



Non-steroidal anti-inflammatory drugs and Analgesics Exposures Prior To Hospital Admission For Acute Liver Injury

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Abstract

Background: Hepatic injury is one of the major drug safety issues. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with liver injury. **Objectives:** To quantify exposure to NSAIDs/analgesics prior to hospital admission for acute liver injury (ALI) in the French National healthcare systems database, SNDS. **Methods:** All hospital admissions for ALI (K71.1.,2,.6,.9, K72.0) over 2010-2014 were identified in SNDS (66 million persons). Previous diagnoses of liver disease/liver injury were excluded. Exposures of interest were systemic NSAIDs (ATC codes M01A), non-overdose paracetamol (N02AA, N02BE) and tramadol (N02AX02) dispensed from 7 to 60 days before hospital admission, to avoid indication and protopathic biases. Reference populations were a) the whole French population over the study period, extrapolated from the 1/97th permanent representative sample, EGB in a case-population analysis; b) 5 controls/case from EGB, matched on age and gender, using the same index date for the case-control analysis. Results are provided as a) number of cases per million users (MPt) or patient-years (MPY) with 95% confidence interval [95%CI], b) Odds Ratios (OR) [95% CI], compared to non-exposure. **Results:** 4807 ALI were matched to 24035 controls. 3619 cases and 12793 controls had been dispensed any drug within 7-60 days before admission (OR 3.1 [2.9-3.4]). 815 cases had been exposed to an NSAID (from 228 for ibuprofen to 5 for nimesulide, among 18 NSAIDs with at least 5 exposed cases); 1698 cases had been exposed to paracetamol, 162 to tramadol. Rates of hospital admission were 75/MPY [65-84] or 18/MPt [16-20] for any NSAID, and ranged from 300/MPY [120-617] for mefenamic acid to 38/MPY [11-88] for nimesulide, or from 14/MPt [9.5-19] for celecoxib to 2.7/MPt [0.9-6.3] for nimesulide. Other individual NSAIDs were ibuprofen 8.9 / MPt [7.6-10.2], diclofenac 8.7/MPt [7.2-10.4]. Paracetamol (alone or in combination) association with ALI was 105/MPY [95-117], 32/MPt [28-35], tramadol used alone 91/MPY [77-106], 19/MPt [16-22]. OR from the case-control analysis were 1.4 [1.3-1.5] for any NSAID, from 3.5 [1.3-9.2] for mefenamic acid, to 0.6 [0.25-1.6] for nimesulide, 1.4 [1.2-1.6] for ibuprofen, diclofenac 1.5 [1.3-1.9], celecoxib 2.1 [1.4-3.2], etoricoxib 2.1 [1.1-4.2]; OR for paracetamol was 1.95 [1.8-2.1], tramadol 2.3 [1.9-2.8]. **Conclusion:** The risk of hospital admission for hepatic injury was lower for NSAIDs than analgesics. There were no striking differences between NSAIDs. Risk of ALI after NSAIDs was generally lower than for all drugs combined.

1. Gulmez SE, et al. Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. *Drug Saf.* 2013;36(2):135-44.
2. Gulmez SE, et al. Risk of hospital admission for liver injury in users of NSAIDs and nonoverdose paracetamol: Preliminary results from the EPIHAM study. *Pharmacoepidemiol Drug Saf.* 2018;27(11):1174-81.

Declaration of Interest Statement

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Background

- Acute Liver Injury (ALI) is a major source of drug-induced regulatory action, drug-induced hospital admissions and burden of care.
- To our knowledge, hepatotoxicity studies were based on identification of individual cases and concerned a few hundred cases.
- A previous field study (SALT) exhaustively explored the acute liver failure leading to liver transplantation in 7 countries. The EPIHAM study was conducted in order to identify drugs with less severe hepatotoxicity, still resulting in hospital admission using the French nationwide claims database.

Objectives

To quantify exposure to Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics prior to hospital admission for ALI in the French National healthcare systems database SNDS.

Methods

- **Study design**
 - Case-population study of adults with a 1st hospitalization for ALI from 2010 to 2014.
 - Case-control study of adults exposed to interest drugs from 2010 to 2014.
- **Data source:** the SNDS French nationwide claims database which covers 99% of the French population and the EGB 1/97th permanent representative sample of SNDS.
- **Study population**
 - **Case** identified in SNDS among adult patients with a 1st hospital admission from 2010 to 2014 with main diagnosis of acute toxic liver injury (ICD-10 codes K71.1, K71.2, K71.6, K71.9) or hepatic failure (ICD-10 code K72.0) (Figure 1).
 - **Reference population** identified in EGB among adult patients affiliated at least one day for each year considered to the national healthcare insurance system for salaried workers (CNAMTS), extrapolated to the whole French population.
 - **Control** identified in EGB among adult patients affiliated to the CNAMTS and hospitalized between 2010 and 2014 for a reason other than ALI. Control were matched on age and gender using the same index date with a ratio of 5 controls / case identified (Figure 2).

- **Index date:** Date of first hospital admission for ALI.
- **Exposure**
 - **Case:** systemic NSAID (ATC code M01A), non-overdose paracetamol (N02AA, N02BE) and tramadol (N02AX02) dispensing between 7 and 60 days preceding the date of 1st hospital admission for ALI (to avoid indication and protopathic bias).
 - **Reference population:** number of patients with at least one interest drug dispensed over the study period (2010-2014), extrapolated to the whole French population.
 - **Control:** systemic NSAID (ATC code M01A), non-overdose paracetamol (N02AA, N02BE) and tramadol (N02AX02) dispensing in the same period as the identified cases.
- **Data analysis**
 - Incidence rate of ALI: number of exposed cases over the study period per million users (MP) or patient-years (MPY) with 95% confidence intervals ([case-population analysis](#)).
 - Risk of ALI in exposed patients (Odds Ratio – OR, conditional logistic regression) compared to non-exposed patients ([case-control analysis](#)).

Results

➤ Identification of ALI cases – Case-population analysis

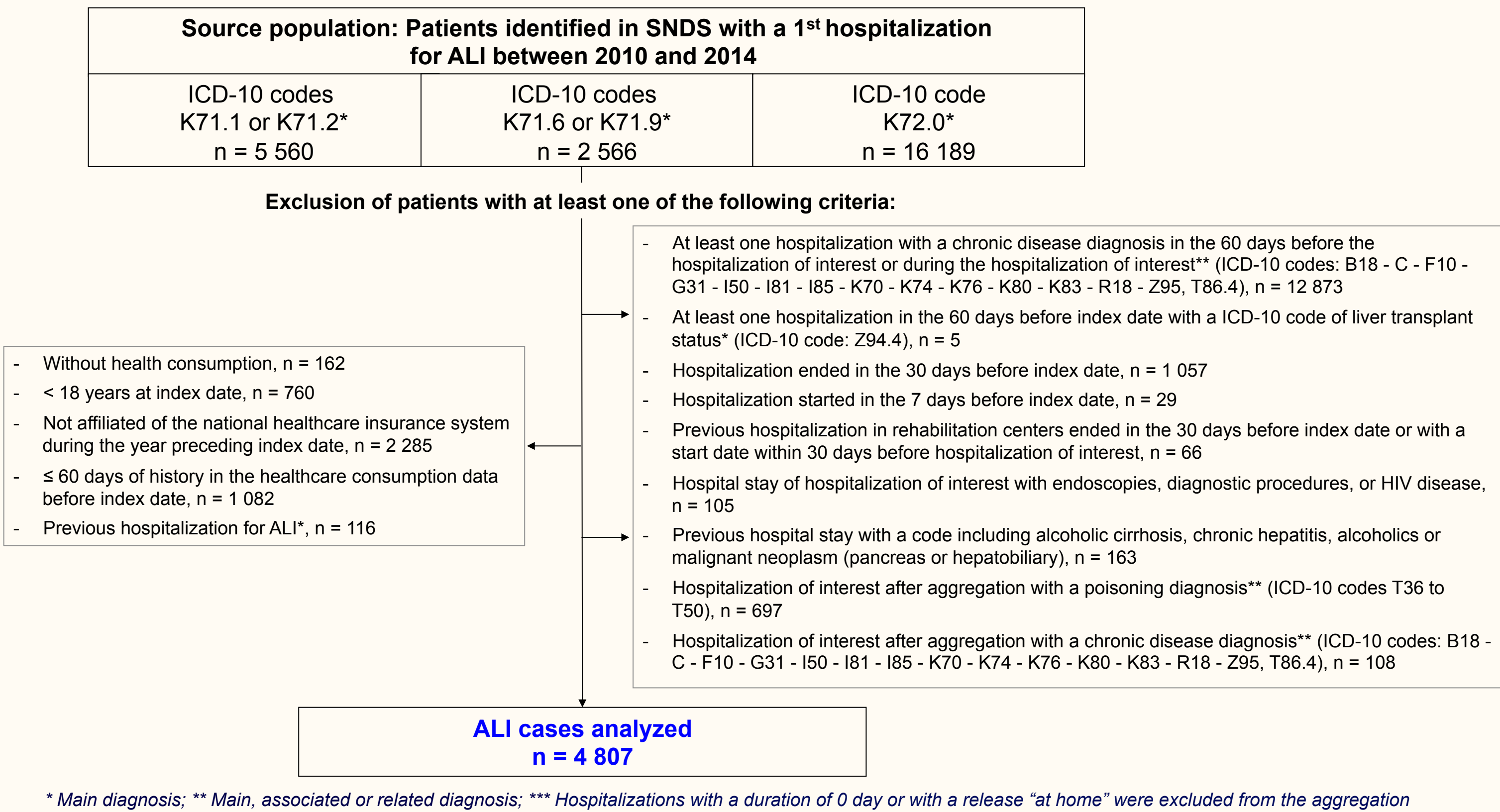


Figure 1. Identification procedure of ALI cases in SNDS between 2010 and 2014

➤ Exposure of adult ALI cases

- 17% of cases were exposed to at least one NSAID (among NSAIDs with at least 5 exposed cases). Exposure ranged from 228 cases for ibuprofen to 5 cases for nimesulide (Table 1).
- 35.3% of cases were exposed to paracetamol and 3.4% to tramadol.

➤ Incidence of hospitalization for ALI

- For NSAIDs, event rates per MPY ranged from 300 [120-617] for mefenamic acid to 38 [11-88] for nimesulide and per MP from 14 [9.5-19] for celecoxib to 2.7 [0.9-6.3] for nimesulide.
- For paracetamol (alone and combinations), event rate was 105 [95-117] per MPY and 32 [28-35] per MP. For tramadol, event rate was 91 [77-106] per MPY and 19 [16-22] per MP.

Table 1. NSAIDs and analgesics exposure of adult ALI cases within 7 and 60 days preceding the index date and incidence of hospitalizations for ALI between 2010 and 2014

Drugs dispensed within 7-60 days before index date	Case n = 4 807	Case / million patients [95% CI]	Case / million patients-year [95% CI]
M01A - NSAIDs, n (%)	815 (17.0)	18.34 [16.31 ; 20.43]	75.48 [65.70 ; 83.95]
M01AE01 - Ibuprofen	228 (4.7)	8.85 [7.63 ; 10.18]	126.39 [109.50 ; 146.00]
M01AE03 - Ketoprofen	153 (3.2)	8.10 [6.83 ; 9.52]	68.63 [58.40 ; 80.30]
M01AB05 - Diclofenac	117 (2.4)	8.69 [7.18 ; 10.42]	59.56 [47.45 ; 73.00]
M01AE02 - Naproxen	71 (1.5)	8.57 [6.69 ; 10.81]	66.39 [51.10 ; 83.95]
M01AE11 - Tiaprofenic acid	47 (1.0)	5.79 [4.25 ; 5.70]	237.30 [175.20 ; 313.90]
M01AC01 - Piroxicam	45 (0.9)	7.77 [5.67 ; 10.40]	78.15 [58.40 ; 105.85]
M01AE09 - Flurbiprofen	41 (0.9)	12.27 [8.80 ; 16.65]	148.77 [105.85 ; 200.75]
M01AH01 - Celecoxib	33 (0.7)	13.83 [9.51 ; 19.42]	53.38 [36.50 ; 76.65]
M01AB55 - Diclofenac, combinations	18 (0.4)	9.99 [5.92 ; 15.79]	81.35 [47.45 ; 127.75]
M01AX01 - Nabumetone	13 (0.3)	6.00 [3.19 ; 10.26]	59.12 [32.85 ; 102.20]
M01AX02 - Niflumic acid	13 (0.3)	4.68 [2.49 ; 8.00]	117.10 [62.05 ; 200.75]
M01AH05 - Etoricoxib	12 (0.2)	10.84 [5.60 ; 18.93]	69.21 [36.50 ; 120.45]
M01AB16 - Aceclofenac	11 (0.2)	4.47 [2.23 ; 8.00]	45.37 [21.90 ; 80.30]
M01AG01 - Mefenamic acid	7 (0.1)	10.95 [4.40 ; 22.56]	299.64 [120.45 ; 616.85]
M01AC06 - Meloxicam	7 (0.1)	6.56 [2.63 ; 13.50]	72.21 [29.20 ; 149.65]
M01AC02 - Tenoxicam	6 (0.1)	6.84 [2.51 ; 14.90]	70.19 [25.55 ; 153.30]
M01AX17 - Nimesulide	5 (0.1)	2.68 [0.87 ; 6.26]	37.90 [10.95 ; 87.60]
N02 - Analgesics, n (%)	1 954 (40.6)	35.90 [32.15 ; 39.7]	87.28 [76.65 ; 84.90]
N02AA/N02BE - Paracetamol	1 698 (35.3)	31.84 [28.49 ; 35.24]	104.90 [94.90 ; 116.80]
N02BE01 - Paracetamol	1 495 (31.1)	28.74 [25.70 ; 31.84]	104.55 [94.90 ; 116.80]
N02AX02 - Tramadol	162 (3.4)	18.54 [15.70 ; 21.72]	91.22 [76.65 ; 105.85]

* Taking into account the extrapolation of patient number for the reference population in the EGB database between 2010 and 2014

➤ Identification of controls – Case-control analysis

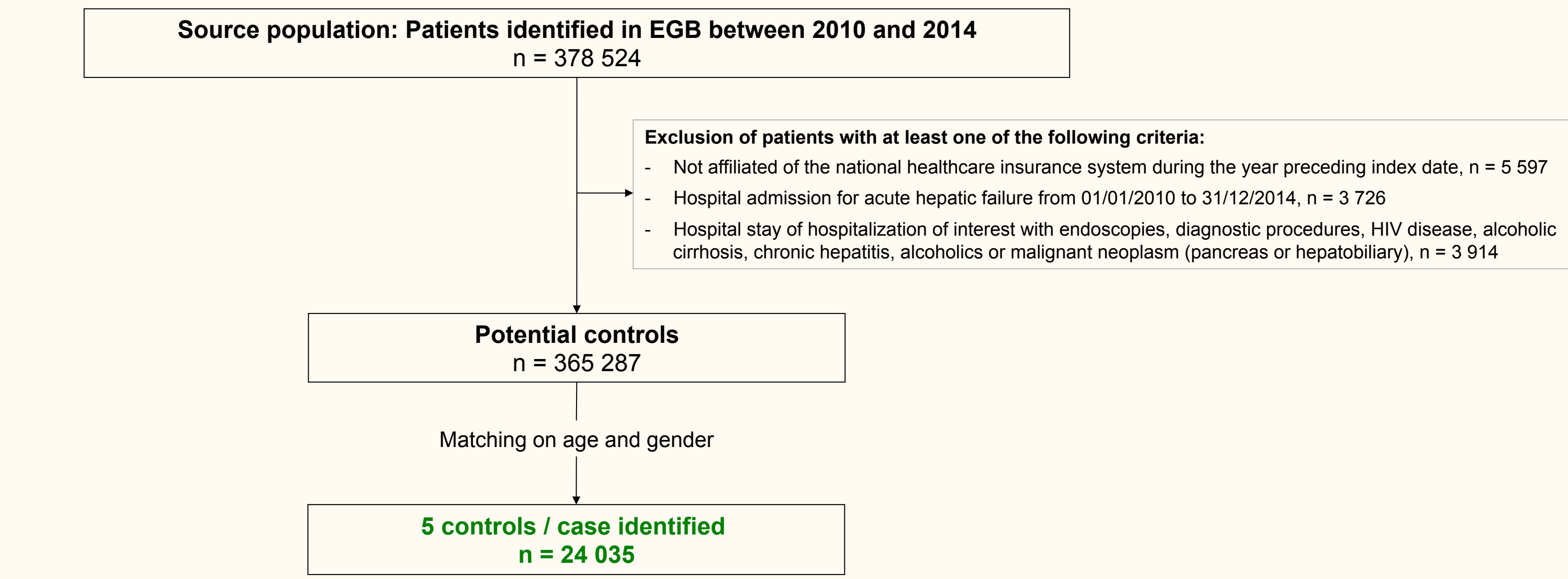


Figure 2. Identification procedure of controls in EGB between 2010 and 2014

➤ Risk of hospital admission for ALI

- For NSAIDs, OR was 1.4 [1.3-1.5] and ranged from 3.5 [1.3-9.2] for mefenamic acid to 0.6 [0.2-1.6] for nimesulide (Figure 3).
- The OR was 1.8 [1.7-2.0] for paracetamol and 2.3 [1.9-2.8] for tramadol.

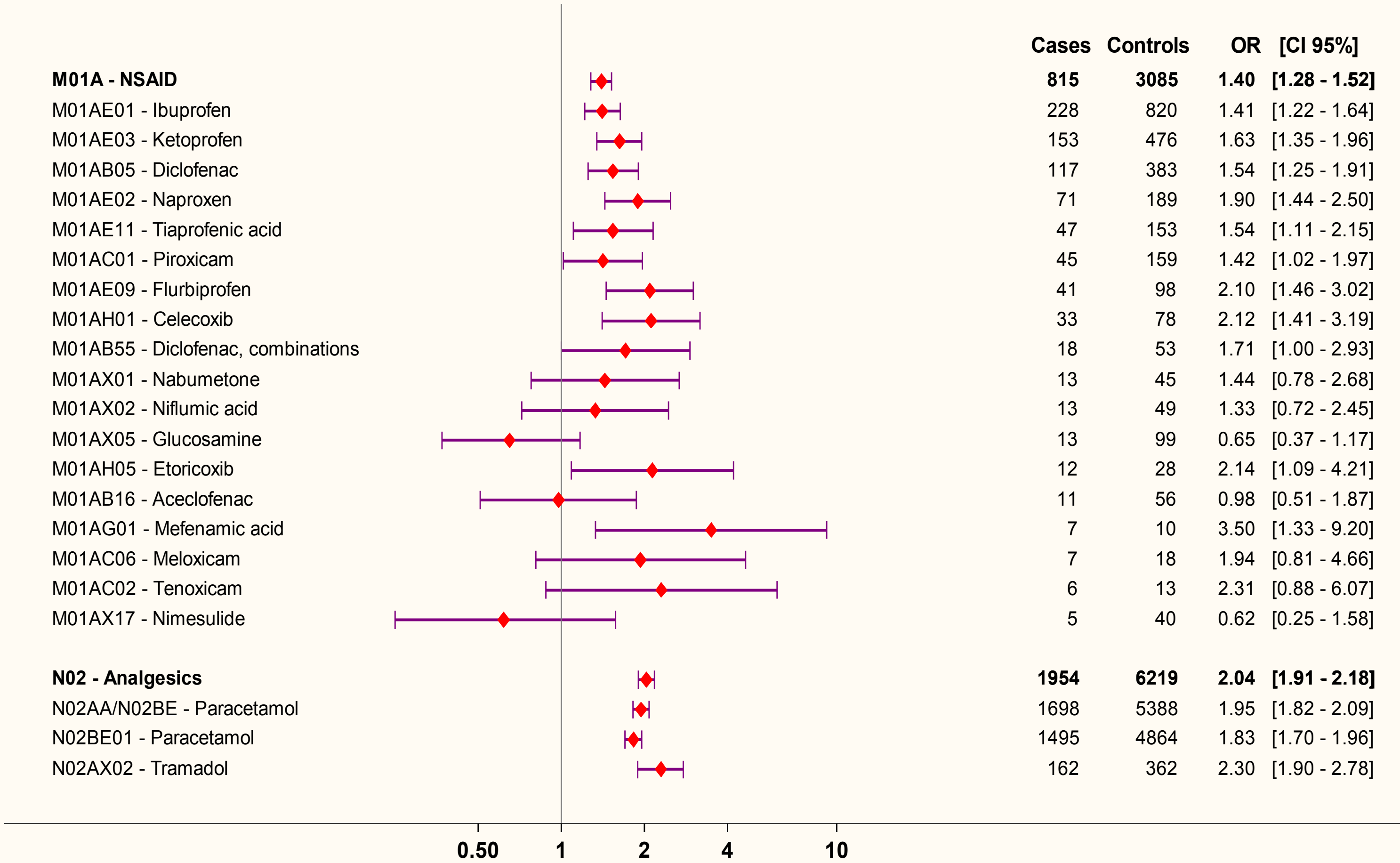


Figure 3. Risk of hospital admission for ALI between 2010 and 2014

Conclusion

- The hospitalization risk for ALI was lower for NSAIDs than for analgesics (1.40 and 2.04 respectively) with no major difference between the most commonly used NSAIDs (1.41 for ibuprofen, 1.63 for ketoprofen and 1.54 for diclofenac).
- Analgesics (paracetamol, tramadol) appear to be associated with a risk at least equal to or greater than NSAIDs (overdoses excluded).

