Universidad
de Alcalá

Ph.D. Program in Health Sciences

PHARMACOEPIDEMIOLOGY OF BENZODIAZEPINES AND ITS

ASSOCIATION WITH HIP/FEMUR FRACTURES: A

METHODOLOGICAL EVALUATION.

DOCTORAL THESIS

GEMA REQUENA RODRÍGUEZ

Directors: Francisco José de Abajo Iglesias

María Consuelo Huerta Álvarez

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A mis padres

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LIST OF ABBREVIATIONS USED

ACE: Angiotensin-Converting Enzyme

ADEs: Adverse Drugs Events

ADRs: Adverse Drugs Reactions

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)

AHC: Almere Health Care

AIS: Additional Information Service

AOR: Adjusted odds ratio

ATC: Anatomical Therapeutic Chemical

BIFAP: Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria

BMD: Bone Mineral Density

BMI: Body Mass Index

BZD: Benzodiazepines

CEIFE: Centro Español de Investigación FarmacoEpidemiológica (Spanish Centre for Pharmacoepidemiological Research)

CHN: Clinical history number

CI: Confidence Interval (95%CI)

CNS: Central Nervous System

COPD: Chronic Obstructive Pulmonary Disease

CPRD: Clinical Practice Research Datalink

CVA: Cerebrovascular disease

CXO: Case crossover

DBs: Databases

DDD: Defined Daily Dose

DKMA: The Danish national registries

DMARDs: Disease-Modifying Anti-Rheumatic Drugs

DPC: Data processing centre

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EPIC: Cegedim Strategic Data: CSD Medical Research UK (formerly known as EPIC)

EU : European Union

EUROSTAT: Statistical Office of the European Communities

FTP: File transfer protocol

GABA: γ-aminobutiric acid

GP: General practitioner

GPRD: General Practice Research Database

HNU: The general practitioners of Utrecht

HR: Hazard Ratio

HRT: Hormone replacement therapy

IBD: Inflammatory Bowel Disease

ICD: International Statistical Classification of Diseases and Related Health Problems

ICPC-2: International Classification of Primary Care

IHD: Ischaemic heart disease

INE: Instituto Nacional de Estadística (National Statistics Institute)

INPS: In Practice Systems Ltd.

IPCI: Integrated Primary Care Information

IQR: Interquartile

IR: Incidence Rate

IRR: Incidence Rate Ratio

LRJG: Leidsche Rijn Julius Health Centre

MEMO: Tayside Medicines Monitoring Unit

MHRA: Medicines and Healthcare products Regulatory Agency

NCC: Nested Case-Control

NHS: National Health Service

NIHR: National Institute for Health Research

NL: The Netherlands

NPCRD: Netherlands Primary Care Research Database

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

OMI-AP: Organización y Management Informático-Atención Primaria

OMOP: Observational Medical Outcomes Partnership

OR: Odds Ratio

PC: Primary Care

PoM: Prescription-only medicines

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PPI: Proton Pump Inhibitor

PR: Prevalence Rates

PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

p_y: Person-years

Rx: Prescription

SCCS: Self-Controlled Case Series

SD: Standard deviation

SSI: National Institute for Health Data and Disease Control

TE: Treatment episode

THIN: The Health Improvement Network

UK: The United Kingdom

WHO: World Health Organization

WG1: Working group 1

WP2: Work package 2

RESUMEN

Objetivo: El objetivo general de este trabajo de investigación es evaluar la asociación entre el uso de benzodiacepinas (BZD) y las fracturas de cadera/fémur, bajo un punto de vista metodológico, comparando los resultados obtenidos con diferentes diseños de estudios, y analizando la consistencia de los métodos empleados, como parte del proyecto Europeo PROTECT (http://www.imi-protect.eu/).

Metodología: Utilizando la misma fuente de datos BIFAP, una base de datos nacional de atención primaria, se realizaron dos diseños tradicionales, un estudio de cohorte y un caso-control anidado (NCC) para investigar la posible asociación entre BZD y fármacos relacionados y fracturas de cadera/fémur. Los resultados de estos diseños se compararon entre ellos y también con los obtenidos en dos diseños más novedosos de sólo casos: un estudio de casos cruzados (CXO) y uno de series de casos auto-controlados (SCCS).

La población en el estudio de cohorte estaba formada por pacientes de 18 años o más, con al menos un año de registro con el médico, que no habían usado BZD o fármacos relacionados en los seis meses previos a la entrada del estudio (1ª receta de BZD), considerándose así "nuevos" usuarios, y sin fractura de cadera/fémur en los 12 meses antes de entrar para asegurar casos "incidentes" durante el periodo de estudio: 1/01/2001-31/12/2009. Para el NCC, los casos seleccionados en el estudio de cohorte se emparejaron con un máximo de cuatro controles por sexo, edad y tiempo de seguimiento dentro del periodo de estudio usando un muestreo por densidad de incidencia. Para los diseños de sólo casos, la población se seleccionó de toda la base de datos. Se consideró que tenían el evento de interés aquellos pacientes con un registro de una nueva fractura de cadera/fémur identificada con el código CIAP-2, L75 durante el periodo de estudio. La exposición se midió por prescripciones de BZD o fármacos relacionados. El tiempo de seguimiento total de cada paciente se dividió según su estado de exposición en periodos de uso actual, uso reciente, uso pasado o no uso (periodo anterior a la 1ª receta de BZD en el periodo de estudio, para los diseños de sólo casos). Una extensa lista de potenciales confusores (co-medicación, co-morbilidades y variables de estilos de vida) se fueron añadiendo

progresivamente a los modelos, primero se incluyó sólo la edad y finalmente todas las co-variables en un modelo completo.

Para evaluar el riesgo de tener una fractura de cadera/fémur asociada con BZD o fármacos relacionados en el estudio de cohorte, se hizo un análisis de riesgos proporcionales de Cox actualizando las variables confusoras cada 182 días. En el NCC y en el CXO se hizo una regresión logística condicional, y finalmente, una regresión de Poisson condicional en el SCCS. En este último diseño se investigó la posible dependencia de la exposición con el evento, separando un periodo de 30 días previo a la exposición de la categoría de referencia. Todos los análisis se hicieron con Stata v11®.

Resultados: El uso actual de BZD y fármacos relacionados se asoció en todos los diseños con la fractura de cadera/fémur, sin embargo los estudios tradicionales (cohorte y NCC) dieron estimadores de riesgo más bajos (HR=1.17, 1.07-1.28 y OR= 1.19, 1.06-1.32) que los obtenidos con los diseños de sólo casos (OR$_{CXO}$ = 1.47, 1.29-1.67 e IRR$_{SCCS}$= 1.64, 1.48-1.81, respectivamente). El riesgo en el SCCS se obtuvo cuando el periodo de pre-exposición fue separado de la categoría de referencia. El uso concomitante de ansiolíticos e hipnóticos, presentó el mayor riesgo de fractura en todos los diseños, (HR=1.21, 1.01-1.43; OR$_{NCC}$=1.48, 1.20-1.84; OR$_{CXO}$=3.03, 2.30-4.00; IRR$_{SCCS}$=2.22, 1.75-2.82) comparado con el uso de ansiolíticos o hipnóticos por separado. Respecto a la duración de tratamiento con BZD, no se observó riesgo en el primer mes de tratamiento (HR=0.98, 0.83-1.15; OR$_{NCC}$=1.03, 0.82-1.30; IRR$_{SCCS}$=1.11, 0.96-1.29). En el estudio de cohorte se vio que altas dosis de BZD estaban relacionadas con un mayor riesgo, pero no se observó diferencia en cuanto a la vida media.

Conclusiones: El uso de BZD y fármacos relacionados aumenta moderadamente el riesgo de fracturas de cadera/fémur, esto fue un hallazgo constante en los cuatro diseños empleados. Los diseños de sólo casos dieron estimadores de riesgo mayores que los obtenidos en los diseños tradicionales, lo que se podría interpretar como un mejor control por factores de confusión que son difíciles de medir en los tradicionales. El riesgo de tener una fractura de cadera/fémur fue mayor cuando ansiolíticos e hipnóticos se tomaban

concomitantemente. No se observó una tendencia clara de riesgo asociado a la duración del tratamiento, en particular, no se encontró efecto al principio del tratamiento. El uso de BZD estaba condicionado a la fractura de cadera/fémur lo que puede suponer un sesgo importante en el diseño SCCS. Este sesgo puede ser corregido cuando el periodo de pre-exposición asociado con un aumento de riesgo se identifica y se separa del periodo de referencia.

ABSTRACT

Objective: The general objective of this research is to assess the association between benzodiazepines (BZD) use and hip/femur fracture under a methodological point of view. The main goal is to compare findings obtained by different study designs, and evaluate the consistency of methods employed. This research is part of the European project PROTECT (http://www.imi-protect.eu/).

Methodology: From the same data source BIFAP, a national primary care database, two traditional designs, a cohort and a nested case-control (NCC) studies were performed to investigate the potential association between BZD and related drugs with hip/femur fractures and results from those designs were compared between them and with the ones obtained from the novel case-only designs: a case crossover (CXO) and a self-controlled case series (SCCS).

The cohort study population was comprised by patients aged 18 years or older, registered at least for 1 year with the GP, having 6 months free of exposure before the start date (1st BZD prescription) to be considered "new" users, and without a hip/femur fracture within 12 months before entry to ensure "incident" cases during the study period: 1/01/2001-31/12/2009. For the NCC, all cases selected in the cohort study were matched by sex, age and time of follow up within the study period up to four controls using a risk-set sampling method. For the case-only designs, population was selected from BIFAP. Patients with a recorded diagnosis of a new event of hip/femur fracture during the study period were considered to have the outcome of interest and it was searched using the ICPC-2, code L75. The exposure was measured with prescriptions of BZD or related drugs, and the total person-time of each person was divided according their exposure status into periods of current, recent, past or non use (period before first prescription within the study period for the case-only designs). An extensive list of potential confounders (co-medications, co-morbidities and life-style factors) was employed, and they were added to the analytical models progressively, first only age was included and finally all covariates into a full model. To evaluate the risk of having a hip/femur fracture associated with BZD or related drugs, in the cohort study a time varying analysis was done every 182 days, using Cox proportional hazard models. In the NCC and the CXO designs a

conditional logistic regression was employed to examine the risk of hip fracture with BZD. And finally, a conditional Poisson regression model was utilized in the SCCS. The potential dependence of the exposure with the event was explored in this design, separating a pre-exposure time of 30 days from the baseline. All analysis were done using Stata, v11®.

Results: Current use of BZD or related drugs was associated in all designs with the outcome of interest however traditional studies (Cohort and NCC) yielded lower estimates (HR=1.17, 1.07-1.28 and OR= 1.19, 1.06-1.32) than those obtained with the case-only designs (OR_{CXO}= 1.47, 1.29-1.67 and IRR_{SCCS}= 1.64, 1.48-1.81, respectively). The risk in the SCCS was obtained once the pre-exposure period was excluded from the baseline or reference period. The concomitant use of anxiolytics and hypnotics showed the highest risk across all designs (HR=1.21, 1.01-1.43; OR_{NCC}=1.48, 1.20-1.84; OR_{CXO}=3.03, 2.30-4.00; IRR_{SCCS}=2.22, 1.75-2.82), compared with the use of anxiolytic or hypnotic separately. Regarding duration of treatment with BZD, no risk was observed during the first month (HR=0.98, 0.83-1.15; OR_{NCC}=1.03, 0.82-1.30; IRR_{SCCS}=1.11, 0.96-1.29). In the cohort study high doses were associated with a higher risk, but no difference was observed according to the half-life of BZD and related drugs.

Conclusions: The use of BZD and related drugs moderately increases the risk of hip/femur fractures and this was consistently found across the four analytical designs performed. Case-only designs yielded estimates higher than the obtained in the traditional designs, allegedly because of a better control for confounding factors that are difficult to measure in traditional designs. The risk of having a hip/femur fracture was higher when anxiolytics and hypnotics were taken concomitantly. No clear trend of risk was observed with duration of use, in particular, a short-term effect was not observed. The exposure was heavily dependent on the event and this may introduce an important bias in the SCCS design. Such bias may be corrected when the pre-exposure period associated with an increased risk is well characterized and excluded from the period used as the reference.

INTRODUCTION

1. INTRODUCTION

1.1 HIP FRACTURES

Hip fractures represent a major public health challenge in developed countries, due to the increasing age of the population. In 2000, there were almost one million patients with an episode of hip fracture in the European Union, and it has been predicted that this figure will increase more than two-fold in the coming fifty years (1).

The increasing trend of the incidence of hip fractures, along with associated morbidity complications, dependence and mortality (2, 3) make this condition a major public health concern. In addition, hospital resources for injury-related admissions are one of the major causes of total healthcare costs in Europe (4). The burden of hip fractures, in terms of disability and healthcare budget, is higher than for common cancers, such as breast or prostate, and myocardial infarction (5). Osteoporosis affects millions of patients worldwide, and hip fractures are considered the most serious outcome.

1.1.1 Definition. Types of hip fractures

A fracture is a break, which occurs when the continuity of bone tissues or bony cartilage is disrupted or broken. There are many different types of fractures which include:

- Simple or Closed: A fracture that does not produce an open wound in the skin.
- Compound or Open: A fracture in which there is an external wound leading to the break in the bone.
- Comminuted: A fracture in which the bone is splintered or crushed.
- Complete: A fracture in which the bone is entirely broken across.
- Incomplete: A fracture that does not entirely destroy the continuity of the bone.
- Depressed fracture: A fracture in which a fragment is depressed.

- Greenstick: A fracture in which one side of a bone is broken, the other being bent.

The hip joint is formed by the *acetabulum* of the pelvis and the proximal femur. The joint is surrounded by a capsule which reaches the trochanteric line completely covering the head and the femoral neck. The *femoral head* is attached to the rest of the femur by a short section of bone called the *femoral neck*. The bump on the outside of the femur just below the femoral neck is called the *greater trochanter* (6). See Figure 1 for anatomy of hip joint.
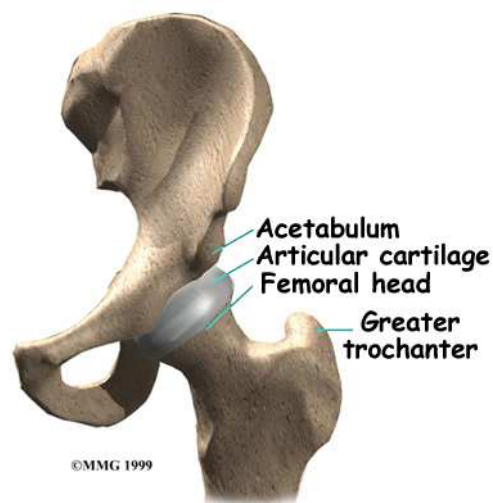
Retrieved from http://www.eorthopod.com.-Orthogate- A patient's guide to hip fracture

Figure 1- Hip joint anatomy

Hip fractures occur in the proximal (upper) portion of the femur, just outside the area where the femoral head (ball) meets the acetabulum (socket) within the pelvis, typically resulting from a fall or minor trauma in old people with osteoporotic bone. Those fractures may be caused by twisting the hip while weight bearing, trips, or a fall from standing height. The actual fall is often secondary to the fracture. Most hip/femur fractures in younger people are the result of high-energy trauma like road motor-vehicle collisions.

The anatomical relationship with the capsule is important from the point of view of classification of hip fractures, thus two main types of hip fractures are:

-Intracapsular fractures are those located in the femoral neck.

-Extracapsular fractures are located in the trochanteric and subtrochanteric hip regions.

Capital fractures are rare, and located in the femoral head. This distinction is important because in intracapsular fractures, such as fractures of the femoral neck, vascularization may be interrupted causing risk of avascular necrosis and pseudoarthrosis. This is the most common hip fracture, which occurs primarily in the elderly and is often associated with osteoporosis. It is also important to know the degree of displacement, which is correlated with the risk of complications and determines the type of treatment performed.

In the extracapsular fractures, the break line is placed outside of the hip joint capsule. There are three types depending on the affected area: transcervical, intertrochanteric and subtrochanteric fractures. See Figure 2.

Retrieved from https://www.stjohnprovidence.org/ProvidenceOrthopedics/HipFracture/
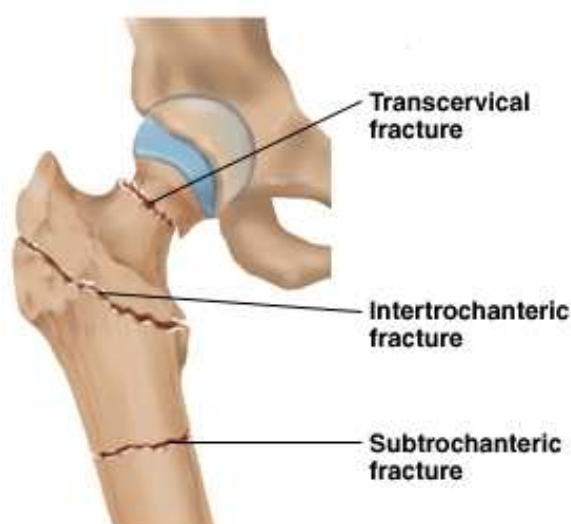
Figure 2- Types of extracapsular hip fractures

Here it is important to know whether or not they are stable, given that the degree of stability increases inversely with the degree of comminution. A fracture is stable provided the end of the fractured bone is in its correct anatomical alignment, in other words, the transmission line loads from calcar to the diaphysis femoral is kept (7).

Simple radiographs may confirm the diagnosis of a fracture, thus there is another classification according to their appearance on radiographs:

1. Intracapsular fractures

1.1) Pauwels classifies fractures according to the obliquity or angle of the fracture:

I -   30 degrees from horizontal

II - 50 degrees from horizontal

III - 70 degrees from horizontal

1.2) Garden classification is based on the radiographic appearance of the fracture:

I -   Incomplete or impacted fracture

II -   Complete fracture without displacement

III -   Complete fracture with partial displacement

IV -   Complete fracture with full displacement, continuity of fragments is disrupted

In view of the differences between different observers in classifying the same fracture it is preferable and more practical to sort intracapsular hip fractures into non displaced (Garden I and II) and displaced (Garden III and IV) (8).

2. Extracapsular fractures

2.1 **Intertrochanteric** fractures are those located between the base of the femoral neck and lesser trochanter. Also *pertrochanteric* fractures are those in which the fracture line is at intertrochanteric line level. There are many classifications, e.g. the one by Boyd & Griffin:

1. Simple fracture that extends along the intertrochanteric line from the greater to the lesser trochanter.

2. Comminuted fractures, the main fracture being along the intertrochanteric line, but with multiple fractures in the cortex.

3. Fractures that are basically subtrochanteric with at least one fracture passing across the proximal end of the shaft just distal to or at the lesser trochanter.

4. Fractures of the trochanteric region and the proximal shaft, with fracture in at least two planes, one of which usually is the sagittal plane and may be difficult to see on routine anteroposterior radiographs.

Or the Evans classification based on direction of fracture (9):

Type I: Fracture line extends upwards and outwards from the lesser trochanter (stable).

Type Ia: Undisplaced two-fragment fracture

Type Ib: Displaced two-fragment fracture

Type Ic: Three-fragment fracture without posterolateral support, owing to displacement of greater trochanter fragment

Type Id: Three-fragment fracture without medial support, owing to displaced lesser trochanter or femoral arch fragment

Type Ie: Four-fragment fracture without postero-lateral and medial support (combination of Type III and Type IV)

Type II: Fracture line extends downwards and outwards from the lesser trochanter (reversed obliquity/unstable). These fractures are unstable and have a tendency to drift medially.

2.2 **Subtrochanteric** fractures are located in the area around the lesser trochanter from its upper edge up to 5cm below it. The most commonly used classification is that of Fielding who divided them into three groups:

I- Fracture at the level of the lesser trochanter

II- Fracture within 2.5 cm of the lesser trochanter

III- Fracture between 2.5 and 5 cm of the lesser trochanter

1.1.2 Management and treatment of hip/femur fractures

Depending on the type of fracture, the management and treatment will vary, as well as the recovery time. Patients with a hip/femur fracture have the typical symptoms of any fracture. Besides pain and local tenderness, they often show external rotation and shortening of the affected limb. Hip/femur fractures in adults mostly require surgery depending on the location, type of fracture and mainly on the general condition of the patient, associated pathology etc. Thus, steps to follow in the management of a hip fracture are:

1) Pain relief with analgesics and immobilization
2) Stabilization of the associated pathology
3) Surgical intervention
4) Rehabilitation

In general, Garden Stage I fractures are the only ones that may not require surgical fixation. With this fracture, the person is on bed rest for 3 weeks and should perform only mild hip and knee exercise. After 3 weeks sitting and crutch ambulation is allowed, but full weight bearing must be avoided for 8 weeks (10).

In the intracapsular fractures, there is a risk that the blood supply may be interrupted, which is vital to the femoral neck, resulting in vascular necrosis. As consequence, death of bone tissue occurs, resulting in pain and limited mobility. Therefore, the treatment of choice tends to be the replacement of the head and neck of the femur. Surgically treated by hemiarthroplasty (replacing half of the joint) or total hip arthroplasty (replacement of the entire joint) (6).

Extracapsular fractures retain sufficient irrigation and they are surgically treated by open reduction and internal fixation. For internal fixation of those fractures, screws, pins and plates are often used and failure of the fixation device and mal-union are the most common complications. Among them, subtrochanteric fractures are the least common and most unstable traumatic fractures, also the most difficult to treat because of the high mechanical stresses in this area of the femur. They are normally the result of direct trauma of

considerable force, and are the most frequent femoral fractures in the younger population (11).

1.1.3 Epidemiology of hip fractures

In general, hip fractures increase exponentially with age regardless of sex, the average age in which hip fractures occur being about 80 years, in industrialised countries (12). Overall 80% of hip fractures occur in women, partly explained by their superior longevity over men. Factors such as race and ethnicity also affect the incidence rates of hip fractures, being higher in white than black or Asian populations (13). Although it might be related to urbanisation, because higher hip fractures rates have been seen in non rural areas compared to rural. Other conditions such as seasonality and climate seem to play a role, since in winter and temperate climates more hip fractures have been observed, but mostly indoors, which probably is associated with vitamin D levels (14).

Most hip fractures which occur in people over 65 are generally due to falls from their own height. These kind of fractures are considered "low-trauma" fractures, defined as those resulting from falls from standing height and less severe trauma, whereas hip/femur fractures in young people are often considered as "high-trauma" fractures, defined as those caused by motor vehicle crashes and falls from greater than standing height (15), where there is often involvement of other organs and systems, and are therefore not subject of this study.

Commonly, falls are the precipitating factor in the loss of mobility and independence among the elderly. In the 4 months following a fracture, an increase of mortality ranging from 12% to 35% was observed, in comparison to subjects of the same age who had not suffered fractures. And only 50% of these patients achieve a functional level comparable to the one they had prior to the fracture (16). A systematic literature review showed that patients who experienced hip/femur fractures had a substantial excess risk of death compared with the general population, that risk was greater during the first year after the fracture, ranging from 8.4% to 36 % (17). It was also observed that mortality was higher among men than women, although they were younger at the time of the fracture. So the cumulative mortality during the first year after a hip/femur fracture

compared with the general population was 37% in men and 26% in women. In general, overall mortality risk increased with age and with co-medication, but was higher in men (18).

1.1.4 Risk Factors

As the population over 65 years are the most affected by these types of fractures, there are numerous intrinsic risk factors associated with age and some also related to gender. Among typical problems of aging, it is worth mentioning visual and hearing impairment, loss of reflexes, loss of bone mass, urinary incontinence, mental deterioration, and a wide range of conditions that may contribute to a greater or lesser extent to the falls suffering by the elderly. There are some fixed risk factors associated with hip/femur fractures such as (1) the ones presented in Table 1.

Table 1- Fixed risk factors associated with hip/femur fractures

Age
• Female gender
• Family history
• Previous fracture
• Race/ethnicity
• Menopause/hysterectomy
• Long term glucocorticoid therapy
• Rheumatoid arthritis
• Primary/secondary hypogonadism in men

These are, at the same time, risk factors for developing osteoporosis. It is well known that people with this condition have bones that are more porous and fragile, and the risk of fracture is greatly increased, the hip/femur fracture being the most serious consequence. Approximately 6 % of men and 21 % of women

aged 50–84 years have osteoporosis affecting 27.6 million men and women in the European Union (EU) in 2010 (19).

In that sense, progress has been made recently in Europe, mainly in the measurement of bone mineral density (BMD), diagnosis of osteoporosis, assessment of risk fracture, interventions to reduce the risk of fractures and creation of practice guidelines. According to the World Health Organization (WHO) criteria, osteoporosis is defined as a BMD of 2.5 standard deviations or more below the average value for young healthy women (a T-score of -2.5). This measurement has provided a diagnosis threshold, as well as an indication for pharmacological treatment (19). The problem is that not all countries have the same facilities and this measure is not available everywhere. And more importantly, there are factors other than BMD that contribute to fracture risk. These independent risk factors can be used to support BMD test results, or used to predict fracture risk in the absence of BMD tests. Thus, a fracture risk assessment tool FRAX® has been developed for use in primary care settings to support the identification of those at risk for fracture and the selection of appropriate treatment. These factors include age, bone mineral density, body mass index, prior fragility fracture, over use of oral glucocorticoids, parental history of fracture, current smoking, alcohol intake and rheumatoid arthritis. Clinical practitioners simply enter an individual's risk factors into the FRAX® tool. Please see in Figure 3 below an example of the questionnaire of this web-based tool, available at www.shef.ac.uk/FRAX.

Figure 3- FRAX tool questionnaire.

Apart from Osteoporosis, a wide range of pathologies have been investigated for their possible association with hip/femur fractures, either because they directly affect bone metabolism, or because they somehow alter the balance and facilitate the falls in these elderly patients.

Among those pathologies would highlight neurological diseases: Parkinson's disease (20, 21), Alzheimer's (22), multiple sclerosis (23), epilepsy (24); cardiovascular diseases (stroke (25, 26)) ; metabolic diseases: diabetes mellitus (27), hyperthyroidism (28), respiratory diseases: chronic obstructive pulmonary disease (29, 30), musculoskeletal disorders (rheumatoid arthritis, arthrosis, chronic inflammations, etc.) (31), renal disorders (32), gastrointestinal disorders (inflammatory bowel disease, malabsorption) (33) and haematological diseases (anaemia) (34).

Besides the aforementioned intrinsic factors, physiological and pathological ones, there are other extrinsic factors to evaluate presented in Table 2.

Table 2- Extrinsic risk factors associated with hip/femur fractures

Toxic habits	Dietary habits	Environment	Life-styles	Therapies
Alcohol	Low calcium intake	Climate conditions	Lack of exercise	Drugs
Smoking	Vitamin D deficiency	Pavements, rugs, poor lighting	Immobilization	Herbal medicines
Drug abuse	Eating disorders	Lack of handrails, unsafe stairs	Sedentary life	Interactions

It is important to draw attention to the pharmacological factors, because there is a high prevalence of co-medication among the elderly. Furthermore, with some particular drugs, such as oral corticosteroids, it has been shown that a relevant fraction of hip fractures was attributable to that treatment (35). The truth is that there are copious risk factors associated with hip fractures, however the drug treatment received largely affect that risk. As consequence, the role of pharmacoepidemiology is crucial in this assessment.

1.2 PHARMACOEPIDEMIOLOGY

While it is true that in recent decades the life expectancy in the population has increased considerably, so there is a significant increase in the consumption of drugs. Nowadays, there are many more pharmacological options than there were before, and that has allowed people to live longer. It is definitely a step forward to be able to treat and combat diseases that previously could not be fought, but at the same time it is a double-edged sword, since no drug is free from damage. Adverse drugs reactions (ADRs) increase each year, as well as the incidence of significant morbidity and even mortality due to them. Also, medication errors contribute significantly to this burden of disease.

In a recent study about emergency hospitalizations for adverse drug events in older Americans (36), 265,802 emergency department visits for adverse drug events occurred annually from 2007 through 2009 among adults 65 years of age or older. An estimated 37.5% of those visits required hospitalization and nearly half of the hospitalizations were among adults 80 years of age or older.

Besides, there is an additional problem, 40% of adults older than 65 years of age take in general between 5 and 9 drugs, and around 18% take more than 10 drugs. Poly-pharmacy has been associated with an increased risk of having an ADR nearly by seven fold in elderly patients compare to young people (37).

There is a close relation between aging, multiple pathology, high drug consumption and prolonged treatments. In Spain, 37% of all hospitalizations in 2005 were patients older than 65 years, and demographics projections indicate that in 2020, chronic pathologies will represent more than 60% of diseases (38).

Hospital admissions due to adverse drug reactions could be avoidable and preventable with a deep knowledge of drug safety profiles. As a result, the need for pharmacoepidemiology will increase exponentially in the near future worldwide.

1.2.1 Concept and importance

Pharmacoepidemiology is defined as the study of the use of and effects of drugs in large numbers of people (39). It aims to describe, explain, control and predict the effects and uses of pharmacologic treatments in a defined time, space and population. It is a evolving discipline between clinical pharmacology and epidemiology (40).

The field of pharmacoepidemiology is relatively new and concerns itself primarily with the study and quantification of adverse drug reactions (ADRs) and patterns of drug use in a population. According to the Spanish Royal Decree 577/2013, of 26th July, regulating pharmacovigilance of medicinal products for human use, an *adverse reaction* is defined as "*any noxious and unintended response to a medicinal product*".

Adverse drugs events (ADEs), in contrast, describe an injury resulting from administration of a drug, which might be temporarily associated but not necessarily causally related, this term implies that the relationship may be coincidental or that the event is not caused solely by the drug itself but rather may relate to the circumstances surrounding use of the drug (41).

ADRs have been divided into type A and B reactions. Type A reactions are expected exaggerations of a drug's known pharmacologic effects. Thus, they normally are dose-dependent, predictable, and preventable. Most type A reactions are identified prior to drug marketing and are listed in a product's labeling. Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacologic action of a drug. They usually are not related to dose, unpredictable and uncommon, and potentially are more serious than type A reactions. They may be due to what are known as *hypersensitivity reactions* or *immunologic reactions.* Type B reactions are the more difficult to predict or even detect, and represent a major focus of pharmacoepidemiological studies of ADRs (42). See Table 3.

Table 3- Summary of features of Adverse Drug Reactions: type A and B

Type A	Type B
Dose dependent	Not related to dose
Predictable	Unpredictable
Preventable	Idiosyncratic
Identified prior drug marketing	Uncommon
Listed in the product label	Unexpected and serious

Similarly, according to the Spanish Royal Decree 577/2013 of 26th July, regulating pharmacovigilance of medicinal products for human use, *Pharmacovigilance* is defined as "*public health activity aimed at identifying, quantifying, assessing, and preventing the risks associated with the use of marketed medicinal products.*" That usually includes a continuous monitoring for unexpected effects and other safety-related aspects of marketed drugs. Hence, the main importance of pharmacoepidemiology is as a tool of pharmacovigilance.

Clinical trials are carried out before a drug reaches the market, however, among limitations of premarketing trials could be cited the following:

- Limited duration, usually short studies
- Limited sample size
- Limited comparison groups, especially for new drugs
- Narrow defined population, often not covering special groups as children, females with child bearing potential, persons with multiple diseases, or limited life expectancy.
- Ethical issues

Therefore, knowledge of drugs after approval is limited as it is not possible to detect all potential risks and benefits during premarketing studies. Those effects occurring after chronic use or with a long latency period are unlikely to be detected as well as those with a frequency of less than 1/1000 (43). To address

the limitations of pre-marketing studies, spontaneous reporting systems are in place as a requirement for post marketing surveillance in all member states from the European Union. However, to determine causation in case reports of adverse reactions can be problematic due to numerous issues such as lack of information about co-medications and co-morbidities of the patient.

Hypotheses can be tested with pharmacoepidemiological studies, and permit a better assessment of the risk/benefit balance of marketed drugs, because only after a drug is used widely by the general population can some effects be observed. They are needed for evaluating drug safety and effectiveness in situations where it is either infeasible or unethical to assign patients randomly to active treatment or placebo (41).

1.2.2 Drugs associated with hip/femur fractures

An extensive list of drugs has been investigated in relation with their potential association with hip/femur fractures. Among them, some drugs have been considered to have a strong relationship with these types of fractures and so it has been confirmed in many publications, whereas other drug associations have shown discrepancies between different published results.

It is not surprising to see that the most widely investigated drugs among people suffering from hip/femur fractures were those employed to treat common pathologies of the elderly, as a result, the following drugs have been studied for their potential association with hip fractures, some of them increasing the risk of fractures, some decreasing the risk and some without presenting any association with fractures:

- Drugs affecting central nervous system: Antidepressants (44, 45); antipsychotics (46), although lithium was associated with a decreased risk of fractures (47); anti-Parkinson drugs (48); anticonvulsants(49); Benzodiazepines and related drugs (50-52)
- Glucocorticoids by systemic route (inhaled corticosteroids (53) have been shown not to increase the risk); bronchodilators(54)

- Cardiovascular drugs: Antihypertensive drugs (55); diuretics (56), in general, do not cause falls and thiazides, in particular, may help prevent fractures, however loop diuretics may affect fracture risk (57); antiarrythmics (58) treatment with amiodarone may have an increased risk of fracture, whereas digoxin may reduce fracture risk; anticoagulants (59); statins (60) seem to be associated with reduced fracture risk despite controversial results.

- Thiazolidinediones (61); other antidiabetic drugs such as metformin and sulphonylureas were associated with a significantly decreased risk of any fracture (62), however no change in fracture risk was associated with the use of insulin or other antidiabetic drugs.

- Hormone replacement therapy (HRT) showed a decline of incidence of hip fractures (63); thyroid hormones (64); antithyroid drugs (65); disease-modifying anti-rheumatic drugs (DMARDs) (66); aromatase inhibitors (59).

- Proton pump inhibitors, recently it was seen that there was no increased risk of fracture contrary to first published articles (67-69); sedating antihistamines (70). Their association with fractures is controversial.

- Non-Steroidal Anti-Inflammatory drugs(NSAIDs) (71); morphine/opiates (72).

- Treatments for osteoporosis which are associated with a reduced risk of fracture: biphosphonates, raloxifene, (73, 74) although recent results are controversial (75). Similarly, some articles about vitamin D and calcium supplements have recently shown that they do not prevent hip fractures (76, 77). (Summary in Table 4).

Table 4- Summary of drugs whose association with risk of hip/femur fractures has been studied.

	Increase risk	No change risk	Decrease risk
Central Nervous System	Antidepressants, antipsychotics, anti-Parkinson drugs, anticonvulsants, benzodiazepines and related drugs		Lithium
Corticoids	Oral glucocorticoids, bronchodilators	Inhaled glucocorticoids	
Cardiovascular drugs	Antihypertensives, loop diuretics, antiarrythmics: amiodarone, anticoagulants	Diuretics in general	Thiazides, digoxin, statins
Antidiabetics	Thiazolidinediones	Insulin and other antidiabetic drugs	Metformin and sulphonylureas
Hormones	Thyroid hormones, antithyroid drugs, Disease-Modifying Anti-Rheumatic drugs (DMARDs), aromatase inhibitors		Hormone Replacement Therapy (HRT)
Analgesics	Non-Steroidal Anti-inflammatory drugs (NSAIDs), morphine, opiates		
Other	Sedating antihistamines	Proton Pump Inhibitors (PPIs)	
Treatment for Osteoporosis		Vitamin D and Calcium supplements	Biphosphonates, raloxifen, etc.

1.2.3 Plausible mechanisms of action

There are two plausible mechanisms of action directly related with a fracture, either falls or bone mass loss. Some drugs have been related with the bone mineral density, reducing bone mass and therefore increasing the risk of fractures. Glucocorticoids are well known drugs causing osteoporotic fractures, but it is observed also in women treated with aromatase inhibitors for breast cancer, in men receiving anti-androgen therapy for prostate cancer, in postmenopausal women treated with high doses of thyroxine, and in men and women treated with thiazolinediones for type 2 diabetes mellitus. Bone loss with fractures also occurs in patients treated with drugs targeting the immune system, such as calcineurin inhibitors, antiretroviral drugs, selective inhibitors of serotonin reuptake, anticonvulsants, loop diuretics, heparin and oral anticoagulants (59). However, drugs affecting the central nervous system, sympathetic activity, vasomotor response, cardiac function, or volume regulation are thought to be more related to falls.

With the pathology of hip/femur fracture, there is an added factor which is the effect of age, as they mainly occur in the elderly. This group of people have a reduced functional reserve, and their secondary homeostatic responses may be impaired (39). Thus, elderly subjects may show an increased sensitivity to the side effects of many drugs. For example, individuals with chronic liver or lung disease may exacerbate postural changes in blood pressure with antihypertensive drugs, diuretics, etc. being common, postural hypotension among them. Or they sometimes exhibit extreme sensitivity to drugs that depress central nervous system function, such as benzodiazepines and opiates. Variability in pharmacokinetics and pharmacodynamics will contribute to variability in drug response, hence in drug effect (78).

Among all possible drugs associated with hip/femur fractures, benzodiazepines and related drugs were selected in this research for their potential relation with hip/femur fractures and because they are one of the most common treatments employed in the general population.

1.3 BENZODIAZEPINES AND RELATED DRUGS

1.3.1 Chemical characteristics

Benzodiazepines (BZD) are composed of a benzene ring fused to a seven-member 1,4 diazepine ring. Most contain a 5-aryl substituent ring. They differ in the chemical nature of the substituent groups at positions 1, 2, 3, 4 of the diazepine ring, position 7 of the benzene ring, and position 2 of the 5-aryl substituent ring (79). See the structure in Figure 4.
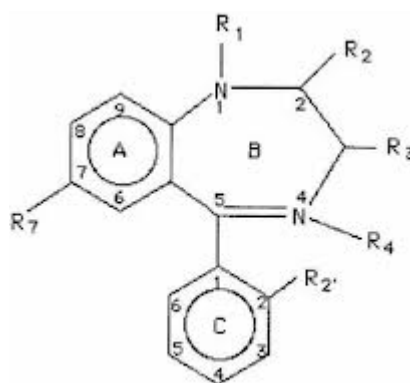
Retrieved from Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th Edition

Figure 4- The structure of the benzodiazepines

A large number of non-benzodiazepine synthesized compounds compete for binding at specific sites in the central nervous system (CNS). These include pyrazolopyrimidines (e.g. zaleplon), imidazopyridines (e.g. zolpidem), cyclopyrrolones (e.g. zopiclone) and thiazoles (e.g. clomethiazole) among others. Although these compounds do not have the same chemical structure as benzodiazepines, their therapeutic actions are similar due to their agonist effects on the benzodiazepine receptor, and therefore they have been included in this research.

1.3.2 Pharmacological properties. Mechanism of action

All effects of the BZD result from actions of these drugs on the CNS. The main effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and anticonvulsant activity. All of the BZD have very

similar pharmacological profiles, but drugs differ in selectivity and clinical usefulness varies considerably.

BZD are believed to exert most of their effects by interacting with inhibitory neurotransmitter receptors directly activated by γ-aminobutiric acid (GABA). These receptors are membrane-bound proteins that can be divided into two major subtypes: $GABA_A$ and $GABA_B$ receptors. BZD act only at the ionotropic $GABA_A$, binding directly to a specific site that is distinct from that of GABA binding on the receptor chloride channel complex. BZD do not activate $GABA_A$ receptors, only modulate the effects of GABA. BZD-receptor ligands can act as agonists, antagonists or inverse agonists at the BZD receptor site, depending on the compound. Agonists will increase the amount of chloride current generated by $GABA_A$-receptor activation, whereas inverse agonists will decrease it. And both effects can be blocked by antagonists such as flumazenil, which is used clinically to reverse the effects of high doses of BZD (79).

Each $GABA_A$ receptor is believed to consist of homologous subunits, most of them are composed for: α, β, and γ subunits, and the subtype of each one ($α_1$, $α_2$, $α_3$, $β_1$, $γ_1$, etc.) determines BZD pharmacology. Consequently, $GABA_A$-receptor subunits are responsible for particular effects of BZD, as McKernan's study revealed that the $α_1$ subtype mediated the sedative, but not the anxiolytic effects of BZD (80).

In addition to their action on the central nervous system, BZD have a dose-dependent ventilatory depressant effect and they also cause a modest reduction in arterial blood pressure and an increase in heart rate as a result of a decrease of systemic vascular resistance (81). See $GABA_A$-receptor structure in Figure 5.
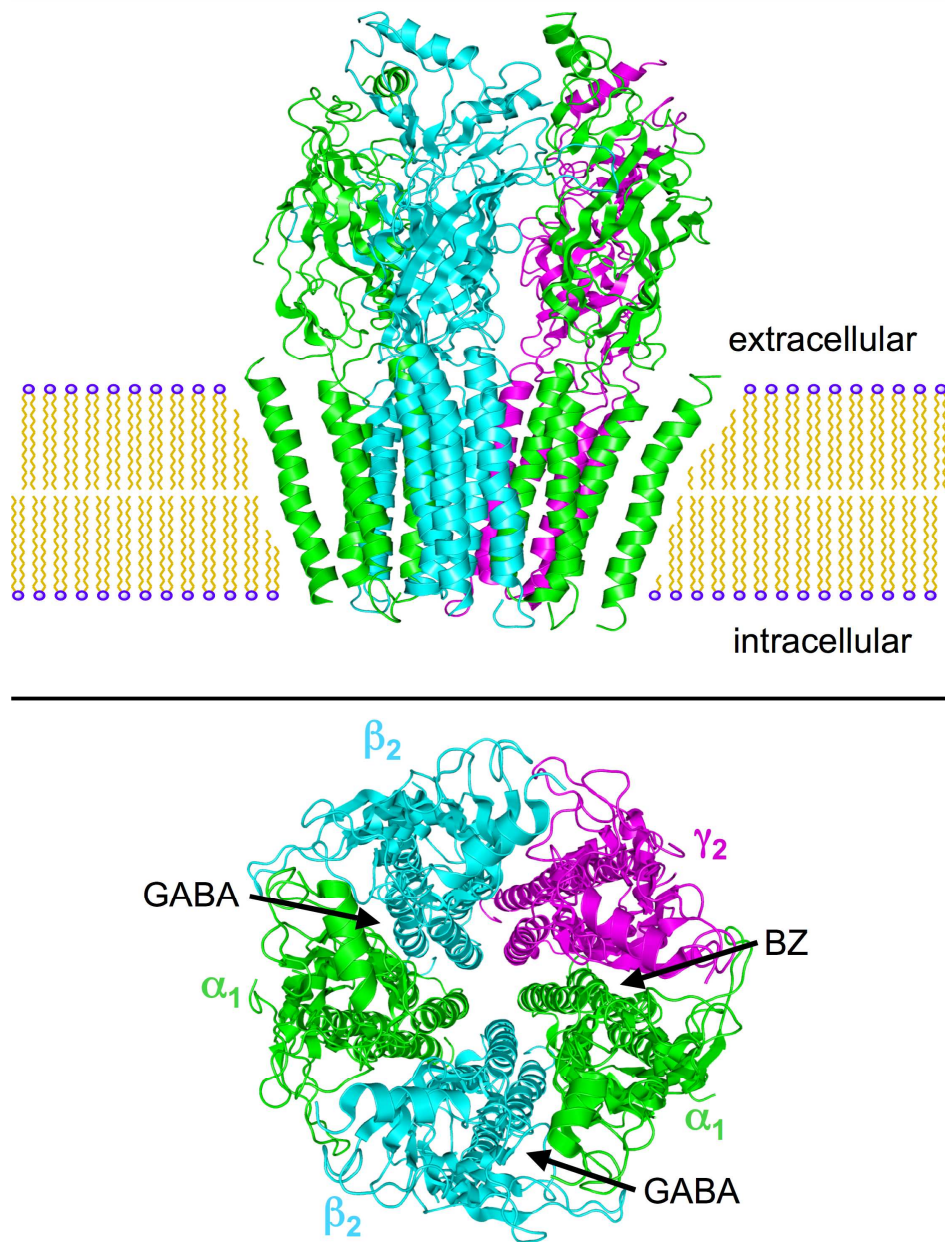
Retrieved from http://en.wikipedia.org/wiki/File:NAchR_2BG9.png

Figure 5- Structure of GABA$_A$ receptor

1.3.3 Pharmacokinetic features

Most of the BZD are not adequate for administration by intramuscular route because it is painful and irregular plasmatic levels are reached, though midazolam is an exception. Some can be administrated by intravenous route under emergency situations, e.g. diazepam and midazolam, but the usual route of administration for BZD is oral. They are well absorbed taking from 30 to 240 minutes according to the active ingredient. All BZD are completely absorbed, with the exception of clorazepate which is first decarboxylated in gastric juice and then absorbed. Some reach the systemic circulation only in the form of active metabolites (e.g. flurazepam). BZD and their active metabolites bind to plasma proteins, in varying degrees depending of their lipid solubility, ranging from 70% (alprazolam) to 99% (diazepam) (79).

Accordingly, there is a rapid uptake of BZD into the brain and other highly perfused organs, followed by redistribution into tissues less well perfused such as muscle and fat. Concentration in the cerebrospinal fluid is similar to the concentration of free drug in plasma. They cross the placental barrier and are secreted into breast milk.

Most BZD are metabolized extensively by enzymes in the cytochrome P450 family, particularly CYP3A4 and CYP2C19, so drugs that act as inhibitors of those enzymes may affect the metabolism of BZD. In general their metabolism occurs in three stages:

1- N-desalkylation: Modification and/or removal of the substituent at position 1 (or 2) of the diazepine ring.
2- Hydroxylation at position 3 giving 3-hydroxyl active compounds.
3- Conjugation with glucuronic acid, or glucuronidation, giving inactive products.

The *α-hydroxylated* products (e.g. α-hydroxyalprazolam, α-hydroxytriazolam) are very active but are metabolized very rapidly by conjugation and no present accumulation of active metabolites (79).

Based on their elimination half-lives, which is the time taken for half of the dose of BZD to be eliminated or metabolised, the BZD may be divided into three categories: Short-acting <6 hours (e.g. midazolam, zolpidem, zoplicone); Intermediate acting from 6 to 24 hours (e.g. lorazepam, bromazepam); and Long-acting >24 hours (e.g. flurazepam, diazepam) (82).

1.3.4 Adverse effects and Interactions.

Relatively common side effects of BZD are weakness, headache, blurred vision, vertigo, nausea and vomiting, epigastric distress, and diarrhoea; joint pains, chest pains, allergic reactions and incontinence may occur in some patients. Also, they may cause paradoxical or disinhibition effects although they are rare and dose-related.

Chronic use poses a risk for development of dependence and abuse, and the use of high doses over prolonged periods can lead to more severe symptoms after discontinuing the drug, including agitation, depression, panic, paranoia, myalgia, muscle twitches and even convulsions and delirium (79).

Main interactions are of pharmacodynamic nature when other depressors of CNS are administrated jointly. The interaction with ethanol may be especially serious, as it increases both the rate of absorption of BZD and the associated CNS depression. Antihistaminic sedative drugs, analgesics with sedatives, opiates or anaesthetics are other examples of this interaction. Also it has been described that BZD in combination with valproate may cause psychotic episodes.

Pharmacokinetic interactions are of less magnitude than with other psycothropic drugs. Cimetidine, oral contraceptives, erythromycin, fluvoxamine, fluoxetine, dextropropoxyphene, ketoconazole, and ritonavir inhibit the metabolism of those BZD metabolised by the CYP3A4 increasing their plasmatic levels. These interactions may be significant in the elderly and patients with chronic liver disease (83). Lorazepam, lormetazepam and oxazepam are only conjugated and present a lesser range of interactions.

BZDs should be used with caution in patients with chronic obstructive pulmonary disease (COPD), or obstructive sleep apnea since they may compromise breathing. Similarly, patients with hepatic insufficiency the half-life of some BZD may be prolonged, and in general the intensity and incidence of CNS toxicity increase with age (82).

1.3.5 Epidemiology of BZD and related drugs use

The BZD and related drugs use varies between countries as different patterns of prescription exist worldwide, however, a higher use in women than in men has been observed as well as an increase of use with age (84-86).

During the last decade the use of BZD and related drugs has increased in different parts of the world, exhibiting a rising trend of use. An example is the United States (87) where a high prevalence and increasing trend of BZD use was observed (41.8% in 2004 to 48.8% in 2009). In Europe, that trend was remarkably observed in Spain, where the use of anxiolytic and hypnotic drugs rose from 56.7 Defined Daily Doses (DDD) per 1,000 inhabitants per day in 2000 to 89.3 in 2012, representing an increase of 57.4% (88).

In contrast, certain European countries with a high prevalence of the use of BZD and related drugs now show a decline in its consumption due to regulatory actions that have been implemented. This is the case in France (89) and Denmark (90) whereas other countries, such as the Netherlands (NL), present a fairly stable use of these drugs (91).

Regarding which BZD and related drugs are the most employed, again it depends on the country, but it could be said that those with short and intermediate half-life (<24h) are more used than those with long half-life (>24h) (92). Similarly, the use of anxiolytics or hypnotics as classified by Anatomical Therapeutic Chemical (ATC) classification system (N05B or N05C respectively) seems to follow a tendency, being the Mediterranean countries where consumption of anxiolytics is higher (93) (Figure 6).
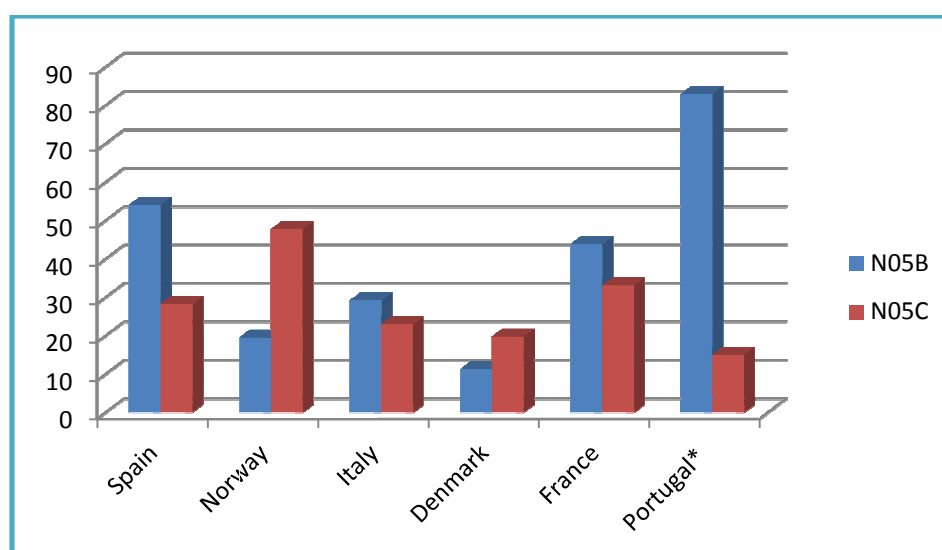
Figure 6- Consumption of anxiolytics (N05B) and hypnotics (N05C) in different European countries in 2010.

1.4 ELECTRONIC HEALTHCARE RECORDS DATABASES

The use of computerized databases has been one of the most important developments in the field of pharmacoepidemiology, allowing efficient and rapid responses in line with the required timeframe in pharmacovigilance to make decisions.

1.4.1 General characteristics

Healthcare records databases are collections of clinical records with a specific well defined structure and purpose. Initially they were created to collect administrative information systematically, generated by the request for payments, or claims, for clinical services and therapies, mainly to control the use and costs of health services, managed by insurance companies or regional health centres. These databases include information at patient-level, on demographics, drug prescriptions, specialist referrals, hospital admissions, hospital discharge diagnoses, operations, ambulatory care, etc.(94, 95).

There are many types of databases, such as disease registries, laboratory databases, census deaths, etc. But that information would need to be linked to drug exposure and diagnosis data to be useful for pharmacoepidemiological research. Hence, two main types of databases are contemplated, electronic medical records and record linkage of administrative health records (96). Medical record databases are generated from the electronic clinical records kept by medical practices. Usually general practitioners (GPs) enter information from the patient such as past medical history, smoking history, out-patient conditions diagnosed by the general practitioner, and procedures performed by the GP. Information on prescribed drugs is to generate prescriptions, not represent drugs dispensed. They may also enter conditions diagnosed by outpatient specialists or information from referral reports or hospital discharge letters. Some databases include laboratory results, and they may also record alcohol use and body mass index, although this is missing in many cases (97).

Record linkage databases link patient's information that is stored separately. They are used mostly for payment, accounting, and fiscal functions related to healthcare services. Providers of those health services such as pharmacies, physicians, hospitals, and laboratories submit information about patients to be paid for their services. As a result, out-patient visits or hospitalizations include diagnoses data and pharmacy services contain details of drugs dispensed.

In medical records databases, data are normally entered by the GP or primary care physician so drugs prescribed by specialists may be incomplete, whereas in record linkage databases, all drugs prescribed by any physician are recorded, as long as it is dispensed by a pharmacy that presents the bill to the administrative system (97).

The main advantages of automated databases, in general, are the following (94):

- Investigators have rapid and easy access to inpatient and outpatient or primary care records.
- They usually cover large populations enough to detect an adverse effect that occurs with a very low incidence, e.g. rare events.

- They allow studies to be performed relatively quickly and cheaply since data have already been collected.
- They may provide time trends, because information from several years is available.
- Information is collected from routine clinical practice, so evaluation of drugs is within common conditions of use.
- It is possible to analyze special populations at risk such as pregnant women, children, the elderly, diabetic patients, etc. who may be excluded from randomised trials.

Similarly, the main disadvantages of automated databases, in general, are the following:

- Incomplete data, information on potential confounding variables may not be collected (e.g. exercise, diet).
- Private sector consultations can be missed.
- The level of detail is limited because they were created for other purposes.

Nowadays, electronic healthcare records databases are progressing considerably, and tend to obtain a full coverage of health data at patient level through data linkage with other databases such as death registries; census; disease registries; hospital; pharmacy; and laboratory databases. They aim to provide the most complete picture of a patient's clinical profile, with the whole medical history and life styles collected for each individual registered, to achieve high quality pharmacoepidemiological studies.

Some countries (Denmark, Sweden and Finland) have a unique personal identifier that is used in many different registers and this allows many registers to be linked. However in other countries some concerns exist about data confidentiality, therefore the quality and availability of these kinds of data is related to the specific type of health system in each country.

1.4.2 BIFAP Database

In a country like Spain, with a public health system, the GP in primary care is the gateway to the national health services. They have information at individual level such as clinical history, diagnoses, operations, treatments and general health problems. Besides, most of the prescriptions from the National Health System are written by GPs. As a consequence, information managed in primary care contains all key elements for pharmacoepidemiological research: symptoms; diagnoses; exploratory data; demographic data; laboratory results; surgical procedures; and treatments prescribed.

1.4.2.1 Definition, Rationale and Objectives

In 2000, the Spanish Agency of Medicines and Medical Devices (AEMPS) in collaboration with the Spanish Centre for Pharmacoepidemiological Research (CEIFE) began the development of a national primary care database for pharmacoepidemiological research, called "***B**ase **d**e **d**atos para la **I**nvestigación **F**armacoepidemiológica en **A**tención **P**rimaria*" BIFAP. It might be defined as a public database with anonymised clinical information provided by primary care physicians of the Spanish National Health System (NHS).

The idea of creating a national database for pharmacoepidemiological research was very interesting in order to contribute to the international effort in the assessing of drug safety. Also, information from foreign data sources can be of limited validity, since drugs marketed and their conditions of use may differ across countries. The effects of drugs might also vary according to genetic, environmental and sociological factors, so it would depend on the population involved (98).

The main objective was to create an efficient data source to perform pharmacoepidemiological investigations in Spain and to detect and analyze signals raised by the Spanish Pharmacovigilance System. Thus, drug safety studies to test hypotheses of causal associations or to confirm signals detected in pharmacovigilance systems together with drug effectiveness studies (efficacy under normal conditions of use) were the intention for this database.

1.4.2.2 Coverage, structure and data collected

At 2009, BIFAP included information of more than 3.5 million of patients, covering 6.9% of the Spanish population. From those, 3,180,161 patients contained valid information to participate in research studies, with a time of follow up in the database of 11,526,376 person-years. That database (2009) was employed for this doctoral research.

Currently, BIFAP includes information of 4,187,465 million patients, covering 8.6% of the Spanish population. Those data are provided voluntarily by 2,235 primary care physicians (1,959 GPs and 276 paediatricians) of the NHS, with the collaboration of ten Autonomous Communities. From those, 3,963,538 patients contain valid information to participate in research studies, with a time of follow up in the database of 19,976,344 person-years. The population in BIFAP database is representative of the Spanish population and reflects a similar distribution of age and sex to the general population. Figure 7 below is from www.bifap.org the Spanish website; it shows general population data from the National Statistics Institute (INE) compared to the registered population in BIFAP, in the year 2011, regarding age and sex distribution.

Comparación población INE- BIFAP Año 2011

Instituto Nacional Estadística (INE): datos del padrón del año 2011
Datos BIFAP: pacientes válidos (TIS/Inactivos) con seguimiento en el año 2011
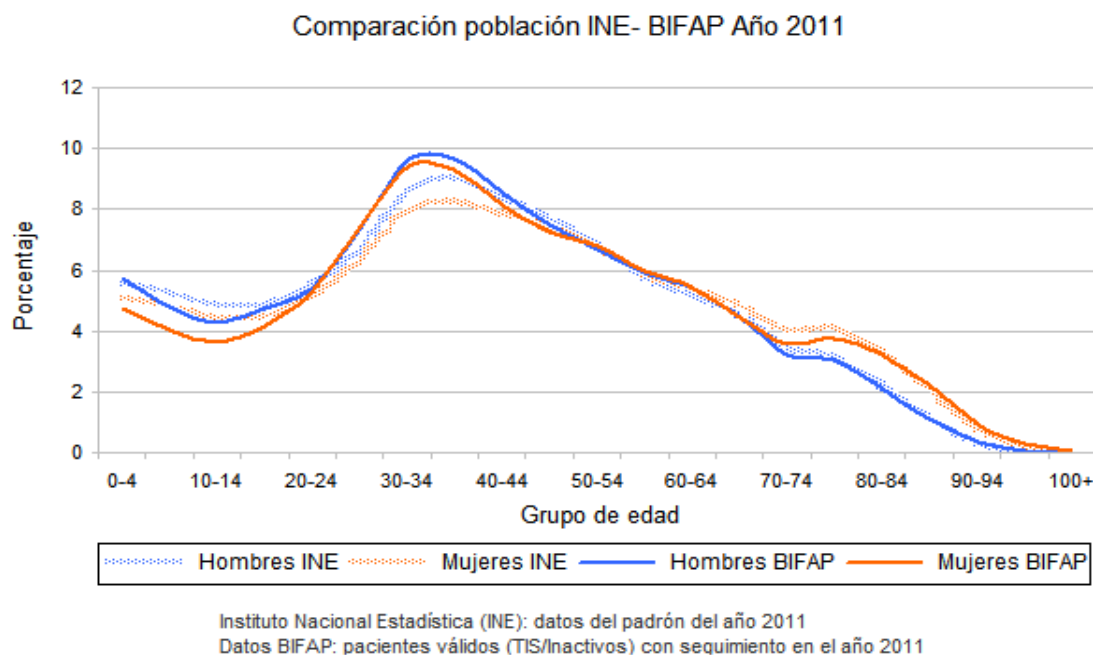
Figure 7- Comparative of the Spanish and BIFAP populations in 2011

The information contained in BIFAP is the following (98):

1. Administrative data (admission/discharge dates) and demographics (sex and date of birth)
2. Morbidity events:
   - Diseases/symptoms leading to patient consultation.
   - Starting date of first diagnosis of chronic and recurrent illnesses.
   - Significant results of complementary tests.
   - Events or disorders giving rise to admission, referral to the Emergency Service or to a specialist, and essential data derived from the latter (new diagnoses, interventions, results of specialized tests, etc.)
3. Prescriptions: drug, quantity, dosage, date and instructions for use.
4. Pregnancy and its outcome
5. Deaths
6. Other data of clinical or epidemiological interest (vaccinations, height, weight, smoking, alcohol abuse)

Each healthcare practice participant has a software named OMI-AP (*Organización y Management Informático - Atención Primaria*) that allows diagnoses introduced by GPs to be linked to a given ICPC code. In addition, the physician can modify in real time the literal string offered by the OMI-AP software to better describe the disease of interest. In BIFAP, all literals with a frequency of more than 50 entries in the diagnosis table are included in "BIFAP thesaurus" as a extra level of granularity in the taxonomy by adding a fourth digit to the linked ICPC code (hereinafter ICPC BIFAP code). These codes represent about 90% of the total number of diagnoses included in BIFAP database. Those codes with a number "0" added to the ICPC code are diagnoses that did not meet previous criteria to be included in BIFAP thesaurus, giving a heterogeneous list of diagnoses which are expected to be correctly linked to the ICPC. To optimize this assignation, additional computational rules automatically redirect literals to the proper ICPC BIFAP code even in the case that this literal is originally linked to other ICPC code in the OMI-AP source. In addition to the table containing diagnosis, as commented before, free text GP notes linked to the episode (diagnosis) are stored in a different table (GP free-text comments table).

Data are periodically exported (twice a year) to the data processing centre (DPC) located in the Spanish Medicines Agency (AEMPS). The exportation process does not include any personal data that could identify patients. In addition, a high level of encrypting is performed at origin. Once data are at the AEMPS they are processed for a second dissociation of personal data. In this step, also physicians and healthcare practices identification is dissociated, so that the researcher has no access to the identification data of patient, GP or healthcare practice. The BIFAP Unit however, may identify the GP and healthcare practice but not the patient. A random code is assigned to each patient, therefore, all data are completely anonymised (Figure 8).

CHN: clinical history number

FTP: File Transfer Protocol, way to share files over the net
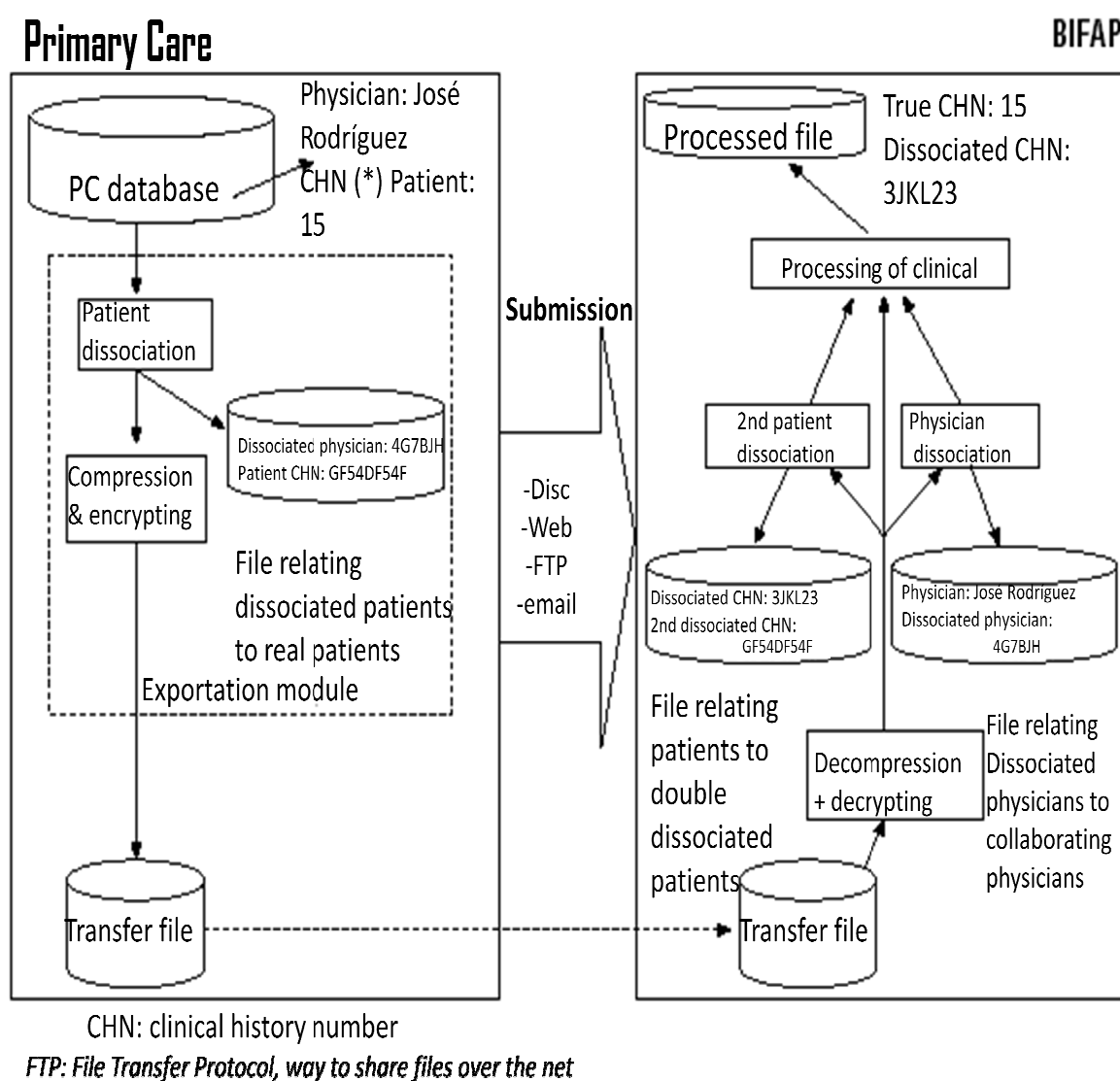
Retrieved from Salvador Rosa, A. et al with permission.

Figure 8- Information flow in the BIFAP database: dissociation procedure.

1.4.2.3 Quality Standards and Validation studies

Data in the DPC are subject to automated controls to verify information received. From a qualitative and quantitative point of view, mean values of data received and population indicators are taken as reference, among other systematic quality controls in place to reach an up-to-standard level. Once that level is achieved a patient is considered valid for investigating purposes.

A scientific committee with representation by the principal scientific societies in the field of primary care, including GPs, primary care paediatricians, specialists in bioethics, specialists in primary care computerization and pharmacoepidemiologists, supervise the activities carried out, provide counselling on specific aspects, contribute suggestions, and ensure adhesion to legislation and to current recommendations in matters of data protection (98).

Several validation studies were performed within BIFAP database, with positive results (www.bifap.org). Some of them comprised correlation of the BIFAP registries with anonymous copies of clinical reports to ensure existing health records. Another type of validation involved a selected sample of patients by disease or medication code, verifying a concordance of diagnoses and prescribed drugs. For both methods a concordance of over 90% was needed to be considered adequate. Finally, another way to validate diagnoses collected in BIFAP is through revision of the patient's clinical profile, including free text that GPs may add and confirming criteria used to assign a particular code or diagnosis.

Moreover, study results obtained within the BIFAP database have been compared with gold standards, national statistics surveys, scientific publications, disease registries, and so on, giving perfectly comparable results. Thus, results from this database may well be compared with other data sources and with other databases from other countries, as it has been shown in different international studies where BIFAP took part. By all the above, BIFAP is considered as a valid tool for pharmacoepidemiological research.

1.4.3 Other databases

The first databases employed for pharmacoepidemiological purposes were health maintenance organizations such as *Group Health Cooperative of Puget Sound* (1945) that covers part of the population of the state of Washington; universal care systems as *Saskatchewan* (1962) from Canada; or federal state programs like *Medicaid* (1965) which is a joint federal state program for financing medical care for qualifying poor persons in the United States (99).

Then appeared databases where health information was collected by the primary care physician, especially in countries with public health systems. Thus, in 1987 a British automated healthcare database was created with the aim of generating useful clinical data for research purposes, named *General Practice Research Database* (GPRD). It comprises computerized medical records of GPs, and contains data from over 600 practices based throughout the United Kingdom, providing information on 12.5 million patients, of which 5 million are currently active. Data covers 8% of the British population. Recently it has changed the name, being now the *Clinical Practice Research Datalink* (CPRD) defined as the new English NHS observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) (100). Data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death. Validity of a wide range of drug exposure data is routinely tested. Furthermore, validation studies are conducted regularly by comparing CPRD data to written notes of general practitioners. Recent additions to the database include external record linkage to other national health services datasets, such as the national Hospital Episode Statistics (with extended data on all hospitalisations) and Death Certificates, increased availability of free text information via a new automated system, the possibility of genetic linkage studies, prospective data collections such as questionnaires, copies of patient–based correspondence, the conduct of multi-country studies, and performing randomization studies within the database.

Similarly, sharing characteristics and content, another British healthcare records database is *The Health Improvement Network* (THIN) (101). It is collaboration between two companies, In Practice Systems Ltd. (INPS), developer of Vision software used by GPs in the United Kingdom (UK), and Cegedim Strategic Data: CSD Medical Research UK (formerly known as EPIC), provider of access to data for use in medical research. Data are collected during routine practice and regularly delivered to THIN database. THIN data collection prospectively started in 2003 – although all prior computerised data were extracted from each practice since they started medical record computerisation). It currently contains electronic medical records of almost 8 million patients (more than 3 million active patients) collected from over 386 general practices in the UK, some of them overlap with the ones employed by GPRD. THIN database consequently covers more than 5.7% of the population in the UK. Patient data are arranged in four standardised (Patient, Medical, Therapy and Additional Health Data and one linked (postcode variable indicators) files per practice. Further information is possible to obtain via the Additional Information Service (AIS) including: questionnaires completed anonymously by the patient or GP, copies of patient-based correspondence, a specified intervention (e.g. a laboratory test to confirm diagnosis) and death certificates.

In the Netherlands (NL) there are other healthcare records databases that have been used for pharmacoepidemiological research, such as *Mondriaan databases*. The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma (102). Under the umbrella of Mondriaan, the participating databases currently include: the Netherlands Primary Care Research database (NPCRD), The Almere Health Care (AHC) database, The General Practitioners of Utrecht (HNU) database and The Leidsche Rijn Julius Health Centre (LRJG) database. The cumulative number of persons having data in Mondriaan reached around 1.4 million comprising mainly of GP data complemented by pharmacy dispensing data and linkages to survey data. The four databases within Mondriaan have different starting dates and scope of data. NPCRD is the Netherlands Information Network of General Practice and it holds a longitudinal data on morbidity, prescription, and referrals. The GPs record data on all patient contacts, including diagnoses, referrals and prescriptions. The AHC

is a GP and pharmacy database. The HNU is a GP database set up in 1995 and includes data dating till the end of 2005. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables.

In the same way, *The IPCI project (Integrated Primary Care Information*) initially aimed to assess whether the electronic patient records of Dutch general practitioners contain sufficient data to perform studies in the area of post marketing surveillance. Due to the collection of data on the indication of therapy and the detailed information on measurements, contacts, referrals and exams, the usage of data has been extended to clinical epidemiology (incidence and natural history of disease) (103).

As record linkage databases, a noteworthy other Dutch database broadly used: *PHARMO Database Network*, which compiles information from many databases to get global patient-level information as complete as possible. Among databases employed are: GP database, In and Out patient pharmacy, hospitalisations, mortality register, clinical laboratory, etc. In 1993, the PHARMO record linkage systems was established as an updateable working system covering a population of approximately 300,000 inhabitants. In 1999, the PHARMO Institute was established and first pharmacoepidemiological studies were performed. Since then, more than 750 scientific studies have been performed (104).

The *Danish national registries* (105-107) maintained by the National Institute for Health Data and Disease Control (SSI), contain information on all hospital contacts since 1995, medication dispensing on a pharmacy level linked to individuals who redeemed the prescription from 1994 onwards, causes of death for the entire population and contact information of visits to GPs as well as specialist in private care. Likewise the *Tayside Medicines Monitoring Unit (MEMO)* is a validated record linkage database, community-based representing all socioeconomic groups. Its longitudinal data of dispensed prescribing and health outcomes over a 15-year period gives the capabilities for a variety of population-based research(108).

In general, the use of e-healthcare records databases is increasing nowadays for pharmacoepidemiology research, and it tends to improve day by day.

JUSTIFICATION

2. JUSTIFICATION

The global aging population, especially in developed countries, is a matter of concern among health authorities. It has been estimated that the number of yearly hip fractures only in the EU, is expected to be more than double over the next 50 years (1).

In recent years there have been an increasing number of studies describing that the secular trends in the incidence of hip fractures have levelled off (109-111), or started to decline, since the late nineties (112) in some European countries. Allegedly this would be the result of the effectiveness of national campaigns to prevent both osteoporosis and falls (113). A call to update the data for as many countries as possible has been made (114) in order to check whether this favourable trend is consistent.

Moreover, BZD and related drugs are one of the most commonly prescribed drugs worldwide, especially to the elderly. Their use represents a public health problem due to inappropriate use and dependence. Knowledge of their prevalence of use can be employed to guide research initiatives, intervention programs, and policy decisions. Globally, during the last decade the prevalence of use of BZD and related drugs was quite high and some policies were implemented to try to diminish their use (115, 116). An update of current situation of use of BZD and related drugs is needed and a comparison with other European countries is desirable.

The association between risk of hip fractures and use of BZD has been investigated by several epidemiological studies (51, 117-119) but there are still some controversial issues. For instance, Cumming et al after reviewing eleven epidemiological studies found that results were not consistent: four case-control hospital-based studies and one study from nursing homes did not show an association between increased hip fracture risk and BZD use, whereas the remaining six found an association (50).

The reasons for the inconsistencies found may, in part, be explained by the diverse methodological approaches, mainly different designs; operative definitions of outcome, exposure, confounders and analytical strategies. Therefore, investigating the association of hip fracture with the use of BZD and related drugs, from the perspective of four different designs (cohort study, nested case-control study, case crossover and self-controlled case series) within the same database population, would allow evaluation of the consistencies and discrepancies that may arise attributable to study design.

This research is part of the European project PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) (http://www.imi-protect.eu/), work package two (WP2) which aims to define methodological standards for the design and analysis of pharmacoepidemiological studies using electronic healthcare records databases to allow more comparability.

HYPOTHESIS

3. HYPOTHESIS

3.1 MAIN HYPOTHESIS:

There is an association between the use of BZD and related drugs and the risk to develop a hip/femur fracture but the design chosen has an impact on the results obtained.

3.2 SECONDARY HYPOTHESES:

- The use prevalence of BZD and related drugs in Spain is high and has increased over time, while in other European countries the pattern is different.
- There is a decreasing trend of hip/femur fractures in Spain and other European countries during the last decade.

OBJECTIVES

4. OBJECTIVES

4.1 GENERAL OBJECTIVE

The primary general objective of this research is to assess the association between BZD use and hip/femur fracture under a methodological point of view. The main goal is to compare findings obtained by different study designs, and evaluate the consistency of methods employed. Hence, from the same data source BIFAP, two traditional designs, a cohort and a nested case-control (NCC) studies were performed to investigate the potential association between BZD with hip/femur fractures and results from those designs were compared between them and with the ones obtained from the novel case-only designs: a case crossover (CXO) and a self-controlled case series (SCCS).

4.2 SPECIFIC OBJECTIVES

4.2.1 Descriptive studies.

1. Estimate the incidence rates and trends of hip/femur fractures in Spain, and compare with the ones from other European countries.
2. Estimate the prevalence of BZD and related drugs use in Spain and compare with the ones from other European countries.

4.2.2 Analytical studies:

4.2.2.1 Cohort study

3. Describe characteristics of BZD and related drugs users cohort.
4. Calculate the incidence rates of hip/femur fracture associated with the exposure to BZD and related drugs overall and by age and sex.
5. Estimate the relative risk of having a hip/femur fracture associated with BZD both crude and adjusted by potential confounding factors.
6. Investigate whether the risk of developing a hip/femur fracture associated with BZD and related drugs varies or not with the type of

ATC group (anxiolytics or hypnotics); duration of treatment; half-life of the drugs, daily dose and individual drugs.

4.2.2.2 NCC study

7. Describe characteristics of cases and controls.
8. Estimate the relative risk of having a hip/femur fracture associated with BZD and related drugs (crude and adjusted by potential confounding factors).
9. Estimate the relative risk by duration of treatment and type of ATC group (anxiolytics or hypnotics).

4.2.2.3 Case only designs

10. Describe characteristics of cases selected in each design.
11. Estimate relative risks of having a hip/femur fracture associated with the exposure to BZD and related drugs (crude and adjusted by potential time-varying confounding factors), in both CXO and SCCs.
12. Investigate whether the risk varies or not with the ATC group (anxiolytics or hypnotics) in both CXO and SCCS designs.
13. Test whether exposure is event-dependent in the SCCS and examine whether the length of the "pre-exposure" window affects the relative risk estimate.

4.2.2.4 Comparison across designs

14. Compare the adjusted relative risks of current use of BZD and related drugs of having a hip/femur fracture across designs.

PATIENTS AND METHODS

5. PATIENTS AND METHODS

5.1 STUDY DESIGNS

Two descriptive studies to assess the current situation of the incidence of hip/femur fractures and the prevalence of BZD and related drugs use in Spain were carried out using the database BIFAP. Following the same protocol, same descriptive studies were done in other six European databases from Denmark, Germany, the Netherlands, and the United Kingdom, as part of the European Project PROTECT WP2-working group 1 (WP2-WG1). Data from those studies were used to compare with the ones obtained in this research (120, 121).

In addition, four analytical epidemiological designs have been conducted. Two using traditional designs, cohort and nested case-control studies, and two novel designs, a case crossover and a self-controlled case series. All studies were registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (122).

5.1.1 Cohort Study

A cohort study is an analytical observational study in which subjects do not have the outcome of interest at the start of the study and they are selected on the basis of their exposure. A cohort generally indicates a group of people who share a common characteristic. Once the cohort is selected, people are followed during a period of time to determine the occurrence of the outcome of interest and to compare the incidence of the outcome among exposed and unexposed subjects. It is an analytical study because it aims to identify and quantify associations, test hypotheses and identify causes.

There are two main types of cohort studies based on when and how they are enrolled into the study: a) Prospective studies, where the outcome of interest has not occurred at the time of starting the study; b) Historical o retrospective studies, where the outcome of interest has already occurred when the researcher starts the investigation. In that case, disease-registries or electronic healthcare records databases are normally employed. As well, a cohort may be open or closed,

depending on whether subjects can be added to the cohort or not, once the cohort has been defined and the follow up has begun. The key difference between them is that in the closed cohorts, the time of follow up is the same for all subjects assuming no losses of follow up, and it allows calculate cumulative incidence of the outcome of interest, whereas in the open or dynamic cohorts, the time of follow up is different for every subject, and "person-time" should be used in the analysis.

The major advantages of the cohort studies are the followings:

- A temporal sequence between exposure and outcome can be established
- They are useful to study rare exposures, i.e. a specific chemical product
- A range of outcomes associated with the exposure can be studied
- Information on confounding factors can be obtained
- Useful for estimating the risk of disease, the incidence rate and/or relative risks. Time-to-event analysis is possible as well
- Less prone to selection and information biases as compared to other designs

In contrast, main disadvantages are:

- Losses during the follow up time can impact in the risk estimates, in particular, if losses are differential with respect to the exposure status
- Large study size is required, in particular when the outcomes are rare or present a long latency
- High cost and time consuming
- More complex analysis than other designs, in particular when time varying variables are to be considered.

Traditionally, cohort studies have been considered highly inefficient to be used in pharmacoepidemiology due the low frequency of drug adverse reactions. The use of electronic healthcare records databases, however, has made them much more feasible, although the quality of information recorded may be an issue for specific purposes, and information about potential confounders might be not

recorded. In this research the study design was a retrospective cohort of BZD and related drugs users.

5.1.2 Nested Case-Control (NCC) Study

A case-control study is an analytical observational study in which subjects are defined by the outcome of interest, not by exposure. A group of individuals who have the outcome of interest (cases) and a group of individuals who do not have the outcome of interest (controls) are identified. Then both groups are compared to assess their exposure to a particular factor.

In a "nested" case-control study, cases arise during a cohort study, and a sample of members of that cohort unaffected by the outcome of interest can be used as controls. This design offers advantages over a case-control study (123) because data on exposures is likely to have already been collected, hence less money and time need to be employed, and more important, cases and controls come from the same source population, in this research a cohort of users of BZD and related drugs.

Both, cases and controls have to meet same inclusion/exclusion criteria except for the outcome itself. A precise case definition is required at the beginning of the study, and it has to be decided whether cases will be prevalent or incident. A problem with prevalent cases is that they may change exposure habits as consequence of the disease, and more severe cases might be underrepresented (124). In this research only incident cases were used.

One common approach to select controls in this type of design is matching each case to a few set of controls on the basis of some factors that might be related with the outcome and the exposure, usually sex, age, place, or calendar time. As a consequence of matching the effect of those factors chosen for cannot be studied, so it is important to select them carefully. Normally a conditional logistic regression is performed to analyse matched case-control studies, to account for the matched nature of the population, and the outcome measure obtained is the odds ratio (OR) of exposure. When controls are randomly sampled from the same data source where cases came from, and they are

selected by incidence density sampling, which implies sampling from those who are at risk at the time of case occurrence, the OR is an unbiased estimate of the rate ratio (125).

In general, main advantages (124) of this design are the following:

- They may be less expensive and time consuming than cohort studies.
- Rare diseases or diseases with long latency or induction periods are more feasible to be explored.
- It is possible to investigate multiple exposures within the same study
- When a risk set sampling is used to select the controls, the OR is an unbiased estimate of the incidence rate ratio.
- In "nested" case-control designs, information on exposures have been collected before cases had been diagnosed, and may be less prone to bias.

As general limitations can be cited:

- Prone to selection bias, especially when controls are not a random sample from the case source population.
- Prone to information bias: recall and observer bias, although it depends on the data source.
- Information on exposure and outcome is collected at the same time, therefore a causal relation is difficult to ascertain, especially in those studies which the selection of patients was based on interviews.
- Rare exposures can be difficult to explore (huge sample size).
- Disease incidence or prevalence cannot be estimate directly, but it may be calculated in the nested studies.

Therefore, performing a "nested" case-control design may prevent some of the biases mentioned above.

5.1.3 Case Crossover (CXO) Study

The case crossover method was developed by Maclure (1991), to investigate the effect of transient exposures on the risk of acute events, especially to investigate risk factors that might trigger a myocardial infarction (126). It arose from the difficulty of finding healthy controls representative of the general population, presence of selection bias in hospital controls and the need to response rapidly to serious acute events.

Apart from studying immediate determinants of myocardial infarction, such as physical exertion, anger, cocaine use, sexual activity, etc (127); it has been applied as well to study drug adverse reactions as the risk of acute coronary events in patients with erectile dysfunction exposed to sildenafil (128); toxic epidermal necrolysis with nevirapine or the risk of flare of inflammatory bowel disease with antibiotic use, for instance (129, 130).

The CXO follows the logic of a matched case-control study, retrospective study where events are fixed and exposure is random. The particularity is that controls come from the follow up time or person-time of cases before the event happens. Namely, controls are periods of time where person who developed the event of interest still had not developed at that time. This provides a set of matched variables corresponding to the event of interest and to control periods that may be analysed as a matched case-control study.

The key feature of this design is that each case acts as its own control. It uses the difference in exposure rates just before the event (case) with those at other time (controls) to estimate an odds ratio of the outcome associated with exposure. In pharmacoepidemiology all control moments are selected prior to the outcome event, because changes in patient´s medical condition may alter the therapy they are being prescribed (131). Likewise, when the analysis employed is a conditional logistic regression with more than one control moment, distribution of exposures must be exchangeable between those periods to emulate a case-control design where the order of controls is irrelevant (132).

Concisely, assumptions required for this method are the following:

- Onset of the event must be acute

- Exposure should be intermittent (only discordant pairs contribute to the estimate) and with stable prevalence over time

- The effect of the exposure must be transient with no carry over effect

- Probability of exposure should be the same in all control moments

This method presents several advantages over other designs:

- Only cases are necessary, therefore, costs are lower

- All individual confounders that do not vary with time such as genetic factors, social status, sex, race, etc are implicitly controlled for

- Comparisons are intra-subjects instead of inter-subjects

- Simpler to design than a case-control as there is no possibility of selection bias to select controls

- Provides a quantified, statistically valid effect estimate

- Ethical benefits without selection of controls

In contrast, main limitations of this method are:

- Time varying confounders should be taken into account

- Distribution of exposure should be exchangeable over time

- Exposure need to be transient, not valid for chronic treatments

- The need to infer the length of control periods might over or infra estimate the association

5.1.4 Self-Controlled Case Series (SCCS) Study

The self-controlled case series method was developed by Farrington (1995) to study the association between vaccination and adverse events arisen in the 90's. This method was initially thought to avoid confounding factors not controlled by other designs such as cohort or case-control designs, because the exposure to vaccines was not uniform, and the population from which the cases arise may not be well known (133) or even with a high vaccine coverage it was hard to find appropriate non-exposed controls. Another key factor was the need to give a response as quick as possible after the event was known and the classical methods required a prolonged time span than was normally affordable. For those reasons the "case series" method was created.

Although initially this method was thought to investigate the effect of vaccination and acute potential adverse events, later on, it has been applied in other areas of pharmacoepidemiology (134, 135), to investigate transient exposures with acute and non-acute (136, 137) outcomes, employing only individuals who experienced the outcome of interest.

The self-controlled case series method follows the cohort design approach, where an event may occur randomly during the observation period, and the follow up of each patient is divided according exposure status. It offers the possibility to investigate the association between time varying exposure and acute outcome events. Since only cases are sampled, the probability an event occurs is related to the individual's time of exposure. The method is derived from a Poisson model by conditioning on the individual total number of events and its exposure history. It is self-matched and hence all age-independent confounders are implicitly controlled for (138). 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 (139).

Three key assumptions are required by this method to be applicable (140):

1- Events arise in a non-homogeneous Poisson process, therefore rare non-recurrent events may be analysed with this method. In case recurrent events are not independent, as may be the case of hip/femur fractures, but the occurrence of a first event is rare; the method can be applied using just the first event. So, considering a hip/femur fracture as a rare event, only first fractures will be used.

2- 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.

3- The occurrence of the event of interest must not censor or affect the observation period. This assumption might be violated in case the event is death, and a single exposure has occurred. It could be considered the event as rare, and taking the observation period as the time from exposure to the end of the *planned* observation period. In summary, the key features of this method are the following:

- Only cases are required.
- It is a conditional cohort method.
- Follow-up is not censored at the time of the event.
- It can be applied with independent recurrent events, or rare non-recurrent events.
- Analysis is self-matched, removing the effect of fixed confounders.

Consequently, main advantages of this method are:

- All fixed variables such as socio-economic status, gender, severity of underlying disease, location, etc, are controlled by design.
- Only cases are sampled, hence data collection and cost are reduced.
- It provides consistent estimates of the relative incidence.
- Temporal variations and age can be included in the model, having high efficiency comparative to cohort studies.
- Independent recurrent events can be studied.
- Dependent recurrent events, if the occurrence of the event is considered rare, can also be studied taking into account only the first event.

In contrast, main limitations are the following:

- The probability of exposure and the follow up time should be independent of the occurrence of the event, if not, the estimates may be biased (unless results are properly corrected for).
- It only provides estimates of relative incidence, not absolute incidence.
- It requires variability in the time or age of the event (not all events happen at the same time or age)
- It cannot be used when the event only occurs a long time after the exposure.
- The occurrence of an event must not censor or affect the observation period thus it is not good for mortality studies, although a modified form can be used.

5.2 DATA SOURCE

Data employed in all designs came from the Spanish *Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria*, BIFAP, which has been described previously (see Introduction, section 1.4.2). It is a national electronic healthcare records database from primary care, operated by the Spanish Medicines Agency (AEMPS), which aims to promote public health performing pharmacoepidemiological studies to evaluate the safety and effectiveness of medicines in Spain.

This database collects data from practices or health centres; at 2009, included information of more than 3.5 million of patients, covering 6.9% of the Spanish population. Those data are provided voluntarily by primary care physicians (general practitioners or primary paediatricians) of the National Health System, with the collaboration of nine Autonomous Communities. From those, 3,180,161 patients contained valid information to participate in research studies, with a follow up time in the database of 11,526,376 person-years. All information is anonymised, containing clinical data related to health issues, prescription records, and general characteristics data.

For the two descriptive studies performed, data from the following data sources were used to compare with the Spanish ones, following same protocol: The Danish national registries (DKMA) (http://www.dkma.dk) (http://www.sst.dk), the German: Bavarian Association of Statutory Health Insurance Physicians database (Bavarian Claims) (http://subs.emis.de/LNI/Proceedings/) , the Dutch Mondriaan project (http://www.projectmondriaan.nl) with two databases: Netherlands Primary Care Research Database (NPCRD), and Almere Health Care group (AHC) http://www.zorggroep-almere.nl), and two databases from the UK, the Clinical Practice Research Datalink (CPRD) (formerly known as the General Practice Research Database, GPRD) (http://www.cprd.com) and The Health Improvement Network (THIN) (http://www.thin-uk.com). More detailed can be found in the articles (120, 121, 141)

5.2.1 Period of data collection

The study period for all designs was considered from the 1st January 2001 until 31st December 2009. The start date or left censoring date was the latest of the following: 1st January 2001; the date that a practice was enrolled into the database (BIFAP); the date that a patient was registered in a practice; or the date that a practice became up to research standards.

In the same way, the end date or right censoring date was the earliest of the following: 31st December 2009; the date a patient died; the date a patient was transferred out of the practice; the date that the practice left BIFAP; or the latest recorded event date.

5.3 STUDY POPULATION

5.3.1 Descriptive study designs

The study population consisted of all patients included in the period of valid data collection with the criteria of left and right censoring dates cited above. The only difference between the two descriptive studies was that the study period for the incidence of hip/femur fractures was from 1st January 2003 to 31st December 2009, whereas for the prevalence of BZD and related drugs use the study period was from 1st January 2001 to 31st December 2009 due to the availability of data in the different European data sources to allow comparison between them.

5.3.2 Cohort and NCC designs

From all patients comprised in the period of valid data collection, those who had at least one year of enrolment with the GP, were aged 18 years or older, and had at least one BZD or related drugs prescription, were included in the cohort study. The date of the BZD or related drug prescription was considered the *start date* in the cohort study. Patients with a recorded prescription within six months before left censoring date were excluded to restrict the analysis to new users only. In addition, patients with a code of hip/femur fracture within the year before the start date were also excluded. The reason for that criterion is because it was established a minimum of 12 months as gap between fractures to be considered

as a new event. Besides, when the hip/femur fracture occurred the same day that the first BZD prescription, those patients were disregarded because temporality between exposure and event was ambiguous, thus, the cohort follow up started on the following day of BZD prescription, day 1 not on day 0.

All patients identified were followed until one of the following events occurred: (a) occurrence of Hip/femur fracture, (b) death, (c) transfer out practice, (d) practice left the database, (e) end of the database collection and (f) end of study period, whichever came first. Cases identified in the cohort study were then used for the NCC design, being the date on which the hip/femur fracture occurred, the *index date*. For the NCC design a random sample around 10,000 patients from the cohort study was selected according to a risk set sampling (see section 5.4.2).

5.3.3 CXO and SCCS designs

From all patients comprised in the period of valid data collection, those who had at least one year of enrolment with the GP, were ≥18 years old, and were 12 months free of hip/femur fracture before the start date were included in the study population. All patients had to have a record/diagnosis of hip/femur fracture during the study period (1st Jan 2001-31st Dec 2009), and although in both designs it was required to have at least one BZD or related drug prescription during the study period, only for the SCCS was required to be free of those prescriptions within six months before the start date to restrict population to new users. This criteria was not applied for the CXO in order to give cases occurring at the beginning of follow up the same opportunity to be exposed to BZD (in both case and control moments), and therefore to avoid bias. As restricting to have a BZD prescription six months before the start date, for those who had a hip/femur fracture close to that date, would be necessarily unexposed.

Patients could entry at any time they fulfilled the criteria above. It had not to be necessarily the first hip/femur fracture that occurred in that patient but the first occurred after satisfying those criteria. The start date was the date patients met the cited criteria. The index date was the date on which the hip/femur fracture occurred.

In the SCCS, all "cases" were followed starting on the day after of the start date, until one of the following events occurred: (a) death, (b) transfer out practice, (c) practice left the database, (d) end of the database collection and (e) end of study period, whichever came first. For the CXO, hip/femur fracture was the index date, and the exposure of the "cases" was explored at four control moments.

A diagram with period of valid data collection and source population for all performed studies can be found in Figure 9.
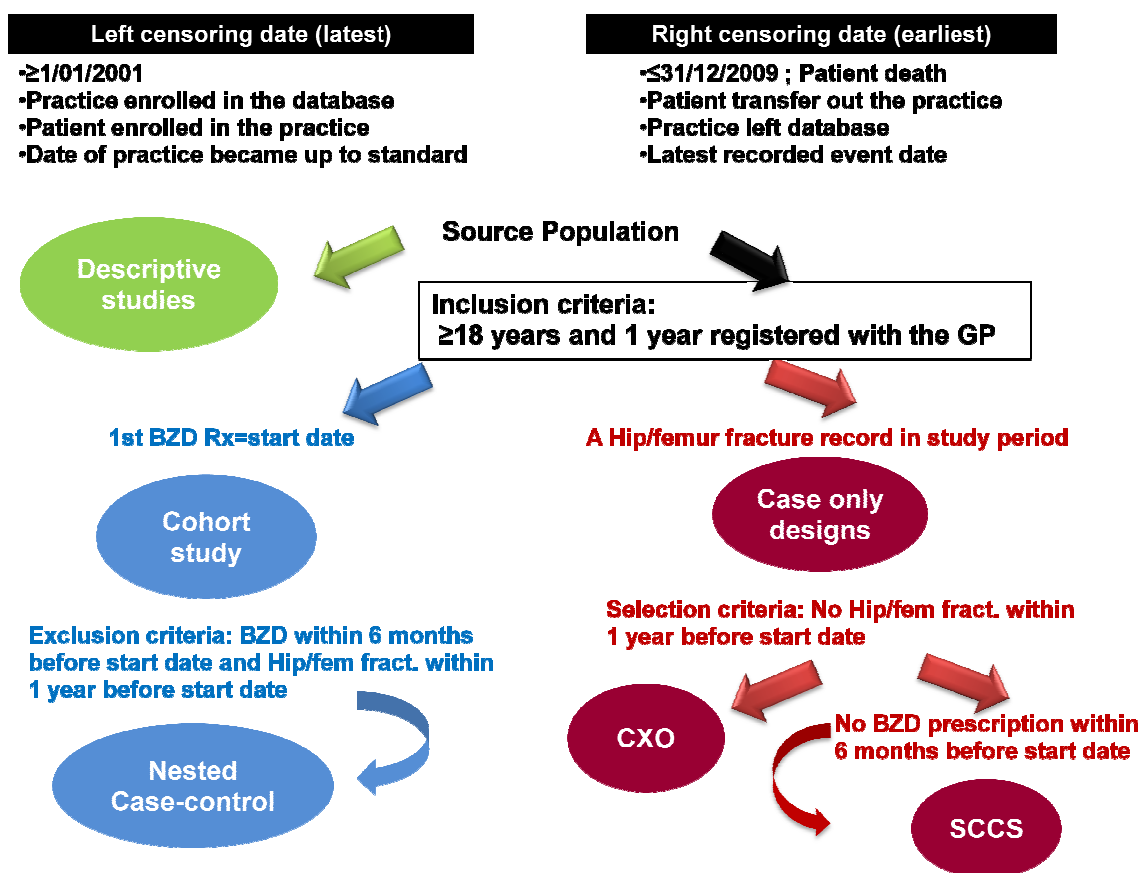
Figure 9- Source population for all studies designs

5.4 OUTCOME DEFINITION

Fractures of the acetabulum (socket) and other pelvic fractures (ilium, ischium, or pubis) are not considered to be hip fractures and have not been included in this study. However, femur fractures have been included since the nomenclature of health problems used by GPs taking part in BIFAP is the ICPC-2 classification which only use a code for "femur fracture" (L75), which includes all hip fractures: femoral head, femoral neck, intertrochanteric, subtrochanteric, etc. defined as a fracture of the proximal femur in the cervix or in the trochanteric region, So, the term "hip/femur" fracture was considered to be the operational outcome definition for this research. In addition, some authors have suggested to use all femur fractures in surveillance programs in order to avoid a misclassification of disease by miscoding (142).

Thus, patients with a recorded diagnosis of a new event of hip/femur fracture during the study period were considered to have the outcome of interest, regardless of whether they had a history of past fractures. For a current fracture to be considered a new event, a minimum of 12 months should have elapsed between the two episodes. That was an inclusion criterion for all designs, except for the descriptive study of incidence rates of hip/femur fractures where patients with a history of past hip/femur fractures ever before the study period were excluded to increase the likelihood of including incident episodes only.

The outcome was searched in BIFAP database using the International Classification of Primary Care: ICPC-2, code L75 "*Fractura de fémur*" and free text: "fractura cadera" or "fractura femur" or "fractura femoral".

5.4.1 Case ascertainment and validation

The same "case" definition was applied for all designs. A validation of cases ascertainment was performed in the four analytical studies. For instance, patients, who after reviewing their automated clinical records had a hip/femur fracture due to a major trauma such as road traffic accidents, were not included in any design. As a result of the validation process around 30% of cases were excluded, of them, about 15% were fractures due to major trauma; about 60%

were other diagnoses (no fractures) and other fractures (e.g. pelvis fracture); and about 25% were prevalent cases (hip fractures before study period) or the date of fractures was unknown.

5.4.2 Selection of Controls for the NCC design

A risk set sampling method was employed to select the controls. Therefore, cases were compared with a set of patients at risk to develop a hip/femur fracture at the same moment the cases occurred. Those controls might become a case afterwards, so they could be re-sampled at different moments in time (until they became a case). Each case of hip/femur fracture was matched to up to four controls by sex, age (± 2 years age-band), and follow up time (+/-6 months) defined as the time contribution of each patient from the start date to the index date (hip/femur fracture date). Index date was the same date for each case and its matched controls. Matching by similar age was given priority against follow-up time. Then controls were selected progressively by follow-up time relaxing day by day up to a maximum of six months.

5.4.3 Cases and Controls dates for the CXO design

The date of the first diagnosis of the hip/femur fracture within the study period was considered the index date. Each case served as its own control, e.g., contributed to one case moment and up to four control moments. The case moment was defined as the index date. The control moments were defined at 91, 182, 273 and 365 days prior to the index date as represented in Figure 10.
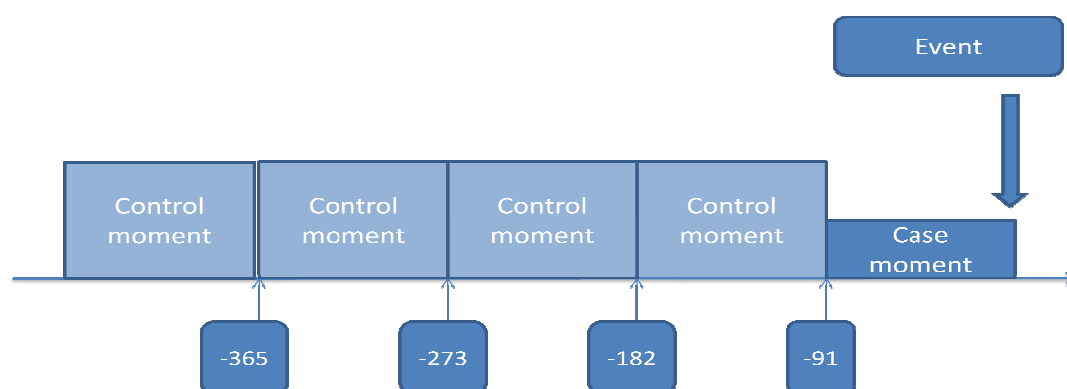
Figure 10- Case and control moments defined in the CXO design

5.5 EXPOSURE DEFINITION

5.5.1 General criteria for all designs

To ascertain the exposure of interest the Anatomical Therapeutic Chemical (ATC) classification system was used (http://www.whocc.no/atc_ddd_index/). In that system the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels. Thus, 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. BZD primarily used in other indications (e.g. tetrazepam used as muscle relaxant, clonazepam used in epileptic patients) were not included in this study. A complete list of codes employed is available in Appendix A.

The prescription of the drug of interest was the indicator of exposure for the descriptive study of prevalence of BZD and related drugs use.

For the analytical designs, the complete person-time of patients was divided according to their exposure. Thus, duration of each prescription was estimated based on the prescribed amount and daily dose. In case of unknown data, the most recent previous prescription was used to estimate it. When that was not possible, population-mode specific for each presentation of pharmaceutical form was employed.

A treatment episode (TE) was defined as a series of subsequent prescriptions and according to the method described in Gardarsdottir et al (143). In case a subsequent prescription is collected before the theoretical end date, with another ATC or different active ingredient, the patient is considered to have changed therapy and the remaining days from the prior prescription are disregarded (Fig.11, Method 1). However, if the subsequent BZD prescription collected before the theoretical end of the current one is from the same drug (active ingredient), the number of overlapping days is added to the theoretical end date of the repeat

prescription (Fig. 11, Method 2).
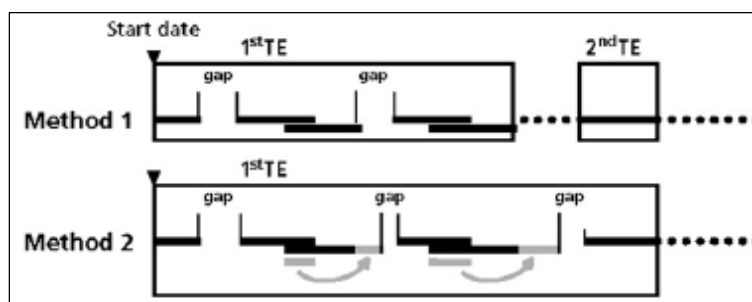
Retrieved from H. Gardarsdottir et al. Journal of Clinical Epidemiology (2010).

Figure 11- Method of Gardarsdottir et al. to define length of treatment episodes

A new TE was considered when an interval of more than 30 days occurred between the theoretical end date of a prescription and the dispensing date of the subsequent prescription for the same patient.

Total person-time of each person was divided according their exposure status into periods of current, recent and past use (Figure 12) for cohort and NCC designs that started with a prescription of BZD or related drugs.
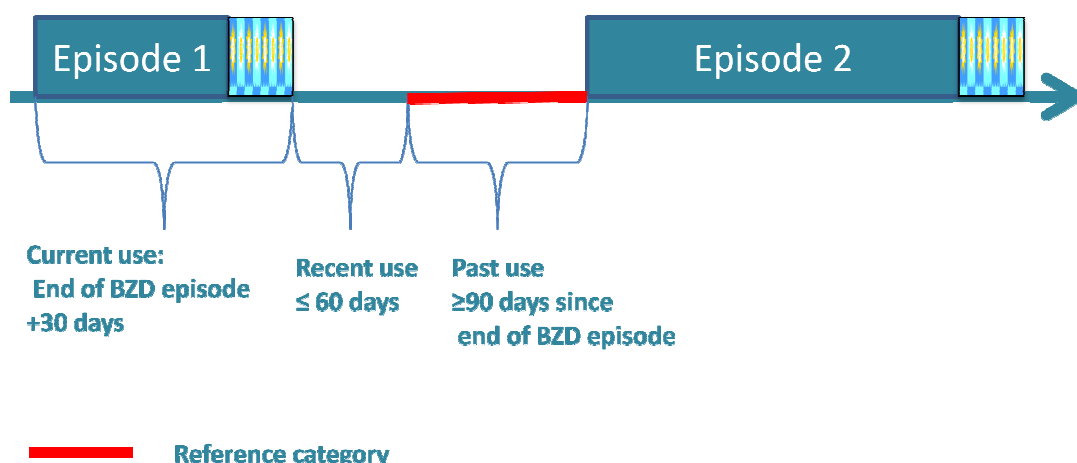
Figure 12- Person-time divided into exposure status for Cohort and NCC

- **Current use** defined as the period from the start of a BZD or related drug prescription until 30 days after the estimated end date of the supply.

- **Recent use** defined as the period up to 60 days after current use.

- **Past use** defined as the period after recent use until the patient became a new user or the end of follow-up. This period was considered as the *reference category*.

The period of *Recent use* after treatment was included because there is a natural uncertainty about the exact date that treatment is stopped, and this period represents a gradual shift from full exposure, followed by a washout period, and finally to an entirely unexposed state (*Non use* or *Past use*).

Likewise, for cases and controls in the NCC, the exposure was defined as *current use* when a prescription lasted until the index date or ended within the 30 days before (-1 to -30) index date, *recent use* when the most recent prescription ended within the 31 and 90 days before the index date, and *past use* when the most recent prescription ended before 91 days prior to the index date.

For the case only designs, an extra period of *Non use* (Figure 13) was also considered because the start date of those studies was not necessarily coincident with a BZD or related drug prescription.

- **Non use** defined as the period between the start date and the first BZD or related drug within the study period. This period together with the past use was considered as baseline or *reference category*.
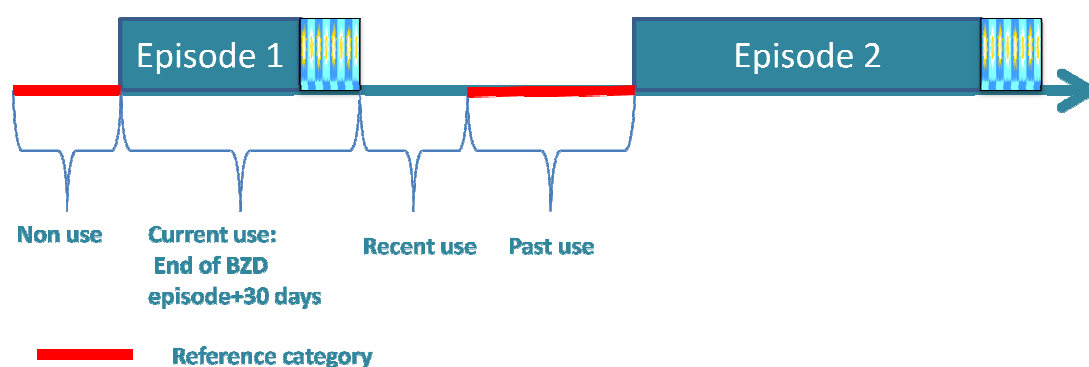
Figure 13- Person-time divided into exposure status for CXO and SCCS

Among current users, the exposure was stratified according the following factors:

1. **Duration of use** was classified into five categories: 0-30, 31-60, 61-182, 183-365 and > 365 days.

2. **Type of BZD** was divided per ATC group as:

   a) Single use of anxiolytics (ATC N05BA)

   b) Single use of hypnotics (ATC N05CD, N05CF and N05CM02)

   c) Use of both, anxiolytics and hypnotics

Among those with only one active ingredient further stratifications according to individual drugs, dose and half-life were explored:

3. **Individual BZD** or related drugs:

   a) Anxiolytics -Benzodiazepine derivatives (N05BA):

   - Lorazepam

   - Bromazepam

   - Diazepam

   - Alprazolam

   - Others: Clobazam, Clotiazepam, Pinazepam, Oxazepam, Chlordiazepoxide, Prazepam, Potassium Clorazepate, Ketazolam, and Halazepam.

   b) Hypnotics and sedatives - Benzodiazepine derivatives (N05CD):

   - Lormetazepam

- Flurazepam

- Loprazolam

- Others: Midazolam, Triazolam, Brotizolam, Flunitrazepam, Quazepam, Temazepam and Nitrazepam.

    c) Hypnotics and sedatives - Benzodiazepine related drugs (N05CF):

- Zolpidem

- Others: Zopiclone and Zaleplon

    d) Other hypnotics and sedatives (N05CM02):

- Clomethiazole

4. **Dose** of current single users was classified with the Defined Daily Dose (DDD) as the number of DDDs per day. For instance, assuming that the DDD for diazepam is 10mg, a prescription of 30 tablets of diazepam 5mg, lasting a period of 30 days, it would be a dose of 5mg/day, so to calculate the DDD, it would be 5/10=0.5 DDD. Thus, doses were considered:

- **Low doses** <1DDD

- **Medium doses** =1 DDD

- **High doses** >1 DDD

5. **Half life** was classified as (144, 145):

- **Short**: <8h

- **Intermediate**: 8-24h

- **Long**: >24h

A list of BZD and related drugs, DDD, Half-life and Recommended Daily Dose is available in Appendix A.

From all these stratifications, individual BZD, dose and half-life were explored only in the cohort study. Stratification according type of ATC group (anxiolytic or hypnotic drug) was performed in all designs as follows:

- For the Cohort study the stratification was done relating to the use of single anxiolytics or hypnotics in the current period, and for the SCCS was done within each time risk window (see below).

-For the NCC and CXO this stratification was done according to the BZD prescriptions within the previous 90 days.

Finally, duration of use was performed in all but the CXO design, because in case a hip/femur fracture occurred at 1st January 2001, a period of time of at least 15 months prior index date would be necessary to explore duration of use; 12 months to explore duration and 3 months to have at least one control moment. In BIFAP data available before year 2000 are scarce, so it was decided not to perform this stratification for this design.

5.5.2 Specific criteria for SCCS design.

For the SCCS, the time risk windows chosen to investigate the exposure were similar to the duration periods: 1-30, 31-60, 61-182, 183-365 and >365 days. However, one key assumption of this design is that the exposure must not be affected by the occurrence of an event. That is not completely clear for this pair event-drug, because the prescription of a BZD or related drug might be altered by the occurrence of a hip/femur fracture, in both directions:

- The GP may be prone to prescribe BZD after the occurrence of the event as anxiolytic or sedative effect; in that case results obtained could be biased downwards, and therefore underestimate.
- On the contrary, the GP may avoid prescribing BZD after the occurrence of the event because the potential risk of falls; in that case, results obtained could be biased upwards, and therefore overestimate.

In case the event restricts the exposure, events are unlikely to occur in the immediate pre-exposure period time, this effect would deplete the baseline incidence and hence exaggerate the relative incidence. Similarly, if the event increases the exposure, this effect over the baseline would understate the relative incidence.

To investigate the possible event-exposure dependence, a sensitivity analysis was performed creating a "pre-exposure" period of 30 days (normal length of a BZD or related drug prescription) before each beginning treatment episode, to

remove this time from baseline and correct for the potential effect that this dependence might cause (Figure 14).
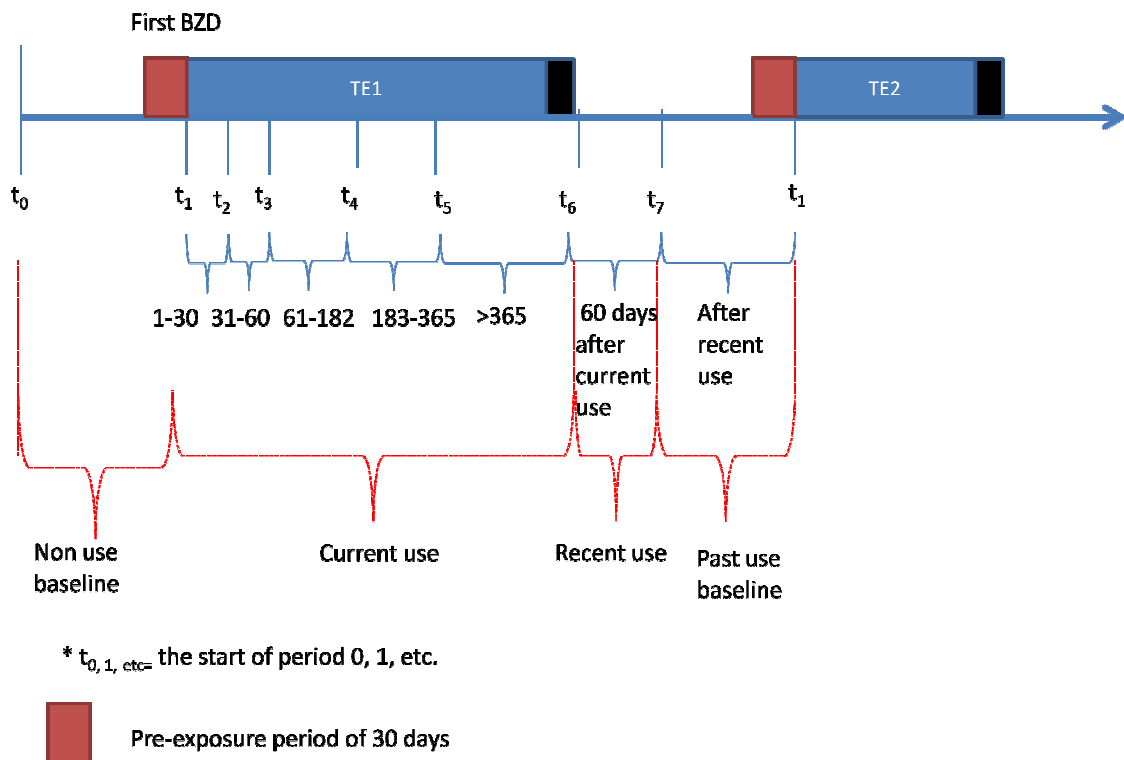
Figure 14- Sensitivity analysis creating a pre-exposure time risk window

5.6 COVARIATES DEFINITION

Information of age, sex and life-style factors such as weight, height, body mass index, smoking or alcohol abuse was extracted from patient's record in BIFAP, for every design. In addition, some drugs and diseases were considered potential confounders based on the published knowledge of risk factors for hip/femur fractures, and information about them was extracted as well.

Among **co-medications**, already described and referenced previously, were included the following presented in Table 5:

Table 5- Co-medication covariates

Co-medications
Oral Glucocorticoids
Bisphosphonate use
Raloxifene
Strontium ranelate
Parathyroid hormone
Calcium & vitamin D
Calcitonin
Antidepressants
Antipsychotics/lithium
Anti-Parkinson drugs
Anticonvulsants
Inhaled glucocorticoids
Bronchodilators
Antihypertensive drugs
Diuretics
Anti-arrhythmics
Sedating Antihistamines
Hormone replacement therapy (HRT)
Thyroid hormones
Antithyroid drugs
Disease-modifying anti-rheumatic drugs (DMARDs)
Thiazolidinediones
Other antidiabetics
Antiemetic (Metoclopramide)
Anticoagulants
Morphine/opiates
Non-steroidal anti-inflammatory drugs (NSAIDs)
Statins
Proton pump inhibitors (PPIs)
Aromatase Inhibitors

The exposure was measured by absence or presence of prescriptions of those drugs within six months (variable: "yes"/"no"; being "no" the reference category). To exclude sporadic use, two or more prescriptions of NSAIDs were needed to be considered exposed; and for Oral Glucocorticoids, prescriptions for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) were required to be considered exposed, so no prescriptions or treatments for less than 3 months were considered not exposed (Reference category).

Among **<u>co-morbidities</u>**, already described and referenced previously, were included the following presented in Table 6:

Table 6- Co-morbidities as covariates

Co-morbidities
Previous fracture
Rheumatoid arthritis
Osteoporosis
Paget's disease
Anaemia
Epilepsies/seizures
Syncope
Ischaemic heart disease
Cerebrovascular disease
Malignant neoplasms
Inflammatory bowel disease
Obstructive airway disease
Liver disease
Chronic renal failure
Mental disorders (without depression)
Dementia and/or Alzheimer's

They were included totally or partially as potential confounders depending on the design. All of them were searched in BIFAP database using ICPC-2. The exposure was measured by absence or presence of recorded codes of these variables ("yes"/"no"; being "no" the reference category). Codes, descriptions and variable values for all potential confounders are described in Appendix B.

5.7 DATA ANALYSIS

All analyses were performed using Stata software, version 11® (StataCorp, College Station, TX).

5.7.1 Descriptive Studies Analysis

5.7.1.1 Incidence of hip/femur fractures by sex and age per year

Annual incidence rates (IRs) of hip/femur fractures were calculated for the whole study population. The numerator comprised all first ever recorded cases of hip/femur fracture and the denominator was the total number of person-years of follow up. Annual IR among people aged 50 years or older were calculated separately, as most fractures occurring before this age are primarily due to trauma and many studies use this age limit (146, 147).

For the comparison of the IRs estimates with other European databases and over time, a direct sex and age standardization was carried out using the European Union population in 2008 (EUROSTAT) as the standard (http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database).

Age (in 10-year bands) and sex specific IRs over the study period were also calculated. Age of patients was computed at midyear within each calendar year of the study period. The incidence rate ratios (IRRs) and their 95% confidence intervals (95%CI) were calculated to assess the effect of sex on different age groups.

To quantify the trend over the study period a linear regression analysis for both crude and standardized rates was performed, defining the annual IR as the dependent variable and the calendar year as the independent variable. The respective slope (β coefficient) was considered as the average change per year over the study period. This annual change was also expressed as a percentage of IR using the first year as reference. The null hypothesis of $\beta=0$ was tested using the t test. A p value <0.05 was considered significant. The 95% CI of the slope was also calculated.

5.7.1.2 Prevalence of BZD and related drugs use

Annual period prevalence was estimated by dividing the number of patients that received one or more prescriptions by the total number of person-years of

follow-up of all patients in every calendar year of the study period. Patients having more than one prescription in a particular year were counted only once. Due to the dynamic nature of the database, where patients have variable durations of follow-up time, person-years were considered as the most appropriate denominator. Prevalence rates (PRs) were standardized using the Eurostat 2008 population as before. Specific PRs were also provided by separate therapeutic groups (anxiolytics (N05BA) and hypnotics (N05CD, N05CF and N05CM02), age groups (in ten-year categories) and sex.

5.7.2 Analytical studies

5.7.2.1 Description of study populations

In each design, study population was described in terms of age, gender, life styles factors, co-medications and co-morbidities. Proportions of subjects for each variable were calculated. Distribution by sex and age was also estimated by categorized age variable in 10 years band up to last category of 90+. Co-medications were investigated within the 6 previous months and co-morbidities any time before.

5.7.2.2 Incidence Rates of hip/femur fractures associated with BZD

IRs of hip/femur fracture were calculated only in the Cohort study. Numerator was the total number of patients with a hip/femur fracture, and denominator was the person-years that each person contributed in the cohort. IRs were calculated separately by exposure status in current, recent and past users, overall and by sex and age in 10-years band.

5.7.2.3 Measure of the crude association of potential risk factors with hip/femur fractures

In the following analytical designs the independent association for life-style factors, co-medications and co-morbidities was examined:

a)   For the cohort study, crude Hazard Ratios (HRs) were calculated

using Cox regression analyses.

b) For the NCC and CXO crude odds ratios (ORs) were calculated using conditional logistic regression.

5.7.2.4 Risk of having a hip/femur fracture associated with BZD crude and adjusted by potential confounding factors

For each study design different incremental models were run to evaluate the adjusted risk of having a hip/femur fracture associated with BZD, taking into account different confounding factors.

In the **Cohort study**, a time varying analysis was done. All potential confounder variables were measured/updated whenever a patient changed between exposure status (current/recent/past) or at 182 days intervals in case a patient had a current or past period longer than 182 days. Besides crude analysis, five time dependent Cox proportional hazards models were run to calculate adjusted HRs and CI 95% as follows:

1) Model "age": adjusted analysis by age (as continuous variable)

2) Model A: adjusted analysis by age and sex

3) Model B: adjusted analysis by model A plus well known risk factors for fracture such as previous fractures, glucocorticoids use, rheumatoid arthritis and lifestyle factors (bmi, smoking, alcohol abuse).

4) Model C: adjusted analysis adding to model B risk factors immediately related to the outcome such as osteoporosis, Paget´s disease, biphosphonate, raloxifene, strontium ranelate, parathyroid hormone, vitamin D and analogues and calcitonin use.

5) Model D: adjusted analysis adding to model C other drugs and diseases associated with fractures in the past, such as antidepressants, or ischaemic heart disease (see Table 5 and 6).

In addition, to examine which variables were those that most affected to the association of BZD with the event of interest stepwise models were performed. After backward and forward analyses, the resultant variables were included in a new model, and those ones that did not change more than 5% the estimator of the exposure variable were eliminated. Interaction terms between variables were also explored. Finally, the most parsimonious model was obtained with the following variables: age, sex, previous fractures, glucocorticoids, antidepressants, anti-Parkinson drugs and the interaction between antidepressants with anti-Parkinson drugs.

In the **NCC study**, conditional logistic regression analysis was used to estimate the risk of hip/femur fracture associated with the use of BZD and related drugs adjusting for confounding variables. The risk was calculated in terms of ORs with corresponding 95% CI.

Co-morbidities were measured any time before the index date, and co-medications were measured within 6 months before the index date. In addition, a sensitivity analysis measuring co-medication within the 30 days previous to the index date was performed in order to obtain a closer measure for co-medication.

Regarding incremental models to adjust by potential confounders, only model B, C and D were run, since age and sex were matching variables for cases and controls.

Similarly, stepwise models were executed to investigate variables that most affected to the association of BZD with the event.

In the **CXO study**, conditional logistic regression analysis was used to estimate the risk in terms of ORs with corresponding 95%CI, similarly than the NCC analysis. The main difference with the only cases studies is that their analysis is within not between subjects so all intra-individual confounding factors are implicitly controlled for in both case only designs. Therefore, only co-medication was included in the adjusted model, and variables were measured at index date and at each control moment, that is at -91, -182, -273 and -365 days.

Similarly, stepwise models were executed to investigate co-medication variables that most affected to the association of BZD with the event.

In the **SCCS study**, conditional Poisson regression analysis was used to estimate the relative risk in terms of IRRs with corresponding 95%CI, to account for the matched nature of the data in accordance with standard practice for the SCCS method (148). This method has the benefit of allowing for exploration of changes in risk with duration of exposure, and it approaches cohort designs in terms of statistical power.

In this study, only age was considered as potential confounder. 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 were created for patients up to 59 years of age: 30-34, 35-39, 40-44, 45-49, 50-54, and 55-59. Then one-year age bands was created for patients from 60 to 95 years, after which the final age band summarised age for the oldest age group (>95 years). Thus, 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.

Relative incidence rates were calculated by comparing the rate of hip/femur fractures experienced during risk periods with the rate of events during baseline time that is, periods of past use or not use (see Figure 14). For this analysis only the first event (hip/femur fracture) that occurred within the study period was taken into account.

A sensitivity analysis was performed taking into account a new risk window up to 30 days just before the beginning of each treatment episode, estimating the IRRs in the same way than before. Besides, to inspect whether the length of that "pre-exposure" time risk window, affected the risk of developing a hip/femur fracture, the analysis was repeated with two additional and different lengths. Thus, one shorter than previously, with a length of 15 days, and one longer than initially, with a length of 60 days, were analysed.

5.7.2.5 Risk of having a hip/femur fracture associated with the type of BZD; duration of treatment; active ingredient; doses and half-life.

To investigate whether the risk of having a hip/femur fracture was related to the type of BZD or related drug taken, current use was stratified according to the use of anxiolytics or hypnotics in all designs. Similar analyses than explained previously were carried out among current users:

a) For the cohort design, a Cox or proportional hazards regression was used. In this analysis, the rate is allowed to vary continuously over time and hazard ratios (HRs) are the effects of different explanatory variables on the risk of having the event.

b) For the SCCS same conditional Poisson regression analysis was employed, with and without adjusting by age but now considering for each period time of exposure if they were taking only anxiolytics, hypnotics or both.

c) For the NCC and CXO, same conditional logistic regression analysis was used, exploring now the type of BZD or related drug taken within the previous 90 days for both designs.

Duration of treatment was explored for all but the CXO design as it has been explained before. Same mentioned analyses were performed for each one, dividing the length of treatment episode in 5 categories: 0-30, 31-60, 61-182, 183-365 and >365 days, which were the risk time windows for the SCCS study.

And finally, just for the cohort study, a Cox was defined for active ingredient, doses and half-life separately, using past use as category of reference. All these variables have been described in detail in section 5.5 among current users.

RESULTS

6. RESULTS

6.1 DESCRIPTIVE STUDIES

6.1.1 Incidence rates and trends of hip/femur fractures

The standardized IRs of hip/femur fracture for the population aged 50 years or older were 2-3 times higher than the ones for the general population, ranging from 15-25 per 10,000 py in the UK, the NL, and Spain to 52 per 10,000 py in Denmark, and around 30 per 10,000 py in Germany (Table 7). Standardized IRs for the general population can be found in the Appendix C-Additional tables from descriptive studies.

Time trends

A significant trend in standardized IRs in people aged 50 years or older was only observed for the British CPRD (+0.7% per year; $p<0.01$) and the Danish database (-1.4% per year; $p< 0.01$) (Table 7). For the remainder of databases no significant trend was observed.

Sex and age-specific IRs of hip/femur fracture

The crude and age-standardized IRs were 2-3 times higher in women than in men for the whole population and for the population aged 50 years or older, over the study period and across all databases (Figure 15). The IRs of hip/femur fractures grew exponentially from the age of 50 years for both females and males (Figure 16), which was a constant feature for all databases (DBs) and for the whole study period.

Table 7- IRs and time trends: population ≥50 years old in all databases.

	2003	2004	2005	2006	2007	2008	2009	Slope (95% CI)	V[#]
BIFAP									
No. fractures	1,298	1,643	1,638	1,629	1,558	1,350	1,027	-	
Person-years	475,139	588,242	616,300	589,588	554,287	472,785	369,872	-	
IR per 10,000py	27.32	27.93	26.58	27.63	28.11	28.55	27.77	0.15 (-0.14, 0.43)	**0.5**
Standardized IR	26.94	27.13	25.60	26.42	26.49	27.05	26.33	-0.04 (-0.32, 0.24)	**(-) 0.1**
CPRD									
No. fractures	2,858	3,087	3,139	3,265	3,295	3,367	3,291	-	
Person-years	1,327,959	1,406,185	1,447,563	1,476,874	1,475,205	1,470,594	1,446,832	-	
IR per 10,000py	21.5	22.0	21.7	22.1	22.3	22.9	22.7	0.22 (0.12, 0.32)*	1.0
Standardized IR	21.47	21.99	21.65	22.07	22.22	22.67	22.29	0.16 (0.04, 0.27)*	0.7
THIN									
No. fractures	2,614	2,734	2,831	2,785	2,830	2,899	2,839		
Person-years	1,241,173	1,259,016	1,270,685	1,284,095	1,294,565	1,302,336	1,288,704		
IR per 10,000py	21.1	21.7	22.3	21.7	21.9	22.3	22.0	0.13 (-0.04, 0.30)	0.6
Standardized IR	21.01	21.79	22.36	21.76	21.92	22.33	22.11	0.14 (-0.04, 0.32)	0.7
AHC									
No. fractures	45	39	60	51	45	47	-		
Person-years	23,883	25,935	28,039	30,293	32,657	35,583	-		
IR per 10,000py	18.8	15.0	21.4	16.8	13.8	13.2	-	-1.04 (-2.89, 0.80)	(-) 5.5
Standardized IR	26.84	21.75	32.43	25.85	20.24	19.75	-	-1.33 (-4.43, 1.77)	(-) 5.0
NPCRD									
No. fractures	157	101	77	82	124	107	74		
Person-years	103,010	64,504	62,856	52,701	76,946	60,608	45,969		
IR per 10,000py	15.24	15.66	12.25	15.56	16.12	17.65	16.10	0.37 (-0.38, 1.13)	2.4
Standardized IR	14.43	15.02	11.74	14.86	14.42	17.76	16.40	0.5 (-0.30, 1.31)	3.5
DKMA									
No. fractures	9,031	9,277	9,206	9,041	8,905	9,036	8,814		
Person-years	1,810,178	1,831,556	1,843,587	1,861,768	1,878,628	1,901,823	1,912,890		
IR per 10,000py	49.9	50.7	49.9	48.6	47.4	47.5	46.1	-0.72 (-1.03, -0.42)*	(-) 1.4
Standardized IR	53.39	54.27	53.51	52.02	50.88	50.97	49.54	-0.74 (-1.07, -0.42)*	(-) 1.4
BAVARIAN									
No. fractures	-	-	-	12,868	11,787	12,928	-	-	-
Person-years$	-	-	-	3,885,264	3,938,210	3,988,146	-	-	-
IR per 10,000py	-	-	-	33.12	29.93	32.42	-	-	-
Standardized IR	-	-	-	31.08	27.82	29.94	-	-	-

*95% CI: Confidence Interval; * p < 0.05 ; V[#] % Variation: (Slope/2003 IR)*100*
$ Incidence per 10,000 Insured persons in BAVARIAN, not enough data to assess time trends

A) Males
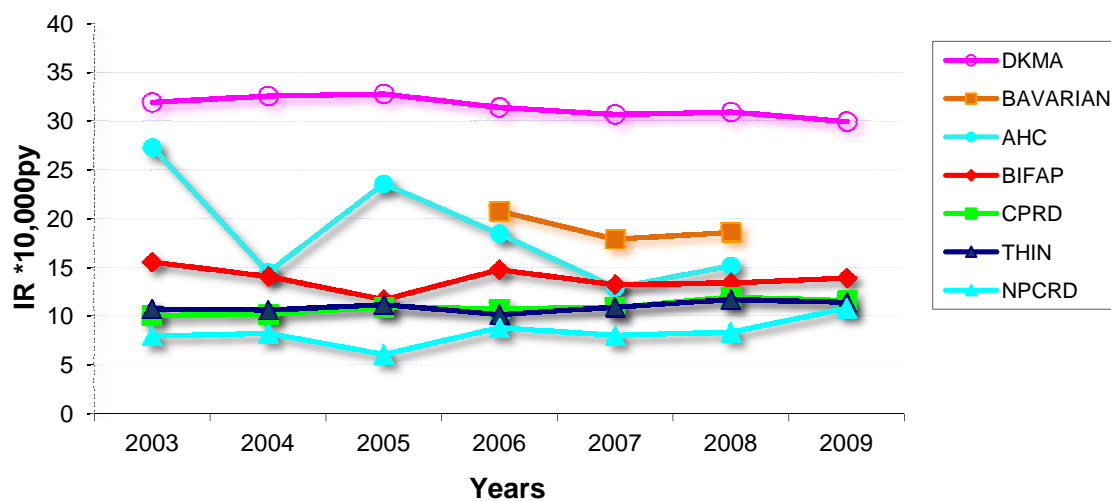
B) Females
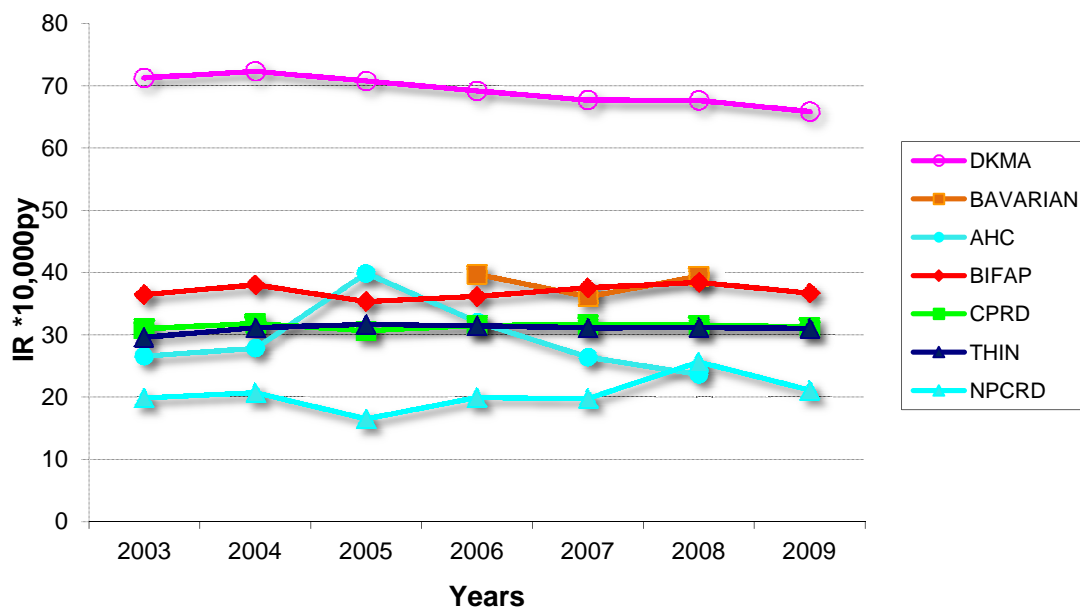
Figure 15- Age-standardized IRs of hip/femur fracture in males and females aged over 50 years old, and trends over time.
(Note that the scale used in females is double than the one used in males)

A) Males
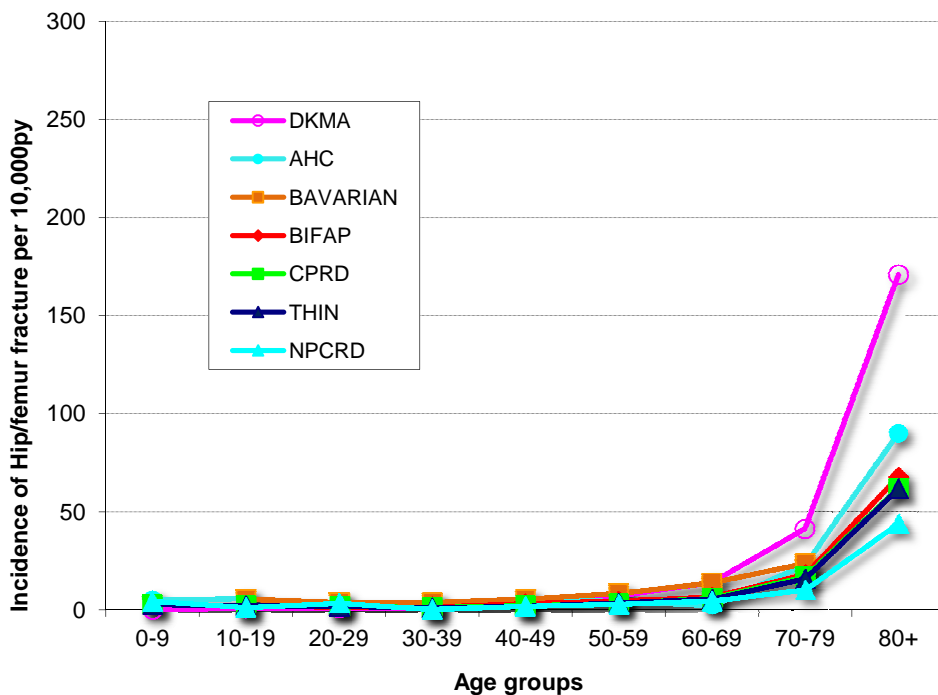
B) Females
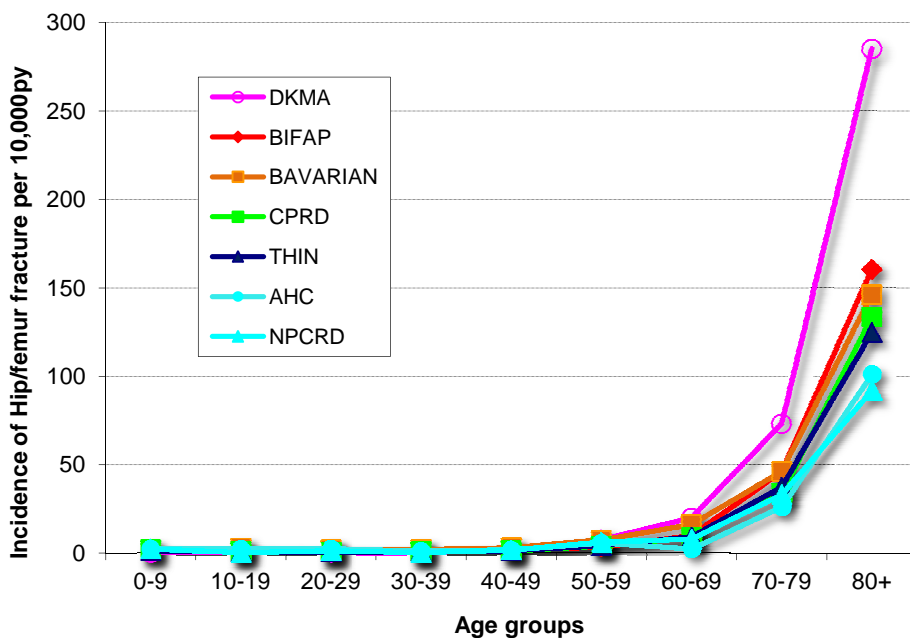
Figure 16- IRs of hip/femur fracture by age groups in males and females across databases in 2008.

The median standardized IRR of females vs males was strongly dependent on age: for age groups less than 50 years the IRR of females vs. males were consistently below 1, but then increased gradually reaching the maximum at the age 70-79 and then declined (Figure 17).
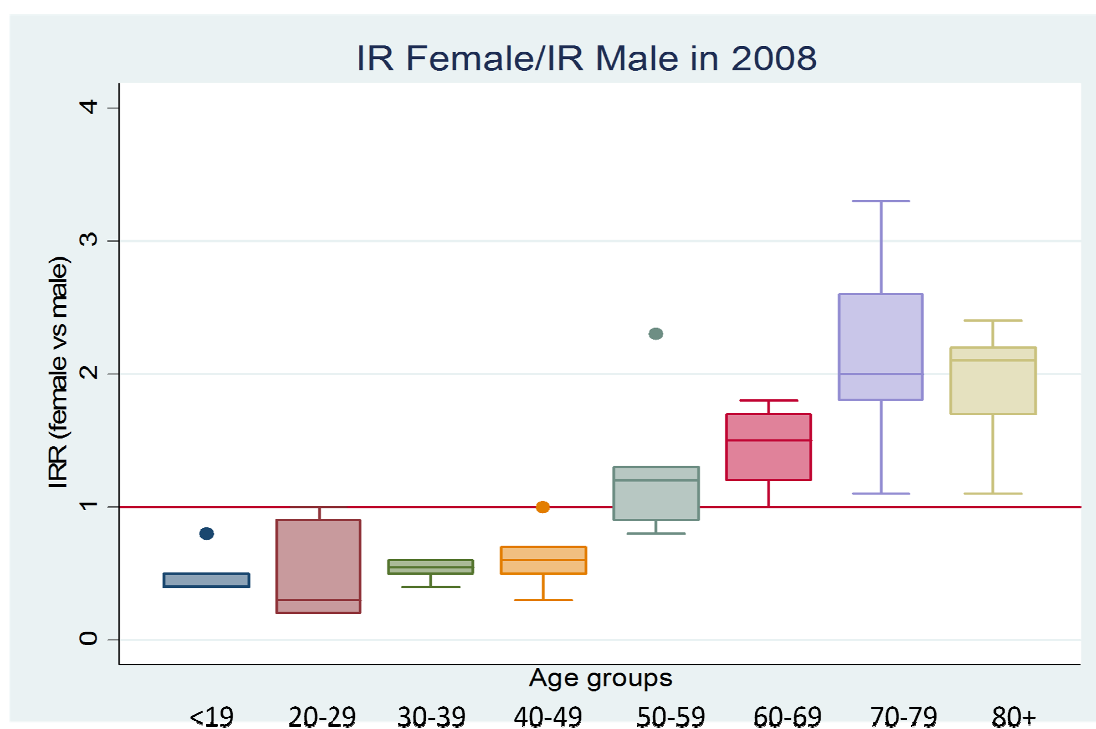
Figure 17- Box-plot showing 2008 IRRs of hip/femur fracture in females vs. males in the participating databases and their relation with age.

(Boxes represent the 25-75 percentiles; the bar within the box represents the median value).

6.1.2 Prevalence of BZD and related drug use

Prevalence rates (PRs), crude as well as age- and sex-standardized ones, are presented in Figure 18. Crude rates showed the highest prevalence of use in the BIFAP database (around 1,600 per 10,000 person-years) and the lowest in the German (Bavarian) and the British (CPRD and THIN) databases (around 570 per 10,000 person-years). The standardization did not substantially change the observed differences.

Prevalence rates by ATC group: anxiolytics (N05B) or hypnotics (N05C)

The prevalence of BZD and related drugs classified as anxiolytics showed in the BIFAP database a PR of use 4-times higher than hypnotics during the whole study period (i.e. 1439.3 vs. 363.2 per 10,000 person-years for 2008), a PR 1.4 times higher in the Bavarian database (i.e. 347.8 vs. 266.4 per 10,000 person-years for 2008) and 1.2 times higher in the Mondriaan-AHC database (i.e. 666.7 vs. 457.0 per 10,000 person-years for 2008). While in the Danish (DKMA), and the UK databases (CPRD and THIN), PR for hypnotics outweighed that of anxiolytics, around 1.2 to 1.5 times higher (i.e. 436.7 vs. 523.6, 302.8 vs. 355.6, and 291.5 vs. 359.6 per 10,000 person-years, respectively for 2008). Almost no differences were observed between anxiolytic or hypnotic drugs for the Mondriaan-NPCRD database (Figure 19).

A) Crude
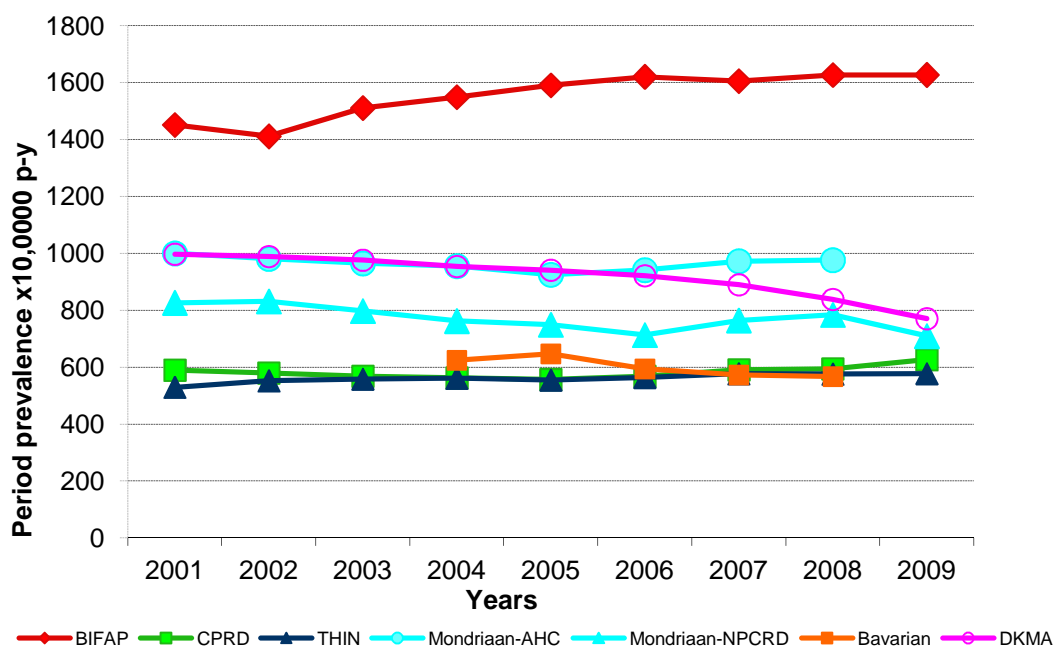
B) Standardized
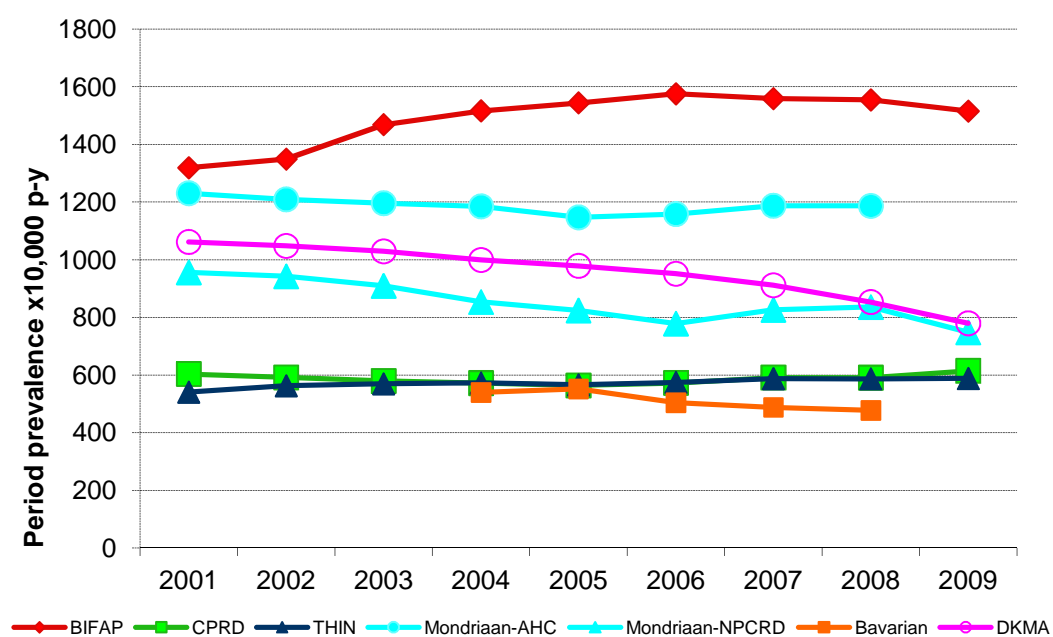
Figure 18- PRs of BZD and related drugs use by year in all databases

A) Anxiolytics (N05BA)
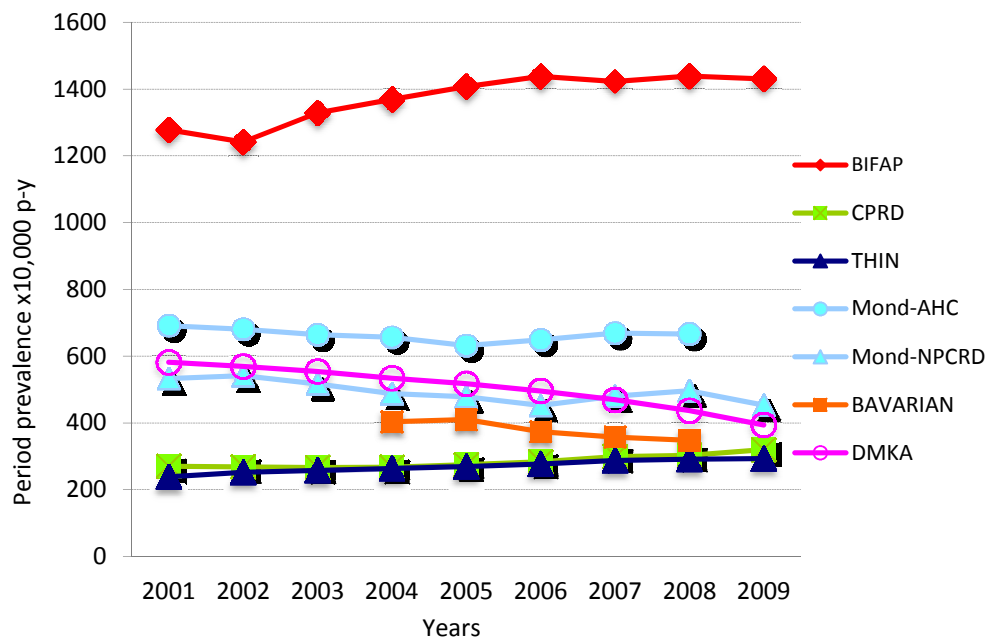
B) Hypnotics (N05C)
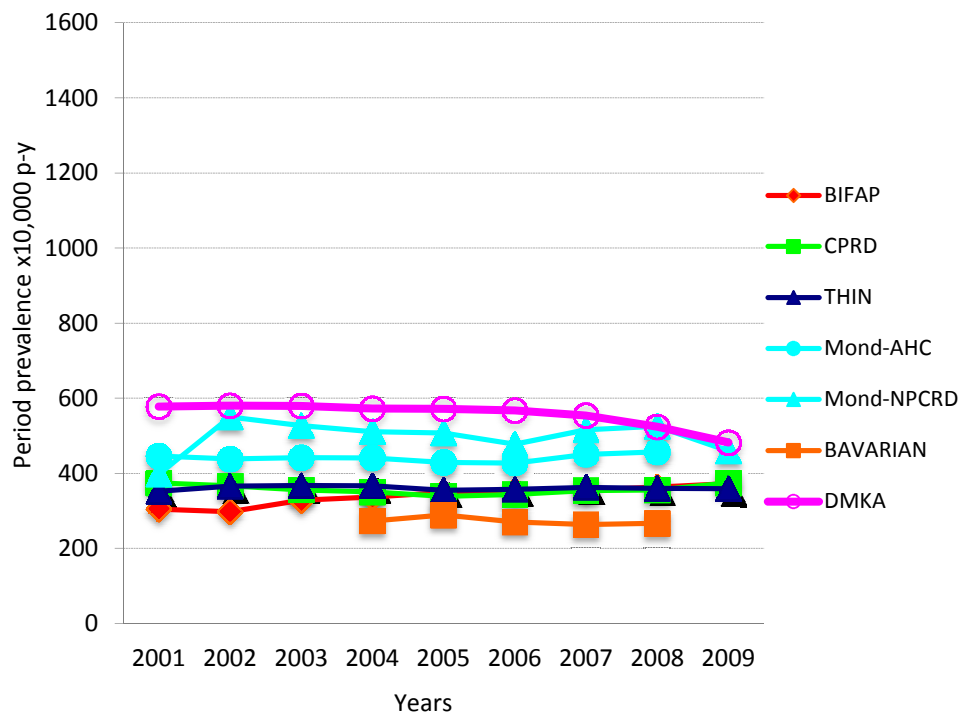
Figure 19- PRs of BZD and related drugs use by ATC group

Prevalence rates by age and sex

The prevalence of BZD and related drugs prescriptions increased steadily with age in all databases both in females and in males, although the slopes were higher in females (Figure 20).

A) Females
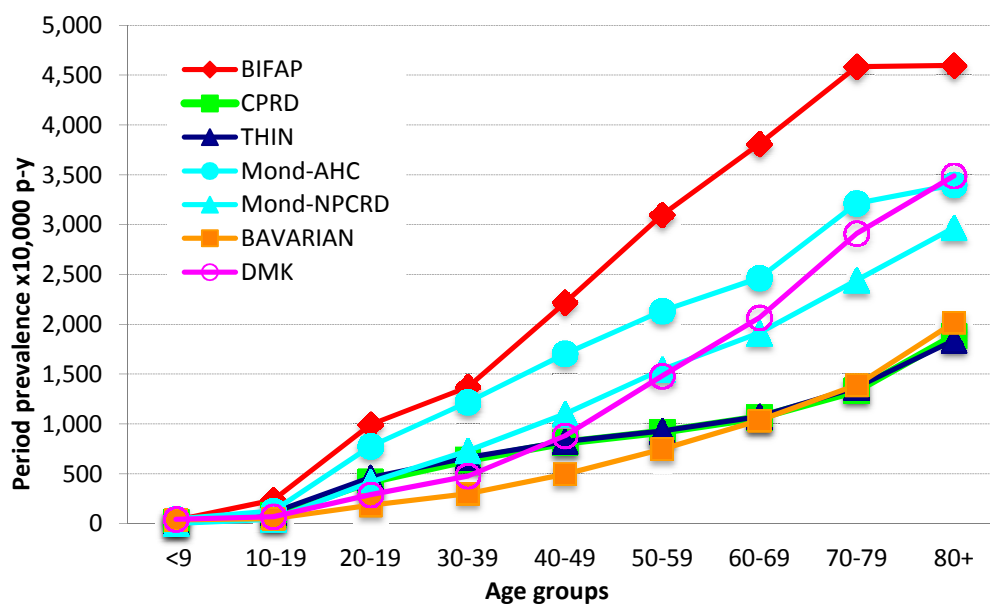
B) Males
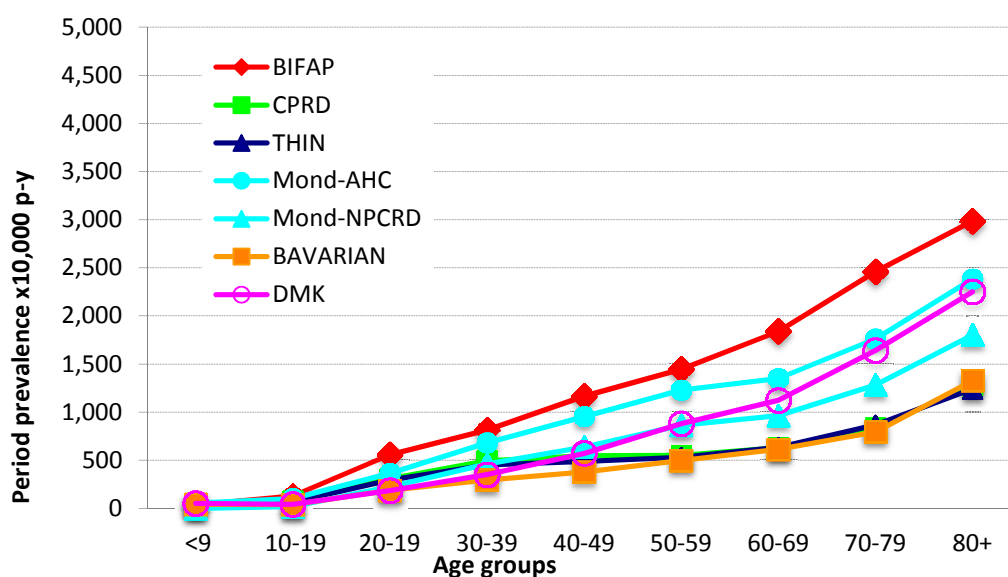
Figure 20- PRs of BZD and related drugs use by sex and age for 2008

This was observed in all age categories from 20 years and older. For all databases, the age-specific prevalence rates were about 1.5 to 2 times greater for women than for men, and this difference was particularly notorious in patients over 50 years of age.

6.2 ANALYTICAL STUDIES

6.2.1 Cohort study

From BIFAP, following the inclusion and exclusion criteria explained in section 5.3.2, a initial study cohort was selected. Then, after a case ascertainment and validation process, a final study cohort was reached (Figure 21).
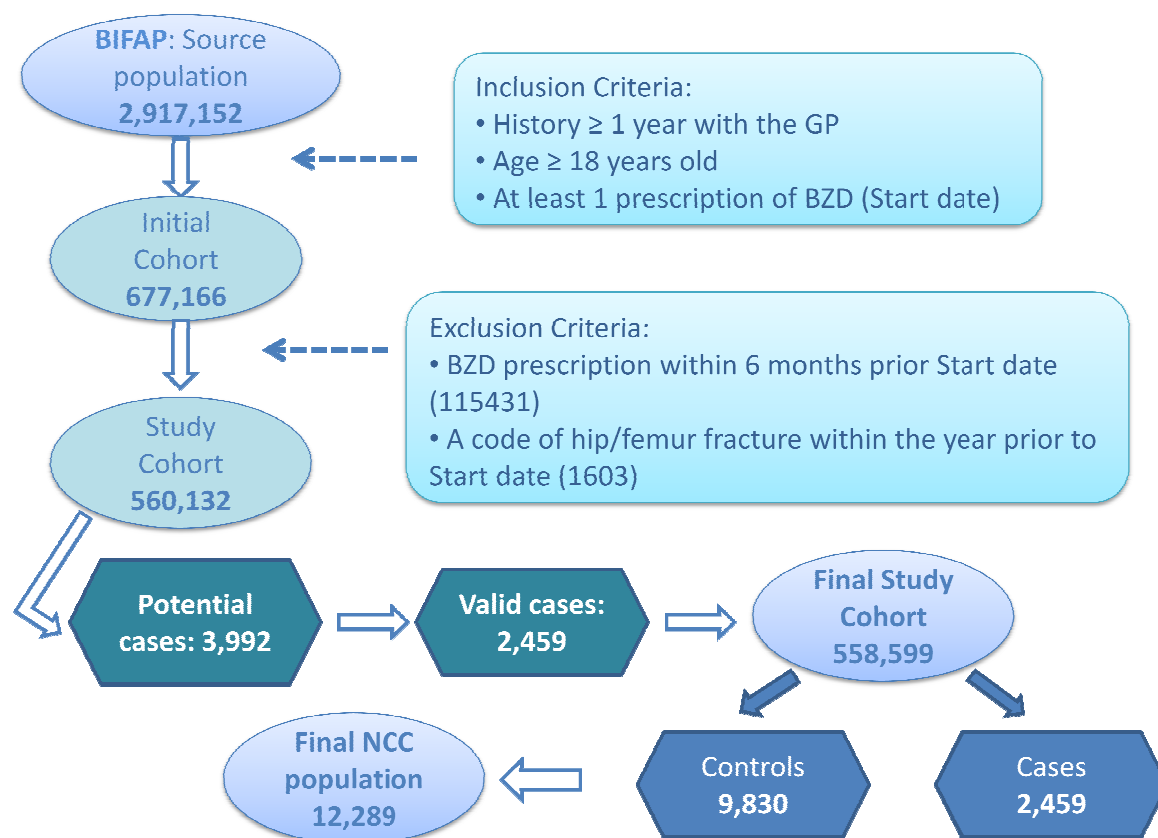
Figure 21- Flow chart of inclusion and exclusion criteria as well as final Cohort and NCC populations

6.2.1.1 Characteristics of the Cohort study population

Final cohort of BZD or related drugs users was composed of 558,599 patients. Age ranged from 18-107 years old, with a mean=52.0 ± 17.1 and 66% were women. Information about life-styles factors, distribution by sex and age in 10-years band categories was collected and presented in Table 8a and co-medication and co-morbidities are presented in Table 8b, together with the crude hazard ratio (HR) for hip/femur fracture estimates with those covariates.

Table 8a- Life-style characteristics and crude hazard ratio (HR) for hip/femur fracture estimates in the cohort

Cohort Population		N=558,599 (100%)	HR	95%CI
Mean Age (SD) years		52.0 (17.1)		
Age range (min - max)		18-107		
Age group (years)*				
18 - 29		75,264 (13.5)		
30 - 39	**18-39**	105,270 (18.9)	0.42	0.31-0.57
40 - 49		107,332 (19.2)		
50 - 59	**40-59**	98,620 (17.7)	1.00ǂ	
60 - 69		71,976 (12.9)		
70 - 79	**60-79**	62,765 (11.2)	9.39	8.00-11.02
80 - 89		31,475 (5.6)		
90+	**80+**	5,897 (1.1)	50.26	42.84-58.96
Sex				
Male		192,519 (34.5)	1.00ǂ	
Female		366,080 (65.5)	1.75	1.59-1.92
Smoking				
Yes		84,224 (15.1)	1.00ǂ	
No		173,543 (31.1)	0.2	0.17-0.24
Ex Fumador		8,240 (1.5)	0.37	0.26-0.53
Unknow		292,592 (52.4)	0.5	0.46-0.55
Alcohol Use				
Yes		17,380 (3.1)		
No / Unknown		541,219 (96.9)		
Body Mass Index (BMI)				
< 18.5 kg/m2, %		3,838 (0.7)	1.61	1.14-2.28
18.5-24,9 kg/m2, %		69,796 (12.5)	1.00ǂ	
25-30 kg/m2, %		92,072 (16.5)	0.99	0.88-1.12
>30 kg/m2, %		74,693 (13.4)	0.75	0.65-0.86
Unknown %		318,200 (57.0)	0.74	0.67-0.83

* Different age groups were created to calculate proportions N (%), and hazard ratios (HRs) in bold type;

SD=Standard Deviation; ǂ Reference category

The complete list of co-medications and co-morbidities was examined. As a result, the drugs most used in this population were: proton pump inhibitors; antihypertensive drugs [including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta blocking agents, calcium channel blockers and other antihypertensive drugs]; and non-steroidal anti-inflammatory drugs (NSAIDs), considered as exposed only if the patient had two or more prescriptions of those drugs; followed by statins, diuretics, antidepressants, and bronchodilators.

The following medication was taken by more than 2% of the population, but in lower percentages than the ones mentioned before: other antidiabetics 4.7%; morphine/opiates 4.2%; antipsychotics/lithium 3.4%; vitamin D plus Calcium and analogues 3.1%; thyroid hormones 2.7%; anticoagulants 2.5%; anticonvulsants 2.2%; and antiemetic 2.0%.

In the same way, the most prevalent diseases in this population were: malignant neoplasms; anaemia; syncope; ischaemic heart disease (IHD); previous fractures; osteoporosis; cerebrovascular disease (CVA); and chronic obstructive pulmonary disease (COPD). The rest of morbidities explored were suffered by less than 2% of the population (see Table 8b).

Table 8b- Co-medications and co-morbidities and crude hazard ratio (HR) for hip/femur fracture estimates in the cohort

Cohort Study Population	N=558,599 (100%)	HR	95%CI
Oral Glucocorticoids*	2,671 (0.5)	3.09	2.55-3.73
Bisphosphonates	9,855 (1.8)	2.69	2.32-3.11
Raloxifene	3,907 (0.7)	0.5	0.28-0.88
Strontium ranelate	478 (0.1)	1.95	1.04-3.62
Parathyroid hormone	65 (0.0)	5.88	2.44-14.15
Vitamin D+Calcium and analogues	17,153 (3.1)	2.15	1.47-3.15
Calcitonin	1,450 (0.3)	3.44	2.38-4.96
Antidepressants	39,868 (7.1)	1.87	1.72-2.04
Antipsychotics / Lithium	19,050 (3.4)	2.62	2.32-2.95
Anti-Parkinson drugs	2,991 (0.5)	6.27	5.27-7.45
Anticonvulsants	12,498 (2.2)	2.76	2.44-3.12
Inhaled glucocorticoids	9,175 (1.6)	1.54	1.22-1.95
Bronchodilators**	34,043 (6.1)	1.73	1.53-1.95
Anti-arrhytmics	3,209 (0.6)	3.62	2.86-4.57
Sedating antihistamines	3,891 (0.7)	2.35	1.78-3.11
Antihypertensive drugs†	93,745 (16.8)	3.06	2.83-3.31
Diuretics	43,976 (7.9)	3.82	3.51-4.15
Hormone Replacement Therapy (HRT)	6,789 (1.2)	0.21	0.10-0.45
Thyroid hormones	14,966 (2.7)	1.19	0.99-1.43
Antithyroid drugs	946 (0.2)	2.05	1.19-3.53
Disease-modifyng anti-rheumatic drugs	2,730 (0.5)	1.64	1.13-2.38
Thiazolidinediones	845 (0.2)	2.25	1.30-3.88
Other antidiabetics	26,009 (4.7)	2.77	2.48-3.09
Antiemetic (Metoclopramide)	11,307 (2.0)	1.54	1.23-1.92
Anticoagulants	14,119 (2.5)	3.55	3.14-4.02
Morphine / opiates	23,164 (4.2)	2.73	2.45-3.05
NSAIDs (≥ 2 prescriptions)	62,915 (11.3)	1.15	1.04-1.26
Statins	45,161 (8.1)	1.39	1.25-1.55
Proton pump inhibitors (PPI)	97,741 (17.5)	2.55	2.35-2.76
Aromatase Inhibitors	806 (0.1)	3.48	2.33-5.20
Osteoporosis	22,494 (4.0)	3.11	2.51-3.85
Paget's disease	432 (0.1)	2.96	0.74-11.84
Previous fractures	24,635 (4.4)	3.41	2.79-4.17
Rheumatoid arthritis	2,886 (0.5)	1.92	0.92-4.04
Anaemia	34,196 (6.1)	2.05	1.56-2.69
Epilepsies/ seizures	5,013 (0.9)	1.63	0.90-2.95
Syncope	28,322 (5.1)	1.73	1.31-2.28
Ischaemic heart disease (IHD)	26,919 (4.8)	2.22	1.93-2.54
Cerebrovascular disease (CVA)	17,294 (3.1)	5.32	4.44-6.38
Malignant neoplasms	34,367 (6.2)	2.66	2.19-3.23
Inflammatory bowel disease (IBD)	2,396 (0.4)	1.65	0.74-3.67
Obstructive airway disease (COPD)	15,383 (2.8)	3.01	2.33-3.89
Liver disease	8,699 (1.6)	1.87	1.17-2.97
Chronic renal failure	4,688 (0.8)	6.35	4.64-8.67
Mental disorders_no_depression	8,005 (1.4)	1.08	0.62-1.86
Dementia and/ or Alzheimer's	5,732 (1.0)	11.25	8.90-14.20

*Exposed to oral glucocorticoids for > 3 months

**Including Beta-2-adrenoceptors agonist and Anticholinergics

† Including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta blocking agents, calcium channel blockers and other antihypertensive drugs

6.2.1.2 Incidence rates of hip/femur fractures associated with BZD.

Total person-time of the whole cohort was 1,695,045 person-years (py), with a mean of follow up time of 1,491.9 ± 782.9 days (4.1 years), ranged from 1 day to 3,285 days (8.99 years). There were 2,459 valid cases of hip/femur fracture (0.44%), giving an incidence rate (IR) of 14.5 per 10,000 py, (95%CI: 13.94-15.09). The mean time to a fracture (among cases) was 884.3 ± 705.4 days (range: 1 day to 3,114 days).

The highest overall crude IR was observed among current users of BZD 24.4 cases per 10,000 py, (95%CI: 23.10-25.73) decreasing to 8.7 cases per 10,000 py (95%CI: 8.10-9.28) for past users. Similarly, women exhibited higher IRs than men in all exposure categories, being the highest IR among current users, and decreasing in recent and past periods of use (Figure 22). Regarding age distribution, the number of incident cases of hip/femur fracture increased exponentially with age regardless the exposure, while it is true that among current users and recent users the incidence of hip/femur fracture was higher than in past users. Low IRs were observed under 50-59 age category, but then increased sharply in the elderly.

IRs of hip/femur fractures across exposure categories (current, recent or past use) by sex are presented in Figure 22; and IRs according to age distribution are represented in Figure 23.
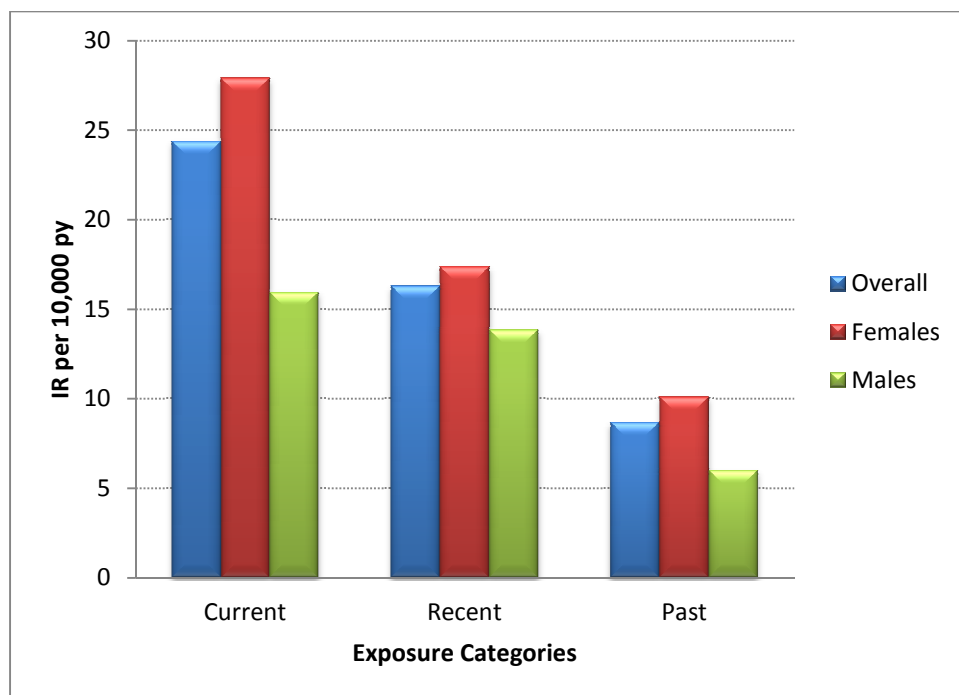
Figure 22- IRs of hip/femur fractures across exposure categories by sex.
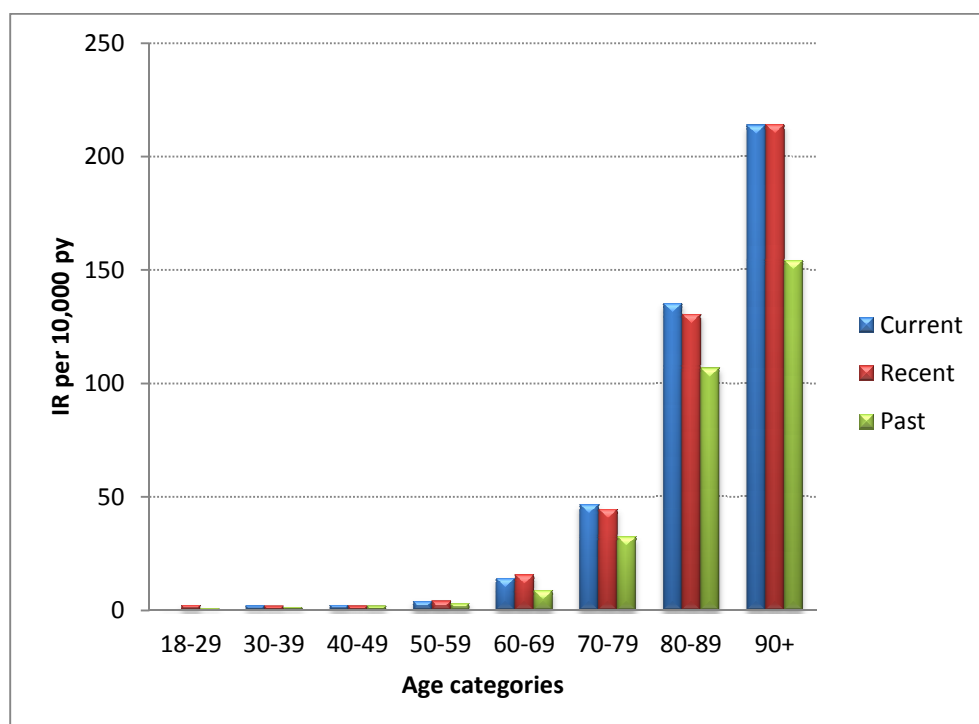
Figure 23- IRs of hip/femur fractures across exposure categories by age.

6.2.1.3 Crude association of potential risk factors with hip/femur fractures

In univariate Cox regression models (Table 8a) crude hazard ratios (HRs) of having a hip/femur fracture were higher in females and older people as it was expected. Those with a low body mass index (BMI <18.5 kg/m^2) were the ones that showed risk associated to hip/femur fractures, taking as reference category BMI between 18.5 and 24.9 kg/m^2. Smoking was not associated with the risk of having the event of interest.

Among co-morbidities, diseases that showed the highest HRs were dementia and/or Alzheimer's with 11.25 (95%CI: 8.90-14.20) followed by chronic renal failure and cerebrovascular disease, with 6.35 (95%CI: 4.64-8.67) and 5.32 (95%CI: 4.44-6.38) respectively. Then, with a hazard ratio around 3, were previous fractures, osteoporosis, Paget's disease (although it was not statistically significant due to the low proportion of patients with this disease) and COPD. Complete information can be found in Table 8b.

Among co-medications, drugs presented the highest crude HRs were anti-Parkinson drugs and parathyroid hormone with 6.27 (95%CI: 5.27-7.45) and 5.88 (95%CI: 2.44-14.15) respectively, followed by diuretics; anti-arrhythmic drugs; anticoagulants; aromatase inhibitors; calcitonin; glucocorticoids; and antihypertensive drugs, ranged between 3.06 and 3.82. Complete information can be found in Table 8b.

6.2.1.4 Crude and adjusted HRs of having a hip/femur fracture associated with the duration of treatment with BZD; type of BZD; individual drugs; doses and half-life.

Adjusted risk of hip/femur fractures by all potential confounding factors was explored according to recency (current, recent or past use). Also, among current users the effect of duration of treatment, type of BZD taken, individual drug, dose and half-life was examined. Five different models of adjustment were performed (see section 5.7.2.4). In Table 9 it is shown the two models with the major changes: "age-adjusted" model and the "fully-adjusted" (model D) together with

the crude estimates. A table with the rest of adjusting models can be found in the Appendix D.

Table 9- Crude and adjusted HRs of hip/femur fracture

COHORT			Crude			"Age-adjusted" model			"Fully-adjusted" model D		
	Cases	P_y	HR	(95%)CI		HR	(95%)CI		HR	(95%)CI	
PAST	851	980,993.2	1	-	-	1	-	-	1	-	-
RECENT	268	164,513.1	1.89	1.64	2.17	1.38	1.20	1.58	1.26	1.09	1.44
CURRENT	1,340	549,538.7	2.83	2.60	3.09	1.39	1.28	1.52	1.17	1.07	1.28
By Duration											
Current 0-30d	184	117,683.0	1.80	1.53	2.11	1.14	0.97	1.34	0.98	0.83	1.15
Current 31-60d	179	100,432.9	2.06	1.75	2.43	1.28	1.08	1.50	1.10	0.93	1.29
Current 61-180d	267	117,810.3	2.59	2.26	2.98	1.25	1.09	1.44	1.04	0.91	1.20
Current 181-365d	212	67,096.9	3.64	3.13	4.23	1.54	1.32	1.79	1.27	1.09	1.48
Current >365	498	146,515.6	3.93	3.52	4.39	1.59	1.42	1.78	1.33	1.18	1.48
Type of BZD by ATC											
Current both	159	56,050.1	3.29	2.77	3.90	1.63	1.37	1.93	1.21	1.01	1.43
Single use of anxiolytics	894	418,895.8	2.48	2.26	2.73	1.37	1.24	1.50	1.17	1.07	1.29
Single use of hypnotics	287	74,592.8	4.46	3.90	5.11	1.36	1.19	1.56	1.16	1.01	1.33
By Individual drugs											
Anxiolytics (N05BA)	838	377,824.1	2.58	2.34	2.84	1.39	1.26	1.53	1.20	1.09	1.33
Lorazepam	453	134,490.5	3.90	3.48	4.37	1.58	1.41	1.77	1.34	1.19	1.50
Bromazepam	171	96,793.9	2.05	1.74	2.41	1.11	0.95	1.31	1.01	0.86	1.19
Diazepam	92	60,637.8	1.76	1.42	2.18	1.36	1.10	1.69	1.23	0.99	1.53
Alprazolam	56	41,301.8	1.57	1.20	2.06	1.31	1.00	1.72	1.06	0.81	1.39
Others	66	44,600.1	1.72	1.33	2.21	1.27	0.99	1.64	1.08	0.84	1.40
Hypnotics (N05CD)	166	43,777.9	4.40	3.72	5.20	1.35	1.14	1.60	1.22	1.03	1.44
Lormetazepam	150	36,888.9	4.70	3.95	5.59	1.47	1.23	1.75	1.32	1.11	1.57
Flurazepam	3	1,969.8	1.76	0.57	5.48	0.80	0.26	2.49	0.74	0.24	2.29
Loprazolam	3	2,270.2	1.53	0.49	4.75	0.43	0.14	1.32	0.42	0.13	1.29
Others	10	2,649.0	4.37	2.34	8.15	1.07	0.58	2.01	0.91	0.49	1.70
Hypnotics (N05CF)	58	24,166.3	2.79	2.14	3.64	1.07	0.82	1.40	0.98	0.75	1.29
Zolpidem	57	22,092.1	2.99	2.28	3.91	1.17	0.89	1.53	1.08	0.82	1.41
Others	1	2,074.2	0.56	0.08	3.97	0.19	0.03	1.35	0.17	0.02	1.21
Other N05CM02	54	3,857.3	16.28	12.36	21.44	2.17	1.64	2.86	1.31	0.97	1.78
By Half Life											
Short <8h	125	33,015.9	4.40	3.64	5.31	1.38	1.14	1.66	1.09	0.90	1.32
Intermediate 8-24h	850	323,139.3	3.05	2.77	3.36	1.40	1.27	1.54	1.22	1.10	1.34
Long >24h	141	93,470.2	1.75	1.47	2.10	1.31	1.10	1.57	1.16	0.97	1.39
By Dose (last Rx)											
Low dose (< 1DDD)	630	248,270.9	2.95	2.66	3.27	1.42	1.28	1.57	1.21	1.09	1.35
Medium dose (=1DDD)	135	56,427.9	2.78	2.32	3.33	1.19	0.99	1.42	1.06	0.89	1.28
High dose (>1DDD)	76	31,462.5	2.80	2.22	3.55	1.75	1.38	2.21	1.42	1.12	1.80
Missing	275	113,464.2	2.83	2.47	3.25	1.35	1.17	1.55	1.18	1.03	1.35

P_y= person-years; Rx= Prescription; Others (N05BA): Clobazam, Clotiazepam, Pinazepam, Oxazepam, Chlordiazepoxide, Prazepam, Clorazepate, Ketazolam and Halazepam; Others (N05CD): Midazolam, Triazolam, Brotizolam, Flunitrazepam, Quazepam, Nitrazepam, and Temazepam; Others (N05CF): Zopiclone and Zaleplon; N05CM02: Clomethiazole

Use of BZD or related drugs: Crude HRs estimates showed a strong association with the current use of these drugs (2.83; 95%CI: 2.60-3.09). After adjusting by age and by all covariates (full model D), risk estimates of hip/femur fractures associated with current and recent users were similar, (1.17, 95%CI: 1.07-1.28) and (1.26, 95%CI: 1.09-1.44) respectively.

Duration of treatment: Crude HRs exhibited an increased risk of hip/femur fractures with the *duration* of treatment, short treatments 1.8 (95%CI: 1.53-2.11) and for long treatments (>365 days), 3.93 (95%CI: 3.52-4.39). Adjusted HRs showed same trend than crude estimates, however, the risk of having a hip/femur fracture dropped dramatically and became non-significant for duration periods shorter than six months (see Table 9).

Type of BZD classified by ATC subgroup: The crude risk was almost two fold higher with hypnotics than with anxiolytics, being 4.46 (95%CI: 3.90-5.11) and 2.48 (95%CI: 2.26-2.73), respectively, and the risk of taking both types of BZD was in-between (3.29, 95%CI: 2.77-3.90). Whereas after adjusting by age, the highest risk was exhibited by the use of both, anxiolytics and hypnotics as well as after adjusting by all covariates (full model D). No difference was observed between the single use of anxiolytics and the single use of hypnotics in the adjusted estimates.

Individual BZD or related drug: Crude estimates for individual drugs demonstrated that anxiolytics presented lower risk than hypnotics in general, being lorazepam the drug with the highest risk among them (HR=3.90; 95%CI: 3.48-4.37), followed by bromazepam, (HR= 2.05; 95%CI: 1.74-2.41). Though after adjusting with the full model, bromazepam showed no risk, and diazepam marginal increased risk (1.23; 95%CI: 0.99-1.53). Lorazepam exhibited still the highest risk of all individual drugs, (HR=1.34; 95%CI: 1.19-1.50).

Among hypnotics (N05CD) the most used drug was lormetazepam showing a crude HR of 4.70 (95%CI: 3.95-5.59) and a full adjusted HR of 1.32 (95%CI: 1.11-1.57). From other hypnotic groups, zolpidem (N05CF) showed no risk after full adjustement (HR=1.08; 95%CI: 0.82-1.41), while zopiclone and zaleplon hardly had any exposed cases. The highest risk was seen with clomethiazole

(N05CM02), being 3 times higher than the risk group of N05CD, but it is remarkable the HR sharply fell after adjustment from 16.28 (95%CI: 12.36 -21.44) to 1.31 (95%CI: 0.97-1.78). While the risk observed with lormetazepam was present after adjusting (1.32; 95%CI: 1.11-1.57).

Half-life of BZD: In crude estimates, BZDs with shortest half-lives (<8h) presented the higher risks, while those with long half-lives (>24h) the lowest. This trend disappeared once estimates were age- or fully-adjusted, where the highest risk was presented by BZD with intermediate half-lives.

Dose of BZD: No dose effect was detected in the crude estimates. In contrast, BZD at high doses (>1DDD) showed the highest risk after age- and full-adjustment.

In addition half-life and doses of single use of anxiolytics and hypnotics was explored separately. No risk was found associated with half-life either. Regarding dose, high doses of anxiolytics and low doses of hypnotics accounted for the highest risk associated with hip/femur fractures. The analyses of doses using last instead of first prescriptions yielded similar results. Tables for the mentioned additional analyses can be found in the Appendix D.

6.2.1.5 Stepwise analysis

After running the most parsimonious model obtained only with the following variables: age, sex, previous fractures, glucocorticoids, antidepressants, anti-Parkinson drugs and the interaction between antidepressants with anti-Parkinson drugs, the estimates observed were slightly higher than those obtained with the full model "D", changing the estimate for recent users from 1.26 (95%CI: 1.09-1.44) to 1.30 (95%CI: 1.13-1.49) and for current users from 1.17 (95%CI: 1.07-1.28) to 1.24 (95%CI: 1.13-1.35). This analysis was only performed for the main exposure to BZD and related drugs, using past use as reference category.

6.2.2 NCC study

The cases and controls for this study were selected from the cohort study. See flow chart in Figure 21 with the source population and criteria applied for the final population.

6.2.2.1 Characteristics of cases and controls at index date

Final NCC study population was comprised of 12,289 patients (2,459 cases and 9,830 controls). Cases and controls were matched by sex, age and follow-up (time between start and index date). About 44% of patients were between 80-89 years old, with a mean=78.5 ± 12.5 and 78% were women. Distribution by sex and age in 10-years band categories is presented in Table 10a. About half of patients had less than 2 years of follow up, and 37% between 2-4 years.

Table 10a- Age, sex and follow up time for cases and controls

NCC population	Cases N=2,459	Cases (100%)	Controls N=9,830	Controls (100%)
Age in years at index date				
18-29 y	11	0.45	44	0.45
30-39 y	39	1.59	156	1.59
40-49 y	53	2.16	212	2.16
50-59 y	97	3.94	388	3.95
60-69 y	198	8.05	792	8.06
70-79 y	651	26.47	2604	26.49
80-89 y	1071	43.55	4284	43.58
³ 90 y	339	13.79	1350	13.73
Mean (SD) of age	78.55 (12.54)	-	78.53 (12.52)	-
Sex				
Female	1927	78.37	7702	78.35
Male	532	21.63	2128	21.65
Time window (Median, IQR)†	1.94 (0.84-3.64)		1.93 (0.84-3.65)	
<2 years	1255	51.04	5014	51.01
2-4 years	907	36.88	3633	36.96
5-7 years	286	11.63	1143	11.63
8> years	11	0.45	40	0.41

SD=Standard deviation; IQR=interquartiles; (†) Cases and Controls are matched by sex, age and follow up (time between start and index date)

The complete list of co-medications and co-morbidities was examined as well. Broadly, cases showed a higher prevalence of drug use than controls, with the exception of antihypertensive drugs; diuretics; antipsychotics/lithium; other antidiabetics; non-steroidal anti-inflammatory drugs; statins; and bronchodilators which presented a similar prevalence, and raloxifen and HRT which presented a lower prevalence among cases than controls (see Table 10b).

Similarly, the prevalence of co-morbidities was higher in cases than controls, showing big differences for previous fractures (19.8 vs. 9.7%) and dementia and/or Alzheimer's (10.7 vs. 6.5%). Other frequent co-morbidities presented in this population were osteoporosis; anaemia; syncope; malignant neoplasms; cerebrovascular disease; ischemic heart disease and chronic obstructive pulmonary disease.

Table 10b- Co-medication and co-morbidities from cases and controls and crude association with hip/femur fractures

NCC study population	Cases N	Cases %	ControlsN	Controls%	CrudeOR	95% (CI)	p-value
Co-medication							
Glucocorticoids*	52	2.11	122	1.24	1.71	1.24-2.37	0.001
Bisphosphonates	201	8.17	650	6.61	1.27	1.07-1.50	0.005
Raloxifene	10	0.41	91	0.93	0.43	0.22-0.83	0.012
Strontium ranelate	12	0.49	36	0.37	1.34	0.69-2.60	0.383
Parathyroid hormone	6	0.24	8	0.08	3.19	1.06-9.56	0.039
Vitamin D+Ca	279	11.35	1016	10.34	1.12	0.97-1.29	0.134
Calcitonin	34	1.38	77	0.78	1.78	1.19-2.68	0.005
Antidepressants	795	32.33	2022	20.57	1.88	1.70-2.08	< 0.001
Antipsychotics / Lithium	312	12.69	805	8.19	1.64	1.42-1.89	< 0.001
Anti-Parkinson drugs	140	5.69	229	2.33	2.56	2.06-3.19	< 0.001
Anticonvulsants	308	12.53	742	7.55	1.77	1.53-2.04	< 0.001
Inhaled glucocorticoids	67	2.72	330	3.36	0.80	0.61-1.05	0.111
Bronchodilators*	313	12.73	1225	12.46	1.03	0.90-1.17	0.708
Anti-arrhytmics	74	3.01	220	2.24	1.36	1.04-1.77	0.026
Sedating antihistamines	49	1.99	170	1.73	1.16	0.84-1.59	0.375
Antihypertensive drugs*	1200	48.80	4917	50.02	0.95	0.87-1.04	0.270
Diuretics	784	31.88	3144	31.98	0.99	0.90-1.10	0.901
HRT	7	0.28	29	0.30	0.96	0.41-2.26	0.931
Thyroid hormones	125	5.08	473	4.81	1.06	0.87-1.30	0.568
Antithyroid drugs	13	0.53	53	0.54	0.98	0.53-1.80	0.951
DMARDs	28	1.14	63	0.64	1.79	1.14-2.81	0.011
Thiazolidinediones	14	0.57	30	0.31	1.87	0.99-3.52	0.054
Other antidiabetics	372	15.13	1310	13.33	1.16	1.03-1.32	0.019
Antiemetic	78	3.17	213	2.17	1.47	1.13-1.92	0.004
Anticoagulants	309	12.57	914	9.30	1.41	1.23-1.62	< 0.001
Morphine / opiates	405	16.47	977	9.94	1.80	1.59-2.05	< 0.001
NSAIDs	477	19.40	1662	16.91	1.19	1.06-1.33	0.003
Statins	412	16.75	1969	20.03	0.80	0.71-0.90	< 0.001
PPI	1197	48.68	4191	42.63	1.30	1.19-1.42	< 0.001
Aromatase Inhibitors	23	0.94	57	0.58	1.63	1.00-2.66	0.050
Co-morbidities							
Osteoporosis	417	16.96	1302	13.25	1.36	1.20-1.54	< 0.001
Paget's disease	10	0.41	38	0.39	1.05	0.52-2.11	0.885
Previous fractures	487	19.80	957	9.74	2.30	2.04-2.59	< 0.001
Rheumatoid arthritis	38	1.55	116	1.18	1.31	0.91-1.90	0.146
Anaemia	418	17.00	1229	12.50	1.46	1.29-1.66	< 0.001
Epilepsies/ seizures	44	1.79	107	1.09	1.66	1.17-2.38	0.005
Syncope	374	15.21	1180	12.00	1.33	1.17-1.51	< 0.001
IHD	305	12.40	1261	12.83	0.96	0.84-1.10	0.559
CVA	306	12.44	820	8.34	1.58	1.37-1.81	< 0.001
Malignant neoplasms	371	15.09	1134	11.54	1.37	1.20-1.55	< 0.001
IBD	18	0.73	36	0.37	2.02	1.14-3.56	0.016
COPD	216	8.78	692	7.04	1.29	1.10-1.53	0.002
Liver disease	62	2.52	178	1.81	1.41	1.05-1.88	0.023
Chronic renal failure	118	4.80	406	4.13	1.16	0.94-1.44	0.158
Mental disorders	65	2.64	148	1.51	1.78	1.32-2.39	< 0.001
Dementia / Alzheimer's	264	10.74	635	6.46	1.77	1.52-2.06	< 0.001

*same variables and conditions for all studies (see Table 8b)

6.2.2.2 Crude association of potential risk factors with hip/femur fractures.

Crude odds ratios (ORs) of co-medication and co-morbidities were estimated and presented in Table 10b. Among co-morbidities, diseases that showed the highest ORs were previous fractures (2.30, 95%CI: 2.04-2.59) intestinal bowel disease (2.02, 95%CI: 1.14-3.56), mental disorders without depression (1.78, 95%CI: 1.32-2.39), dementia and/or Alzheimer's (1.77, 95%CI: 1.52-2.06), epilepsies/seizures (1.66, 95%CI: 1.17-2.38) and cerebrovascular disease (1.58, 95%CI: 1.37-1.81). Among co-medications, drugs presenting the highest ORs were parathyroid hormone and anti-Parkinson drugs with 3.19 (95%CI: 1.06-9.56) and 2.56 (95%CI: 2.06-3.19) respectively, followed by antidepressants; thiazolidinediones (although no statistically significant); morphine/opiates; disease-modifying anti-rheumatic drugs; calcitonin; glucocorticoids; antipsychotic/lithium; and aromatase inhibitors, ranged between 1.63 and 1.88. The rest of co-medication and co-morbidities with an OR less than 1.5 can be found in the Table 10b.

6.2.2.3 Risk of hip/femur fracture associated with BZD and related drugs

Crude and adjusted (model D) ORs of having a hip/femur fracture associated with the use of BZD and related drugs, are shown in Table 11. Risk estimates for specifics aspects of current use such as duration of treatment and type of BZD by ATC group were presented as well. Different groups of potential confounding factors were included in their respective conditional logistic models (models B, C and D). Tables with the rest of the models can be found in the Appendix E.

A sensitivity analysis measuring co-medication 30 days previous to the index date was also performed and presented in Table 11.

Table 11- Risk estimates of hip/femur fracture associated with BZD, and by duration and type of ATC group in the NCC.

NCC	Cases(%)	Controls(%)	NCC Crude*		Full model		Sensitivity full**	
			OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Past use (ref.)	851 (34.6)	3,949 (40.2)	1.00		1.00		1.00	
Recent use	268 (10.9)	934 (9.5)	1.39	1.18-1.63	1.30	1.10-1.54	1.36	1.15-1.61
Current use	1,340 (54.5)	4,947 (50.3)	1.30	1.17-1.43	1.14	1.02-1.26	1.19	1.06-1.32
By Duration								
Current 0-30d	184 (13.7)	786 (15.9)	1.06	0.86-1.32	1.03	0.82-1.30	1.06	0.84-1.33
Current 31-60d	179 (13.4)	686 (13.9)	1.26	1.02-1.56	1.19	0.95-1.48	1.22	0.98-1.53
Current 61-182d	267 (19.9)	1,058 (21.4)	1.20	1.02-1.41	1.04	0.88-1.24	1.09	0.92-1.29
Current 183-365	212 (15.8)	660 (13.3)	1.51	1.27-1.80	1.30	1.08-1.56	1.37	1.14-1.65
Current >365d	498 (37.2)	1,757 (35.5)	1.34	1.17-1.53	1.14	0.99-1.31	1.20	1.04-1.38
By ATC drug								
Use of both	161 (12)	407 (8.2)	1.87	1.53-2.28	1.40	1.13-1.73	1.48	1.20-1.84
Anxiolytics	894 (66.7)	3,476 (70.3)	1.23	1.10-1.37	1.11	0.99-1.25	1.17	1.04-1.31
Hypnotics	285 (21.3)	1,064 (21.5)	1.28	1.09-1.49	1.10	0.94-1.30	1.13	0.96-1.33

Crude: adjusted only for matching factors (age, sex and index date)
**Sensitivity Analysis: Full model but co-medication variables were measured at 30 days from index date.

Recency of use of BZD or related drug: The full-adjustment for all potential risk factors hardly changed the OR associated with current use as compared with the crude one (adjusted only for the matching factors), indicating that the matching factors (in particular age) were the most relevant confounding factors. To note, recent users presented slightly higher ORs than current users.

Duration of treatment: No clear trend was observed with duration of treatment. In particular, there was no short term effect.

Type of BZD classified by ATC: In this design, the highest risk of having a hip/femur fracture was associated with the use of both anxiolytic and hypnotics. Risk estimates for the use of anxiolytic or hypnotic separately were quite similar.

The sensitivity analysis in the NCC, showed no material differences (Table 11).

6.2.2.4 Stepwise analysis

A more parsimonious model was obtained with only the following variables: previous fractures, glucocorticoids, antidepressants, anticonvulsants and morphine/opiates. The analysis yielded similar ORs estimates than those obtained with the full model: current use, 1.14 (95%CI: 1.03-1.26) and recent use, 1.29 (95%CI: 1.09-1.52).

6.2.3 CXO study

6.2.3.1 Characteristics of the CXO study population at index date

From 5,705 patients available in BIFAP who fulfilled the required criteria, 293 were unable to participate in the study because it was not possible to find a control moment for them. Thus, the final CXO study population was comprised of 5,412 patients with a recorded diagnosis of hip/femur fracture, and at least one control moment; from them, 95% had two, 90% had three and 85% had four control moments respectively. From those cases, 1,368 had not a prescription of BZD or related drug before the recorded code of hip/femur fracture. And only 1,820 discordant pairs were included in the analysis. Mean age of patients were 78.3 ± 13.1 years old, and 78% were women. The index date was the hip/femur fracture date, and the four controls moments were at -91, -182, -273, -365 days. A flow chart with the source population, inclusion and exclusion criteria, case ascertainment and final populations for case only designs is presented in Figure 24.

Flowchart contents:

BIFAP: Source population 2,917,152

Hip/femur fractures identified during study period: 1/01/2001-31/12/2009

Initial Cohort 13,382

No Hip/femur fracture code 1 year before

No Hip/femur fracture code 1 year before
No BZD 6 months before

CXO Initial 13,233

SCCS Initial 11,906

At least one BZD Rx within study period

At least one BZD Rx within study period

8,034

6,285

Validation Process

CXO final 5,705

SCCS final 4,450

Figure 24- Flow chart of CXO and SCCS final populations

The sample size for the SCCS design was lower than for the CXO due to the additional requirement of no BZD use six months before start date. Distribution by gender, mean age in years and co-morbidities any time before the hip/femur fracture is presented in Table 12.

The most frequent co-morbidities presented by this population were: previous fractures (18.7%), anaemia (16.2%), and osteoporosis (15.6%), followed by malignant neoplasms (13.5%); syncope (12.3%); ischemic heart disease (12.2%); cerebrovascular disease (11.4%); dementia and/or Alzheimer's (10.5%) and chronic obstructive pulmonary disease (7.8%).

Table 12- Gender distribution, and co-medication used by CXO population.

CXO Population	N=5,412	100%
Age, mean (S.D.)	78.27 (13.11)	
Gender		
Female	4,224	78.05
Male	1,188	21.95
Co-morbidities (anytime before)		
Osteoporosis	844	15.59
Paget's disease	24	0.44
Previous fractures	1,010	18.66
Rheumatoid arthritis	80	1.48
Anaemia	879	16.24
Epilepsy/Seizures	94	1.74
Syncope	665	12.29
Ischaemic heart disease (IHD)	661	12.21
Cerebrovascular disease (ACV)	617	11.40
Malignant neoplasms	731	13.51
Inflammatory bowel disease (IBD)	30	0.55
Chronic Obstructive Pulmonary Disease (COPD)	423	7.82
Liver disease	136	2.51
Chronic renal failure	254	4.69
Mental disorders (without depression)	139	2.57
Dementia and/or Alzheimer's	566	10.46

SD=Standard deviation

Regarding the most used drugs, 40% of this population was using antihypertensive drugs at index date (hip/femur fracture); 37% were taking proton pump inhibitors; and around 25% were using diuretics and antidepressants. In less proportion, but more than 8% of the population were using other antidiabetics; statins; morphine/opiates; bronchodilators; non-steroidal anti-inflammatory drugs; anticoagulants; antipsychotics / lithium; anticonvulsants and vitamin D plus calcium and analogues (Table 13).

Table 13- Co-medication and its crude association with hip/femur fracture in the CXO population

Co-medication use*	Case M N(%)	Control M1 N(%)	Control M2 N(%)	Control M3 N(%)	Control M4 N(%)	∑ control (date1-4) N(%)	OR	95% CI
Glucocorticoids	97(1.8)	85(1.6)	77(1.5)	71(1.5)	71(1.5)	304(1.5)	1.72	1.17-2.54
Bisphosphonates	304(5.6)	308(5.7)	285(5.5)	258(5.3)	241(5.2)	1,092(5.5)	1.26	0,97-1,65
Raloxifene	22(0.4)	19(0.4)	23(0.5)	19(0.4)	20(0.4)	81(0.4)	1.11	0,41-3,01
Strontium ranelate	11(0.2)	15(0.3)	15(0.3)	14(0.3)	12(0.3)	56(0.3)	0.48	0,15-1,49
Parathyroid hormone	9(0.2)	3(0.1)	6(0.1)	4(0.1)	3(0.1)	16(0.1)	14.24	1,65-122,94
Vitamin D/Calcium	451(8.3)	434(8.0)	431(8.4)	393(8.1)	380(8.3)	1,638(8.2)	1.12	0,93-1,34
Calcitonin	54(1.0)	49(0.9)	42(0.8)	44(0.9)	37(0.8)	172(0.9)	1.39	0,89-2,16
Antidepressants	1,332(24.6)	1,297(24.0)	1,182(23.0)	1,063(21.8)	969(21.1)	4,511(22.5)	1.72	1,49-1,98
Antipsychotics	481(8.9)	441(8.2)	394(7.7)	364(7.5)	312(6.8)	1,511(7.5)	1.54	1,30-1,83
Anti-Parkinson drugs	262(4.8)	260(4.8)	234(4.6)	217(4.5)	200(4.4)	911(4.6)	1.97	1,28-3,02
Anticonvulsants	463(8.6)	465(8.6)	404(7.9)	358(7.4)	335(7.3)	1,562(7.8)	1.52	1,23-1,88
Inhaled glucocortic.	113(2.1)	132(2.4)	122(2.4)	109(2.2)	104(2.3)	467(2.3)	0.67	0,46-0,96
Bronchodilators	526(9.7)	537(9.9)	490(9.5)	459(9.4)	429(9.3)	1,915(9.6)	1.11	0,92-1,34
Anti-arrhythmics	131(2.4)	122(2.3)	108(2.1)	97(2.0)	94(2.0)	421(2.1)	1.90	1,17-3,09
Sedating Antihistamines	67(1.2)	73(1.4)	60(1.2)	49(1.0)	47(1.0)	229(1.1)	1.22	0,84-1,78
Antihypertensives	2,615(40)	2,240(41.4)	2,119(41.2)	1,989(40.8)	1,855(40.3)	8,203(41.0)	0.95	0,84-1,09
Diuretics	1,385(25.6)	1,422(26.3)	1,311(25.5)	1,231(25.3)	1,146(24.9)	5,110(25.5)	1.11	0,97-1,27
HRT	10(0.2)	6(0.1)	10(0.2)	9(0.2)	11(0.2)	36(0.2)	1.16	0,38-3,50
Thyroid hormones	205(3.8)	198(3.7)	197(3.8)	175(3.6)	156(3.4)	726(3.6)	1.53	1,03-2,26
Antithyroid drugs	23(0.4)	21(0.4)	27(0.5)	20(0.4)	18(0.4)	86(0.4)	1.07	0,44-2,62
DMARDs	42(0.8)	47(0.9)	43(0.8)	49(1.0)	38(0.8)	177(0.9)	0.80	0,42-1,50
Thiazolidinediones	22(0.4)	19(0.4)	19(0.4)	18(0.4)	17(0.4)	73(0.4)	2.02	0,76-5,38
Other antidiabetics	718(13.3)	764(14.1)	737(14.3)	695(14.3)	646(14.1)	2,842(14.2)	0.68	0,54-0,85
Antiemetics	83(1.5)	81(1.5)	70(1.4)	59(1.2)	50(1.1)	260(1.3)	1.24	0,93-1,64
Anticoagulants	509(9.4)	452(8.4)	396(7.7)	384(7.9)	342(7.4)	1,574(7.9)	1.96	1,62-2,37
Morphine/opiates	613(11.3)	552(10.2)	491(9.5)	439(9.0)	378(8.2)	1,860(9.3)	1.88	1,61-2,20
NSAIDs	514(9.5)	567(10.5)	535(10.4)	490(10.1)	487(10.6)	2,079(10.4)	0.85	0,74-0,98
Statins	680(12.6)	735(13.6)	680(13.2)	648(13.3)	612(13.3)	2,675(13.4)	0.87	0,70-1,06
PPIs	2,015(31.2)	1,986(36.7)	1,794(34.9)	1642	1498	6920(34.6)	1.56	1,40-1,74
Aromatase Inhibitors	34(0.6)	37(0.7)	39(0.8)	35	30	141(0.7)	0.77	0,35-1,69

M=moment; M1= moment 1 etc.
*Exposure: at least a prescription within the previous 91 days. Reference category: non-use in the 91 days window. (Glucocorticoids and NSAIDs were measured as in the rest of designs).

6.2.3.2 Crude association of potential risk factors with hip/femur fractures.

As a case only design, this study based its analysis on comparison within individuals hence all intrinsic potential confounding factors were controlled for by design. Thus, the association with the outcome was not measured for any of the co-morbidities because they were considered conditions that do not vary within each patient (in a limit time span). Instead, co-medications were considered time-varying variables. Crude odds ratios (ORs) of co-medication were estimated and presented in Table 13. Among drugs that showed the highest ORs were parathyroid hormone with an OR of 14.24 but very wide 95%CI: 1.65-122.94, because the number of patients who took this drug was very small; thiazolidinediones, 2.02 although was not statistically significant 95%CI: 0.76-5.38; anti-Parkinson drugs 1.97 (95%CI: 1.28-3.02); anticoagulants 1.96 (95%CI: 1.62-2.37); anti-arrhythmics 1.90 (95%CI: 1.17-3.09); morphine/opiates 1.88 (95%CI: 1.61-2.20); antidepressants 1.72 (95%CI: 1.49-1.98); and glucocorticoids 1.72 (95%CI: 1.17-2.54); followed by proton pump inhibitors, antipsychotics/lithium; thyroid hormones and anticonvulsants, ranged between 1.56 and 1.52. The rest of co-medications with an OR less than 1.5 can be found in the Table 13.

6.2.3.3 Risk of hip/femur fracture associated with BZD and related drugs

There was only one adjusted model for this design, including all co-medications, named as full model. Table 14 summarizes crude and adjusted risk estimates of having a hip/femur fracture associated with BZD or related drugs use. Risk estimates by type of ATC group were presented as well. A table with the complete model for the CXO design can be found in the Appendix F.

Table 14- Risk estimates of hip/femur fracture associated with BZD use, and type of BZD by ATC group in the CXO design

CXO	Crude		Full model*	
	OR	95% CI	OR	95% CI
No use/past use	*Reference*		*Reference*	
Recent use	1.88	1,62-2,18	1.69	1,46-1,97
Current use	1.70	1,50-1,92	1.47	1,29-1,67
Type of BZD by ATC group				
Both	3.62	2,77-4,75	3.03	2,30-4,00
Anxiolytics	1.42	1,23-1,63	1.24	1,07-1,43
Hypnotics	2.09	1,64-2,67	1.82	1,42-2,33

*Full model: adjusted by all co-medication

The ORs observed for current and recent use of BZD and related drugs indicated a relevant association between the exposure and the outcome, in the crude and adjusted estimates.

Regarding the type of BZD by ATC group, patients who took both, anxiolytics and hypnotics, had higher risk than those who took them separately.

6.2.3.4 Stepwise analysis

A more parsimonious model was built with the following variables: antidepressants, antipsychotics; anticoagulants; morphine/opiates; and proton pump inhibitors. The analysis was run for the main exposure, giving similar results than the full model. Current use, OR=1.45 (95%CI: 1.28-1.65) and recent use, 1.71 (95%CI: 1.47-1.98).

6.2.4 SCCS study

A common flow chart with the source population, inclusion and exclusion criteria, case ascertainment and final populations for case only designs was presented in Figure 24.

6.2.4.1 Baseline characteristics of the SCCS study population

Final SCCS study population was composed of 4,450 patients who had a recorded diagnosis of hip/femur fracture and at least one prescription of BZD or related drug within the observation period (1/01/2001-31/12/2009). 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 age of 74.5 ± 13.6 years old and a mean age at first exposure of 76.4 ± 13.6 years old. About 77% were women. From all cases, 35% had a hip/femur fracture during the exposure to BZD or related drug, with a median duration of exposure to BZD of 360 days. Distribution by sex and age in 10-years band categories and co-morbidities at baseline are presented in Table 15.

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 of these patients collected at baseline, the most used drugs were antihypertensives (21.6%); diuretics (12.8%); and proton pump inhibitors (11.8%). Followed by other antidiabetics; antidepressants; non-steroidal anti-inflammatory drugs; statins; and bronchodilators, in a proportion between 5-10%. Information about all co-medication can be found in Table 16.

Table 15- Baseline characteristics and co-morbidities of SCCS population

Total SCCS population	N=4,450	100%
Age		
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_depresion	49	1.10
Dementia and/ or Alzheimer's	174	3.91

* Observation period is from start date until the end of observation: patient died, leave the practice or the practice leave the database (end of data collection) or end of the study period.

Table 16- Co-medication at baseline of SCCS population

Total SCCS population	N=4,450	100%
Co-medication		
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	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-arrhytmics	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 antidiabetics	340	7.64
Antiemetic	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

6.2.4.2 Relative IRs of hip/femur fractures associated with BZD and related drugs, and with the type of BZD by ATC group.

Crude and adjusted by age incidence rate ratios (IRRs) of hip/femur fracture comparing exposed/unexposed periods were estimated. To investigate the effect of taking one type of BZD or another on the risk of having a hip/femur fracture, exposure was divided according ATC groups in single use of anxiolytics, single use of hypnotics or use of both. Results were presented in Table 17.

Crude analysis:

- No risk of having a hip/femur fracture was observed in current use periods to BZD: 1.02 (0.94-1.11), while a small increased risk was observed in recent use periods: 1.14 (95%CI: 1.00-1.30).
- Estimates across exposure time period windows subdividing the current use in five risk strata illustrated that no risk appeared in the SCCS analysis up to six months of treatment.
- Only the use of both, anxiolytics and hypnotics exhibited a risk associated with hip/femur fractures: 1.48; 95%CI: 1.18-1.86.

Adjusted analysis by age:

- No association was observed over current or recent use periods.
- No association was observed in any time window of current use.
- Similarly, no risk was found as it was stratified by type of BZD.

Table 17- Risk of having a hip/femur fracture associated with BZD use, and type of drug by ATC group in the SCCS

SCCS			Model Crude			Model Adjusted by age		
Exposure	Cases	Py	IRR	IC(95%)		IRR	IC(95%)	
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								
Use of Both	187	314,002	1.48	1.18	1.86	1.02	0.81	1.30
Use of Anxiolytics	1,023	1,985,997	1.01	0.91	1.11	0.80	0.72	0.88
Use of Hypnotics	333	645,533	0.96	0.82	1.13	0.72	0.61	0.84

6.2.4.3 Potential exposure-event dependence and impact of different length periods of pre-exposure.

To examine whether the exposure was dependent on the event, a pre-exposure time risk window was created with a length of 30 days, because it was considered as normal length for a BZD prescription. The rationale to do that was explained in section 5.5.2 (Specific criteria for the SCCS design). A significant risk was now observed across all exposure period time windows of approximately 1.44 of median value, even after controlling by age. The markedly highest risk was exhibited by the new created pre-exposure time window, with 6.47 (95%CI: 5.91-7.09) adjusted by age, and the lowest by recent use, with 1.21 (95%CI: 1.03-1.42).

In addition, a shorter window of 15 days and a longer window of 60 days were created. Changes in the length of the pre-exposure time risk window, had a relevant impact on the risk of having a hip/femur fracture associated to all exposure time periods. Thus, risks obtained with pre-exposure time of 60 days were higher than those obtained with 30 days, and these in turn were higher than those obtained with 15 days, along the different exposure categories. Likewise, risk associated with recent use increased when pre-exposure period was considered.

Examining the risk associated with pre-exposure, the highest risk was observed with a length of 15 days, giving a value of 8.32 (95%CI: 7.54-9.18). Table 18 represents a comparison between IRRs in the model adjusted by age with different lengths in the pre-exposure risk period.

Complete tables for each pre-exposure time window (crude and adjusted) can be found in the Appendix G.

Table 18- Comparison of IRRs of hip/femur fracture changing the length of pre-exposure time risk window to 15 days, 30 days and 60 days.

Exposure	Model Adjusted by age			Model Adjusted by age			Model Adjusted by age		
	IRR_{15*}	IC(95%)		IRR_{30}	IC(95%)		IRR_{60}	IC(95%)	
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 1-30d	1.26	1.09	1.46	1.40	1.21	1.62	1.52	1.31	1.77
Current 31-60d	1.35	1.16	1.57	1.49	1.28	1.74	1.62	1.39	1.89
Current 61-182d	1.24	1.08	1.41	1.37	1.20	1.57	1.49	1.30	1.71
Current 183-365d	1.38	1.18	1.60	1.53	1.32	1.79	1.67	1.43	1.95
Current >365d	1.26	1.08	1.47	1.42	1.22	1.65	1.55	1.33	1.81
Current use	1.29	1.18	1.41	1.43	1.31	1.57	1.56	1.42	1.72

*$IRR_{15, 30, 60}$, this sub-index indicates the length of the risk window in days

6.2.4.4 Post hoc analysis to explore the risk in the pre-exposure period

Two unexpected findings were observed, an elevated risk just before the exposure, and a lower risk in the recent period whereas it was found constantly higher than current use along the other designs and before this pre-exposure time were created. Therefore, in order to explore those findings further two post hoc analyses were performed:

a) Exploring the risk at seven days before the exposure, but separating two pre-exposure periods, one created from baseline only, and the other created from recent use periods. See Figure 25 for clarification.

Investigation of the risk observed before the exposure
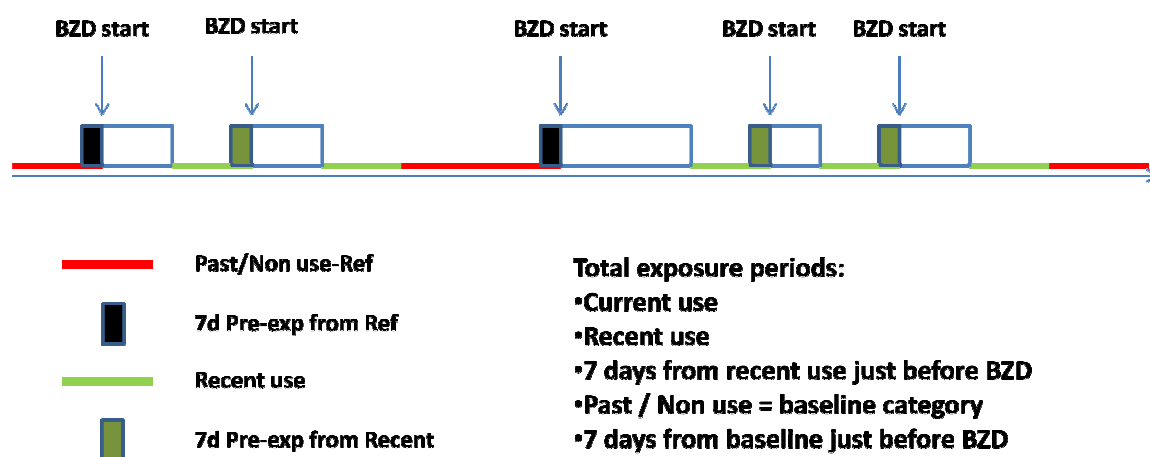
Figure 25- Two pre-exposure periods created at 7 days before the exposure

Both pre-exposure periods showed important increased risks being 15.28 (95%CI: 13.69-17.05) when patient were in a past or non use period, and 5.17 (95%CI: 4.09-6.55) as they were within a recent period. There was no risk in the recent period resulting from the exclusion of the week before the exposure. And the risk in current use drop to 1.12 (95%CI: 1.02-1.23). See Table 19 for results.

Table 19- IRRs with two different pre-exposure periods at 7 days

Exposure	Cases	Py	Adjusted Model		
			IRR	IC(95%)	
Past/non use	2,192	5,113,236	1.00		
Pre-Exp -baseline 7d	423	56,528	**15.28**	13.69	17.05
Recent use	212	441,528	1.03	0.89	1.19
Pre-Exp -recent 7d	80	35,284	**5.17**	4.09	6.55
Current 1-30d	213	213	1.11	0.96	1.29
Current 31-60d	201	201	1.18	1.02	1.38
Current 61-182d	314	314	1.07	0.94	1.23
Current 183-365d	246	246	1.19	1.02	1.39
Current >365d	569	569	1.08	0.93	1.25
Current use	1,543	1,543	**1.12**	1.02	1.23

b) Exploring the risk at baseline (past/non use) before the exposure, dividing the time before the exposure in periods of 7 days up to no risk was found. Then, remove this time from baseline and repeat the analysis.

The baseline time before the exposure was studied up to 210 days. A decreasing curve was observed, with lower risks as long as pre-exposure 7-day interval moved away the starting of current use (Figure 26).

Baseline risk before the exposure

7 days intervals before the exposure
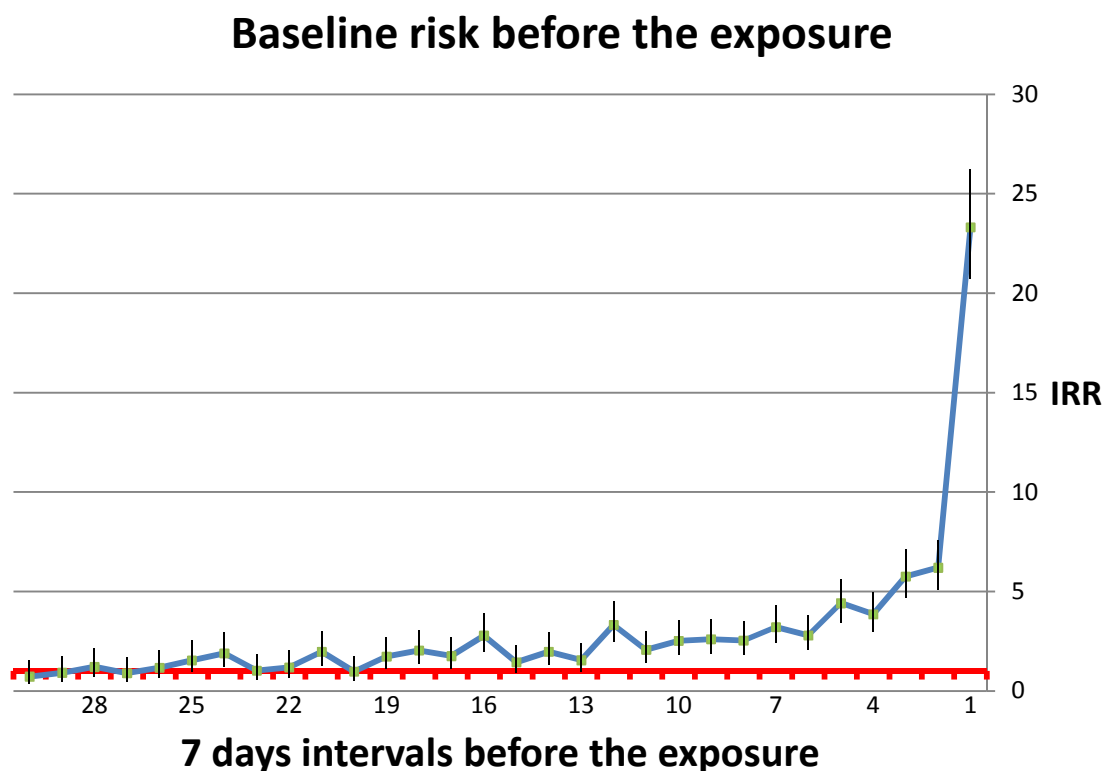
Figure 26- Risk at baseline before the exposure

Note, 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 IRR=1.

From the 27th interval (IRR= 0.9; 95%CI: 0.46-1.72) onwards no risk was observed. Hence the whole period between that interval and the exposure was removed from baseline creating a separate category called "182-day pre-exposure time". Crude and adjusted IRRs as well as the risk stratified by type of BZD (anxiolytics or hypnotics) for this post-hoc analysis can be found in Table 20.

Crude post-hoc analysis:

- Estimates across exposure time period windows dividing the exposure in five risk strata exhibited high risk of hip/femur fracture associated with the use of BZD.

- Estimates across exposure categories aggregated in current, recent or past use demonstrated the highest risk at 7 days before the exposure

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within a recent period (9.37; 95%CI: 7.38-11.90), whereas the rest of the recent period showed the lowest risk (1.71; 95%CI: 1.47-1.99).

- The risk associated with current use of BZD and related drugs was 2.10 (95%CI: 1.91-2.31).
- The use of both, anxiolytics and hypnotics exhibited the highest risk associated with hip/femur fractures: 3.12; 95%CI: 2.49-3.91.

Post-hoc analysis adjusted by age:

- Estimates across exposure time periods windows , aggregated in current, recent or past use, and stratified by type of BZD, were in the same line as commented before, but the magnitude of the estimates were slightly lower after adjusting by age. Thus, the risk associated with current use was 1.64 (95%CI: 1.48-1.81), with recent use 1.47 (95%CI: 1.26-1.71) and the risk at 7 days before exposure within recent use was 7.51 (95%CI: 5.91-9.56).
- Similarly, the use of both, anxiolytics and hypnotics exhibited the highest risk associated with hip/femur fractures: 2.22; 95%CI: 1.75-2.82.

Table 20- Risk of having a hip/femur fracture associated with BZD use, and type of drug by ATC group. Post-hoc analysis.

SCCS Analysis without baseline risk	Cases	Py	Crude Model			Model Adjusted by age		
Exposure	Cases	Py	IRR	IC(95%)		IRR	IC(95%)	
Past/Non use (ref)	1,315	4,109,390	1.00			1.00		
182-day pre-exposure	1,300	1,060,374	3.95	3.63	4.29	3.68	3.38	4.01
Recent use	212	441,528	1.71	1.47	1.99	1.47	1.26	1.71
Pre-exp 7d-Recent	80	35,284	9.37	7.38	11.90	7.51	5.91	9.56
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								
Use of Both	187	314,002	3.12	2.49	3.91	2.22	1.75	2.82
Use of Anxiolytics	1,023	1,985,997	2.06	1.85	2.30	1.65	1.47	1.85
Use of Hypnotics	333	645,533	1.95	1.66	2.29	1.48	1.25	1.75

In addition, representing those patients who started a treatment episode of BZD and related drugs within two months around the hip/femur fracture date (from -60 days to +60 days, being the 0=fracture date), it was seen that 431 (36%) patients started before the hip/femur fracture and 754 (64%) started after the fracture, showing a peak around 10-20 days after the fracture (Figure 27).
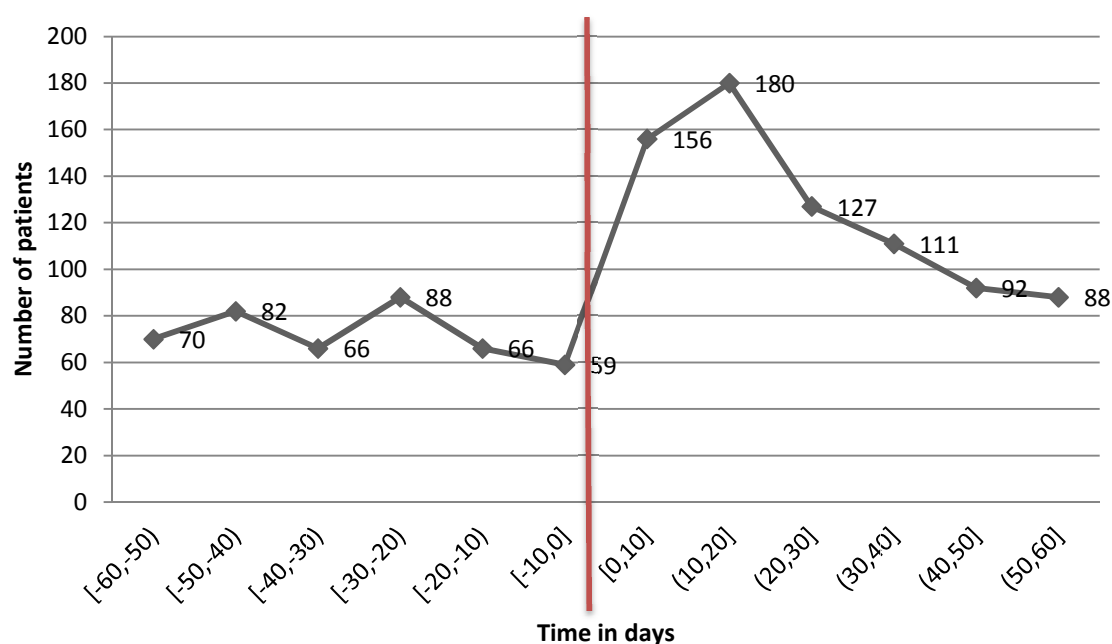
Figure 27- People started a BZD treatment before and after the hip fracture

6.3 COMPARISON OF RISK OF HIP/FEMUR FRACTURES ASSOCIATED WITH THE USE OF BZD AND RELATED DRUGS ACROSS DESIGNS

A comparison of the risks of having a hip/femur fracture associated with the exposure to BZD or related drugs across designs, is presented in Figure 28.

To allow better comparison, results from the SCCS design were presented aggregated in just one current category of use. All estimates were obtained from the full adjusted model in each design, and for the NCC, the sensitivity analysis and for the SCCS the post-hoc analysis were used.
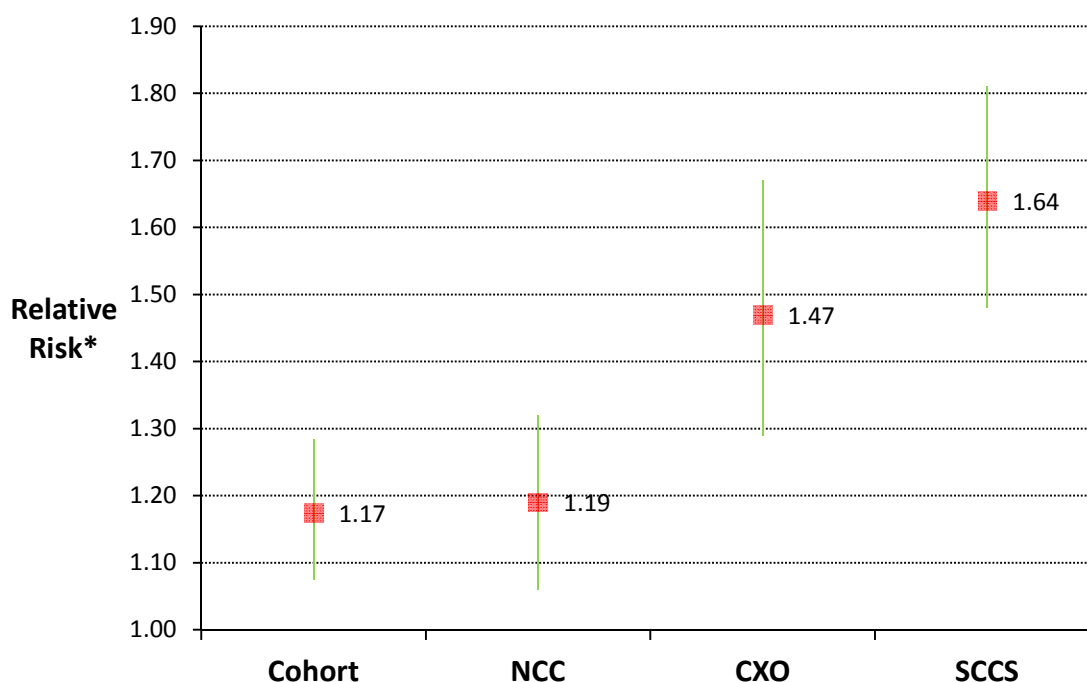
Cohort (HRs); NCC and CXO (ORs); SCCS (IRRs).All results are full adjusted estimates. The sensitivity analysis for the NCC and the post-hoc for the SCCS are shown. (Please note the scale of vertical axis starts at the relative risk null value which is equal to 1).

Figure 28 Comparison of risk of hip/femur fracture associated with BZD use in all designs

Current use of BZD or related drugs was associated in all designs with the outcome of interest however traditional studies (Cohort and NCC) yielded lower estimates (1.17, 95%CI: 1.07-1.28 and 1.19, 95%CI: 1.06-1.32) than those obtained with the case-only designs (1.47, 95%CI: 1.29-1.67 and 1.64, 95%CI: 1.48-1.81 respectively).

To investigate the effect of taking one type of BZD or another on the risk of having a hip/femur fracture, exposure was divided according ATC groups in use of anxiolytics, use of hypnotics or use of both. The Table 21 is a summary presenting this stratification for crude and adjusted analysis in all designs. Like in the previous figure, results came from the sensitivity NCC and post-hoc SCCS analyses.

Crude and adjusted estimates of the use of both types of BZD showed the highest risk across all designs, compared with the use of anxiolytic or hypnotic separately. Regarding the risk of the use of anxiolytics or hypnotics, once obtained adjusted estimates, in the cohort and NCC studies were fairly similar (1.17-1.16 and 1.17-1.13, anxiolytic-hypnotics respectively); whereas for the case only designs, results were contradictory. In the SCCS, the risk of hip/femur fracture associated with anxiolytic use (1.65, 95%CI: 1.47-1.85) was higher than the risk obtained with hypnotic use (1.48, 95%CI: 1.25-1.75) in contrast with the CXO where the risk of hypnotics use (1.82, 95%CI: 1.42-2.33) outweighed by large the risk of anxiolytics (1.24, 95%CI: 1.07-1.43).

In common, all designs exhibited risk associated with the use of BZD and related drugs, although risk estimates in the traditional designs were lower than those obtained in the case only designs. For instance, comparing the results from the cohort with the ones from the SCCS, there was a big difference in the magnitude: 1.17 (95%CI: 1.07-1.28) and 1.64 (95%CI: 1.48-1.81) respectively. Similarly, the ORs from NCC and CXO were 1.19 (95%CI: 1.06-1.32) and 1.47 (95%CI: 1.29-1.67) for current use in full models, respectively. In addition, in all designs was observed that, taking both anxiolytics and hypnotics showed the highest risk.

Regarding differences observed, apart from the magnitude of the estimates, it was the big variation found in the CXO with the use of hypnotics and anxiolytics, whereas in the other designs those estimates were much more similar.

Table 21- Risk of hip/femur fracture by ATC: Anxiolytics/Hypnotics in all designs, crude and adjusted.

	Cohort Crude			Cohort Adjusted*			NCC Crude **			NCC Adjusted*			CXO Crude			CXO Adjusted*			SCCS Crude			SCCS Adjusted*		
	HR	95%CI		HR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		IRR	95%CI		IRR	95%CI	
Past/non use	1.00			1.00			1.00			1.00			1.00			1.00			1.00			1.00		
Recent use	1.89	1.64	2.17	1.26	1.09	1.44	1.39	1.18	1.63	1.36	1.15	1.61	1.88	1.62	2.18	1.69	1.46	1.97	1.71	1.47	1.99	1.47	1.26	1.71
Current use	2.83	2.60	3.09	1.17	1.07	1.28	1.30	1.17	1.43	1.19	1.06	1.32	1.70	1.50	1.92	1.47	1.29	1.67	2.10	1.91	2.31	1.64	1.48	1.81
Type of BZD by ATC																								
Use of Both	3.29	2.77	3.90	1.21	1.01	1.43	1.87	1.53	2.28	1.48	1.20	1.84	3.62	2.77	4.75	3.03	2.30	4.00	3.12	2.49	3.91	2.22	1.75	2.82
Anxiolytics	2.48	2.26	2.73	1.17	1.07	1.29	1.23	1.10	1.37	1.17	1.04	1.31	1.42	1.23	1.63	1.24	1.07	1.43	2.06	1.85	2.30	1.65	1.47	1.85
Hypnotics	4.46	3.90	5.11	1.16	1.01	1.33	1.28	1.09	1.49	1.13	0.96	1.33	2.09	1.64	2.67	1.82	1.42	2.33	1.95	1.66	2.29	1.48	1.25	1.75

*Cohort and NCC adjusted by full model; CXO adjusted by co-medication; SCCS adjusted by age. The NCC results come from the sensitivity analysis and the SCCS results come from the post-hoc analysis.

**Crude: adjusted only for matching factors (age, sex and index date)

DISCUSSION

7. DISCUSSION

One research question in the same source population has been analysed with four different methodological designs. Results of this research are going to be discussed initially for the descriptive studies, as an overview of the current situation of the incidence of hip/femur fractures and the exposure to BZD and related drugs, in Spain compared with other European countries. Then, an evaluation of findings from analytical designs, with a comparison between them is going to be presented. Strengths and limitations of all studies will be addressed, as well as the contribution of this study to the scientific community.

7.1 DESCRIPTIVE STUDIES

7.1.1 Incidence of hip/femur fractures

The main findings of this study were as follows: 1) Denmark showed age- and sex- standardized IRs of hip/femur fractures two times higher than those observed in the UK, the NL and Spain while Germany yielded IRs in between; 2) in all countries, IRs were about 2-3 times greater in females than in males and grew exponentially with age regardless sex; both patterns were constant in all databases; and 3) significant trends in standardized IRs over time were observed only in two databases (slight increasing trend in the British CPRD and a decreasing trend in the Danish databases), both among the general population and among the population aged 50 years or older.

Denmark showed the highest IRs throughout the study period with figures rather similar in the population aged 50 years or older (45 per 10,000 py) (149). The two UK databases participating in the present study yielded almost identical results and were similar to the ones reported for England (10.2 per 10,000 py) using hospital admission rates (150). The IRs from the Spanish database in people aged 50 years or older are also similar to the ones reported by Hernández et al (110) using hospital discharge data from Cantabria in 2002 (25,9 per 10,000 persons) and to the ones reported in Catalonia (151) using GP

records in 2009 (22.3 per 10,000 py). The two databases from the NL provided standardized IRs that fluctuated greatly over the study period probably due to the small numbers of hip/fractures that they had, yielding lower values than those based on hospital registries (152). Apparently until 2009 there was an under-registration of ICPC codes in the NL that improved significantly after a national campaign, making more similar the IRs of hip/femur fractures between the hospital registries and NPCRD database in 2010-11 (121). Finally, IRs from the Bavarian claims database were marginally lower than in other studies (109, 153), that might be due to differences in data sources employed (national hospital discharge diagnosis opposed to outpatient diagnosis). Therefore, in general, the data provided in the present study seem to be consistent with results from previous studies using different data sources.

The IRs of hip/femur fractures increased exponentially with age for both males and females, as observed in other studies, which may be partly explained by the progressive bone mass reduction with ageing (154), but also by the accumulation of other risk factors, such as disability and increasing risk of falls, as well as increasing use of drugs acting at the central nervous system (e.g. antidepressants, hypno-sedatives, anti-Parkinson drugs, opioids), the cardiovascular system (e.g. antihypertensives, diuretics) or drugs affecting the bone mineral density (e.g. corticosteroids, glitazones, SSRIs).

The female to male IR ratios steadily increased with age among the population over 50 years but declined at older ages (≥80 years) probably indicating that males approximate females in bone mineral density and major risk factors at very old ages (155). This pattern was consistent across most databases and over the whole study period, and is in accordance with previously published results (147, 156, 157). Conversely, men presented higher IRs than women under the age of 50 years old, most probably due to the greater incidence of trauma-related fractures among males (158).

Time trend analyses showed no decreasing trend in the standardized IRs over time in most databases, with the exception of the Danish database. Thus, the general picture is of a rather stable situation which appears to date back to the nineties, as shown by previous reports in the same countries (2, 150). Denmark was the only country which showed a steady decline over the study period, in particular among the population 70-79 years old, in both males and females. This tendency is shared by other Nordic countries (159), as well as by the US (160); Australia (161); Canada (162) and Scotland (163). This decline in the Nordic countries might be attributable to a better management of osteoporosis (earlier screening, diagnosis and treatment of patients at risk) (164) and a combination of healthier diet, increase of physical activity, and educative measures to prevent falls (165).

7.1.2 Prevalence of BZD and related drugs use

The main findings of this study were as follows: 1) Spain exhibited the highest PRs compared to the other European countries, and it was the only one that presented an increased trend of BZD and related drug use over the study period (2001-2009); 2) PRs of BZD use were about 2 times greater in females than in males and grew steadily with age; both patterns were shared by all databases; and 3) decreasing trends of use were observed in Denmark, Germany and the Netherlands.

Remarkable differences were found in prevalence rates (PRs) of BZD and related drugs use, which were not attributable to differences in age or sex distribution in the participant populations. Most published studies included psychotropic drugs, not only BZD and related, applied different exposure definitions, and obtained information from questionnaires (84, 91, 166), making difficult a proper comparison between studies (167). Diverse prescription habits (168, 169) and attitudes of patients towards mental health help-seeking might explain those differences. A European study performed to explore this issue, showed that Spanish participants were keener to seek mental aid than for

instance the German ones (170). And this factor of seeking help for emotional problems is one of the most important independent predictor for BZD and antidepressant prescriptions (84).

The increasing trend observed in Spain was consistent with results from other studies (83, 171). Recent research suggests that the current economic crisis might be negatively affecting population mental health (172). Therefore, a further increase in the PRs of BZD use could be anticipated. In contrast, databases from Denmark, Germany and one from the NL (NPCRD), yielded a decreasing trend of use of BZD and related drugs. Such trend might reflect initiatives taken by official bodies (115) and the scientific community (173, 174), in order to rationalize the use of BZD in those countries.

With regards to the differences in use of anxiolytics and hypnotics found, several explanations are plausible. Firstly, the prescription of anxiolytics or hypnotics is influenced by marketing preferences and physician habits rather than by real pharmacological differences. Thus, in Spain lorazepam is generally the BZD most prescribed and, although classified among anxiolytics, it is widely used at low doses to induce sleep, in particular among the elderly (175); its special hepatic metabolism (glucuronidation pathway) which does not generate relevant active metabolites nor has relevant pharmacokinetics interactions with other (drugs or herbal) medicines (176) is usually referred to as an advantage in several practice guidelines. Therefore, indication for this type of drug is not always followed strictly and patients with insomnia are treated in a similar percentage with anxiolytics and hypnotics (177). Moreover, anxiety and insomnia seem to be intertwined over time (178) and the choice of the BZD may depend on the most predominant disorder as well as the physician experience (179).

As an overview of the situation in Spain, the incidence rate of hip/femur fractures remained rather stable taking up an intermediate position among the other European countries analyzed. However, the prevalence of use of BZD

and related drugs in this country was the highest compared to the other European countries, and it was the only one which exhibited an increasing trend.

7.2 ANALYTICAL STUDIES

7.2.1 Cohort study

In this study, crude IRs of hip/femur fracture increased exponentially with age regardless the exposure, and it was higher in females than in males in all exposure categories. Current use of BZD and related drugs accounted for the highest overall crude IR (24.38 per 10,000 py) and it was decreasing with past use. IRs obtained were higher than the obtained for the general population in the descriptive study of incidence of hip/femur fracture performed, (about 10.44 per 10,000py)(121), possibly due to the population was a cohort of users of BZD and related drugs, instead of general population.

Potential risk factors of hip/femur fractures identified in this study are in line with the ones described in the literature. Thus, having a low body mass index, dementia and/or Alzheimer's, cerebrovascular disease, osteoporosis or previous fractures, among others, were associated with an increased risk of hip fractures (25, 180, 181). Similarly, medication such as anti-Parkinson drugs, parathyroid hormones, diuretics, anticoagulants, glucocorticoids, antihypertensives, etc were associated with an increased risk as well (182). The increased risk associated with some drugs used in the prevention of osteoporotic fractures (e.g. parathyroid hormone, biphosphonates, vitamin D and calcium) should be interpreted as a confounding by indication.

Cox proportional hazards incremental models with time-dependent covariates were employed to estimate the risk of hip/femur fracture associated with BZD and related drugs use. Taking the past use as reference category, and comparing crude with the age-adjusted model, HRs demonstrated that the age was a factor strongly related with the outcome. However, the rest of

covariates in the subsequent models did not seem to act as relevant confounding factors. Even after performing an stepwise analysis, the only variables which seemed to affect more the association between hip/femur fracture and the use of BZD and related drugs, were age, sex, previous fractures, oral glucocorticoids, antidepressants and anti-Parkinson drugs. One reason could be that all those variables are related to age hence once age is controlled for the estimates are indirectly adjusted for the rest of covariates as well. Another explanation would be that in this study, a cohort of current users are compared with themselves when they are not using the drug of interest, so the intrinsic characteristics of the past users are the same and therefore many co-morbidities and chronic treatments are adjusted by design. Once all covariates were included in the model, HRs for current use of BZD (1.17, 95%CI: 1.07-1.28) were comparable than those obtained in another cohort study (183) with similar characteristics (1.24, 95%CI: 1.06-1.44).

Contrary to what was expected, the risk observed immediately after the treatment with BZD, that is, in the washout or *recent* period, was similar to the one obtained for current use when the model was age or fully-adjusted. Albeit a residual increased risk might be due to some treatments which are prescribed to take them on request, and patients classified as unexposed could be misclassified for this reason, the risk should be similar in both periods, not higher. This finding was common to all designs except for the SCCS, where, it was further investigated and an explanation is presented below, being applicable to all.

Regarding *duration of treatment*, crude estimates showed an increasing trend of risk with longer periods of treatment, whereas no short-term effect was observed, in particular when adjusting by all covariates. The short-term effect of BZD and related drugs has not been observed in a consistent manner across the different studies published so far. Some studies found the higher risk at the beginning of the treatment (183, 184) others found fluctuation of risk along the periods of use (185) and others after 14 days (186). From a pharmacological

point of view, it is reasonable to think that at the beginning of the treatment the patient may be more vulnerable to the adverse effects of the drug, and therefore more prone to sedation, confusion, dizziness, which may impair body balance and the risk of fall and subsequently the risk of hip/femur fractures. After continual use for a few weeks patients may develop some tolerance to these adverse effects reducing such a risk.

However, the lack of short-term effect may also have a plausible explanation: at the beginning of treatment patients received lower doses of BZD, and they escalated to higher doses afterwards leading to higher risks. This idea is supported by standard guidelines for the rational use of BZD where is indicated that dosage should be adjusted in the elderly, usually to half the recommended adult dose (187). Also, some authors have pointed out (186) that clinicians and patients could be more vigilant or alert at the beginning of treatment, and such vigilance may decrease as time goes by.

Concerning *doses*, findings from this study are consistent with previous reports (117, 145, 184, 186, 188, 189) showing that high doses of BZD and related drugs were associated with higher risk of hip fractures.

The effect of *half-life* has been largely studied giving controversial results. In this study no differential effect was shown according to drug half-life. Many previous studies found higher risk of falls and hip fractures with the use of long-acting BZD (99, 180, 190) and it seems to be plausible because of the potential accumulation of those drugs might cause prolonged drug activity. However, it has been shown in many others (92, 117, 183, 191, 192) that a high risk of hip fractures was still present for the short-acting BZD and related drugs.

There could be several explanations for this finding; one would be that the use of hypnotics with short-acting half-life could increase the rate of falls occurring over night as Ray et al (118) already pointed out. Also, it has been suggested (51) that short-acting BZD could imply more rapid tolerance, and

more cognitive impairment resulting in higher risk of hip fractures. Another possible explanation would be a potential confounding by indication, because patients with more severe conditions would be more frequently prescribed short-acting BZD to avoid the high risk implicit with long-acting drugs (191).

With respect to the risk observed with *individual drugs*, lorazepam was the anxiolytic with the highest risk and lormetazepam the highest among hypnotic drugs, followed by the non-BZD drug clomethiazole. However, results relating to this aspect are very disparate, for instance the risk found for flurazepam by Sylvestre and Tamblyn (189, 193) was 2.83 (95%CI: 1.45-4.34) and 2.2 (95%CI: 1.39-3.47), respectively; and for diazepam and zolpidem by Finkle (119) were 1.97 (95%CI: 1.22-3.18) and 2.55 (95%CI: 1.78-3.65). In contrast, in this study an increased risk was not observed with flurazepam or zolpidem, and the risk associated with diazepam was marginally non-significant. The high risk observed with clomethiazole, and the remarkable fall after adjustment is suggesting that physicians are particularly prone to prescribe this drug to the elderly. This could indicate the different pattern of use of BZD and related drugs in different countries, as only three cases were taking flurazepam and the use of "z" drugs is lower compare to other countries. In addition, differences in potential confounders might yield substantial changes in the estimates.

Finally, as regards the *type of BZD or related drug*, classified as anxiolytic, hypnotic or both, the highest risk after adjusting for all covariates was found in patients taking both anxiolytics and hypnotics, similarly to findings from other authors (184). An explanation for this might be patients with more severe underlying conditions are prescribed both types of drugs instead of just one, as a result the risk of hip fractures in those patients would be higher.

The risk for anxiolytics and hypnotics separately was quite similar. Most published articles did not examine the risk by type of BZD, making for difficult comparison, only Guo et al (194), found similar results but were not statistically significant: anxiolytics 1.41 (95%CI: 0.90-2.19) and hypnotics 1.15 (0.78-1.69).

7.2.2 NCC study

The crude association of potential risk factors with hip/femur fractures in this study with cases and controls were similar to the ones found in the cohort study and is also in line with other published studies (184). Apart from the ones mentioned in the cohort study discussion, intestinal bowel disease, mental disorders and epilepsies/seizures were independently associated with hip fractures, as it was seen in previous reports (24, 195, 196). Similarly, medication such as morphine/opiates (72), disease-modifying anti-rheumatic drugs (66), calcitonin (197) and aromatase inhibitors (59), were also associated with an increased risk of hip/femur fractures.

Conditional logistic regression was employed to estimate the risk of hip/femur fracture associated with the use of BZD and related drugs. Despite age and gender were used as matching variables, a difference in the ORs estimates was observed between crude and full adjusted model, indicating that some co-morbidities and co-medications were acting as potential confounders. Similarly to the cohort study, as a more parsimonious model was obtained, only the following variables were included: previous fractures, oral glucocorticoids, antidepressants, anticonvulsants and morphine/opiates. This probably indicates that only a few covariates were having an independent role in the estimates obtained.

A fully-adjusted odds ratio (AOR) of 1.14, 95%CI: 1.02-1.26 was found for the current use of BZD and related drugs, and it was comparable to the ones obtained by Zint et al (184): 1.2 (95%CI: 1.1-1.2) and Sgadari et al (198): 1.10 (95%CI: 0.98-1.20) with similar designs.

BZD usage and the other covariates were measured within 180 days before index date, to be comparable with the cohort study, but in addition a sensitivity analysis was done measuring the exposure to BZD and co-medication within 30 days before index date. As a result an AOR of 1.19, 95%CI: 1.06-1.32 was

obtained for the current use of BZD, which was slightly higher than the previous one but still comparable with the same published reports.

Regarding *duration of treatment,* crude and adjusted estimates suggested neither short-term effect nor a trend with the continuous use of BZD, in contrast with the cohort study where an increasing trend was observed. However, in the NCC cases were matched with controls on follow-up and this might hinder the possibility of observing a trend.

Also many discrepancies can be found in the literature. Thus, Chang et al (51) found a risk particularly high during the first month (AOR = 5.6, 95%CI: 2.7-11.8) of exposure to BZD; Zint et al (184) found an AOR = 2.1 (95%CI: 1.5, 2.8) for BDZ use initiated within 14 days preceding the index date; Wang et al (185) found fluctuation, with a significant increased risk during the initial 2 weeks of use (60% increase) and after more than 1 month of continuous use (80% increase) but not for 2-4 weeks of continuous use.

Possible explanations for increasing or decreasing the risk with duration of treatment have been discussed previously. While it is true that most published studies observed risk at the beginning of the treatment, particular characteristics of the design (e.g. selection of controls from hospital) or the number of covariates included in the logistic regression model to adjust for may yield very different results.

A summary with studies which have explored duration of BZD and related drugs use is presented in Table 22.

Table 22- Published studies which have explored duration of BZD use

Author	Title	Design	Population	Results	Observations
Chang, C. M. et al, 2008	BZD and risk of hip fractures in older people: a nested case-control study in Taiwan	NCC	217 cases, 214 controls	AOR 1st month=5.6 (2.7-11.8)	Using nonusers as reference group, use of BZD was significantly associated with hip fractures (AOR,1.7, 95% CI, 1.2-2.5). Such risks appear to be particularly high during the first month (AOR = 5.6, 95% CI = 2.7-11.8) of exposure.
Zint, K. et al. 2010	Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with BZD use in older adults	NCC	17,198 cases, 85,198 controls	AOR 1st month=2.1 (1.57-2.8)	While the adjusted relative risk (RR) for overall BDZ use and hip fracture was 1.16 (95% confidence interval 1.10, 1.22), for BDZ use initiated within 14 days preceding the index date was 2.1 (1.5, 2.8).
van der Hooft, C. S. et al. 2008	Inappropriate BZD use in older adults and the risk of fracture	NCC	200 cases, 2,678 controls	AOR (14-90 days)=2.15	Daily dose and longer duration of use (>14 days) is associated with higher risk of fracture, irrespective of he type of benzodiazepine prescribed.
Wang, P. S. et al 2001	Hazardous BZD regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture	C-C	1,222 cases, 4,888 controls	AOR (14 days) =1.6; AOR (>28days)=1.8	Significantly increased adjusted risks of hip fracture were seen during the initial 2 weeks of use (60% increase) and after more than 1 month of continuous use (80% increase) but not for 2-4 weeks of continuous use.
Berry, S. D. et al 2013	Non-BZD sleep medication use and hip fractures in nursing home residents	CXO	15,528	OR=2.2	The risk for hip fracture was elevated among users of a non-BZD hypnotic drug (OR, 1.66; 95% CI, 1.45-1.90). The association between non-BZD hypnotic drug use and hip fracture was some greater in new users (OR, 2.20; 95% CI, 1.76-2.74).
Neutel, C. I. et al 2002	Medication use and risk of falls	CXO	227	OR=11.4	The highest OR was for BZD at OR = 1.8 (unadjusted). Residents starting a new BZD/antipsychotic were at very high risk (OR = 11.4) for experiencing a fall.
Hoffmann, F. et al 2006	New use of BZD and the risk of hip fracture: A case-crossover study	CXO	1,630	OR (first 5days)=3.4	Odds ratio (OR) of hip fracture was highest during the initial 5 days of new use (OR: 3.43; 95% CI 1.15-10.20) and then declined to a non-significant OR of 1.59 (95% CI 0.96-2.63) after 30 days.
Wagner, A. K. et al. 2004	BZD use and hip fractures in the elderly: who is at greatest risk?	Cohort	125,203 (2,312 cases)	IRR (14 days)=2.05	Exposure to any BZD (IRR, 1.24; 95% CI, 1.06-1.44), during the first 2 weeks after starting a BZD (IRR, 2.05; 95% CI, 1.28-3.28), during the second 2 weeks (IRR, 1.88; 95% CI, 1.15-3.07), and for continued use (IRR, 1.18; 95% CI, 1.03-1.35).
Ray, W.A. et al. 2000	BZD and the risk of falls in nursing home residents	Cohort	2,510	RR (7days)=2.96	The rate of falls was greatest in the 7 days after the BZD was started (RR, 2.96 [2.33-3.75]) but remained elevated (1.30 [1.17-1.44]) after the first 30 days of therapy.

Finally, as regards the *type of BZD or related drug*, classified as anxiolytic, hypnotic or both, the highest risk of having a hip/femur fracture was found taking both types of drugs, for crude and full AOR estimate. This result was similar to the one found in the cohort study, but with a higher difference between taking both (AOR = 1.40, 95%CI: 1.13-1.73) and taking separately anxiolytics (AOR = 1.11, 95%CI: 0.99-1.25) or hypnotics (AOR = 1.10, 95%CI: 0.94-1.30). Prescription of both drugs might be related to patients with more severe conditions, as it has been said before, with the corresponding increase of risk. Similarly, Herings et al (117) found an OR = 2.5; 95%CI: 1.3-4.9 with the concomitant use of several BZD.

Between anxiolytics and hypnotics taken separately there was no difference in the main analysis, alike the cohort study.

7.2.3 CXO study

The crude association of co-medication as potential risk factors with hip/femur fractures yielded similar results than the two previous studies.

Odds ratios (ORs) of hip fracture were estimated using conditional logistic regression models by comparing the exposure to BZD and related drugs during 1 to 90 days before the hip fracture (hazard period) with the exposure during four backward consecutive 90-days time windows (91 to 182, 183 to 273, 274 to 365 and 366 to 457 days before the hip fracture, control periods). A crude OR of 1.70, 95%CI: 1.50-1.92, and a full AOR of 1.47, 95%CI: 1.29-1.67 was found for the current use of BZD and related drugs. Other CXO studies showed high risk estimates as well, hence, Neutel et al (199), found a crude OR = 1.7, 95%CI: 1.0-2.9, for exposure to BZD, similar to the crude estimate obtained. In the same way, Berry et al (200) found an AOR = 1.66, 95%CI: 1.45-1.90 associated with the use of non-BZD hypnotics.

Concerning the *type of BZD or related drug*, the highest risk was observed taking both type of drugs, anxiolytics and hypnotics, similarly than in the other designs. As falls and fractures are dose-related adverse effects, the use of several drugs is equivalent to the use of a higher dose. Yet again, this could partly be related to the higher severity of the underlying conditions of these patients.

Looking at the type of drugs separately, the risk associated with hypnotics was higher than for anxiolytics for crude and AOR, whereas in the other designs this risk was similar or slightly higher with anxiolytics. No clear explanation can be provided for this finding. A published case crossover study (200) found a risk of hip/femur fracture of 2.20, 95%CI: 1.76-2.74, in new users of hypnotics (Z drugs), which is aligned with the magnitude of the result obtained for hypnotics separately.

7.2.4 SCCS study

In this study, crude incidence rate ratios (IRRs) of hip/femur fracture associated with BZD and related drugs was observed only after the first six months of treatment and in the recent use category, which was a period up to two months after the current exposure to BZD. Once the analysis was adjusted by age, no risk was found in any exposure category, or in the recent use.

This drug-event pair has been explored in the study of Madigan et al (201), to evaluate the heterogeneity of databases, as part of the Observational Medical Outcomes Partnership (OMOP) project. In seven out of ten DBs they found no risk of hip fracture associated with BZD use, when a SCCS was employed.

Such a lack of effect may be related to the strong dependence of event and exposure. As it has clearly been shown, patients who sustained a hip/femur fracture were frequently prescribed a BZD or a related drug after such event (as new treatment, not as treatment continuation). This dependence between the

exposure and the outcome represents a violation of one of the key assumptions that this design must fulfil, as consequence, to overcome this problem a pre-exposure period over which there was an increased risk was identified. First, a "pre-exposure" period of 30 days was created taking that time from the baseline (past/non use) or recent use periods, as a new different category, and results changed radically. Separating this period, risk associated with exposure to BZD was found in all current use windows. Usually, the reference category is the one with the lowest risk, in this case was past/non use, because the hypothesis was to investigate the possible association between the exposure to BZD and hip/femur fractures, so it was assumed the unexposed periods, after a washout time, as reference category. Since that period with high risk was included in the baseline, all results were underestimated, because the risk was higher in the denominator yielding necessarily lower estimates.

Gibson et al (148) used a pre-exposure time as well, obtaining similar results, the highest risk was observed in that pre-exposure time, and then was progressively decreasing in recent and past use. The outcome was not the same, because their outcome was motor vehicle crashes, not hip/femur fractures, but design and results are comparable.

After exploring the length of this pre-exposure time window, it was seen that the shorter windows (7 or 15 days) presented higher risk than the longer ones (30 and 60 days). This is the mirror image of the high number of new users of BZD and related drugs found after a hip/femur fracture. Implications of this finding are critical, because it reveals dependence between the exposure and the event, and the results without separating this time from the reference category were biased. Similar situation with a SCCS design and hip/femur fracture as an outcome was observed by Lai C et al (202) where they examined prescriptions of alpha blockers following hip/femur fractures.

Further exploring the baseline risk before the exposure, it was found that apart from the intense risk just before the exposure, there was some risk up to

182 days before. Once this period was removed, the results in the SCCS were similar to the ones found in the CXO, IRR=1.64 (95%CI: 1.48-1.81) and OR=1.47 (95%CI: 1.29-1.67), respectively.

Another finding observed was that contrary to the rest of the designs, and after creating the pre-exposure time, not before, the risk observed in recent use was lower than the risk observed in current use. This finding was further explored post-hoc. When the risk in recent periods was investigated, windows of seven days just before the exposure showed a remarkable risk, leaving the rest of the period without it. This finding may partly explain the constant high risk observed in recent periods across designs. Most of the patients take intermittently BZD and related drugs, being frequent periods of current-recent-current-recent- and so on. Consequently, if the exposure is conditioned by the event, as it has been shown with this design, it would be reasonable to obtain higher risk during recent periods than during current use.

7.2.5 Comparison across designs and literature review

All designs showed an increased risk associated with current use of BZD and related drugs as a group. However, they differ in the magnitude of HRs: traditional designs presented lower values than case-only designs. Interestingly, traditional designs are consistent with each other and so case-only designs (after adjusting for the pre-exposure in the SCCS). This is a major finding of the present research.

The lack of a gold standard does not allow identification of which of these estimates was closer to the true HR value, though it should be noted that traditional designs might still have some residual confounding due to factors difficult to adjust for, such as severity of underlying diseases, or frailty. Such factors may increase the risk of fall and fractures and, for this reason, physicians could be reluctant to prescribe them BZD and related drugs, or use them at lower doses. As a result, it could lead to an underestimation of HR. In

case-only designs, these personal factors are implicitly controlled for by design and then a greater HR could be obtained.

The experience of comparing different designs using the same source population is very limited. The OMOP project (201), studied this drug-event pair employing a SCCS and a cohort design within the same data source, and compare the results across ten DBs. In general, results were similar to the ones obtained in this research, before taking into account the pre-exposure period, that is, no risk was found in the SCCS design in 7 out of 10 data sources, in contrast with the cohort design where no risk was found in 3 out of 7 data sources.

There are some other publications comparing designs yielding different results. In most articles, the estimates with case only designs were lower than the obtained with cohort or case-control designs. Thus, Douglas et al (203) studied the association between exposure to proton pump inhibitor (PPI), and incident myocardial infarction in patients taking clopidogrel and aspirin with two different designs, a SCCS and a cohort study. They obtained and age-adjusted IRR=0.75 (95%CI: 0.55-1.01) with the SCCS, and an adjusted HR=1.30 (95%CI: 1.12-1.50) with the cohort study. Similarly, Hebert et al (204), compared a case-control with a CXO design, studying the effect of BZD on elderly drivers. The case-control approach showed an increased rate of motor vehicle crashes associated with the use of BZD, OR=1.45 (95%CI: 1.12-1.88) whereas the CXO found no association, OR=0.99 (95%CI: 0.83-1.19). And Ravera et al (205), compared different designs to study the risk of motor vehicle accidents associated with psychtropic drugs, obtaining that the result that CXO did not show any statistically significant association with any drug, for instance for anxiolytics AOR=0.95 (95%CI: 0.68-1.31) whereas the case-control found an AOR=1.54 (95%CI: 1.11-2.15) for the same drug.

Other studies however, found similar associations such as Ramsay et al, (123) who found similar risk estimates of pneumonia associated with the use of

proton pump inhibitors, in a new-users cohort (RR=3.24, 95%CI: 2.50-4.19) and in a SCCS (IRR=3.07, 95%CI: 2.69-3.50). Alike Andrews et al (206) who compared three study designs to investigate the association between autism and MMR vaccine, obtaining the following: Cohort, RR=0.92 (95%CI: 0.68-1.24); the NCC, OR=0.88, (95%CI: 0.67-1.15) and the SCCS, IRR=0.94 (95%CI: 0.60-1.47).

7.3 STRENGTHS AND LIMITATIONS

7.3.1- Data source

The BIFAP database employed provided a large study sample, with nationwide coverage and quality standards, showing internal and external validity for pharmacoepidemiologic research. Population registered in BIFAP database are representative of the Spanish population with a similar distribution by age and sex (Figure 7). Moreover, results from previous studies performed within BIFAP (207-209) have been comparable with other scientific publications, proving an external validity of those data.

The use of electronic records to ascertain the exposure, allows eliminating errors in measurement of drug use due to inadequate patient´s recall. Also, validation processes of codes used to ascertain the outcome were in place to ensure the inclusion of valid cases for all designs. This validation is recommended when a coding system is employed as outcome definition (210) and it is a normal practice for BIFAP database (211, 212).

In addition, this population-based data source provided appropriate person-time denominators and conferred good statistical power due to the large size of population included and followed over long periods of time.

As limitations of the data source, similarly than in other primary care databases, would be the incomplete data on potential confounding variables, for instance, alcohol use, smoking or BMI. Also, some variables such as

socioeconomic status, exercise or diet are not systematically recorded. In the same way, as it was commented in section 7.2, some personal characteristics of patients such as quality of life, frailty, dependence, social networks etc, which may have a relevant impact on their health status, are not usually recorded in DBs, being therefore a major limitation of studies performed with them. Precisely for these reasons there is an increasing interest in pharmacoepidemiology to use case-only designs, to overcome such limitations linked to the residual confounding by personal characteristics that hardly vary over time.

Finally, BIFAP only has information on prescriptions written by GPs. Over the counter drugs or drugs prescribed outside the primary care setting (hospital prescriptions) are not systematically recorded in this DB.

7.3.2 Classification of the exposure

The exposure was defined in all designs as a prescription of BZD or related drug recorded in the database; implications for this definition are the following:

First, a prescription is not the same as dispensing or consumption. Patients may receive a prescription but never exchange it in the pharmacy for the medication, or once dispensed they may not be fully adherent, so a misclassification of exposure could exist.

Secondly, the duration of prescriptions might not be precise, thus, patients with a treatment theoretically ended, could be still exposed and vice versa. Despite of this potential misclassification might be present, it would be non-differential, affecting to cases and no cases in the same manner, and therefore is not expected to alter the results.

Finally, although this medication is acquired by prescription only (PoM), some patients might obtain them privately and as a result, not be included in the primary care database. In Spain, the vast majority of population use the public

health system, and the percentage of patients with private prescriptions would be low.

7.3.3 Outcome identification and ascertainment

In a primary care database, the case identification depends on the selection of the relevant diagnostic codes used by GPs to record the event (213). In BIFAP the coding system employed is the ICPC-2. It is known that the granularity of such a system is not as great as others (ICD, Read codes, etc.) and this may, to some extent, reduce the specificity of the codes used. When this happens there may be as a result some misclassification of the outcome that may have an impact on the study power and on the magnitude of the true effect (206). Presumably, however, such a misclassification is non-differential according to the exposure. In order to limit that error a manual review of the individual clinical records of potential cases was performed, and only validated cases were included in these studies, strengthening the specificity of the case definition.

On the other hand, the use of the outcome "hip/femur" fracture might provide a less comparable definition with respect to other studies which only focused on "hip" fractures. However, some authors (142, 214) have recommended the use of this broader outcome for monitoring hip fractures, even when using hospital records, as "there is often miscoding between fractures of the neck of the femur and fractures of other parts or unspecified parts of the femur". However, this limitation is less important when the data are referred to population 50 years or older, as 90% of femur fractures beyond this age are of osteoporotic nature and mostly affect the neck or intertrochanteric sites (215).

7.3.4 Confounding by indication

This bias might be present in this investigation because as Barlett et al (216) already pointed out patients with pre-existing conditions that increase the risk of injurious falls (arthritis, depression, alcohol abuse) are significantly more likely

to receive a new prescription for a BZD. And, on the contrary, GPs might tend to avoid prescribing BZD to patients with more severe conditions.

This confounding by indication cannot be rule out, and might explain part of the risk observed once the risk from baseline was removed. However, in all designs patients with at least one prescription of BZD or related drugs were included, and analyses were adjusted by a number of chronic illnesses and a large list of co-medications, minimizing such bias.

7.3.5 Selection of cases/controls

Albeit the outcome of interest requires hospitalization, a population-based data source was preferred than a hospital-based, avoiding the difficulty of finding appropriate controls in a hospital. For the NCC, cases and controls were selected from the same cohort study population. Controls were randomly sampled from the underlying cohort at the time a case occurred (hip/femur fracture or index date). This approach is called "risk set sampling" and it assures that patients selected as controls are representative of the underlying population, so the ORs obtained are unbiased estimates of the incidence rate ratios (213), allowing a better comparison across designs.

Cases were matched to four controls, who were similar for three matching criteria to cases: sex, age and time of follow up within the study. In doing so, it was improved statistical efficiency, and the power for detecting an effect was increased, as well as controlling for those matching factors. Matching by follow-up time, however, may have had an impact on the HRs estimated by duration effect of BDZ and related drugs, as follow-up may be somewhat correlated with duration of treatment. Then, HRs may be distorted to the null value as controls are forced to match cases on this factor.

7.3.6 Selection of covariates

Co-morbidities and co-medications were searched in the database to include this information as potential confounders, as well as age, gender and life-style factors.

The use of health care services or number of visits to the GP in the last year is normally used as an approximate variable or 'proxy' to estimate health condition of the study population, because subjects who consult more frequently are more likely to be diagnosed with any problems they have and to be treated (213). However, this covariate was not included in this research due to the extensive list of potential diseases and treatments evaluated.

Albeit a large number of potential confounding factors were adjusted for in the analyses, the results may still be influenced by other potential confounders not included in the analyses, e.g. diet, physical activity, etc. Though it was seen that the main differences in the analyses were found when age was included in the model, and with the rest of covariates small changes were observed.

7.3.7- Study designs

Cohort study

Selecting a cohort of users of BZD or related drugs, all patients were exposed at least once to the drug of interest. Hence, comparison between cohort members, was more similar than if an external cohort of non users had been used, minimizing this way the confounding by indication that otherwise would arise.

Moreover, a "new-user" design was performed establishing as inclusion criteria to be six months free of the exposure of interest before the start date, alike "incident" cases were looked for, being twelve months without the outcome of interest before the start date. Prevalent users may introduce bias if risk varies with time, and covariates may be affected by the use of that drug (217).

Prevalent cases may have changed their habits and treatments because the disease, and reverse causality might occur. By doing this, biases from prevalent users or cases were avoided.

A potential bias in cohort studies is the loss of people during the follow up. Many reasons can make a patient leave the study, they may die, leave the practice, move to another city, etc. But when the losses are related with the exposure, outcome or both, this can bias the measurement of effect of the exposure. In this research the cohort was comprised by a dynamic population, (BIFAP database) so losses were not specifically related with the exposure or the outcome, similarly affecting to all population.

NCC study

Using a "nested" case-control design overcomes some biases that a traditional case-control might present. Thus, controls were selected from the same source population than cases, minimizing the selection bias. Information on exposures were obtained before cases were diagnosed, hence it was less prone to bias. And selecting controls with a risk set sampling method provided unbiased estimates of the risk ratios.

Other strength of this design is that allows for a more accurate ascertainment of the time-varying confounders, due to the proximity of the index date, making possible to investigate the use of co-medication one month before the hip/femur fracture.

And finally, cohort and NCC approaches produced very similar findings (213), which make easier the comparison between those designs.

CXO study

The main strength of this design is to eliminate control selection bias and between-person confounding by constant characteristics, such chronic

diseases. As a case-only design, cases act as their own controls with the mentioned strengths that it entails (section 5.1.3).

The CXO method assumes that the baseline risk for an exposure is constant, and this assumption was tested using four control periods of three months each starting immediately prior to the at-risk period. This consideration improved the precision of the effect size, by using several control time periods per case, and achieved greatest efficiency by using the whole year prior to the event (218).

As limitation, estimates obtained from a conditional logistic model could be biased if the distribution of exposures in the time periods was not exchangeable (219), but in this study that condition was met.

SCCS study

Similarly than with the CXO design, the major advantage is that confounding by differences between patients is removed, using a within-person comparison. Other strengths of this design can be found in section 5.1.4.

It has been often said, that results from this approach would be likely more accurate than the obtained with more traditional designs, as they removed selection and indication bias that otherwise would be present (134).

A main limitation is that the occurrence of the event should not affect the probability of exposure. In case this happens, it can be corrected removing that pre-exposure time that might induce a prescription from the calculation of the baseline incidence rate, preventing any spurious inflation of this estimate (148); as it was done in this research.

Another potential limitation would be the adjustment for more confounding factors such as co-medications in the analysis (220). However, in this particular investigation, age was the principal confounding factor, and it has shown that adding a broad list of co-medications barely affected the results. Once age was

controlled for, the estimates were indirectly adjusted for the rest of covariates as well.

7.4 CONTRIBUTION OF THIS RESEARCH TO THE SCIENTIFIC KNOWLEDGE

Findings from this investigation are consistent with other study reports (192) and provide evidence for the validity of the results obtained. Nevertheless, due to the observational nature of these data, causality cannot be guaranteed though evidence for causality is at least as strong here as in most other observational studies and should be interpreted in light of the limitations already discussed.

This drug event pair has been heavily studied because of the wide use of BZD and related drugs and the public health impact of this increasing outcome nowadays. However, different results have been published worldwide. Findings of this research are consistent with two recently published meta-analyses (92, 192) and suggest that the use of BZD increases moderately the risk of hip/femur fracture. Such increased risk is dependent on dose.

This thesis makes an important methodological contribution to pharmacoepidemiological research, illustrating all similarities and discrepancies found between four different designs in response to a single study question, and employing the same data source. There is, worldwide, limited experience in doing that and in Spain is the first investigation of its kind.

In this study a reciprocal association between exposure to BDZ and related drugs and the occurrence of hip/femur fracture has been observed. In pharmacoepidemiology the influence of the event on the exposure is rarely analysed. As has been shown, when the event determines the exposure it is necessary to be cautious in using designs in which current use experience is compared to past use within the same population. The approach used in the present research may be applied in further investigations.

In addition this is the first time that the risk at baseline has been explored, yielding explanations for the risk observed in a period after exposure, that otherwise only assumptions could have been done.

CONCLUSIONS

8. CONCLUSIONS

1- Spain exhibited intermediate values of IRs of hip/femur fractures compared to other European countries, and no trend was shown over 2003-2009.

2- The high prevalence of use of BZD and related drugs and the increasing trend observed in Spain compared to other European countries during the last decade requires a careful assessment and implementation of effective measures.

3- Incidence rates of hip/femur fractures associated with exposure to BZD increased exponentially with age, and it was higher in females than in males after 50 years of age, in all exposure categories.

4- The use of BZD and related drugs moderately increases the risk of hip/femur fractures and this was consistently found across the four analytical designs performed.

5- Half-life appeared not to have a relevant impact on the effect while high doses were associated with the highest risk.

6- The risk of having a hip/femur fracture was higher when anxiolytics and hypnotics were taken concomitantly.

7- No clear trend of risk was observed with duration of use, in particular, a short-term effect was not observed.

8- The hypnotics that showed the greatest risk were lormetazepam and clomethiazole, and among the anxiolytics, lorazepam and diazepam.

9- The exposure was heavily dependent on the event and this may introduce an important bias in the SCCS design. Such bias may be corrected when the pre-exposure period associated with an increased risk is well characterized and excluded from the period used as the reference.

10- The increased risk associated with pre-exposure can be an explanation for the increased risk associated with recent use in the designs performed in this research, although this should be further explored.

11- Case-only designs yielded estimates higher than the obtained in the traditional designs, allegedly because of a better control for confounding factors that are difficult to measure in traditional designs.

12- This research had not been feasible without employing an electronic primary care database with national coverage as BIFAP, demonstrating the importance of this kind of data source for pharmacoepidemiological research, particularly in Spain.

REFERENCES

9. REFERENCES

1.   Osteoporosis in the European Union in 2008: Ten years of progress and ongoing challenges: International Osteoporosis Foundation 2008 [02/10/2012]. Available from: http://www.sante.public.lu/publications/maladies-traitements/osteoporose/osteoporosis-eu-2008/osteoporosis-eu-2008.pdf.

2.   Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002 May 18;359(9319):1761-7. PubMed PMID: 12049882. Epub 2002/06/07. eng.

3.   Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ. 2000 Feb 5;320(7231):341-6. PubMed PMID: 10657327. Pubmed Central PMCID: 27279. Epub 2000/02/05. eng.

4.   Polinder S, Meerding WJ, van Baar ME, Toet H, Mulder S, van Beeck EF, et al. Cost estimation of injury-related hospital admissions in 10 European countries. The Journal of trauma. 2005;59(6):1283-90; discussion 90-1. PubMed PMID: 16394898.

5.   Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012 Sep;23(9):2239-56. PubMed PMID: 22419370. Pubmed Central PMCID: 3421108. Epub 2012/03/16. eng.

6.   Alvaro A. Guia basica de traumatologia. Hospital San Vicente de Paul, 2008.

7.   De Miguel Herrero I. CCE. Fracturas de cadera: técnica quirúrgica y carga precoz. Patología del Aparato Locomotor. 2006;4((2)):108-15.

8.   van Embden D, Roukema GR, Rhemrev SJ, Genelin F, Meylaerts SA. The Pauwels classification for intracapsular hip fractures: is it reliable? Injury. 2011 Nov;42(11):1238-40. PubMed PMID: 21146815.

9.   One O. Intertrochanteric fractures-Evans classification 2012 [Mar 2013]. Available from:
http://www.orthopaedicsone.com/display/Main/Intertrochanteric+fractures+-+Evans+classification.

10.   Therapy Information Services I. TIS Chapter 7- The Hip 1998 [Mar 2013]. Available from: http://www.therapyedu.com/ortho/chapter7.htm.

11.   Ruiz de la Cuesta Madruga F, et al. Fracturas subtrocantéreas de fémur. Clavo de Zickel. Rev Esp Cirugía Osteoarticular. 1980;15(086):139-51.

12.   Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011 Jan;45(1):15-22. PubMed PMID: 21221218. Pubmed Central PMCID: 3004072. Epub 2011/01/12. eng.

13.   Wright NC, Saag KG, Curtis JR, Smith WK, Kilgore ML, Morrisey MA, et al. Recent trends in hip fracture rates by race/ethnicity among older US adults. J Bone Miner Res. 2012 Nov;27(11):2325-32. PubMed PMID: 22692958. Epub 2012/06/14. eng.

14.   Kanis J. Assessment of osteoporosis at the primary health care level: on behalf of the World Health Organization Scientific Group (WHO); 2007 [Nov 2012]. Available from:
http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf.

15.   Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, et al. High-trauma fractures and low bone mineral density in older women and men. JAMA. 2007 Nov 28;298(20):2381-8. PubMed PMID: 18042915.

16.   Alvarez-Nebreda ML, Jimenez AB, Rodriguez P, Serra JA. Epidemiology of hip fracture in the elderly in Spain. Bone. 2008 Feb;42(2):278-85. PubMed PMID: 18037366. Epub 2007/11/27. eng.

17.   Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009 Oct;20(10):1633-50. PubMed PMID: 19421703.

18.   Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing. 2010 Mar;39(2):203-9. PubMed PMID: 20075035.

19.   Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management,

epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013 Dec;8(1-2):136. PubMed PMID: 24113837.

20.   Walker RW, Chaplin A, Hancock RL, Rutherford R, Gray WK. Hip fractures in people with idiopathic Parkinson's disease: incidence and outcomes. Movement disorders : official journal of the Movement Disorder Society. 2013 Mar;28(3):334-40. PubMed PMID: 23389925.

21.   Bhattacharya RK, Dubinsky RM, Lai SM, Dubinsky H. Is there an increased risk of hip fracture in Parkinson's disease? A nationwide inpatient sample. Movement disorders : official journal of the Movement Disorder Society. 2012 Sep 15;27(11):1440-3. PubMed PMID: 22744727.

22.   Tolppanen AM, Lavikainen P, Soininen H, Hartikainen S. Incident hip fractures among community dwelling persons with Alzheimer's disease in a Finnish nationwide register-based cohort. PLoS One. 2013;8(3):e59124. PubMed PMID: 23527106. Pubmed Central PMCID: 3601105.

23.   Bazelier MT, van Staa TP, Uitdehaag BM, Cooper C, Leufkens HG, Vestergaard P, et al. Risk of fractures in patients with multiple sclerosis: a population-based cohort study. Neurology. 2012 Jun 12;78(24):1967-73. PubMed PMID: 22592374. Pubmed Central PMCID: 3369507.

24.   Souverein PC, Webb DJ, Petri H, Weil J, Van Staa TP, Egberts T. Incidence of Fractures among Epilepsy Patients: A Population-based Retrospective Cohort Study in the General Practice Research Database. Epilepsia. 2005;46(2):304-10.

25.   Sennerby U, Melhus H, Gedeborg R, Byberg L, Garmo H, Ahlbom A, et al. Cardiovascular diseases and risk of hip fracture. JAMA. 2009 Oct 21;302(15):1666-73. PubMed PMID: 19843901. Epub 2009/10/22. eng.

26.   Pouwels S, Lalmohamed A, Leufkens B, de Boer A, Cooper C, van Staa T, et al. Risk of hip/femur fracture after stroke: a population-based case-control study. Stroke. 2009 Oct;40(10):3281-5. PubMed PMID: 19661475. Epub 2009/08/08. eng.

27.   Schwartz AV, Ewing SK, Porzig AM, McCulloch CE, Resnick HE, Hillier TA, et al. Diabetes and change in bone mineral density at the hip, calcaneus, spine, and radius in older women. Frontiers in endocrinology. 2013;4:62. PubMed PMID: 23755040. Pubmed Central PMCID: 3667237.

28.   Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk--a meta-analysis. Thyroid : official journal of the American Thyroid Association. 2003 Jun;13(6):585-93. PubMed PMID: 12930603.

29.   Martin Escudero JC. [Chronic obstructive pulmonary disease and risk of fractures]. Revista clinica espanola. 2011 Oct;211(9):455-7. PubMed PMID: 21696720. Enfermedad pulmonar obstructiva cronica y riesgo de fracturas.

30.   Diez-Manglano J, Lopez-Garcia F, Barquero-Romero J, Galofre-Alvaro N, Montero-Rivas L, Almagro-Mena P, et al. [Risk of osteoporotic fracture and hip fracture in patients with chronic obstructive pulmonary disease]. Revista clinica espanola. 2011 Oct;211(9):443-9. PubMed PMID: 21899835. Riesgo de fractura osteoporotica y de cadera en pacientes con enfermedad pulmonar obstructiva cronica.

31.   Tebe C, del Rio LM, Casas L, Estrada MD, Kotzeva A, Di Gregorio S, et al. Risk factors for fragility fractures in a cohort of Spanish women. Gac Sanit. 2011 Nov-Dec;25(6):507-12. PubMed PMID: 21955641. Epub 2011/10/01. Factores de riesgo de fracturas por fragilidad en una cohorte de mujeres espanolas. spa.

32.   Pouwels S, Bazelier MT, de Boer A, Weber WE, Neef CK, Cooper C, et al. Five-year fracture risk estimation in patients with Parkinson's disease. Bone. 2013 Jun 22;56(2):266-70. PubMed PMID: 23800516.

33.   Vestergaard P, Mosekilde L. Fracture risk in patients with celiac Disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. Am J Epidemiol. 2002 Jul 1;156(1):1-10. PubMed PMID: 12076883.

34.   van Staa TP, Leufkens HG, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. Bone. 2002 Oct;31(4):508-14. PubMed PMID: 12398948. Epub 2002/10/26. eng.

35.   van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. Public health impact of adverse bone effects of oral corticosteroids. Br J Clin Pharmacol. 2001 Jun;51(6):601-7. PubMed PMID: 11422020. Pubmed Central PMCID: 2014495.

36.   Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011 Nov 24;365(21):2002-12. PubMed PMID: 22111719.

37.   ElDesoky ES. Pharmacokinetic-pharmacodynamic crisis in the elderly. American journal of therapeutics. 2007 Sep-Oct;14(5):488-98. PubMed PMID: 17890940.

38.   Cuevas C NM, Benavente MJ. El sistema de información para la administración de medicamentos a pacientes hospitalizados. En: Carnicero J (Coordinador). La gestión del medicamento en los Servicios de Salud. Informes SEIS (8). . Pamplona: Sociedad Española de Informática de la Salud, 2008.

39.   Strom B L KSEaHS. Pharmacoepidemiology. 5th ed: Wiley-Blackwell; 2012.

40.   Hartzema AG, Porta M. S. and Tilson H. H. Pharmacoepidemiology: An introduction. 2nd ed: Harvey Whitney Books; 1991.

41.   Stergachis A, Hazlet T. Pharmacoepidemiology. Pharmacotherapy A Pathophysiologic Approach: McGraw-Hill; 2005. p. 115-23.

42.   Joseph T. DiPiro RLT, Gary C. Yee, Gary R. Matzke and Barbara G. Wells. Pharmacotherapy: A Pathophysiologic Approach. 6th ed: MCGRAW-HILL; 2005.

43.   Etminan M, Gill S, Fitzgerald M, Samii A. Challenges and opportunities for pharmacoepidemiology in drug-therapy decision making. J Clin Pharmacol. 2006 Jan;46(1):6-9. PubMed PMID: 16397278. Epub 2006/01/07. eng.

44.   Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. Age Ageing. 2013 Jul;42(4):514-20. PubMed PMID: 23438446.

45.   Eom CS, Lee HK, Ye S, Park SM, Cho KH. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. J Bone Miner Res. 2012 May;27(5):1186-95. PubMed PMID: 22258738.

46.   Rigler SK, Shireman TI, Cook-Wiens GJ, Ellerbeck EF, Whittle JC, Mehr DR, et al. Fracture risk in nursing home residents initiating antipsychotic medications. Journal of the American Geriatrics Society. 2013 May;61(5):715-22. PubMed PMID: 23590366. Pubmed Central PMCID: 3656141.

47.   Vestergaard P, Rejnmark L, Mosekilde L. Reduced relative risk of fractures among users of lithium. Calcif Tissue Int. 2005 Jul;77(1):1-8. PubMed PMID: 16007481.

48.   Arbouw ME, Movig KL, van Staa TP, Egberts AC, Souverein PC, de Vries F. Dopaminergic drugs and the risk of hip or femur fracture: a population-based case-control study. Osteoporos Int. 2011 Jul;22(7):2197-204. PubMed PMID: 20967420. Pubmed Central PMCID: 3106160.

49.   Mezuk B, Morden NE, Ganoczy D, Post EP, Kilbourne AM. Anticonvulsant use, bipolar disorder, and risk of fracture among older adults in the Veterans Health Administration. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2010 Mar;18(3):245-55. PubMed PMID: 20224520.

50.   Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs. 2003;17(11):825-37. PubMed PMID: 12921493. Epub 2003/08/19. eng.

51.   Chang CM, Wu EC, Chang IS, Lin KM. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2008 Aug;16(8):686-92. PubMed PMID: 18669947. Epub 2008/08/02. eng.

52.   Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: a meta-analysis. Osteoporos Int. 2013 Sep 7. PubMed PMID: 24013517.

53.   de Vries F, Pouwels S, Lammers JW, Leufkens HG, Bracke M, Cooper C, et al. Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study. J Intern Med. 2007 Feb;261(2):170-7. PubMed PMID: 17241182. Epub 2007/01/24. eng.

54.   de Vries F, Pouwels S, Bracke M, Leufkens HG, Cooper C, Lammers JW, et al. Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study. Pharmacoepidemiol Drug Saf. 2007 Jun;16(6):612-9. PubMed PMID: 16998945.

55.   Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med. 2012 Dec 10;172(22):1739-44. PubMed PMID: 23165923.

56.   Cumming RG. Epidemiology of medication-related falls and fractures in the elderly. Drugs & aging. 1998 Jan;12(1):43-53. PubMed PMID: 9467686.

57.   Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in patients treated with loop diuretics. J Intern Med. 2006 Jan;259(1):117-24. PubMed PMID: 16336519.

58.   Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in patients treated with amiodarone or digoxin for cardiac arrhythmias: a nation-wide case-control study. Osteoporos Int. 2007 Apr;18(4):409-17. PubMed PMID: 17093893.

59.   Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. The American journal of medicine. 2010 Oct;123(10):877-84. PubMed PMID: 20920685.

60.   Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA. 2000 Jun 28;283(24):3211-6. PubMed PMID: 10866868. Epub 2000/06/24. eng.

61.   Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med. 2009 Sep;6(9):e1000154. PubMed PMID: 19787025. Pubmed Central PMCID: 2741577. Epub 2009/09/30. eng.

62.   Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005 Jul;48(7):1292-9. PubMed PMID: 15909154.

63.   Meyer HE, Lofthus CM, Sogaard AJ, Falch JA. Change in the use of hormone replacement therapy and the incidence of fracture in Oslo. Osteoporos Int. 2009 May;20(5):827-30. PubMed PMID: 18563511. Epub 2008/06/20. eng.

64.   Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. BMJ. 2011;342:d2238. PubMed PMID: 21527461. Pubmed Central PMCID: 3084377.

65.   Vestergaard P, Rejnmark L, Mosekilde L. Influence of hyper- and hypothyroidism, and the effects of treatment with antithyroid drugs and levothyroxine on fracture risk. Calcif Tissue Int. 2005 Sep;77(3):139-44. PubMed PMID: 16151671.

66.   Roussy JP, Bessette L, Bernatsky S, Rahme E, Lachaine J. Biologic disease-modifying anti-rheumatic drugs and the risk of non-vertebral osteoporotic fractures in patients with rheumatoid arthritis aged 50 years and over. Osteoporos Int. 2013 Sep;24(9):2483-92. PubMed PMID: 23504029.

67.   Pouwels S, Lalmohamed A, Souverein P, Cooper C, Veldt BJ, Leufkens HG, et al. Use of proton pump inhibitors and risk of hip/femur fracture: a population-based case-control study. Osteoporos Int. 2011 Mar;22(3):903-10. PubMed PMID: 20585937. Pubmed Central PMCID: 3034906.

68.   Reyes C, Formiga F, Coderch M, Hoyo J, Ferriz G, Casanovas J, et al. Use of proton pump inhibitors and risk of fragility hip fracture in a Mediterranean region. Bone. 2013 Feb;52(2):557-61. PubMed PMID: 23023097.

69.   Cea-Soriano L, Johansson S, Garcia Rodriguez LA. Risk factors for falls with use of acid-suppressive drugs. Epidemiology. 2013 Jul;24(4):600-7. PubMed PMID: 23676267.

70.   Abrahamsen B, Vestergaard P. Proton pump inhibitor use and fracture risk - effect modification by histamine H1 receptor blockade. Observational

case-control study using National Prescription Data. Bone. 2013 Nov;57(1):269-71. PubMed PMID: 23973557.

71.   Vestergaard P, Hermann P, Jensen JE, Eiken P, Mosekilde L. Effects of paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and opioids on bone mineral density and risk of fracture: results of the Danish Osteoporosis Prevention Study (DOPS). Osteoporos Int. 2012 Apr;23(4):1255-65. PubMed PMID: 21710339.

72.   Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. J Intern Med. 2006 Jul;260(1):76-87. PubMed PMID: 16789982.

73.   Abelson A, Ringe JD, Gold DT, Lange JL, Thomas T. Longitudinal change in clinical fracture incidence after initiation of bisphosphonates. Osteoporos Int. 2010 Jun;21(6):1021-9. PubMed PMID: 19722103. Pubmed Central PMCID: 2861765. Epub 2009/09/02. eng.

74.   Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, et al. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Miner Res. 2008 Jan;23(1):112-20. PubMed PMID: 17892376.

75.   Erviti J, Alonso A, Oliva B, Gorricho J, Lopez A, Timoner J, et al. Oral bisphosphonates are associated with increased risk of subtrochanteric and diaphyseal fractures in elderly women: a nested case-control study. BMJ Open. 2013;3(1). PubMed PMID: 23370011. Pubmed Central PMCID: 3563115. Epub 2013/02/02. eng.

76.   Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. Journal of women's health. 2013 Nov;22(11):915-29. PubMed PMID: 24131320. Pubmed Central PMCID: 3882746.

77.   Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014 Jan 11;383(9912):146-55. PubMed PMID: 24119980.

78.   Longo F K, Hauser, Jameson, Loscalzo. Harrison's Principles of Internal Medicine. 18th ed2012.

79.   Gilman G. The Pharmacological Basis of Therapeutics. 10th ed2001.

80.   McKernan RM, Rosahl TW, Reynolds DS, Sur C, Wafford KA, Atack JR, et al. Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. Nat Neurosci. 2000 Jun;3(6):587-92. PubMed PMID: 10816315. Epub 2000/05/18. eng.

81.   Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Handbook of experimental pharmacology. 2008 (182):335-60. PubMed PMID: 18175099.

82.   Florez J AJaMA. Farmacología Humana. 4th ed: Masson; 2004.

83.   Garcia del Pozo J, de Abajo Iglesias FJ, Carvajal Garcia-Pando A, Montero Corominas D, Madurga Sanz M, Garcia del Pozo V. [The use of anxiolytic and hypnotic drugs in Spain (1995-2002)]. Rev Esp Salud Publica. 2004 May-Jun;78(3):379-87. PubMed PMID: 15293958. Utilizacion de ansioliticos e hipnoticos en Espana (1995-2002).

84.   Demyttenaere K, Bonnewyn A, Bruffaerts R, De Girolamo G, Gasquet I, Kovess V, et al. Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD). J Affect Disord. 2008 Sep;110(1-2):84-93. PubMed PMID: 18329721. Epub 2008/03/11. eng.

85.   van Hulten R, Leufkens HG, Bakker A. Usage patterns of benzodiazepines in a Dutch community: a 10-year follow-up. Pharmacy world & science : PWS. 1998 Apr;20(2):78-82. PubMed PMID: 9584341.

86.   Kjosavik SR, Ruths S, Hunskaar S. Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database. Pharmacoepidemiol Drug Saf. 2009 Jul;18(7):572-8. PubMed PMID: 19402032.

87.   Wu CH, Wang CC, Katz AJ, Farley J. National trends of psychotropic medication use among patients diagnosed with anxiety disorders: results from

medical expenditure panel survey 2004-2009. Journal of anxiety disorders. 2013 Mar;27(2):163-70. PubMed PMID: 23428605.

88.   (AEMPS). SAfMaMD. Uso de Benzodiacepinas en España (2000-2012) 2013 [2013]. Available from:
http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/ansioliti cos_hipnoticos-2000-2012.pdf.

89.   Lasserre A, Younes N, Blanchon T, Cantegreil-Kallen I, Passerieux C, Thomas G, et al. Psychotropic drug use among older people in general practice: discrepancies between opinion and practice. The British journal of general practice : the journal of the Royal College of General Practitioners. 2010 Apr;60(573):e156-62. PubMed PMID: 20353661. Pubmed Central PMCID: 2845506.

90.   Authority DHaM. The consumption of benzodiazepines and benzodiazepine related drugs 2007 [cited 2014]. Available from:
http://sundhedsstyrelsen.dk/en/medicines/consumption-analyses/the-consumption-of-benzodiazepines-and-benzodiazepine-related-drugs.

91.   Sonnenberg CM, Bierman EJ, Deeg DJ, Comijs HC, van Tilburg W, Beekman AT. Ten-year trends in benzodiazepine use in the Dutch population. Soc Psychiatry Psychiatr Epidemiol. 2012 Feb;47(2):293-301. PubMed PMID: 21258999. Pubmed Central PMCID: 3259393. Epub 2011/01/25. eng.

92.   Khong TP, de Vries F, Goldenberg JS, Klungel OH, Robinson NJ, Ibanez L, et al. Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and the United States. Calcif Tissue Int. 2012 Jul;91(1):24-31. PubMed PMID: 22566242. Pubmed Central PMCID: 3382650. Epub 2012/05/09. eng.

93.   Vicente Sanchez MP, Macias Saint-Gerons D, de la Fuente Honrubia C, Gonzalez Bermejo D, Montero Corominas D, Catala-Lopez F. [Trends of use of anxiolytics and hypnotics in Spain from 2000 to 2011]. Rev Esp Salud Publica. 2013 May-Jun;87(3):247-55. PubMed PMID: 23892676. Evolucion del uso de medicamentos ansioliticos e hipnoticos en Espana durante el periodo 2000-2011.

94.   Strom BL. Pharmacoepidemiology. 4th ed2005.

95.   Perez-Gutthann S, Garcia Rodriguez LA, de Abajo Iglesias FJ, Varas-Lorenzo C, Gutierrez Cornejo L, Castellsague J. Farmacoepidemiologia. La epidemiologia aplicada a la seguridad y gestion de los medicamentos y al desarrollo farmaceutico. In: Panamericana EM, editor. Tratado de Medicina Farmaceutica2010. p. 649-60.

96.   (ENCePP) TENoCfPaP. Guide on Methodological Standards in Pharmacoepidemiology (Revision 1). EMA/95098/2010, Feb 2013.

97.   Hennessy S. Use of health care databases in pharmacoepidemiology. Basic & clinical pharmacology & toxicology. 2006 Mar;98(3):311-3. PubMed PMID: 16611207.

98.   Salvador Rosa A, Moreno Perez JC, Sonego D, Garcia Rodriguez LA, de Abajo Iglesias FJ. [The BIFAP project: database for pharmaco-epidemiological research in primary care]. Atencion primaria / Sociedad Espanola de Medicina de Familia y Comunitaria. 2002 Dec;30(10):655-61. PubMed PMID: 12525343. Epub 2003/01/15. El Proyecto BIFAP: Base de datos para la Investigacion Farmacoepidemiologica en Atencion Primaria. spa.

99.   Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol. 1989 Apr;129(4):837-49. PubMed PMID: 2646920. Epub 1989/04/01. eng.

100.   Clinical Practice Research Datalink (CPRD) 2012 [Oct 2012]. Available from: http://www.cprd.com/intro.asp.

101.   The Health Improvement Network website (THIN) [Nov 2012]. Available from: http://www.thin-uk.com/.

102.   The Mondriaan Project 2011 [Oct 2012]. Available from: http://www.projectmondriaan.nl/.

103.   Erasmus M. IPCI (Integrated Primary Care Information) 2013 [Feb 2013]. Available from: http://www.erasmusmc.nl/med_informatica/research/555688/?lang=en.

104.   PHARMO I. PHARMO Institute for Drug Outcomes Research 1999 [cited 2013]. Available from: http://www.pharmo.nl.

105.   Authority DHaM. Register of Medicinal Product Statistics [Oct 2012]. Available from: http://www.dkma.dk/en/topics/statistics,-prices-and-reimbursement/statistics-and-analyses/about-the-register-of-medicinal-product--tatistics-.

106.   Authority DHaM. The civil registration system [Oct 2012]. Available from: http://www.sst.dk/Indberetning%20og%20statistik/Sundhedsstyrelsens%20registre/CPR-registeret.aspx.

107.   Authority DHaM. National Patient Registry [Oct 2012]. Available from: http://www.sst.dk/Indberetning%20og%20statistik/Landspatientregisteret.aspx.

108.   Li Wei JPaTMM. The Tayside Medicines Monitoring Unit (MEMO). In: John Wiley & Sons L, editor. Pharmacoepidemiology2005.

109.   Mann E, Meyer G, Haastert B, Icks A. Comparison of hip fracture incidence and trends between Germany and Austria 1995-2004: an epidemiological study. BMC Public Health. 2010;10:46. PubMed PMID: 20113471. Pubmed Central PMCID: 2831031. Epub 2010/02/02. eng.

110.   Hernandez JL, Olmos JM, Alonso MA, Gonzalez-Fernandez CR, Martinez J, Pajaron M, et al. Trend in hip fracture epidemiology over a 14-year period in a Spanish population. Osteoporos Int. 2006;17(3):464-70. PubMed PMID: 16283063. Epub 2005/11/12. eng.

111.   Lyritis GP, Rizou S, Galanos A, Makras P. Incidence of hip fractures in Greece during a 30-year period: 1977-2007. Osteoporos Int. 2012 Oct 13. PubMed PMID: 23064370. Epub 2012/10/16. Eng.

112.   Korhonen N, Niemi S, Parkkari J, Sievanen H, Palvanen M, Kannus P. Continuous decline in incidence of hip fracture: nationwide statistics from Finland between 1970 and 2010. Osteoporos Int. 2012 Oct 30. PubMed PMID: 23108781. Epub 2012/10/31. Eng.

113.   Lakatos P, Balogh A, Czerwinski E, Dimai HP, Hans D, Holzer G, et al. New considerations on the management of osteoporosis in Central and Eastern Europe (CEE): summary of the "3rd Summit on Osteoporosis-CEE", November 2009, Budapest, Hungary. Arch Osteoporos. 2011 Dec;6(1-2):1-12. PubMed PMID: 22886098. Epub 2012/08/14. eng.

114.   Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporos Int. 2011 May;22(5):1277-88. PubMed PMID: 21461721. Epub 2011/04/05. eng.

115.   Authority DHaM. Effective effort against the excessive use of benzodiazepines in Denmark. 2009 [2013]. Available from: http://laegemiddelstyrelsen.dk/en/topics/statistics,-prices-and-reimbursement/statistics-and-analyses/analyses/consumption-analyses/effective-effort-against-the-excessive-u--in-denmark.

116.   (afssaps) Afdssdpds. État des lieux de la consommation des benzodiazépines en France. Jan 2012.

117.   Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. Arch Intern Med. 1995 Sep 11;155(16):1801-7. PubMed PMID: 7654115. Epub 1995/09/11. eng.

118.   Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. Journal of the American Geriatrics Society. 2000 Jun;48(6):682-5. PubMed PMID: 10855607. Epub 2000/06/16. eng.

119.   Finkle WD, Der JS, Greenland S, Adams JL, Ridgeway G, Blaschke T, et al. Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. Journal of the American Geriatrics Society. 2011 Oct;59(10):1883-90. PubMed PMID: 22091502.

120.   Huerta C A-KV, Requena G, Oliva B, Alvarez Y et al. Prevalence of use of benzodiazepines and related drugs in seven European databases: A cross-national descriptive study from the PROTECT-EU Project. 29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management 2013.

121.   Requena G, Abbing-Karahagopian V, Huerta C, De Bruin ML, Alvarez Y, Miret M, et al. Incidence Rates and Trends of Hip/Femur Fractures in Five

European Countries: Comparison Using E-Healthcare Records Databases. Calcif Tissue Int. 2014 Apr 1. PubMed PMID: 24687523.

122.   ENCePP ENoCfPaP. ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) [Oct 2012]. Available from: http://www.encepp.eu/encepp/studiesDatabase.jsp.

123.   Ramsay EN, Pratt NL, Ryan P, Roughead EE. Proton pump inhibitors and the risk of pneumonia: a comparison of cohort and self-controlled case series designs. BMC medical research methodology. 2013 Jun 24;13(1):82. PubMed PMID: 23800078. Pubmed Central PMCID: 3699413.

124.   Lucianne Bailey KV, Julia Langham and Daniel Chandramohan. Introduction to Epidemiology: Open University Press; 2005.

125.   Richardson DB. An incidence density sampling program for nested case-control analyses. Occup Environ Med. 2004 Dec;61(12):e59. PubMed PMID: 15550597. Pubmed Central PMCID: 1740694. Epub 2004/11/20. eng.

126.   Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991 Jan 15;133(2):144-53. PubMed PMID: 1985444.

127.   Maclure M, Mittleman MA. Should we use a case-crossover design? Annual review of public health. 2000;21:193-221. PubMed PMID: 10884952.

128.   Mittleman MA, Maclure M, Glasser DB. Evaluation of acute risk for myocardial infarction in men treated with sildenafil citrate. The American journal of cardiology. 2005 Aug 1;96(3):443-6. PubMed PMID: 16054479.

129.   Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, Naldi L, Viboud C, Roujeau JC, et al. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. Aids. 2001 Sep 28;15(14):1843-8. PubMed PMID: 11579247.

130.   Aberra FN, Brensinger CM, Bilker WB, Lichtenstein GR, Lewis JD. Antibiotic use and the risk of flare of inflammatory bowel disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005 May;3(5):459-65. PubMed PMID: 15880315.

131.   Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. Stat Methods Med Res. 2009 Feb;18(1):53-65. PubMed PMID: 18765504. Epub 2008/09/04. eng.

132.   Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. Vaccine. 2004 May 7;22(15-16):2064-70. PubMed PMID: 15121324.

133.   Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Statistics in medicine. 2006 May 30;25(10):1768-97. PubMed PMID: 16220518.

134.   Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol. 2003 Jul 1;158(1):77-84. PubMed PMID: 12835289. Epub 2003/07/02. eng.

135.   Hubbard R, Lewis S, West J, Smith C, Godfrey C, Smeeth L, et al. Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network. Thorax. 2005 Oct;60(10):848-50. PubMed PMID: 16055620. Pubmed Central PMCID: 1747199. Epub 2005/08/02. eng.

136.   Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, Li J, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet. 1999 Jun 12;353(9169):2026-9. PubMed PMID: 10376617.

137.   Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. Vaccine. 2001 Jun 14;19(27):3632-5. PubMed PMID: 11395196.

138.   Farrington CPaW, H. J. Semiparametric analysis of case series data. Journal of the Royal Statistical Society. 2006 Nov 2006;55(5):553-94.

139.   Hocine MN, Chavance M. [The case series method]. Revue d'epidemiologie et de sante publique. 2010 Dec;58(6):435-40. PubMed PMID: 21094004. La methode de la serie de cas.

140.   Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res. 2009 Feb;18(1):7-26. PubMed PMID: 18562396. Epub 2008/06/20. eng.

141.   Abbing-Karahagopian V, Kurz X, de Vries F, van Staa TP, Alvarez Y, Hesse U, et al. Bridging Differences in Outcomes of Pharmacoepidemiological Studies: Design and First Results of the Protect Project. Curr Clin Pharmacol. 2013 Nov 11. PubMed PMID: 24218995.

142.   Balasegaram S, Majeed A, Fitz-Clarence H. Trends in hospital admissions for fractures of the hip and femur in England, 1989-1990 to 1997-1998. J Public Health Med. 2001 Mar;23(1):11-7. PubMed PMID: 11315687. Epub 2001/04/24. eng.

143.   Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol. 2010 Apr;63(4):422-7. PubMed PMID: 19880282. Epub 2009/11/03. eng.

144.   Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA. 1989 Dec 15;262(23):3303-7. PubMed PMID: 2573741. Epub 1989/12/15. eng.

145.   Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ, 3rd. Psychotropic drug use and the risk of hip fracture. N Engl J Med. 1987 Feb 12;316(7):363-9. PubMed PMID: 2880292. Epub 1987/02/12. eng.

146.   Lalmohamed A, Welsing PM, Lems WF, Jacobs JW, Kanis JA, Johansson H, et al. Calibration of FRAX (R) 3.1 to the Dutch population with data on the epidemiology of hip fractures. Osteoporos Int. 2012 Mar;23(3):861-9. PubMed PMID: 22120910. Pubmed Central PMCID: 3277691. Epub 2011/11/29. eng.

147.   Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006 Dec;17(12):1726-33. PubMed PMID: 16983459. Epub 2006/09/20. eng.

148.   Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use

of prescription medications and the risk of motor vehicle crashes. Am J Epidemiol. 2009 Mar 15;169(6):761-8. PubMed PMID: 19181876. Epub 2009/02/03. eng.

149.   Giversen IM. Time trends of age-adjusted incidence rates of first hip fractures: a register-based study among older people in Viborg County, Denmark, 1987-1997. Osteoporos Int. 2006;17(4):552-64. PubMed PMID: 16408148. Epub 2006/01/13. eng.

150.   Wu TY, Jen MH, Bottle A, Liaw CK, Aylin P, Majeed A. Admission rates and in-hospital mortality for hip fractures in England 1998 to 2009: time trends study. J Public Health (Oxf). 2011 Jun;33(2):284-91. PubMed PMID: 20926392. Epub 2010/10/12. eng.

151.   Pages-Castella A, Carbonell-Abella C, Aviles FF, Alzamora M, Baena-Diez JM, Laguna DM, et al. "Burden of osteoporotic fractures in primary health care in Catalonia (Spain): a population-based study". BMC Musculoskelet Disord. 2012;13:79. PubMed PMID: 22639802. Pubmed Central PMCID: 3489545. Epub 2012/05/30. eng.

152.   Goettsch WG, de Jong RB, Kramarz P, Herings RM. Developments of the incidence of osteoporosis in The Netherlands: a PHARMO study. Pharmacoepidemiol Drug Saf. 2007 Feb;16(2):166-72. PubMed PMID: 16700086. Epub 2006/05/16. eng.

153.   Icks A, Haastert B, Wildner M, Becker C, Meyer G. Trend of hip fracture incidence in Germany 1995-2004: a population-based study. Osteoporos Int. 2008 Aug;19(8):1139-45. PubMed PMID: 18087659. Epub 2007/12/19. eng.

154.   Poole KE, Compston JE. Osteoporosis and its management. BMJ. 2006 Dec 16;333(7581):1251-6. PubMed PMID: 17170416. Pubmed Central PMCID: 1702459. Epub 2006/12/16. eng.

155.   De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA. Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ. 1997 Jul 26;315(7102):221-5. PubMed PMID: 9253270. Pubmed Central PMCID: 2127146. Epub 1997/07/26. eng.

156.   Johnell O, Gullberg B, Allander E, Kanis JA. The apparent incidence of hip fracture in Europe: a study of national register sources. MEDOS Study Group. Osteoporos Int. 1992 Nov;2(6):298-302. PubMed PMID: 1421798. Epub 1992/11/01. eng.

157.   Dolan P, Torgerson DJ. The cost of treating osteoporotic fractures in the United Kingdom female population. Osteoporos Int. 1998;8(6):611-7. PubMed PMID: 10326069. Epub 1999/05/18. eng.

158.   Tafuri S, Martinelli D, Balducci MT, Fortunato F, Prato R, Germinario C. Epidemiology of femoral neck fractures in Puglia (Italy): an analysis of existing data. Ig Sanita Pubbl. 2008 Sep-Oct;64(5):623-36. PubMed PMID: 19188938. Epub 2009/02/04. Epidemiologia delle fratture del collo del femore in Puglia attraverso l'analisi dei dati correnti. ita.

159.   Nilson F, Moniruzzaman S, Gustavsson J, Andersson R. Trends in hip fracture incidence rates among the elderly in Sweden 1987-2009. J Public Health (Oxf). 2012 Jun 29;35(1):125-31. PubMed PMID: 22753444. Epub 2012/07/04. Eng.

160.   Adams AL, Shi J, Takayanagi M, Dell RM, Funahashi TT, Jacobsen SJ. Ten-year hip fracture incidence rate trends in a large California population, 1997-2006. Osteoporos Int. 2012 Feb 21;24(1):373-6. PubMed PMID: 22349963. Epub 2012/02/22. Eng.

161.   Pasco JA, Brennan SL, Henry MJ, Nicholson GC, Sanders KM, Zhang Y, et al. Changes in hip fracture rates in southeastern Australia spanning the period 1994-2007. J Bone Miner Res. 2011 Jul;26(7):1648-54. PubMed PMID: 21445981. Epub 2011/03/30. eng.

162.   Leslie WD, Sadatsafavi M, Lix LM, Azimaee M, Morin S, Metge CJ, et al. Secular decreases in fracture rates 1986-2006 for Manitoba, Canada: a population-based analysis. Osteoporos Int. 2011 Jul;22(7):2137-43. PubMed PMID: 21069292. Epub 2010/11/12. eng.

163.   Holt G, Smith R, Duncan K, Hutchison JD, Reid D. Changes in population demographics and the future incidence of hip fracture. Injury. 2009 Jul;40(7):722-6. PubMed PMID: 19426972. Epub 2009/05/12. eng.

164.   Greene D, Dell RM. Outcomes of an osteoporosis disease-management program managed by nurse practitioners. J Am Acad Nurse Pract. 2010 Jun;22(6):326-9. PubMed PMID: 20536631. Epub 2010/06/12. eng.

165.   PASEO (Physical Activity among SEdentary Older people): EU Commission, Executive Agency for Health and Counsumers (EAHC); 2009 [cited November 2012]. Available from: http://www.paseonet.org/the_project.html.

166.   Ohayon MM LM. Use of psychotropic medication in the general population of France, Germany, Italy and the United Kingdom. J Clin Psychiatry. 2002;63:817-25.

167.   Zandstra SM, Furer JW, van de Lisdonk EH, van't HM, Bor JH, van Weel C, et al. Different study criteria affect the prevalence of benzodiazepine use. Soc Psychiatry Psychiatr Epidemiol. 2002 Mar;37(3):139-44. PubMed PMID: 11990011. Epub 2002/05/07. eng.

168.   Pharoah PD, Melzer D. Variation in prescribing of hypnotics, anxiolytics and antidepressants between 61 general practices. The British journal of general practice : the journal of the Royal College of General Practitioners. 1995 Nov;45(400):595-9. PubMed PMID: 8554839. Pubmed Central PMCID: 1239434.

169.   Tsimtsiou Z, Ashworth M, Jones R. Variations in anxiolytic and hypnotic prescribing by GPs: a cross-sectional analysis using data from the UK Quality and Outcomes Framework. The British journal of general practice : the journal of the Royal College of General Practitioners. 2009 Jun;59(563):e191-8. PubMed PMID: 19520017. Pubmed Central PMCID: 2688068.

170.   ten Have M, de Graaf R, Ormel J, Vilagut G, Kovess V, Alonso J, et al. Are attitudes towards mental health help-seeking associated with service use? Results from the European Study of Epidemiology of Mental Disorders. Soc Psychiatry Psychiatr Epidemiol. 2010 Feb;45(2):153-63. PubMed PMID: 19381427. Pubmed Central PMCID: 2820660.

171.   (AEMPS). SAfMaMD. Uso de Benzodiacepinas en España (1992-2006) 2007 [cited 2013]. Available from:

http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/ansioliti cos_hipnoticos.pdf.

172. Gili M, Roca M, Basu S, McKee M, Stuckler D. The mental health risks of economic crisis in Spain: evidence from primary care centres, 2006 and 2010. European journal of public health. 2013 Feb;23(1):103-8. PubMed PMID: 23132877.

173. Laroche ML, Charmes JP, Bouthier F, Merle L. Inappropriate medications in the elderly. Clinical pharmacology and therapeutics. 2009 Jan;85(1):94-7. PubMed PMID: 18987619.

174. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Deutsches Arzteblatt international. 2010 Aug;107(31-32):543-51. PubMed PMID: 20827352. Pubmed Central PMCID: 2933536.

175. Rayon P, Serrano-Castro M, del Barrio H, Alvarez C, Montero D, Madurga M, et al. Hypnotic drug use in Spain: a cross-sectional study based on a network of community pharmacies. Spanish Group for the Study of Hypnotic Drug Utilization. The Annals of pharmacotherapy. 1996 Oct;30(10):1092-100. PubMed PMID: 8893114.

176. Menkes D. Hypnosedatives and anxiolytics: Chapter on Benzodiazepines. . Meyler's Side Effects of Drugs: International Encyclopaedia of Adverse Drug Reactions and Interactions. 14th ed. The Netherlands: Aronson JK (ed.) 2000. p. 124.

177. Ohayon MM, Caulet M, Arbus L, Billard M, Coquerel A, Guieu JD, et al. Are prescribed medications effective in the treatment of insomnia complaints? Journal of psychosomatic research. 1999 Oct;47(4):359-68. PubMed PMID: 10616230.

178. Jansson-Frojmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. Journal of psychosomatic research. 2008 Apr;64(4):443-9. PubMed PMID: 18374745.

179.   Hayward RA, Jordan KP, Croft P. The relationship of primary health care use with persistence of insomnia: a prospective cohort study. BMC family practice. 2012;13:8. PubMed PMID: 22340760. Pubmed Central PMCID: 3293729.

180.   Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995 Mar 23;332(12):767-73. PubMed PMID: 7862179. Epub 1995/03/23. eng.

181.   Sato Y. [Dementia and fracture]. Clinical calcium. 2010 Sep;20(9):1379-84. PubMed PMID: 20808046.

182.   Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs & aging. 2012 May 1;29(5):359-76. PubMed PMID: 22550966.

183.   Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med. 2004 Jul 26;164(14):1567-72. PubMed PMID: 15277291. Epub 2004/07/28. eng.

184.   Zint K, Haefeli WE, Glynn RJ, Mogun H, Avorn J, Sturmer T. Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults. Pharmacoepidemiol Drug Saf. 2010 Dec;19(12):1248-55. PubMed PMID: 20931664.

185.   Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001 Jun;158(6):892-8. PubMed PMID: 11384896. Epub 2001/06/01. eng.

186.   van der Hooft CS, Schoofs MW, Ziere G, Hofman A, Pols HA, Sturkenboom MC, et al. Inappropriate benzodiazepine use in older adults and the risk of fracture. Br J Clin Pharmacol. 2008 Aug;66(2):276-82. PubMed PMID: 18460035. Pubmed Central PMCID: 2492915.

187.   Ashton PCH. Guidelines for the Rational Use of Benzodiazepines 2000 [26/07/2012]. Available from: http://www.benzo.org.uk/asgr.htm.

188. Vestergaard   P, Prieto-Alhambra D, Javaid MK, Cooper C. Fractures in users of antidepressants and anxiolytics and sedatives effects of age and dose. Bone. 2012;50, Supplement 1(0):S143-S4.

189. Tamblyn R, Abrahamowicz M, du Berger R, McLeod P, Bartlett G. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users. Journal of the American Geriatrics Society. 2005 Feb;53(2):233-41. PubMed PMID: 15673346. Epub 2005/01/28. eng.

190. Berdot S, Bertrand M, Dartigues J-F, Fourrier A, Tavernier B, Ritchie K, et al. Inappropriate medication use and risk of falls - A prospective study in a large community-dwelling elderly cohort. BMC Geriatr. 2009;9(1):30. PubMed PMID: doi:10.1186/1471-2318-9-30.

191. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. Journal of the American Geriatrics Society. 2001 Dec;49(12):1685-90. PubMed PMID: 11844004.

192. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: a meta-analysis. Osteoporos Int. 2014 Jan;25(1):105-20. PubMed PMID: 24013517.

193. Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr. 2011 Nov 8:1-10. PubMed PMID: 22059800. Epub 2011/11/09. Eng.

194. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. Am J Epidemiol. 1998 Nov 1;148(9):887-92. PubMed PMID: 9801019.

195. Sánchez Cano D CRJ, Ríos Fernández R, Ortego Centeno N. Bone mineral metabolism in inflammatory bowel disease. Rev Osteoporos Metab Miner. 2009;1(1):21-8.

196. Pouwels S, van Staa TP, Egberts AC, Leufkens HG, Cooper C, de Vries F. Antipsychotic use and the risk of hip/femur fracture: a population-based

case-control study. Osteoporos Int. 2009 Sep;20(9):1499-506. PubMed PMID: 19156348. Pubmed Central PMCID: 2728222. Epub 2009/01/22. eng.

197.   Bakhireva LN, Shainline MR, Carter S, Robinson S, Beaton SJ, Nawarskas JJ, et al. Synergistic effect of statins and postmenopausal hormone therapy in the prevention of skeletal fractures in elderly women. Pharmacotherapy. 2010 Sep;30(9):879-87. PubMed PMID: 20795843.

198.   Sgadari A, Lapane KL, Mor V, Landi F, Bernabei R, Gambassi G. Oxidative and nonoxidative benzodiazepines and the risk of femur fracture. The Systematic Assessment of Geriatric Drug Use Via Epidemiology Study Group. Journal of clinical psychopharmacology. 2000 Apr;20(2):234-9. PubMed PMID: 10770463.

199.   Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf. 2002 Mar;11(2):97-104. PubMed PMID: 11998544. Epub 2002/05/10. eng.

200.   Berry SD, Lee Y, Cai S, Dore DD. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. JAMA internal medicine. 2013 May 13;173(9):754-61. PubMed PMID: 23460413. Pubmed Central PMCID: 3676706.

201.   Madigan D, Ryan PB, Schuemie M, Stang PE, Overhage JM, Hartzema AG, et al. Evaluating the impact of database heterogeneity on observational study results. Am J Epidemiol. 2013 Aug 15;178(4):645-51. PubMed PMID: 23648805. Pubmed Central PMCID: 3736754.

202.   Lai C-LK, R. N-C.; Chen, H-M.; Wu, C-F.; Huang, H-C.; Wang, C-H.; Lai, C-L.; Chang, C-H.; Chen, M-F.; Lai, M-S. Relative Risk of Hip/Femur Fractures during the Initiation Period of alpha-Blockers Therapy in Male Elders. 29th ICPE-Montreal2013. p. 56.

203.   Douglas IJ, Evans SJ, Hingorani AD, Grosso AM, Timmis A, Hemingway H, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. BMJ. 2012;345:e4388. PubMed PMID: 22782731. Pubmed Central PMCID: 3392956.

204.   Hebert C, Delaney JA, Hemmelgarn B, Levesque LE, Suissa S. Benzodiazepines and elderly drivers: a comparison of pharmacoepidemiological study designs. Pharmacoepidemiol Drug Saf. 2007 Aug;16(8):845-9. PubMed PMID: 17563091. Epub 2007/06/15. eng.

205.   Ravera S, van Rein N, de Gier JJ, de Jong-van den Berg LT. A comparison of pharmacoepidemiological study designs in medication use and traffic safety research. Eur J Epidemiol. 2012 Jun;27(6):473-81. PubMed PMID: 22576759. Pubmed Central PMCID: 3382653.

206.   Andrews N. Epidemiological designs for vaccine safety assessment: methods and pitfalls. Biologicals : journal of the International Association of Biological Standardization. 2012 Sep;40(5):389-92. PubMed PMID: 21985898.

207.   Hernandez-Diaz S, Garcia Rodriguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC medicine. 2006;4:22. PubMed PMID: 16987411. Pubmed Central PMCID: 1590044.

208.   Gil M, Oliva B, Timoner J, Macia MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study. Br J Clin Pharmacol. 2011 Dec;72(6):965-8. PubMed PMID: 21627676. Pubmed Central PMCID: 3244644.

209.   de Abajo FJ, Gil MJ, Garcia Poza P, Bryant V, Oliva B, Timoner J, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. Pharmacoepidemiol Drug Saf. 2014 Apr 1. PubMed PMID: 24692325.

210.   Shapiro S. The role of automated record linkage in the postmarketing surveillance of drug safety: a critique. Clinical pharmacology and therapeutics. 1989 Oct;46(4):371-86. PubMed PMID: 2535647.

211.   Chacon Garcia A, Ruigomez A, Garcia Rodriguez LA. [Incidence rate of community acquired pneumonia in a population cohort registered in BIFAP]. Atencion primaria / Sociedad Espanola de Medicina de Familia y Comunitaria. 2010 Nov;42(11):543-9. PubMed PMID: 20833449. Incidencia de neumonia

adquirida en la comunidad en la cohorte poblacional de la base de datos en atencion primaria (BIFAP).

212.   de Abajo FJ, Gil MJ, Bryant V, Timoner J, Oliva B, Garcia-Rodriguez LA. Upper gastrointestinal bleeding associated with NSAIDs, other drugs and interactions: a nested case-control study in a new general practice database. Eur J Clin Pharmacol. 2013 Mar;69(3):691-701. PubMed PMID: 22955795.

213.   Smeeth L, Donnan PT, Cook DG. The use of primary care databases: case-control and case-only designs. Fam Pract. 2006 Oct;23(5):597-604. PubMed PMID: 16787956. Epub 2006/06/22. eng.

214.   Evans JG, Seagroatt V, Goldacre MJ. Secular trends in proximal femoral fracture, Oxford record linkage study area and England 1968-86. J Epidemiol Community Health. 1997 Aug;51(4):424-9. PubMed PMID: 9328551. Pubmed Central PMCID: 1060513. Epub 1997/08/01. eng.

215.   Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011 May 5;364(18):1728-37. PubMed PMID: 21542743. Epub 2011/05/06. eng.

216.   Bartlett G, Abrahamowicz M, Grad R, Sylvestre MP, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. BMC family practice. 2009;10:1. PubMed PMID: 19126237. Pubmed Central PMCID: 2627814. Epub 2009/01/08. eng.

217.   Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003 Nov 1;158(9):915-20. PubMed PMID: 14585769.

218.   Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. Am J Epidemiol. 1995 Jul 1;142(1):91-8. PubMed PMID: 7785679.

219.   Vines SK, Farrington CP. Within-subject exposure dependency in case-crossover studies. Statistics in medicine. 2001 Oct 30;20(20):3039-49. PubMed PMID: 11590631.

220.   Simpson SE, Madigan D, Zorych I, Schuemie MJ, Ryan PB, Suchard MA. Multiple self-controlled case series for large-scale longitudinal

observational databases. Biometrics. 2013 Dec;69(4):893-902. PubMed PMID: 24117144.

221.   WHO CCfDSMNIoPH. Codes for drugs: ATC/DDD Index 2011. 2011 [cited 2013 January 17 2013]. Available from:

http://www.whocc.no/atc_ddd_index/

222.   WONCA ICC. ICPC – 2 International Classification for Primary Care Online. [cited 2013 January 16 2013]. Available from:

http://www.globalfamilydoctor.com/wicc/sensi.html.

APPENDICES

10. APPENDICES

APPENDIX A

List of BZD, DDD, half-life and recommended daily dose

N05B Anxiolytics (221)
N05BA   Benzodiazepine derivatives

ATC code	Name	Defined Daily Dose DDD	Recom mended Daily Dose†	U	Adm. R	Half-life*
N05BA01	diazepam	10		mg	O	Long (>24)
		10		mg	P	
		10		mg	R	
N05BA02	chlordiazepoxide	30		mg	O	Long (>24)
		50		mg	P	
N05BA03	medazepam	20		mg	O	Long (>24)
N05BA04	oxazepam	50		mg	O	Intermediate (8-24)
N05BA05	potassium clorazepate	20		mg	O	Long (>24)
N05BA06	lorazepam	2.5		mg	O	Intermediate (8-24)
		2.5		mg	SL	
N05BA07	adinazolam					Short (<8)
N05BA08	bromazepam	10		mg	O	Intermediate (8-24)
N05BA09	clobazam	20		mg	O	Intermediate (8-24)
N05BA10	ketazolam		15	mg		Intermediate (8-24)
N05BA11	prazepam	30		mg	O	Long (>24)
N05BA12	alprazolam	1		mg	O	Intermediate (8-24)
N05BA13	halazepam	0.1		g	O	Long (>24)
N05BA14	pinazepam		5	mg		Intermediate (8-24)
N05BA15	camazepam	30		mg	O	Intermediate (8-24)
N05BA16	nordazepam	15		mg	O	Long (24)
N05BA17	fludiazepam	0.75		mg	O	Long (>24)
N05BA19	etizolam		0.5	mg		Short (<8)
N05BA21	clotiazepam		10	mg		Short (<8)
N05BA56	lorazepam, combinations					

* **Half life** definitions: Short (<8); Intermediate (8-24), Long (>24)
† If there is no information on DDD, the recommended daily dose will be used to approach the DDD.

N05C Hypnotics and sedatives (221)
N05CD   Benzodiazepine derivatives

ATC code	Name	Defined Daily Dose (DDD)	U	AdmR	Half-life *
N05CD01	flurazepam	30	mg	O	Long (>24)
N05CD02	nitrazepam	5	mg	O	Long(>24)
N05CD03	flunitrazepam	1	mg	O	Intermediate (8-24)
		1	mg	P	
N05CD04	estazolam	3	mg	O	Intermediate (8-24)
N05CD05	triazolam	0.25	mg	O	Short(<8)
		0.2	mg	SL	
N05CD06	lormetazepam	1	mg	O	Intermediate(8-24)
N05CD07	temazepam	20	mg	O	Intermediate(8-24)
N05CD08	midazolam	15	mg	O	Short(<8)
		15	mg	P	
N05CD09	brotizolam	0.25	mg	O	Short (<8)
N05CD10	quazepam	15	mg	O	Long(>24)
N05CD11	loprazolam	1	mg	O	Intermediate(8-24)

* **Half life** definitions: Short (<8); Intermediate (8-24), Long (>24)

N05CF   Benzodiazepine related drugs

ATC code	Name	Defined Daily Dose (DDD)	U	Half-life*
N05CF01	zopiclone*	7.5	mg	Short (<8)
N05CF02	zolpidem*	10	mg	Short (<8)
N05CF03	zaleplon	10	mg	Short (<8)

* **Half life** definitions: Short (<8); Intermediate (8-24), Long (>24)

N05CM   Other hypnotics and sedatives

ATC code	Name	Defined Daily Dose (DDD)*	U	Half-life
N05CM02	Clomethiazole	1,5	g	O
		1,5	g	P

* **Half life** definitions: Short (<8); Intermediate (8-24), Long (>24)

APPENDIX B

Codes for potential confounders

1) Well known risk factors for fracture (222)

Weight, height, BMI, smoking and alcohol

Weight	This should be entered in kg.
Height	This should be entered in cm.
BMI	Calculated as weight in kilograms divided by height squared in meters. Categories: <18.50; 18.50-24.99; 25.00-30;>30 Reference category: 18.50-24.99
Smoking	Enter no/yes/ex-smoker/unknown. Reference category: No
Alcohol	Enter non use/use/ unknown. Reference category: Non use

Previous fractures

ICPC codes	
L75	Fracture: femur
L74	Fracture: hand/foot bone
L73	Fracture: tibia/fibula
L72	Fracture: radius/ulna
L76	Fracture: other

Glucocorticoids

ATC code	
H02AB	. Glucocorticoids

Equivalent anti-inflammatory doses of corticosteroids to Prednisolone 5 mg (Fte: British National Formulary. BMJ Group and RPS Publishing BNF, London 2009)	= Cortisone acetate 25 mg
	= Deflazacort 6 mg
	= Dexamethasone 750 micrograms
	= Hydrocortisone 20 mg
	= Methylprednisolone 4 mg
	= Triamcinolone 4 mg

Rheumatoid arthritis

ICPC-2	TITLE
L88	Rheumatoid/seropositive arthritis

2) Risk factors immediately related to the outcome

Osteoporosis and Paget´s disease

ICPC-2	TITLE
L95	Osteoporosis
L99	No specific code (Musculoskeletal disease)

Biphosphonates, raloxifene, parathyroid hormones and analogues, strontium ranelate, vitamin D and analogues and calcitonin

ATC code	
M05BA01	etidronic acid
M05BA02	clodronic acid
M05BA03	pamidronic acid
M05BA04	alendronic acid
M05BA05	tiludronic acid
M05BA06	ibandronic acid
G03XC01	raloxifene
H05AA	Parathyroid hormones and analogues
M05BX03	Strontium ranelate
A11CC04	calcitriol
A11CC05	colecalciferol
	calcium+ colecalciferol
A11CC06	calcifediol
H05BA	Calcitonin preparations

3) Other drugs associated with fractures

Antidepressants

ATC code	
N06AA	Non-selective monoamine reuptake inhibitors
N06AB	Selective serotonin reuptake inhibitors

Antipsychotic drugs/lithium

ATC code	
N05A	Antipsychotics
N05AA	Phenothiazines with aliphatic side-chain
N05AB	Phenothiazines with piperazine structure
N05AC	Phenothiazines with piperidine structure
N05AD	Butyrophenone derivatives
N05AE	Indole derivatives
N05AF	Thioxanthene derivative
N05AG	Diphenylbutylpiperidine derivatives
N05AH	Diazepines, oxazepines, thiazepines and oxepines
N05AL	Benzamides
N05AN	Lithium
N05AX	Other antipsychotics

Anti-Parkinson drugs

ATC code	
N04	Anti-Parkinson drugs
N04A	Anticholinergic agents
N04AA	Tertiary amines
N04AB	Ethers chemically close to antihistamines
N04AC	Ethers of tropine or tropine derivatives
N04B	Dopaminergic agents
N04BA	Dopa and dopa derivatives
N04BB	Adamantane derivatives
N04BC	Dopamine agonists
N04BD	Monoamine oxidase B inhibitors
N04BX	Other dopaminergic agents

Antiepileptic drugs (anticonvulsants)

ATC code	
N03A	Antiepileptics
N03AA	Barbiturates and derivatives
N03AB	Hydantoin derivatives
N03AC	Oxazolidine derivatives
N03AD	Succinimide derivatives
N03AE	Benzodiazepine derivatives
N03AF	Carboxamide derivatives
N03AG	Fatty acid derivatives
N03AX	Other antiepileptics

Inhaled glucocorticoids

ATC code	
R03BA	Glucocorticoids
R03BA01	Beclometasone
R03BA02	Budesonide
R03BA03	Flunisolide
R03BA04	Betamethasone
R03BA05	Fluticasone
R03BA06	Triamcinolone
R03BA07	Mometasone
R03BA08	Ciclesonide

Sedating antihistamines

ATC code	
N05BB	Diphenylmethane derivatives (sedating)

Bronchodilators

ATC code	
	Beta-2-adrenoreceptor agonists
R03A	Adrenergics, inhalants
R03AC	Selective beta-2-adrenoreceptor agonists
R03AK	Adrenergics and other drugs for obstructive airway diseases
R03C	Adrenergics for systemic use
R03CC	Selective beta-2-adrenoreceptor agonists
R03B	Other drugs for obstructive airway diseases, inhalants
R03BB	Anticholinergics

Antiarrhythmics

ATC code	
C01B	Antiarrhythmics, class I and III
C01BA	Antiarrhythmics, class Ia
C01BB	Antiarrhythmics, class Ib
C01BC	Antiarrhythmics, class Ic
C01BD	Antiarrhythmics, class III

Antihypertensives

ACE Inhibitors

ATC code	
C09	Agents acting on the renin-angiotensin system
C09A	ACE inhibitors, plain
C09AA	ACE inhibitors, plain
C09B	ACE inhibitors, combinations
C09BA	ACE inhibitors and diuretics
C09BB	ACE inhibitors and calcium channel blockers

Angiotensin II antagonists

ATC code	
C09	Agents acting on the renin-angiotensin system
C09C	Angiotensin II antagonists, plain
C09CA	Angiotensin II antagonists, plain
C09D	Angiotensin II antagonists, combinations
C09DA	Angiotensin II antagonists and diuretics
C09DB	Angiotensin II antagonists and calcium channel blockers
C09DX	Angiotensin II antagonists, other combinations

Beta blocking agents

ATC code	
C07A	Beta blocking agents
C07AA	Beta blocking agents, non-selective
C07AB	Beta blocking agents, selective
C07AG	Alpha and beta blocking agents
C07B	Beta blocking agents and thiazides
C07BA	Beta blocking agents, non-selective, and thiazides
C07BB	Beta blocking agents, selective, and thiazides
C07BG	Alpha and beta blocking agents and thiazides
C07C	Beta blocking agents and other diuretics
C07CA	Beta blocking agents, non-selective, and other diuretics
C07CB	Beta blocking agents, selective, and other diuretics
C07CG	Alpha and beta blocking agents and other diuretics
C07D	Beta blocking agents, thiazides and other diuretics
C07DA	Beta blocking agents, non-selective, thiazides and other diuretics
C07DB	Beta blocking agents, selective, thiazides and other diuretics
C07F	Beta blocking agents and other antihypertensives
C07FA	Beta blocking agents, non-selective, and other antihypertensives
C07FB	Beta blocking agents, selective, and other antihypertensives

Calcium channel blockers

ATC code	
C08	Agents acting on the renin-angiotensin system
C08C	Selective calcium channel blockers with mainly vascular effects
C08CA	Dihydropyridine derivatives
C08CX	Other selective calcium channel blockers with mainly vascular effects
C08D	Selective calcium channel blockers with direct cardiac effects
C08DA	Phenylalkylamine derivatives
C08DB	Benzothiazepine derivatives
C08E	Non-selective calcium channel blockers
C08EA	Phenylalkylamine derivatives
C08EX	Other non-selective calcium channel blockers
C08G	Calcium channel blockers and diuretics
C08GA	Calcium channel blockers and diuretics

Other antihypertensives

ATC code	
C02A	Antiadrenergic agents, centrally acting
C02AA	Rauwolfia alkaloids
C02AB	Methyldopa
C02AC	Imidazoline receptor agonists
C02C	Antiadrenergic agents, peripherally acting
C02CA	Alpha-adrenoreceptor antagonists
C02CC	Guanidine derivatives
C02D	Arteriolar smooth muscle, agents acting on
C02DA	Thiazide derivatives
C02DB	Hydrazinophthalazine derivatives
C02DC	Pyrimidine derivatives
C02DD	Nitroferricyanide derivatives
C02DG	Guanidine derivatives
C02K	Other non-selective calcium channel blockers
C02KA	Alkaloids, excluding rauwolfia
C02KB	Tyrosine hydroxylase inhibitors
C02KC	MAO inhibitors
C02KD	Serotonin antagonists
C02KX	Other antihypertensives
C02L	Calcium channel blockers and diuretics
C02LA	Rauwolfia alkaloids and diuretics in combination
C02LB	Methyldopa and diuretics in combination
C02LC	Imidazoline receptor agonists in combination with diuretics
C02LE	Alpha-adrenoreceptor antagonists and diuretics
C02LF	Guanidine derivatives and diuretics
C02LG	Hydrazinophthalazine derivatives and diuretics
C02LK	Alkaloids, excluding rauwolfia, in combination with diuretics
C02LL	MAO inhibitors and diuretics
C02LN	Serotonin antagonists and diuretics
C02LX	Other antihypertensives and diuretics

Diuretics

ATC code	
C03A	Low-ceiling diuretics, thiazides
C03AA	Thiazides, plain
C03AB	Thiazides and potassium in combination
C03AH	Thiazides, combinations with psycholeptics and/or analgesics
C03AX	Thiazides, combinations with other drugs
C03B	Low-ceiling diuretics, excluding thiazides
C03BA	Sulfonamides, plain
C03BB	Sulfonamides and potassium in combination
C03BC	Mercurial diuretics
C03BD	Xanthine derivatives
C03BK	Sulfonamides, combinations with other drugs
C03BX	Other low-ceiling diuretics
C03C	High-ceiling diuretics
C03CA	Sulfonamides, plain
C03CB	Sulfonamides and potassium in combination
C03CC	Aryloxyacetic acid derivatives
C03CD	Pyrazolone derivatives
C03CX	Other high-ceiling diuretics
C03D	Potassium-sparing agents
C03DA	Aldosterone antagonists
C03DB	Other potassium-sparing agents
C03E	Diuretics and potassium-sparing agents in combination
C03EA	Low-ceiling diuretics and potassium-sparing agents
C03EB	High-ceiling diuretics and potassium-sparing agents
C03X	Other diuretics
C03XA	Vasopressin antagonists

Hormone replacement therapy

ATC code	
G03C	Estrogens
G03CA	Natural and semi synthetic estrogens, plain
G03CX	Other estrogens
G03D	Progestogens
G03DA	Pregnen-(4) derivatives
G03DC	Estren derivatives
G03F	Progestogens and estrogens in combination
G03FA	Progestogens and estrogens, fixed combinations
G03FB	Progestogens and estrogens, sequential preparations

Thyroid hormones

ATC code	
H03A	Thyroid preparations
H03AA	Thyroid hormones

Anti-thyroid drugs

ATC code	
H03B	Antithyroid preparations
H03BA	Thiouracils
H03BB	Sulphur-containing imidazole derivatives
H03BC	Perchlorates
H03BX	Other antithyroid preparations

Disease modifying anti-rheumatic drugs

ATC code	
Gold	
M01CB03	Auranofin
M01CB02	Sodium aurothiomalate
Penicillamine	
M01CC01	Penicillamine
Antimalarials	
P01BA01	Chloroquine
P01BA02	Hydroxychloroquine sulphate
Drugs affecting the immune response	
L04AX01	Azathioprine
L04AD01	Cyclosporine
L04AA13	Leflunomide
L01BA01/L01AX03	Methotrexate
Cytokine modulators	
L04AA24	Abatacept
L04AB04	Adalimumab
L04AC03	Anakinra
L04AB01	Etanercept
L04AB02	Infliximab
L01XC02	Rituximab
Sulfasalazine	
A07EC01	Sulfasalazine

Thiazolidinediones

ATC code	
A10BG	Thiazolidinediones

Other antidiabetics

ATC code	
A10A	Insulins and analogues
A10AB	Insulins and analogues for injection, fast-acting
A10AC	Insulins and analogues for injection, intermediate-acting
A10AD	Insulins and analogues for injection, interm-acting combined with fast-acting
A10AE	Insulins and analogues for injection, long-acting
A10AF	Insulins and analogues for inhalation
A10B	Blood glucose lowering drugs, excluding insulins
A10BA	Biguanides
A10BB	Sulfonamides, urea derivatives
A10BC	Sulfonamides (heterocyclic)
A10BD	Combinations of oral blood glucose lowering drugs
A10BF	Alpha glucosidase inhibitors
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10BX	Other blood glucose lowering drugs, excluding insulins
A10X	Other drugs used in diabetes
A10XA	Aldose reductase inhibitors

Antiemetic (metoclopramide)

ATC code	
A03F	Propulsives
A03FA	Propulsives
A03FA01	Metoclopramide

Anticoagulants

ATC code	
B01AA	Vit K antagonist
B01AB	Heparin group

Opioids (including morphine)

ATC code	
N02A	Opioids
N02AA	Natural opium alkaloids
N02AB	Phenylpiperidine derivatives
N02AC	Diphenylpropylamine derivatives
N02AD	Benzomorphan derivatives
N02AE	Oripavine derivatives
N02AF	Morphinan derivatives
N02AG	Opioids in combination with antispasmodics
N02AX	Other opioids

Non-steroidal anti-inflammatory drugs

ATC code	
M01A http://www.whocc.no/atc_ddd_index/?code=M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M01AA	Butylpyrazolidines
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other antiinflammatory and antirheumatic agents, non-steroids

Statins

ATC code	
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin
C10AA07	rosuvastatin
C10AA08	pitavastatin

Proton pump inhibitors

ATC code	
A02BC01	omeprazole
A02BC02	pantoprazole
A02BC03	lansoprazole
A02BC04	rabeprazole
A02BC05	esomeprazole

Aromatase inhibitors

ATC code	
L02BG	Enzyme inhibitors
L02BG01	aminoglutethimide
L02BG02	formestane
L02BG03	anastrozole
L02BG04	letrozole
L02BG05	vorozole
L02BG06	exemestane

4) Other diseases associated with fractures

ICPC codes	
B80	Iron Deficiency anaemia
B81	Anaemia, Vitamin B12/folate def
B82	Anemia other inespecify
N07	Convulsion/seizure
N88	Epilepsy
A06	Syncope
K74	Ischaemic heart disease with angina
K75	Acute Myocardial Infarction
K76	Ischaemic heart disease without angina
K90	Stroke/Cerebrovascular accident
K91	Cerebrovascular Disease
A79	Malignancy NOS
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malignant neoplasm digest other/NOS
F74	Neoplasm of the eye/adnexa
H75	Neoplasm of ear
K72	Neoplasm cardiovascular
L71	Malignant neoplasm musculoskeletal
N74	Malignant neoplasm nervous system
R84	Malignant neoplasm bronchus/lung
R85	Malignant neoplasm respiratory, other
S77	Malignant neoplasm of the skin
T71	Malignant neoplasm thyroid
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
W72	Malignant neoplasm relate to pregnancy
X75	Malignant neoplasm cervix
X76	Malignant neoplasm breast female
X77	Malignant neoplasm genital other (f)
Y77	Malignant neoplasm prostate
Y78	Malignant neoplasm male genital other
D94	Chronic enteritis/Ulcerative colitis
R79 (old R91)	Chronic bronchitis
R95	Emphysema/chronic obstructive pulmonary disease
D97	Liver disease NOS
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis (excluding depression)
P80	Personality disorder
P98	Psychosis nos/other
P99	Psychological disorders other
P70	Dementia

APPENDIX C

Additional tables from descriptive studies

Table A1- Incidence of hip/femur fracture by sex and age for 2008 in different databases (per 10,000 py)

MALES	BIFAP	CPRD	NPCRD	AHC	THIN	DKMA	BAVARIAN
0-9	2.71	2.53	4.10	4.90	2.48	0	
10-19	1.78	1.97	1.02	5.55	1.99	0.68	5.28*
20-29	1.21	1.69	3.19	2.21	1.62	0.77	3.78
30-39	1.47	1.04	0.00	1.92	0.80	0.71	3.48
40-49	2.95	1.96	1.59	4.76	1.62	2.64	5.19
50-59	4.21	2.90	2.61	4.11	3.26	7.07	8.11
60-69	6.29	5.73	4.26	2.15	5.22	13.66	13.58
70-79	17.82	16.73	9.93	22.70	15.65	41.06	23.53
80+	67.55	61.82	43.72	89.84	61.62	170.72	70.29

FEMALES	BIFAP	CPRD	NPCRD	AHC	THIN	DKMA	BAVARIAN
0-9	1.18	1.61	2.19	2.06	1.15	0.06	
10-19	0.66	0.74	0.00	1.99	0.46	0.46	2.80*
20-29	1.11	0.30	1.01	2.14	0.30	0.22	1.65
30-39	0.85	0.65	0.00	0.87	0.47	0.26	1.76
40-49	1.99	1.10	1.56	1.54	1.22	1.45	2.90
50-59	3.16	3.87	6.01	5.44	3.95	7.43	7.17
60-69	9.75	8.73	7.76	2.17	9.01	19.71	15.95
70-79	45.76	33.80	32.94	25.81	37.24	72.97	45.98
80+	160.27	133.34	91.86	101.01	124.67	284.92	145.93

* *Data grouped from 0-19 years*

Table A2- IRs and time trends: general population in all databases

	2003	2004	2005	2006	2007	2008	2009	Slope (95% CI)	V#
BIFAP									
No. fractures	1,503	1,847	1,871	1,805	1,745	1,498	1,137	-	
Person-years	1,397,047	1,742,682	1,840,894	1,776,966	1,680,082	1,416,105	1,091,342	-	
IR per 10,000py	10.76	10.60	10.16	10.16	10.39	10.58	10.42	-0.03 (-0.15, 0.09)	(-) 0.3
Standardized IR	11.04	10.85	10.39	10.42	10.52	10.68	10.37	-0.08 (-0.18, 0.02)	(-) 0.7
CPRD									
No. fractures	3,147	3,375	3,465	3,611	3,629	3,677	3,600	-	
Person-years	3,640,845	3,847,614	3,932,917	3,972,745	3,901,072	3,830,411	3,640,820	-	
IR per 10,000py	8.64	8.77	8.81	9.09	9.30	9.60	9.89	0.21 (0.16, 0.26)*	2.4
Standardized IR	8.46	8.60	8.56	8.77	8.80	8.94	8.89	0.08 (0.05, 0.11)*	0.9
THIN									
No. fractures	2,880	3,018	3,126	3,060	3,142	3,189	3,101		
Person-years	3,579,571	3,647,552	3,643,259	3,675,595	3,699,299	3,713,072	3,667,410		
IR per 10,000py	8.09	8.36	8.58	8.33	8.49	8.59	8.46	0.05 (-0.17, 0.12)	0.6
Standardized IR	8.22	8.53	8.76	8.49	8.64	8.73	8.58	0.05 (-0.03, 0.13)	0.6
AHC									
No. fractures	55	55	78	65	65	77	-		
Person-years	106,545	114,024	120,932	127,565	133,824	142,231	-		
IR per 10,000py	5.16	4.82	6.45	5.10	4.86	5.41	-	0.00 (-0.45, 0.45)	0.0
Standardized IR	10.27	9.01	12.71	10.11	8.48	8.80	-	-0.33 (-1.39, 0.73)	(-) 3.2
NPCRD									
No. fractures	196	113	84	90	137	119	88		
Person-years	272,655	173,315	164,399	135,386	192,507	154,675	11,4214		
IR per 10,000py	7.19	6.52	5.11	6.65	7.12	7.69	7.70	0.21 (-0.20, 0.62)	2.9
Standardized IR	6.77	6.05	4.64	5.85	5.84	7.24	7.16	0.17 (-0.28, 0.62)	2.5
DKMA									
No. fractures	9,316	9,568	9,477	9,291	9,180	9,296	9,113		
Person-years	5,207,838	5,223,111	5,209,669	5,210,109	5,209,064	5,222,891	5,207,078		
IR per 10,000py	17.89	18.32	18.19	17.83	17.62	17.80	17.50	-0.10 (-0.20, 0.01)	(-) 0.6
Standardized IR	19.60	19.93	19.62	19.04	18.68	18.68	18.25	-0.27 (-0.38, -0.15)*	(-) 1.4
BAVARIAN									
No. fractures	-	-	-	15,196	13,997	15,154	-	-	-
Person-years$	-	-	-	10,387,207	10,395,597	10,415,393	-	-	-
IR per 10,000py	-	-	-	14.63	13.46	14.55	-	-	-
Standardized IR	-	-	-	13.39	12.13	12.91	-	-	-

*95% CI: Confidence Interval; * p < 0.05 ; V# % Variation: (Slope/2003 IR)*100*
$ Incidence per 10,000 Insured persons in BAVARIAN, not enough data to assess time trends
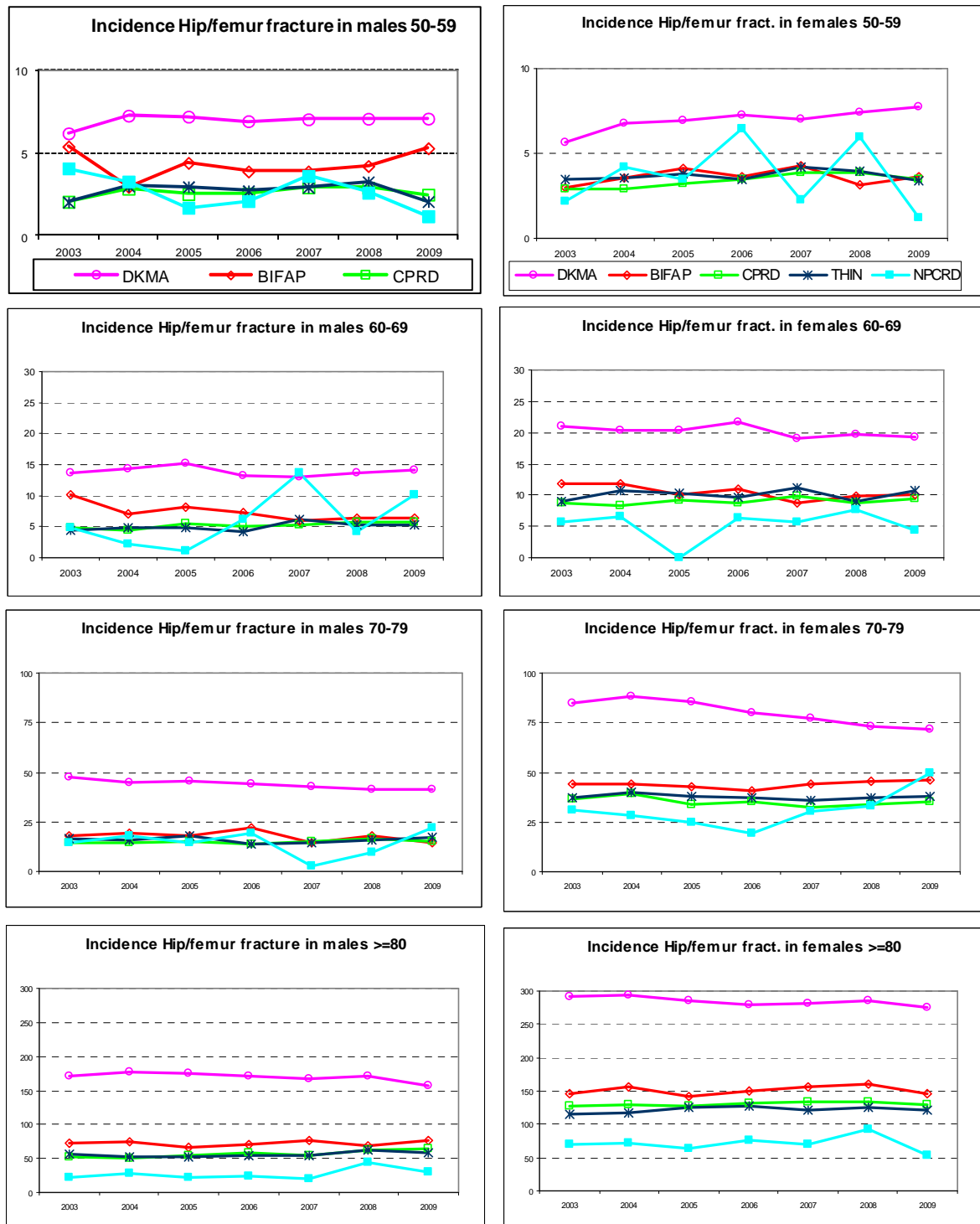
Figure A1- Trends over the study period of sex and age-specific

Note that the scale used in the y-axis has been accommodated to better observed the trends and vary by age groups.

APPENDIX D

Additional tables from cohort study

Table A3- Adjusted HRs of hip/femur fracture

COHORT	Model "A"			Model "B"			Model "C"		
	HR	(95%)CI		HR	(95%)CI		HR	(95%)CI	
PAST	1	-	-	1	-	-	1	-	-
RECENT	1.36	1.19	1.56	1.35	1.18	1.55	1.35	1.18	1.55
CURRENT	1.37	1.25	1.49	1.35	1.23	1.47	1.34	1.23	1.46
By Duration									
Current 0-30d	1.12	0.96	1.32	1.08	0.92	1.27	1.07	0.91	1.26
Current 31-60d	1.26	1.07	1.48	1.21	1.03	1.43	1.20	1.02	1.42
Current 61-180d	1.24	1.07	1.42	1.19	1.04	1.37	1.18	1.03	1.36
Current 181-365d	1.52	1.30	1.76	1.50	1.28	1.74	1.49	1.28	1.74
Current >365	1.55	1.39	1.73	1.55	1.39	1.74	1.55	1.39	1.73
Type of BZD by ATC									
Current both	1.59	1.34	1.88	1.56	1.32	1.85	1.56	1.31	1.84
Single use of anxiolytics	1.34	1.22	1.47	1.32	1.20	1.45	1.31	1.19	1.44
Single use of hypnotics	1.36	1.18	1.55	1.33	1.16	1.53	1.33	1.16	1.52
By Individual drugs									
Anxiolytics (N05BA)	1.36	1.24	1.50	1.34	1.22	1.48	1.34	1.21	1.47
Lorazepam	1.55	1.39	1.75	1.52	1.35	1.71	1.51	1.35	1.70
Bromazepam	1.08	0.92	1.28	1.08	0.91	1.27	1.07	0.91	1.26
Diazepam	1.33	1.07	1.65	1.33	1.07	1.65	1.32	1.06	1.64
Alprazolam	1.27	0.97	1.67	1.27	0.97	1.67	1.26	0.96	1.65
Others	1.25	0.97	1.61	1.24	0.96	1.59	1.23	0.96	1.58
Hypnotics (N05CD)	1.34	1.13	1.58	1.32	1.12	1.57	1.32	1.11	1.56
Lormetazepam	1.45	1.22	1.73	1.43	1.20	1.70	1.43	1.20	1.70
Flurazepam	0.80	0.26	2.48	0.80	0.26	2.49	0.80	0.26	2.48
Loprazolam	0.42	0.13	1.29	0.42	0.14	1.31	0.42	0.13	1.29
Others	1.06	0.57	1.98	1.04	0.56	1.94	1.04	0.56	1.94
Hypnotics (N05CF)	1.07	0.82	1.39	1.07	0.82	1.40	1.07	0.82	1.39
Zolpidem	1.17	0.89	1.52	1.17	0.89	1.53	1.17	0.89	1.52
Others	0.19	0.03	1.33	0.19	0.03	1.33	0.19	0.03	1.32
Other N05CM02	2.21	1.68	2.92	2.03	1.54	2.69	2.04	1.54	2.70
By Half-life									
Short <8h	1.38	1.14	1.67	1.35	1.11	1.63	1.34	1.11	1.62
Intermediate 8-24h	1.37	1.25	1.51	1.35	1.23	1.49	1.35	1.22	1.48
Long >24h	1.29	1.08	1.54	1.28	1.07	1.53	1.27	1.06	1.52
By Dose (last prescription)									
Low dose (< 1DDD)	1.39	1.25	1.54	1.37	1.23	1.52	1.36	1.23	1.51
Medium dose (=1DDD)	1.17	0.98	1.41	1.17	0.97	1.40	1.16	0.97	1.39
High dose (>1DDD)	1.73	1.37	2.19	1.71	1.35	2.17	1.71	1.35	2.16
Missing	1.33	1.16	1.52	1.31	1.14	1.50	1.30	1.13	1.49

Model "A" : adjusted analysis by age and sex; Model "B": adjusted analysis by model A plus well known risk factors for fracture such as previous fractures, glucocorticoids use, rheumatoid arthritis and lifestyle factors (bmi, smoking, alcohol abuse); Model" C": adjusted analysis adding to model B risk factors immediately related to the outcome such as osteoporosis, Paget´s disease, biphosphonate, raloxifene, strontium ranelate, parathyroid hormone, vitamin D and analogues and calcitonin use.

Table A4- HRs of hip fractures by doses at first and last prescription and by anxiolytics and hypnotics

COHORT	Model "Age"			Model "A"			Model "B"			Model "C"			Full Model "D"		
	HR	(95%)CI		HR	(95%)CI		HR	(95%)CI		HR	(95%)CI		HR	(95%)CI	
By Dose (last Rx															
Low dose (< 1DDD)	1.42	1.28	1.57	1.39	1.25	1.54	1.37	1.23	1.52	1.36	1.23	1.51	1.21	1.09	1.35
Medium dose (=1DDD)	1.19	0.99	1.42	1.17	0.98	1.41	1.17	0.97	1.4	1.16	0.97	1.39	1.06	0.89	1.28
High dose (>1DDD)	1.75	1.38	2.21	1.73	1.37	2.19	1.71	1.35	2.17	1.71	1.35	2.16	1.42	1.12	1.80
Missing	1.35	1.17	1.55	1.33	1.16	1.52	1.31	1.14	1.5	1.3	1.13	1.49	1.18	1.03	1.35
By Dose only anxiolytic (last Rx)															
Low dose (< 1DDD)	1.36	1.22	1.52	1.33	1.20	1.48	1.32	1.18	1.47	1.31	1.18	1.46	1.18	1.06	1.32
Medium dose (=1DDD)	1.86	1.32	2.61	1.82	1.30	2.55	1.82	1.30	2.55	1.80	1.29	2.53	1.53	1.09	2.15
Hight dose (>1DDD)	2.23	1.60	3.09	2.18	1.57	3.03	2.13	1.53	2.97	2.12	1.53	2.95	1.59	1.14	2.21
Missing	1.31	1.12	1.53	1.29	1.10	1.50	1.27	1.09	1.48	1.26	1.08	1.47	1.16	0.99	1.35
By Dose only hypnotic (last Rx)															
Low dose (< 1DDD)	2.15	1.67	2.75	2.16	1.69	2.77	2.04	1.59	2.61	2.04	1.59	2.61	1.52	1.17	1.98
Medium dose (=1DDD)	1.06	0.86	1.30	1.04	0.85	1.29	1.04	0.84	1.28	1.03	0.84	1.27	0.96	0.78	1.18
Hight dose (>1DDD)	1.46	1.06	2.01	1.45	1.05	2.00	1.45	1.05	2.00	1.45	1.05	2.00	1.29	0.94	1.78
Missing	1.46	1.14	1.86	1.46	1.14	1.86	1.43	1.12	1.83	1.42	1.12	1.82	1.26	0.98	1.60
By Dose (1st Rx)															
Low dose (< 1DDD)	1.42	1.28	1.58	1.39	1.26	1.55	1.37	1.24	1.52	1.37	1.23	1.52	1.21	1.09	1.35
Medium dose (=1DDD)	1.19	0.99	1.42	1.17	0.98	1.41	1.17	0.97	1.40	1.16	0.97	1.39	1.06	0.89	1.28
Hight dose (>1DDD)	1.72	1.36	2.19	1.70	1.34	2.16	1.68	1.32	2.14	1.68	1.32	2.13	1.39	1.09	1.77
Missing	1.35	1.17	1.55	1.33	1.16	1.52	1.31	1.14	1.50	1.30	1.13	1.49	1.18	1.03	1.35
By Dose only anxiolytic (1st Rx)															
Low dose (< 1DDD)	1.37	1.23	1.52	1.34	1.20	1.49	1.32	1.19	1.47	1.31	1.18	1.46	1.19	1.07	1.33
Medium dose (=1DDD)	1.80	1.28	2.54	1.76	1.25	2.48	1.76	1.25	2.49	1.75	1.24	2.47	1.48	1.05	2.09
Hight dose (>1DDD)	2.18	1.56	3.05	2.14	1.53	2.99	2.09	1.50	2.92	2.08	1.49	2.91	1.56	1.11	2.18
Missing	1.31	1.12	1.53	1.29	1.10	1.50	1.27	1.09	1.48	1.26	1.08	1.47	1.16	0.99	1.35
By Dose only hypnotic (1st Rx)															
Low dose (< 1DDD)	2.14	1.67	2.75	2.16	1.68	2.77	2.03	1.58	2.61	2.03	1.58	2.61	1.52	1.17	1.97
Medium dose (=1DDD)	1.07	0.87	1.31	1.06	0.86	1.30	1.05	0.85	1.29	1.05	0.85	1.29	0.97	0.79	1.20
Hight dose (>1DDD)	1.43	1.03	1.99	1.42	1.02	1.97	1.42	1.02	1.97	1.42	1.02	1.97	1.26	0.91	1.76
Missing	1.46	1.14	1.86	1.46	1.14	1.86	1.43	1.12	1.83	1.42	1.12	1.82	1.26	0.98	1.60

Rx= Prescription

Table A5- HRs by half-life in anxiolytics and hypnotics separately

COHORT	Model "Age"			Model "A"			Model "B"			Model "C"			Full Model "D"		
	HR	(95%)CI		HR	(95%)CI		HR	(95%)CI		HR	(95%)CI		HR	(95%)CI	
By Half-life															
Short <8h	1.38	1.14	1.66	1.38	1.14	1.67	1.35	1.11	1.63	1.34	1.11	1.62	1.09	0.90	1.32
Intermediate 8-24h	1.40	1.27	1.54	1.37	1.25	1.51	1.35	1.23	1.49	1.35	1.22	1.48	1.22	1.10	1.34
Long >24h	1.31	1.10	1.57	1.29	1.08	1.54	1.28	1.07	1.53	1.27	1.06	1.52	1.16	0.97	1.39
By Half-life only anxiolytic															
Short <8h	1.12	0.46	2.69	1.09	0.45	2.64	1.10	0.46	2.66	0.81	0.33	1.95	0.80	0.33	1.94
Intermediate 8-24h	1.40	1.27	1.55	1.37	1.24	1.52	1.35	1.22	1.50	1.00	0.87	1.15	0.96	0.83	1.11
Long >24h	1.33	1.11	1.60	1.31	1.09	1.57	1.30	1.09	1.56	0.96	0.78	1.18	0.94	0.76	1.15
By Half-life only hypnotic															
Short <8h	1.39	1.15	1.69	1.39	1.15	1.69	1.36	1.12	1.65	1.01	0.81	1.25	0.87	0.70	1.08
Intermediate 8-24h	1.38	1.17	1.65	1.37	1.15	1.63	1.35	1.14	1.61	1.00	0.82	1.22	1.00	0.82	1.22
Long >24h	0.76	0.25	2.37	0.76	0.25	2.37	0.76	0.25	2.37	0.56	0.18	1.76	0.56	0.18	1.74

APPENDIX E

Additional tables from the NCC study

Table A6- Model B and C with risk estimates of hip/femur fracture associated with BZD, and by duration and type of ATC group

NCC	Model B		Model C	
	OR	(95%CI)	OR	(95%CI)
Past use (ref.)	1		1	
Recent use	1.28	1.16-1.42	1.28	1.16-1.42
Current use	1.36	1.15-1.60	1.35	1.15-1.60
By Duration				
Current 0-30d	1.1	0.88-1.36	1.09	0.88-1.36
Current 31-60d	1.27	1.03-1.57	1.27	1.02-1.57
Current 61-182d	1.18	1.00-1.39	1.18	1.00-1.39
Current 183-365	1.48	1.24-1.76	1.48	1.24-1.77
Current >365d	1.32	1.16-1.51	1.31	1.15-1.50
By ATC drug				
Use of both	1.82	1.49-2.22	1.82	1.49-2.23
Anxiolytics	1.22	1.09-1.36	1.22	1.09-1.36
Hypnotics	1.26	1.08-1.48	1.27	1.08-1.48

Model "B": adjusted by well known risk factors for fracture such as previous fractures, glucocorticoids use, rheumatoid arthritis and lifestyle factors (bmi, smoking, alcohol abuse); Model" C": adjusted analysis adding to model B risk factors immediately related to the outcome such as osteoporosis, Paget´s disease, biphosphonate, raloxifene, strontium ranelate, parathyroid hormone, vitamin D and analogues and calcitonin use.

Table A7- Sensitivity analysis. Model B and C with risk estimates of hip/femur fracture associated with BZD, by duration and type of ATC

NCC Sensitivity analysis	Model B		Model C	
	OR	(95%CI)	OR	(95%CI)
Past use (ref.)	1		1	
Recent use	1.28	1.16-1.42	1.28	1.16-1.42
Current use	1.36	1.15-1.61	1.36	1.15-1.60
By Duration				
Current 0-30d	1.1	0.88-1.36	1.1	0.88-1.36
Current 31-60d	1.27	1.03-1.57	1.27	1.03-1.58
Current 61-182d	1.18	1.00-1.39	1.18	1.00-1.40
Current 183-365	1.48	1.24-1.77	1.49	1.24-1.78
Current >365d	1.32	1.16-1.51	1.32	1.15-1.50
By ATC drug				
Use of both	1.83	1.50-2.24	1.83	1.50-2.25
Anxiolytics	1.22	1.09-1.36	1.22	1.09-1.36
Hypnotics	1.26	1.08-1.47	1.27	1.08-1.48

Sensitivity Analysis: Full model but co-medication variables were measured at 30 days from index date. Model "B": adjusted by well known risk factors for fracture such as previous fractures, glucocorticoids use, rheumatoid arthritis and lifestyle factors (bmi, smoking, alcohol abuse); Model" C": adjusted analysis adding to model B risk factors immediately related to the outcome such as osteoporosis, Paget´s disease, biphosphonate, raloxifene, strontium ranelate, parathyroid hormone, vitamin D and analogues and calcitonin use.

APPENDIX F

Additional tables from the CXO study

Table A8- Risk estimates of hip/femur fracture associated with BZD use, and type of BZD by ATC

CXO	Cases date N(%)	Contr. Date1 N(%)	Contr. Date2 N(%)	Contr. Date3 N(%)	Contr. Date4 N(%)	∑control 1-4 N(%)	Crude OR	95% CI	AOR	95% CI
Non use/past	2,493(46.1)	2,607(48.2)	2,524(49.1)	2,459(50.5)	2,338(50.8)	9,928(49.6)	*1.00*		*1.00*	
Recent use	367(6.8)	259(4.8)	268(5.2)	234(4.8)	259(5.6)	1,020(5.1)	1.88	1,62-2,18	1.69	1,46-1,97
Current use	2,552(47.2)	2,546(47.0)	2,353(45.7)	2,180(44.7)	2,002(43.5)	9,081(45.3)	1.70	1,50-1,92	1.47	1,29-1,67
Type of BZD used										
Both	750(29.4)	715(28.1)	659(28.0)	615(28.2)	568(28.4)	2,557(28.2)	3.62	2,77-4,75	3.03	2,30-4,00
Anxiolytics	1,449(56.8)	1,495(58.7)	1,388(59.0)	1,293(59.3)	1,171(58.5)	5,347(58.9)	1.42	1,23-1,63	1.24	1,07-1,43
Hypnotics	353(13.8)	336(13.2)	306(13.0)	272(12.5)	263(13.1)	1,177(13.0)	2.09	1,64-2,67	1.82	1,42-2,33

AOR-adjusted for all co-medication

APPENDIX G

Additional tables from the SCCS study

Table A9- IRRs of hip/femur fracture with pre-exposure time risk window of 15 days

Exposure	Cases	Py	Model Crude			Model Adjusted by age		
			IRR	IC(95%)		IRR	IC(95%)	
Past/non use	2,066	5,051,344	1.00			1.00		
Pre-Exposure 15d	646	187,471	9.28	8.43	10.23	8.32	7.54	9.17
Current 1-30d	213	409,985	1.43	1.23	1.65	1.26	1.09	1.46
Current 31-60d	201	362,943	1.53	1.32	1.78	1.35	1.16	1.57
Current 61-182d	314	614,880	1.47	1.29	1.68	1.24	1.08	1.41
Current 183-365d	246	437,601	1.76	1.51	2.04	1.38	1.18	1.60
Current >365d	569	1,120,123	2.03	1.77	2.33	1.26	1.08	1.47
Recent use	195	407,761	1.28	1.10	1.49	1.13	0.97	1.32
Current use	1,543	2,945,532	1.60	1.47	1.74	1.29	1.18	1.41
Type of BZD by ATC								
Use of Both	187	314,002	2.33	1.86	2.91	1.71	1.35	2.16
Use of Anxiolytics	1,023	1,985,997	1.58	1.43	1.75	1.31	1.18	1.45
Use of Hypnotics	333	645,533	1.47	1.26	1.72	1.15	0.98	1.35

Table A10- IRRs of hip/femur fracture with pre-exposure time risk window of 30 days

Exposure	Cases	Py	Model Crude			Model Adjusted by age		
			IRR	IC(95%)		IRR	IC(95%)	
Past/non use	1,898	4,941,761	1.00			1.00		
Pre-Exposure 30d	837	343,657	7.17	6.55	7.84	6.47	5.91	7.09
Current 1-30d	213	409,985	1.58	1.36	1.83	1.40	1.21	1.62
Current 31-60d	201	362,943	1.69	1.45	1.97	1.49	1.28	1.74
Current 61-182d	314	614,880	1.63	1.43	1.86	1.37	1.20	1.57
Current 183-365d	246	437,601	1.95	1.68	2.27	1.53	1.32	1.79
Current >365d	569	1,120,123	2.27	1.97	2.60	1.42	1.22	1.65
Recent use	172	361,158	1.37	1.16	1.60	1.21	1.03	1.42
Current use	1,543	2,945,532	1.77	1.62	1.93	1.43	1.31	1.57
Type of BZD by ATC								
Use of Both	187	314,002	2.59	2.07	3.23	1.91	1.51	2.42
Use of Anxiolytics	1,023	1,985,997	1.76	1.59	1.94	1.45	1.31	1.61
Use of Hypnotics	333	645,533	1.62	1.39	1.90	1.28	1.09	1.50

Table A11- IRRs of hip/femur fracture with pre-exposure time risk window of 60 days

Exposure	Cases	Py	Model Crude			Model Adjusted by age		
			IRR	IC(95%)		IRR	IC(95%)	
Past/non use	1,706	4,744,140	1.00			1.00		
Pre-Exposure 60d	1,059	599,271	5.57	5.11	6.06	5.06	4.64	5.52
Current 1-30d	213	409,985	1.72	1.48	2.00	1.52	1.31	1.77
Current 31-60d	201	362,943	1.85	1.59	2.15	1.62	1.39	1.89
Current 61-182d	314	614,880	1.78	1.56	2.03	1.49	1.30	1.71
Current 183-365d	246	437,601	2.13	1.83	2.48	1.67	1.43	1.95
Current >365d	569	1,120,123	2.48	2.16	2.86	1.55	1.33	1.81
Recent use	142	303,165	1.41	1.18	1.68	1.25	1.05	1.49
Current use	1,543	2,945,532	1.94	1.77	2.12	1.56	1.42	1.72
Type of BZD by ATC								
Use of Both	187	314,002	2.85	2.28	3.56	2.10	1.66	2.66
Use of Anxiolytics	1,023	1,985,997	1.92	1.73	2.12	1.58	1.42	1.76
Use of Hypnotics	333	645,533	1.77	1.51	2.07	1.39	1.18	1.63