 (0.96-10.67)
Others, n (%)	1 (1.0)	1,098 (7.5)	0.15 (0.02-1.08)	0.15 (0.02-1.11)
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	20 (25.6)	5,260 (36.1)	1 (reference)	1 (reference)
Oxicams, n (%)	14 (17.9)	3,393 (23.3)	1.09 (0.55-2.15)	1.08 (0.54-2.13)
Acetic acid derivatives and related substances, n (%)	12 (15.4)	3,380 (23.2)	0.93 (0.46-1.91)	0.90 (0.44-1.84)
Fenamates, n (%)	16 (20.5)	673 (4.6)	6.25 (3.22-12.13)*	5.62 (2.77-11.38)*
Propionic acid derivatives, n (%)	12 (15.4)	692 (4.7)	4.56 (2.22-9.37)*	4.34 (2.11-8.96)*
Butylpyrazolidines, n (%)	0 (0.0)	68 (0.5)	NA	NA
Others, n (%)	4 (5.1)	1,114 (7.6)	0.94 (0.32-2.77)	0.95 (0.32-2.78)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S6c Reporting odds ratios of anaphylactic shock for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=122)	Non-cases (n=60,551)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	89 (73.0)	41,385 (68.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	33 (27.0)	19,166 (31.7)	0.80 (0.54-1.19)	0.85 (0.57-1.27)
5-10 years	Cases (n=99)	Non-cases (n=14,620)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	63 (63.6)	8,188 (56.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	36 (36.4)	6,432 (44.0)	0.73 (0.48-1.10)	0.79 (0.52-1.19)
10-15 years	Cases (n=78)	Non-cases (n=14,580)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	52 (66.7)	8,488 (58.2)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	26 (33.3)	6,092 (41.8)	0.70 (0.44-1.12)	0.77 (0.48-1.25)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S6d Reporting odds ratios of anaphylactic shock for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=122)	Non-cases (n=60,528)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	17 (13.9)	27,072 (44.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	23 (18.9)	12,452 (20.6)	2.94 (1.57-5.51)*	2.97 (1.59-5.57)*
Zomepirac, n (%)	13 (10.7)	1,609 (2.7)	12.87 (6.24-26.54)*	8.84 (4.20-18.62)*
Tolmetin, n (%)	9 (7.4)	514 (0.8)	27.88 (12.37-62.85)*	20.47 (8.95-46.78)*
Sulindac, n (%)	4 (3.3)	2,131 (3.5)	2.99 (1.01-8.89)*	2.75 (0.92-8.19)
Piroxicam, n (%)	2 (1.6)	2,650 (4.4)	1.20 (0.28-5.21)	1.11 (0.26-4.80)
Mefenamic acid, n (%)	10 (8.2)	903 (1.5)	17.64 (8.05-38.62)*	12.83 (5.75-28.63)*
Meloxicam, n (%)	1 (0.8)	2,130 (3.5)	0.75 (0.10-5.62)	0.67 (0.09-5.01)
Etoricoxib, n (%)	4 (3.3)	1,781 (2.9)	3.58 (1.20-10.64)*	3.25 (1.09-9.67)*
Loxoprofen, n (%)	15 (12.3)	670 (1.1)	35.65 (17.73-71.69)*	28.55 (14.05-58.00)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S7a Reporting odds ratios of hypersensitivity reactions for NSAIDs according to cyclooxygenase selectivity stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	621 (40.1)	21,737 (81.0)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	804 (51.9)	3,771 (14.0)	7.46 (6.68-8.33)*	6.21 (5.54-6.98)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	123 (7.9)	1,338 (5.0)	3.22 (2.63-3.94)*	2.90 (2.36-3.55)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	10 (3.4)	283 (13.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	268 (91.2)	1,675 (79.3)	4.53 (2.38-8.62)*	4.49 (2.35-8.58)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	16 (5.4)	155 (7.3)	2.92 (1.29-6.59)*	2.97 (1.30-6.77)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	7 (2.5)	139 (4.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	263 (93.6)	2,548 (89.1)	2.05 (0.95-4.43)	1.71 (0.79-3.71)
Non-coxib NSAIDs with COX- 2 preference, n (%)	11 (3.9)	174 (6.1)	1.26 (0.47-3.32)	1.04 (0.39-2.78)
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
Non-US countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age-and sex- adjusted ROR (95% CI)
Coxibs, n (%)	1,605 (60.6)	19,006 (64.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	720 (27.2)	7,376 (24.9)	1.16 (1.05-1.27)*	1.02 (0.92-1.12)
Non-coxib NSAIDs with COX- 2 preference, n (%)	323 (12.2)	3,249 (11.0)	1.18 (1.04-1.33)*	1.04 (0.92-1.18)
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age-and sex- adjusted ROR (95% CI)
Coxibs, n (%)	619 (43.8)	3,974 (36.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	412 (29.2)	3,792 (34.8)	0.70 (0.61-0.80)*	0.68 (0.60-0.78)*

Non-coxib NSAIDs with COX-2 preference, n (%)	381 (27.0)	3,130 (28.7)	0.78 (0.68-0.90)*	0.75 (0.65-0.86)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=1,523)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age-and sex- adjusted ROR (95% CI)
Coxibs, n (%)	708 (46.5)	4,426 (44.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	453 (29.7)	3,526 (35.3)	0.80 (0.71-0.91)*	0.74 (0.65-0.84)*
Non-coxib NSAIDs with COX-2 preference, n (%)	347 (22.8)	1,968 (19.7)	1.10 (0.96-1.27)	1.04 (0.90-1.20)
Unknown potency, n (%)	15 (1.0)	73 (0.7)	1.29 (0.73-2.25)	1.25 (0.71-2.21)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S7b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	621 (40.1)	21,737 (81.0)	1 (reference)	1 (reference)
Oxicams, n (%)	55 (3.6)	505 (1.9)	3.81 (2.85-5.09)*	3.59 (2.68-4.81)*
Acetic acid derivatives and related substances, n (%)	719 (46.4)	2,997 (11.2)	8.40 (7.49-9.41)*	6.93 (6.15-7.80)*
Fenamates, n (%)	7 (0.5)	126 (0.5)	1.95 (0.91-4.18)	1.70 (0.79-3.66)
Propionic acid derivatives, n (%)	140 (9.0)	1,422 (5.3)	3.45 (2.85-4.17)*	2.88 (2.37-3.51)*
Butylpyrazolidines, n (%)	6 (0.4)	58 (0.2)	3.62 (1.56-8.42)*	3.01 (1.28-7.05)*
Others, n (%)	0 (0.0)	1 (0.0)	NA	NA
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	10 (3.4)	283 (13.4)	1 (reference)	1 (reference)
Oxicams, n (%)	47 (16.0)	572 (27.1)	2.33 (1.16-4.67)*	2.29 (1.14-4.62)*
Acetic acid derivatives and related substances, n (%)	184 (62.6)	446 (21.1)	11.68 (6.07- 22.45)*	11.27 (5.83- 21.77)*
Fenamates, n (%)	7 (2.4)	51 (2.4)	3.88 (1.41-10.67)*	3.23 (1.16-9.02)*
Propionic acid derivatives, n (%)	16 (5.4)	159 (7.5)	2.85 (1.26-6.43)*	2.90 (1.28-6.59)*
Butylpyrazolidines, n (%)	0 (0.0)	12 (0.6)	NA	NA
Others, n (%)	30 (10.2)	590 (27.9)	1.44 (0.69-2.99)	1.48 (0.71-3.08)
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	7 (2.5)	139 (4.9)	1 (reference)	1 (reference)
Oxicams, n (%)	36 (12.8)	427 (14.9)	1.67 (0.73-3.85)	1.50 (0.65-3.46)
Acetic acid derivatives and related substances, n (%)	203 (72.2)	1,947 (68.1)	2.07 (0.96-4.48)	1.67 (0.77-3.63)
Fenamates, n (%)	1 (0.4)	9 (0.3)	2.21 (0.24-19.93)	1.96 (0.22-17.87)
Propionic acid derivatives, n (%)	1 (0.4)	16 (0.6)	1.24 (0.14-10.74)	1.03 (0.12-9.03)
Butylpyrazolidines, n (%)	0 (0.0)	0 (0.0)	NA	NA
Others, n (%)	33 (11.7)	323 (11.3)	2.03 (0.88-4.70)	1.90 (0.82-4.14)
Non-United States Countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	1,605 (60.6)	19,006 (64.1)	1 (reference)	1 (reference)
Oxicams, n (%)	316 (11.9)	4,765 (16.1)	0.79 (0.69-0.89)*	0.72 (0.63-0.82)*
Acetic acid derivatives and related substances, n (%)	328 (12.4)	2,302 (7.8)	1.69 (1.49-1.92)*	1.51 (1.33-1.72)*

Fenamates, n (%)	135 (5.1)	773 (2.6)	2.07 (1.71-2.50)*	1.57 (1.29-1.91)*
Propionic acid derivatives, n (%)	167 (6.3)	1,021 (3.4)	1.94 (1.63-2.30)*	1.65 (1.39-1.97)*
Butylpyrazolidines, n (%)	50 (1.9)	640 (2.2)	0.93 (0.69-1.24)	0.79 (0.59-1.06)
Others, n (%)	47 (1.8)	1,124 (3.8)	0.50 (0.37-0.67)*	0.45 (0.33-0.60)*
5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	619 (43.8)	3,974 (36.5)	1 (reference)	1 (reference)
Oxicams, n (%)	300 (21.2)	2,437 (31.5)	0.56 (0.49-0.65)*	0.59 (0.51-0.69)*
Acetic acid derivatives and related substances, n (%)	52 (3.7)	406 (3.7)	0.82 (0.61-1.11)	0.94 (0.69-1.27)
Fenamates, n (%)	114 (8.1)	497 (4.6)	1.47 (1.18-1.84)*	1.02 (0.81-1.28)
Propionic acid derivatives, n (%)	255 (18.1)	2,056 (18.9)	0.80 (0.68-0.93)*	0.73 (0.62-0.86)*
Butylpyrazolidines, n (%)	21 (1.5)	102 (0.9)	1.32 (0.82-2.13)	1.18 (0.73-1.91)
Others, n (%)	51 (3.6)	428 (3.9)	0.77 (0.57-1.04)	0.75 (0.55-1.02)
10-15 years	Cases (n=1,532)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	708 (46.5)	4,426 (44.3)	1 (reference)	1 (reference)
Oxicams, n (%)	388 (25.5)	2,556 (25.6)	0.95 (0.83-1.08)	0.95 (0.83-1.09)
Acetic acid derivatives and related substances, n (%)	130 (8.5)	1,112 (11.1)	0.73 (0.60-0.89)*	0.71 (0.58-0.87)*
Fenamates, n (%)	134 (8.8)	545 (5.5)	1.54 (1.25-1.89)*	1.00 (0.81-1.24)
Propionic acid derivatives, n (%)	78 (5.1)	609 (6.1)	0.80 (0.62-1.03)	0.72 (0.56-0.92)*
Butylpyrazolidines, n (%)	10 (0.7)	58 (0.6)	1.08 (0.55-2.12)	0.92 (0.46-1.82)
Others, n (%)	75 (4.9)	687 (6.9)	0.68 (0.53-0.88)*	0.67 (0.52-0.87)*

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S7c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide group stratified by reporting countries

United States				
0-5 years	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,214 (78.4)	20,711 (77.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	334 (21.6)	6,135 (22.9)	0.93 (0.82-1.05)	1.02 (0.90-1.16)
5-10 years	Cases (n=294)	Non-cases (n=2,113)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	237 (80.6)	1,437 (68.0)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	57 (19.4)	676 (32.0)	0.51 (0.38-0.69)*	0.51 (0.37-0.70)*
10-15 years	Cases (n=281)	Non-cases (n=2,861)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	238 (84.7)	2,294 (80.2)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	43 (15.3)	567 (19.8)	0.73 (0.52-1.02)	0.82 (0.58-1.15)
Non-United States Countries				
0-5 years	Cases (n=2,648)	Non-cases (n=29,631)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,400 (52.9)	18,149 (61.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,248 (47.1)	11,482 (38.7)	1.41 (1.30-1.53)*	1.42 (1.31-1.54)*
5-10 years	Cases (n=1,412)	Non-cases (n=10,900)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	869 (61.5)	5,708 (52.4)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	543 (38.5)	5,192 (47.6)	0.69 (0.61-0.77)*	0.78 (0.70-0.88)*
10-15 years	Cases (n=1,532)	Non-cases (n=9,993)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	880 (57.8)	5,128 (51.3)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	643 (42.2)	4,865 (48.7)	0.77 (0.69-0.86)*	0.88 (0.79-0.99)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S7d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by reporting countries

United States				
Individual NSAIDs	Cases (n=1,548)	Non-cases (n=26,846)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	342 (22.1)	16,106 (60.0)	1 (reference)	1 (reference)
Celecoxib, n (%)	260 (16.8)	5,517 (20.6)	2.22 (1.88-2.62)*	2.21 (1.87-2.60)*
Zomepirac, n (%)	405 (26.2)	805 (3.0)	23.69 (20.18-27.82)*	18.09 (15.26-21.44)*
Tolmetin, n (%)	134 (8.7)	233 (0.9)	27.08 (21.35-34.36)*	22.85 (17.92-29.14)*
Sulindac, n (%)	71 (4.6)	843 (3.1)	3.97 (3.04-5.17)*	3.68 (2.82-4.80)*
Piroxicam, n (%)	47 (3.0)	411 (1.5)	5.39 (3.91-7.42)*	5.19 (3.76-7.15)*
Mefenamic acid, n (%)	1 (0.1)	7 (0.0)	6.73 (0.83-54.83)	4.10 (0.94-34.05)
Meloxicam, n (%)	8 (0.5)	94 (0.4)	4.01 (1.93-8.32)*	3.62 (1.74-7.52)*
Etoricoxib, n (%)	0 (0.0)	1 (0.0)	NA	NA
Loxoprofen, n (%)	0 (0.0)	9 (0.0)	NA	NA
Non-US countries				
Individual NSAIDs	Cases (n=2,647)	Non-cases (n=29,609)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	497 (18.8)	10,144 (34.3)	1 (reference)	1 (reference)
Celecoxib, n (%)	810 (30.6)	5,888 (19.9)	2.81 (2.50-3.15)*	2.78 (2.48-3.13)*
Zomepirac, n (%)	115 (4.3)	297 (1.0)	7.90 (6.26-9.98)*	6.55 (5.16-8.30)*
Tolmetin, n (%)	41 (1.5)	115 (0.4)	7.28 (5.04-10.51)*	5.68 (2.91-8.25)*
Sulindac, n (%)	95 (3.6)	1,126 (3.8)	1.72 (1.37-2.16)*	1.57 (1.25-1.98)*
Piroxicam, n (%)	117 (4.4)	2,077 (7.0)	1.15 (0.94-1.41)	1.06 (0.86-1.30)
Mefenamic acid, n (%)	135 (5.1)	770 (2.6)	3.58 (2.92-4.39)*	2.71 (2.20-3.34)*
Meloxicam, n (%)	125 (4.7)	1,904 (6.4)	1.34 (1.10-1.64)*	1.19 (0.97-1.46)
Etoricoxib, n (%)	132 (5.0)	1,652 (5.6)	1.63 (1.34-1.99)*	1.49 (1.22-1.82)*
Loxoprofen, n (%)	120 (4.5)	556 (1.9)	4.41 (2.55-5.47)*	3.73 (2.99-4.64)*

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S8a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity stratified by age

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,125 (43.5)	16,358 (66.7)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,153 (44.5)	5,860 (23.9)	2.86 (2.62-3.12)*	2.85 (2.61-3.11)*
Non-coxib NSAIDs with COX-2 preference, n (%)	311 (12.0)	2,296 (9.4)	1.97 (1.72-2.25)*	1.92 (1.68-2.20)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	460 (37.1)	2,271 (33.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	480 (38.7)	2,718 (40.1)	0.87 (0.76-1.00)	0.88 (0.77-1.01)
Non-coxib NSAIDs with COX-2 preference, n (%)	300 (24.2)	1,779 (26.3)	0.83 (0.71-0.98)*	0.84 (0.71-0.98)*
Unknown potency, n (%)	0 (0.0)	3 (0.0)	NA	NA
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	500 (37.8)	2,395 (33.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	549 (41.5)	3,404 (48.1)	0.77 (0.68-0.88)*	0.78 (0.68-0.89)*
Non-coxib NSAIDs with COX-2 preference, n (%)	264 (19.9)	1,239 (17.5)	1.02 (0.87-1.20)	1.02 (0.86-1.20)
Unknown potency, n (%)	11 (0.8)	41 (0.6)	1.29 (0.66-2.52)	1.32 (0.67-2.58)
≥60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,963)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,101 (68.5)	24,385 (76.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	371 (23.1)	5,287 (16.5)	1.55 (1.38-1.76)*	1.54 (1.37-1.74)*
Non-coxib NSAIDs with COX-2 preference, n (%)	135 (8.4)	2,291 (7.2)	1.31 (1.09-1.57)*	1.30 (1.08-1.56)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	169 (36.3)	1,986 (31.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	200 (42.9)	2,749 (44.0)	0.86 (0.69-1.06)	0.86 (0.69-1.06)
Non-coxib NSAIDs with COX-2 preference, n (%)	97 (20.8)	1,506 (24.1)	0.76 (0.58-0.98)*	0.76 (0.59-0.99)*
Unknown potency, n (%)	0 (0.0)	1 (0.0)	NA	NA
10-15 years	Cases	Non-cases	Crude ROR	Sex-adjusted ROR

	(n=480)	(n=5,775)	(95% CI)	(95% CI)
Coxibs, n (%)	215 (44.8)	2,170 (37.6)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	167 (34.8)	2,670 (46.2)	0.63 (0.51-0.78)*	0.64 (0.52-0.79)*
Non-coxib NSAIDs with COX-2 preference, n (%)	94 (19.6)	903 (15.6)	1.05 (0.82-1.36)	1.06 (0.82-1.36)
Unknown potency, n (%)	4 (0.8)	32 (0.6)	1.26 (0.44-3.60)	1.27 (0.44-3.61)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S8b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by age

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,125 (43.5)	16,358 (66.7)	1 (reference)	1 (reference)
Oxicams, n (%)	245 (9.5)	2,491 (10.2)	1.43 (1.24-1.65)*	1.40 (1.21-1.62)*
Acetic acid derivatives and related substances, n (%)	810 (31.3)	2,789 (11.4)	4.22 (3.83-4.66)*	4.16 (3.76-4.59)*
Fenamates, n (%)	109 (4.2)	502 (2.0)	3.16 (2.55-3.92)*	3.04 (2.45-3.78)*
Propionic acid derivatives, n (%)	224 (8.7)	1,428 (5.8)	2.28 (1.96-2.66)*	2.36 (2.02-2.75)*
Butylpyrazolidines, n (%)	44 (1.7)	399 (1.6)	1.60 (1.17-2.20)*	1.64 (1.19-2.25)*
Others, n (%)	32 (1.2)	547 (2.2)	0.85 (0.59-1.22)	0.84 (0.59-1.21)
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	460 (37.1)	2,271 (33.5)	1 (reference)	1 (reference)
Oxicams, n (%)	228 (18.4)	1,879 (27.8)	0.60 (0.51-0.71)*	0.61 (0.51-0.72)*
Acetic acid derivatives and related substances, n (%)	177 (14.3)	343 (5.1)	2.55 (2.07-3.13)*	2.59 (2.22-3.19)*
Fenamates, n (%)	107 (8.6)	388 (5.7)	1.36 (1.08-1.72)*	1.33 (1.05-1.69)*
Propionic acid derivatives, n (%)	207 (16.7)	1,310 (19.3)	0.78 (0.65-0.93)*	0.79 (0.66-0.94)*
Butylpyrazolidines, n (%)	11 (0.9)	88 (1.3)	0.62 (0.33-1.16)	0.66 (0.35-1.25)
Others, n (%)	50 (4.0)	492 (7.3)	0.50 (0.37-0.68)*	0.50 (0.37-0.68)*
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	500 (37.8)	2,395 (33.8)	1 (reference)	1 (reference)
Oxicams, n (%)	316 (23.9)	1,548 (21.9)	0.98 (0.84-1.14)	0.98 (0.84-1.15)
Acetic acid derivatives and related substances, n (%)	259 (19.6)	1,702 (24.0)	0.73 (0.62-0.86)*	0.74 (0.63-0.87)*
Fenamates, n (%)	128 (9.7)	481 (6.8)	1.28 (1.03-1.58)*	1.24 (1.00-1.55)*
Propionic acid derivatives, n (%)	58 (4.4)	411 (5.8)	0.68 (0.51-0.91)*	0.68 (0.51-0.91)*
Butylpyrazolidines, n (%)	8 (0.6)	48 (0.7)	0.80 (0.38-1.70)	0.84 (0.39-1.79)
Others, n (%)	55 (4.2)	494 (7.0)	0.53 (0.40-0.72)*	0.53 (0.40-0.71)*
≥ 60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,936)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	1,101 (68.5)	24,385 (76.3)	1 (reference)	1 (reference)
Oxicams, n (%)	126 (7.8)	2,779 (8.7)	1.00 (0.83-1.21)	1.00 (0.83-1.21)
Acetic acid derivatives and related substances, n (%)	237 (14.7)	2,510 (7.9)	2.09 (1.81-2.42)*	2.07 (1.79-2.40)*
Fenamates, n (%)	33 (2.1)	397 (1.2)	1.84 (1.28-2.64)*	1.79 (1.25-2.57)*
Propionic acid derivatives, n (%)	83 (5.2)	1,015 (3.2)	1.81 (1.44-2.28)*	1.81 (1.43-2.28)*
Butylpyrazolidines, n (%)	12 (0.7)	299 (0.9)	0.89 (0.50-1.59)	0.90 (0.50-1.61)
Others, n (%)	15 (0.9)	578 (1.8)	0.58 (0.34-0.96)*	0.57 (0.34-0.95)*
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)

Coxibs, n (%)	169 (36.3)	1,986 (31.8)	1 (reference)	1 (reference)
Oxicams, n (%)	119 (25.5)	2,130 (34.1)	0.66 (0.52-0.84)*	0.66 (0.52-0.84)*
Acetic acid derivatives and related substances, n (%)	59 (12.7)	509 (8.2)	1.36 (1.00-1.86)	1.36 (1.00-1.86)
Fenamates, n (%)	14 (3.0)	160 (2.6)	1.03 (0.58-1.82)	1.03 (0.58-1.81)
Propionic acid derivatives, n (%)	64 (13.7)	905 (14.5)	0.83 (0.62-1.12)	0.84 (0.63-1.14)
Butylpyrazolidines, n (%)	10 (2.1)	26 (0.4)	4.52 (2.14-9.53)*	4.55 (2.16-9.61)*
Others, n (%)	31 (6.7)	526 (8.4)	0.69 (0.47-1.03)	0.69 (0.46-1.02)
10-15 years	Cases (n=480)	Non-cases (n=5,775)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Coxibs, n (%)	215 (44.8)	2,170 (37.6)	1 (reference)	1 (reference)
Oxicams, n (%)	108 (22.5)	1,435 (24.8)	0.76 (0.60-0.97)*	0.77 (0.60-0.97)*
Acetic acid derivatives and related substances, n (%)	74 (15.4)	1,357 (23.5)	0.55 (0.42-0.72)*	0.56 (0.43-0.74)*
Fenamates, n (%)	7 (1.5)	73 (1.3)	0.97 (0.44-2.13)	0.98 (0.45-2.16)
Propionic acid derivatives, n (%)	21 (4.4)	214 (3.7)	0.99 (0.62-1.58)	1.01 (0.63-1.61)
Butylpyrazolidines, n (%)	2 (0.4)	10 (0.2)	2.02 (0.44-9.27)	2.01 (0.44-9.25)
Others, n (%)	53 (11.0)	516 (8.9)	1.04 (0.76-1.42)	1.04 (0.76-1.43)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S8c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide group stratified by age group

<60 years old				
0-5 years	Cases (n=2,589)	Non-cases (n=24,514)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,749 (67.6)	17,418 (71.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	840 (32.4)	7,096 (28.9)	1.18 (1.08-1.29)*	1.14 (1.05-1.24)*
5-10 years	Cases (n=1,240)	Non-cases (n=6,771)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	844 (68.1)	3,978 (58.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	396 (31.9)	2,793 (41.2)	0.67 (0.59-0.76)*	0.67 (0.59-0.77)*
10-15 years	Cases (n=1,324)	Non-cases (n=7,079)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	865 (65.3)	4,539 (64.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	459 (34.7)	2,540 (35.9)	0.95 (0.84-1.07)	0.95 (0.84-1.07)
≥60 years old				
0-5 years	Cases (n=1,607)	Non-cases (n=31,963)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	865 (53.8)	21,442 (67.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	742 (46.2)	10,521 (32.9)	1.75 (1.58-1.93)*	1.75 (1.58-1.93)*
5-10 years	Cases (n=466)	Non-cases (n=6,242)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	262 (56.2)	3,167 (50.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	204 (43.8)	3,075 (49.3)	0.80 (0.66-0.97)*	0.80 (0.66-0.97)*
10-15 years	Cases (n=480)	Non-cases (n=5,775)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	253 (52.7)	2,883 (49.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	227 (47.3)	2,892 (50.1)	0.89 (0.74-1.08)	0.89 (0.74-1.07)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S8d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by age group

<60 years old				
Individual NSAIDs	Cases (n=2,588)	Non-cases (n=24,499)	Crude ROR (95% CI)	Sex-adjusted ROR (95% CI)
Rofecoxib, n (%)	425 (16.4)	10,699 (43.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	496 (19.2)	4,095 (16.7)	3.05 (2.67-3.49)*	2.93 (2.56-3.36)*
Zomepirac, n (%)	450 (17.4)	809 (3.3)	14.00 (12.05-16.28)*	13.78 (11.85-16.03)*
Tolmetin, n (%)	141 (5.4)	236 (1.0)	15.04 (11.95-18.93)*	15.05 (11.94-18.96)*
Sulindac, n (%)	99 (3.8)	833 (3.4)	2.99 (2.38-3.77)*	2.84 (2.26-3.58)*
Piroxicam, n (%)	103 (4.0)	1,102 (4.5)	2.35 (1.88-2.94)*	2.29 (1.83-2.87)*
Mefenamic acid, n (%)	107 (4.1)	441 (1.8)	6.11 (4.84-7.71)*	5.79 (4.59-7.32)*
Meloxicam, n (%)	99 (3.8)	1,003 (4.1)	2.49 (1.98-3.12)*	2.37 (1.88-2.97)*
Etoricoxib, n (%)	83 (3.2)	781 (3.2)	2.68 (2.09-3.42)*	2.61 (2.04-3.33)*
Loxoprofen, n (%)	89 (3.4)	306 (1.2)	7.32 (5.67-9.45)*	7.26 (5.62-9.38)*
≥ 60 years old				
Individual NSAIDs	Cases (n=1,607)	Non-cases (n=31,956)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	414 (25.8)	15,551 (48.7)	1 (reference)	1 (reference)
Celecoxib, n (%)	574 (35.7)	7,310 (22.9)	2.95 (2.59-3.36)*	2.94 (2.58-3.34)*
Zomepirac, n (%)	70 (4.4)	293 (0.9)	8.97 (6.79 (11.86)*	9.00 (6.81-11.89)*
Tolmetin, n (%)	34 (2.1)	112 (0.4)	11.40 (7.67-16.94)*	11.51 (7.74-17.12)*
Sulindac, n (%)	67 (4.2)	1,136 (3.6)	2.22 (1.70-2.89)*	2.19 (1.68-2.85)*
Piroxicam, n (%)	61 (3.8)	1,386 (4.3)	1.65 (1.26-2.18)*	1.65 (1.26-2.18)*
Mefenamic acid, n (%)	29 (1.8)	226 (1.1)	3.24 (2.19-4.80)*	3.15 (2.13-4.66)*
Meloxicam, n (%)	34 (2.1)	995 (3.1)	1.28 (0.90-1.83)	1.28 (0.90-1.83)
Etoricoxib, n (%)	49 (3.0)	872 (2.7)	2.11 (1.56-2.86)*	2.14 (1.58-2.89)*
Loxoprofen, n (%)	31 (1.9)	259 (0.8)	4.50 (3.06-6.61)*	4.59 (3.12-6.75)*

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S9a Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on cyclooxygenase selectivity stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	1,508 (55.2)	26,022 (71.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	935 (34.2)	7,348 (20.2)	2.20 (2.02-2.39)*	1.87 (1.71-2.04)*
Non-coxib NSAIDs with COX-2 preference, n (%)	291 (10.6)	3,090 (8.5)	1.63 (1.43-1.85)*	1.44 (1.26-1.65)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	413 (40.5)	2,814 (33.3)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	357 (35.0)	3,595 (42.5)	0.68 (0.58-0.79)*	0.68 (0.58-0.79)*
Non-coxib NSAIDs with COX-2 preference, n (%)	249 (24.4)	2,038 (24.1)	0.83 (0.70-0.98)*	0.78 (0.66-0.92)*
Unknown potency, n (%)	0 (0.0)	2 (0.0)	NA	NA
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	508 (45.0)	3,123 (36.9)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	375 (33.2)	3,853 (45.5)	0.60 (0.52-0.69)*	0.53 (0.46-0.61)*
Non-coxib NSAIDs with COX-2 preference, n (%)	238 (21.1)	1,441 (17.0)	1.02 (0.86-1.20)	0.94 (0.79-1.11)
Unknown potency, n (%)	9 (0.8)	46 (0.5)	1.20 (0.59-2.47)	1.14 (0.55-2.35)
Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	505 (51.8)	14,934 (72.8)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	366 (37.6)	4,022 (19.6)	2.69 (2.34-3.09)*	2.39 (2.07-2.76)*
Non-coxib NSAIDs with COX-2 preference, n (%)	103 (10.6)	1,549 (7.6)	1.97 (1.58-2.45)*	1.84 (1.48-2.29)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	153 (36.7)	1,506 (31.2)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	174 (41.7)	2,021 (41.8)	0.85 (0.68-1.06)	0.82 (0.65-1.03)
Non-coxib NSAIDs with COX-2 preference, n (%)	90 (21.6)	1,305 (27.0)	0.68 (0.52-0.89)*	0.66 (0.50-0.86)*
Unknown potency, n (%)	0 (0.0)	2 (0.0)	NA	NA
10-15 years	Cases	Non-cases	Crude ROR	Age-adjusted

	(n=460)	(n=4,605)	(95% CI)	ROR (95% CI)
Coxibs, n (%)	170 (37.0)	1,479 (32.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	193 (42.0)	2,369 (51.4)	0.71 (0.57-0.88)*	0.70 (0.56-0.87)*
Non-coxib NSAIDs with COX-2 preference, n (%)	91 (19.8)	730 (15.9)	1.09 (0.83-1.42)	1.04 (0.79-1.37)
Unknown potency, n (%)	6 (1.3)	27 (0.6)	1.93 (0.79-4.75)	1.91 (0.77-4.72)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

Table S9b Reporting odds ratios of hypersensitivity reactions for any NSAIDs based on chemical group stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	1,508 (55.2)	26,022 (71.4)	1 (reference)	1 (reference)
Oxicams, n (%)	272 (9.9)	2,477 (9.5)	1.35 (1.18-1.54)*	1.24 (1.08-1.41)*
Acetic acid derivatives and related substances, n (%)	603 (22.1)	2,687 (10.1)	2.82 (2.55-3.12)*	2.40 (2.16-2.66)*
Fenamates, n (%)	112 (4.1)	641 (1.8)	3.02 (2.45-3.71)*	2.36 (1.91-2.91)*
Propionic acid derivatives, n (%)	169 (6.2)	1,468 (4.0)	1.99 (1.68-2.35)*	1.67 (1.41-1.98)*
Butylpyrazolidines, n (%)	33 (1.2)	414 (1.1)	1.38 (0.96-1.97)	1.15 (0.80-1.65)
Others, n (%)	37 (1.4)	751 (2.1)	0.85 (0.61-1.19)	0.78 (0.56-1.09)
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	413 (40.5)	2,814 (33.3)	1 (reference)	1 (reference)
Oxicams, n (%)	237 (23.3)	2,531 (30.0)	0.64 (0.54-0.76)*	0.68 (0.58-0.81)*
Acetic acid derivatives and related substances, n (%)	87 (8.5)	605 (7.2)	0.98 (0.77-1.26)	1.03 (0.80-1.33)
Fenamates, n (%)	69 (6.8)	413 (4.9)	1.14 (0.87-1.50)	0.79 (0.59-1.05)
Propionic acid derivatives, n (%)	146 (14.3)	1,336 (15.8)	0.75 (0.61-0.91)*	0.65 (0.53-0.80)*
Butylpyrazolidines, n (%)	9 (0.9)	54 (0.6)	1.14 (0.56-2.32)	0.97 (0.47-1.99)
Others, n (%)	58 (5.7)	696 (8.2)	0.57 (0.43-0.76)*	0.60 (0.45-0.81)*
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	508 (45.0)	3,123 (36.9)	1 (reference)	1 (reference)
Oxicams, n (%)	285 (25.2)	1,919 (22.7)	0.91 (0.78-1.07)	0.89 (0.76-1.04)
Acetic acid derivatives and related substances, n (%)	149 (13.2)	1,862 (22.0)	0.49 (0.41-0.60)*	0.43 (0.35-0.53)*
Fenamates, n (%)	79 (7.0)	434 (5.1)	1.12 (0.87-1.45)	0.69 (0.52-0.90)*
Propionic acid derivatives, n (%)	34 (3.0)	409 (4.8)	0.51 (0.36-0.73)*	0.44 (0.30-0.63)*
Butylpyrazolidines, n (%)	5 (0.4)	30 (0.4)	1.03 (0.40-2.65)	0.84 (0.32-2.21)
Others, n (%)	70 (6.2)	686 (8.1)	0.63 (0.48-0.82)*	0.62 (0.47-0.81)*
Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	505 (51.8)	14,934 (72.8)	1 (reference)	1 (reference)
Oxicams, n (%)	82 (8.4)	1,810 (8.8)	1.34 (1.06-1.70)*	1.28 (1.01-1.62)*
Acetic acid derivatives and related substances, n (%)	256 (26.3)	1,800 (8.8)	4.21 (3.59-4.93)*	3.80 (3.23-4.46)*
Fenamates, n (%)	19 (2.0)	269 (1.3)	2.09 (1.30-3.35)*	1.78 (1.10-1.87)*
Propionic acid derivatives, n (%)	86 (8.8)	1,027 (5.0)	2.48 (1.95-3.14)*	2.09 (1.64-2.66)*
Butylpyrazolidines, n (%)	16 (1.6)	291 (1.4)	1.63 (0.98-2.71)	1.43 (0.86-2.39)
Others, n (%)	10 (1.0)	374 (1.8)	0.79 (0.42-1.49)	0.73 (0.39-1.38)
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)

Coxibs, n (%)	153 (36.7)	1,506 (31.2)	1 (reference)	1 (reference)
Oxicams, n (%)	91 (2.18)	1,497 (31.0)	0.60 (0.46-0.78)*	0.60 (0.46-0.79)*
Acetic acid derivatives and related substances, n (%)	50 (12.0)	346 (7.2)	1.42 (1.01-2.00)*	1.46 (1.04-2.06)*
Fenamates, n (%)	32 (7.7)	155 (3.2)	2.03 (1.34-3.08)*	1.45 (0.94-2.22)
Propionic acid derivatives, n (%)	66 (15.8)	938 (19.4)	0.69 (0.51-0.94)*	0.66 (0.48-0.89)*
Butylpyrazolidines, n (%)	9 (2.2)	63 (1.3)	1.41 (0.69-2.88)	1.13 (0.55-2.34)
Others, n (%)	16 (3.8)	329 (6.8)	0.48 (0.28-0.81)*	0.48 (0.28-0.81)*
10-15 years	Cases (n=460)	Non-cases (n=4,605)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Coxibs, n (%)	170 (37.0)	1,479 (32.1)	1 (reference)	1 (reference)
Oxicams, n (%)	113 (24.6)	1,090 (23.7)	0.90 (0.70-1.16)	0.93 (0.72-1.20)
Acetic acid derivatives and related substances, n (%)	90 (19.6)	1,291 (28.0)	0.61 (0.47-0.79)*	0.59 (0.45-0.78)*
Fenamates, n (%)	36 (7.8)	140 (3.0)	2.24 (1.50-3.34)*	1.72 (1.14-2.59)*
Propionic acid derivatives, n (%)	20 (4.3)	241 (5.2)	0.72 (0.45-1.17)	0.65 (0.40-1.06)
Butylpyrazolidines, n (%)	4 (0.9)	29 (0.6)	1.20 (0.42-2.46)	0.98 (0.34-2.83)
Others, n (%)	27 (5.9)	335 (7.3)	0.70 (0.46-1.07)	0.74 (0.49-1.14)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S9c Reporting odds ratios of hypersensitivity reactions for any NSAIDs according to the presence/absence of sulfonamide group stratified by sex

Females				
0-5 years	Cases (n=2,734)	Non-cases (n=36,460)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,659 (60.7)	24,659 (67.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	1,075 (39.3)	11,801 (32.4)	1.35 (1.25-1.47)*	1.40 (1.29-1.52)*
5-10 years	Cases (n=1,019)	Non-cases (n=8,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	633 (62.1)	4,686 (55.5)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	386 (37.9)	3,763 (44.5)	0.76 (0.66-0.87)*	0.87 (0.76-0.99)*
10-15 years	Cases (n=1,130)	Non-cases (n=8,463)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	672 (59.5)	4,796 (56.7)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	3,667 (43.3)	3,667 (43.3)	0.89 (0.79-1.01)	1.03 (0.91-1.18)
Males				
0-5 years	Cases (n=974)	Non-cases (n=20,505)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	582 (59.8)	14,574 (71.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	392 (40.2)	5,931 (28.9)	1.66 (1.45-1.89)*	1.75 (1.54-2.00)*
5-10 years	Cases (n=417)	Non-cases (n=4,834)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	269 (64.5)	2,663 (55.1)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	148 (35.5)	2,171 (44.9)	0.68 (0.55-0.83)*	0.71 (0.58-0.88)*
10-15 years	Cases (n=460)	Non-cases (n=4,605)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	282 (61.3)	2,790 (60.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	178 (38.7)	1,815 (39.4)	0.97 (0.80-1.18)	1.08 (0.89-1.32)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S9d Reporting odds ratios of hypersensitivity reactions for individual NSAIDs within 5 years after market approval stratified by sex

Females				
Individual NSAIDs	Cases (n=2,733)	Non-cases (n=36,449)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	594 (21.7)	16,323 (44.8)	1 (reference)	1 (reference)
Celecoxib, n (%)	709 (25.9)	7,729 (21.2)	2.52 (2.25-2.82)*	2.53 (2.26-2.84)*
Zomepirac, n (%)	295 (10.8)	758 (2.1)	10.70 (9.14-12.52)*	7.96 (6.76-9.37)*
Tolmetin, n (%)	78 (2.9)	246 (0.7)	8.71 (6.67-11.39)*	6.92 (5.28-9.08)*
Sulindac, n (%)	104 (3.8)	1,393 (3.8)	2.05 (1.65-2.54)*	1.92 (1.54-2.38)*
Piroxicam, n (%)	120 (4.4)	1,607 (4.4)	2.05 (1.68-2.51)*	1.92 (1.57-2.36)*
Mefenamic acid, n (%)	106 (3.9)	562 (1.5)	5.18 (4.15-6.48)*	4.11 (3.28-5.16)*
Meloxicam, n (%)	99 (3.6)	1,353 (3.7)	2.01 (1.61-2.51)*	1.82 (1.46-2.27)*
Etoricoxib, n (%)	93 (3.4)	1,039 (2.8)	2.46 (1.96-3.09)*	2.25 (1.79-2.82)*
Loxoprofen, n (%)	59 (2.2)	357 (1.0)	4.54 (3.41-6.05)*	3.78 (2.82-5.05)*
Males				
Individual NSAIDs	Cases (n=974)	Non-cases (n=20,494)	Crude ROR (95% CI)	Age-adjusted ROR (95% CI)
Rofecoxib, n (%)	159 (16.3)	10,013 (48.9)	1 (reference)	1 (reference)
Celecoxib, n (%)	276 (28.3)	3,761 (18.3)	4.62 (3.79-5.64)*	4.77 (3.91-5.82)*
Zomepirac, n (%)	124 (12.7)	445 (2.2)	17.55 (13.62-22.61)*	14.51 (11.19-18.80)*
Tolmetin, n (%)	39 (4.0)	160 (0.8)	15.35 (10.46-22.52)*	12.93 (8.77-19.05)*
Sulindac, n (%)	44 (4.5)	594 (2.9)	4.67 (3.31-6.58)*	4.57 (3.24-6.45)*
Piroxicam, n (%)	42 (4.3)	883 (4.3)	3.00 (2.12-4.24)*	2.89 (2.04-4.09)*
Mefenamic acid, n (%)	19 (2.0)	226 (1.1)	5.29 (3.23-8.67)*	4.52 (2.75-7.43)*
Meloxicam, n (%)	22 (2.3)	657 (3.2)	2.11 (1.34-3.32)*	2.02 (1.28-3.18)*
Etoricoxib, n (%)	25 (2.6)	628 (3.1)	2.51 (1.63-3.85)*	2.45 (1.59-3.77)*
Loxoprofen, n (%)	32 (3.3)	237 (1.2)	8.50 (5.69-12.70)*	7.75 (5.18-11.60)*

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

Table S10a Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs based on cyclooxygenase selectivity

0-5 years	Cases [‡] (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	3,622 (59.5)	39,347 (72.1)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	1,929 (31.7)	10,742 (19.7)	1.95 (1.84-2.07)*	1.69 (1.59-1.80)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	537 (8.8)	4,496 (8.2)	1.30 (1.18-1.43)*	1.16 (1.06-1.28)*
Unknown potency, n (%)	0 (0.0)	0 (0.0)	NA	NA
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	804 (37.5)	4,082 (32.5)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	828 (38.6)	5,319 (42.3)	0.79 (0.71-0.88)*	0.79 (0.71-0.88)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	514 (24.0)	3,168 (25.2)	0.82 (0.73-0.93)*	0.80 (0.71-0.90)*
Unknown potency, n (%)	0 (0.0)	4 (0.0)	NA	NA
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	846 (39.5)	4,434 (35.4)	1 (reference)	1 (reference)
NSAIDs with poor selectivity, n (%)	844 (39.4)	5,946 (47.5)	0.74 (0.67-0.83)*	0.70 (0.63-0.78)*
Non-coxib NSAIDs with COX- 2 preference, n (%)	435 (20.3)	2,065 (16.5)	1.10 (0.97-1.25)	1.05 (0.92-1.19)
Unknown potency, n (%)	19 (0.9)	69 (0.6)	1.44 (0.86-2.41)	1.41 (0.84-2.37)

Abbreviations: COX = cyclooxygenase; NA = non-applicable; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant (p<0.05)

[‡] broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest.

Table S10b Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs based on chemical group

0-5 years	Cases (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	3,622 (59.5)	39,347 (72.1)	1 (reference)	1 (reference)
Oxicams, n (%)	527 (8.7)	5,114 (9.4)	1.12 (1.02-1.23)*	1.03 (0.94-1.14)
Acetic acid derivatives and related substances, n (%)	1,223 (20.1)	5,123 (9.4)	2.59 (2.42-2.78)*	2.24 (2.08-2.41)*
Fenamates, n (%)	157 (2.6)	884 (1.6)	1.93 (1.62-2.29)*	1.52 (1.27-1.81)*
Propionic acid derivatives, n (%)	406 (6.7)	2,344 (4.3)	1.88 (1.68-2.10)*	1.62 (1.44-1.81)*
Butylpyrazolidines, n (%)	94 (1.5)	660 (1.2)	1.55 (1.24-1.93)*	1.34 (1.08-1.68)*
Others, n (%)	59 (1.0)	1,113 (2.0)	0.58 (0.44-0.75)*	0.52 (0.40-0.68)*
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	804 (37.5)	4,082 (32.5)	1 (reference)	1 (reference)
Oxicams, n (%)	460 (21.4)	3,896 (31.0)	0.60 (0.53-0.68)*	0.63 (0.56-0.71)*
Acetic acid derivatives and related substances, n (%)	256 (11.9)	832 (6.6)	1.56 (1.33-1.83)*	1.67 (1.42-1.96)*
Fenamates, n (%)	131 (6.1)	538 (4.3)	1.24 (1.01-1.52)*	0.89 (0.72-1.10)
Propionic acid derivatives, n (%)	361 (16.8)	2,125 (16.9)	0.86 (0.75-0.99)*	0.81 (0.70-0.93)*
Butylpyrazolidines, n (%)	25 (1.2)	110 (0.9)	1.15 (0.74-1.79)	1.04 (0.67-1.63)
Others, n (%)	109 (5.1)	990 (7.9)	0.56 (0.45-0.69)*	0.57 (0.46-0.71)*
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Coxibs, n (%)	846 (39.5)	4,434 (35.4)	1 (reference)	1 (reference)
Oxicams, n (%)	524 (24.4)	2,883 (23.0)	0.95 (0.85-1.07)	0.96 (0.85-1.08)
Acetic acid derivatives and related substances, n (%)	380 (17.7)	3,012 (24.1)	0.66 (0.58-0.75)*	0.63 (0.55-0.72)*
Fenamates, n (%)	148 (6.9)	541 (4.3)	1.43 (1.18-1.74)*	0.98 (0.80-1.20)
Propionic acid derivatives, n (%)	100 (4.7)	604 (4.8)	0.87 (0.69-1.09)	0.79 (0.63-0.99)*
Butylpyrazolidines, n (%)	12 (0.6)	56 (0.4)	1.12 (0.60-2.10)	0.97 (0.51-1.82)
Others, n (%)	134 (6.3)	984 (7.9)	0.71 (0.59-0.87)*	0.72 (0.59-0.88)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

† broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest.

Table S10c Reporting odds ratios of hypersensitivity reactions using broad scope definition for any NSAIDs according to the presence/absence of sulfonamide group

0-5 years	Cases (n=6,088)	Non-cases (n=54,585)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	3,935 (64.6)	37,539 (68.8)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	2,153 (35.4)	17,046 (31.2)	1.21 (1.14-1.27)*	1.23 (1.17-1.30)*
5-10 years	Cases (n=2,146)	Non-cases (n=12,573)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,387 (64.6)	6,864 (54.6)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	759 (35.4)	5,709 (45.4)	0.66 (0.60-0.72)*	0.72 (0.65-0.79)*
10-15 years	Cases (n=2,144)	Non-cases (n=12,514)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Non-sulfonamide NSAIDs, n (%)	1,300 (60.6)	7,240 (57.9)	1 (reference)	1 (reference)
Sulfonamide NSAIDs, n (%)	844 (39.4)	5,274 (42.1)	0.89 (0.81-0.98)*	1.00 (0.91-1.10)

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

† broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest.

Table S10d Reporting odds ratios of hypersensitivity reactions using broad scope definition for individual NSAIDs within 5 years after market approval

Individual NSAIDs	Cases (n=6,087)	Non-cases (n=54,563)	Crude ROR (95% CI)	Age- and sex- adjusted ROR (95% CI)
Rofecoxib, n (%)	1,750 (28.7)	25,339 (46.4)	1 (reference)	1 (reference)
Celecoxib, n (%)	1,442 (23.7)	11,033 (20.2)	1.89 (1.76-2.04)*	1.89 (1.75-2.03)*
Zomepirac, n (%)	602 (9.9)	1,020 (1.9)	8.55 (7.64-9.56)*	6.69 (5.96-7.51)*
Tolmetin, n (%)	194 (3.2)	329 (0.6)	8.54 (7.10-10.26)*	7.10 (5.89-8.56)*
Sulindac, n (%)	205 (3.4)	1,930 (3.5)	1.54 (1.32-1.79)*	1.42 (1.22-1.66)*
Piroxicam, n (%)	276 (4.5)	2,376 (4.4)	1.68 (1.47-1.92)*	1.58 (1.38-1.81)*
Mefenamic acid, n (%)	151 (2.5)	762 (1.4)	2.87 (2.39-3.44)*	2.27 (1.89-2.73)*
Meloxicam, n (%)	155 (2.5)	1,976 (3.6)	1.14 (0.96-1.35)	1.03 (0.87-1.22)
Etoricoxib, n (%)	182 (3.0)	1,603 (2.9)	1.64 (1.40-1.93)*	1.54 (1.31-1.81)*
Loxoprofen, n (%)	153 (2.5)	532 (1.0)	4.16 (3.46-5.02)*	3.66 (3.03-4.42)*

Abbreviations: COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs; ROR = reporting odds ratio

*statistically significant ($p < 0.05$)

‡broad scopes include all possible terms that are often less likely to represent the outcome of interest but give high sensitivity for the case of interest.