# IMPACT OF PRE-EXPOSURE TIME BIAS IN SELF-CONTROLLED CASE SERIES WHEN THE EVENT CONDITIONS THE EXPOSURE: HIP FEMUR FRACTURE AND USE OF BENZODIAZEPINES AS A CASE STUDY.

Running Title: Pre-exposure time bias in self-controlled case series

**Authors**: *Gema Requena[1], Ian J Douglas[2], Consuelo Huerta[3], and Francisco de Abajo[1,4].*

**Affiliation:**

1. Department of Biomedical Sciences (Pharmacology), School of Medicine, University of Alcalá (IRYCIS), Madrid, Spain (*)
2. London School of Hygiene and Tropical Medicine (LSHTM), London, UK
3. Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Agency of Medicines and Medical Devices, Madrid, Spain
4. Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain

(*) G Requena was a researcher from the University of Alcalá (Madrid, Spain) when this study was performed, now is an employee of GSK (London, UK).

**Author for correspondence:**
Francisco de Abajo
Facultad de Medicina y Ciencias de la Salud
Universidad de Alcalá Ctra. Madrid-Barcelona, km 33.2
28871 Alcalá de Henares Madrid, Spain
E-mail: francisco.abajo@uah.es

**Key words**: Self-controlled case series; benzodiazepines; hip fractures; methods; pre-exposure time; bias.

**Key points**:

1- The self-controlled case series (SCCS) design is increasingly used in pharmacoepidemiology, but it is important to check its assumptions in order to avoid biased estimates.

2- In the SCCS a large bias can be introduced when the assumption that the event does not alter the probability of subsequent exposure is not met.

3- When the event may condition the exposure it is necessary to compute the relative risk excluding a pre-exposure time from the reference category.

4- Hip fractures and use of benzodiazepines have a temporally limited bidirectional causal relationship and we used this case study to assess the magnitude of bias introduced in a SCCS and explore ways to correct it.

5- Implications of this finding are critical, because it reveals dependence between the exposure and the event which provokes an important bias towards the null when this is not taken into account.

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**ABSTRACT (249/250)**

***Background:*** In self-controlled case series (SCCS) the event should not condition the probability of subsequent exposure. If this assumption is not met, an important bias could take place. The association of hip/femur fracture (HFF) and use of benzodiazepines (BDZ) has a bidirectional causal relationship and can serve as case study to investigate the impact of this methodological issue.

***Objectives:*** To assess the magnitude of bias introduced in a SCCS when HFF conditions the posterior exposure to BDZ and explore ways to correct it.

***Methods***: 4,450 cases of HFF who had at least one BZD prescription were selected from the primary care health record database BIFAP. Exposure to BZD was divided into non-use, current, recent and past use. Conditional Poisson regression was used to estimate incidence rate ratios (IRR) of HFF among current vs. non-use/past, adjusted for age. To investigate possible event-exposure dependence, a pre-exposure time of different lengths (15, 30 and 60 days) was excluded from the reference category to evaluate the IRR.

***Results***: IRR of HHF for current use was 0.79 (0.72-0.86); removing 30 days IRR was 1.43 (1.31-1.57). Removing 15 days, IRR was 1.29 (1.18-1.41) and removing 60 days, IRR was 1.56 (1.42-1.72). A pre-exposure period up to 182 days was necessary to remove such effect giving an IRR of 1.64 (1.48-1.81).

***Conclusions***: HFF remarkably conditioned the use of BDZs resulting in seriously biased IRRs when this association was studied through a SCCS design. The use of pre-exposure periods of different lengths helped to correct this error.

## 1. INTRODUCTION

The self-controlled case series (SCCS) method was developed initially to investigate the effect of vaccination and acute potential adverse events[1], but it has been applied later on in other areas of pharmacoepidemiology[2], to investigate transient exposures with acute and non-acute outcomes, employing only individuals who experienced the outcome of interest.

The SCCS design follows the cohort design approach, where events occur randomly during the observation period, and the follow up of each patient is divided according to exposure status. A key difference from a traditional cohort is that all patients in an SCCS have both the exposure and the outcome of interest. The rate of outcomes during exposed time is compared against the rate in unexposed time to determine if there is an association with the exposure. The method is derived from a Poisson model by conditioning on the individual total number of events and exposure history. It is self-matched and hence all time invariant confounders are implicitly controlled for[3]. As a consequence of this conditioning, the effects of fixed covariates cancel out, so that the method has a particular advantage compared with cohort and case-control studies[4] and it is being used increasingly in pharmacoepidemiology [5-11]. Potential confounders that change over time and are measurable can also be controlled for.

Among the assumptions required by this method, one is that the occurrence of an event must not alter the probability of subsequent exposure. To ensure this assumption, a "pre-exposure" time risk window can be created to examine whether the exposure depends or not on the occurrence of the outcome. As the selection of that risk window may impact the estimates, it is important to assess different period lengths to observe the effect[12].

This assumption and the one that the event does not influence the length of observation period, have been explored recently by Whitaker et al.[13] to investigate the robustness of results obtained using SCCS when these two assumptions are not met.

In a previous study within the IMI-PROTECT project comparing case-only designs[10], we observed this pre-exposure time bias and the aim of the present study is to measure and characterise the impact of this bias and show how to correct it. We explored the risk in the reference category to avoid the under/over estimation of the relative risk if the assumption above is not met. As a case study we used the well-

established association of benzodiazepines and related drugs (BZD) with hip/femur fractures (HFF), as it is normally a transient exposure and with this design some confounding such as frailty could be addressed.

## 2. METHODS

### 2.1 Data source

The study was performed in the Spanish BIFAP database. It is an electronic healthcare records database from primary care, operated by the Spanish Medicine Agency (AEMPS), with fully anonymised clinical information. BIFAP contains demographic and administrative data; medical information including diagnosis, test results and referrals; prescriptions; deaths; and other data on smoking, weight, height and alcohol abuse. For this study, data up to 2009 was used, with information from about 4 million patients. Systematic quality controls are in place to reach an up-to-standard level valid for research and several validation studies[14-17] have been performed with this database (http://www.bifap.org/summary.php).

### 2.2 Study population

The study period was considered from the 1st January 2001 until 31st December 2009. We included all patients who had a recorded diagnosis of HFF ("cases") and had at least one prescription of BZD during the study period. In many studies the index date coincides with the start date, but in this study design, the event will occur randomly during the study period, and not at the start date, that is why we named them differently. The start date was the date patients met the following criteria: 1) At least one year of enrolment with the general practitioner (GP); 2) age ≥18 years old; and 3) 12 months free of hip/femur fracture (HFF) and 6 months free of exposure to BZD before the start date. And the index date was the date on which the HFF occurred. The outcome was searched in the BIFAP database using the International Classification of Primary Care: ICPC-2, code L75 and then validated through manual review.

### 2.3 Exposure definition

To ascertain the exposure of interest the Anatomical Therapeutic Chemical (ATC) classification system was used (http://www.whocc.no/atc_ddd_index/). All drugs pertaining to ATC codes N05BA (Anxiolytics - Benzodiazepine derivatives), N05CD (Hypnotics and sedatives - Benzodiazepine derivatives), N05CF (Hypnotics and sedatives - Benzodiazepine related drugs) and N05CM02 (Other hypnotics and sedatives - Clomethiazole) were included as exposure of interest.

Duration of each prescription was estimated based on the prescribed amount and daily dose. The expected duration of use was calculated following the methods described by Gardarsdottir et al [18]. When a gap of more than 30 days occurred between the theoretical end date of a prescription and the date of the subsequent prescription, exposure was deemed to be discontinuous and a new treatment episode was considered.

The person-time of each patient was divided according to their exposure into periods of current, recent, past and non-use. Thus, current use was the period from the start of a BZD prescription until 30 days after the estimated end date of the supply and it was further divided into five risk time windows: 1-30, 31-60, 61-182, 183-365 and >365 days; recent use was the period up to 60 days after current use; past use was the period after recent use until the patient became again a current user or the end of follow-up; non-use was the period between the start date and the first BZD prescription within the study period (supplementary Figure 1s). Combined non-use and past use were considered the reference category. Among current users, the exposure was stratified by the type of BZD: anxiolytics, hypnotics or both.

**2.4 Potential confounders**

Age was considered as the only potential confounder, assuming it accounts for most unmeasured time varying effects, if any.

**2.5 Analysis**

A conditional Poisson regression analysis was used to estimate the relative risk in terms of incidence rate ratios (IRRs) with corresponding 95%CI [19]. Small age bands were created to allow adequate adjustment. A first age band was created for 18-29 years of age, and then 5-year age bands for patients up to 59 years of age, and finally one-year age bands for patients from 60 to 95 years, after which the final age band summarised age for the oldest age group (>95 years). The observation period of each participant was divided into risk windows according to their exposure to BZD and was further divided to control for age.

Initially, IRRs were calculated by comparing the rate of HFF experienced during exposure periods with the rate of events during periods of past/non-use. For this analysis, only the first event (HFF) that occurred within the study period was considered, to meet the SCCS method assumption that events are independent.

Then, to investigate the possible event-exposure dependence, a "pre-exposure" period of 30 days (normal length of a BZD prescription) was created before each beginning treatment episode, to remove this time from the reference category and correct for the potential effect that this dependence might cause (Supplementary - Figure 1s). The IRRs were estimated in the same way as before, excluding this pre-exposure time from the reference category.

Besides, to examine whether the length of that "pre-exposure" time risk window affected the risk of developing an HFF, the analysis was repeated with two different lengths. One shorter than previously with a length of 15 days, and one longer with a length of 60 days.

Additionally, we estimated the extension of the risk in the reference category (past/non-use), dividing the time before the exposure in periods of 7 days until the pre-exposure IRR was ≤ 1. We then removed this time from the reference category and repeated the analysis. All analyses were performed using STATA v11®.

## 3. RESULTS

The final study population was made up of 4,450 patients who had a recorded diagnosis of HFF and at least one prescription of BZD within the observation period. Patients had a median duration of the observation period of 1,956 days (5.4 years).

Age ranged from 18-106 years old, with a mean (± SD) age of 74.5 (13.6) years old and a mean (± SD) age at first exposure of 76.4 (13.6) years old. About 77% were women. From all cases, 35% had an HFF during the exposure to BZD, with a median duration of exposure to BZD of 360 days. Distribution by sex and age in 10-years band categories, co-morbidities and co-medications at baseline are shown in **Table 1**. Osteoporosis; previous fractures; malignant neoplasms; ischemic heart disease; cerebrovascular disease; chronic obstructive pulmonary disease and anaemia, were the most frequent co-morbidities for this study population.

Regarding co-medication collected at baseline, the most used drugs were antihypertensives (21.6%); diuretics (12.8%); and proton pump inhibitors (11.8%), followed by glucose-lowering drugs; antidepressants; non-steroidal anti-inflammatory drugs; statins; and bronchodilators, in a proportion between 5-10%.

### 3.1. Risk of HFF associated with BZD use

Crude and adjusted by age IRRs of HFF comparing exposed/unexposed periods were estimated in the absence of a pre-exposure window. A reduced risk of HFF was observed in the adjusted analysis over all time windows of current use [0.79 (0.72, 0.86)]. Similarly, a reduced risk was observed for use of anxiolytics or hypnotics when stratified by type of BZD [1.02 (0.81, 1.30)] (**Table 2**).When we examined whether the exposure was dependent on the event, excluding a time window of 30 days from the reference category, a remarkable pre-exposure risk was found (IRR adjusted by age= 6.47 (95%CI: 5.91-7.09), giving an increased risk of HFF associated with BZD of 1.43 (1.31, 1.57). In addition, changes in the length of the pre-exposure time risk window had a relevant impact on the risk of having an HFF associated to current use of BZD, reaching an adjusted IRR of 1.56 (1.42, 1.72) when the pre-exposure time considered was 60 days (**Table 3**).

### 3.2. Estimating the extension of the pre-exposure time.

We divided the pre-exposure time in periods of 7 days until no increased risk was found. Then, we removed this time from the reference category and repeated the analysis. The time before the exposure was studied up to 210 days. A decreasing curve was observed, with lower 'pre-exposure' risks as long as the pre-exposure 7-day interval moved away of the starting of current use (**Figure 1**).

Beyond the 26th interval (IRR= 0.9; 95%CI: 0.46-1.72) no increased 'pre-exposure' risk was observed. Hence the whole period between that interval and the exposure (182 days) was removed from the reference category.

### 3.3. Risk of HFF associated with BZD after adjusting for the pre-exposure time

In the adjusted analysis, the risk associated with current use was 1.64 (95%CI: 1.48-1.81). The current use of both, anxiolytics and hypnotics exhibited a higher risk of HFF (2.22; 95%CI: 1.75-2.82), as compared to the current use of either single subgroup (**Table 4**).

### 3.4. Assessment of BZD use before and after the HFF

Among 1,185 patients who had an HFF and use of BZD within ±2 months around the HFF date, we observed that 36% patients started before and 64% started after the HFF, showing a peak around 10-20 days after the event (**Figure 2**).

## 4. DISCUSSION

In the present study we found that many patients who sustained an HFF were newly prescribed a BZD after such event. This dependence between the exposure and the outcome represents a violation of one of the key assumptions of the SCCS design. Consequently, we observed that the risk of the reference period was contaminated with a high pre-exposure risk, increasing the risk of the reference category and diluting the risks of all other exposure categories. When such pre-exposure time was removed from the reference period, we corrected for this bias and the risk associated with current use reversed from a protective association to the expected harmful increased risk.

The association of BZD use and HFF is an important public health problem which has been addressed multiple times with different designs. Most studies obtained an increased risk, but the magnitude of the effect varies considerably. In the PROTECT project[20] one of the objectives was to investigate this event-pair association (BZD-HFF) employing different designs and databases. As a result, we carried out a cohort study, and a nested case-control (NCC) study, in 3 different databases (BIFAP- Spain; CPRD-UK and Mondriaan-Netherlands) and compared our estimates with other published cohort and case-control studies. The pooled risk of 22 studies, including published cohort and case-control studies[21 22] and the results from our three cohort studies, was 1.33 (1.23–1.43) with $I^2$ = 84.2%[23]. This association was also explored in the Observational Medical Outcomes Partnership (OMOP) project [24]. Interestingly, in seven out of ten DBs the researchers found no risk of hip fracture associated with BZD use when a SCCS was employed, similar to our initial results. Such a lack of effect may be related to the strong dependence of event and exposure, as we have shown.

This phenomenon has also been described in other settings. Gibson et al [19], in a study of motor vehicle crashes and use of medications, found the highest risk in the pre-exposure time category, including the date of the first prescription, and then progressively decreased in recent and past use. This marked association of all medications in the 28 days up to and including the date of the first prescription, is consistent with the issue of prescriptions as a consequence of involvement in a motor vehicle crash.

After exploring the length of the pre-exposure time window, we observed that the closer time window (7 or 15 days), the higher risks found (7 days >15 days >30 days >60 days), reflecting the high number of new users of BZD found after a hip/femur fracture. A similar situation with SCCS design and hip/femur fracture as an outcome was observed by Lai C et al [25] where they examined prescriptions of alpha blockers following hip/femur fractures.

Further exploring the risk before the exposure, it was found that apart from the intense risk just before the exposure, there was some 'pre-exposure' risk up to 182 days prior to the exposure. Once this period was removed, the results in the SCCS were similar to the ones found in a case crossover (CXO) design, performed as part of the same project (PROTECT) where we compared different designs across different databases thus, for the SCCS we observed an IRR=1.64 (95%CI: 1.48-1.81) and for the CXO, an OR=1.47 (95%CI: 1.29-1.67).

We have demonstrated the importance of exploring the assumptions in this study design and would recommend evaluating this potential bias whenever a SCCS is conducted. For this we would suggest estimating first the IRR of the event of interest associated with a particular exposure, and then repeat this calculation removing an estimate time window from the reference time (e.g. the standard length of the exposure prescription, in our case it was 30 days). If the IRRs before and after removing that time window are very different, this may indicate that the exposure is conditioned by the event and results may be biased. Histograms, plotting the number of outcomes centred around the day of exposure can also be informative (ref https://www.crcpress.com/Self-Controlled-Case-Series-Studies-A-Modelling-Guide-with-R/Farrington-Whitaker-Weldeselassie/p/book/9781498781596).

The main limitations of the study are as follows: 1) The exposure to BZD was based on prescription dates, rather than the precise use dates, which is common in databases used in pharmacoepidemiology; It is therefore possible that exposure periods are misclassified to some extent, with both exposed and unexposed periods affected to some degree. The effect of this misclassification, if non-differential with respect to the outcome, would bias results towards the null, and so it is possible that we have underestimated any real effect of treatment with BZD, 2) Results from this study might not be extrapolated to other settings and certainly not be generalised to other drug-event pairs.

## 5. CONCLUSIONS

Case-only designs may offer better control for time invariant confounding factors than traditional designs and are a useful choice when intrinsic factors may represent relevant confounding, and when the effects of transient exposures are to be measured. However, care is needed to ensure the underlying assumptions of these designs are met. A specific assumption of SCCS design is that the event should not alter the probability of being exposure. When this is not met, the reference period could be spuriously associated with an increased/decreased 'pre-exposure' risk and, as a result, the risks of all other exposure categories would be under/overestimated. A thorough exploration of the appropriate pre-exposure period length is required to account for this.

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***Table 1- Baseline characteristics of the study population.***

| **Total SCCS population** | **N=4,450** | **%** |
|---|---|---|
| **Age (years)** | | |
| 18 - 29 | 57 | 1.28 |
| 30 - 39 | 100 | 2.25 |
| 40 - 49 | 134 | 3.01 |
| 50 - 59 | 254 | 5.71 |
| 60 - 69 | 540 | 12.13 |
| 70 - 79 | 1,531 | 34.4 |
| 80 - 89 | 1,563 | 35.12 |
| 90+ | 271 | 6.09 |
| **Sex** | | |
| Male | 1,038 | 23.33 |
| Female | 3,412 | 76.67 |
| **Co-morbidities** | | |
| Osteoporosis | 385 | 8.65 |
| Paget's disease | 12 | 0.27 |
| Previous fractures | 383 | 8.61 |
| Fractures during BZD exposure | 1,543 | 34.67 |
| Rheumatoid arthritis | 47 | 1.06 |
| Anaemia | 230 | 5.17 |
| Epilepsies/ seizures | 49 | 1.10 |
| Syncope | 133 | 2.99 |
| IHD | 341 | 7.66 |
| CVA | 317 | 7.12 |
| Malignant neoplasms | 372 | 8.36 |
| IBD | 13 | 0.29 |
| COPD | 248 | 5.57 |
| Liver disease | 60 | 1.35 |
| Chronic renal failure | 81 | 1.82 |
| Mental disorders (no depression) | 49 | 1.10 |
| Dementia and/ or Alzheimer's disease | 174 | 3.91 |
| **Co-medications** | | |
| Glucocorticoids | 33 | 0.74 |
| Bisphosphonates | 92 | 2.07 |
| Raloxifene | 10 | 0.22 |
| Strontium ranelate | 0 | 0.00 |
| Parathyroid hormone | 1 | 0.02 |
| Vitamin D + Ca supplements | 179 | 4.02 |
| Calcitonin | 37 | 0.83 |
| Antidepressants | 316 | 7.10 |
| Antipsychotics/ Lithium | 132 | 2.97 |
| Anti-Parkinson drugs | 87 | 1.96 |
| Anticonvulsants | 105 | 2.36 |
| Inhaled glucocorticoids | 85 | 1.91 |

| | | |
|---|---|---|
| Bronchodilators | 235 | 5.28 |
| Anti-arrhythmics | 52 | 1.17 |
| Sedating antihistamines | 24 | 0.54 |
| Antihypertensive drugs | 962 | 21.62 |
| Diuretics | 570 | 12.81 |
| HRT | 14 | 0.31 |
| Thyroid hormones | 62 | 1.39 |
| Antithyroid drugs | 9 | 0.20 |
| DMARDs | 27 | 0.61 |
| Thiazolidinediones | 2 | 0.04 |
| Other glucose-lowering drugs | 340 | 7.64 |
| Antiemetics | 41 | 0.92 |
| Anticoagulants | 156 | 3.51 |
| Morphine/ opiates | 156 | 3.51 |
| NSAIDs | 311 | 6.99 |
| Statins | 271 | 6.09 |
| PPIs | 526 | 11.82 |
| Aromatase Inhibitors | 11 | 0.25 |

*Abbreviations: BZD: Benzodiazepines and related drugs; IHD: Ischemic Heart disease; CVA: Cerebrovascular accident; IBD: Inflammatory bowel disease; COPD: Chronic Obstructive Pulmonary Disease; HRT: Hormone-replacement therapy; DMARDs: Disease-modifying antirheumatic drugs; NSAIDs: Non-steroidal anti-inflammatory drugs; PPIs: Proton-pump inhibitors.*

***Table 2- Risk of hip-femur fracture associated with benzodiazepine use overall in different current use windows and according to the ATC subgroup when no pre-exposure period was considered.***

| SCCS | | | Model Crude | | | Model Adjusted by age | | |
|---|---|---|---|---|---|---|---|---|
| **Exposure** | **Cases** | **Py** | **IRR** | **95%** | **CI** | **IRR** | **95%** | **CI** |
| **Past/Non use (ref)** | 2,615 | 5,169,764 | 1.00 | | | 1.00 | | |
| **Recent use** | 292 | 476,812 | 1.14 | 1.00 | 1.29 | 0.97 | 0.85 | 1.10 |
| **Current 1-30d** | 213 | 409,985 | 0.92 | 0.80 | 1.07 | 0.79 | 0.68 | 0.92 |
| **Current 31-60d** | 201 | 362,943 | 0.99 | 0.85 | 1.15 | 0.85 | 0.73 | 0.99 |
| **Current 61-182d** | 314 | 614,880 | 0.93 | 0.82 | 1.06 | 0.75 | 0.66 | 0.86 |
| **Current 183-365d** | 246 | 437,601 | 1.11 | 0.95 | 1.29 | 0.83 | 0.71 | 0.96 |
| **Current >365d** | 569 | 1,120,123 | 1.28 | 1.12 | 1.47 | 0.73 | 0.63 | 0.84 |
| **Current use** | 1,543 | 2,945,532 | 1.02 | 0.94 | 1.11 | 0.79 | 0.72 | 0.86 |
| **Type of BZD by ATC subgroup** | | | | | | | | |
| **Current use of anxiolytics** | 1,023 | 1,985,997 | 1.01 | 0.91 | 1.11 | 0.80 | 0.72 | 0.88 |
| **Current use of hypnotics** | 333 | 645,533 | 0.96 | 0.82 | 1.13 | 0.72 | 0.61 | 0.84 |
| **Current use of both** | 187 | 314,002 | 1.48 | 1.18 | 1.86 | 1.02 | 0.81 | 1.30 |

***Table 3- Comparison of incidence rate ratios (IRRs) of hip/femur fracture associated with benzodiazepine current use adjusted by age with different lengths of the pre-exposure time: 15, 30, and 60 days.***

| SCCS | Pre-exposure time 15 days | | | Pre-exposure time 30 days | | | Pre-exposure time 60 days | | |
|---|---|---|---|---|---|---|---|---|---|
| **Exposure** | **$IRR_{15*}$** | **95% CI** | | **$IRR_{30}$** | **95% CI** | | **$IRR_{60}$** | **95% CI** | |
| **Past/non use** | 1.00 | | | 1.00 | | | 1.00 | | |
| **Recent use** | 1.13 | 0.97 | 1.32 | 1.21 | 1.03 | 1.42 | 1.25 | 1.05 | 1.49 |
| **Pre-Exposure** | **8.32** | 7.54 | 9.17 | **6.47** | 5.91 | 7.09 | **5.06** | 4.64 | 5.52 |
| **Current use** | 1.29 | 1.18 | 1.41 | 1.43 | 1.31 | 1.57 | 1.56 | 1.42 | 1.72 |

***Table 4- Risk of hip-femur fracture associated with the use of benzodiazepine and related drugs, when a pre-exposure period of 182 days was excluded.***

| SCCS Analysis without pre-exposure risk | | | Crude Model | | | Model Adjusted by age | | |
|---|---|---|---|---|---|---|---|---|
| **Exposure** | **Cases** | **Py** | **IRR** | **(95%) CI** | | **IRR** | **(95%) CI** | |
| **Past/Non use** | 1,315 | 4,109,390 | 1.00 (ref.) | | | 1.00 (ref.) | | |
| **182-day pre-exposure** | 1,300 | 1,060,374 | 3.95 | 3.63 | 4.29 | 3.68 | 3.38 | 4.01 |
| **Current 1-30d** | 213 | 409,985 | 1.86 | 1.60 | 2.17 | 1.60 | 1.37 | 1.87 |
| **Current 31-60d** | 201 | 362,943 | 2.00 | 1.71 | 2.34 | 1.71 | 1.46 | 2.00 |
| **Current 61-182d** | 314 | 614,880 | 1.92 | 1.67 | 2.21 | 1.56 | 1.36 | 1.80 |
| **Current 183-365d** | 246 | 437,601 | 2.31 | 1.98 | 2.70 | 1.75 | 1.49 | 2.06 |
| **Current >365d** | 569 | 1,120,123 | 2.71 | 2.35 | 3.13 | 1.62 | 1.38 | 1.89 |
| **Current use** | 1,543 | 2,945,532 | 2.10 | 1.91 | 2.31 | 1.64 | 1.48 | 1.81 |
| **Type of BZD by ATC subgroup** | | | | | | | | |
| **Current use of anxiolytics** | 1,023 | 1,985,997 | 2.06 | 1.85 | 2.30 | 1.65 | 1.47 | 1.85 |
| **Current use of hypnotics** | 333 | 645,533 | 1.95 | 1.66 | 2.29 | 1.48 | 1.25 | 1.75 |
| **Currrent use of both** | 187 | 314,002 | 3.12 | 2.49 | 3.91 | 2.22 | 1.75 | 2.82 |

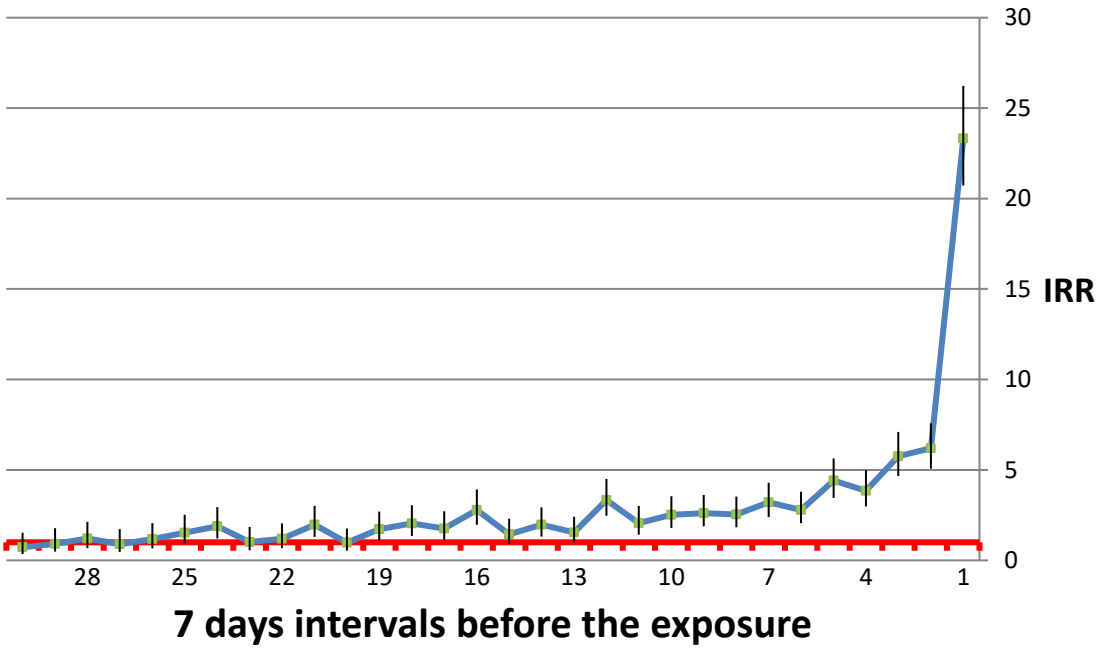


***Figure 1- Risk before the exposure to benzodiazepine. The scale starts at exposure time (0) and then 30 intervals of 7 days before that day are presented. The red line indicates the value of Incidence Rate Ratio (IRR)=1.***

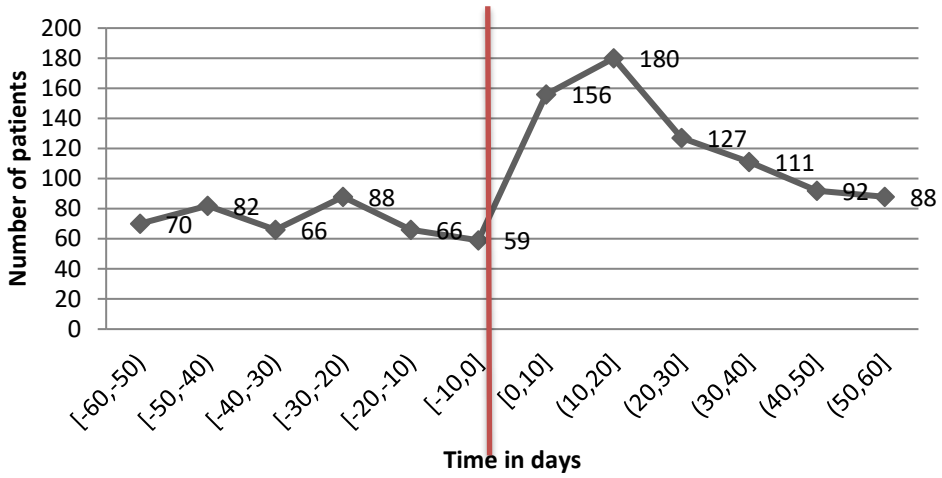


***Figure 2 - People started a BZD treatment before and after the hip/femur fracture. The red line indicates the time of hip/femur fracture.***

**SUPPLEMENTARY MATERIAL**

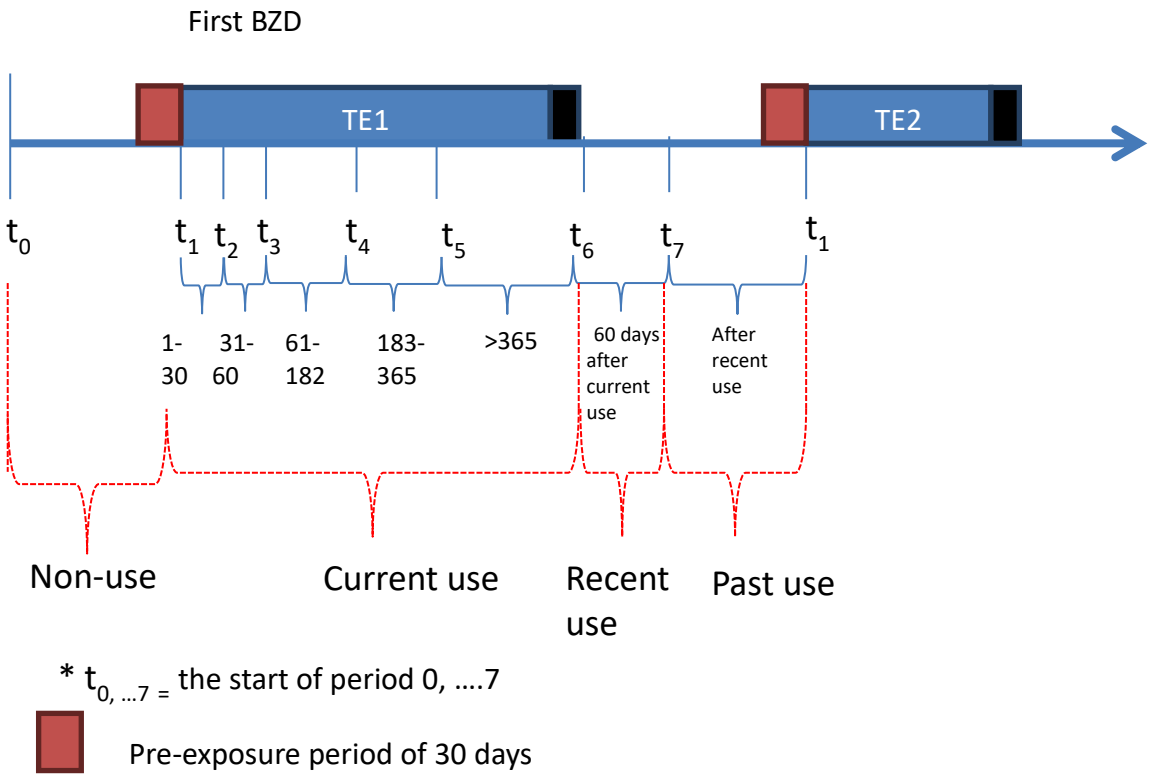


**Figure 1s- Person-time divided into exposure status and accounting for a pre-exposure time window**