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Screening anxiolytics, hypnotics, antidepressants and neuroleptics for bone fracture risk among elderly: a nation-wide dynamic multivariate self-control study using the SNDS claims database.

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Abstract *Background and Purpose* Existing screening works provide point estimates for drug-outcome pairs risk assessment. We propose a flexible approach based on dynamic risk estimates to support alert generation while providing additional information on risk qualification (delay, shape) and LOD-specific biases. We illustrate this approach by studying the longitudinal effect of anxiolytic, hypnotic, antidepressant, and neuroleptic molecules on fractures using SNDS, a French large healthcare claims database.

Methods We follow French new users who were 65 y.o. or older in 2014 for up to four years. We use ConvSCCS, a flexible longitudinal model based on self-control case series. This model alleviates several observational claims data issues and does not require precise assumptions on risk timings. The presence of eventual indication biases is assessed by estimating dynamic pre-exposure relative risks.

Results Pre-exposure risk estimates suggest the presence of confounding by indication in anxiolytics, hypnotics and neuroleptics estimates, while it is not the case for antidepressants. Tricyclic antidepressants exhibit lower relative risk than other antidepressants. Zolpidem relative risk is consistently higher than Zopiclone across all sensitivity analyses.

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Conclusion This approach complements existing screening methods as well as clinical or observational risk quantification studies by providing granular and dynamic risk estimates for many molecules using a single model. It could be used to map molecules and adverse events, pointing out the presence of eventual biases or associations for further investigation.

Keywords Large Observational Database · Dynamic analysis · Adverse drug reaction screening · Elderly · Fracture · Anxiolytics · Hypnotics · Antidepressants · Neuroleptics

Key Points

- Our screening methodology estimates pre and post-exposure dynamic relative risk to go beyond existing approaches relying on point estimates.
- We perform a screening on all anxiolytic, hypnotic, antidepressant and neuroleptic (AHAN) molecules for bone fracture using a single flexible model on four years of SNDS data.
- Our results shed lights on the dynamics associating AHANs to fractures in claims data, and are consistent with the fragmented, existing literature.

1 Introduction

Observational healthcare data volume and availability increased over the last years carrying the hope of improving Adverse Drug Reactions (ADRs) screening. ADRs screening is defined as “drug-related risk identification and alert generation” in Bezin et al [5]. In this setup, there are no precise hypotheses regarding suspected ADRs, and the screening algorithm is designed to assess several drug exposures effect on an identified event of interest.

Observational data peculiar characteristics and ADRs various dynamics [13] make this task particularly difficult. Indeed, observational healthcare data, such as Electronic Healthcare Records (EHRs) and claims data are often collected for economic concerns rather than epidemiological purposes. As a result, such data reflect as much the data recording process and care providers economic considerations as patients’ health status [19], and can mis-represent some populations due to eventual geographic or healthcare affordability constraints [23].

First screening approaches exploiting claims data relied on re-purposing classical models to study many drug-outcome *pairs* (see examples in Ryan et al [36] or Thurin et al [41]). They produced simple statistical models and designs, contrasting with the tailored analyses observational data would require to handle its specific biases [23]. More recent works alleviate some of these issues, either thanks to careful designs [42] or mixed effects bayesian models [14]. However, these approaches produce point estimates relying on strong temporal dynamics assumptions.

In this work, we use ConvSCCS [26], a recent flexible conditional Poisson model (also known as Self-Control Case Series - SCCS) which does not require precise assumptions on risk timings, provide dynamic risk estimates, and allows for estimating many molecules associated risk within a single model. Combined with a careful study design, we aim to provide detailed information on the underlying dynamics of several drug exposures association with a target event.

We use this methodology to screen potential associations between anxiolytic, hypnotic, antidepressant and neuroleptic (AHAN) molecules use and fractures among the elderly using data from the *Système National des Données de Santé* (SNDS, formerly known as SNI-IRAM), a French large observational database containing most of the population’s health-

care claims and hospital discharges. While SNDS is often used to perform drug safety studies [5, 44], it has been used only very recently to perform ADR screening Thurin et al [41].

AHANs and fracture risk associations have already been investigated at different levels of granularity and scopes in numerous clinical and observational studies. Fractures among the elderly are a prominent public health issue as they are associated with high morbidity and mortality [9, 47]. They can be caused by reduced bone mineral density or postural instability [2], both of which might be influenced by the use of AHANs. Meta-analyses, such as Seppala et al [40] or Woolcott et al [51], reviewed a very large corpus of papers investigating such associations. These works highlight how hard establishing a broad mapping of fracture risk and molecules association can be, as most studies scope is limited to a single drug or drug class. To raise the level of evidence, Seppala et al [40] calls for studies investigating pharmacological subgroups rather than large drug classes, as well as duration effects, which is precisely what we are trying to achieve.

We aim to assess the capabilities of our approach to estimate the duration effects of all the molecules belonging to AHAN classes using a single statistical model while assessing the presence of eventual database-specific biases.

2 Materials and methods

2.1 Data Source

This study is based on data from the SNDS, a nation-wide claims and hospital discharge database containing of 98.8% of French population healthcare reimbursements [5, 44]. When working on adult subjects, this database has virtually no turnover apart from subjects moving abroad, resulting in almost no censorship due to loss in follow-up. Besides basic demographic information (gender, birth date), it contains timestamped outpatients dispensed drugs, procedures and long-term diseases, and inpatients procedures and diagnoses [44].

2.2 Study design

The study was conducted as a self-control study on new-user data. To enter the cohort, subjects had to be (1) covered by the universal health insurance coverage, which is the case for 98.8% of France inhabitants [44], (2) 65 y.o. or older on 1 January 2015, (3) receive their first outpatient target drug prescription at least 365 days after study start on 1 January 2014 to prevent prevalent users or to provide a sufficient wash-out delay. Restriction to 65+ y.o. patients result in a more homogeneous population in terms of professional activity (retirees), behaviour (response to a fall, sport practice) and characteristics (bone density), all of which might have an effect on fracture risk. Cohort entry was 1 January 2014 when all these conditions were met. Cohort exit was defined as (1) death; or (2) end of the study period, 31 December 2017.

As we performed the analysis with an SCCS model, only cases were used to fit the statistical model. We used a one-year time-window (entry condition (3)) as a control period common to all subjects. To ensure we do not bias fracture risk during the control period, patients with a history of fracture during this first year were not excluded.

2.3 Case definition

We extracted fracture events following the algorithm presented in Bouyer et al [7]. Fractures from public and private hospitalisations were extracted using International Classification of Diseases 10th revision (ICD10) codes of stay diagnoses, while non-hospitalised fractures were extracted based on outpatients' medical procedures using CCAM (French Common Classification of Medical Acts) codes matching plastered or orthopedic immobilisation and fracture reduction. Extracted events were categorised by fracture site and severity. Fracture severity was computed as an index ranging from 1 to 4: (1) there was no hospital admission due to the fracture, (2) fractured patients were hospitalized but did not have surgery, (3) fractured patients were hospitalised and a surgery dedicated to the fracture was performed and (4) indicates that the patient died during the hospital stay following its fracture.

As a fracture can generate multiple events in the healthcare system, we considered same-site fracture events within a 4-month window following the first event as the initial fracture subsequent events. To be consistent with our statistical analysis (see Section 2.5), we only studied the first fracture event of each subject.

2.4 Exposure definition

AHANs dispensations were identified using codes from the Anatomical Therapeutic Chemical (ATC) classification system. We selected psychotropic drugs excepted those commonly used for acute psychiatric indications or anaesthesia, listed in Appendix, Tables 4 to 7.

We focused on fractures resulting from falls, and thus on short or mid-term adverse reactions to AHANs use [2]. We used binary indicators of exposure starting times in combination with a flexible model, which has been shown to be the best modeling assumption when the ADRs' true forms and prescribed doses are unknown [13], which is the case in SNDS [5, 44].

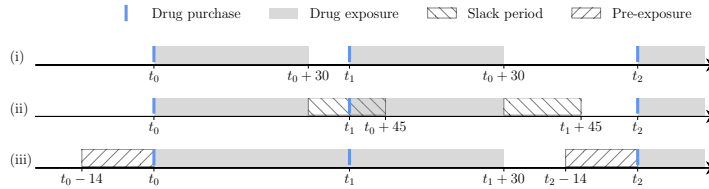


Fig. 1 Illustration of drug exposures computation. Exposures are assumed to last for 30 days (90 days for large drug packaging) after drug purchases (i). A slack period is added (ii) to account for slight variability in drug purchasing dates. Exposures which overlap with other exposures or other exposures' slack period are merged (iii). Once the merging is done, 14-day pre-exposure periods are added before each exposure starting points (iii).

Exposure start and end time were computed as follows: (1) drug exposure was considered to start at the drug dispensation date. (2) subjects were assumed to use at most one drug dose per day, resulting in 30 or 90-day exposures depending on the drug packaging. (3) When a given exposure plus a 15-day slack period overlapped with another exposure, they were merged, thus considered as a single exposure. This slack period was used to account for small drug adherence variability across patients. The size of this delay was chosen to fit

most regular users while remaining conservative, given the short half-life of the molecules under study [50]. (4) Pre-exposure risk periods covering 14 days preceding exposure start were defined to account for eventual confounding by indication.

As a result, patients could have been exposed multiple times to each molecule. Exposure and pre-exposure define two distinct sets of risk periods for each molecule, the reference period being non-exposed time. Note that pre and post-exposure risk periods were not stopped during hospitalisations as our statistical model requires risk periods of a minimal fixed length (see Section 2.5). Exposure computation is illustrated Figure 1.

2.5 Statistical Analysis

We aim to detect eventual association between fracture risk and drug exposure without precise prior knowledge on risk timing or shape. To do so, we used ConvSCCS [26], a flexible conditional Poisson model (also known as Self-Control Case Series – SCCS) allowing to estimate longitudinal variations of the risk resulting from each exposure. As in any SCCS model, patients are their own control and the model is robust to non-longitudinal confounding [26]. The new-user cohort design allowed us to use the first year of study as the control period, which also alleviated the prevalent user bias stated in Madigan et al [23]. Such design performs well on claims databases [22, 36] which do not contain enough information on patients’ demographics and life habits to find matching control patients [44].

ConvSCCS estimates a longitudinal relative risk curve (RRC) for each studied molecule, modeling the risk dynamics during risk periods. The length of those RRCs can be at most the minimal length of the considered exposure type [26]. Our risk periods definition resulted in 14-day pre-exposure and 30-day post-exposure RRCs for each molecule. We used daily data, which is the lowest temporal granularity available in SNDS. To avoid obtaining noisy estimates, RRCs variation were penalised as described in Morel et al [26]. Group Lasso penalisation cancels out RRCs close to one, providing feature selection. Total Variation penalisation controls RRCs discontinuities, leading the model to automatically select an optimal risk periods partition, as illustrated in Figure 2.

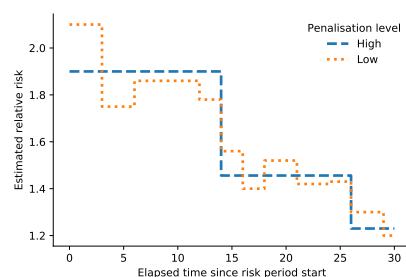


Fig. 2 Illustration of the Total Variation penalisation effect. Assuming a risk period starting at 0 and lasting for 30 days, ConvSCCS will estimate a 30-day piece-wise constant relative risk curve. The total size of the jumps is controlled by the level of Total Variation penalisation. A low (resp. high) level of penalisation results in more (resp. less) detailed relative risk curves, illustrated by the orange small dashes (resp. blue long dashes) curve. The aim of the model fitting algorithm is to reach a good balance between the detail level and the smoothness of the estimated relative risk curves.

Reported 95% confidence intervals were estimated using parametric bootstrap as described in Morel et al [26], and statistical power was approximated as described in Wasserman [48].

2.6 Sensitivity and subgroup analysis

To assess the robustness of our results, the following analyses were carried out:

- (1) *Single fractures*: exclusion of patients with more than one fracture or hospital admission with fracture diagnosis over the observation period. Multiple fractures might reflect patients affected by osteoporosis or fractures resulting from severe crashes. Approximately 16% of the patients experienced two or more fractures during the observation period (see Table 2).
- (2) *65-85 y.o.*: analysis on the 65-85 y.o. subgroup. The average age of the elderly moving into retirement homes is 85 years old [28], in which case drug purchase data might be less precise [44].
- (3) *Epileptic patients exclusion*: this condition is an indication for some of the molecules under study thus leading to an eventual confounding [9, 39].
- (4) *Gender*: analysis of men and women subgroups. Bone density variations related to gender might lead to differences in fracture risks [38]. Differences between men and women subgroups regarding associations between fractures and antidepressants have been reported in Vermeeren [45].
- (5) *Additional control drugs*: add exposures to other drugs which might have an influence on fractures. Additional molecules or group of molecules were opioids, proton pump inhibitors [39] ; loop diuretics, digitalis, digoxin [47] ; and anti-hypertensive drugs [9]. Exposures to these molecules or groups of molecules were simply used as additional features, not to filter prevalent users.
- (6) *Fracture severity*: restriction to a subset of fractures depending on their severity. We restricted the fracture definition to severity 1, 1 or 2 and 3. The severity 4 fractures subgroup was not considered as a very high correlation between death date and event date violates a ConvSCCS assumption (see discussion in Section 4.2).
- (7) *Specific fracture sites*: restriction to hip, wrist or spine fracture.

Sensitivity analysis resulted in numerous RRCs, the all-fracture scenario being the reference analysis. To ease results reading and interpretation, we report the differences between reference RRCs and those estimated in sensitivity experiments using the following method: (i) We consider only RRCs for which at least one value is significantly different from reference estimates based on 95% bootstrap confidence intervals. (ii) Some sensitivity analysis experiments result in smaller datasets with only a few patients exposed to some molecules. RRCs estimated with low power ($< .2$) are excluded from the comparison, to avoid considering estimates to be “unstable” when a poor estimate is caused by the lack of data. (iii) We then compute the mean relative error,

$$\bar{re} = T^{-1} \sum_{t=1}^T \frac{\theta_t - \theta_t^{ref}}{\theta_t^{ref}},$$

between the RRCs $\theta = (\theta_1, \dots, \theta_T)$ selected in step (i) and the corresponding reference estimates $\theta^{ref} = (\theta_1^{ref}, \dots, \theta_T^{ref})$, where T is the length of the considered risk period.

2.7 Software

Cases and exposures extraction from SNDS was performed using the SCALPEL3 library [4], while the statistical model was fitted using the Tick library [3]. Both libraries are open-source and freely available. The code used to produce the results presented in this paper is available at <https://github.com/X-DataInitiative/AHANScreening>.

3 Results

From a source population containing 13,762,623 patients of 65 y.o. or older, we extracted 126,567 fracture cases among 1,969,587 patients exposed to AHANs between 1 January 2015 and 31 December 2017 but not exposed in 2014 (see flow chart Figure 3). An overview of the studied cohort demographic characteristics is presented in Tables 1 and 2. Exclusion of subjects not exposed to AHANs did not result in major demographic changes (see Table 2). Restriction of the cohort to cases only led to an over-representation of 85+ y.o. patients (57% vs. 32%), women (72% vs. 58%), antidepressants (44% vs. 31%) and neuroleptics (21% vs. 7%) users as compared to the study population (see Table 1).

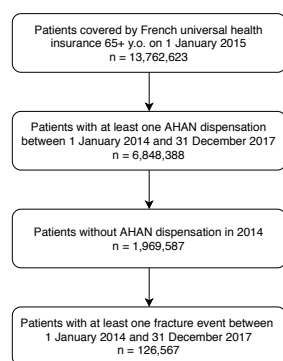


Fig. 3 Flow chart of the study population. Subjects were first selected based on their consumption of Anxiolytics, Hypnotics, Antidepressants or Neuroleptics (AHANs). The cohort was then restricted to fracture cases.

Our model produces a set of two relative risk curves (RRCs) for each molecule. The post-exposure RRC express the evolution of the relative risk $t = [0, \dots, 30]$ periods after exposure start. The coefficient associated with $t = 0$ represent the instantaneous relative risk, i.e. the risk associated to the day of exposure initiation. Pre-exposure RRCs describe relative risk dynamics during the two weeks preceding exposure start, with $t = [-1, \dots, -14]$. More details regarding RRCs interpretation are provided in Section 4. Estimated relative risk curves (RRCs) are compiled Figure 4 to 11. Please note that the longitudinal variation of the risk is controlled by the model penalisation and is not the result of explicit assumptions.

3.1 All fractures

Fractures RRCs before and after the drug exposure start are compiled in Figures 4 to 7. With the exception of diazepam, anxiolytics post-exposure RRCs (Figure 4) are either flat,

Table 1 Demographics and Anxiolytics, Hypnotics, Antidepressants or Neuroleptics use by fracture adverse event. The first column reports the number of 65+ y.o. new users patients cohort in the listed subgroups. The second (resp. third) column reports the number of patients with at least one fracture (resp. hip fracture) during the observation period within the study cohort and the associated subgroups. Figures in parenthesis represent the relative size (%) of a subgroup with respect to its population (*n*).

	Study population (%)		Fracture cases (%)		Hip fracture cases (%)	
<i>n</i>	1,969,587	(100.0)	126,567	(100.0)	46,699	(100.0)
Women	1,136,695	(57.7)	90,340	(71.4)	33,370	(71.5)
Age (years)						
[65-70[576,854	(29.3)	17,123	(13.5)	2,755	(5.9)
[70-75[395,883	(20.1)	14,872	(11.8)	3,373	(7.2)
[75-80[366,227	(18.6)	19,858	(15.7)	6,102	(13.1)
[80-85[316,085	(16.1)	27,895	(22.0)	11,053	(23.7)
[85-90[204,989	(10.4)	27,544	(21.8)	13,060	(28.0)
[90-95[93,195	(4.7)	16,252	(12.8)	8,685	(18.6)
[95-100[13,594	(0.7)	2,585	(2.0)	1,411	(3.0)
> 100	2,760	(0.1)	438	(0.4)	260	(0.6)
Exposed to anxiolytics	1,381,068	(70.1)	83,581	(66.0)	30,013	(64.3)
Exposed to hypnotics	519,548	(26.4)	38,291	(30.3)	14,682	(31.4)
Exposed to antidepressants	603,511	(30.6)	50,937	(40.3)	20,493	(43.9)
Exposed to neuroleptics	144,303	(7.3)	18,464	(14.6)	9,554	(20.5)

Table 2 Demographics of fractured patients. The first column reports the number of 65+ y.o. SNDS French patients who experienced a fracture during the observation period for each population subgroup. The second column reports the number of these patients who were also exposed to one of the Anxiolytic, Hypnotic, Antidepressant or Neuroleptic (AHAN) molecules under study. The last column reports similar figures when restricting the population to new users (i.e. patients who were not users during the first year of study). Figures in parenthesis represent the relative size (%) of a subgroup with respect to its population (*n*).

	Fractured 65+ y.o. patients (%)		Patients exposed to AHANs (%)		2015 new-users (%)	
<i>n</i>	729,647	(100.0)	513,303	(100.0)	126,567	(100.0)
with hip fracture	263,402	(36.1)	194,827	(38.0)	46,699	(36.9)
with multiple fractures	112,162	(15.4)	84,175	(16.4)	20,342	(16.1)
Women	549,795	(75.4)	398,847	(77.7)	90,340	(71.4)
Age (years)						
[65-70[98,289	(13.5)	58,179	(11.3)	17,123	(13.5)
[70-75[83,654	(11.5)	54,025	(10.5)	14,872	(11.8)
[75-80[110,948	(15.2)	77,931	(15.2)	19,858	(15.7)
[80-85[153,538	(21.0)	113,022	(22.0)	27,895	(22.0)
[85-90[159,192	(21.8)	119,223	(23.2)	27,544	(21.8)
[90-95[101,589	(13.9)	75,146	(14.6)	16,252	(12.8)
[95-100[18,644	(2.6)	13,303	(2.6)	2,585	(2.0)
> 100	3,793	(0.5)	2,474	(0.5)	438	(0.3)

between 1.2 and 1.7, or decreasing over 30 days, starting between 1.8 and 2.5 to fall between 1 and 1.5. Diazepam post-exposure RRC is also decreasing, starting much higher at 6.0 to level at 2, thirty days after exposure start. Other than buspirone, all anxiolytics pre-exposure risks are almost always significantly higher than 1, with three distinct profiles: increasing pre-exposure RRC (diazepam), decreasing RRCs starting between 1.9 and 3 before plummeting to 1 in 5 to 10 days and constant RRCs between 1.1 and 2.7.

Hypnotics RRCs (Figure 5) are either constant, with similar profiles, or U-shaped in the case of zopiclone and zolpidem, for which post-exposure relative risk decreases in 10 to 15 days before increasing slightly. Zolpidem post-exposure relative risks are higher than zopiclone's. Both molecules have sharp decreasing pre-exposure RRCs. Temazepam and bromides RRCs are non-significant (at 95%).

Antidepressants RRCs (Figure 6) can be separated in two groups. The first group, consisting of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tetracyclic antidepressants (TTCAs) exhibit decreasing post-exposure RRCs for most of the molecules. Those RRCs range from 1.5 to 2.5. SSRIs relative risk stays high (> 1.5) during 30 days following exposure start, while RRCs of TTCAs are non-significant 12 days after exposure start for mianserin, and 22 days after exposure start for mirtazapine. Among these molecules, fluoxetine, paroxetine, and duloxetine have a constant relative risk of similar magnitude, while fluvoxamine, moclobemide and milnacipran exhibit very low relative risks (between 1 and 1.2). These molecules pre-exposure RRCs tend to be either decreasing or flat, but are always lower than 1 in the few days preceding the exposure starting time.

The second group, made of tricyclic antidepressants (TCAs) and other antidepressants has constant post-exposure RRCs, either ranging from 1.5 to 2.0 or non-significant. Those molecules have flat, non-significant pre-exposure RRCs, excepted amitriptyline and agomelatine. Amitriptyline's pre-exposure relative risks start at around 1.5 in the 14 to 7 days before exposure starts, and non-significant 7 to 0 days before exposure start, while agomelatine's is constant, lower than one.

Most of neuroleptics RRCs are constant over the considered risk periods. Cyamemazine, haloperidol, and risperidone stand out, with post exposures starting between 1.7 and 2.4, decreasing towards a relative risk between 1.2 and 1.5, 30 days after exposure start. These three molecules exhibit similar pre-exposure RRCs, starting around 1.5 and decreasing to a non-significant relative risk or slightly less than in the case of cyamemazine. Other neuroleptics RRCs are either non-significant or constant, with a relative risk ranging from 1.1 to 1.6. They exhibit non-significant pre-exposure RRCs excepted for loxapine and tiapride, whose pre-exposure RRCs start around two, to non-significant levels a few days before exposure starting time.

3.1.1 Hip fracture

Restricting the study population to hip fractures resulted in 46,699 cases. RRCs are represented Figures 8 to 11. The smaller number of cases seems to result in a slight loss of power, leading to non-significant RRCs in some cases (such as clomipramine), flatter RRCs (escitalopram) or wider confidence intervals (mirtazapine).

Diazepam post-exposure RRC is now significantly lower, but still high starting at 2.5 to level-off around 1.5 after one week. Estimated RRC increases for dosulepin with a RR of 1.6 (1.2 previously) and duloxetine with RRC around 2.4 (1.7 previously). Other molecules post-exposure RRCs are overall stable with respect to the all-fracture analysis. A noticeable decrease in pre-exposure relative risk can be observed, especially among anxiolytics (Figure 8) and hypnotics (Figure 9), resulting in several non-significant pre-exposures RRCs. It is not the case for neuroleptics (Figure 11) for which pre-exposure does not vary nor increases in the case of haloperidol.

3.1.2 Sensitivity analysis

The relative differences between RRCs of the reference all-fracture analysis and those estimated in sensitivity experiments are reported in Figure 12. RRCs excluded from the comparison due to low power ($< .2$) are hatched on the graphical representation. Detailed relative risk estimates for these sensitivity analyses are provided in Supplementary Materials, Figures 38 to 49. Pre-exposure and post-exposure RRCs are overall stable with respect to

population design variations (experiments 1 to 4 defined in Section 2.6), with more variability when restricting the population to men. Adding control drugs slightly shifted downwards anxiolytics and Zopiclone and Zolpidem post-exposure RRCs, and their pre-exposure RRCs even more. Changing target event definition using specific fracture sites or fracture severity introduce some variations in post-exposure estimates, and heavily affects pre-exposure relative risks. Defining the target event as wrist fracture or low severity fractures leads to a smaller population ($n = 9,722$), resulting in low power estimates.

4 Discussion

4.1 Key results

We presented a methodology designed to perform large scope screening studies using claims data. It relies on using ConvSCCS [26], a flexible SCCS model, with binary drug exposures. The flexibility of the model allows to estimate risk dynamics without prior assumption on the risk shape, and prevent risk dilution when the risk window is larger than the actual risk [26]. Binary exposures encode the starting times of exposures, which has been show to be an optimal choice when combined with a flexible model in situations where reliable prior knowledge is unavailable [13]. A new-user design prevents the risk dynamics estimated by the model to be affected by prevalent drug use, starting before the observation period. In addition to post-exposure risk, we also estimate pre-exposure flexible risk curves to highlight the presence of eventual biases linked to specific care pathways or database-specific biases.

We applied this approach on observational claims data from SNDS [44]. To our knowledge, only [41] performed ADRs screening on the full scale SNDS database, using a methodology based on point estimates, similarly to Ryan et al [34]. Dynamic risk estimation produced more detailed information than binary answers sought by screening algorithms based on point estimates. Rather than pursuing a fully automated alert generation system, our approach fosters human interpretation of data-mined patterns.

We evaluate our screening approach by studying AHANs for bone fracture risk. Some works on ADRs screening such as Ryan et al [36] evaluated the performance of their methodology by comparing their results to an adverse drug reaction database [35] containing established positive and negative association. While this approach is appealing because of its convenience, the reliability of such datasets have been criticized by Hauben et al [17] as some associations appear to have been mis-classified. In place of this evaluation scheme, we evaluate our screening methodology by comparing our results to existing works on AHANs. We compare our relative risk estimates and dynamics to meta-analyses and to results obtained with other methodologies.

Overall, results from the main analysis (presented in Figures 4 to 11) seem consistent with meta-analyses compiled in Table 3. Our estimates for benzodiazepines were slightly higher than pooled odds ratios (ORs) when considering all studies [6, 40, 51], but they were close to pooled ORs restricted to studies providing adjusted ORs [40]. Note that grouping individual molecules into large categories might result in an averaging effect, smoothing out risk estimates [45]. Results for each molecule class are discussed below.

Table 3 Meta-analyses and reviews on fracture and Anxiolytics, Hypnotics, Antidepressants or Neuroleptics (AHANs) eventual association. (*CI: Confidence Interval, OR: Odds Ratio, RR: Relative Risk, TCA: tricyclic antidepressant, SSRI: selective serotonin reuptake inhibitor*)

Study	Methodology	Target event	Results
Bloch et al [6]	Meta-analysis	Falls	Heterogeneity across reviewed studies on hypnotics. Pooled ORs (95% CI): benzodiazepines 1.61 (1.35-1.93), hypnotics 1.53 (1.40-1.68), antidepressants 1.59 (1.43-1.75), antipsychotics 1.37 (1.16-1.61).
Graham et al [16]	Review	Hip or femur fractures	Antipsychotic drug use OR varying from 1.2 to 3 depending on studies. No dose relationship, schizophrenia is a confounding factor.
Seppala et al [40]	Meta-analysis	Falls	Heterogeneity across reviewed studies. Pooled ORs on all studies (95% CI): benzodiazepines 1.38 (1.17-1.63), antidepressants 1.35 (1.28-1.42), antipsychotics 1.43 (1.15-1.77). Pooled ORs on adjusted studies: benzodiazepines 1.81 (1.05-3.16), TCAs 1.41 (1.07-1.86), SSRIs 2.02 (1.85-2.20), antipsychotics 1.54 (1.28-1.85).
Vestergaard [46]	Review	Fractures	Only Amitriptyline is associated with fracture risk among TCA (RR = 1.3), SSRIs are associated with an increased risk overall, especially in the 14 first days post-exposure (RR = 6.3 tapering off to 1.3 after 42 days).
Woolcott et al [51]	Meta-analysis	Falls	Heterogeneity across reviewed studies. Pooled ORs (95% CI): benzodiazepines 1.57 (1.43-1.72), hypnotics 1.47(1.35-1.62) antidepressants 1.68 (1.47-1.91), neuroleptics 1.59 (1.37-1.83).

4.2 Limitations

Confounding by indication SNDS does not allow to make a distinction between a drug effect and its indication, which might bias the estimated associations [44]. We used pre-exposure RRCs to assess biases resulting from LOD-specific care pathways. Such use of pre-exposure risk windows is not new [30, 32, 33], especially when using flexible dynamic models. A pre-exposure RRC above one might indicate the presence of indication bias. In this case, the molecule is likely to be prescribed in reaction to the target event occurrence. On the contrary, pre-exposures RRCs below one might highlight protective environments such as hospitals, preventing patients to experience the studied event. It highlights situations where patients are prescribed a molecule during a hospital stay and buy the said molecule at discharge. Both effects can be mixed when the studied event is likely to cause an hospitalization, resulting in a pre-exposure RRC starting above one and decreasing sharply (see zolpidem for example). This interpretation was consistent with sensitivity analysis experiments restricting fracture definition to a given severity level. Sensitivity analysis results summarised Figure 12 showed that pre-exposure RRCs were lower than the all-fracture study when considering only fractures requiring surgery (severity 3), and conversely when

considering fractures which did not require surgery (severity 1 or 2) or did not require hospitalisation (severity 1). While pre-exposure estimates do not prevent biases resulting from such dynamics, they allow for contextualising screening results thus helping to design further confirmation studies.

Comorbidities and unobserved confounding Potential biases linked to impaired vision, low BMI, physical or instrumental disability, cognition impairment, Parkinson’s disease or rheumatic diseases [9] have a slow evolution. They might result in almost-static individual effects, which should not have a significant impact on our results thanks to self-controlled designs ability to ignore unmeasured non-longitudinal biases [12]. Results were robust to the exclusion of 1678 epileptic patients as shown in Figure 12 (see Figures 21 to 53 for more details). Depression might also be considered as a comorbidity [9] and lead to an eventual confounding by indication but antidepressant pre-exposure RRCs did not suggest the presence of short-term indication biases.

Fracture definition We studied the first fracture event of each case rather than studying recurrent fractures. Results were robust to the exclusion of the 20,342 patients who experienced more than one fracture over the observation period (see Figure 12). We also controlled for an eventual measurement bias by restricting the analysis to hip, wrist, or spine fractures. Due to a small number of cases, restriction to wrist fracture resulted in low power estimates for many molecules. Restriction to spine fractures resulted in higher anxiolytic and hypnotic pre and post-exposure RRCs indicating a stronger indication bias for these molecules in this subgroup, especially in the case of diazepam. Conversely, restriction to hip fractures resulted in lower pre-exposure RRCs and a lower diazepam post-exposure RRC, while other post-exposure RRCs were comparable with the reference analysis.

Population selection Restriction to women resulted in slightly lower post-exposure RRCs and lower pre-exposure RRCs, and conversely for men, which might be explained by differences in fractures site repartition between men and women as a larger proportion of men experienced spine (+6%) or ribs (+3%) fractures. Post-exposure RRCs were robust to the exclusion of 85+ y.o. subjects.

Model assumptions ConvSCCS relies on three assumptions: (1) exposure times are independent of outcome times, (2) the observation period of each patient is independent of its outcome times, (3) outcome times follow a Poisson process conditionally on the exposure times. Assumption (3) is verified by design as we consider only the first fracture event. Assumption (2) was assessed by looking at the distribution of the gaps between event times and time to death [49]. In our reference analysis, 7.35% of the cases event times were eventually correlated to time of death, which seems reasonable. Excluding 85+ y.o. patients or high severity fractures reduced this proportion while producing in similar results (see Figure 58 in Supplementary materials for more details). Assumption (1) is not likely to be verified as pre-exposure RRCs suggested the presence of confounding by indication. While pre-exposures help to capture this effect at least partially, we cannot rule out an eventual bias in post-exposure RRCs.

Statistical power When our model estimation procedure leads to flat RRCs for some molecules, it does not necessarily mean that the risk is actually flat. It can be the result of a lack of statistical power when too few patients are exposed to a molecule and risk variations are small.

RRCs estimated to be constant over the risk period can be interpreted as an “average risk” over the risk period, similarly to regular SCCS models. In addition, low statistical power might lead to non-significant relative risks for some molecules. In these cases, we conclude to an absence of detection rather than an absence of risk. While using a large observational database brings more cases, and thus more power, longitudinal screening of many molecules is data intensive. Indeed, it relies on the estimation of many parameters as it cannot take advantage of precise prior assumptions regarding RRCs shapes.

Scalability While the statistical model has no particular issue in terms of scalability, relying on a new-user design might result in too few available subjects when working on many molecules with only a few years of data.

Long term ADRs The study described in this paper focuses on short term associations, and cannot detect long term associations in its current form. However, the statistical model used in this study can do so when adopting different exposure and risk window definitions [26].

4.3 Interpretation

Anxiolytics All anxiolytics exhibited a positive association with fracture risk, either constant or decreasing over time. Decreasing of post-exposure RRCs follow two scenarios: (1) the molecules can be prescribed for short-duration treatments (<30 days, including a drug withdrawal phase [21]), in this case, the effect might disappear at the end of the treatment. The decline of the risk can be smooth, as withdrawal might be implemented by slowly decreasing the doses patients are using. (2) There can be some form of tolerance as described in Vermeeren [45]. The tolerance can be pharmacokinetic when it results from a lesser absorption with use, pharmacodynamic when the response to the molecule decreases with use, or behavioural when the brain gradually learns to overcome drug-induced impairments. As the estimated curves express an averaged effect over the studied population, they can express dynamics resulting from both scenarios. Several anxiolytic pre-exposure RRCs (such as clorazepate potassium or clobazam) indicated a potential indication bias [11]. In some cases such as oxazepam or etifoxine, a sharp decrease in pre-exposure risk highlighted the presence of care pathways in which fracture is probably followed by a hospital admission of two to ten days and a subsequent anxiolytic prescription. Such pathways might occur when anxiolytics are used to manage anxiety following the event leading to the fracture, or patient agitation in the case of fractures that cannot be immobilised such as head or torso fractures. This was confirmed by sensitivity analysis experiments restricted to specific fracture severity levels (see Figure 12 ; and Figures 38 to 49 in Supplementary Materials for more details). Similar dynamics of anxiolytic prescriptions following car crashes or fracture events were also observed in other studies [15, 33].

Our risk estimates were consistent with meta-analysis adjusted pooled Odds Ratios (ORs) [40], excepted for diazepam, for which estimated RRC was considerably higher than other benzodiazepines in the all-fracture analysis. While a similarly high diazepam RR has also been found in studies focusing on car crashes [15], it is likely to be the result of a strong indication bias in our case. Indeed, pre-exposure RRC of diazepam was much higher (peaking at 9) than what can be observed for other anxiolytics. Results from our sensitivity analysis showed that this bias was particularly important when restricting the study to spine fractures with a peak RR around 42 (see Figure 12 ; or Figure 54 in Supplementary Materials for more details). This strong association can be explained by prescriptions of diazepam

aiming to control spasticity after spinal cord injury [8, 24]. These biases almost disappeared when restricting the study to hip fractures. Adding control drugs (experiment 5) also resulted in a lower diazepam pre-exposure RRC, suggesting a potential co-prescription bias with opioids (see Figure 12 ; or Figure 35 in Supplementary Materials for more details). Note that such co-prescription bias might be also affect other anxiolytics and hypnotics pre-exposure RRCs (see Figure 12). As a result, diazepam relative risk was probably overestimated when spine fractures were included in cases definition and opioids exposure were not controlled in the model.

Hypnotics Hypnotic benzodiazepines exhibited lower RRCs than anxiolytic benzodiazepines which can be consistent with their recommended use, at bedtime. Their side effects such as drowsiness or dizziness might be less likely to lead to fractures than anxiolytic benzodiazepines which are used during daytime [45].

However, zopiclone and zolpidem association with fracture risk was similar or even higher than anxiolytics. Those two molecules have been extensively investigated as a group (“Z-drugs”) or individually [43]. However, they seem to have been compared only once in Pierfitte et al [31] when it comes to fracture association. Pierfitte et al [31] also find odds ratio twice as high for zolpidem compared to zopiclone’s, but they relied on a very small sample (less than 70 patients exposed to each molecule, among whom there are at most 15 cases) which might result in large confidence intervals and possibly low power.

Despite variations in pre-exposure risk, zolpidem post-exposure RRC was always found to be higher than zopiclone’s across all sensitivity analysis experiments. This might be explained by zolpidem’s sharper plasma concentration-time curve compared to zopiclone [10] and more impairing reported side effects, such as “strong visual disturbances and changes in perception” for zolpidem while “tiredness, dry mouth, metallic taste” were reported for zopiclone [10]. This result might also indicate a misuse of zolpidem [25] in France.

Antidepressants Antidepressants RRCs were consistent with the results presented in reviews [40, 46]. The increase in relative risks after exposure was smaller among tricyclic antidepressants (TCAs) than selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and tetracyclic antidepressants (TTCAs). We also observed decreasing RRCs for citalopram, escitalopram, sertraline, mianserin, mirtazapine, and venlafaxine similarly to Hubbard et al [20]. However, we estimated a constant RRC for amitriptyline while Hubbard et al [20] found a decreasing RR. Amitriptyline pre-exposure RRC was above one, indicating a potential confounding by indication, perhaps resulting from its use in neuropathic pain management, especially after spinal cord injury [1]. Aside from amitriptyline, pre-exposure RRCs were either non-significant or below 1, which suggest post-hospitalization prescriptions but no indication bias. Such care pathways are likely as SSRIs [27] or mirtazapine [18] might be prescribed in reaction to post-myocardial infarction for example.

Neuroleptics Similarly to [32], neuroleptic pre-exposure RRCs suggested the presence of indication bias which might be explained by the use of some neuroleptics in neuropathic pain management [29]. Our post-exposure risk estimates were consistent with Pratt et al [32], while our pre-exposure risks were slightly lower. We have not found a clear pattern relating estimated RRCs to neuroleptic sub-classes or their mechanism of action.

Hip fracture Restricting the study to hip fractures resulted in a sharp decrease of pre-exposure RRCs with respect to the reference analysis. It can be explained by a larger proportion of hospitalized fractures when restricting the cases to hip fractures, shifting the whole RRC downward. However, pre-exposure RRCs decrease was not as important when restricting the study to hospitalized fractures (severity 3), suggesting another source of pre-exposure RRC diminution. This subgroup age repartition is slightly skewed towards older subjects (see Table 1) for whom benzodiazepine prescription are not recommended by the French Health Authority (HAS) [37], probably resulting in a lesser confounding by indication.

5 Conclusion

We showed that our approach mixing cautious study design and an easy-to-tune flexible statistical algorithm can be used to produce large scope results highlighting eventual associations and indication or database-specific dynamic biases. Our approach is easy to implement as it relies on open-source, scalable libraries. It does not require much fine-tuning, it can handle large populations and many molecules, it relies on a few ascertainable assumptions and provides easily interpretable results. Our cohort construction and exposure and event definitions help to mitigate some of the database biases, without injecting over-restrictive prior knowledge to retain model plasticity. Flexible dynamic pre and post-exposure relative risk curves provide information on healthcare pathways, helping to highlight large observational databases specific biases. While the properties of our approach make it robust to some biases and can detect additional ones, its result should still be interpreted with care, and rely on the co-operation of medical experts and statisticians. We believe it can be used effectively to perform risk detection on large sets of molecules while contextualizing these risks so as to ease further confirmation studies.

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Author contributions MM, AG, ML, FL, DPN, YS, EB, SG contributed to the research plan. MM, ML, FL, DPN, YS contributed to the study design. MM drafted the manuscript, YS performed data extraction, MM and YS conducted the analyses. MM, BB, ML, FL, DPN and YS contributed to the interpretation of the results. All authors reviewed the manuscript and approved the final version.

Compliance with Ethical Standards

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Conflict of Interest M. Morel, B. Bouyer, A. Guilloux, M. Laanani, F. Leroy, D. P. Nguyen, Y. Sebiat, E. Bacry and S. Gaiffas declare that they have no conflict of interest.

Ethical approval Use of SNDS observational data was approved by the CNIL.

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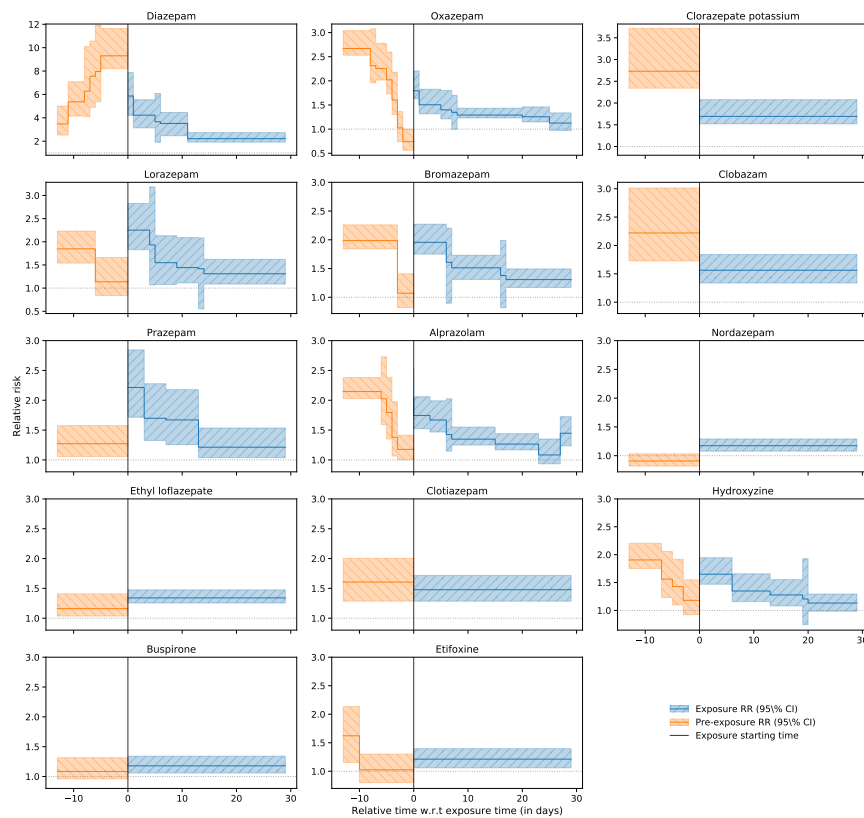


Fig. 4 Fracture relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

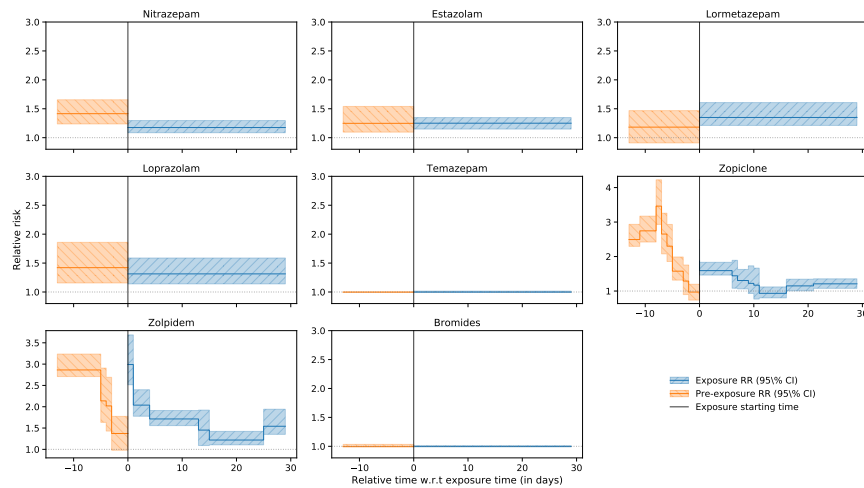


Fig. 5 Fracture relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

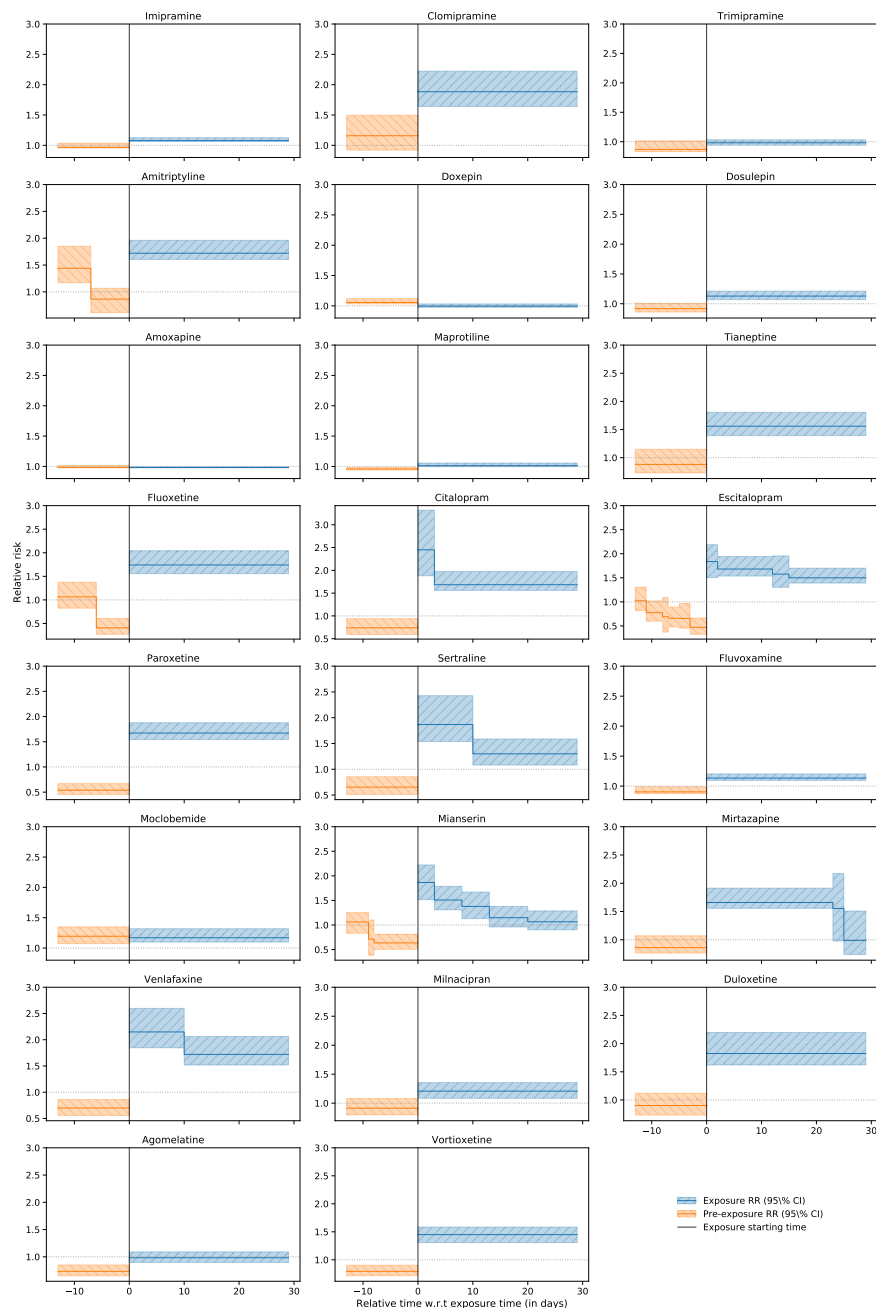


Fig. 6 Fracture relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

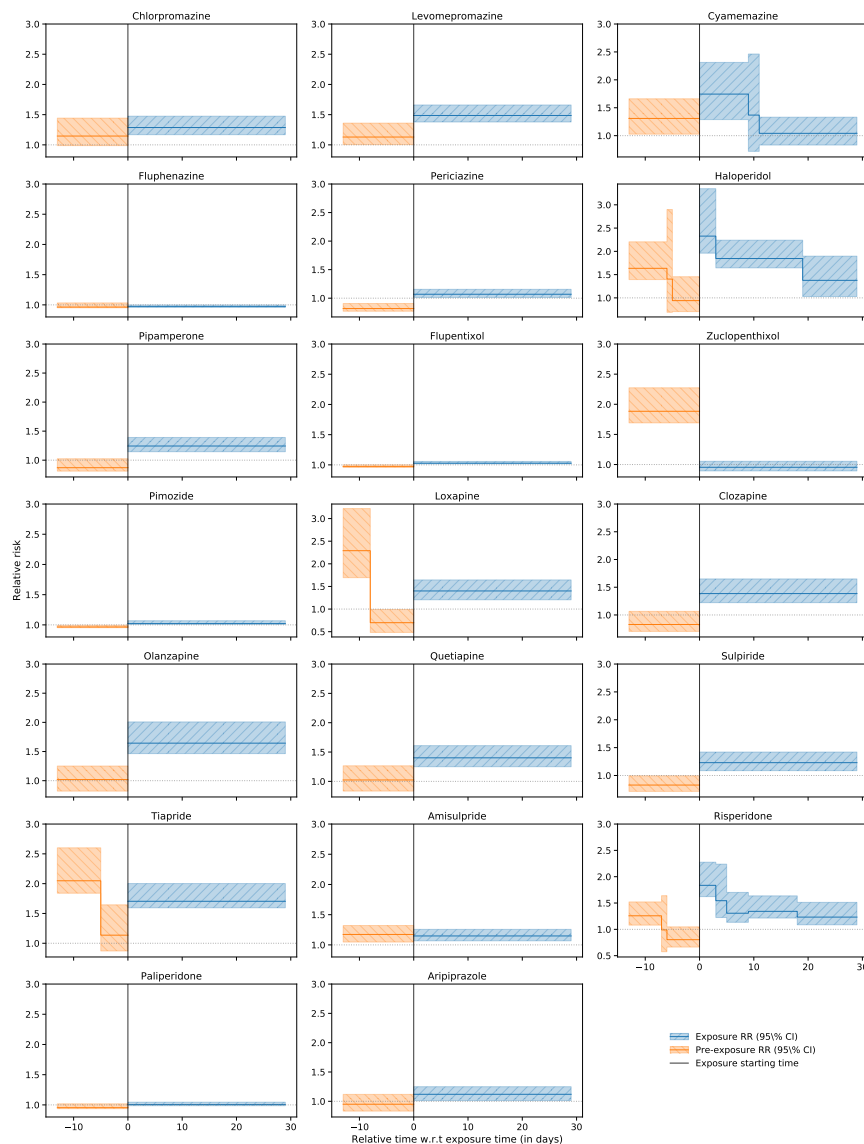


Fig. 7 Fracture relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

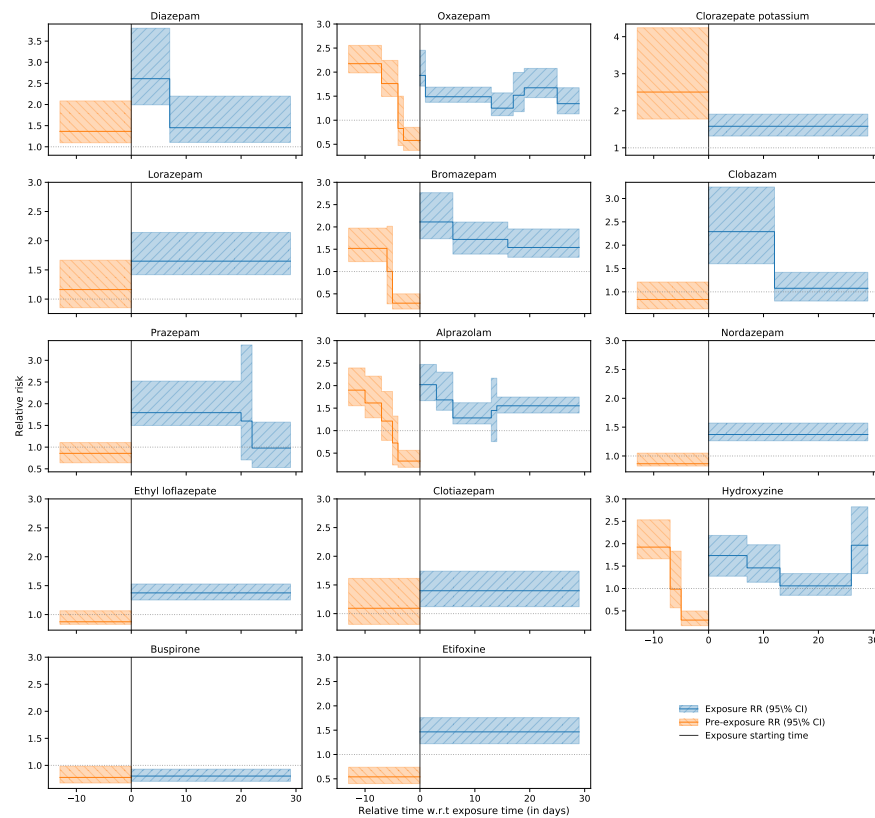


Fig. 8 Hip fracture relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

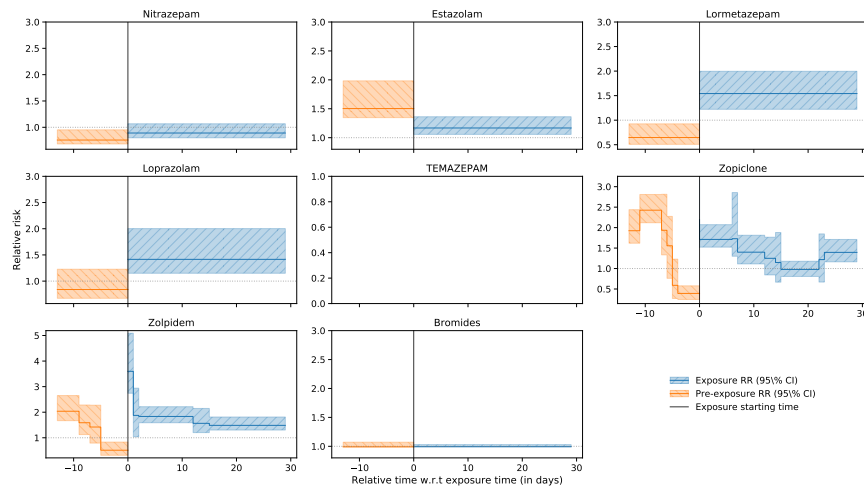


Fig. 9 Hip fracture relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

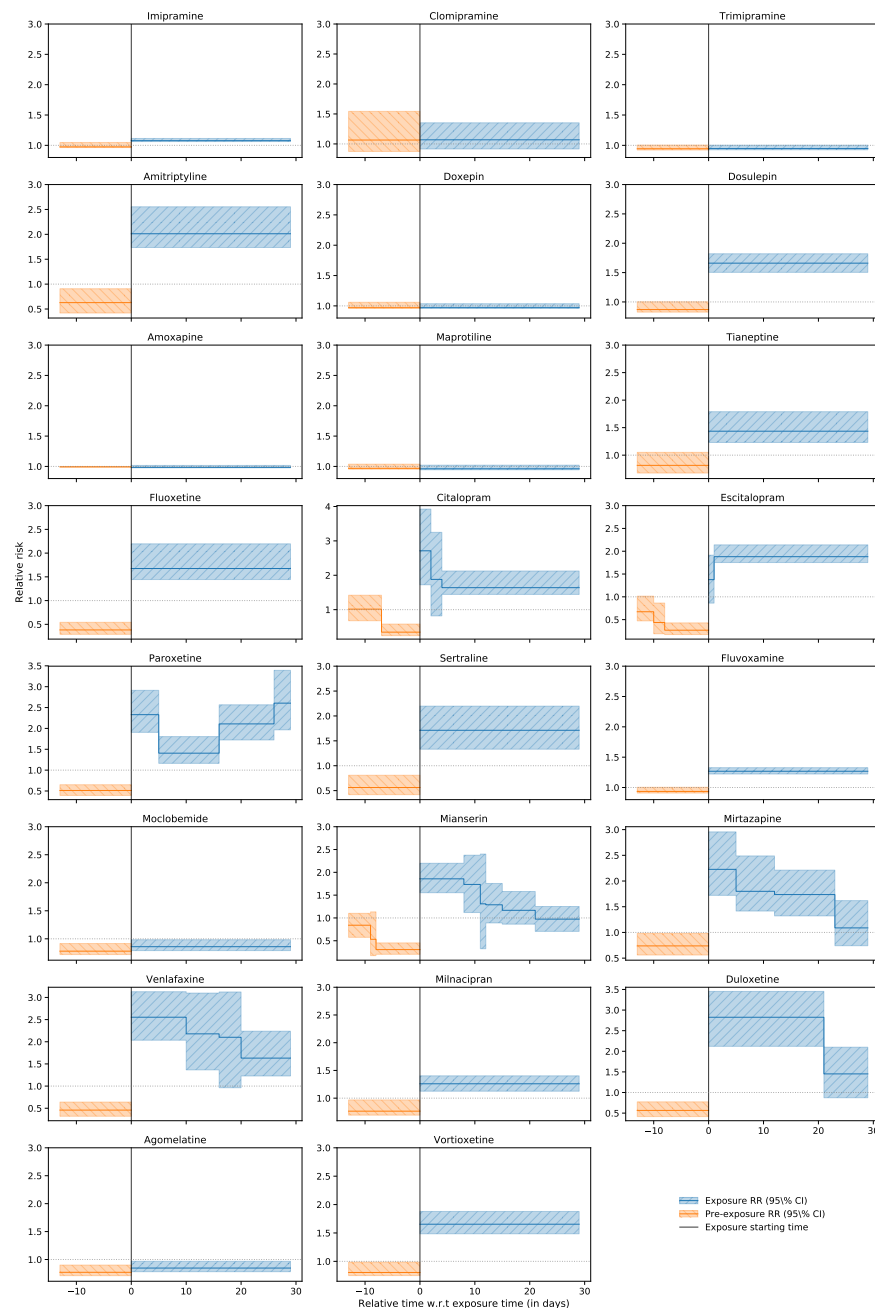


Fig. 10 Hip fracture relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

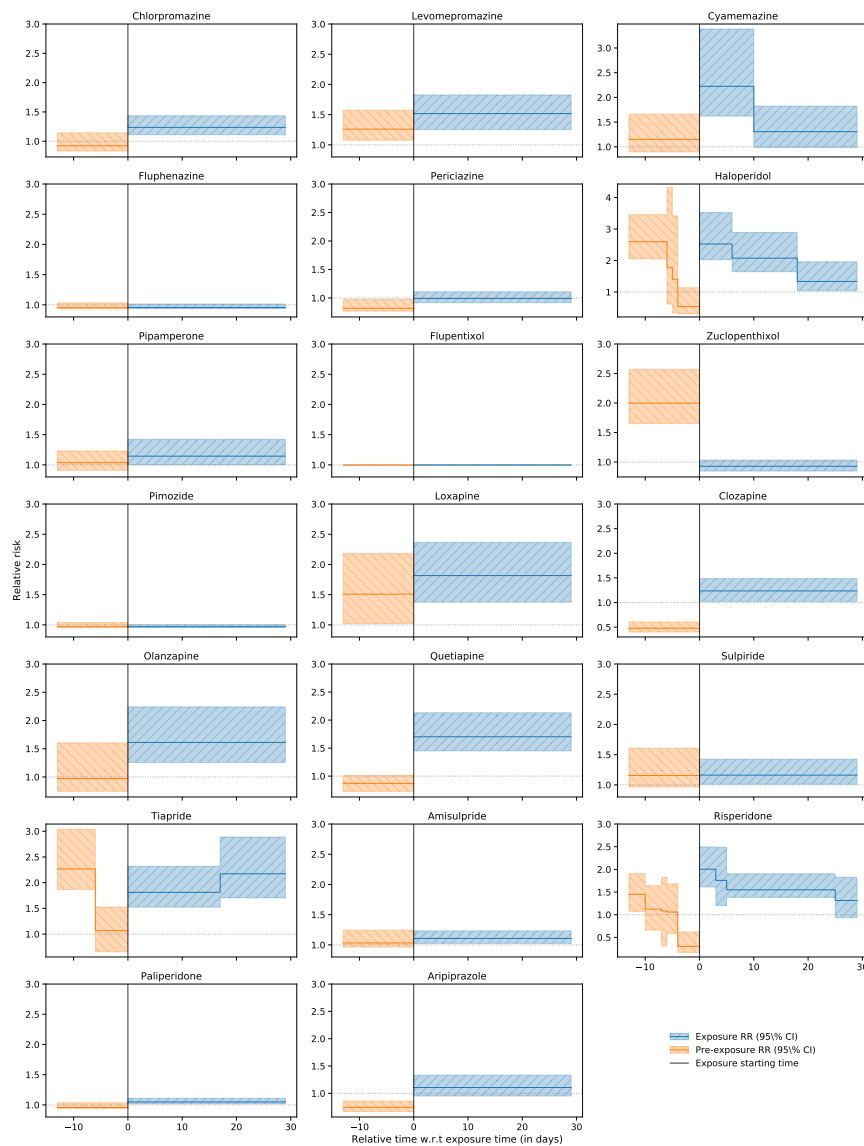


Fig. 11 Hip fracture relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

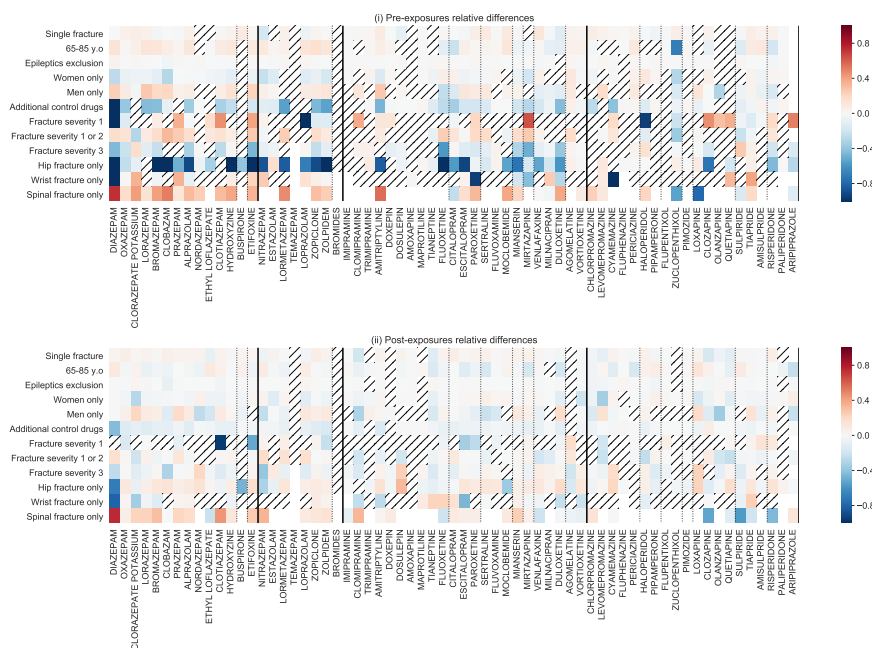


Fig. 12 Summary of the significant changes in terms of mean relative difference over sensitivity analysis experiments. The top (resp. bottom) heatmap represents the relative errors of pre-exposure (resp. post-exposures) relative risks. To ease the reading, the mean relative difference between two relative risk curves are reported only when there is at least one coefficient of these curves being significantly different at 95% confidence with a power greater than 0.2. The darkest squares indicate the most variable results, and the hatched squares indicate relative risk curves for which power is less than 0.2. Errors reported in red (resp. blue) means that the estimated risk is higher (resp. lower) in the experiment than in the all-fracture, reference analysis.

Supplementary Materials

A Codes

Table 4 Anxiolytics: Anatomical Therapeutic Chemical (ATC) codes beginning with N05B*, N05CF*, N05CM11, N05CM16 and N05CX. Midazolam was excluded, at it is mostly used as pre-medication for minor surgery [45].

Molecule	ATC class	Chemical class	ATC Code
DIAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA01
OXAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA04
CLORAZEPATE POTASSIUM	Benzodiazepine derivatives	Benzodiazepines	N05BA05
LORAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA06
BROMAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA08
CLOBAZAM	Benzodiazepine derivatives	Benzodiazepines	N05BA09
PRAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA11
ALPRAZOLAM	Benzodiazepine derivatives	Benzodiazepines	N05BA12
NORDAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA16
ETHYLE LOFLAZEPATE	Benzodiazepine derivatives	Benzodiazepines	N05BA18
CLOTIAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05BA21
HYDROXYZINE	Diphenylmethane derivatives	Diphenylmethane derivatives	N05BB01
BUSPIRONE	Azaspironedione derivatives	Diazinanes	N05BE01
ETIFOXINE	Other anxiolytics	Benzoxazines	N05BX03

Table 5 Hypnotics: Anatomical Therapeutic Chemical (ATC) codes beginning with N05CD*

Molecule	ATC class	Chemical class	ATC Code
NITRAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05CD02
ESTAZOLAM	Benzodiazepine derivatives	Benzodiazepines	N05CD04
LORMETAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05CD06
TEMAZEPAM	Benzodiazepine derivatives	Benzodiazepines	N05CD07
LOPRAZOLAM	Benzodiazepine derivatives	Benzodiazepines	N05CD11
ZOPICLONE	Benzodiazepine derivatives	Benzodiazepines	N05CF01
ZOLPIDEM	Benzodiazepine derivatives	Benzodiazepines	N05CF02
BROMURES	Other	Homogeneous halogens	N05CM11

Table 6 Antidepressants: Anatomical Therapeutic Chemical (ATC) codes beginning with N06A*, excepted Oxitriptan

Molecule	ATC class	Chemical class	ATC Code
IMIPRAMINE	TCA	Benzazepines	N06AA02
CLOMIPRAMINE	TCA	Benzazepines	N06AA04
TRIMIPRAMINE	TCA	Benzazepines	N06AA06
AMITRIPTYLINE	TCA	Dibenzocycloheptenes	N06AA09
DOXEPINE	TCA	Benzazepines	N06AA12
DOSULEPINE	TCA	Benzothiepins	N06AA16
AMOXAPINE	TCA	Benzoxazepines	N06AA17
MAPROTILINE	TCA	Anthracenes	N06AA21
TIANEPTINE	TCA	Fatty Acids	N06AX14
FLUOXETINE	SSRI	Benzene and substituted derivatives	N06AB03
CITALOPRAM	SSRI	Benzene and substituted derivatives	N06AB04
ESCITALOPRAM	SSRI	Benzene and substituted derivatives	N06AB10
PAROXETINE	SSRI	Piperidines	N06AB05
SERTRALINE	SSRI	Tetralins	N06AB06
FLUVOXAMINE	SSRI	Aralkylketone derivative	N06AB08
MOCLOBEMIDE	MAOI RIMA	Benzene and substituted derivatives	N06AG02
MIANSERINE	Tetracyclic	Benzazepines	N06AX03
MIRTAZAPINE	Tetracyclic	Benzazepines	N06AX11
VENLAFAXINE	SNRI	Phenol ethers	N06AX16
MILNACIPRAN	SNRI	Unclassed	N06AX17
DULOXETINE	SNRI	Naphthalenes	N06AX21
AGOMELATINE	Other	Carboxylic acids and derivatives	N06AX22
VORTIOXETINE	Other	Piperidines	N06AX26

Table 7 Neuroleptics: Anatomical Therapeutic Chemical (ATC) codes beginning with N05A* excepted Veralipride, Lithium and Chlorproethazin, as they are mostly used as a mood stabiliser to treat bipolar disorders or schizo-affective disorders rather than depression.

Molecule	ATC class	Chemical class	ATC Code
CHLORPROMAZINE	Phenothiazines with aliphatic side-chain	Benzothiazines	N05AA01
LEVOMEPROMAZINE	Phenothiazines with aliphatic side-chain	Benzothiazines	N05AA02
CYAMEMAZINE	Phenothiazines with aliphatic side-chain	Benzothiazines	N05AA06
FLUPHENAZINE	Phenothiazines with aliphatic side-chain	Benzothiazines	N05AB02
PERICIAZINE	Phenothiazines with aliphatic side-chain	Benzothiazines	N05AC01
HALOPERIDOL	Butyrophenone derivatives	Organoxygen compounds	N05AD01
PIPAMPERONE	Butyrophenone derivatives	Organoxygen compounds	N05AD05
FLUPENTIXOL	Thioxanthene derivatives	Benzothiopyrans	N05AF01
ZUCLOPENTHIXOL	Thioxanthene derivatives	Benzothiopyrans	N05AF05
PIMOZIDE	Diphenylbutylpiperidine derivatives	Benzene and substituted derivatives	N05AG02
LOXAPINE	Diazepines, oxazepines, thiazepines and oxepines	Benzoxazepines	N05AH01
CLOZAPINE	Diazepines, oxazepines, thiazepines and oxepines	Benzodiazepines	N05AH02
OLANZAPINE	Diazepines, oxazepines, thiazepines and oxepines	Benzodiazepines	N05AH03
QUETIAPINE	Diazepines, oxazepines, thiazepines and oxepines	Benzodiazepines	N05AH04
SULPRIDE	Benzamides	Benzene and substituted derivatives	N05AL01
TIAPRIDE	Benzamides	Benzene and substituted derivatives	N05AL03
AMISULPRIDE	Benzamides	Benzene and substituted derivatives	N05AL05
RISPERIDONE	Other	Pyridopyrimidines	N05AX08
PALIPERIDONE	Other	Pyridopyrimidines	N05AX13
ARIPRAZOLE	Other	Diazinanes	N05AX12

B Sensitivity analysis

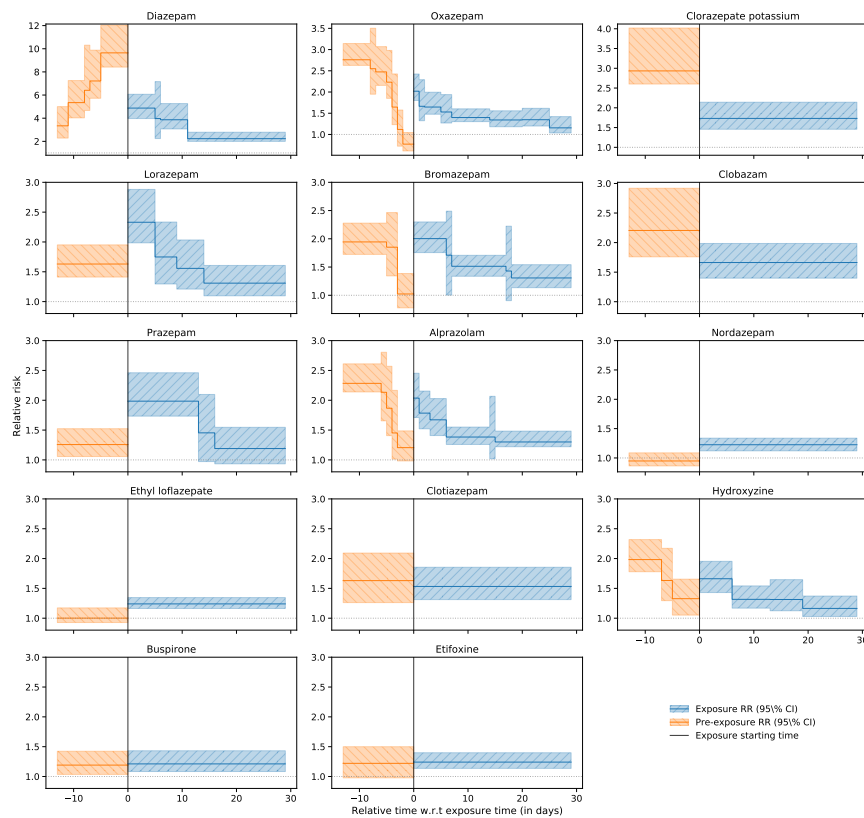


Fig. 13 Fracture relative risk curves estimated before and after anxiolytics exposure on patients having experienced only one fracture during the observation period. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

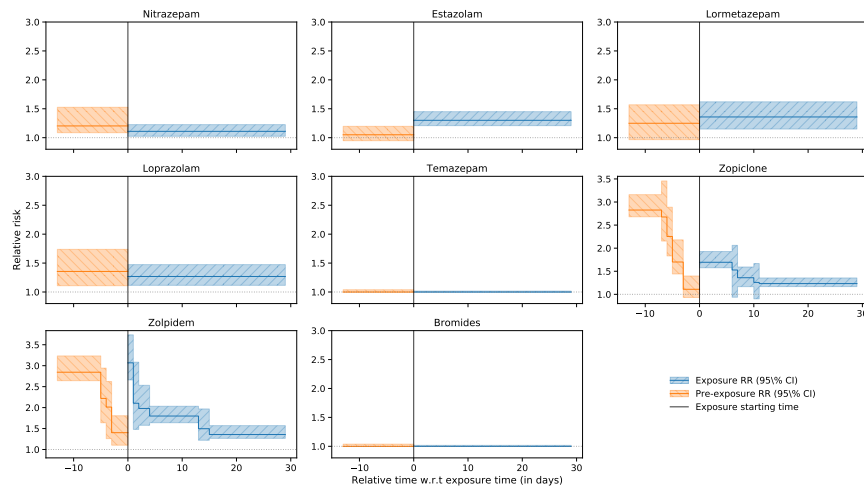


Fig. 14 Fracture relative risk curves estimated before and after hypnotics exposure on patients having experienced only one fracture during the observation period. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

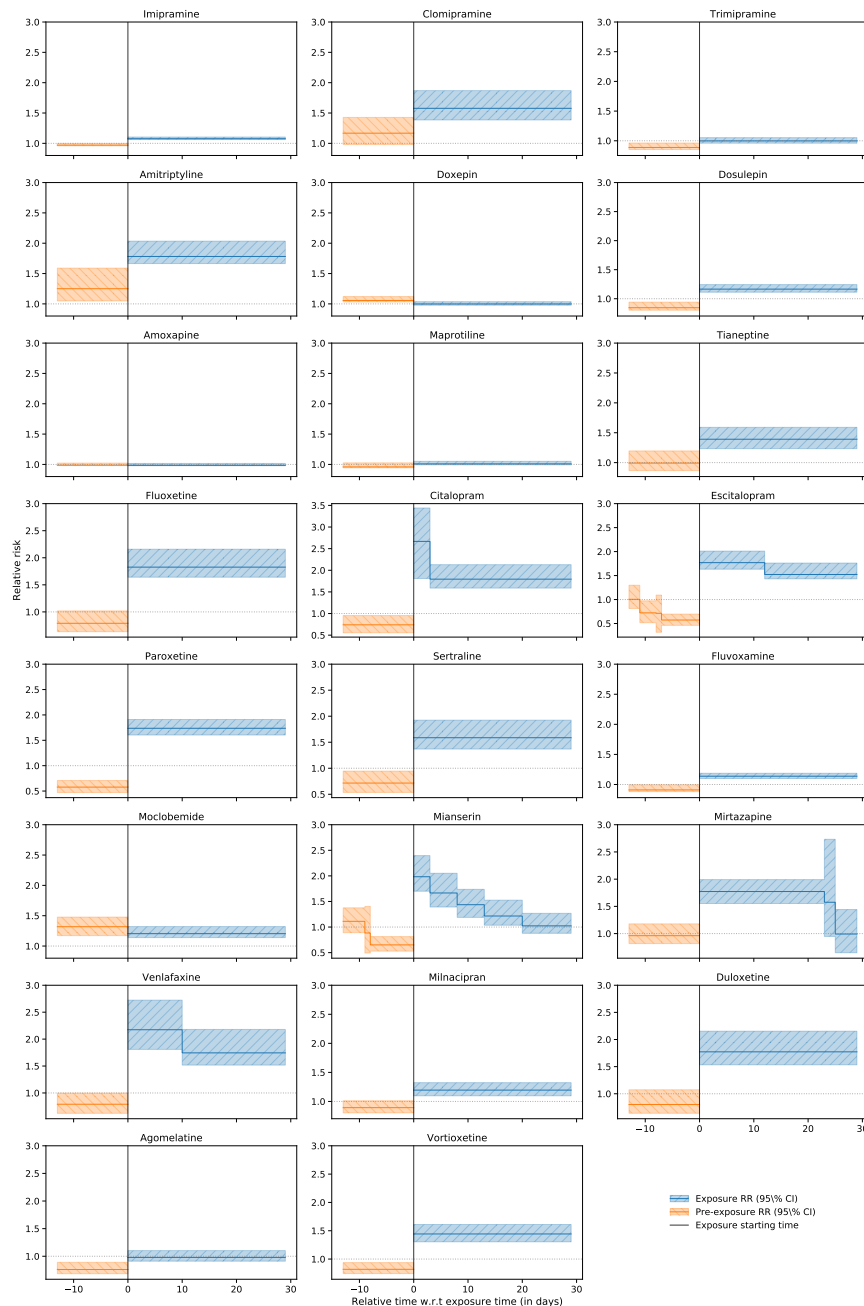


Fig. 15 Fracture relative risk curves estimated before and after antidepressant exposure on patients having experienced only one fracture during the observation period. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

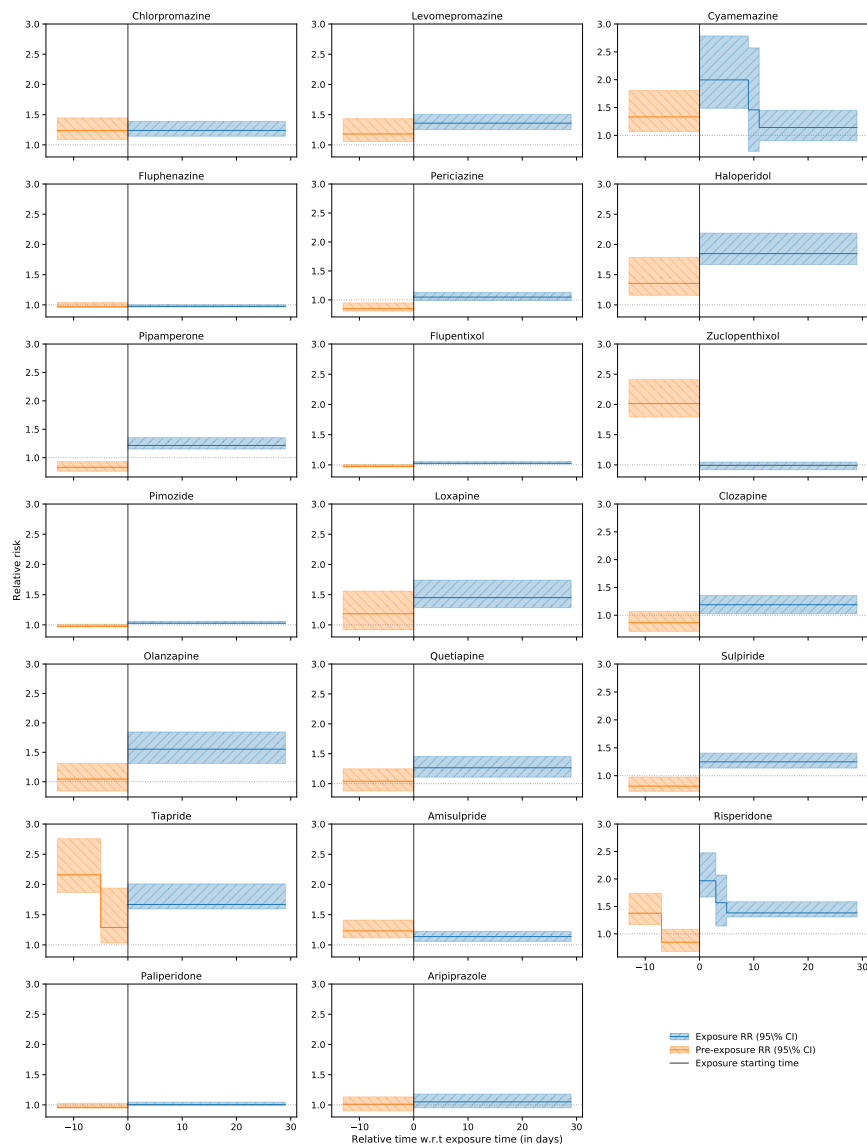


Fig. 16 Fracture relative risk curves estimated before and after neuroleptics exposure on patients having experienced only one fracture during the observation period. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

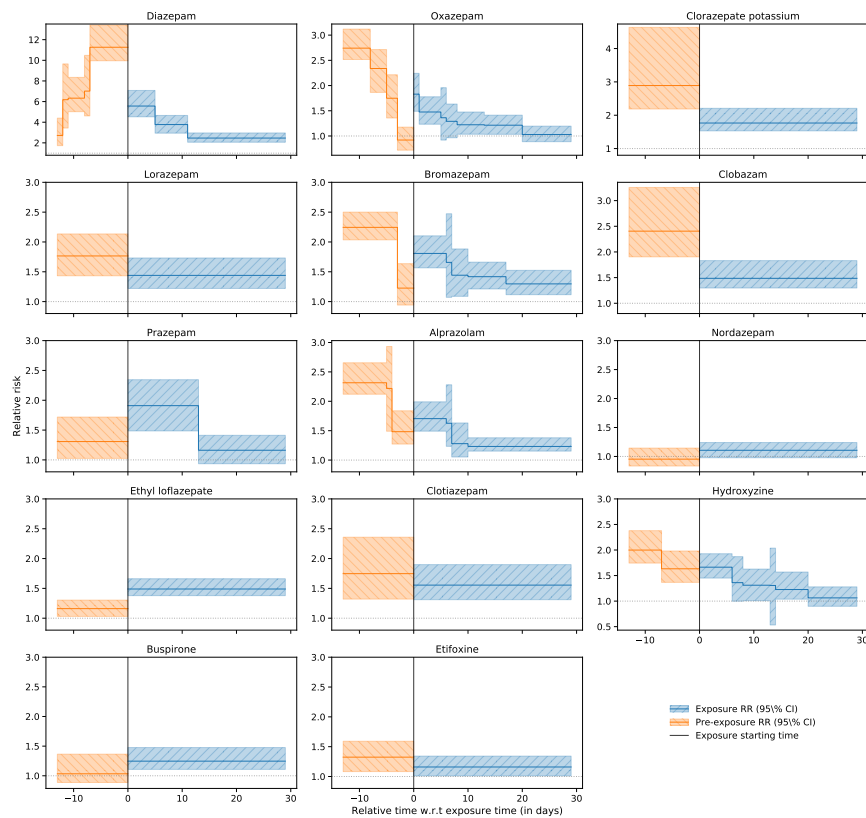


Fig. 17 Fracture relative risk curves estimated before and after anxiolytics exposure on 65 – 85 y.o. patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

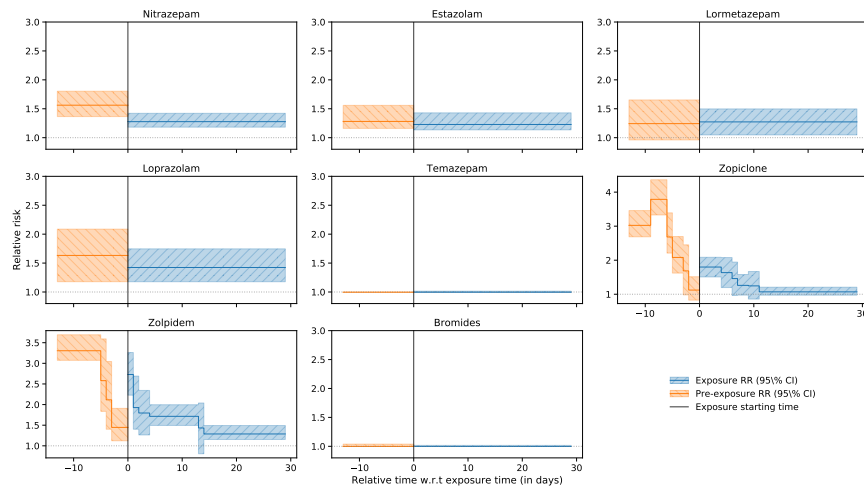


Fig. 18 Fracture relative risk curves estimated before and after hypnotics exposure on 65 – 85 y.o. patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).



Fig. 19 Fracture relative risk curves estimated before and after antidepressant exposure on 65 – 85 y.o. patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

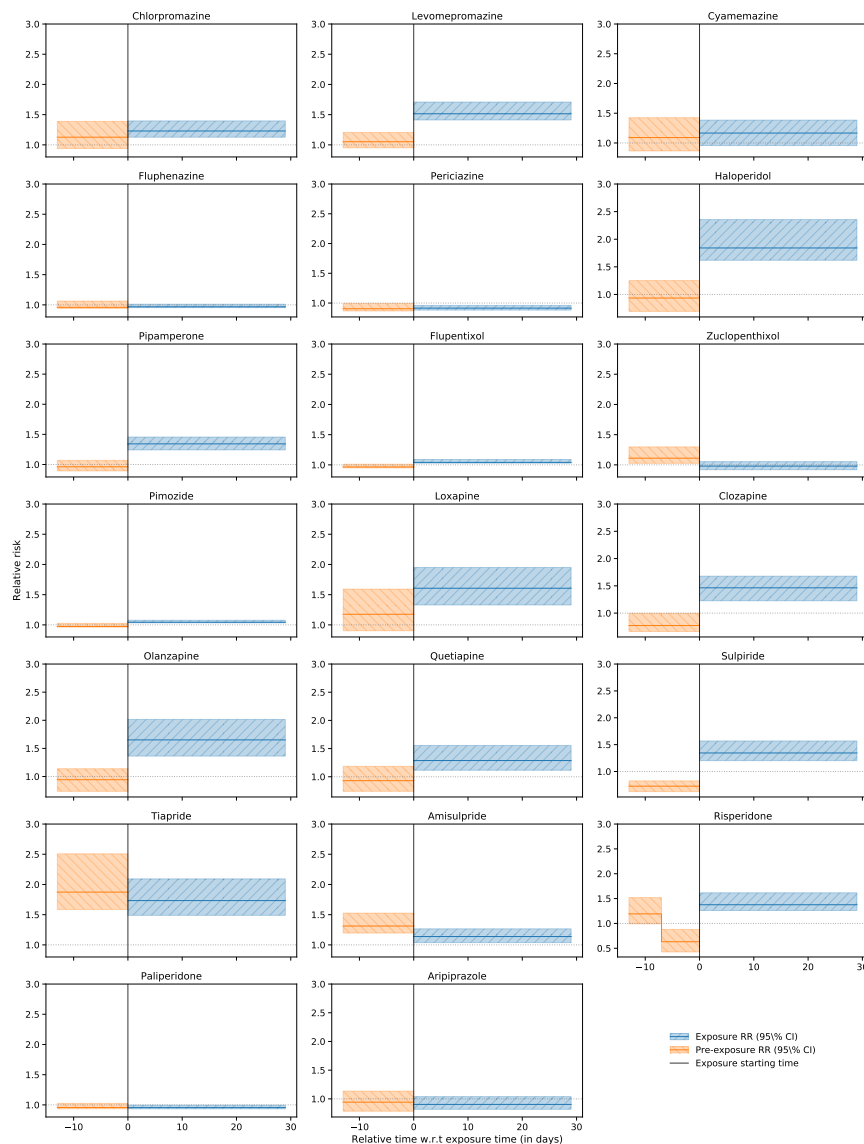


Fig. 20 Fracture relative risk curves estimated before and after neuroleptics exposure on 65 – 85 y.o. patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

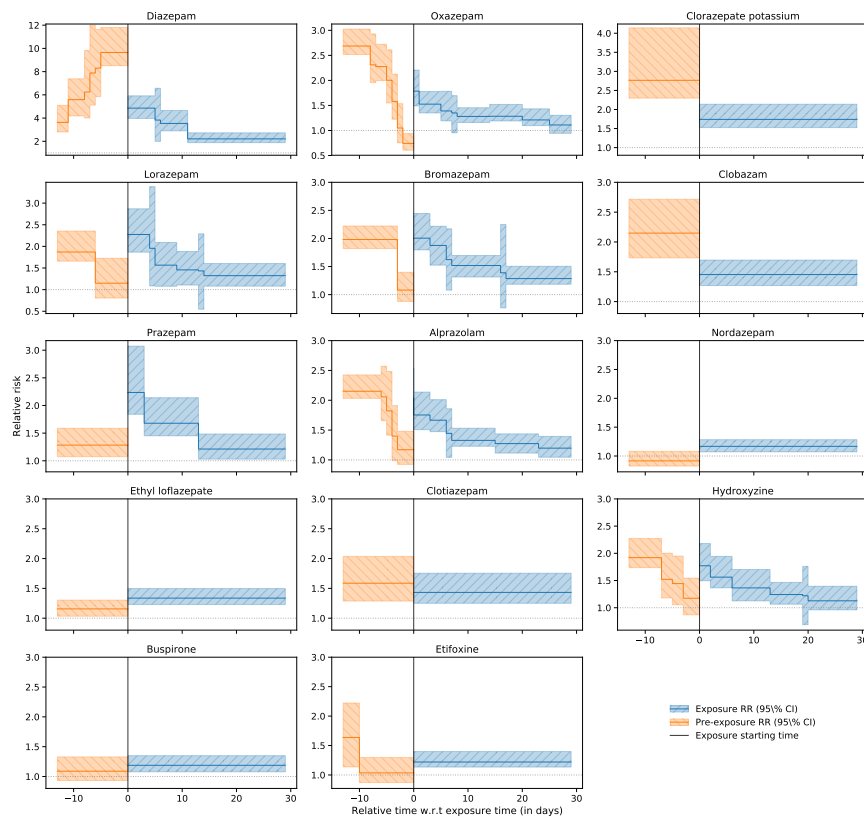


Fig. 21 Fracture relative risk curves estimated before and after anxiolytics exposure on non-epileptic patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

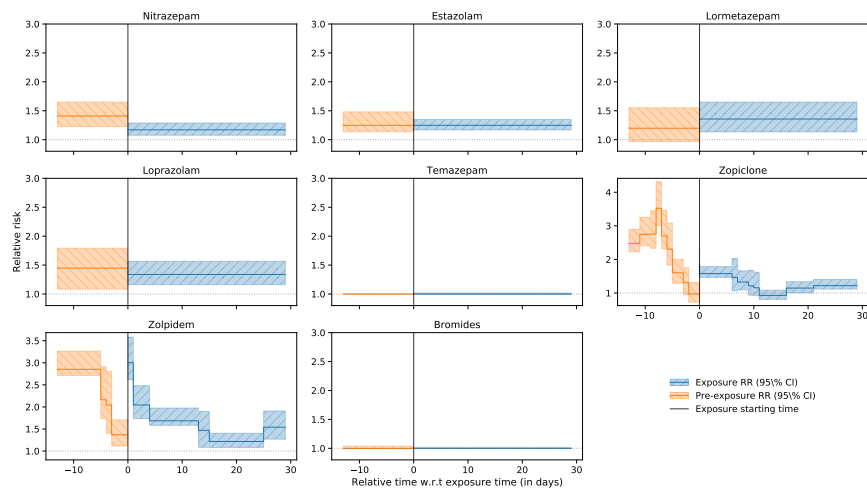


Fig. 22 Fracture relative risk curves estimated before and after hypnotics exposure on non-epileptic patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

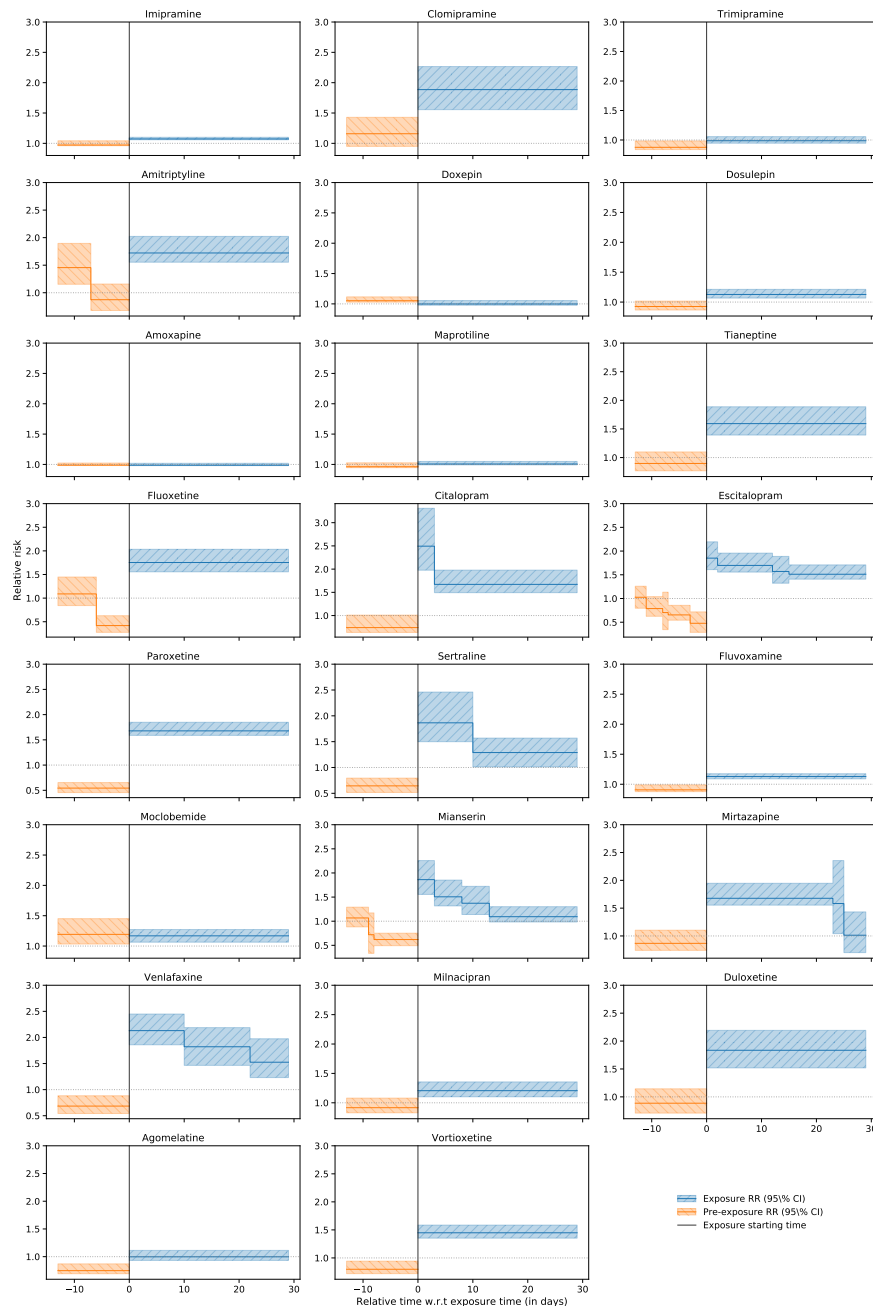


Fig. 23 Fracture relative risk curves estimated before and after antidepressant exposure on non-epileptic patients. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

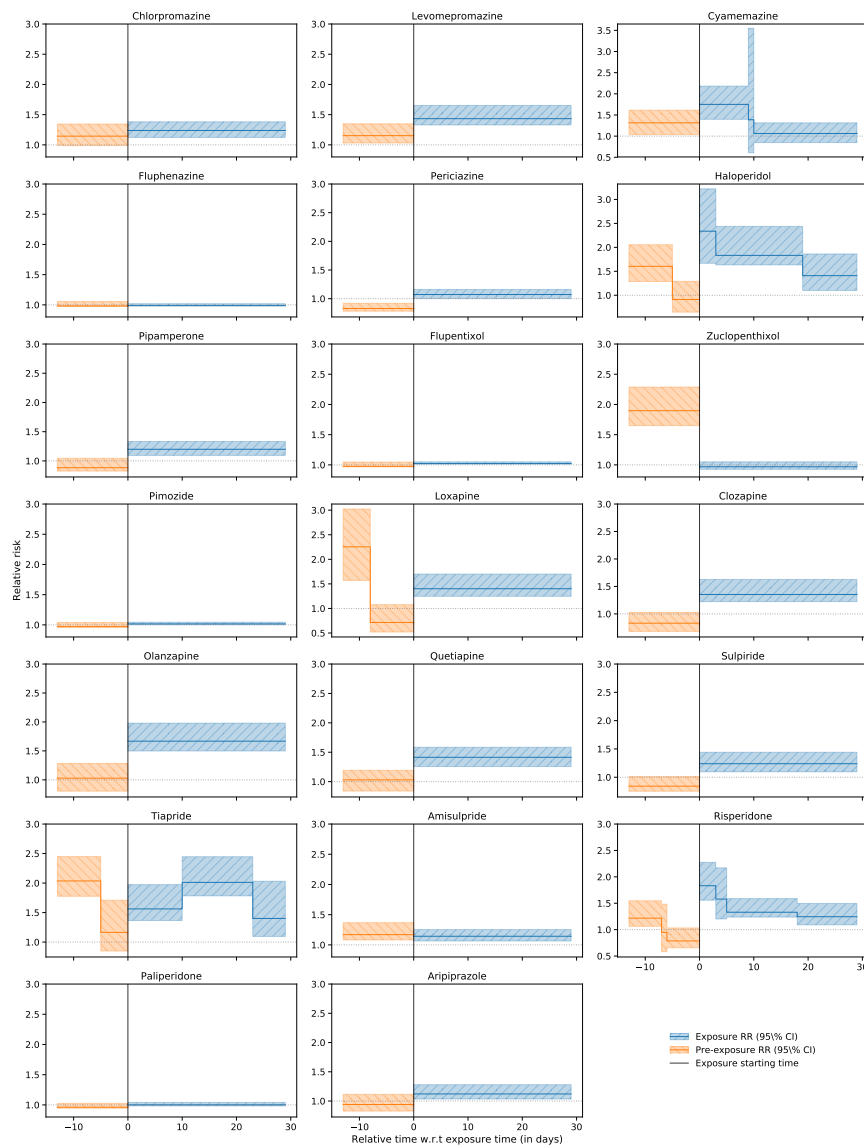


Fig. 24 Fracture relative risk curves estimated before and after neuroleptics exposure after epileptic patients exclusion. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

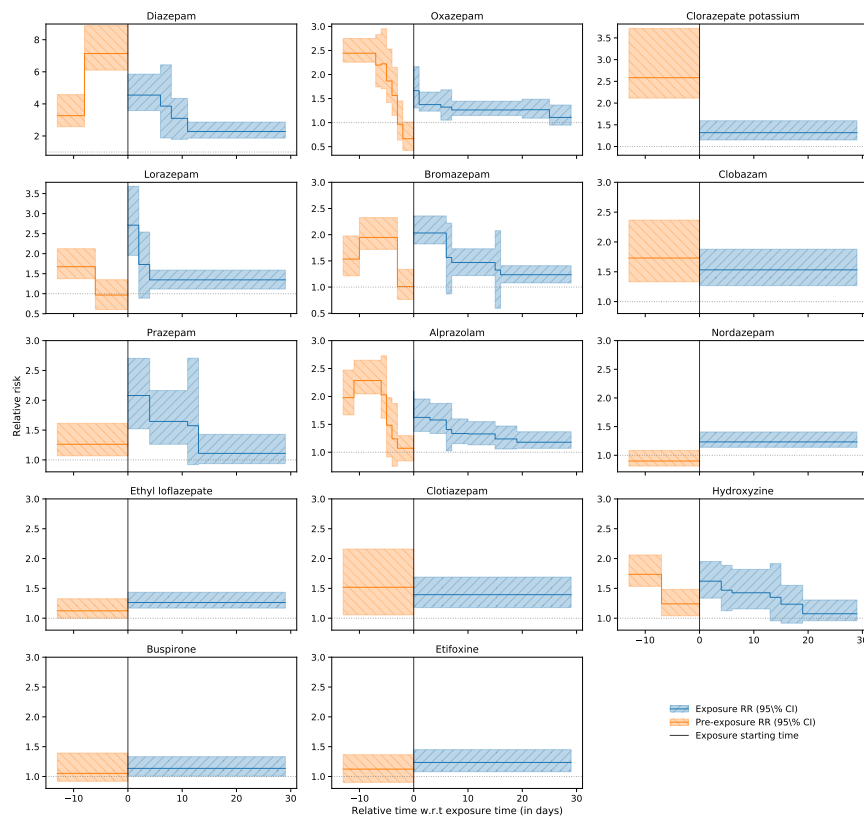


Fig. 25 Fracture relative risk curves estimated before and after anxiolytics exposure on women only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

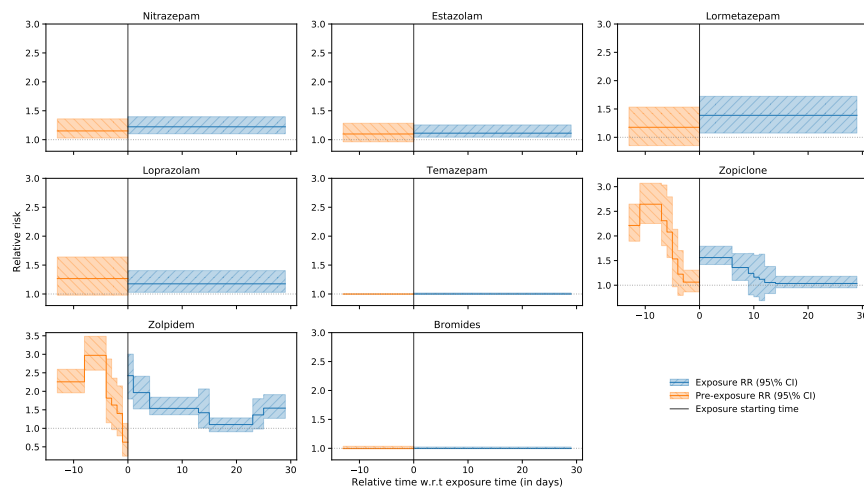


Fig. 26 Fracture relative risk curves estimated before and after hypnotics exposure on women only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

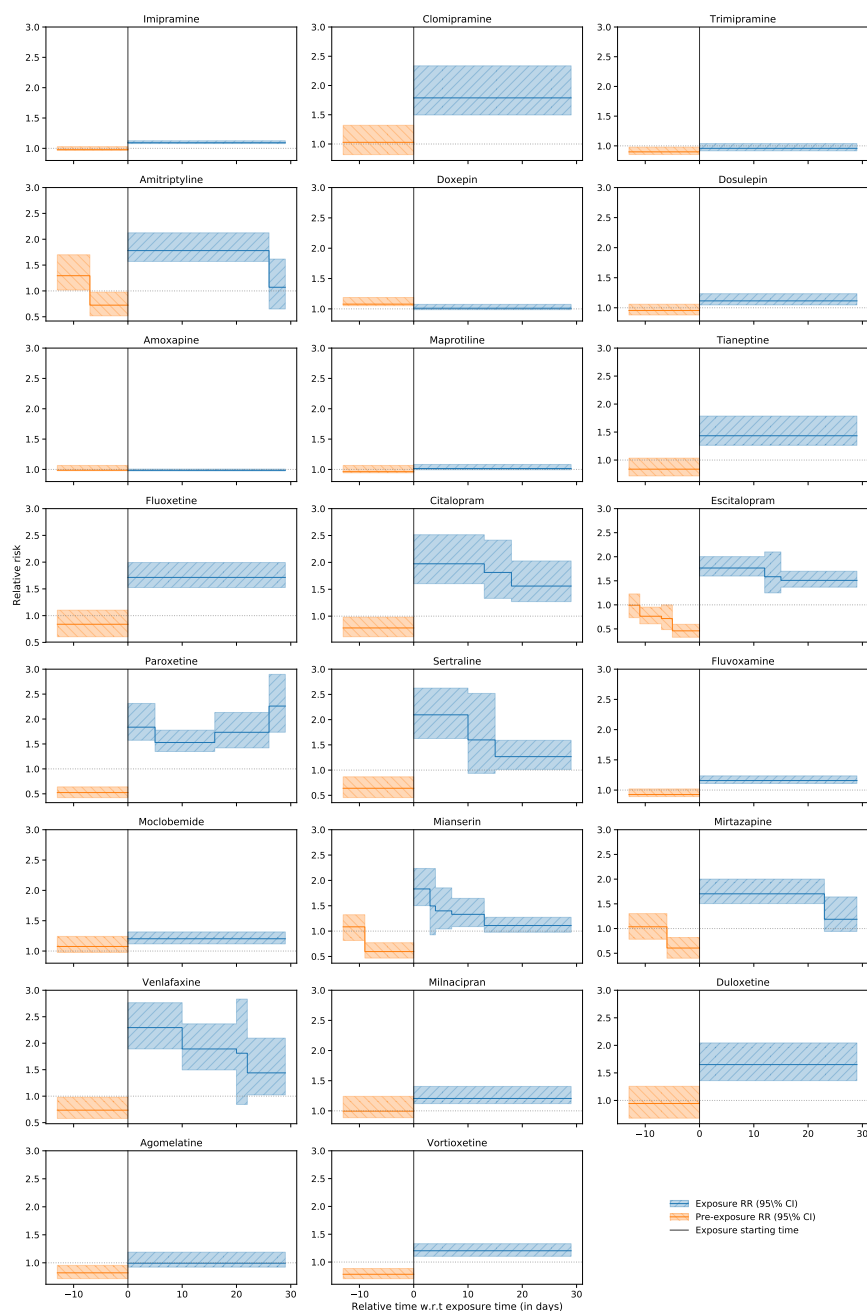


Fig. 27 Fracture relative risk curves estimated before and after antidepressant exposure on women only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

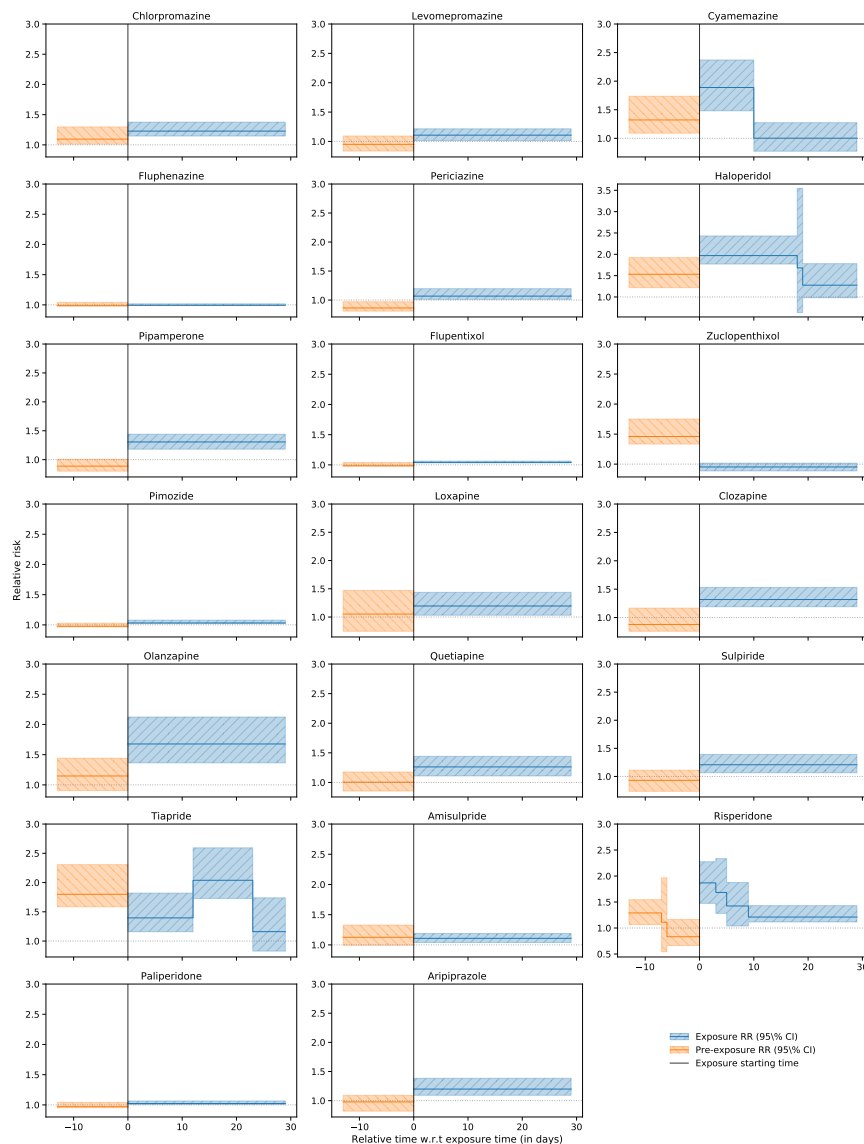


Fig. 28 Fracture relative risk curves estimated before and after neuroleptics exposure on women only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

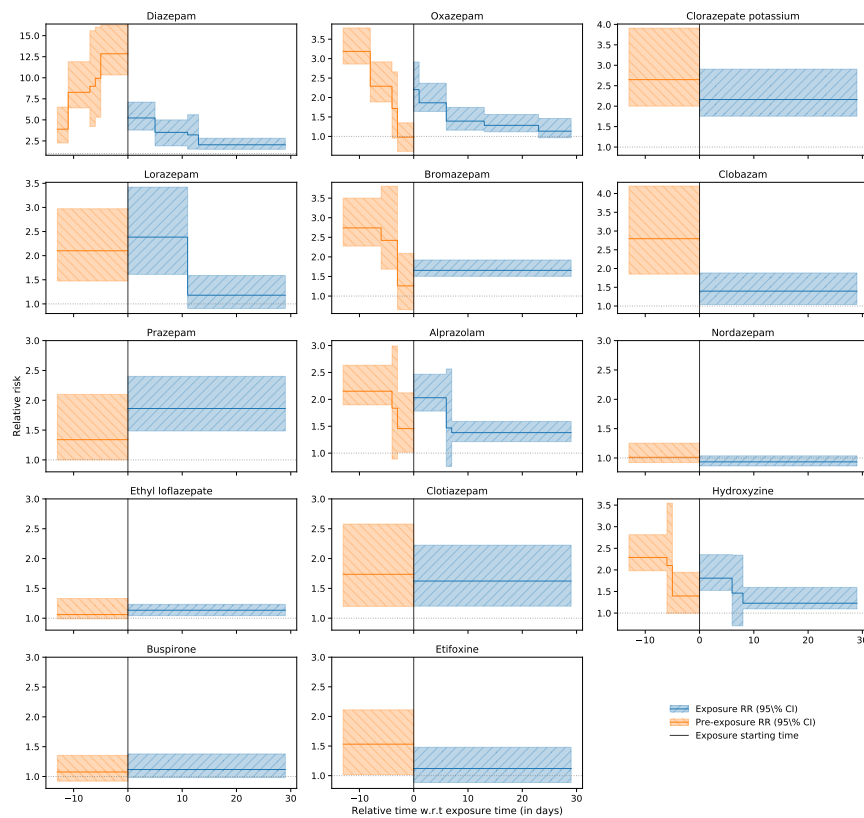


Fig. 29 Fracture relative risk curves estimated before and after anxiolytics exposure on men only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

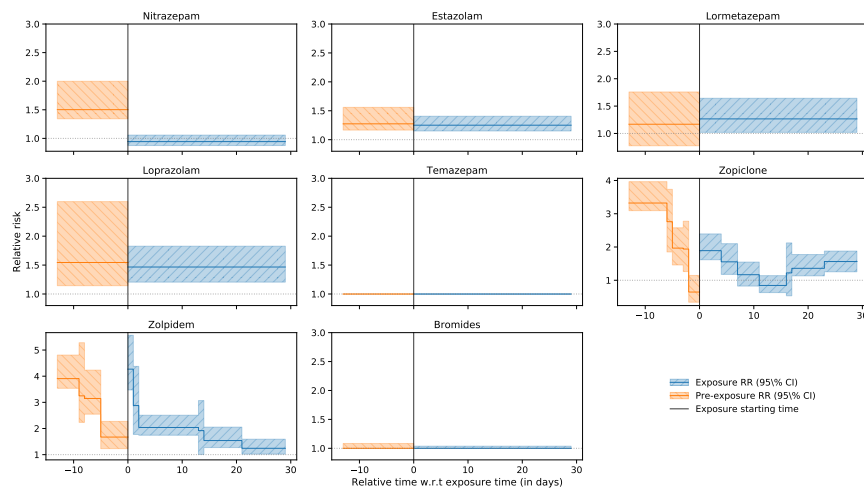


Fig. 30 Fracture relative risk curves estimated before and after hypnotics exposure on men only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).



Fig. 31 Fracture relative risk curves estimated before and after antidepressants exposure on men only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

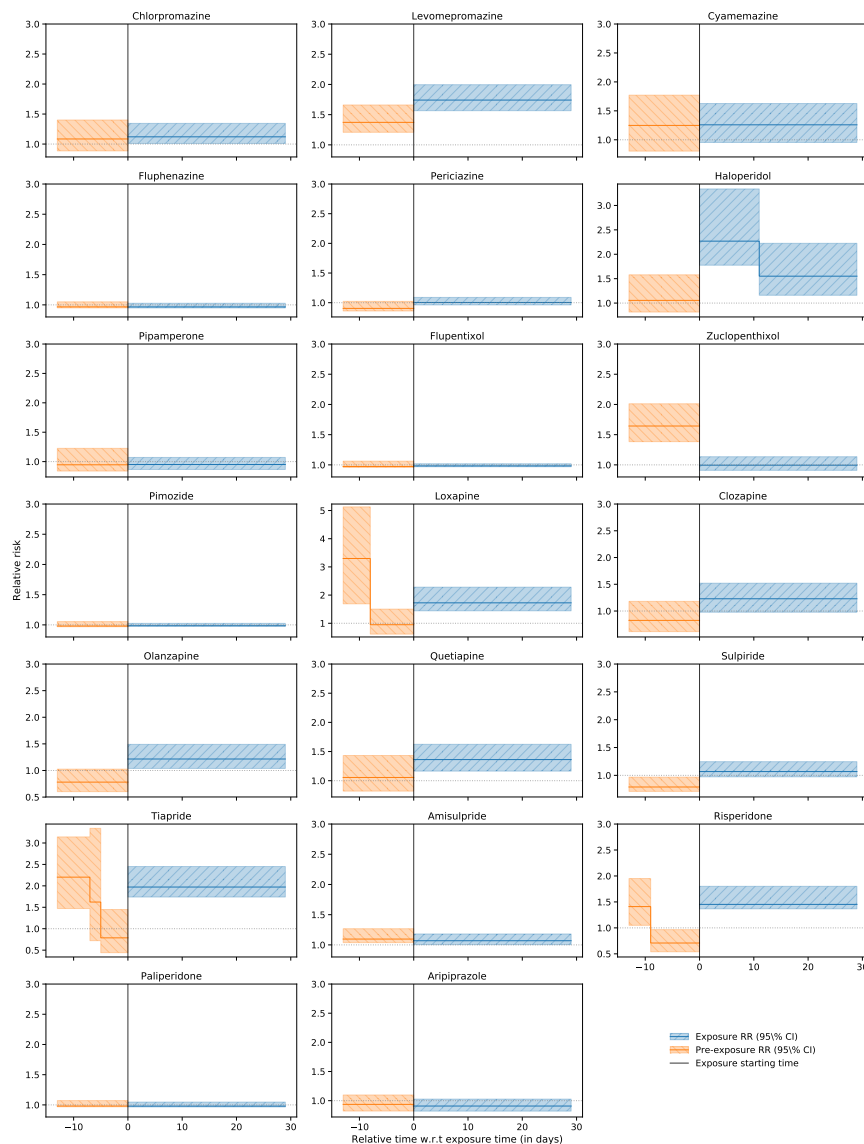


Fig. 32 Fracture relative risk curves estimated before and after neuroleptics exposure on men only. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

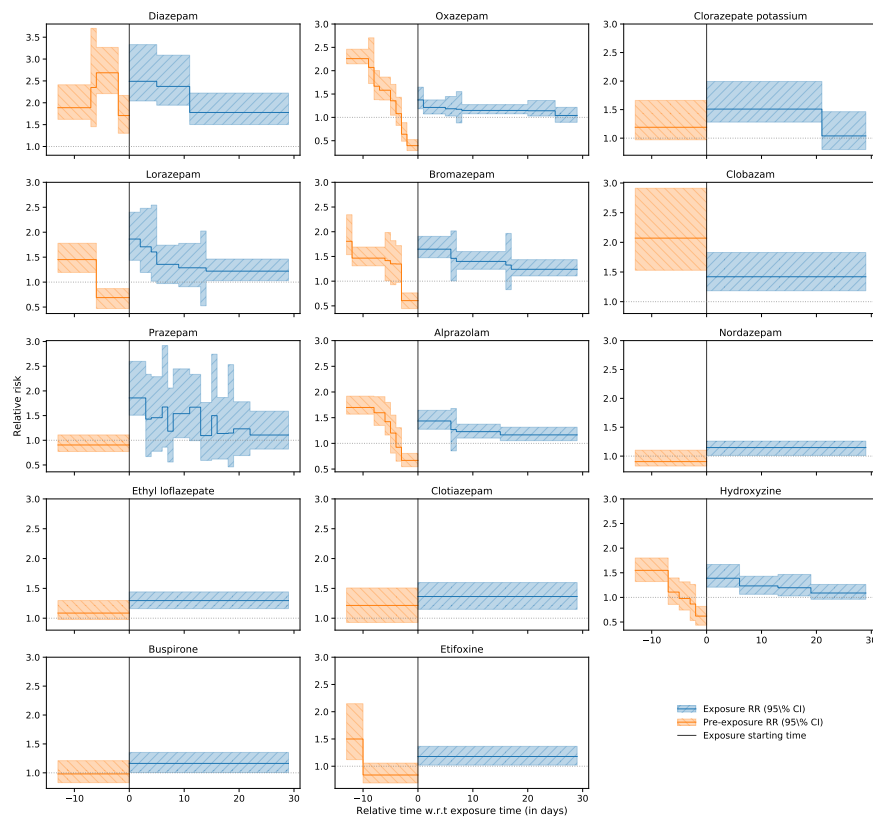


Fig. 33 Fracture relative risk curves estimated before and after anxiolytics exposure when adding additional drugs as control variables. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

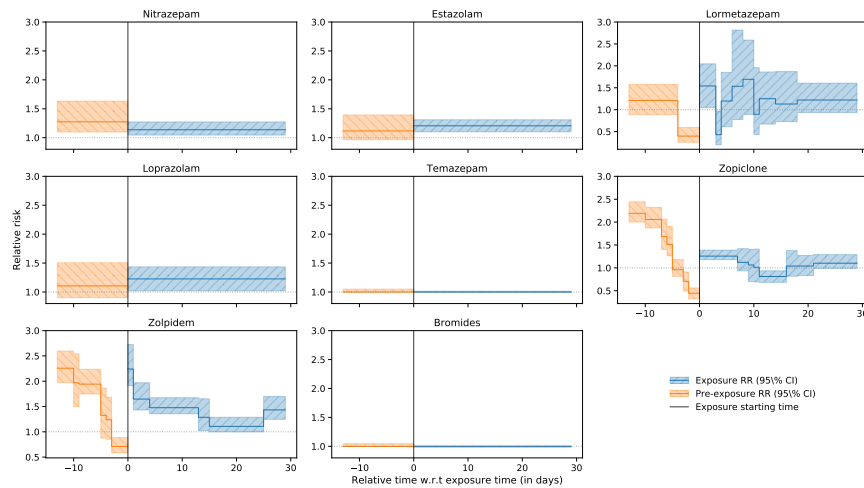


Fig. 34 Fracture relative risk curves estimated before and after hypnotics exposure when adding additional drugs as control variables. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

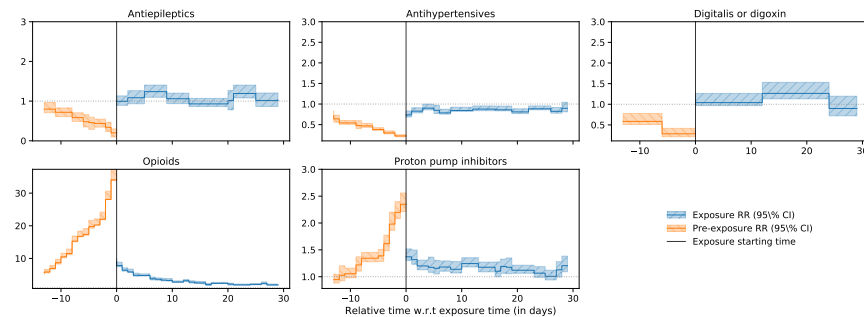


Fig. 35 Fracture relative risk curves estimated before and after exposure to control drugs when adding additional drugs as control variables. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

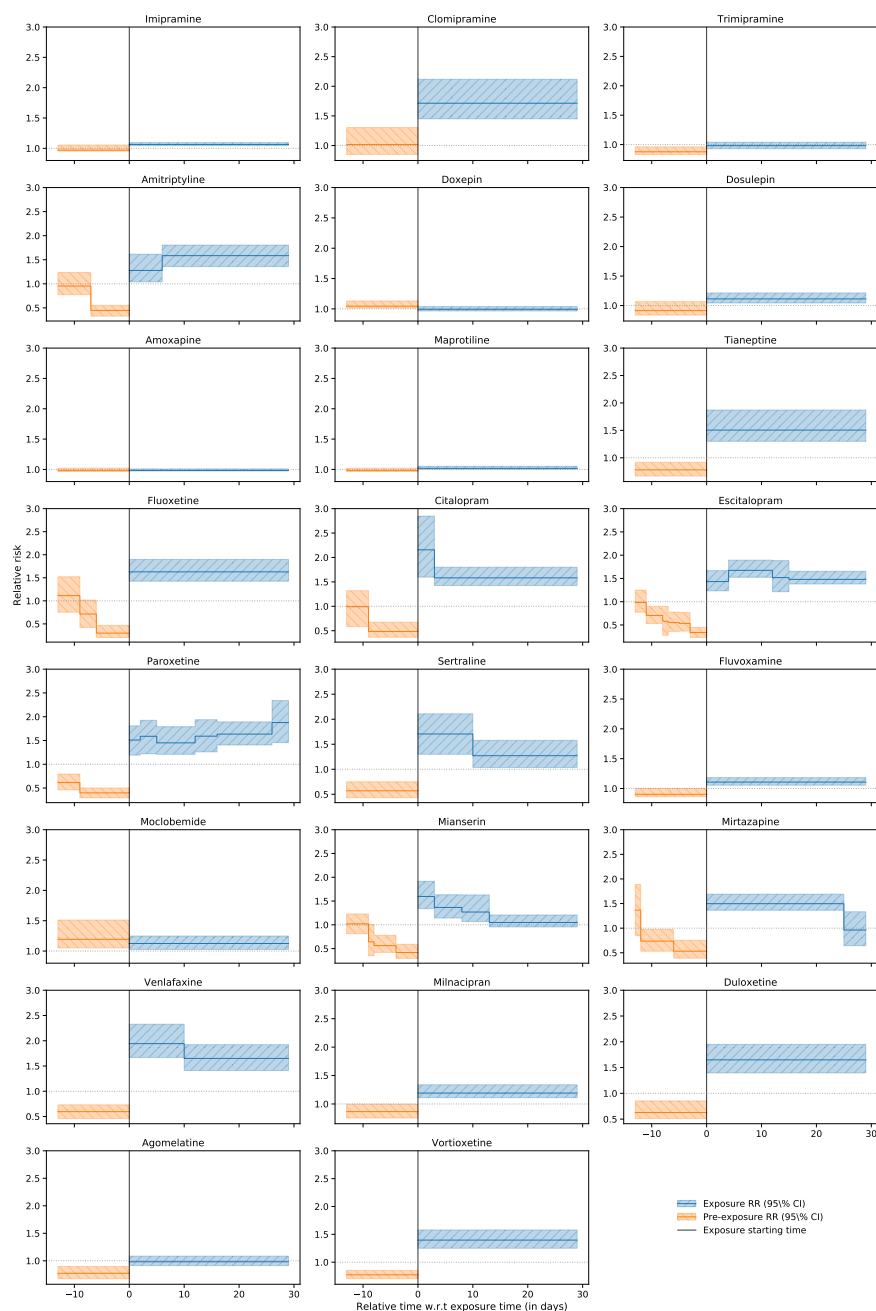


Fig. 36 Fracture relative risk curves estimated before and after antidepressant exposure when adding additional drugs as control variables. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

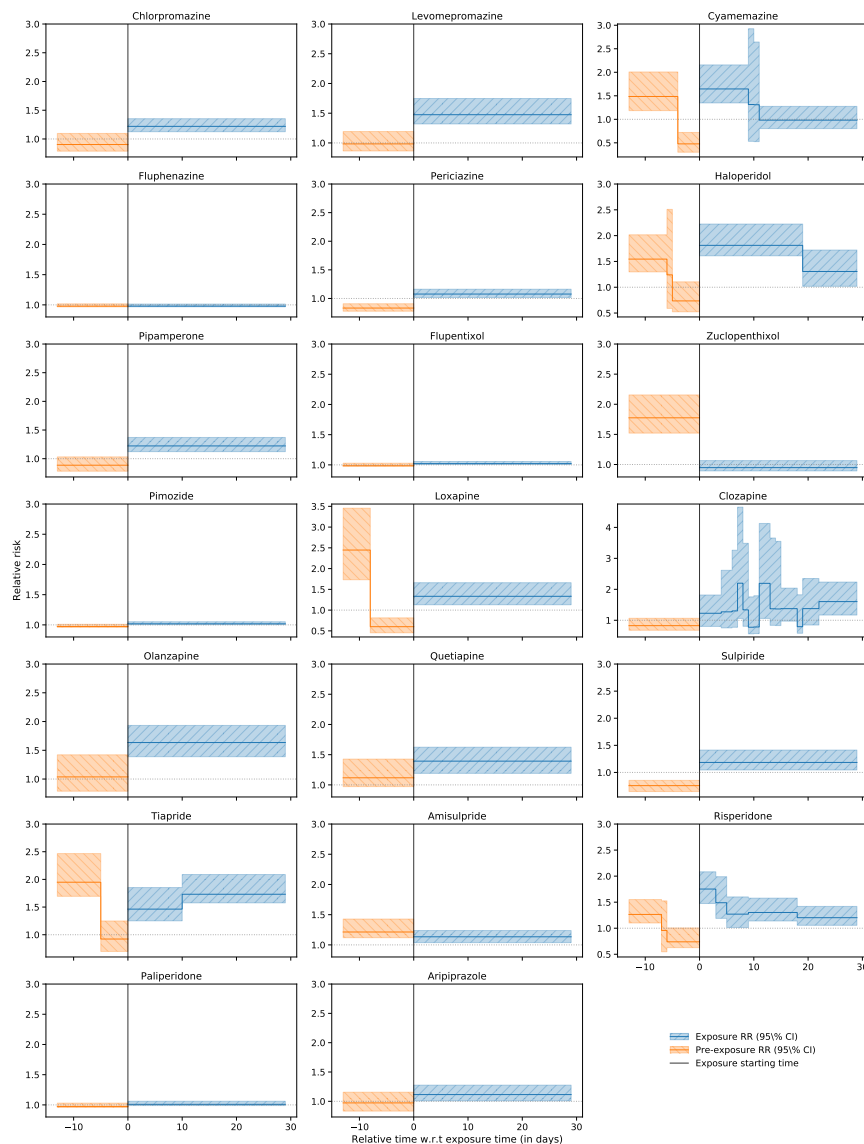


Fig. 37 Fracture relative risk curves estimated before and after neuroleptics exposure when adding additional drugs as control variables. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

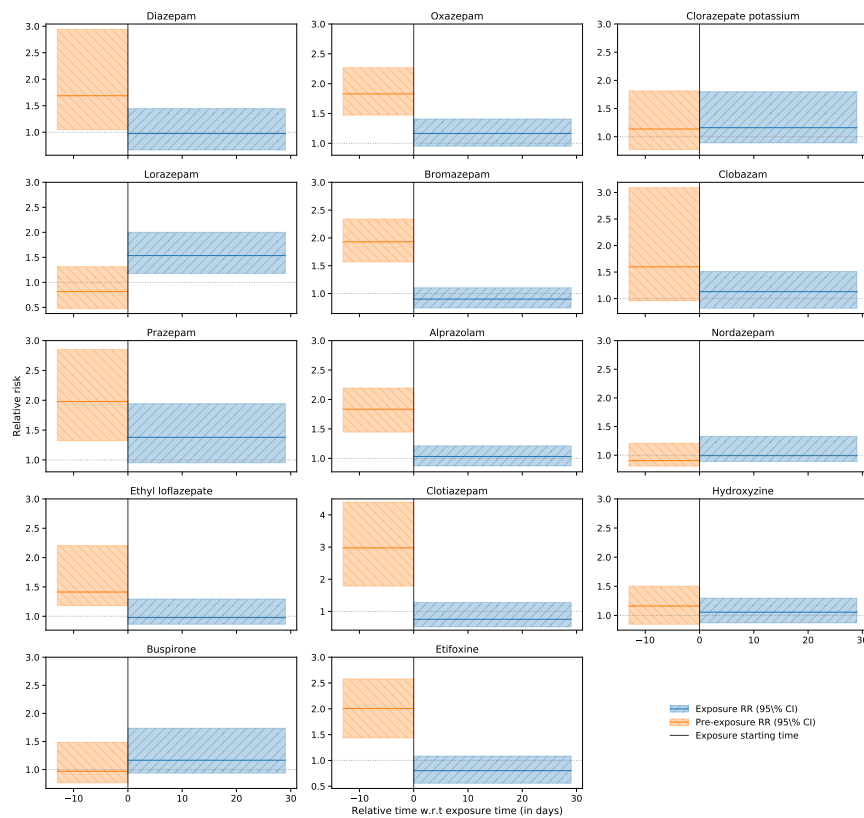


Fig. 38 Non-hospitalised fracture relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

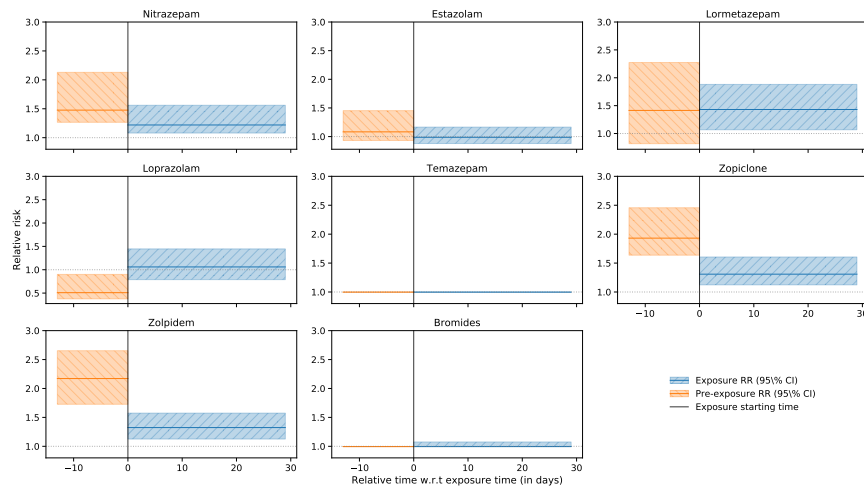


Fig. 39 Non-hospitalised fracture relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).



Fig. 40 Non-hospitalised fracture relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

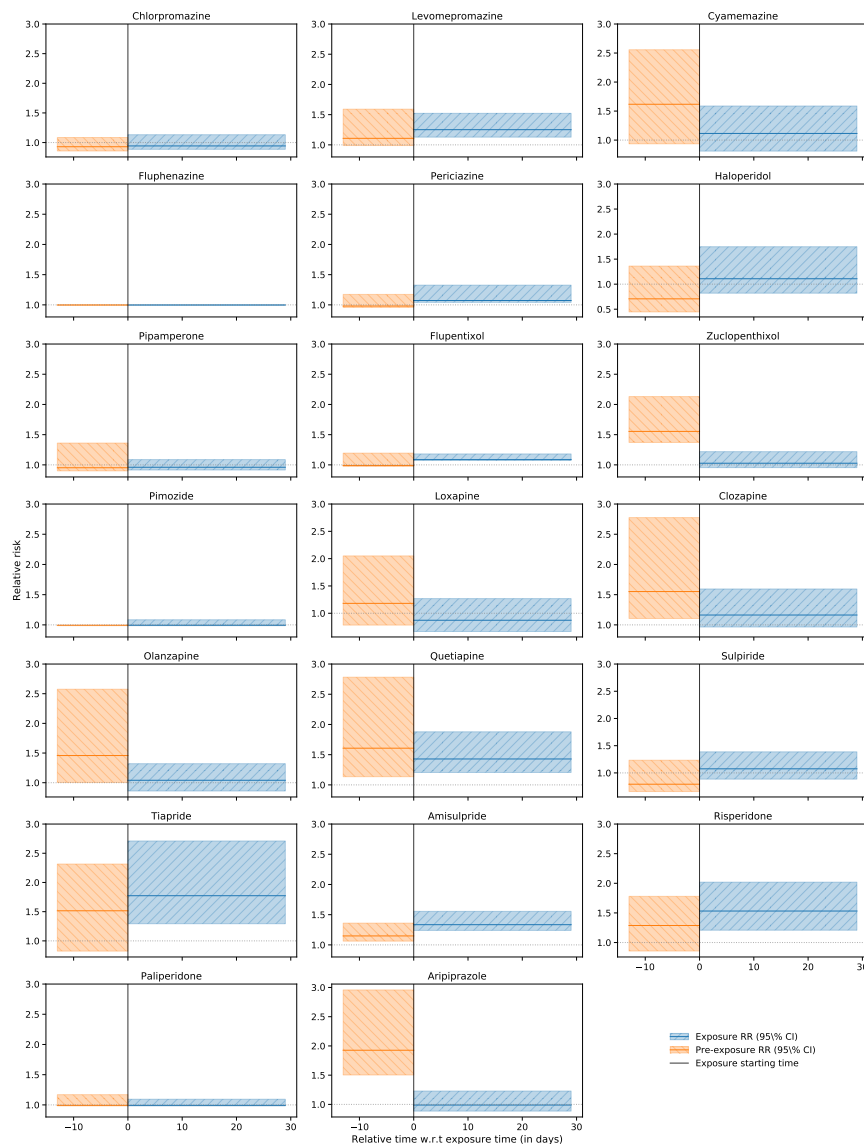


Fig. 41 Non-hospitalised fracture relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

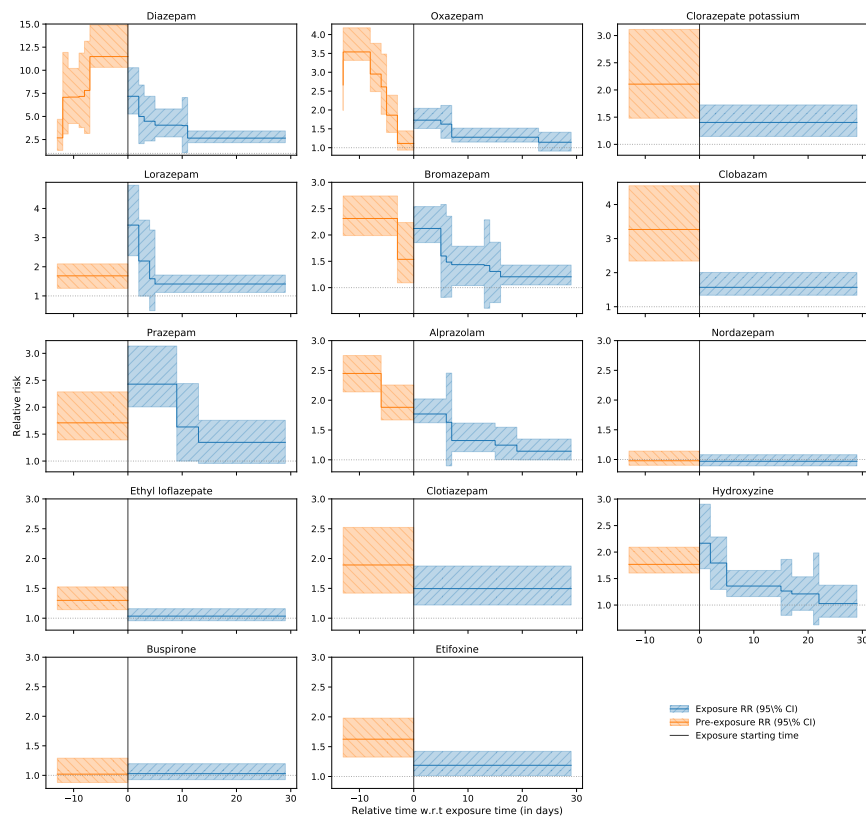


Fig. 42 Fracture without surgery relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

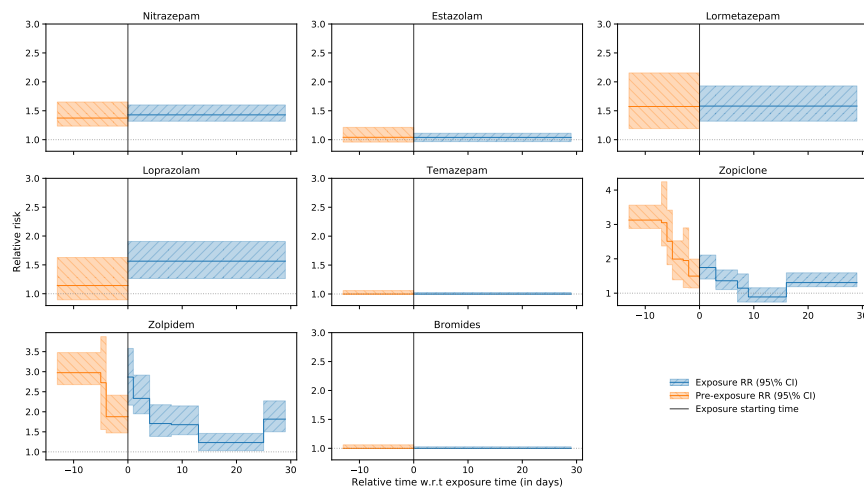


Fig. 43 Fracture without surgery relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).



Fig. 44 Fracture without surgery relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

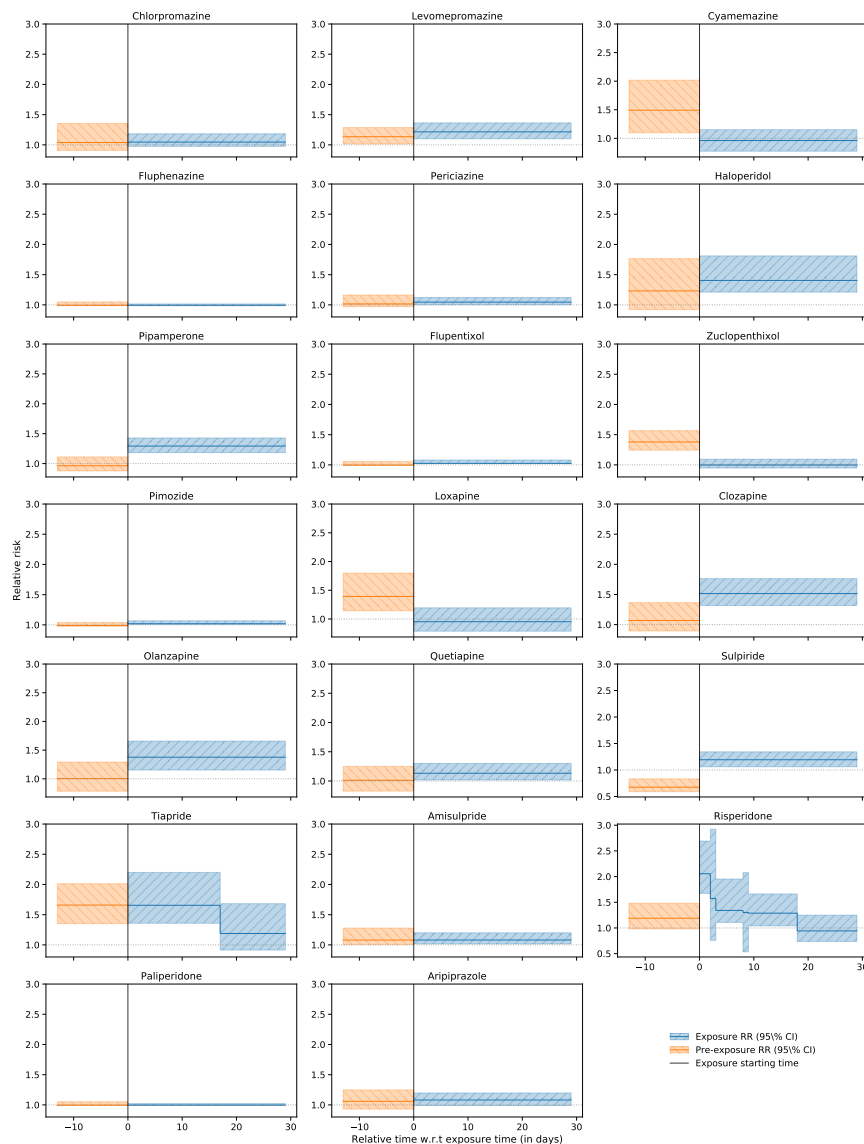


Fig. 45 Fracture without surgery relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

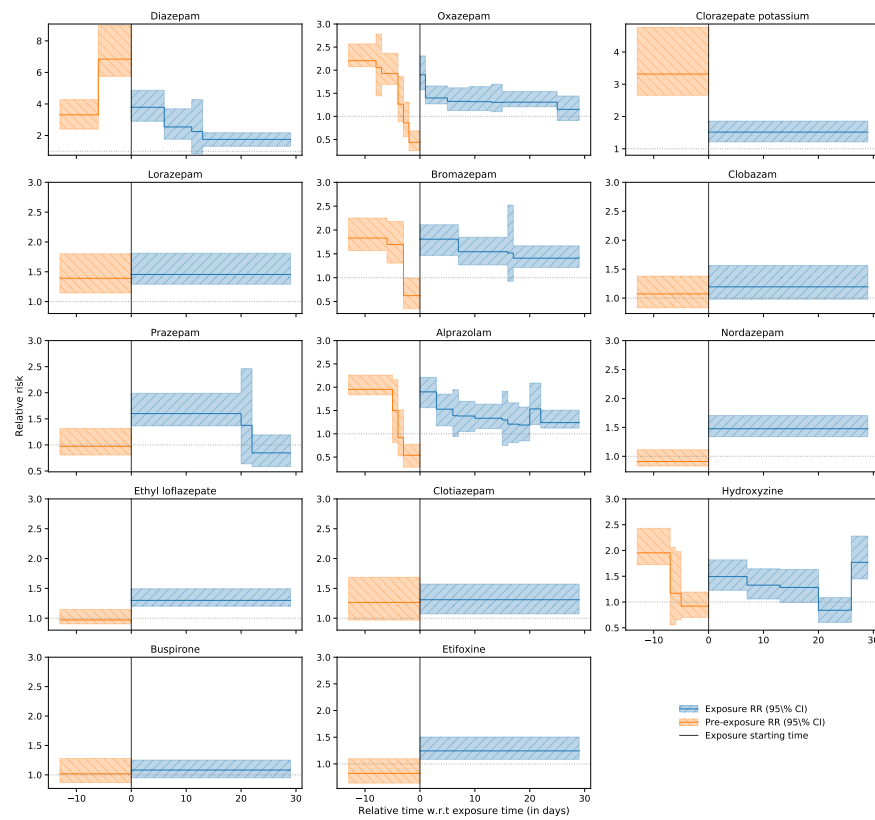


Fig. 46 Fracture relative risk curves estimated before and after anxiolytics exposure after epileptic patients exclusion. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

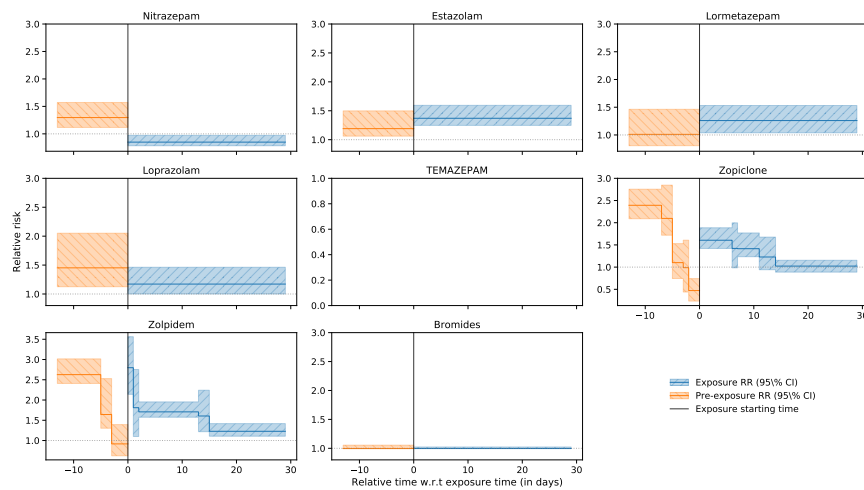


Fig. 47 Fracture requiring surgery relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).



Fig. 48 Fracture requiring surgery relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

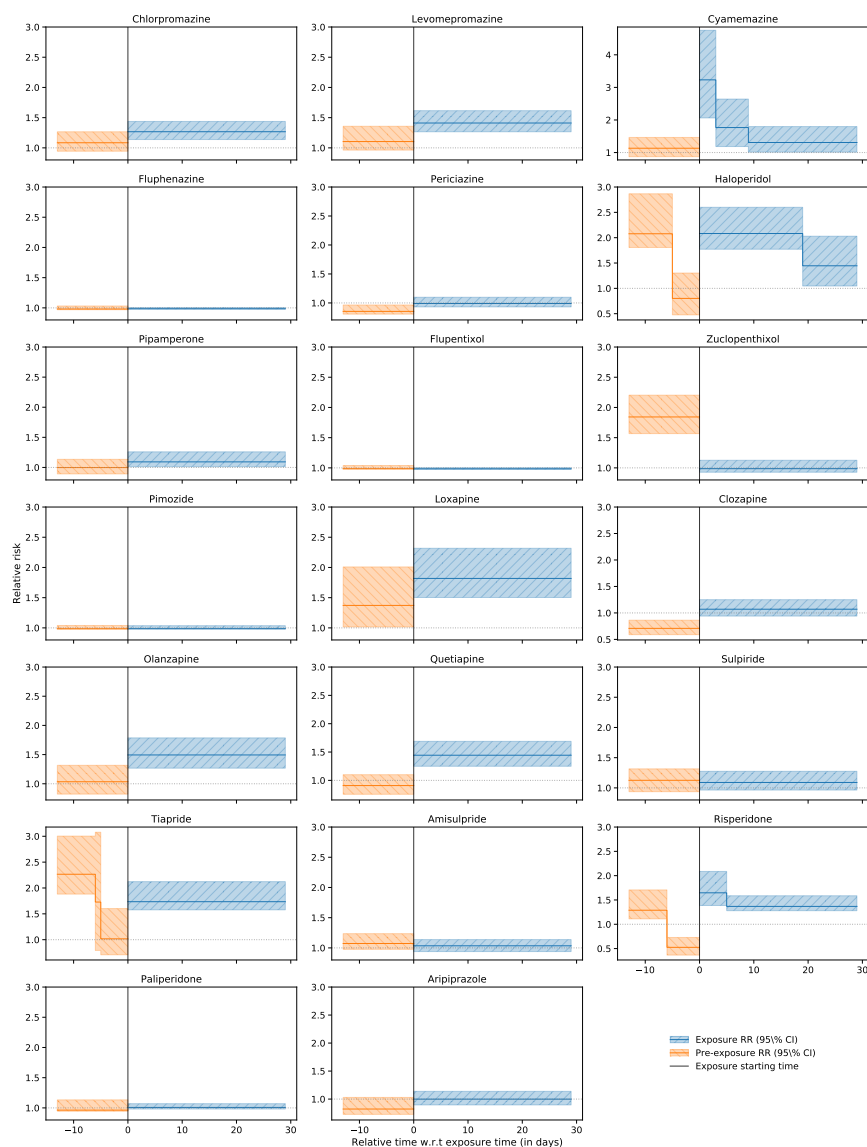


Fig. 49 Fracture requiring surgery relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

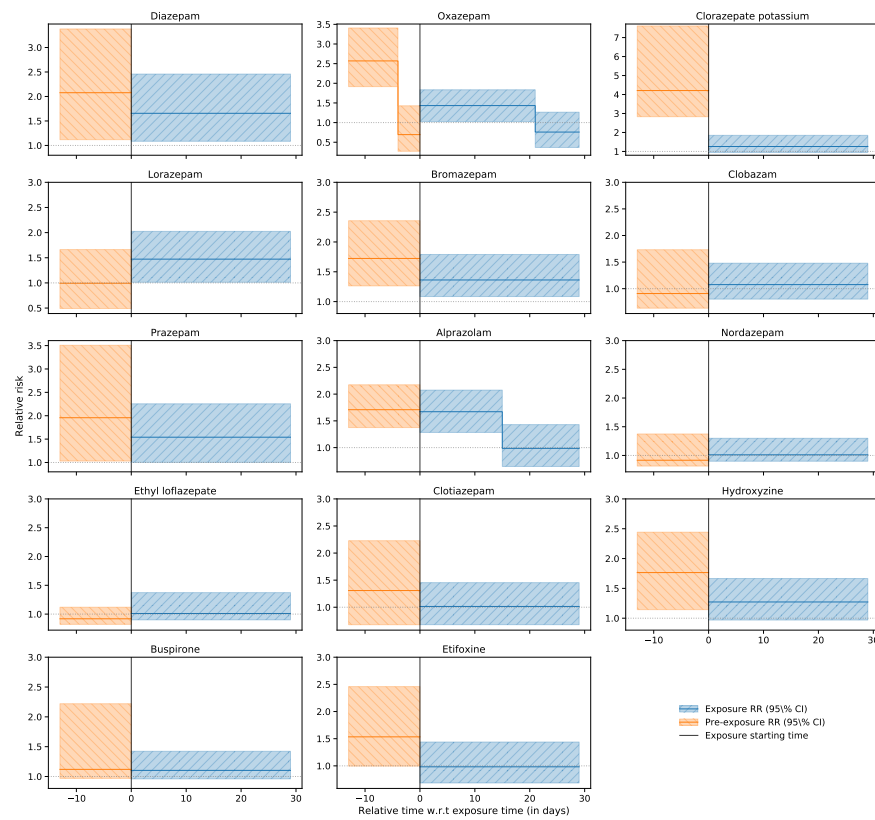


Fig. 50 Wrist fracture relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

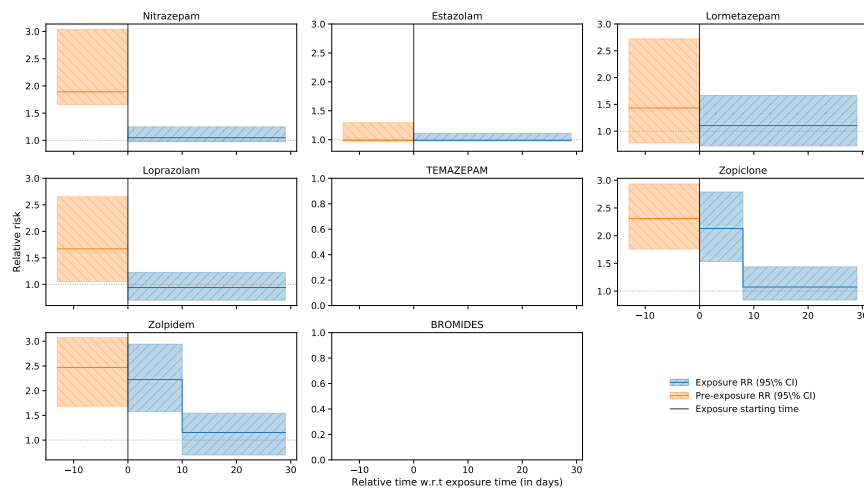


Fig. 51 Wrist fracture relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

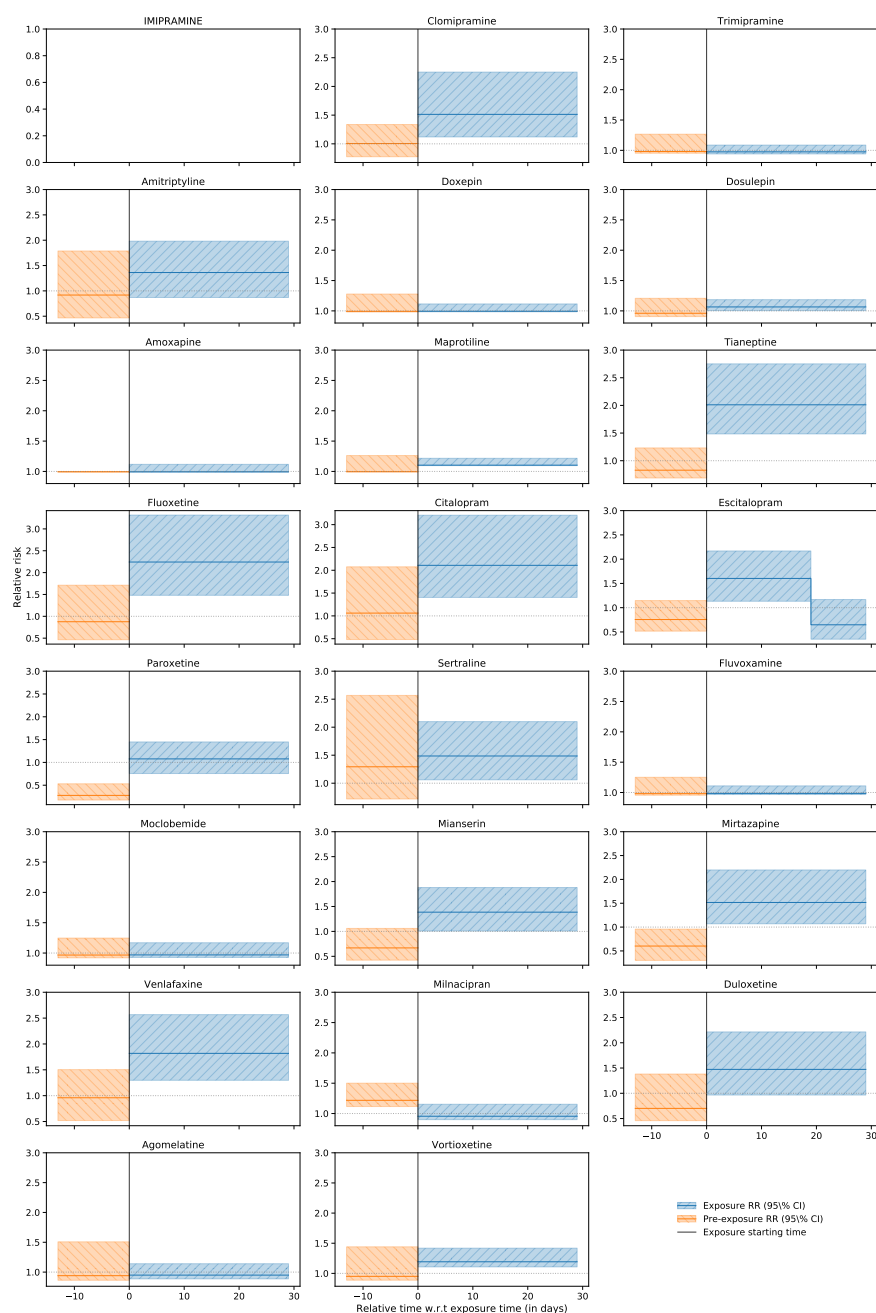


Fig. 52 Wrist fracture relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

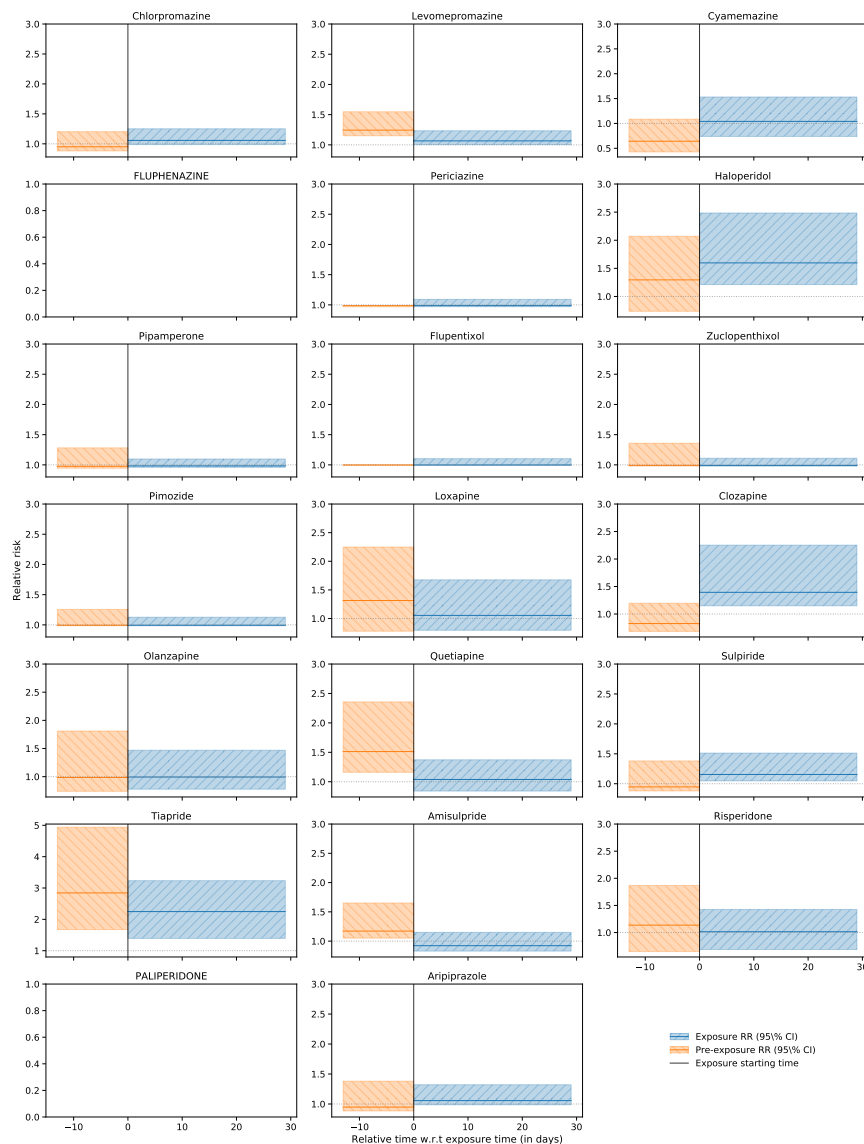


Fig. 53 Wrist fracture relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

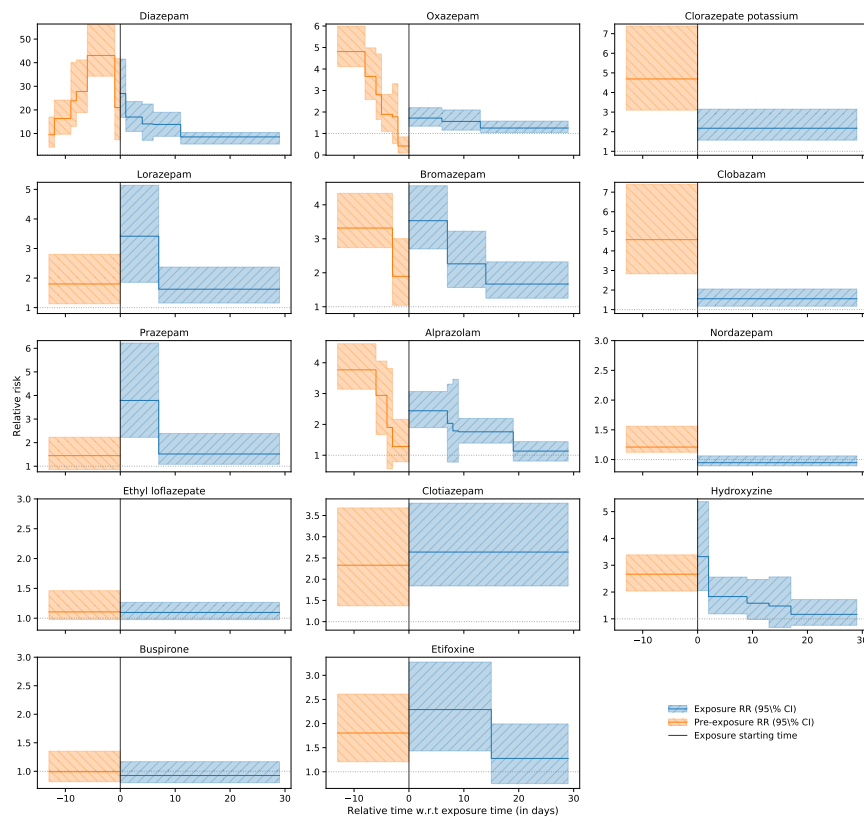


Fig. 54 Spine fracture relative risk curves estimated before and after anxiolytics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

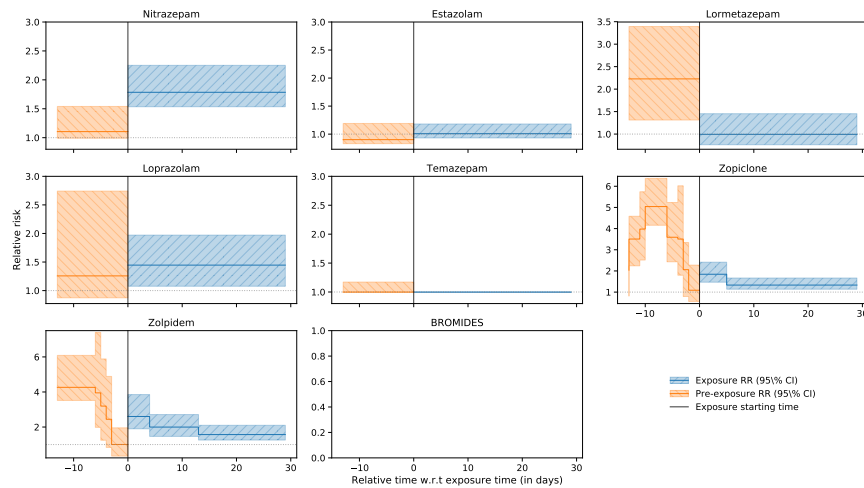


Fig. 55 Spine fracture relative risk curves estimated before and after hypnotics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

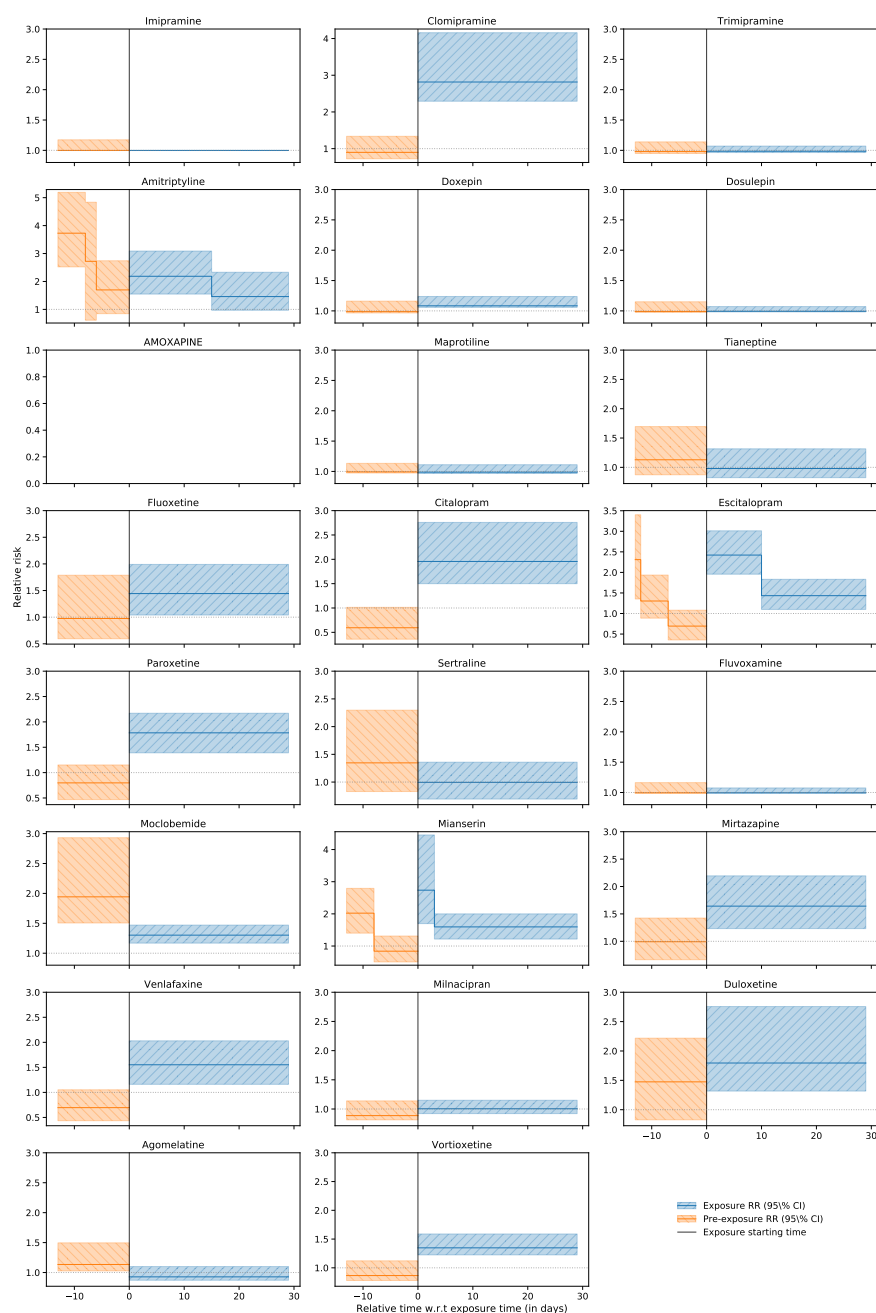


Fig. 56 Spine fracture relative risk curves estimated before and after antidepressant exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched). Molecules considered in the three first rows are tricyclic antidepressants, followed by selective serotonin reuptake inhibitors in rows 4 and 5, and serotonin-norepinephrine reuptake inhibitor row 7.

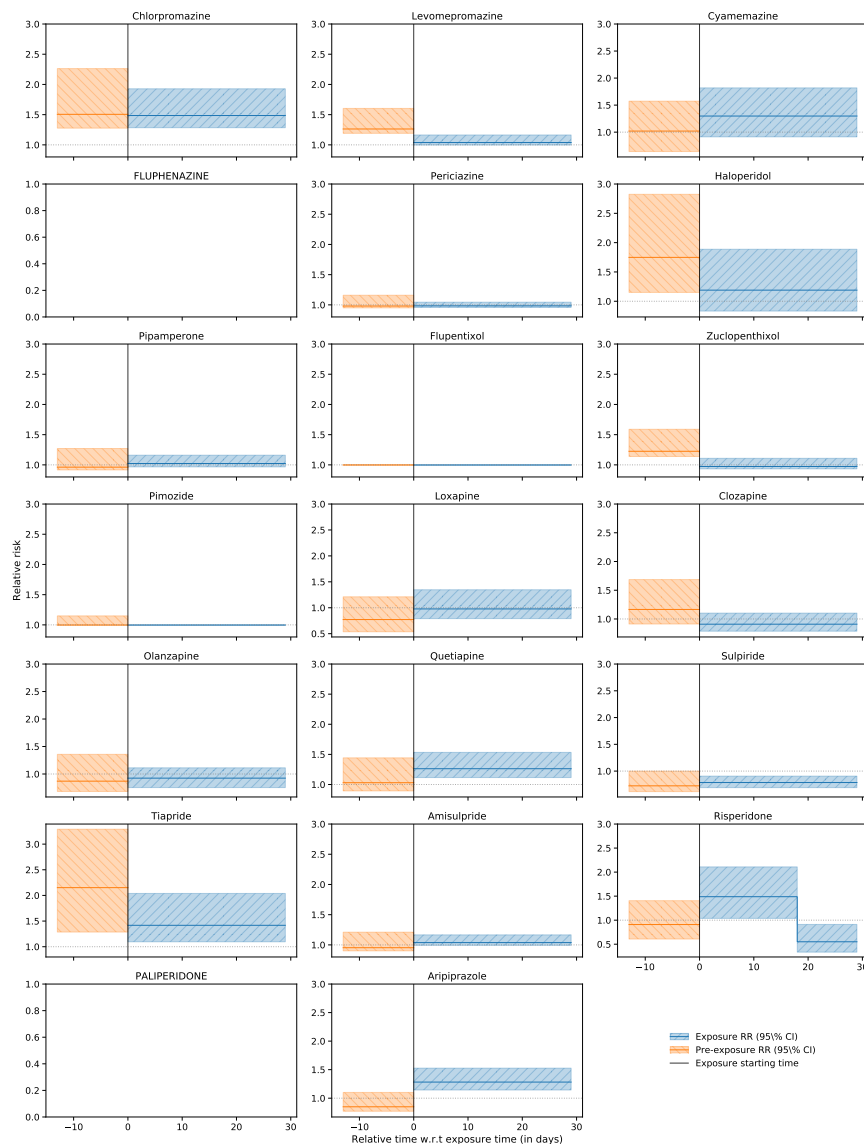


Fig. 57 Spine fracture relative risk curves estimated before and after neuroleptics exposure. Exposure time is represented by the vertical black bar at $x = 0$. Post-exposure (resp. pre-exposure) relative risk is represented in blue (resp. orange) solid lines, with 95% Confidence Intervals (CI) depicted in blue right hatched bands (resp. orange left hatched).

C SCCS assumption assessment

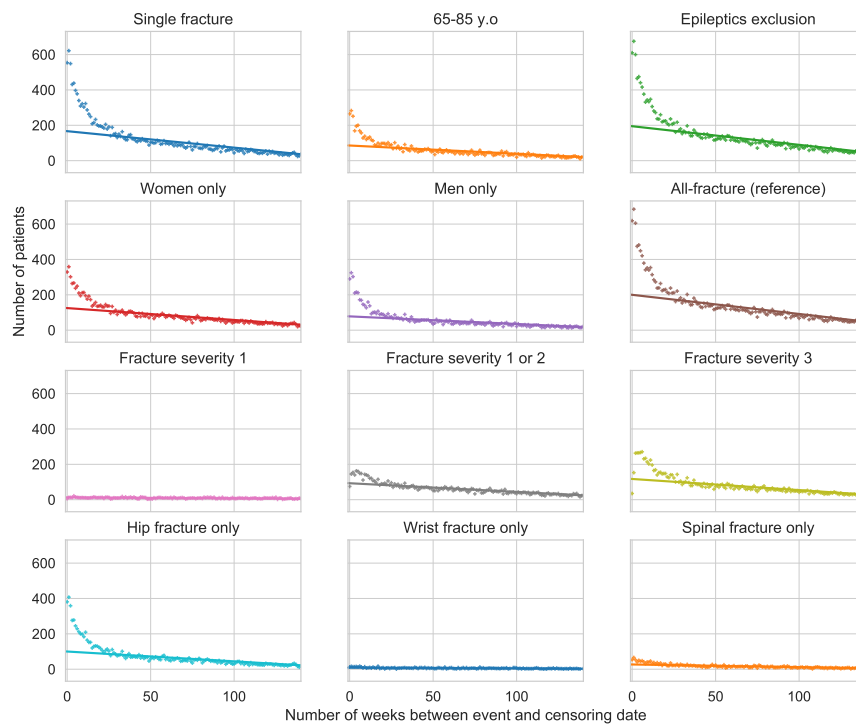


Fig. 58 Robust regression (Huber) of censoring times versus event times. The horizontal axis represents the number of weeks between event date and censoring date, and the vertical axis the corresponding number of patients. Markers represent the patient counts corresponding to each week bucket, and the solid line represents the robust regression line. The closer the points are to the regression lines, the more likely the assumption of independence between event dates and observation dates is. Patients above the regression line are susceptible to have a death event correlated with a fracture event. In the all-fracture (reference) study featured in this paper, 9300 patients (7.35%) death event might be considered to be correlated to their fracture times. Note that the negative gradient of the regression line is explained by the events repartition in the study: if events are assumed to be uniformly distributed across the four years, there are fewer chances to observe events separated by 200 weeks than 25 weeks.