Understanding differences in findings from pharmacoepidemiological studies

The case of antidepressant and benzodiazepine use and hip fracture

Victoria Abbing-Karahagopian

Funding
Most of the studies in this thesis were conducted as part of the IMI-PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.

The IMI-PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. In the context of the IMI Joint Undertaking (IMI JU), the Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, also received a direct financial contribution from Pfizer. The views expressed are those of the authors only and not of their respective institution or company.

Printing of this thesis was kindly supported by the Nederlands Bijwerkingen Fonds [NBF, Dutch side effects fund].

ISBN: 978-94-6169-797-4
Layout and Printing: Optima Grafische Communicatie (www.ogc.nl)
Cover painting by Arthur Pinajian 1914 – 1999.
Courtesy of Pinajian Estate Collection (PinajianArt.com - http://pinajianart.com)

UNDERSTANDING DIFFERENCES IN FINDINGS FROM PHARMACOEPIDEMIOLOGICAL STUDIES

The case of antidepressant and benzodiazepine use and hip fracture

VARIABILITEIT IN UITKOMSTEN VAN FARMACOEPIDEMIOLOGISCH ONDERZOEK:

de associatie tussen antidepressiva- en benzodiazepinegebruik en heupfracturen als casus

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar te
verdedigen op dinsdag 19 januari 2016 des middags te 12.45 uur

door

Victoria Abbing-Karahagopian

geboren op 9 april 1971
te Beiroet, Libanon

Promotoren:	Prof. dr. A.C.G. Egberts
	Prof. dr. H.G.M. Leufkens
Copromotoren:	Dr. M.L. De Bruin
	Dr. T.P. van Staa

In memory of one and a half million Armenians killed
during the Genocide in 1915 by the Ottoman government.

To future generations claiming their right for a dignified life,
education and living their own culture.

TABLE OF CONTENTS

1

Introduction

1.1 General introduction

The first epidemiological studies were performed by John Graunt [1] (early statistical and census methods and concepts of lifetables) in the 17th century, John Snow [2] (the association between water source and the cholera epidemic in London) and Louis Pasteur [3] (principles of preventive medicine through vaccination and the first use of anti-rabies vaccines in humans) later in the 19th century. These studies can be seen as the roots of modern epidemiology [4]. The science and nature of epidemiology has, since then, evolved with respect to study designs, data analysis methods and the collection and availability of data. In addition, specific areas such as environmental, occupational, nutritional, genetic, and pharmacoepidemiology have been developed. The essence of epidemiology has, however, remained the same: the occurrence of outcome(s) as a function of determinant(s) [5]. Pharmacoepidemiology is the study of the effects of drug use in human populations [6] and includes experimental and observational studies during the pre- and the post-approval phases of drugs. Observational pharmacoepidemiological studies are especially valuable for assessing drug effects in the post-approval period in larger populations under real-life situations in contrast to the experimental pre-approval studies conducted in highly selected, closely monitored, relatively small populations for a limited period of time [6].

When a clustering of eight young female patients (age 14-22 old) with vaginal carcinoma was observed in one hospital during a four-year period in the late 1960s in the US, a case-control study was designed to investigate the causes of this rare type of cancer. Birth certificates were used to identify 32 controls born within five days in similar maternity services in the region as the eight cases. This study linked fetal exposure to diethylstilbestrol to this specific form of vaginal cancer [7]. At the same time, the idea of recording patients information electronically instead of using paper notes was just developing which made it possible for a third party (other than the patient and the doctor) to have access to medical information [8]. Apart from information on diagnoses or symptoms (i.e. outcomes) recorded in electronic healthcare records, interest in benefits and risks of drug use in real-world patients (other than those included in clinical trials) and the application of this information in benefit-risk analyses has expanded the use of such electronic databases.

The availability of electronic healthcare record (EHR) databases, alternatively referred to as administrative databases, has greatly contributed to the increased numbers of studies, performed with larger sample sizes and longer follow-up periods in post-approval settings. As opposed to earlier cross-sectional sampled study populations and interview data from surveys, EHR data created the opportunity for a better defined source population and less concerns for response rate and recall bias in observational studies with retrospectively collected data [9,10]. The use of EHR made also more detailed exposure information possible: from simple exposed/not-exposed categorization on the basis of a single recorded prescrip-

tion, to more detailed definitions with respect to time, doses prescribed, estimations of duration of use, and intra-individual changes in time (i.e. switch, stop).

The classic drug safety examples from the 1960s and 1970s - like the association between fetal distilbestrol exposure and adenocarcinoma of the vagina- typically were high relative risks and a low background incidence. An example of low background rate and high absolute risk incurring a very high relative risk (RR) is the association between Stevens Johnson Syndrome and toxic epidermal necrolysis and the use of phenobarbital (RR around 45) [11]. When the excess risk of an event is high this should be usually detected during the pre-authorisation period of the drug [12]. When a medication is long enough in the market and the period of sudden increase in the exposure is ended (i.e. steady state of exposure among the risk and reference windows) the chances of spurious high risk findings (due to the unequal chances of exposure among the two windows) is less [13]. During the last decades, however, observational studies on drug safety issues increasingly reported low relative risks (e.g RR between 1 and 2). As such, the relation between the background risk (high or low) and the absolute risk (high or low) of a health outcome is a function of exposure intensity in the population [14]. The public health impact of adverse events with low RR but with high background risk can be as large as drug safety issues which are rare but have high relative risk. In this case, the consistency of the reported low relative risks in different populations is highly important to reinforce the causal relationship [12]. Moreover, when the estimated RR is low, the challenge for evaluating the effects of bias (whether by confounding indication, prothopatic bias, selection or other) will be also higher. This also hinders policy makers to draw conclusions.

The large number of observational studies has thus resulted in varying, and often contradictory, estimates of risks. This has been discussed in literature in the late 1990s [15]. Few examples of these conflicting findings from studies which have used similar databases are oral bisphosphonates and cancer of oesophagus [16, 17], proton pump inhibitors and hip fracture [18-20] and statins and fractures [21-22]. The variability in the results of the observational studies may be due to several factors such as sampling strategies, population characteristics, study design and method robustness, or clinical differences. The reported risk ratios (RR) in most pharmacoepidemiological studies, such as the examples given above, are usually low (RR in the order of 2 or 3) due to the high background rate of the outcome studied and low absolute risk of the exposure. Wide range of low risk ratios reported by studies using different populations and methodologies leaves us with the challenge of summarising evidence base. Epidemiological reviews and meta-analysis studies may not be enough for summarizing drug-benefit or -risk evidence. There has also been much critique [23] and critical appraisal [24] of meta-analysis methods and the appropriateness of combining oranges with apples to generate a single effectiveness or risk measure.

There are several electronic data sources in Europe, which are increasingly used for observational pharmacoepidemiological research. Age, size and type of such data sources are varied. The need for a systematic investigation on current applied methods in pharmacoepidemiology has become more apparent. A specific need is to have more insight into the use of EHR data and related possibilities and limitations of hypothesis generation (signal detection) and hypothesis testing. As systematic efforts require considerable resources, studying the impact of methods and data sources on the discrepancies among study results in consortia with multi-partnership becomes a logical direction. Accordingly, many systematic and collective efforts in consortia have made their place. Examples of such collaborations are the Observational Medical Outcomes Partnership (OMOP) [25] and the Mini-sentinel projects in the United States, which have already published much of their experiences and findings in peer reviewed publications [26, 27]. The Drug Safety and Effectiveness Network (DSEN) and the Canadian Network for Observational Drug Effect Studies (CNODES) are the Canadian initiatives [28]. Other consortia in Europe and Asia have also aimed at addressing data and methods related issues in pharmacoepidemiology [25, 29, 30]. The EU-ADR [31], VAESCO-Brighton collaboration [32], IMI-ADVANCE [33] and IMI-PROTECT are examples of European initiatives addressing drug and vaccine safety signal detection and pharmacoepidemiology methods. The latter, is discussed further, as it is the context in which the work relating to this thesis was performed.

The IMI-PROTECT Consortium

PROTECT is an acronym for *Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium* (PROTECT). This European project funded by the *Innovative Medicines Initiative* (34) aims at strengthening the monitoring of the benefit-risk balance of medicines in Europe [30]. The consortium consists of 29 public and private partners coordinated by the European Medicines Agency (EMA). It addresses broad issues within post-marketing settings such as new modalities for collecting data for safety and effectiveness studies, acquiring accurate drug utilization data in the countries, investigating methods for signal detection and association testing to enhance benefit-risk models. To achieve its multi-faceted goal, the consortium had initiated several work-packages (WP) dedicated to evaluating existing methods and developing, testing and validating tools for signal detection, pharmacoepidemiological studies, and benefit-risk assessments. These issues were investigated in separate WPs with clearly stated deliverables [30].

Framework for Pharmacoepidemiology Studies

This thesis is within the scope of WP2 (Framework for Pharmacoepidemiology Studies) of PROTECT which aims at developing a methodological framework for pharmacoepidemiology studies to be applied in different databases and investigating discrepancies in results. In addition, WP2 aims at identifying and evaluating statistical methods for conducting

multi-database studies. Within this WP, advantages and limitations of EHR databases in ascertaining adverse events, drug exposure and drug-adverse event associations were addressed with the application of different methodologies. Three working groups making up the WP2 have focused on: methods used in multi-database studies, methods used to control for confounding and methods available for obtaining accurate drug utilization data.

To achieve the overall objectives stated in WP2, and specifically those related to the methods used in multi-database studies, feasibility studies were conducted. These studies would assess the feasibility to ascertain key adverse events with sufficient validity using standard algorithms and applying same definitions in different databases for conducting pharmacoepidemiological studies in multiple databases. Accordingly, two consensus meetings have produced an initial short list of 55 and then a final list of six drug-adverse event pairs as key associations to be studied systematically in different databases. The criteria for selecting the six drug-adverse event pairs included factors related to : public health importance of the adverse event, degree of controversy/ascertainment of the drug-adverse event association, diversity in drug use (chronic/acute) and adverse event type (long-term/short-term) and importance of drug use and adverse event occurrence. The final list of drug-adverse event pairs to be studied in WP2 included:

1. Short-/long-acting beta-2 agonists and acute myocardial infarction
2. Antibiotics and acute liver injury
3. Antidepressant and hip fracture
4. Benzodiazepines and hip fracture
5. Anticonvulsive drugs and suicide/suicidal attempts
6. Calcium channel blockers and cancer

Moreover, databases from different European countries were identified to perform methodological studies on these selected drug-adverse event pairs. The following databases were accessible via the partners in the consortium: Database for pharmacoepidemiology studies in primary care (BIFAP) in Spain, Bavarian Claims Database in Germany, National Databases in Denmark, Clinical Practice Research DataLink (CPRD) and The Health Improvement Network (THIN) in the UK, and the Mondriaan databases in The Netherlands.
The exploration of methodological aspects using the example of antidepressants and benzodiazepines and the risk of fractures, one of the chosen drug-adverse event associations in PROTECT and the focus of this thesis, is further discussed below.

Previous studies on antidepressant and benzodiazepine use and hip fractures

To understand the variability in the results of pharmacoepidemiology studies, we have made a conscious choice of selecting the association between antidepressant and benzodiazepine use and fractures as a case study. Antidepressants are among the most used medication

groups in the world [35, 36]. The first antidepressants in the mid-20th century were the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), followed by the selective serotonin reuptake inhibitors (SSRIs) in the late 1980's and the serotonin-norepinephrine reuptake inhibitors (SNRIs) in the 1990's. Antidepressants are prescribed for various depressive disorders, anxiety disorders, chronic pain, sleeping disorders, eating disorders and alcohol use disorders [37]. Benzodiazepines, its derivatives and related drugs; also referred as anxiolytics and hypnotics are also prescribed for various indications [38] such as anxiety related disorders, insomnia, seizures and epilepsies, and alcohol addiction withdrawal and pre-stressful situations like surgery. Many studies have reported increase in prescribing of antidepressants [39-42] and benzodiazepines [43-45] in the last 20 years in various countries. These studies have used different data ranging from populations described according to narrow definitions of indications to those restricted to certain age groups. Drug utilization studies have reported prevalence of antidepressant or benzodiazepine use using several measures to denote 'drug use'. These measures vary from aggregate level of sales numbers (number of doses sold) to patient level use (number of persons with a medication prescription or dispensation). Given the diversity of these measures and methods used to estimate or infer drug use multi-country comparisons are not straightforward.

Fractures on the other hand are one of the health outcomes with considerable public health burden in several countries worldwide. Appropriate quantification of the frequency of fractures and characterization of patients [46, 47] in terms of age, sex, type of fracture and seasonality is an essential part of suitable assessment of its burden and planning for managed healthcare systems. Several measures of fracture occurrence have been reported using different quantification methods which have introduced not only the challenge of cross-country or regional comparisons but have also produced different estimates for the same country [48-50]. Studies using different methodologies have reported different incidence rates, some of which suggested a decrease in the incidence owing to the effectiveness of public health preventive programs on osteoporosis and falls [51]. However, if quantification methods are different and rates cannot be compared directly, it is a challenge to draw conclusions on the trend of fracture incidence in different countries, let alone implying its decrease to be a result of preventive programs.

Antidepressants and benzodiazepines have both been associated with fractures in several studies as early as in the 1980s [52]. Moreover, each of these medication groups has been hypothesized to be associated with fracture through different biological mechanisms. Antidepressants are hypothesized to affect bone metabolism [53, 54] and bone marrow density (BMD) resulting in osteoporosis or through anticholinergic effects [55] leading to falls and fractures. Benzodiazepines, on the other hand, are known with their anxiolytic and hypnotic effects which may lead to falls and fractures. These two different hypothesized

biological mechanisms are very different in terms of hazard curve per exposure time. Antidepressant effects on BMD may be expected to be after relatively long and chronic use of the medication while, the risk of fracture due to benzodiazepines use, more intermittent, may be expected to be more acute [56, 57].

Numerous literature studies have reported different risk ratios for fractures among antidepressant [58-62] or benzodiazepine [63, 64] users using diverse types and sources of databases. These studies were conducted in different populations, using different databases and study methods. Looking at studies on antidepressant use and fracture and further screening studies which have used the cohort design for example still leaves us with wide ranges of risk estimates. As such, risks estimated for fracture in SSRI users range between 1.01 [65] and 2.40 [66] when only cohort studies are considered. This range is 1.21 [65] and 2.40 [67] in TCA users in cohort studies. This shows that *drug group* and *study design* similarities are not enough to reduce diversity of the reported risk estimates. Exposure definition, matching design [21] may explain some of these discrepancies. Moreover, confounder adjustment may also introduce discrepancies in the reported estimates [68]. Study designs and definitions of cohorts may introduce biases such as immortal time bias and render study results incomparable to each other [69]. Several sources of biases and differences in the study design and conduct can make understanding of the sources of differences and comparison of study results difficult.

OBJECTIVES OF THIS THESIS

The overarching objective of this thesis is to understand the variability in findings of pharmacoepidemiological studies resulting from different choices in study methods.

Specific objectives of the studies throughout this thesis were:

- To evaluate the variability between countries in prevalence of medication use and incidence of health outcome when applying common study methods.
- To understand differences in risk estimates of pharmacoepidemiology association studies when applying common study methods.
- To discuss and test the impact of the complexity of concomitant use of medications that are frequently co-prescribed and are associated with a common adverse event.

OUTLINE OF THIS THESIS

Chapter 1 includes an introduction and a background for the studies in this thesis. ***Chapter 1.1*** provides a general introduction and sets the scene for the context of the thesis: The IMI-PROTECT a European consortium. ***Chapter 1.2*** discusses the rationale and the first results of Work Package 2 of PROTECT.

Chapter 2 focuses on variability of medication use and a health outcome estimated in different populations using different electronic healthcare records. ***Chapter 2.1*** describes the prevalence of antidepressant prescribing in five European countries and seven different databases using common study methods. ***Chapter 2.2*** describes the prevalence of use of benzodiazepines and related drugs applying common study methods. ***Chapter 2.3*** describes the incidence of hip and/or femur fracture in five European countries using common study methods.

Chapter 3 deals with differences in findings of pharmacoepidemiology association studies in general and focuses on the complexity of concomitant exposures and their impact on the estimated risks. ***Chapter 3.1*** explains differences in risk estimates between antidepressant and hip fracture association, in a cohort design, in three European databases by applying common study methods. ***Chapter 3.2*** discusses the complexity of concomitant use of antidepressants and benzodiazepine and its impact on risk estimates for a common adverse event: hip fracture. ***Chapter 3.3*** tests the impact of different definitions of concomitant use of antidepressants and benzodiazepines on the risk estimates for hip/femur fractures.

Finally, *chapter 4* discusses the findings of the studies included in this thesis from a broader perspective.

REFERENCES

1. Rothman KJ. The rise and fall of epidemiology, 1950-2000 A.D. 1981. Int J Epidemiol. 2007;36(4):708-10.
2. Winkelstein W, Jr. A new perspective on John Snow's communicable disease theory. Am J Epidemiol. 1995;142(9 Suppl):S3-9.
3. Schwartz M. The life and works of Louis Pasteur. J Appl Microbiol. 2001;91(4):597-601.
4. Ginzburg R, Rosero E. Risk of fractures with selective serotonin-reuptake inhibitors or tricyclic antidepressants. Ann Pharmacother. 2009;43(1):98-103.
5. Last JM. Dictionary of public health. Am J Prev Med. 2002;23(3):235.
6. Strom BL, Kimmel SE. Pharmacoepidemiology. Fifth ed. Philadelphia, PA: John Wiley &Sons, LTD; 2005.
7. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971;284(15):878-81.
8. Wright A, Sittig DF, McGowan J, Ash JS, Weed LL. Bringing science to medicine: an interview with Larry Weed, inventor of the problem-oriented medical record. J Am Med Inform Assoc. 2014;21(6):964-8.
9. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37.
10. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. Nat Clin Pract Rheumatol. 2007;3(12):725-32.
11. Jick H. The discovery of drug-induced illness. N Engl J Med. 1977;296(9):481-5.
12. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333(24):1600-7.
13. Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. Drug Saf. 2002;25(6):467-71.
14. Wang SV, Schneeweiss S, Maclure M, Gagne JJ. "First-wave" bias when conducting active safety monitoring of newly marketed medications with outcome-indexed self-controlled designs. Am J Epidemiol. 2014;180(6):636-44.
15. Taubes G. Epidemiology faces its limits. Science. 1995;269(5221):164-9.
16. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010;341:c4444.
17. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010;304(6):657-63.
18. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947-53.
19. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy. 2008;28(8):951-9.
20. de Vries F, van Staa TP, Leufkens HG. Proton pump inhibitors, fracture risk and selection bias: three studies, same database, two answers. Osteoporos Int. 2011;22(5):1641-2.
21. de Vries F, de Vries C, Cooper C, Leufkens B, van Staa TP. Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database. Int J Epidemiol. 2006;35(5):1301-8.
22. van Staa TP, Wegman S, de Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. JAMA. 2001;285(14):1850-5.
23. Sharpe D. Of apples and oranges, file drawers and garbage: why validity issues in meta-analysis will not go away. Clin Psychol Rev. 1997;17(8):881-901.
24. Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. Clin Med. 2001;1(6):478-84.

25. Foundation for the National Institutes of Health. Observational Medical Outcomes Partnership [cited 2013 July]. Available from: http://omop.fnih.org/.
26. Mini-Sentinel Publications and Presentations [cited 2015 July 25]. Available from: http://mini-sentinel.org/communications/mini-sentinel_publications/default.aspx.
27. Observational Medical Outcomes Partnership (OMOP): Publications [cited 2015 July 25]. Available from: http://omop.org/PublicationList.
28. Canadian Institutes of Health Research [cited 2015 July 25]. Available from: http://www.cihr-irsc.gc.ca/e/193.html.
29. Kimura T, Matsushita Y, Yang YH, Choi NK, Park BJ. Pharmacovigilance systems and databases in Korea, Japan, and Taiwan. Pharmacoepidemiol Drug Saf.20(12):1237-45.
30. PROTECT-EU. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium [cited 2013 July]. Available from: http://www.imi-protect.eu/.
31. Schuemie MJ, Gini R, Coloma PM, Straatman H, Herings RM, Pedersen L, et al. Replication of the OMOP experiment in Europe: evaluating methods for risk identification in electronic health record databases. Drug Saf. 2013;36 Suppl 1:S159-69.
32. Vaccine Adverse Event Surveillance & Communication. [cited 2015 July 25] Available from: http://vaesco.net/vaesco.html.
33. Accelerated development of vaccine benefit-risk collaboration in Europe (IMI-ADVANCE) [cited 2015 July 25]. Available from: http://www.imi.europa.eu/content/advance.
34. Innovative Medicines Initiative [cited 2015 July 25]. Available from: www.imi.europa.eu
35. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. BMJ. 2009;339:b3999.
36. Alonso MP, de Abajo FJ, Martinez JJ, Montero D, Martin-Serrano G, Madurga M. Evolution of antidepressive drug consumption in Spain. The impact of selective serotonin re-uptake inhibitors. Medicina Clinica. 1997;108(5):161-6.
37. Bourgeois J, Elseviers MM, Van Bortel L, Petrovic M, Vander Stichele RH. The use of antidepressants in Belgian nursing homes: focus on indications and dosages in the PHEBE study. Drugs Aging. 2012;29(9):759-69.
38. Bourgeois J, Elseviers MM, Azermai M, Van Bortel L, Petrovic M, Vander Stichele RR. Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages. Eur J Clin Pharmacol. 2012;68(5):833-44.
39. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatr. 2009;66(8):848-56.
40. McManus P, Mant A, Mitchell P, Britt H, Dudley J. Use of antidepressants by general practitioners and psychiatrists in Australia. Aust N Z J Psychiatry. 2003;37(2):184-9.
41. Hemels ME, Koren G, Einarson TR. Increased use of antidepressants in Canada: 1981-2000. The Ann Pharmacother. 2002;36(9):1375-9.
42. Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998-2010. Br J Psychiatry. 2012;200(5):393-8.
43. Ohayon MM, Caulet M, Priest RG, Guilleminault C. Psychotropic medication consumption patterns in the UK general population. J Clin Epidemiol. 1998;51(3):273-83.
44. 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;18(7):572-8.
45. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck GA. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. Int Clin Psychopharmacol. 2007;22(5):292-8.
46. Pasco JA, Lane SE, Brennan SL, Timney EN, Bucki-Smith G, Dobbins AG, et al. Fracture risk among older men: osteopenia and osteoporosis defined using cut-points derived from female versus male reference data. Osteoporos Int. 2014;25(3):857-62.

47. Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA. The population burden of fractures originates in women with osteopenia, not osteoporosis. Osteoporos Int. 2006;17(9):1404-9.
48. Donaldson LJ, Cook A, Thomson RG. Incidence of fractures in a geographically defined population. J Epidemiol Community Health. 1990;44(3):241-5.
49. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. Bone. 2001;29(6):517-22.
50. Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW. Fracture incidence in England and Wales: a study based on the population of Cardiff. Injury. 1997;28(9-10):655-60.
51. 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;6(1-2):1-12.
52. 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;316(7):363-9.
53. Warden SJ, Robling AG, Sanders MS, Bliziotes MM, Turner CH. Inhibition of the serotonin (5-hydroxytryptamine) transporter reduces bone accrual during growth. Endocrinology. 2005;146(2):685-93.
54. Bliziotes M. Update in serotonin and bone. J Clin Endocrinol Metabol. 2010;95(9):4124-32.
55. Verdel BM, Souverein PC, Egberts TC, van Staa TP, Leufkens HG, de Vries F. Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. Bone. 2010;47(3):604-9.
56. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA. 1989;262(23):3303-7.
57. 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.
58. 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;27(5):1186-95.
59. Oderda LH, Young JR, Asche CV, Pepper GA. Psychotropic-related hip fractures: meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. Ann Pharmacother. 2012;46(7-8):917-28.
60. Rabenda V, Nicolet D, Beaudart C, Bruyere O, Reginster JY. Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int. 2012;24(1):121-37.
61. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int. 2012;23(1):365-75.
62. Wu Q, Qu W, Crowell MD, Hentz JG, Frey KA. Tricyclic antidepressant use and risk of fractures: A meta-analysis of cohort and case-control studies. J Bone Miner Res. 2013;28(4):753-63.
63. 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;91(1):24-31.
64. 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;25(1):105-20.
65. Diem SJ, Blackwell TL, Stone KL, Cauley JA, Hillier TA, Haney EM, et al. Use of antidepressant medications and risk of fracture in older women. Calcif Tissue Int. 2011;88(6):476-84.
66. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998;351(9112):1303-7.
67. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, et al. Predictors of non-

spine fracture in elderly men: the MrOS study. J Bone Miner Res. 2007;22(2):211-9.
68. Klungel OH, Stricker BH, Breteler MM, Seidell JC, Psaty BM, de Boer A. Is drug treatment of hypertension in clinical practice as effective as in randomized controlled trials with regard to the reduction of the incidence of stroke? Epidemiology. 2001;12(3):339-44.
69. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 2007;16(3):241-9.

1.2

Bridging differences in outcomes of pharmacoepidemiological studies: design and first results of the PROTECT project.

Victoria Abbing-Karahagopian, Xavier Kurz, Frank de Vries, Tjeerd P. van Staa, Yolanda Alvarez, Ulrik Hesse, Joerg Hasford, Liset van Dijk, Fancisco J. de Abajo, John G. Weil, Lamiae Grimaldi-Bensouda, Toine C.G. Egberts, Robert F. Reynolds, Olaf H. Klungel.

Current Clinical Pharmacology 2014; 9(2):130-8

ABSTRACT

Background

Observational pharmacoepidemiological (PE) studies on drug safety have produced discrepant results that may be due to differences in design, conduct and analysis. The pharmacoepidemiology work-package (WP2) of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project aims at developing, testing and disseminating methodological standards for design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues using different databases across European countries. This article describes the selection of the safety issues and the description of the databases to be systematically studied.

Methods

Based on two consensus meetings and a literature search, we selected five drug-adverse event (AE) pairs to be evaluated in different databases. This selection was done according to pre-defined criteria such as regulatory and public health impact, and the potential to investigate a broad range of methodological issues.

Results

The selected drug-AE pairs are: 1) inhaled long-acting beta-2 agonists and acute myocardial infarction; 2) antimicrobials and acute liver injury; 3) antidepressants and/or benzodiazepines and hip fracture; 4) anticonvulsants and suicide/suicide attempts; and 5) calcium channel blockers and malignancies. Six European databases, that will be used to evaluate the drug-AE pairs retrospectively, are also described.

Conclusion

The selected drug-AE pairs will be evaluated in PE studies using common protocols. Based on consistencies and discrepancies of these studies, a framework for guiding methodological choices will be developed. This will increase the usefulness and reliability of PE studies for benefit-risk assessment and decision-making.

INTRODUCTION

Randomised Clinical Trials (RCT) of drug adverse events do not optimally reflect real life situations: small sample sizes, highly selected populations and short duration of exposures [1]. During the past decades, it has been realized that adverse drug-events (AE) need to be further evaluated in pharmacoepidemiological (PE) studies [2]. PE methods were, however, still in development and therefore had the potential for reporting biased results. An example is the falsely reported relationship of breast cancer to use of the blood pressure lowering drug reserpine [3]. The growing availability of large routine electronic health record databases has made it possible to study less frequent and less severe AEs. An example is the risk of deep venous thrombosis in users of third generation oral contraceptives [4]. Although (pharmaco)-epidemiological methods have progressed, the challenge of studies of low absolute and relative risks associated with medications may have pushed pharmacoepidemiology to the borders of what can reliably be detected beyond the level of background noise [5]. Furthermore, efforts focusing on evaluation of type A AEs (those with dose dependent and predictably augmented pharmacological effects) and intended effects of drugs have increased the potential for bias [6].

Study conduct and design choices are one of the factors contributing to the diversity and discrepancy of study results. For instance, using the same database (the UK Clinical Practice Research Datalink [7]) and including a large number of patients, two studies that were independently conducted reached very different conclusions [8, 9]. Within the same source study population, discrepant results between studies can be explained by small differences in study design such as different definitions of exposure time windows, confounder selection and age matching [9, 10]. Moreover, exposure-time-dependent hazard functions can substantially affect comparisons between different studies of the same drug [11]. The use of different statistical methods to adjust for confounding is another explanation for dissimilar study results [12]. For instance, in a database study and in simulation studies, systematic differences were found in effect estimates when propensity scores were used compared to logistic regression or Cox-proportional hazards regression [13, 14]. Immortal time bias has been suggested as another important source of variability in results between observational studies on drug effects [15]. Furthermore, several studies that have evaluated the same data source have drawn different conclusions about the plausibility of a pharmacological explanation of an observed association. Among these are: use of inhaled corticosteroids and risk of hip fracture [16, 17], use of beta-blocker and risk of hip fracture [18, 19]; use of oral bisphosphonates and risk of cancer of oesophagus [20, 21]; and more recently, use of proton pump inhibitors and risk of hip fracture [22-25].

The influence of methodological variation should be minimized and quantified, in order to interpret differences in associations between drugs and AEs that arise between types of data sources and healthcare systems in the different countries. A clear interpretation of differences in results between studies performed in the same database, and between different databases, is currently not completely feasible due to these methodological differences. This situation poses difficulties for all stakeholders, such as regulatory agencies, industry, healthcare professionals and patients. Difficulties in interpreting individual and/or groups of observational studies limit their usefulness for decision making on the benefit-risk balance of drugs. These experiences highlight the need to increase understanding of the implications of different methodological choices by investigators and for a framework on PE methodology across different data sources. To understand and subsequently validate differences caused by methodological and non-methodological (data related) factors we have selected five different drug-AE pairs, to be analysed in five different European databases based on a common protocol that includes extensive sensitivity analyses.

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) study is a collaborative European project that addresses limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance [26]. PROTECT is a multinational consortium of 29 partners including academics, regulators, small and medium enterprises (SMEs) and European Federation of Pharmaceuticals Industries and Associations (EFPIA) companies, coordinated by the European Medicines Agency (EMA) with GlaxoSmithKline (GSK) as deputy co-ordinator. The "Framework for pharmacoepidemiology studies" work-package (WP2) of PROTECT, co-led by Utrecht University and Pfizer, aims at developing, testing and disseminating methodological standards for the design, conduct, and analysis of PE studies applicable to different safety issues using different data sources. This article presents the rationale, design and the first results of the WP2 of PROTECT initiative.

METHODS

Selection of drug-AE pairs:

Criteria for the selection of key AEs to evaluate in different databases included: 1) the AE selected having resulted in (major) regulatory decisions such as drug withdrawal or major summary of product characteristics (SmPC) changes; 2) public health impact aspects including seriousness of the event (prioritise more serious events); having variable incidence rates (both rare and common events); and prevalence of drug exposure (commonly used drugs and infrequently used drugs); 3) possibility to investigate a broad range of relevant methodological issues including feasibility to ascertain events in electronic healthcare da-

tabases (events both easy and difficult to ascertain); hazard functions (acute and long-term effects, delayed/transient effects); setting of drug use (in-/outpatient use); type of use (short/long-term, as needed); and different indications of use. All drug-AE pairs needed to fulfil these criteria. Furthermore, at least one drug-AE pair was selected taking into account those chosen by the public-private US initiative Observational Medical Outcomes Partnership (OMOP) in order to facilitate comparison with this initiative [27].

An initial inventory of potential drug-AE pairs was compiled, based on recommendations from public and private partner experts in the field of epidemiology and pharmacovigilance (European and national medicines agencies, pharmaceutical industry and academia). All partners were asked to nominate 10 drug-AE pairs that would fulfil the previously defined criteria for selection. This resulted in an initial list of 55 AEs and >55 individual drugs and drug classes. A first consensus meeting produced five AEs and a limited number (≤ 3) of drugs per AE with high priority. Supported by extensive research of the scientific literature and publicly available information sources, including PubMed, EMA and the US Food and Drug Administration (FDA) websites, each of the criteria for the selected drug-AE pairs was assessed. Subsequent to this assessment, the selection of five drug-AE pairs was finalized in a second consensus meeting.

Databases:

All PROTECT partners who manage or have access to electronic healthcare or reimbursement databases were asked to describe characteristics of these databases. Databases incorporated medical and registry-based data sources, such as the Danish national registries, the Dutch Mondriaan project, the British CPRD and The Health Improvement Network (THIN) databases, the Spanish BIFAP project and the German Bavarian claims database. In addition, the French PGRx case-referent system will be made available to investigate and/or confirm some of the drug-AE pairs. All partners were sent a questionnaire in order to systematically collect the information. Parameters included information on period of data collection, coding systems, accessibility procedures and an extensive list of specific categories for longitudinally collected data such as drug prescribing/dispensing, clinical data, laboratory test data and life style parameters. The databases from the Netherlands, Spain, Denmark, and UK are based on primary care (GP and/or pharmacy) covering all prescription drugs regardless of reimbursement.

Analytical approach

Common study protocols to study each of the drug-AE pairs have been developed and comply with the ENCePP methodological standards (including the ENCePP checklist) and were submitted to the ENCePP registry of studies [28]. These protocols include different study designs such as cohort, case-control, and case-cross-over design. All studies are retro-

spective, based on existing data from the databases described above. We will use data from the period 2001-2009. Inclusion for entry in the cohort studies is that subjects would have to have at least 1 recorded prescription or dispensing of the drug of interest. This approach reduced confounding by indication and still allows comparing between subjects that are on the drug at a certain time during follow-up versus subjects that are not currently on the drug but used the drug in the past. Operational definitions of exposures and outcomes are harmonized as much as possible and varied in a range that reflects the possibilities and limitations of the available databases. For the outcome of liver injury a automated algorithm has been developed taking into account diagnostic codes and laboratory tests. Detailed code lists are available upon request. Exposure will be analysed time-dependently in all studies and some confounders will also be classified time-dependently if appropriate. Different methods for the selection of and control for confounding variables will be applied. Not all databases have the same level of detail with regard to confounders. We will conduct an analysis for each drug-ae pair that includes a minimum set of confounders that all databases have available. In subsequent sensitivity analyses we will also assess the impact of further adjustment for confounders that are available in some, but not all databases. For all databases we will describe exposure to the drugs of interest and for those databases with sufficient information on diagnoses we will describe the outcomes of interest. For the association studies we have implemented a blinding procedure with central results management. Results for each design will be un-blinded only after all databases have been analysed and produce the adjusted association measures.

RESULTS

The drug-AE pairs

The five drug-AE pairs fulfilling the a priori defined criteria are: 1) inhaled long-acting beta-2 agonists and acute myocardial infarction; 2) antimicrobials and acute liver injury; 3) antidepressants and/or benzodiazepines and hip fracture; 4) anticonvulsants (approved for treatment of epilepsy) and suicide/suicide attempts; 5) calcium channel blockers and malignancies. The following information is described for each drug-AE pair: public health impact, drug utilisation, the level of evidence to support a causal association, the proposed pharmacological mechanism(s), and methodological challenges specific for the drug-AE association. Table 1 shows the selected AEs and their characteristics. Table 2 shows the characteristics of the selected drugs. Table 3 displays the drug-AE associations and characteristics such as the range of relative risks; the study designs that have been used to study the association, the main methodological issues, and the suggested hazard function (in relation to onset and offset of the increased risk after initiation or discontinuation of the drug).

Table 1: Selected AE and their characteristics

AE	Non-fatal /fatal incidence		Regulatory triggers/ action	Seriousness	Ascertainment	Feasibility of ascertainment in EHR
Acute myocardial infarction	Non-fatal	803/100,000 hospital discharges due to CHD in 2009 (33)	Drug withdrawal/ Boxed warning (35)	10% disability-adjusted life years lost by CHD in 2010 (33)	Clinical, laboratory and ECG criteria	Moderately easy
	Fatal	76 (range 30-313) / 100,000 in 2010 (34)		28-day case fatality of IHD: 34%-88% (35)		
Idiopathic acute liver injury	Non-fatal	1-41/100,000 person years (36-38)	Drug withdrawal/ Boxed warning (30, 40, 41)	6 months case fatality: 12% (36)	Diverse clinical, laboratory and histological data (43)	Moderately Difficult
	Fatal	10% of all AE (39) 0.8/ million person-years (36)		29% of patients acute jaundice (42)		
Hip fracture	Non-fatal	80-200 /100,000/yr (44)	Warning in product information of	3.3 years: mean interval between fractures (50)	Hospital admission	Easy
	Fatal	20-24% fatality rate within 1 yr (45, 46)	antiretrovirals (47) & thiazolidinediones (48, 49)			
Suicide/suicide attempt	Non-fatal	50-100/100,000/yr attempts (51)	Drug withdrawal/Boxed warning (30)		Cause of death	Difficult
	Fatal	10 /100,000/yr (52)			Hospital admission due to self-harm	
Cancer	Non-fatal	414-600/100,000 new cases/yr (53)	For biologicals (41)	5-year fatality rate: 43%-71% (53)	Tumour diagnosis	Moderately easy
	Fatal	170/100,000/yr (34)			Cancer registry	

AE = adverse event

IHD =Ischemic Heart Diseases or CHD= Coronary Heart Diseases both terms include acute myocardial infarction

EHR = electronic healthcare records

Table 2: Selected medications and their characteristics

Drug	Range prevalence of drug exposure per thousand inhabitants	Most frequent type of use
Short / long acting beta-agonists	66 (54) to 84 (55) /1000	As needed/chronic
Antimicrobials	236 (56) to 344 (54) /1000	Short-term/long-term use
Antidepressants/benzodiazepines		As needed/long-term use
SSRI	30 (56) to 55 (54) /1000	
TCA	15 (56) to 11 (54) /1000	
Benzodiazepines	30 ((56) to 81 (54) /1000	
Anticonvulsants	17 (56) to 22 (55) /1000	Chronic
Calcium channel blockers	45 (55) to 70 (54) /1000	Chronic

SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressants

The databases

General features of the databases participating in PROTECT are presented in Table 4. The six databases contain data from patients from five different European nations: the Danish national registries, the Dutch Mondriaan database, the British CPRD and THIN databases, the Spanish BIFAP project, the German Bavarian claims database. The Danish registries have national coverage, while other databases contain regional data or a representative sample of a total population. All the databases were quite representative of their nation. Most of the databases were established more than 10 years ago with regular and expanding data collection and validation history. Routine checks on quality are performed in all databases. The majority of databases include GP data and two (Danish and CPRD) include registries for and linkages to mortality, cancer, and secondary care data. Three (Danish registries, Mondriaan and Bavarian claims) out of six databases include or had linkages to claims data. A particular characteristic of the Bavarian Claims database is the availability of information on prescriptions and diagnoses in quarters of a calendar year. The exact dates of prescribing and diagnoses are not available. Therefore, we decided to use this database for descriptive purposes only and refrained from conducting association studies for which this information is pivotal. For some databases, linkage to other national registries requires additional procedures and financial compensation. Table 4 briefly describes the participating databases.

DISCUSSION AND UPCOMING STUDIES IN PROTECT

We prioritised five drug-AE associations that are highly relevant from the perspective of various stakeholders including regulatory agencies, patients and the pharmaceutical indus-

Table 3: Drug–AE associations and characteristics

	Relative risk (RR)	Source (type of study)	Main methodological issues	Hazard function
SABA / LABA and AMI	RR > 2 for cardiovascular events vs. placebo (57) ORs 1.7 - 7.3 (new users) for MI vs. non-users (57)	Systematic review (RCT) (Case-control)	Protopathic bias Confounding by indication / severity	Acute onset, transient
	RR = 2.5 for respiratory deaths vs. placebo (58)	Meta-analysis (RCT)		
	salmeterol: all-cause mortality Peto OR =1.3 vs. placebo (59) non-fatal AE OR = 1.2 vs. placebo (59) *formoterol* : non-fatal serious AE OR = 1.6 vs. placebo (60)	Cochrane database systematic review (RCT)		
	OR 1.2 for beta-2 agonists (current users) 2.5 (IHD patients) (61) RR = 1.6 for SABA (heavy users vs. users of <3 months) (62) RR = 1.1 for LABA (heavy users vs. users of <3 months) (62)	Nested case–control cohort		
Antimicrobials and ALI	Elevated liver enzymes, cholestasis, and acute liver failure (for betalactam antimicrobials, macrolides, sufonamides, tetracyclines (63)	Case reports/ retrospective cohort	Definition/measurement of the outcome	Acute/intermediate onset (3-4 weeks) after drug stop
	RRs 2.3 (Amoxicillin without clavulanic acid) 1299.9 (Isoniazid + rifampicin + pyrazinamide) (64)	Case-population	Ascertaining/tracing of exposure (short time window)	
	ORs 5.3 (erythromycin) 94.8 (amoxicillin/clavulanic acid) (37)	Case-control (pop-based)		
Antidepressants/ BZD and hip fracture	RRs 1.2 - 3.7 for TCA users (65) RRs 1.5 - 8.6 for SSRI users (65) RRs 1.5 - 2.0 for hypnotics including BZD (66)	Case-control/ cohort	Exposure classification (for antidepressants) Selection bias Unmeasured confounding	SSRIs: peak at 6–12 months (67) TCA's: peak at 1-2 months (67) BZD: acute
Anticonvulsants and suicide/-attempts	RR = 2 for 11 different groups of the drug (1.5 (psychiatric) 3.5 (epilepsy) risk by indication) (68)	Meta-analysis of RCT	Definition and measurement of outcome	Acute
	RR = 3.1 for current users (lamotrigine, gabapentin, ethosuximide, vigabatrin) (69) OR 2.57 vs. non-users (70)	Nested case-control		
	HRs 1.4 – 2.4 vs. topiramate users (71)	Cohort		
CCB and cancer	RRs 1.7 (vs. non-users) - 2.6 (breast cancer) (72, 73) RR = 2.1 for *verapamil (74)*	Cohort	Long latent period Selection bias Unmeasured confounding	Long-term, delayed

SABA = short acting beta-2 agonists
LABA = long acting beta-2 agonists
(A)MI = (acute) myocardial infarction
CCB = calcium channel blockers
BZD = benzodiazepines
SSRI = selective serotonin reuptake inhibitor
RR = relative risk
AE = adverse event
TCA = tricyclic antidepressants
OR =odds ratio
ALI = acute liver injury
IHD = Ischemic Heart Diseases
HR= hazard ratio

Table 4: Characteristics of participating databases

Database /country	Danish registries (DK)	Mondriaan (NL)	GPRD (UK)	THIN (UK)	BIFAP (ES)	Bavarian claims (DE)
Nr. of persons with historical data (in Millions)	approx. 6	1.4 (GP) 13.5 (pharmacy) 1.2 (claims)	11.2	11	3.2	10.5
Nr. of active persons in 2008 (in millions)	5.2	0.6	4.6	3.8	1.6	9.5
Starting year of data collection	1994 a 1977 b	1991	1987	2003	2001	2001
Nationwide	+	90% of NL (pharmacy)	7% of the UK	6.2% of the UK	7% of Spain	
Representative of nation	+	+	+	+	+e	+c
Type of database						
General practitioner	+	+	+	+	+	+h
Pharmacy	+	+	/ f		/ f	+h
Mortality registry	+	/ linkage	+ g		/	
Cancer registry	+		+ linkage			
Hospitalisation registry	+	/linkage	+ linkage		/	
Specialist/secondary care	+	/	+ linkage			+
Claims	+	+				+
National statistics	+		/			
Surveys		+				
Routine data quality checks	+	+	+	+	+	+
Possibility of prospective data collection among patients in the database d		/	+	+	+	

DK = Denmark, NL = The Netherlands, UK = United Kingdom, ES = Spain, DE = Germany
d = For Interviews, trials, surveys
+ = Data is available / = data is partly available
e = GPs from 9 out of 17 regions in Spain. 15% of the collaborating regions and 7% of the total population. Representative of population attending primary care in Spain (similar age and sex distribution)
a = Medicinal products
f = Prescribed not dispensed
b = Patient registration
g = Contains records of death but is not the official registry
c = Representative of the region
h = Prescriptions and dagnoses are only available per quarter (no exact dates)

try. These associations allow investigation of the influence of variation in methodology. Furthermore, we characterised seven routine electronic healthcare databases from five European countries that will be used for the evaluation of the selected drug-AE associations.

The work of WP2 of PROTECT is in the front line of currently on-going large (inter-) national initiatives such as the Observational Medical Outcomes Partnership (OMOP), FDA Sentinel Initiative [29] and EU-ADR (EU-Adverse Drug Reactions) project [30]. OMOP is a public-private partnership that conducts experiments to assess value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs [31]. Furthermore, OMOP tests approaches for creating the infrastructure for accessing and managing the required data. The FDA Sentinel initiative aims at development of a national electronic safety monitoring system in order to strengthen FDA's ability to monitor post-marketing performance of medical products and to enable FDA to access existing automated healthcare data by partnering with data holders. EU-ADR project is focussing on utilizing electronic healthcare data records and biomedical databases for the early detection of AEs. In the EU-ADR project a list of 23 events were judged as important in pharmacovigilance and three AE (acute myocardial infarction, acute liver injury, and suicidal behaviour/attempt) on this list have also been prioritised in our project. The OMOP project has also defined a list of health outcomes of interest (HOI) and drug pairs to be further investigated. As previously mentioned we included two of these pairs (DILI and antimicrobials, hip fracture and benzodiazepines) in our prioritised list of five drug-AE pairs. Although these projects have a different focus than those of WP2 of PROTECT, the overlap in prioritised AEs (and drugs) will facilitate comparisons.

The strengths of our approach include the development of a common study protocol (that includes variation in methodology e.g. different designs) for five drug-AE associations that will be studied in different databases. In addition, some of our findings will be confirmed in specific registries such as PGRx [32]. Our approach will allow us to distinguish between variation in results due to variation in methodology and those due to database differences. Analysing these discrepancies will provide guidance regarding the optimal methodology for certain safety issues and the optimal selection of appropriate data source(s). The experience obtained in the PROTECT database network will improve the possibilities for multinational database studies for various safety issues, including the investigation of rare serious AE. Finally, other research activities of WP2 of PROTECT will further improve the methodological guidance on pharmacoepidemiological studies. These include an evaluation and improvement of methods to control for confounding such as propensity scores and instrumental variables in simulation studies, and drug utilisation research.

A limitation of our approach may be the scope of the drug-AE pairs and selected healthcare databases. Our findings may not be extendable to other safety issues or other databases that we do not study. However, our selection of drug-AE pairs includes common drug safety issues presenting different methodological challenges. The different types of databases (GP, claims, and registries) owned by PROTECT partners, also make extrapolation of our find-

ings to wider ranges of data sources possible. Furthermore, our findings will be validated by testing different drug-AE pairs in the same databases and confirmation of drug-AE association in specific registries that include more detailed information on outcomes and potential confounding factors.

In conclusion, WP2 of PROTECT will assess the influence of methodological parameters on the association between selected AEs and drug class of interest. The selected AEs include resulted in (major) regulatory decisions such as drug withdrawal or SmPC changes or allow the investigation of a broad range of relevant methodological issues. The anticipated results of this project include the creation of a European database network and further development of methodological standards for the conduct of (multi-) national PE studies. Methodological standards will be included when appropriate in the EMA-based ENCePP guidance on methodological standards. Increasing methodological standards and registration of study protocols may decrease discrepancies in results from these studies, increase transparency and thereby increase the usefulness and reliability of these studies for benefit-risk assessment and decision- making of marketed drugs in Europe and beyond.

REFERENCES

1. Strom BL, Kimmel SE, Hennessy S. Pharmacoepidemiology. 5th ed. Wiley-Blackwell: Oxford 2012.
2. Strom BL. Pharmacoepidemiology: Response to a challenge. Pharmacoepidemiol Drug Saf. 1995; 4: 11-4.
3. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med. 1980; 68: 255-8.
4. Lewis MA. The epidemiology of oral contraceptive use: a critical review of the studies on oral contraceptives and the health of young women. Am J Obstet Gynecol. 1998; 179: 1086-97.
5. Taubes G. Epidemiology faces its limits. Science. 1995; 269: 164-9.
6. Klungel OH, Martens EP, Psaty BM, et al. Methods to assess intended effects of drug treatment in observational studies are reviewed. J Clin Epidemiol. 2004; 57: 1223-31.
7. CPRD. The UK Clinical Practice Research Datalink. http://www.cprd.com/intro.asp (Accessed December 11 2013).
8. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. JAMA. 2000; 283: 3205-10.
9. van Staa TP, Wegman S, de Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. JAMA. 2001; 285: 1850-5.
10. de Vries F, de Vries C, Cooper C, Leufkens B, van Staa TP. Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database. Int J Epidemiol. 2006; 35: 1301-8.
11. Guess HA. Exposure-time-varying hazard function ratios in casecontrol studies of drug effects. Pharmacoepidemiol Drug Saf. 2006; 15: 81-92.
12. Klungel OH, Stricker BH, Breteler MM, Seidell JC, Psaty BM, de Boer A. Is drug treatment of hypertension in clinical practice as effective as in randomized controlled trials with regard to the reduction of the incidence of stroke? Epidemiology. 2001; 12: 339-44.
13. Martens EP, de Boer A, Pestman WR, Belitser SV, Stricker BH, Klungel OH. Comparing treatment effects after adjustment with multivariable Cox proportional hazards regression and propensity score methods. Pharmacoepidemiol Drug Saf. 2008; 17: 1-8.
14. Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Systematic differences in treatment effect estimates between propensity score methods and logistic regression. Int J Epidemiol. 2008; 37: 1142-7.
15. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 2007; 16: 241-9.
16. Hubbard RB, Smith CJ, Smeeth L, Harrison TW, Tattersfield AE. Inhaled corticosteroids and hip fracture: a population-based casecontrol study. Am J Respir Crit Care Med.

2002; 166: 1563-6.

17. van Staa TP, Leufkens B, Cooper C. Bone loss and inhaled glucocorticoids. N Engl J Med. 2002; 346: 533-5.
18. Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of betablockers and risk of fractures. JAMA. 2004; 292: 1326-32.
19. de Vries F, Souverein PC, Cooper C, Leufkens HG, van Staa TP. Use of beta-blockers and the risk of hip/femur fracture in the United Kingdom and The Netherlands. Calcif Tissue Int. 2007; 80: 69-75.
20. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010; 304: 657-63.
21. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010; 341: c4444.
22. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296: 2947-53.

23. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy. 2008; 28: 951-9.
24. de Vries F, van Staa TP, Leufkens HG. Proton pump inhibitors, fracture risk and selection bias: three studies, same database, two answers. Osteoporos Int. 2010; 22: 1641-2.
25. de Vries F, Cooper AL, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. Osteoporos Int. 2009; 20: 1989-98.
26. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT). http://www.imi-protect.eu (Accessed December 11 2013).
27. Foundation for the National Institutes of Health. Observational Medical Outcomes Partnership (OMOP). http://omop.fnih.org (Accessed December 11 2013).
28. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. http://www.encepp.eu (Accessed December 11 2013).
29. The US Food and Drug Administration. FDA's Sentinel Initiative. http://www.fda.gov/Safety/FDAsSentinelInitiative (Accessed December 11 2013).
30. Trifiro G, Pariente A, Coloma PM, et al. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? Pharmacoepidemiol Drug Saf. 2009; 18: 1176-84.
31. Stang PE, Ryan PB, Racoosin JA, et al. Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership. Ann Intern Med. 2010; 153: 600-6.
32. Grimaldi-Bensouda L, Rossignol M, Aubrun E, Benichou J, Abenhaim L. Agreement between patients' self-report and physicians' prescriptions on nonsteroidal anti-inflammatory drugs and other drugs used in musculoskeletal disorders: the international Pharmacoepidemiologic General Research eXtension database. Pharmacoepidemiol Drug Saf. 2012; 21: 753-9.
33. European Heart Network. New European Cardiovascular Disease Statistics 2012. http://www.ehnheart.org/cvd-statistics (Accessed December 11 2013)
34. European Commission Eurostat. Statistics Public Health: main tables. http://epp.eurostat.ec.europa/tgm/table.do?tab=table&init=1&language=en&pcode=tps00119&plugin=1 (Accessed December 11 2013).
35. Health in Europe: Information and Data Interface: cardiovascular diseases https://webgate.ec.europa.eu/sanco/heidi/index.php/Heidi/Major_and_chronic_diseases/Cardiovascular_disease/Ischaemic_heart_disease (Accessed December 11 2013).
36. Ibanez L, Perez E, Vidal X, Laporte JR. Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol. 2002; 37: 592-600.
37. de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol. 2004; 58: 71-80.
38. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002; 36: 451-5.
39. Shapiro MA, Lewis JH. Causality assessment of drug-induced hepatotoxicity: promises and pitfalls. Clin Liver Dis 2007; 11: 477-505.
40. Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963-2004. CMAJ. 2005; 172: 765-7.
41. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, Schellekens H, Leufkens HG, Egberts AC. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA. 2008; 300: 1887-96.
42. Vuppalanchi R, Liangpunsakul S, Chalasani N. Etiology of newonset jaundice: how often is it caused by idiosyncratic druginduced liver injury in the United States? Am J Gastroenterol .2007; 102: 558-62.

43. Slavin DE, Schlichting CL, Freston JW. Rating the severity of the medical consequences of drug-induced liver injury. Regul Toxicol Pharmacol. 2005; 43: 134-40.
44. International Osteoporosis Foundation. Osteoporosis in Europe: Indicators of Progress Outcomes of panel meeting 2005 Nov 10, 2004: http: //www.iofbonehealth.org/osteoporosis-europe-inbdicatorsprogress- 2005 (Accessed December 11 2013).
45. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993; 137: 1001-5. Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc. 2002; 50: 1644-50.
46. Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc. 2002; 50: 1644-50.
47. European Medicines Agency. European Public Assessment Reports (EPAR): antiretroviral: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000797/WC500028102.pdf (Accessed December 11 2013).
48. European Medicines Agency. European Public Assessment Reports (EPAR): pioglitazone: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109185.pdf (Accessed December 11 2013).
49. European Medicines Agency. Summary of product charactersitics: rosiglitazone: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000268/WC00029108.pdf (Accessed December 11 2013).
50. Schroder HM, Petersen KK, Erlandsen M. Occurrence and incidence of the second hip fracture. Clin Orthop Relat Res. 1993; 289: 166-9.
51. Statistics Netherlands: http: //statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71859NED&D1=1,3,5,7-8&D2=12&D3=1&D4=189&D5=l&VW=T (Accessed December 11 2013).
52. European Commission EUROSTAT. Death due to suicide, by gender 2010 November 2012: http: //epp.eurostat.ec.europa/tgm/table.do?tab=table&init=1language=en&pcode=tps00122&plugin=1. (Accessed December 11 2013).
53. Health in Europe: Information and Data Interface: Cancer. http://webgate.ec.europa.eu/sanco/heidi/index.php/Heidi/Major_and_chronic_diseases Cancer#Adult_cancer_survival. (Accessed December 11 2013).
54. Statens Serum Institut. Register of Medicinal Product Statistics. http: //www.medstat.dk/en. (Accessed December 11 2013).
55. Norwegen Prescription Database.: http://www.norpd.no/prevalens. aspx. (Accessed December 11 2013).
56. GIPdatabank. The Drug Information System of the Health Care Insurance Board The Netherland: http://www.gipdatabank.nl. (Accessed December 11 2013).
57. Salpeter SR. Cardiovascular safety of beta(2)-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. Drugs Aging. 2004; 21: 405-14.
58. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006; 21: 1011-9.
59. Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009(3): CD006922.
60. Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2009(2): CD006924.
61. de Vries F, Pouwels S, Bracke M, et al. Use of beta2 agonists and risk of acute myocardial infarction in patients with hypertension. Br J Clin Pharmacol. 2008; 65: 580-6.

62. Zhang B, de Vries F, Setakis E, van Staa TP. The pattern of risk of myocardial infarction in patients taking asthma medication: a study with the General Practice Research Database. J Hypertens. 2009; 27: 1485-92.
63. Neil Kaplowitze LDD. Drug-induced Liver Disease. 1 ed. Informa Healthcare; 2003.
64. Sabate M, Ibanez L, Perez E, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther. 2007; 15: 25: 1401-9.
65. Ginzburg R, Rosero E. Risk of fractures with selective serotoninreuptake inhibitors or tricyclic antidepressants. Ann Pharmacother. 2009; 43: 98-103.
66. Allain H, Bentue-Ferrer D, Polard E, Akwa Y, Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. Drugs Aging. 2005; 22: 749-65.
67. MHRA Medicines and Healthcare products Regulatory Agency. Drug Safety Update Antidepressants: risk of fractures 2010. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON08 5136. (Accessed December 11 2013).
68. US Food and Drug Agency. Statistical Review and Evaluation: Antiepleptic Drugs and Suicidality: http: //www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationd for Patients and Providers/UCM192556.pdf. (Accessed December 11 2013).
69. Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology. 2010; 75: 335-40.
70. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicideralated events in patients treated with antiepileptic drugs. N Engl J Med. 2010; 363: 542-51.
71. Patorno E, Bohn RL, Wahl PM, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA. 2010; 303: 1401-9.
72. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. Lancet. 1996; 348: 493-7.
73. Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL. Use of calcium channel blockers and breast carcinoma risk in postmenopausal women. Cancer. 1997; 80: 1438-47.
74. Beiderbeck-Noll AB, Sturkenboom MC, van der Linden PD, et al. Verapamil is associated with an increased risk of cancer in the elderly: the Rotterdam study. Eur J Cancer. 2003; 39: 98-105.

2

Variability in medication use patterns and health outcomes in Europe

2.1

Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations and methodological implications.

Victoria Abbing-Karahagopian, Consuelo Huerta, Patrick C. Souverein, Francisco J. de Abajo, Hubert G. M. Leufkens, Jim Slattery, Yolanda Alvarez, Montserrat Miret, Miguel Gil, Belén Oliva, Ulrik Hesse, Gemma Requena, Frank de Vries, Marietta Rottenkolber, Sven Schmiedl, Robert F. Reynolds, Raymond G. Schlienger, Mark C. H. de Groot, Olaf H. Klungel, Tjeerd P. van Staa, Liset van Dijk, Toine C. G. Egberts, Helga Gardarsdottir, Marie L. De Bruin.

European Journal of Clinical Pharmacology. 2014; 70(7):849-57

ABSTRACT

Background

Drug utilization studies have applied different methods on various data types to describe medication use which hampers comparisons across populations. The aim of this study was to describe the time trends in antidepressant prescribing in the last decade and the variation in the prevalence, calculated in a uniform manner, in seven European electronic healthcare databases.

Methods

Annual prevalence per 10,000 person-years (PYs) was calculated for 2001-2009 in databases from Spain, Germany, Denmark, the United Kingdom (UK), and the Netherlands. Prevalence data were stratified according to age, sex, antidepressant type (selective serotonin re-uptake inhibitors [SSRIs] or tricyclic antidepressants [TCAs]) and major indications.

Results

The age- and sex-standardized prevalence was lowest in the two Dutch (391 and 429 users per 10,000 PYs) and highest in the two UK (913 and 936 users per 10,000 PYs) populations in 2008. The prevalence in the Danish, German and Spanish populations was 637, 618 and 644 users per 10,000 PY, respectively. Antidepressants were prescribed most often in 20-60 year-olds in the two UK populations compared to the others. SSRIs were prescribed more often than TCAs in all except in the German population. In the majority of countries we observed an increasing trend of antidepressant prescribing over time. Two different methods identifying recorded indications yielded different ranges proportions of patients recorded with the specific indication (15% - 57% and 39% - 69% for depression, respectively).

Conclusion

Despite applying uniform methods, variations in the prevalence of antidepressant prescribing were obvious in the different populations. Database characteristics and clinical factors may both explain these variations.

INTRODUCTION

The objectives of drug utilization research have broadened over the years to include economic and quality aspects of medication prescribing and use [1]. Drug utilization studies, published in the 1980s and 90s, are most often cross-sectional surveys or consist of aggregate country data on drug expenditure or sales volume. The increasing availability of electronic healthcare databases has provided the opportunity for more detailed, longitudinal assessments of drug consumption at patient level and across healthcare settings, regions and countries.

Antidepressants are one of the most widely used drug classes, prescribed for a wide range of indications [2] with a reported increasing trend in use [3-14]. Comparison of results of these studies is difficult due to differences in the methods applied, data sources used and population groups selected. Cross-country comparisons are few and are done mainly in populations with specific indications or ages [15-19]. The aim of this study was to describe the time trends and the variation in the prevalence of antidepressant prescribing across different European settings applying a uniform method for utilization assessment.

METHODS

Study setting and population

For this study, information was obtained from seven European electronic healthcare databases: The Spanish BIFAP Project: Database for Pharmacoepidemiological Research in Primary Care - Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (www.bifap.org); the German database of the National Association of Statutory Health Insurance Physicians of Bavaria - Kassenärztliche Vereinigung Bayerns (www.kvb.de); the Danish Register of Medicinal Products Statistics, National Institute for Health Data and Disease Control referred as Danish national registry in our study (www.ssi.dk); two databases from the United Kingdom: the Clinical Practice Research Datalink (www.cprd.com) and The Health Improvement Network (www.thin-uk.com); and finally, two databases from the Dutch Mondriaan project (www.projectmondriaan.nl): Netherlands Primary Care Research Database (Mondriaan-NPCRD) (http://nivel.nl) and Almere Health Care group (Mondriaan-AHC).

Most of the databases provide primary care prescribing data. Dispensing data is present in the Danish national registry, the German Bavarian claims and the Mondriaan –AHC (for the latter in addition to prescribing data). Some of the databases include/provide links to secondary care data and registries. Characteristics of these databases have been described in details elsewhere [20].

Data were obtained for the period between 1 January 2001 and 31 December 2009. The Bavarian claims database was able to provide valid patient information only from 2004 to 2008, while Mondriaan-AHC provided data from 2001 to 2008. Each patient in the databases was considered from the start of the study period or patient's enrolment into a practice/database, or the moment the practice became up to research standard (where applicable) whichever was the latest. Patients were considered in the study population until they left the practice/database or until the end of the study period whichever came first.

Antidepressant prescribing and data analysis

Antidepressant prescribing was defined as patients having a prescription (dispensed in case of Danish national registry and claimed in case of Bavarian claims database) for a selective serotonin re-uptake inhibitor (SSRI) and/or a tricyclic antidepressant (TCA). Annual period prevalence of antidepressant prescribing was calculated by dividing the number of patients having at least one prescription for an antidepressant in a calendar year by the total number of person-years (PYs) of follow-up in that calendar year in a database during the study period. Because of the dynamic nature of the source population, the denominator was expressed as PYs of follow-up in the given calendar year rather than as persons. Prevalence and 95% confidence intervals (95% CI) of overall antidepressants, as well as, of SSRIs or TCAs were calculated separately. Prevalence was further stratified by age (10-year bands) and sex. Direct standardization of the overall prevalence to age and sex was performed using the distribution of the Eurostat (http://appsso.eurostat.ec.europa.eu) population in 2008 with 27 countries.

Data for the year 2008 (latest calendar year available in all databases) were stratified according to the number of prescriptions 1, 2-4, 5-9 and ≥10 prescriptions) and recorded indications (on the first prescription) classified into four groups: depression (with or without anxiety/sleep disorders); anxiety disorders (without depression, with or without sleep disorder); and sleeping disorders (without anxiety and depression). Different coding systems were used in the databases (ICPC for BIFAP and Mondriaan-NCPRD and AHC; ICD-9 in Bavarian claims and Danish registries and Read codes in CPRD and THIN) (protocol published at (www.encepp.eu). In case of missing information a search was performed within three months before and after the first prescription. An additional analysis was performed by looking for indications recorded any time before (until January 1st 2001) the first prescription.

RESULTS

The age- and sex-standardized prevalence of antidepressant prescribing showed a slightly increasing trend between 2001 and 2009 (Figure 1). The prevalence varied between 359 (Mondriaan-AHC) and 836 (CPRD) patients per 10,000 PYs in 2001 and between 389 (Mondriaan-AHC) and 930 (THIN) patients per 10,000 PYs in 2008. In both UK databases the overall antidepressant use was higher compared to the other databases. The two Dutch Mondriaan databases had lower prevalence in 2008 (376 and 382 patients per 10,000 PYs for Mondriaan-NPCRD and Mondriaan-AHC, respectively); compared to the others (Table 1). The two UK databases showed the highest prevalence (917 and 913 users per 10,000 PYs for THIN and CPRD, respectively) in 2008 among all (Table 1).

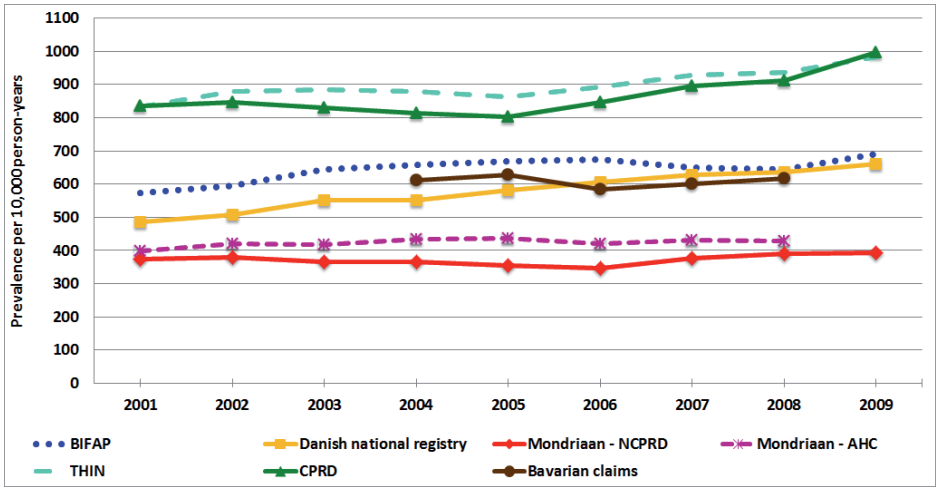


Figure 1: Age- and sex-standardized 1-year period prevalence of antidepressant use by calendar year in seven European databases from 2001–2009

Stratification by sex and age for the year 2008 (Figure 2) showed higher (almost two times) antidepressant prescribing among females than males in all populations. In general, there was an increase in prevalence with increasing age. The Danish national registry showed a marked increase, almost doubling, in prevalence in age groups from 60-69 years to 80^{+} years both in males and females (from 615 to 1403 and from 1013 to 2094 per 10,000 PYs in males and females, respectively). Both UK databases showed higher antidepressant prescribing among age groups from 20 throughout 60 years (more pronounced among females than males) compared to the same age groups in the other databases.

Table 1: Antidepressant use in 2008 in seven European healthcare databases

Database/source	BIFAP	Bavarian claims	Danish national registry	CPRD	THIN	Mondriaan-NPCRD	Mondriaan-AHC
			Antidepressants				
Patients (n)	94,234	594,745	321,811	397,034	340,798	12,412	5,449
Person-years in 2008	1,424,572	8,558,315	5,222,891	4,348,431	3,860,850	330,477	142,819
Crude prevalence /10,000 PY	662	695	616	913	883	376	382
(± 95% CI)	(657-666)	(693-697)	(614-618)	(910-916)	(880-886)	(369-382)	(372-391)
Standardised# prevalence /10,000 PY	644	618	637	913	936	429	391
			Selective serotonin reuptake inhibitors				
Patients *(n)	81,020	283,355	280,184	284,922	232,678	8,671	4,101
Prescriptions (n)	512,408	661,607	1,417,063	1,805,959	1,434,894	41,911	26,051
Crude prevalence /10,000 PY	569	331	536	655	603	262	287
(± 95% CI)	(565-573)	(330-332)	(535-538)	(653-658)	(600-605)	(257-268)	(278-296)
Standardised# prevalence /10,000 PY	553	302	556	657	639	271	311
Prescriptions/user (average)	6.3	2.3	5.1	6.3	6.2	4.8	6.4
Users with one prescription (%)	18	37	27	18	22	15	13
			Tricyclic antidepressants				
Patients * (n)	16,566	372,656	50,803	133,965	128,696	3,979	1,488
Prescriptions (n)	114,664	843,303	259,209	738,003	734,231	16,381	7,942
Crude prevalence per 10,000 PY	116	435	97	308	333	120	104
(± 95% CI)	(115-118)	(434-437)	(96-98)	(306-310)	(332-335)	(117-124)	(99-109)
Standardised# prevalence /10,000 PY	115	382	99	306	354	128	128
Prescriptions/user (average)	6.9	2.3	5.1	5.5	5.7	4.1	5.3
Users with one prescription (%)	27	45	16	33	34	28	25

PY=person-years

* = Patients having one or more prescriptions of SSRI/TCA

= Standardisation according to Eurostat population of 2008

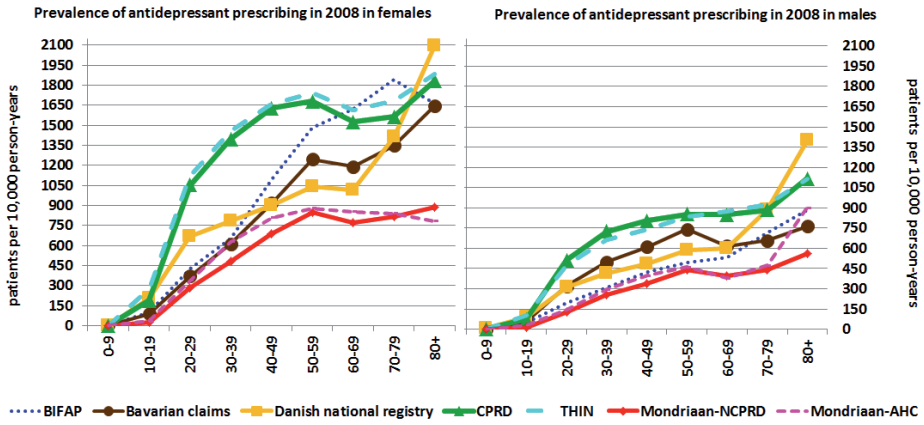


Figure 2: Period prevalence of antidepressant use in 2008 by sex and age in seven European databases

The prevalence of SSRI prescribing showed a slightly increasing trend between 2001 and 2009 in all except in both Dutch databases where it remained stable (Figure 3). The two Dutch and the Bavarian claims databases showed lower prescribing of SSRIs compared to the other databases. Prevalence of TCA prescribing was stable throughout the study period in all databases but was lower than that of SSRI except in the Bavarian claims database (where TCA prescribing was two times higher than SSRI) (Figure 3). The Bavarian claims database showed an increasing SSRI and a decreasing TCA trend (237 to 310 and 450 to 391 per 10,000 PYs for SSRI and TCA from 2004 to 2008, respectively). Both UK databases showed higher TCA prescribing in general compared to TCA prescribing in other databases except for the Bavarian claims.

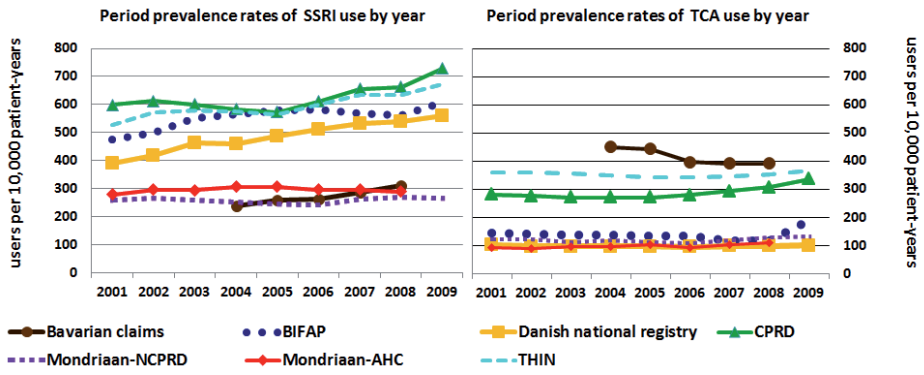


Figure 3: Age and sex standardized prevalence of SSRI and TCA use in seven European healthcare databases from 2001-2009

The average number of prescriptions per patient (Table 1) in 2008 varied between 2.3 and 6.4 in SSRI users and between 2.3 and 6.9 in TCA users with lowest number of prescriptions per patient in the Bavarian claims database. There were fewer patients having only one SSRI prescription compared to those having only one TCA prescription in 2008 in all databases except in the Danish national registry.

Depression was the most frequently recorded indication in all databases amounting up to 57% of the patients as shown in Figure 4. In CPRD, Mondriaan-AHC and THIN databases depression was recorded for only 23%, 15%, and 12% of patients, respectively. In our additional analysis, higher proportions of patients with depression as the registered indication were obtained ranging from 39% to 69% of patients.

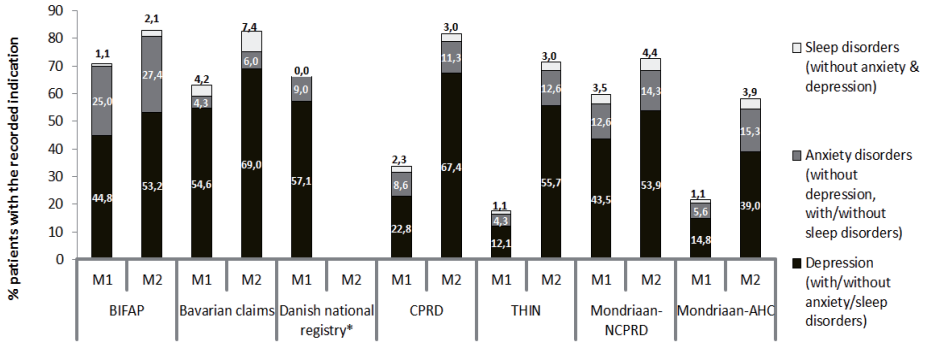


Figure 4 Distribution of major indications recorded for antidepressant use in seven different European healthcare databases in 2008

M1 = Indication assessed in the period 3 months before/after the first antidepressant prescription in 2008

M2 = Indication assessed in the period from the first antidepressant prescription in 2008 going backwards until 1 January 2001 (1 January 2004 in the Bavarian claims)

* Assessment of M2 method in the Danish national registry was not possible

DISCUSSION

This study provides a recent and a distinctive overview of antidepressant prescribing in seven different databases from five European countries assessed according to uniform methods. In the majority of the countries we observed an increasing trend of antidepressant prescribing over time. There were especially between-country variations in the prevalence even after standardization for age and sex. Having applied a uniform method to calculate the prevalence, variations in the results may be evaluated and explained in light of differences in the database characteristics and/or clinical aspects related to antidepressant use.

Comparability of major findings

Due to differences in the reported medication class, selected population, utilization measure and data type in previous studies [10, 16-19, 21-27] no direct comparison can be done with our results. As such, a 40% increase in antidepressant consumption measured in defined daily doses (DDDs) per 1,000 inhabitants from 2000 to 2004 reported in a Spanish study [28) may reflect changes in duration or dose of treatment rather than an increase in prevalence of use. The increase in prevalence in the Spanish BIFAP database between 2001 and 2004 was only 14% in our study.

Our results show that the highest prevalence of antidepressant prescribing was in the UK and the lowest in the Netherlands, with Spain, Denmark and Germany in between. The standardized (for age and sex) prevalence numbers were not essentially different from the non-standardized ones. Characterization of the denominator of the prevalence ratio in databases with dynamic populations and different protocols for recording patient information can be challenging. An example of such a challenge was present in the German Bavarian claims database, where claims are recorded only on a quarterly basis. In the absence of exact dates of prescriptions and number of patient-time contributed per patient per year, the denominator of the prevalence ratio could not be optimally defined. Consequently, in calculating PYs of follow-up in the denominator, 1 year of follow-up was assumed for each patient in this database for a given year instead of the exact amount of time contributed by each patient. This tends to inflate the denominator and underestimate the prevalence. Therefore, such database differences can influence utilization measures even though application of uniform definitions is attempted. To test the stability of the denominator in the calculated prevalence, we also computed the prevalence with the denominator as the population number at June 1 of every calendar year in all the databases (data not shown). Results based on this definition of the prevalence ratio were not essentially different from those presented in our study.

Sex and age stratification

A distinctive feature in our results was the higher prevalence of prescribing in women compared to men. Moreover, there was a steady increase in the prevalence with increasing age. The characteristic increase in the prevalence in patients 70^{+} years in Denmark has also been reported elsewhere [3, 29, 30]. Older patients in Denmark seem to have a higher antidepressant use compared to other European countries possibly indicating a real feature which needs further investigation as noted previously [30].

An increasing use of antidepressants among adolescents and children under the age of 18 years was reported in two studies in CPRD [31, 32] for the period 1992-2001. In our study we observed a relatively stable trend in the prevalence (94 and 81 users per 10,000 PYs

in 2001 and 2009, respectively). A more recent study [33] in THIN (study period 2002 - 2009) reported a significant drop in SSRI use in 2005; around the time of the advice of the Committee on Safety of Medicines (CSM) on antidepressant prescribing to children and adolescents. We also confirmed this drop in SSRI prescribing in our study (92, 75 and 86 users per 10,000 PYs) in 2001, 2005 and 2009, respectively.
A distinctive feature in our results for the UK databases, which is not reported before, was the remarkable difference (higher) in antidepressant prescribing in the age groups 20 throughout 60 years (especially in females) compared to the same age groups in the other databases. This finding calls for more in-depth investigation of indications of use in this large adult age group in the UK.

SSRI versus TCA use

The slight increasing trend in SSRI prescribing during the period from 2001 to 2009 reported in our study adds to the knowledge of the widespread use of SSRIs in contrast to the decreasing use of TCAs [34, 35]. The use of SSRIs outbalancing that of TCAs has been reported in previous studies [3, 16, 29, 36] and is in line with our findings. The higher use of TCAs compared to SSRIs in Germany found in our study, has also been reported in other studies [37, 38]. In a recent study [39], using German statutory claims data for the year 2009, Hoffman et al. have reported that among children and adolescents [12 to 18 years) with a diagnosis of depression the use of SSRIs was higher than TCA use (55.6% vs. 17.9%). In our study, we observed a gradual increase (from 30.8 to 42.6 per 10,000 users) and a decrease (from 38.8 to 33.5 per 10,000 users) in the prevalence of SSRI and TCA from 2004 to 2008, respectively, in the age group 10-19 years in the Bavarian claims database. Our results suggest an appearance of an increasing trend in SSRI and a decreasing trend in TCA use in Germany, similar to that in other European countries. However, this trend does not confirm the large differences between SSRI and TCA use in the same age groups, defined without restrictions according to indication (depression) as reported by Hoffman et al [39]. Moreover, inclusion of data from specialists, which is the case in the Bavarian claims database, might introduce differences in the prevalence. As shown in a French study [40], TCAs (e.g. amitriptyline or clomipramin) were more frequently prescribed by specialists compared to general practitioners. Further analyses are needed to disentangle differences in the prevalence due to prescriber differences, especially owing to somewhat conflicting results reported by a recent Norwegian study on more frequent prescribing of SSRI as initiation therapy by specialists [41].

Number of prescriptions

The proportion of users with only one prescription in a year is an indicator of a patient subgroup in whom treatment is not sustained. This is true unless this single prescription is issued at the end of the calendar year and the patient continues his treatment in the

following year. Information on the treatment duration is important for proper comparison of drug use. The definition of a user as a patient having at least one prescription in a year contributes to the measure of the prevalence while this group is not a regular user. Proportions of patients with one prescription reported in our study for Denmark (27% and 16% for SSRI and TCA users in 2008, respectively) differ from those reported in another study [30] (22% and 33% for SSRI and TCA users in 1995, respectively). This might indicate possible changes in the length of treatment (switching or discontinuation) and not necessarily changes in the prevalence of use.
Similar high proportions of patients with a single prescription, especially of TCA, (in addition to lowest number of prescriptions in general) in Germany are reported in another study using a different claims database [38]. Prescribing large packages of antidepressants in Germany (usually for 90 days) and the high percentage of patients stopping or switching their treatment after a single prescription may explain our results. Such differences in prescribing policies should be taken into account when performing country comparisons.

Indications

The main clinical indication for antidepressant treatment is depression and has been reported to be the most frequent reported indication for antidepressant use [2, 36]. Our sensitivity analyses (see Figure 4) yielded larger proportions (two to fourfold) of patients with recorded indications demonstrating the importance of extensive search criteria. We could not associate the increase in the identified indications with the type of database in our study. Many conditions such as sleeping and anxiety disorders are also known to be co-morbid with depression [42, 43] hence cross-sectional selection of subgroups based on the indication recorded on one prescription may not compose subgroups optimally [44]. The variation in the recording of indications in our study points out that, selection of a population group based on indications may not produce comparable groups in terms of drug use and therefore hinder direct comparison of utilization patterns.

To our knowledge, this is the first study comparing the prevalence of antidepressant prescribing calculated in a uniform manner across different European databases, covering a broad age range, both sexes, major antidepressant groups and without selection criteria on certain indications. Moreover, the databases are population-based reflecting patient specific information in contrast to aggregate sales data calculated per inhabitants of a specific region. Due to application of common methods for calculating such simple measures, our results reflect actual features of utilization or changes in treatment course or intensity of prescribing rather than differences in the methods of calculating the prevalence.

A limitation of our study is the inability to reach complete harmonization definitions which was due to differences in database designs and heterogeneity of level of information. Also,

no comparisons based on prescribed doses and indications could be performed. Inherent differences in the coding systems used in the databases may have also created differences in capturing indications. Furthermore no prescriber characteristics analyses were performed. Having mainly prescribing data, we could not distinguish patients not collecting their prescriptions. This has been shown to amount to 4% in the Dutch databases [45]. Besides that, some of the differences between countries we observed may be influenced by the availability of individual drugs per country and national prescribing guidelines. A separate study on these specific topics would be informative.

Conclusion

In conclusion, our study illustrates that harmonizing methods to describe the prevalence of antidepressant prescribing in electronic healthcare databases may contribute to direct cross-country comparisons. Prescribing differences, after the application of harmonized method, may primarily reflect differences in clinical guidelines among the countries. Direct comparison of results of drug utilization studies may provide a better insight in prescribing practices and hence contribute to better drug safety systems and assessment of future research needs.

REFERENCES

1. Strom B. Pharmacoepidemiology. Fourth ed. England: John Wiley; 2005.
2. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. J Affect Disord. 2007;98(1-2):109-15.
3. Rosholm JU, Andersen M, Gram LF. Are there differences in the use of selective serotonin reuptake inhibitors and tricyclic antidepressants? A prescription database study. Eur J Clin Pharmacol. 2001;56(12):923-9.
4. Development of Drug Utilization Indicators: A feasibility Study Using Existing Aggregated Administrative Databases 2002 [cited December 2012]; Available from: http://www.cihi.ca/CIHI-ext-portal/pdf/internet/PDF_INDI_DRUG_FINAL_REPORT_EN.
5. Exeter D, Robinson E, Wheeler A. Antidepressant dispensing trends in New Zealand between 2004 and 2007. Aust N Z J Psychiatry. 2009;43(12):1131-40.
6. Aguglia E, Ravasio R, Simonetti M, Pecchioli S, Mazzoleni F. Use and treatment modalities for SSRI and SNRI antidepressants in Italy during the period 2003-2009. Curr Med Res Opin. 2012;28(9):1475-84.
7. Smith AJ, Tett SE. How do different age groups use benzodiazepines and antidepressants? Analysis of an Australian administrative database, 2003-6. Drugs Aging. 2009;26(2):113-22.
8. Patten SB, Wang JL, Williams JV, Lavorato DH, Beck CA, Bulloch AG. Frequency of antidepressant use in relation to recent and past major depressive episodes. Can J Psychiatry. 2010;55(8):532-5.
9. Sundell KA, Gissler M, Petzold M, Waern M. Antidepressant utilization patterns and mortality in Swedish men and women aged 20-34 years. Eur J Clin Pharmacol. 2011;67(2):169-78.
10. Volkers AC, Heerdink ER, van Dijk L. Antidepressant use and off-label prescribing in children and adolescents in Dutch general practice (2001-2005). Pharmacoepidemiol Drug Saf. 2007;16(9):1054-62.
11. Athanasopoulos C, Pitychoutis PM, Messari I, Lionis C, Papadopoulou-Daifoti Z. Is Drug Utilization in Greece Sex dependent? A Population-based Study. Basic Clin Pharmacol Toxicol. 2012;112(1):55-62.
12. Parabiaghi A, Franchi C, Tettamanti M, Barbato A, D'Avanzo B, Fortino I, et al. Antidepressants utilization among elderly in Lombardy from 2000 to 2007: dispensing trends and appropriateness. Eur J Clin Pharmacol. 2011;67(10):1077-83.
13. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. Bmj. 2009;339:b3999.
14. Alonso MP, de Abajo FJ, Martinez JJ, Montero D, Martin-Serrano G, Madurga M. [Evolution of antidepressive drug consumption in Spain. The impact of selective serotonin re-uptake inhibitors]. Med Clin (Barc). 1997;108(5):161-6.
15. Lidell E, Luepker R, Baigi A, Lagiou A, Hildingh C. Medication usage among young adult women: a comparison between Sweden, the USA, and Greece. Nurs Health Sci. 2008;10(1):4-10.
16. Bauer M, Monz BU, Montejo AL, Quail D, Dantchev N, Demyttenaere K, et al. Prescribing patterns of antidepressants in Europe: results from the Factors Influencing Depression Endpoints Research (FINDER) study. Eur Psychiatry. 2008;23(1):66-73.
17. Zito JM, Tobi H, de Jong-van den Berg LT, Fegert JM, Safer DJ, Janhsen K, et al. Antidepressant prevalence for youths: a multi-national comparison. Pharmacoepidemiol Drug Saf. 2006;15(11):793-8.
18. Bowers L, Callaghan P, Clark N, Evers C. Comparisons of psychotropic drug prescribing patterns in acute psychiatric wards across Europe. Eur J Clin Pharmacol. 2004;60(1):29-35.

19. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004;(420):55-64.
20. Abbing-Karahagopian V., Kurz X., de Vries F., van Staa T.P., Alvarez Y., Hesse U., et al. Bridging differences in findings from observational pharmacoepidemiological studies: PROTECT project. Curr Clin Pharmacol. 2014;9(2):130-8.
21. Ohayon MM, Caulet M, Priest RG, Guilleminault C. Psychotropic medication consumption patterns in the UK general population. J Clin Epidemiol. 1998;51(3):273-83.
22. Pagura J, Katz LY, Mojtabai R, Druss BG, Cox B, Sareen J. Antidepressant use in the absence of common mental disorders in the general population. J Clin Psychiatry. 2011;72(4):494-501.
23. Paulose-Ram R, Safran MA, Jonas BS, Gu Q, Orwig D. Trends in psychotropic medication use among U.S. adults. Pharmacoepidemiol Drug Saf. 2007;16(5):560-70.
24. Raymond CB, Morgan SG, Caetano PA. Antidepressant utilization in British Columbia from 1996 to 2004: increasing prevalence but not incidence. Psychiatr Serv. 2007;58(1):79-84.
25. Sanyal C, Asbridge M, Kisely S, Sketris I, Andreou P. The utilization of antidepressants and benzodiazepines among people with major depression in Canada. Can J Psychiatry. 2011;56(11):667-76.
26. Sihvo S, Isometsa E, Kiviruusu O, Hamalainen J, Suvisaari J, Perala J, et al. Antidepressant utilisation patterns and determinants of short-term and non-psychiatric use in the Finnish general adult population. J Affect Disord. 2008;110(1-2):94-105.
27. Wittkampf LC, Smeets HM, Knol MJ, Geerlings MI, Braam AW, De Wit NJ. Differences in psychotropic drug prescriptions among ethnic groups in the Netherlands. Soc Psychiatry Psychiatr Epidemiol. 2010;45(8):819-26.
28. Ubeda A, Cardo E, Selles N, Broseta R, Trillo JL, Fernandez-Llimos F. Antidepressant utilization in primary care in a Spanish region: impact of generic and reference-based pricing policy (2000-2004). Soc Psychiatry Psychiatr Epidemiol. 2007;42(3):181-8.
29. Hansen DG, Sondergaard J, Vach W, Gram LF, Rosholm JU, Kragstrup J. Antidepressant drug use in general practice: inter-practice variation and association with practice characteristics. Eur J Clin Pharmacol. 2003;59(2):143-9.
30. Hansen DG, Rosholm JU, Gichangi A, Vach W. Increased use of antidepressants at the end of life: population-based study among people aged 65 years and above. Age Ageing. 2007;36(4):449-54.
31. Hsia Y, Maclennan K. Rise in psychotropic drug prescribing in children and adolescents during 1992-2001: a population-based study in the UK. Eur J Epidemiol. 2009;24(4):211-6.
32. Murray ML, de Vries CS, Wong IC. A drug utilisation study of antidepressants in children and adolescents using the General Practice Research Database. Arch Dis Child. 2004;89(12):1098-102.
33. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One. 2012;7(3):e33181.
34. Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. Br J Psychiatry. 2006;188:354-8.
35. Bramness JG, Walby FA, Tverdal A. The sales of antidepressants and suicide rates in Norway and its counties 1980-2004. J Affect Disord. 2007;102(1-3):1-9.
36. Trifiro G, Barbui C, Spina E, Moretti S, Tari M, Alacqua M, et al. Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004. Pharmacoepidemiol Drug Saf. 2007;16(5):552-9.
37. Fegert JM, Kolch M, Zito JM, Glaeske G, Janhsen K. Antidepressant use in children

and adolescents in Germany. J Child Adolesc Psychopharmacol. 2006;16(1-2):197-206.
38. Ufer M, Meyer SA, Junge O, Selke G, Volz HP, Hedderich J, et al. Patterns and prevalence of antidepressant drug use in the German state of Baden-Wuerttemberg: a prescription-based analysis. Pharmacoepidemiol Drug Saf. 2007;16(10):1153-60.
39. Hoffmann F, Glaeske G, Petermann F, Bachmann CJ. Outpatient treatment in German adolescents with depression: an analysis of nationwide health insurance data. Pharmacoepidemiol Drug Saf. 2012;21(9):972-9.
40. Lapeyre-Mestre M, Desboeuf K, Aptel I, Chale JJ, Montastruc JL. A comparative survey of antidepressant drug prescribing habits of general practitioners and psychiatrists. Clin Drug Investig. 1998;16(1):53-61.
41. Kjosavik SR, Hunskaar S, Aarsland D, Ruths S. Initial prescription of antipsychotics and antidepressants in general practice and specialist care in Norway. Acta Psychiatr Scand. 2011;123(6):459-65.
42. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Goldberg D, Magruder KM, et al. Consensus statement on the primary care management of depression from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1999;60 Suppl 7:54-61.
43. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: A prospective perspective. Am J Psychiatry. 2000;157(1):81-8.
44. Gardarsdottir H, Egberts AC, van Dijk L, Sturkenboom MC, Heerdink ER. An algorithm to identify antidepressant users with a diagnosis of depression from prescription data. Pharmacoepidemiol Drug Saf. 2009;18(1):7-15.
45. van Geffen EC, Gardarsdottir H, van Hulten R, van Dijk L, Egberts AC, Heerdink ER. Initiation of antidepressant therapy: do patients follow the GP's prescription? Br J Gen Pract. 2009;59(559):81-7.

2.2

Exposure to benzodiazepines and related drugs in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project

Consuelo Huerta, Victoria Abbing-Karahagopian, Gema Requena, Belén Oliva, Yolanda Alvarez, Helga Gardarsdottir, Montserrat Miret, Cornelia Schneider, Miguel Gil, Patrick C. Souverein, Marie L. De Bruin, Jim Slattery, Mark C. H. De Groot, Ulrik Hesse, Marietta Rottenkolber, Sven Schmiedl, Dolores Montero, Andrew Bate, Ana Ruigomez, Luis A. García-Rodríguez, Saga Johansson, Frank de Vries, Raymond G. Schlienger, Robert F. Reynolds, Olaf H. Klungel and Francisco J. de Abajo.

Pharmacoepidemiology and Drug Safety. 2015; Jul 7. doi: 10.1002/pds.3825. [Epub ahead of print]

ABSTRACT

Background

Studies on drug utilization usually do not allow for direct cross-national comparison as they applied different methods. This study aimed to compare time trends in benzodiazepine (BZD) prescribing applying a common protocol to all analyses performed in seven European electronic healthcare databases.

Methods

Crude and standardized prevalence rates of drug prescribing from 2001-2009 were calculated in databases from Spain, United Kingdon (UK), The Netherlands, Germany and Denmark. Prevalence was stratified by age, sex, BZD type [(using ATC codes), i.e. BZD-anxiolytics BZD-hypnotics, BZD-related drugs and clomethiazole], indication and number of prescription.

Results

Crude prevalence rates of BZDs prescribing ranged from 570 to 1700 per 10,000 person-years over the study period. Standardization by age and sex did not substantially change the differences. Standardized prevalence rates increased in the Spanish (+13%) and UK databases (+2% and +8%) over the study period, while they decreased in the Dutch databases (-4% and -22%), and in the German (-12%) and Denmark databases (-26%). Prevalence of anxiolytics outweighed that of hypnotics in the Spanish, Dutch and Bavarian databases, but the reverse was shown in the UK and Danish databases. Prevalence rates consistently increased with age and were two-fold higher in women than in men in all databases. A median of 18% of users received 10 or more prescriptions in 2008.

Conclusion

Although similar methods were applied, the prevalence of BZD prescribing varied considerably across different populations. Clinical factors related to BZDs and characteristics of the databases may explain these differences.

INTRODUCTION

BZDs are one of the most widely used drug classes. Their pharmacological properties confer a broad range therapeutic applicability in anxiety, insomnia, panic attacks, epilepsy, muscle spasms and pre-surgical stress [1]. Their use has been a matter of concern among public health regulators in different countries due to the associated risks with long-term exposure [2-4]. Although many drug utilization studies have been published over the last twenty years, that focused on prescribing and use of BZDs in different countries or regions, comparisons are difficult because of differences in methodology. Moreover, only a few studies were designed for direct cross-national comparison [5-9].

Within this context, this study aimed to describe the patterns of BZD prescriptions in different European databases using a common methodology and definitions. We also included in the study the use of hypnotics separately as BZD-related hypnotics (Z-drugs) that have been proposed to replace BZDs for their allegedly better safety profile [10].

The present study is part of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) (http://www.imi-protect.eu/), a European consortium in the field of pharmacoepidemiology and pharmacovigilance, with the general aim of developing a standardized way to conduct pharmacoepidemiological studies that enable comparisons across countries and databases.

PATIENTS AND METHODS

Setting and data collection

Seven databases representing five European countries, participated in this descriptive study: The Spanish "Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria" (BIFAP) [11], the Clinical Practice Research Datalink (CPRD); formerly known as General Practice Research database (GPRD) [12] and the Health Improvement Network (THIN) from the United Kingdom (UK) [13]; two databases participating in the Dutch Mondriaan project: the Netherlands Primary Care Research database (Mondriaan-NPCRD) which is maintained by NIVEL, and the Almere Health Care Group (Mondriaan-AHC) database [14], the Bavarian Association of Statutory Health Insurance Physicians claims database (Bavarian) [15] and, finally, the Danish national registries (DKMA) [16]. All databases participating have been described in detail elsewhere [17]. The study was based on a common protocol and data specifications applied to all analyses in the individual databases.

Source population

The study population consisted of all patients in the corresponding data sources during the period from 1 January, 2001 until 31 December, 2009. For Mondriaan-AHC data for the year 2009 were not available, and for the Bavarian database the study period was shorter (2004-2008). For each database, all patients with valid data within the study period were included. Each patient was followed up from the start of the study period or enrolment of the patient or practice into the database or the practice became up to research standard (whichever occurred last) until the patient left the practice/database or the practice did not contribute further information to the database or the end of the study period (whichever occurred first).

Drugs

The Anatomical Therapeutic Chemical (ATC) Classification System [18] was used for the classification of drugs of interest, i.e.: N05BA (anxiolytics – benzodiazepine derivatives), and hypnotics under N05CD (hypnotics and sedatives – benzodiazepine derivatives) and N05CF (hypnotics and sedatives – benzodiazepine-related drugs or Z-drugs). Although clomethiazole (N05CM02) was not prescribed in the Bavarian and Dutch databases during the study period, this drug was also included due to its use as a hypnotic is non negligible in Spain. BZDs primarily used for other indications (e.g. tetrazepam as muscle relaxant, clonazepam in epilepsy) were not included in our study. Although the available drugs differ among countries, the main drugs are essentially the same (Supplementary Table S1 available at http://doi/10.1002/pds.3825/suppinfo). In the BIFAP, THIN, CPRD, Mondriaan-NPCRD and Bavarian databases the prescription of the drug of interest was the indicator of exposure, while in DKMA the indicator was the dispensing of the drug. In the Mondriaan-AHC database, both prescription and dispensing data were available.

Analysis

In each database the annual period prevalence of BZD prescribing was estimated by dividing the number of patients who received one or more prescription (or dispensing in the case of DKMA or prescription/dispensing in the case of the Mondrian-AHC database) by the total number of person-years of follow-up in every calendar year of the study period (2001-2009). Due to the dynamic nature of the databases, where patients can come in and out and have variable durations of follow-up time, person-years were considered as the most appropriate denominator. In the Bavarian database, only the quarter of the year in which the prescription was written was available, so for this database we used the number of patients at mid-year as the denominator. In calculating annual prevalence for 2008, the number of patients at 1st of June included in different databases was also provided.

In order to adjust for differences in age and sex distribution between databases, we standardized the prevalence rates using the Eurostat 2008 population [19]. Prevalence rate ratios (PRR) were calculated for both crude and standardized rates in order to compare prevalence rates between databases; the median of all prevalence rates in the different databases was used as reference. Specific crude prevalence rates were also provided by separate therapeutic groups (anxiolytics (N05BA) and hypnotics (N05CD, N05CF and N05CM02), age groups (in ten-year categories), and sex. The total number of prescriptions was obtained for the year 2008. Mean prescription per patient was calculated by type of BZD. We also calculated the percentage of prescribing in four categories of number of prescriptions (1, 2-4, 5-9, 10+) among those with at least a prescription.

Finally, the registered indication for prescribing was explored in all databases for 2008. Patients receiving one of the drugs of interest were classified in one of the following mutually exclusive categories: anxiety disorders (alone or with other indication – excluding depression), sleep disorders (alone or with any indication – excluding anxiety and/or depression), depressive disorders (with either or both anxiety and sleep disorders), depressive disorders (alone or with any indication under "other"), other (miscellaneous category including muscular relaxation, alcohol withdrawal or epilepsy) and unknown (codes other than those mentioned above). DKMA reported only one category for depression regardless whether patients additionally had anxiety or sleep disorders. Potential indication was first identified by checking for indication on the prescription date, followed by looking for the indication within a defined time window of three months before and after the date of the prescription. When the link was not available in the data source, only the search in the time window was done. A sensitivity analysis was also performed extending the time window to any time during the study period prior to the prescription date (Supplementary Figure 2.2A).
The study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) registry of studies [20].

RESULTS

Prevalence rates

In 2008 (the last calendar year available in all databases), the seven databases participating in the study provided information from 1.7 million of patients being prescribed BZD, from a total population of more than 24 million persons-years (Table 1).
The overall prevalence rate of BZDs prescriptions varied considerably across databases, with the highest rate in BIFAP database (around 1,600 per 10,000 person-years) and the lowest in the Bavarian and UK databases (around 570 per 10,000 person-years). The standardization by sex and age did not substantially change the observed differences (Table 1).

Table 1. Crude and standardized prevalence rates and prevalence rate ratios of BZDs use in 2008 in the seven participating databases

DBs	BZD prescribing	Persons at 1st June in databases	Person-years in databases	Prevalence rate (per 10,000 p-y)	PRR*	Age and sex standardized prevalence rate (per 10,000 p-y)	Age and sex-standardized PRR*
BIFAP	231,729	1,441,011	1,424,572	1626.7	2.1	1598.1	1.9
CPRD	258,353	4,771,361	4,348,431	594.1	0.8	590.8	0.7
THIN	213,820	3,704,927	3,713,072	575.9	0.7	586.6	0.7
Mondriaan-AHC	13,941	140,818	142,819	976.1	1.2	1186.8	1.4
Mondriaan-NPCRD	25,912	346,332	330,477	784.1	1.0	835.9	1.0
Bavarian†	485,058	8,558,315	8,558,315	566.8	0.7	477.2	0.6
DKMA	437,881	5,242,538	5,222,891	838.4	1.1	853.3	1.0

BZD: benzodiazepine anxiolytics and hypnotics and related drugs; PRR: Prevalence rate ratio

* Reference category to calculate PRR was the median value of all prevalence rates in the databases for 2008.

† Person-years not available, denominator were patients at 1 July; person-years were calculated assuming a complete follow-up

Trends in prevalence rates, crude as well as age- and sex-standardized, are presented in Figure 1. When comparing last to first year available, crude rates showed an increase in BIFAP (+11%), CPRD (+6%) and THIN (+8%); while a decrease was observed in AHC (-2%), NPCRD (-14%), Bavarian (-9%), and DKMA (-23%). When rates were standardized by age and sex, trends showed an increase in BIFAP (+13%), CPRD (+2%) and THIN (+8%) while a decreasing trend was observed in AHC (-4%), NPCRD (-22%), Bavarian (-12%), and DKMA (-26%).

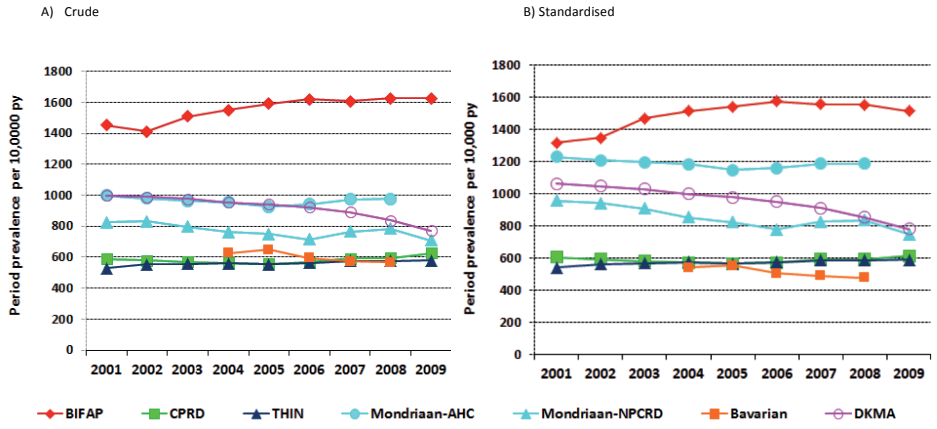


Figure 1. Period prevalence rates of BZDs use by year in the participating databases A) crude rates and B) standardized rates by age and sex

Throughout the study period, the prevalence of prescriptions of BZDs classified as anxiolytics was 4-times higher than that of hypnotics (including BZDs, Z-drugs, and clomethiazole when available) in BIFAP (i.e. 1439.3 *vs.* 363.2 per 10,000 person-years for 2008), 1.3-times higher in the Bavarian database (i.e. 347.8 *vs.* 266.4 per 10,000 person-years for 2008) and 1.5-times higher in the Mondriaan-AHC database (i.e. 666.7 *vs.* 457.0 per 10,000 person-years for 2008), whereas in the UK databases, CPRD and THIN, and in DKM, the prevalence for hypnotics prescriptions outweighed that of anxiolytics, by a factor of approximately 1.2 (i.e. 355.6 *vs.*302.8, 359.6 *vs.* 291.5 and 523.5 *vs.* 436.7, per 10,000 person-years respectively for 2008). Almost no differences were observed for the Mondriaan-NPCRD database. Trends over time were essentially similar for both anxiolytics and hypnotics (Figure 2).

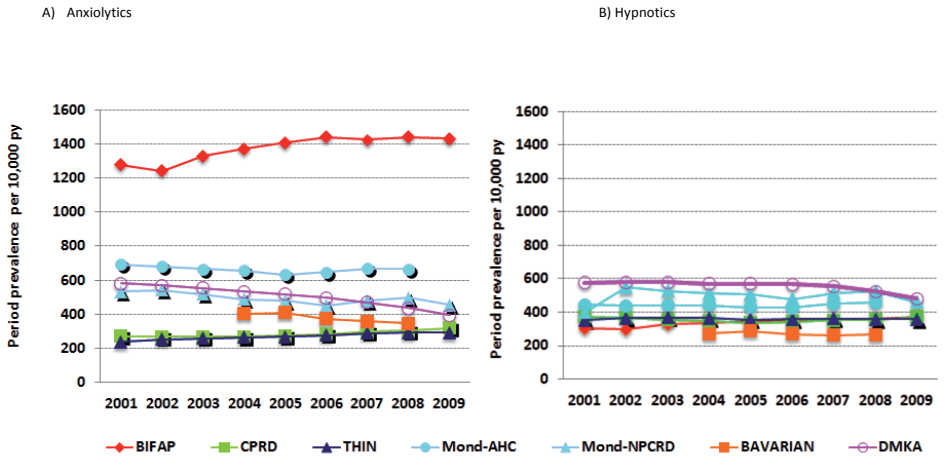


Figure 2. Period prevalence rates of BZDs use according to the ATC classification: A) anxiolytics (N05BA) and B) hypnotics (N05CD, N05CF and N05CM02). Crude rates

Among hypnotics, the prevalence of Z-drugs was higher than BZD-hypnotics in the Bavarian database (2-3 times higher) and DKMA (2-5 times higher) databases for the whole period. For the UK databases, prevalence of Z-drugs prescriptions was lower than BZDs at the start of the study period, but from 2004 onwards, it was steadily higher. In the Spanish and Dutch databases prevalence for BZD-hypnotics was higher than for Z-drugs over the study period (1.5 and 4-6 times, respectively). Clomethiazole use was negligible in the UK databases and DKMA; in the BIFAP database, it represented about 6% of the total use of hypnotics (Fig 3).

Prevalence rates by age and sex

The prevalence of BZDs prescriptions increased steadily with age in all databases both in females and males, although the slopes were higher in females (Figure 4). This was observed

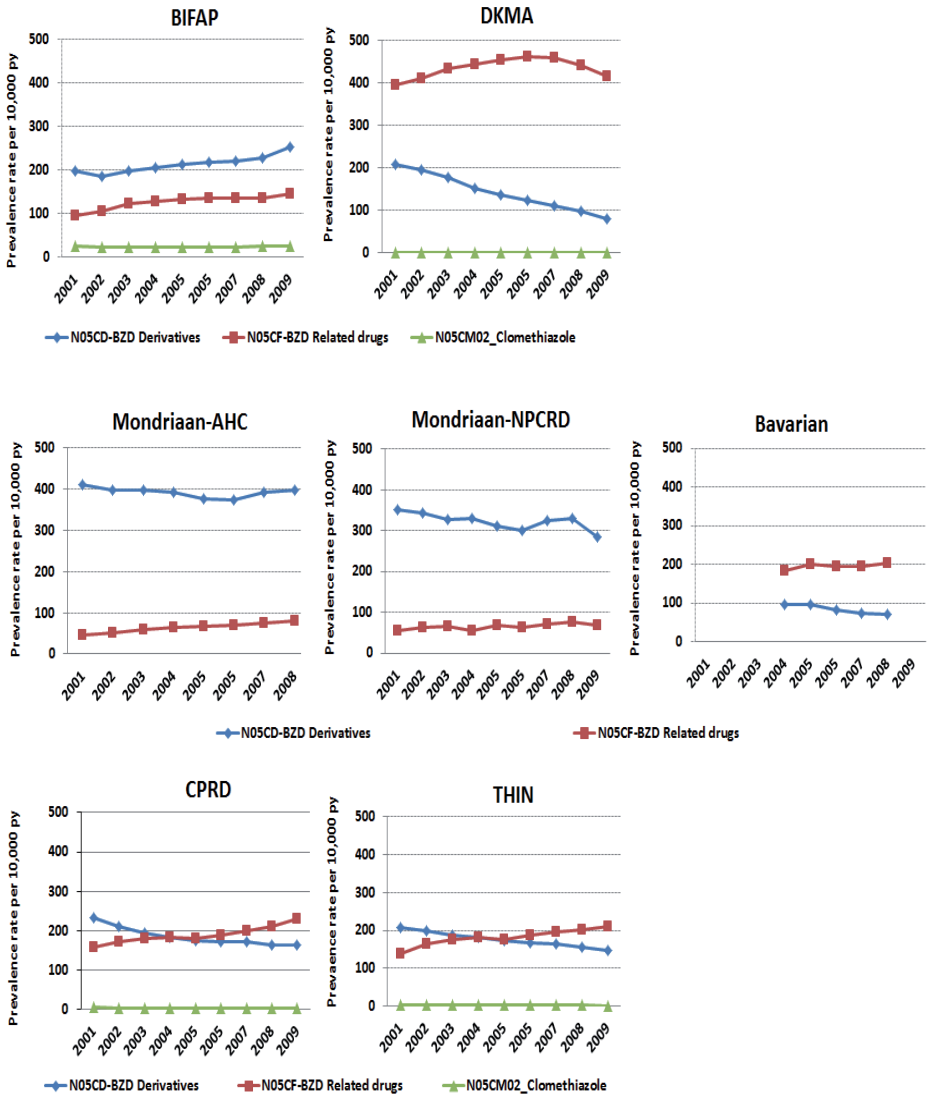


Figure 3. Trends in prevalence of the use of hypnotics (N05CD, N05CF and N05CM02). Crude rates

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

Trends in age-specific prevalence rates showed an important decrease in use in older ages (60 years and older) over the study period in most countries (with the exception of BIFAP),

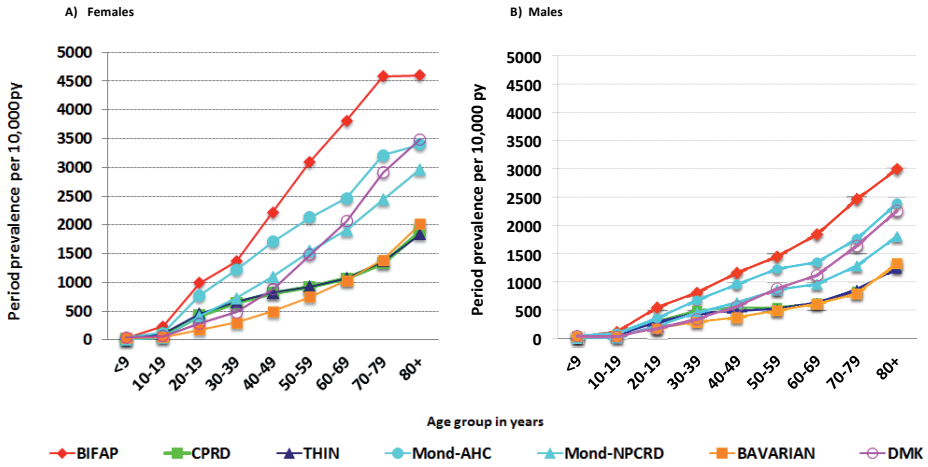


Figure 4. Prevalence use rates of BZDs by sex and age for 2008 in different databases. Crude rates

while prevalence remained stable (or showed a slight increase in some databases) among the younger ones (Supplementary Figure 2.2B), with hardly no differences by sex.

Number of prescriptions

The mean of prescriptions per patient in 2008 was rather similar in the different databases both for anxiolytics (ranged from 4 to 5) and for hypnotics (ranged from 4 to 6). Only the Bavarian databases presented distinct low numbers for anxiolytics and hypnotics (2 and3 respectively). Most patients received 4 or less prescriptions per year in all databases (in 2008; median 66.3%, range 53.7-83.8%). Of note, a considerable proportion of users received 10 or more prescriptions per year (in 2008; median 18.1%, range: 1.9-27.9%) (Table 2).

Potential Indication

In searching for registered indication three months around the first prescription, the linkage of prescriptions with their indication using diagnostic codes proved to be quite difficult in most databases with a percentage of unknown ranging from 21.7% to 82.2%. Among known indications, sleep disorders (without anxiety) were the most often recorded diagnosis temporally related with the prescription, (median 13.3%; range: 7.0%-76%). The recording of anxiety and related disorders also varied among databases (median = 12.7%; range: 1.6%-27.7%) (Figure 5). A sensitivity analysis searching diagnostic codes for indication any time during the study period prior to the prescription date, resulted in a remarkable decrease of the unknown category (Supplementary Figure 2.2A).

Table 2. Number (percentages) of patients by number of prescriptions in the different databases in 2008

	Total patients prescribed BZDs	Patients prescribed by BZD type		Total number of prescriptions by BZD type		Mean of prescriptions per patient by BZD type		Number (percentage†) of patients by number of prescriptions			
		Anx*	Hyp*	Anx	Hyp	Anx	Hyp	1 prescription	2-4 prescriptions	5-9 prescriptions	10+ prescriptions
BIFAP	231,729	205,032	51,746	931,588	265,622	4.5	5.1	68,861 (29.7)	55,659 (24.0)	42,466 (18.3)	64,743 (27.9)
CPRD	258,353	131,658	154,634	613,039	942,286	4.7	6.1	108,790 (42.1)	59,684 (23.1)	34,938 (13.5)	54,941 (21.3)
THIN	213,820	108,237	133,512	496,829	824,111	4.6	6.2	90,281 (42.2)	495,51 (23.17)	30,273 (14.2)	43,715 (20.4)
Mondriaan-AHC	13,941	9,522	6,527	41,858	35,915	4.4	5.5	5,576 (40.0)	3,875 (27.8)	1,962 (14.1)	2,528 (18.1)
Mondriaan-NPCRD	25,912	16,401	12,952	66,875	57,415	4.1	4.4	9,485 (36.6)	9,045 (34.9)	4,124 (15.9)	3,258 (12,6)
Bavarian	485,058	297,670	227,977	662,721	631,397	2.2	2.8	225,048 (46.4)	181,573 (37.4)	69,141 (14.3)	9,296 (1.9)
DKMA	437,881	228,081	273,449	113,177	120,041	5.0	4.4	146,956 (33.6)	143,089 (32.7)	81,056 (18.5)	66,780 (15.2)

Anx: Anxiolytics; Hyp: Hypnotics

* Number of patients prescribed anxiolytic and hypnotic does not add up to total patients prescribed BZDs as some patients can contribute both to anxiolytics and hypnotics prescribing categories.

† Percentage of total patients prescribed BZDs

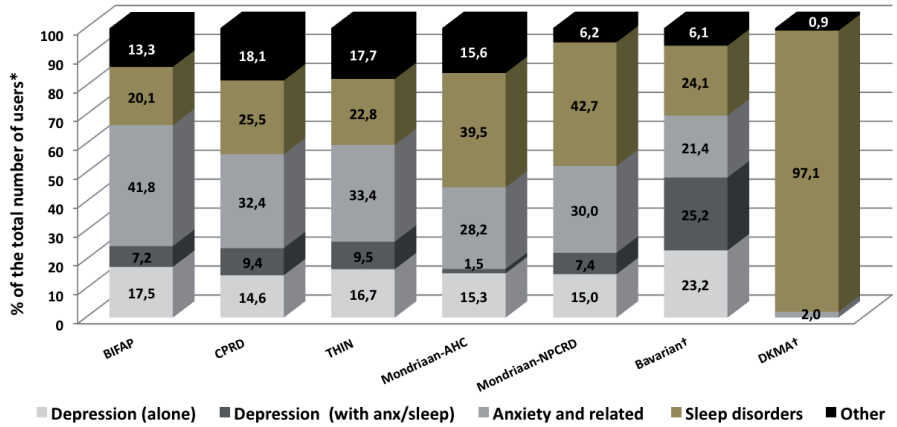


Figure 5. Indications for BZDs in 2008 by searching for registered indications during the 3 months prior to and 3 months post the date of the first BZD prescription in the different databases.
* % Calculated on the total number of users by database excluding category "Unknown" *[Results for "Unknown" were: BIFAP: 78.229 (33.8%); CPRD: 157246 (60.9%); THIN: 135923 (63.6%); Mondriaan-AHC: 11465 (82.2%); Mondriaan-NPCRD: 12172 (47.0%); Bavarian: 172528 (35.6%) and DKMA: 95271 (21.7%)].*
† In the Bavarian and DKMA databases, only the link between prescription and diagnoses was used. DKMA reported only one category for depression regardless patients additionally had anxiety or sleep

DISCUSSION

This collaborative European study provides a unique and updated overview of the prevalence of BZDs prescribing as well as trends over a nine-year period, in large populations derived from seven electronic health databases from five Western European countries. As uniform methods and analysis were applied to the individual databases, variations in results may be explained according to the differences in database characteristics and in clinical aspect related to the use of BZDs.

We found remarkable differences in prevalence rates of BZD use, which are not attributable to differences in age or sex distribution in their respective populations. Although differences across countries in the prevalence of disorders for which these drugs are indicated cannot be ruled out, it seems that most differences can be attributed to diverse prescription habits of physicians, as it has been shown in previous studies even within the same country (21-23). Added to this, the attitudes of patients towards mental health help-seeking can vary across countries, and this may also help to explain the differences in prescribing (24, 9).

To the best of our knowledge, previous collaborative European studies on BZD use are scarce. Only five studies published in the last 15 years were identified, with a cross-national

comparison (5-9). Other published studies are country or region specific (25-32). Most of these studies investigated the broader group of psychotropic medication, including other drugs different from BZDs, which yielded different exposure definitions (5, 6, 8, 28-30). In most, information was obtained from questionnaires (5, 6, 26, 28, 29). Age ranges and study period also varied largely among studies. In sum, all these factors make the comparison with other studies difficult - as already noted in a previous publication. Nonetheless, all studies performed in adults captured two constant elements in BZD use: the higher prevalence in women and the steadily increasing use with age (5, 6, 9, 27, 29, 31, 31).

Our study shows that standardized prevalence rates remained rather stable over the study period in three databases (CPRD, THIN and Mondriaan-AHC), decreased in three (Mondriaan- NPCRD, Bavarian and DKMA) and increased in one (BIFAP). A closer look at the trends by age groups showed that a decreasing trend was the pattern for most databases among the elderly. This is probably the consequence of the initiatives taken by official bodies [2] and the scientific community [34-39], in order to rationalize the use of BZDs. The Spanish BIFAP is the only database where a steady and relevant increase was observed over the study period, which is consistent with results from other studies [3, 25]. Population databases may be an important tool to assess trends and evaluate the effectiveness of prescription recommendations.

With regard to the prevalence of use of anxiolytics and hypnotics, two different patterns were observed. Anxiolytics were more prescribed than hypnotics in three databases (BIFAP, Bavarian and Mondriaan-AHC), which is in line with previous published results [3, 5-9, 25], whereas hypnotics were more used in three other databases (CPRD, THIN and DKMA), as also described previously [2, 6, 29]. These differences may have several explanations. Firstly, the prescription of BZDs and the selection of anxiolytics or hypnotics are influenced by marketing preferences and physician habits rather than by real pharmacological differences. Secondly, it has been described that patients receiving BZDs for insomnia complaints were treated in a similar percentage with anxiolytics and hypnotics [40]. Thirdly, anxiety and insomnia seem to be intertwined over time [41] and the choice of the BZD may depend on the most predominant disorder as well as the physicians' experience [42].

This study also shows the remarkable differences in the market uptake of the newer Z-drugs. It seems that these drugs have been more easily introduced in those countries which showed the most remarkable decreasing trends of BZD prescribing (Denmark and Germany). However, it is important to note that these drugs have not been shown to have a lower risk of fractures requiring hospitalization than benzodiazepines [43], which is one of the major concerns among the elderly, in addition to drug abuse and dependency.

Looking at the number of prescriptions, it seems that the highest percentage of users should be considered sporadic users (only one prescription per year) or short-term users (4 or less prescriptions per year). However, the percentage of regular or chronic users (10 or more prescriptions per year) continues to be quite high, as shown in previous studies [26, 27, 28, 32], and this appears not to be country specific. This matter would deserve a more thorough study in order to analyse the main determinants of chronic use, as a first necessary step to plan interventions to reduce intake.

A remarkably high proportion of prescriptions without any specific recorded indication was observed in the different databases, which was reduced when the search extended to diagnoses recorded any time during the study period prior to the first prescription. This might be explained by the fact that some diagnoses, such as depressive disorders, are registered only once instead of every time a prescription is filled. Among the known indications, most are related with anxiety and sleep disorders, which is an expected result. Of note, half of the patients who were prescribed BZDs in the Bavarian database had a diagnosis classified under depressive disorders (alone or associated) as the main indication, while in the other databases the proportion was around 25%. Differences in the underlying coding systems may explain these results. In addition, the Bavarian database presented the lowest numbers of both the mean prescriptions per patients and the proportion of chronic user. Explanations could be related to differences in benefit and risk perceptions for BZDs and Z-drugs [44]. Furthermore, a relevant proportion of prescriptions from the private healthcare sector, which are not documented in the Bavarian database, have been described for BZDs and Z-drugs, [45]. In addition, a wide regional variation of private prescriptions was found for the Z-drugs zolpidem and zopiclone in Germany [46). Finally, it is possible that this method for assessing indication did not solve the problem. Our conclusion is that indication appears as a major challenge in pharmacoepidemiological studies, moreover in those databases where information on indication is not directly available, creating the need for studies specifically designed to further investigate the recording of indication and making adapted to the specific characteristics of the database.

Important strengths of this study deserve attention. Firstly, this study estimated prevalence rates of BZD use by counting patients with recorded prescriptions, which eliminate measurement errors due to inadequate recall by respondents. Secondly, all databases are population-based providing appropriate denominators in persons and person-years. Thirdly, populations included in most GP-based databases are representative of their respective country population (THIN, CPRD, BIFAP, Mondriaan-NPCRD), although it is not possible to assure that prescription habits of GPs participating in these databases are representative of the national prescribing habits of all GPs; finally, the Danish Registries include the entire

population, and the Bavarian database includes approximately 84% of the population at regional Bavarian level.

Some limitations also need to be addressed. Prescriptions of BZDs outside the primary care setting, such as in-hospital use or private prescribing may not be considered in these databases. Over the counter delivery is not expected to affect results since BZDs are prescription drugs under strict dispensing control in all participating countries. Differences in the coding systems used in the databases may also have produce differences in indication. For those databases registering prescriptions for BZDs, we cannot exclude the possibility that patients did not collect the drug from the pharmacy, this accounted for a 5% in Denmark [47].

In conclusion, this study shows that analysing drug utilization in different databases from different countries according to a common protocol is feasible and valuable and contributes to direct cross-comparison. In addition, differences in prescribing prevalence, after harmonizing methods, may be explained by differences in the databases which may reflect different aspect related to the use of the BZDs, prescribing habits and/or patient perception and other specific characteristics of the databases Appropriate comparison of drug utilization across countries gives the opportunity to answer basic questions about prescribing practices which may also help to inform public health decisions and identify areas in which more research is needed.

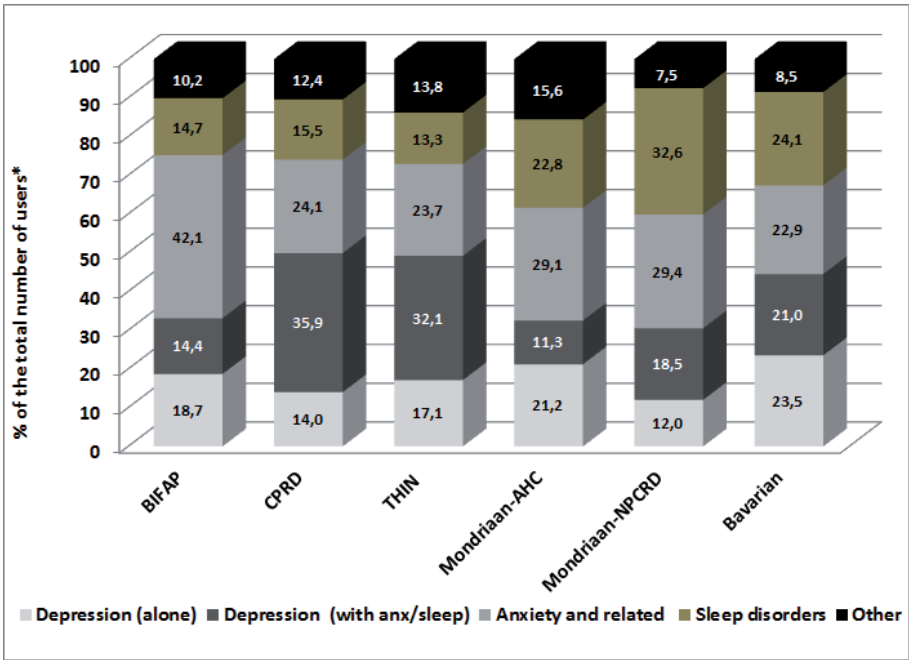
REFERENCES

1. Charney DS, Mihic SJ and Harris RA: Hypnotics and Sedatives. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill; 2006. pp. 401-427.
2. Danish Health and Medicines Authority. Effective effort against the excessive use of benzodiazepines in Denmark. [cited 2012 October]; Available from: http://www.dkma.dk/en/topics/statistics,-prices-and-reimbursement/statistics-and-analyses/analyses/consumption-analyses/effective-effort-against-the-excessive-u—in-denmark
3. Spanish Agency for Medicines and Medical Devices (AEMPS). Uso de Benzodiacepinas en España (1992-2006) [cited October 2012]. Available from: http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/ansioliticos_hipnoticos.pdf
4. Medicines and Healthcare products Regulatory Agency (MHRA). Addiction to benzodiazepines and codeine: supporting safer use. July 2011. [cited 2012 October]. Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123123
5. Linden M, Lecrubier Y, Bellantuono C et al. The prescribing of psychotropic drugs by primary care physicians: an international collaborative study. J Clin Psychopharmacol. 1999;19:132-40.
6. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. J Clin Psychiatry. 2002;63:817-25.
7. van Hulten R, Isacson D, Bakker A, Leufkens HG. Comparing patterns of long-term benzodiazepine use between a Dutch and a Swedish community. Pharmacoepidemiol Drug Saf. 2003;12:49-53.
8. Zito JM, Safer DJ, de Jong-van den Berg LT et al. A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health. 2008, 2:26.
9. Demyttenaere K, Bonnewyn A, Bruffaerts 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;110:84-93.
10. Zammit G. Comparative tolerability of newer agents for insomnia. Drug Saf 2009; 32(9): 735-748
11. BIFAP: A computerized database of medical records of Primary Care in Spain. [cited 2012 October]; Available from: http://www.bifap.org/summary.php.
12. Clinical Practice Research Datalink (CPRD). [cited 2012 October]; Available from: http://www.cprd.co.uk/intro.asp
13. The Health Improvement Network THIN. [cited 2012 October]; Available from: http://www.thin-uk.com/partnership.htm.
14. Project Mondriaan. [cited 2012 October]; Available from: http://www.projectmondriaan.nl.
15. Wirtz, K., Tauscher, M, Zwerenz, M, Munte, A. Data Warehousing for Bavarian Out-Patient Public Health. [cited 2012 October]; Available from: http://subs.emis.de/LNI/Proceedings/Proceedings91/GI-Proceedings-91-23.pdf.
16. Danish Health and Medicines Authority. [cited 2012 October]; Available from: http://www.sst.dk/Indberetning%20og%20statistik/Landspatientregisteret.aspx
17. Abbing-Karahagopian V, Kurz X, de Vries F, van Staa TP, Alvarez Y, et al. Bridging differences in outcomes of pharmacoepidemiological studies: Design and first results of the PROTECT project. Curr Clin Pharmacol. 2014 May;9(2):130-8.
18. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) Classification System. [cited 2013 December]; [Last updated: 2013-12-19];Available from: http://www.whocc.no/atc_ddd_index/
19. EUROSTAT. European Commission; 2008 [cited 2012 October]; Available from: http://

epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database
20. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [cited 2012 October]; Available from: http://www.encepp.eu/index.html
21. Pharoah PD, Melzer D. Variation in prescribing of hypnotics, anxiolytics and antidepressants between 61 general practices. Br J Gen Pract. 1995;45(400):595-9.
22. 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. Br J Gen Pract. 2009;59:e191-8.
23. van der Waals FW, Mohrs J, Foets M. Sex differences among recipients of benzodiazepines in Dutch general practice. BMJ. 1993;307:363-6.
24. Ten Have M, de Graaf R, Ormel J et al.; ESEMeD/MHEDEA 2000 Investigators. 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.
25. Garcia del Pozo J, de Abajo Iglesias FJ, Carvajal Garcia-Pando A et al. Utilizacion de ansioliticos e hipnoticos en Espana (1995-2002). Rev Esp Salud Publica. 2004;78:379-87.
26. Sonnenberg CM, Bierman EJ, Deeg et al. Ten-year trends in benzodiazepine use in the Dutch population. Soc Psychiatry Psychiatr Epidemiol. 2012;47:293-301.
27. van Hulter R, Leufkens HG, Bakker A. Usage patterns of benzodiazepines in a Dutch community: a 10 year follow-up. Pharm World Sci. 1998;20:78-82.
28. Koelch M, Prestel A, Singer H et al. Psychotropic medication in children and adolescents in Germany: prevalence, indications, and psychopathological patterns. J Child Adolesc Psychopharmacol. 2009 Dec;19:765-70.
29. 29 Ohayon MM, Caulet M, Priest RG, Guilleminault C. Psychotropic medication consumption patterns in the UK general population. J Clin Epidemiol. 1998;51:273-83.
30. Hsia Y, Maclennan K. Rise in psychotropic drug prescribing in children and adolescents during 1992-2001: a population-based study in the UK. Eur J Epidemiol. 2009;24:211-6.
31. Kjosavik SR, Ruths S, Hunskaar S. Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription DB. Pharmacoepidemiol Drug Saf. 2009:18(7):572-8.
32. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck GA. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. Int Clin Psychopharmacol. 2007;22:292-8.
33. Zandstra SM, Furer JW, van de Lisdonk EH et al. Different study criteria affect the prevalence of benzodiazepine use. Soc Psychiatry Psychiatr Epidemiol. 2002;37(3):139-44.
34. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol. 2007;63:725-31.
35. Laroche ML, Charmes JP, Bouthier F, Merle L. Inappropriate medications in the elderly. Clin Pharmacol Ther. 2009;85:94-7.
36. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med. 1997 Jul 28;157(14):1531-6.
37. 37 . Fick DM, Cooper JW, Wade WE et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716-24.
38. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997;156:385-91.
39. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010;107:543-51.
40. Ohayon MM, Caulet M, Arbus L et al. Are prescribed medications effective in the treatment of insomnia complaints? Psychosom Res. 1999;47:359-68.

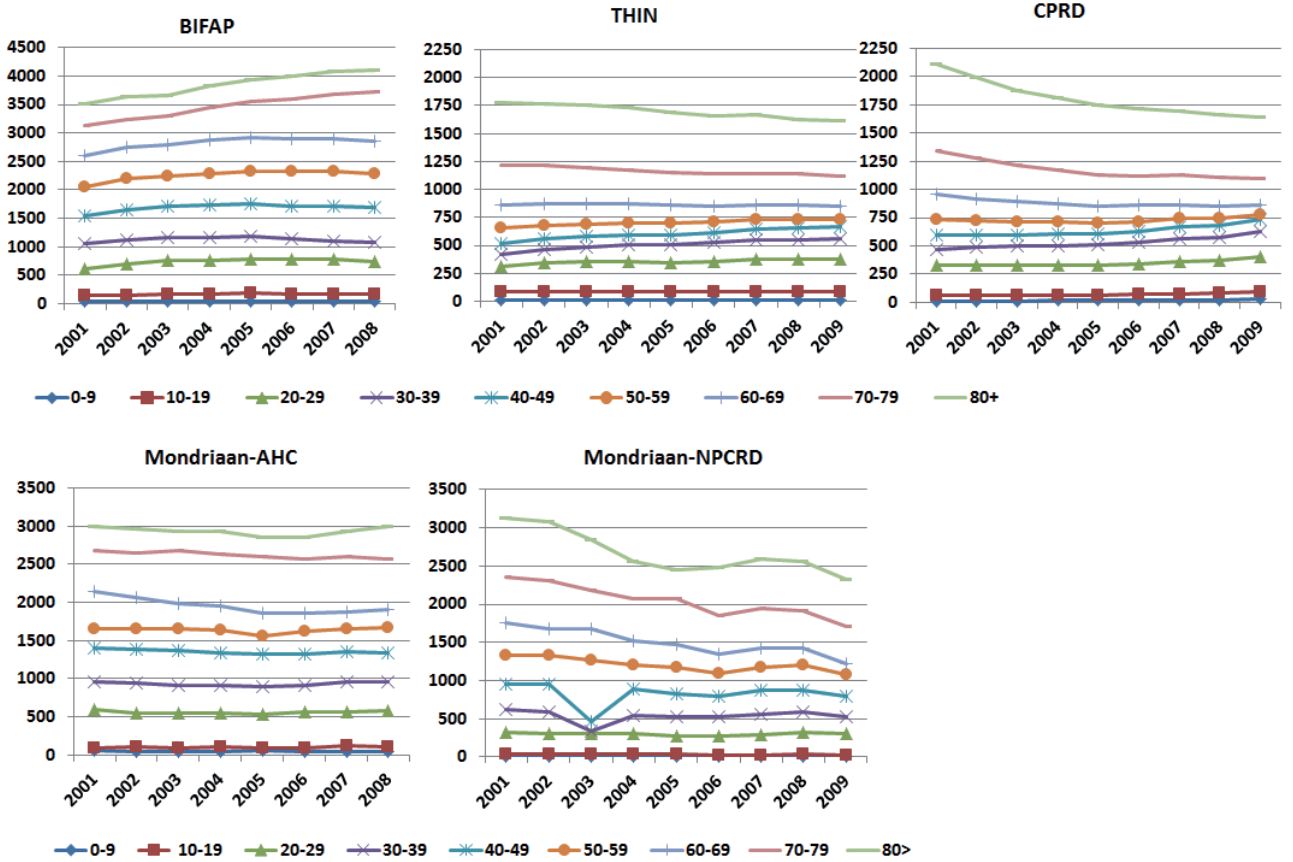
41. Jansson-Fröjmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. J Psychosom Res. 2008;64:443-9.
42. Hayward RA, Jordan KP, Croft P. The relationship of primary health care use with persistence of insomnia: a prospective cohort study. BMC Fam Pract. 2012;13:8.
43. Finkle WD, Der JS, Greenland S et al. Risk of fractures requiring hospitalization after an initial prescription of zolpidem, alprazolam, lorazepam, or diazepam in older adults. J Am Geriatr Soc 2011;59:1883-90.
44. Hoffmann F. Benefits and risks of benzodiazepines and Z-drugs: comparison of perceptions of GPs and community pharmacists in Germany. Ger Med Sci. 2013;18;11:Doc10.
45. Hoffmann F, Glaeske G. [Benzodiazepine hypnotics, zolpidem and zopiclone on private prescriptions: use between 1993 and 2012]. Nervenarzt. 2014;85(11):1402-9. [Article in German but abstract in English].
46. Hoffmann F, Hies M, Glaeske G. Regional variations of private prescriptions for the non-benzodiazepine hypnotics zolpidem and zopiclone in Germany. Pharmacoepidemiol Drug Saf. 2010;19(10):1071-7.
47. Pottegård A, Christensen Rd, Houji A, Christiansen CB, Paulsen MS, Thomsen JL, Hallas J. Primary non- adherence in general practice: a Danish register study. Eur J Clin Pharmacol. 2014;70(6):757-63.

Supplementary Figure 2.2A: Benzodiazepines indication in 2008 by searching any time before first prescription within the study period in the different databases (Sensitivity analysis)
anx= anxiety disorder; sleep= sleep disorder

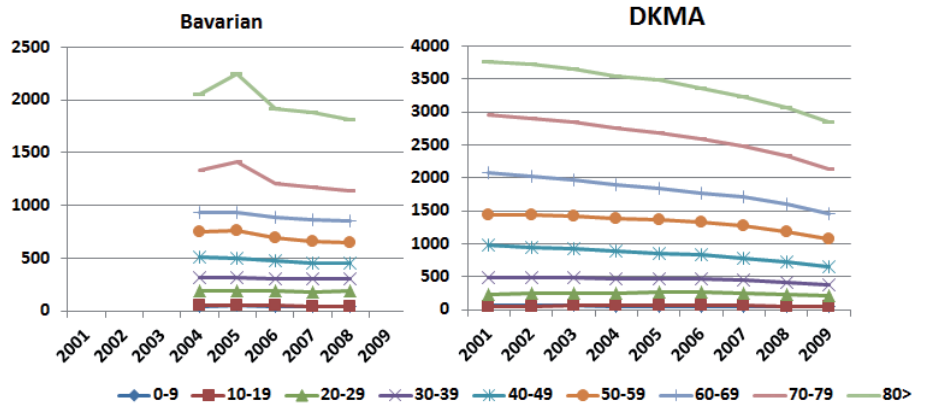


* % Calculated on the total number of users, excluding category 'Unknown' [*Results for "Unknown" were: BIFAP: 47422 (20.5%); CPRD: 58251 (22.5%); THIN: 59113 (27.6%); Mondriaan-AHC: 6777 (48.6%); Mondriaan-NPCRD: 8742 (33.7%) and Bavarian: 70871 (14.6%)]*

Supplementary Figure 2.2B Trends of age-specific prevalence rates. Crude rates.



Supplementary Figure 2.2B Trends of age-specific prevalence rates. Crude rates (continued)



2.3

Incidence rates and trends of hip/femur fractures in five European countries: comparison using e-healthcare records databases

Gemma Requena, Victoria Abbing-Karahagopian, Consuelo Huerta, Marie L. De Bruin, Yolanda Alvarez, Montserrat Miret, Ulrik Hesse, Helga Gardarsdottir, Patrick C. Souverein, Jim Slattery, Cornelia Schneider, Marietta Rottenkolber, Sven Schmiedl, Miguel Gil, Mark de C. H. Groot, Andrew Bate, Ana Ruigómez, Luis A. García Rodríguez, Saga Johansson, Frank de Vries, Dolores Montero, Raymond G. Schlienger, Robert F. Reynolds, Olaf H. Klungel, Francisco J. de Abajo.

Calcified Tissue International. 2014; 94(6):580-9

ABSTRACT

Background

Hip fractures represent a major public health challenge worldwide. Multinational studies using a common methodology are scarce. We aimed to estimate the incidence rates (IR) and trends of hip/femur fractures over the period 2003-2009 in five European countries.

Methods

The study was performed using seven electronic health care record databases (DBs) from Denmark, Germany, the Netherlands, the UK, and Spain based on the same protocol.
Yearly IRs of hip/femur fractures were calculated for the general population and for those aged ≥50 years. Trends over time were evaluated using linear regression analysis for both crude and standardized IRs.

Results

Sex- and age-standardized IRs for the UK, Netherlands, and Spanish DBs varied from 9 to 11 per 10,000 person-years for the general population and from 22 to 26 for those ≥50 years old; the German DB showed slightly higher IRs (about 13 and 30, respectively), whereas the Danish DB yielded IRs twofold higher (19 and 52, respectively). IRs increased exponentially with age in both sexes. The ratio of females to males was ≥2 for patients aged ≥70–79 years in most DBs. Statistically significant trends over time were only shown for the UK DB (CPRD) (+0.7 % per year, P<0.01) and the Danish DB (-1.4 % per year, P<0.01).

Conclusions

IRs of hip/femur fractures varied greatly across European countries. With the exception of Denmark, no decreasing trend was observed over the study period.

INTRODUCTION

Hip fractures represent a major public health challenge in developed countries, due to the increasing age of the population [1]. 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 [2]. The increasing trend of the incidence of hip fractures, along with associated morbidity complications, dependence and mortality [3, 4] 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 [5]. 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 [1]. Osteoporosis affects millions of patients worldwide, and hip fractures are considered the most serious outcome. Distribution of this injury in the world is heterogeneous [1], although Europe holds an important share of all osteoporotic fractures (35%) worldwide [6], including hip fractures (37%).

In recent years an increasing number of studies have reported that secular trends in the incidence of hip fractures have levelled off [7-9], or started to decline, since the late nineties [10] in some European countries. Allegedly, this is the result of the effectiveness of national campaigns to prevent both osteoporosis and falls [2, 11]. A call to update the data for as many countries as possible has been made [12] in order to check whether this favourable trend is consistent. In the present study we aim to describe the incidence of hip and femur fractures across five European countries of different latitudes (Denmark, Germany, the Netherlands, the UK, and Spain) using seven different electronic health care record databases and to compare the rates and trends over the period 2003-2009.

PATIENTS AND METHODS

Data sources

Seven European data sources located in five different countries were used in this study. 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), the Spanish "Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria" (BIFAP; http://www.bifap.org), and two databases from the UK, the Clinical Practice Research Datalink (CPRD) (formerly known as the General Practice Research Database;

http://www.cprd.com) and The Health Improvement Network (THIN; http://www.thin-uk.com).

Four of the databases are nationwide primary care databases covering a part of their country populations: 2% (Mondriaan NPCRD), 5.7% (THIN), 6.8% (BIFAP), and 8% (CPRD). Mondriaan-AHC is a primary care regional database: covering about 200,000 patients from Almere, a newly built city in the Netherlands. The Bavarian claims database includes population-based data on diagnoses and medical services linked to outpatient treatment data through general practitioners (GPs) and specialists, covering 10.5 million people (85% of the Bavarian population). Dates of prescribing and diagnoses are not available in the Bavarian claims database, but only in which quarter of the year a prescription or a diagnosis was registered. And finally, the Danish national registries, maintained by the National Institute for Health Data and Disease Control (SSI), contain information on all hospital contacts since 1995 (inpatient contacts since 1977 and emergency and outpatient contacts since 1995), medication dispensing on a pharmacy level linked to individuals who redeemed the prescription from 1994 onwards [27], causes of death for the entire population (5.3 million inhabitants) and contact information of visits to GPs as well as specialist in private care.

All participating databases fulfil quality standards for pharmacoepidemiology research [13]. A common protocol and data specifications revised and approved by all study participants and by an external committee, was adopted by the seven databases. This study protocol has been registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study registry (http://www.encepp.eu/).

Study population

The study population comprised patients of all age groups within each database, during the study period from 1 January, 2003 to 31 December, 2009, fulfilling the quality criteria of valid registration status established by the respective database owners. Within this period, we selected as start date the latest of the following: the date when the practice became up to a research standard; the date when the practice was enrolled into the database; or the date when a patient was enrolled into a practice or into the database (this does not apply to the Danish data which included all citizens). End of follow-up was defined as the end of the study period or at the earliest of the following events: the patient died, the patient was transferred out, the practice left the database, or the last event was recorded. For the Danish databases follow-up was stopped at the end of the study period or if the patient died or left Denmark. For the Mondriaan AHC database data from 2009 were not available, and the Bavarian Claims database only provided data from 2006 to 2008.

Outcome definition

Although our main interest was hip fracture, defined as a fracture of the proximal femur in the cervix or in the trochanteric region, we considered "any femur fracture" to be the operational outcome definition for this study (hereinafter referred to as "hip/femur" fracture). The main reason was that some of the participating databases (the Dutch NPCRD, AHC and the Spanish BIFAP) use the International Classification of Primary Care (ICPC-2) for disease coding which does not have a specific code for hip fracture, but a broader code for "femur" fracture (L75), and a primary objective of PROTECT was to assure consistency in the outcome definition across databases. Additionally, the use of a broader code may avoid overlooking hip fractures by miscoding [14]. The codes applied for the outcome searching strategy are provided in the published version of this article in the Online Resource I. The coding system was unchanged during the study period in each database.

We included all patients with a first ever diagnosis of hip/femur fracture during the study period. Patients with a history of past hip/femur fracture ever before were excluded to increase the likelihood of including incident episodes only.

Analysis

Annual incidence rates (IR) of hip/femur fractures were calculated for the whole study population. The numerator comprised all newly recorded cases of hip/femur fracture in each year and the denominator was the total number of person-years of follow up. We also calculated the annual IR among people aged 50 years or older separately, as most fractures occurring before this age are primarily due to trauma and many studies use this age limit [15, 16].

For the comparison of the IRs in the whole population and population 50 years or older across databases and over time, we carried out a direct sex and age standardization using the European Union population in 2008 (EUROSTAT) as the standard (http: //epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database).
We also calculated age (in 10-year bands) and sex specific IRs over the study period. 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 within each database.

To quantify the trend over the study period we performed linear regression analysis for both crude and standardized rates in each database, 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 β=0 was tested using the t test. A p value <0.05 was considered significant. The 95% CI of the slope was also calculated.

RESULTS

Incidence rates of hip/femur fractures

The number of fracture episodes and the person-time of observation for each specific database per year, as well as the crude and standardized IRs are described in table 1. The data sources from the UK, the Netherlands (NL) and Spain provided fairly similar standardized IRs, mostly ranging from 7 to 10 per 10,000 person-years (py); Bavarian Claims database displayed rates around 13 per 10,000 py, whereas the Danish database yielded rates approximately twofold higher than most of other databases (around 19 per 10,000 py) (in Supplementary Table 2.3A).

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 to 25 per 10,000 py in the UK, the NL, and Spain to 52 10,000 py in Denmark and around 30 10,000 py in Germany (Table 1).

Time trends

A significant trend in standardized IRs was only observed for the British CPRD (+0.9% per year; p<0.01) and the Danish database (-1.4% per year; p< 0.01) (table 1). When the analysis was restricted to subjects aged 50 years or older similar trends were observed (table 2). For the remainder of databases trends observed were not remarkable and did not reach statistical significance (negative for BIFAP and positive for THIN) or exhibited fluctuations that prevent from identifying a clear trend (for NPCRD and AHC). The short study period available for the Bavarian Claims database precluded any trend analysis.

Sex and age-specific incidence rates of hip/femur fracture

The crude and age-standardized IRs were 2-3 times higher in women than in men for the whole population (data not shown) and for the population aged 50 years or older, over the study period and across all databases (Figure 1). In 2008, the median standardized IRR of females vs. males was 2.4 (range: 1.3-3.3) for the general population and 2.6 (range: 1.6-3.1) for the population aged 50 years or older. This ratio, however, was shown to be 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 declining (Figure 2).

Table 1. Incidence rates and time trends in the population ≥ 50 years old in the participating databases of the study.

	2003	2004	2005	2006	2007	2008	2009	Slope (95% CI)	% variation[#]
BIFAP									
No. fractures	1298	1643	1638	1629	1558	1350	1027	-	
Person-years	475139	588242	616300	589588	554287	472785	369872	-	
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
Standardised 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	2858	3087	3139	3265	3295	3367	3291	-	
Person-years	1327959	1406185	1447563	1476874	1475205	1470594	1446832	-	
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
Standardised 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	2614	2734	2831	2785	2830	2899	2839		
Person-years	1241173	1259016	1270685	1284095	1294565	1302336	1288704		
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
Standardised 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	23883	25935	28039	30293	32657	35583	-		
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	103010	64504	62856	52701	76946	60608	45969		
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
Standardised 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	9031	9277	9206	9041	8905	9036	8814		
Person-years	1810178	1831556	1843587	1861768	1878628	1901823	1912890		
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
Standardised 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	-	-	-	12868	11787	12928	-	-	-
Person-years[$]	-	-	-	3885264	3938210	3988146	-	-	-
IR per 10,000py	-	-	-	33.12	29.93	32.42	-	-	-
Standardized IR	-	-	-	31.08	27.82	29.94	-	-	-

**** p < 0.05 ; [#] % Variation: (Slope/2003 IR)*100***

[$] Incidence per 10,000 Insured persons *BAVARIAN, not enough data to assess time trends*

The IRs of hip/femur fractures grew exponentially at the age of 50 years for both females and males (Figure 3a, b respectively), which was a constant feature for all databases and for the whole study period (Supplementary Table 2.3B).

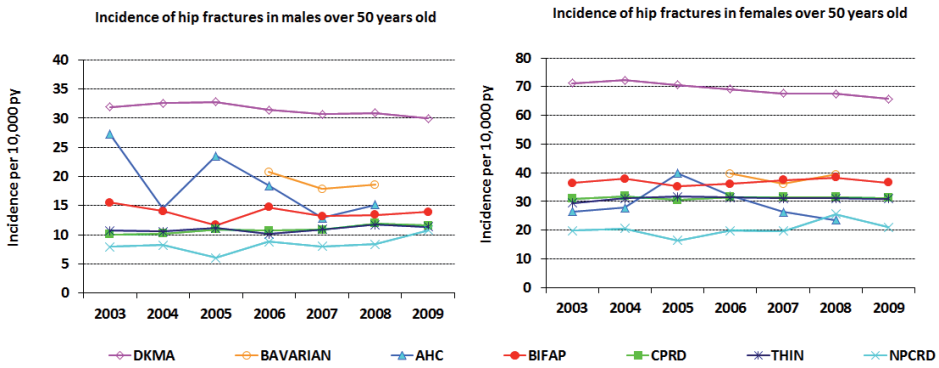


Figure 1. Age-standardized incidence rates of hip/femur fracture by sex in the population aged over50 years old and trends over time.
Note that the scale used in females is double than the one used in males.

Trends of age- and sex-specific IRs over the study period showed that there was no relevant trend in any age group or sex in the British, Dutch and Spanish databases. In the Danish database there were sex- and age-dependent trends: an increasing trend in females 50-59 years old and a decreasing trend in both males and females among the 70-79 age groups; being stable or slightly decreasing among the other age groups (Supplementary Figure 2.3A).

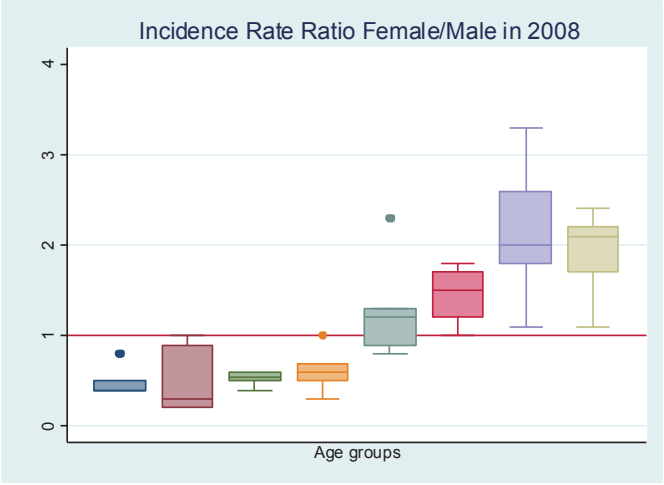


Figure 2. Box-plot showing 2008 incidence rate ratios (IRRs) of hip/femur fracture in females compared to males in the participating databases and their relation with age.
Boxes represent the 25-75 percentiles; the bar within the box represents the median value.

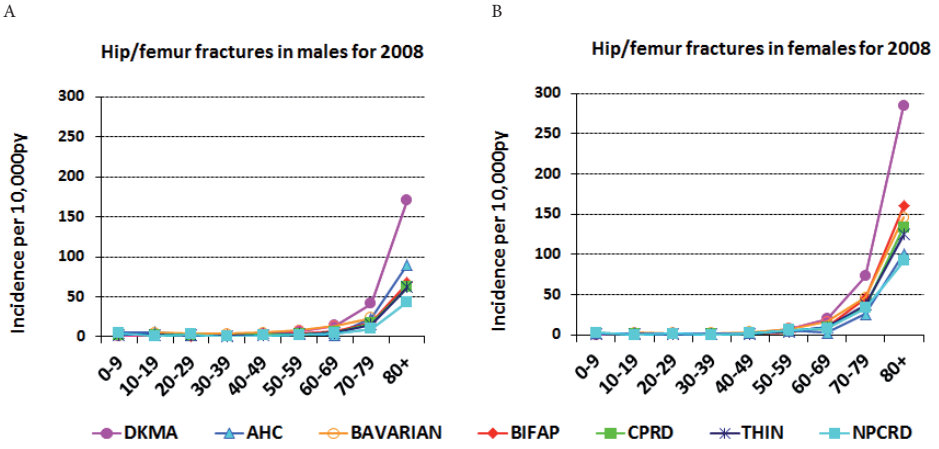


Figure 3: Incidence rates of hip/femur fractures by age groups in females (a) and males (b) in different databases for 2008.

DISCUSSION

To the best of our knowledge this is the first study to provide a direct comparison across European countries of different latitudes, of incidence rates of hip/femur fractures and trends over time, using the same case definition and the same standard population. The main findings of our study were as follows: 1) the age- and sex- standardized IRs of hip/femur fractures in the UK, the NL and Spain were around 7 to 10 per 10,000 py and 2 times lower than the one observed in Denmark (19 per 10,000 py), whereas Germany yielded intermediate IRs (13 per 10,000 py); 2) 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; 3) significant trends in standardized IRs over time were observed only in two databases (increasing trend in the British CPRD and 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 to those already published for the general population (21.1 per 10,000 population) [2] and for the population aged 50 years or older (45 per 10,000 py) [17]. 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 [18]. The IRs from the Spanish database in people aged 50 years or older are also similar to the ones reported by Hernández et al [8] using hospital discharge data from Cantabria in 2002 (25,9 per 10,000 persons) and to the ones reported in Catalonia [19] using GP records in 2009 (22.3 per 10,000 py). The two GP databases from the NL provided standardized IRs that

fluctuated greatly over the study period, showing lower values than those based on hospital registries [15, 20]. One plausible explanation for these results is that there was a slight under-registration of ICPC codes by GPs until 2009 in the Netherlands. This has been proven since after a national campaign to stimulate ICPC coding use in 2010-11, the incidence of hip/femur fractures rose to 13.5 per 10, 0000 population, which is similar to both the hospital registration and the NPCRD Web site. Finally, IRs from the Bavarian claims database were marginally lower than in other studies [7, 11]. That might be due to differences in ICD coding and 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. Also, our data confirm the evidence that European Nordic countries exhibit greater incidence rates of hip/femur fractures than other European countries [1, 22]. There is no clear explanation for that but lifestyle, limited exposure to sunlight and weather conditions may play a role [23, 24]. Regarding this latter factor, some studies performed in Nordic countries observed higher incidence rates in winter than during summer, likely related to the fact that worse weather conditions with slippery roads and pavements increase the risk of falls [25, 26].

The IRs of hip/femur fractures increase with age for both males and females. As in other studies, IRs increased exponentially which is partly explained by the progressive bone mass reduction with ageing [27], 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, antiparkinsonians, 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 at older aged males approximate females in bone mineral density and major risk factors [28]. This pattern was consistent across most databases and over the whole study period, and is in accordance with previously published results [16, 29, 30]. 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 [31].

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 since the nineties, as shown by previous reports in the same countries [3, 18]. Denmark is the only country in our study 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 [32], as well

as by the US [33]; Australia [34]; Canada [35] and Scotland [36]. This decline in the Nordic countries, might be attributable to a better management of osteoporosis (earlier screening, diagnosis and treatment of patients at risk) [37] and, particularly, to a healthier diet, increase of physical activity, and educative measures to prevent falls [38]. Also, a trend to a lower consumption of certain drugs that increase the risk of falls and fractures may also have contributed; as a matter of fact, in a parallel study we have observed an important decreasing trend in the use of benzodiazepines in Denmark during the same time period [39]. In the AHC database there was also the suggestion of a decreasing trend since 1005; but the IRs were based on a small sample of case, and this trend was not observed in the other Dutch database.

Among the strengths of the present study is the use of multiple databases that proved valid for pharmacoepidemiological research [13] including representative populations regarding age and sex. Additionally, a common protocol and data specifications agreed was used by all participants, with consistent criteria for case search and operational case definition which facilitates comparison of results across data sources. The present study is part of a larger research program aimed at describing and analysing the discrepancies found among data sources from different European countries with respect to selected outcomes, drug exposures, and, particularly, with respect to associations between drug exposures and outcomes. Therefore, common analytical procedures were employed in order to minimize methodological discrepancies as much as possible. Nevertheless, each data source has its own limitations with regards to data collection and each country has different health policies and prescription patterns which, among other intrinsic characteristics of populations and their life styles, may contribute to the variability of our results.

As limitations we should mention that IRs of hip/femur fractures reported in this manuscript come from codes recorded in the corresponding databases, and no further validation was performed [40]. This, in particular for the GP-based data sources, may theoretically result in the inclusion of false cases in the numerator leading to an overestimation of the incidence. On the other hand, it could exist as well an under-reporting of hip fractures in the GP databases, because these fractures require hospital admission and some cases, in particular fatal cases, might not be reported to the GP. However, the IRs obtained in the present study were fairly consistent with those published previously by other authors using different data sources (most of them from hospital records), which reinforces the idea that the data provided can be used as reasonably valid estimates for each country. Importantly, the analysis of time trends should not be affected by such potential limitation, as the search criteria were unchanged over the study period. Finally, the use of the outcome "hip/femur" fracture might have inflated the number of cases with respect to other studies which only focused on "hip" fractures. However, it is pertinent to note that some authors [14, 41] 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" [14]. 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 [42].

In conclusion, incidence rates of hip/femur fractures in the European countries that took part in this study were fairly similar, regardless of their latitude, and showed no significant trend, reflecting a rather stable situation. A remarkable exception of this general picture is Denmark, which presented the highest incidence rates, but showed a consistent decline in both males and females aged 70 years or older. Our results confirm the strong relation between this injury and age and sex, largely published in the literature, and gives an updated overview of the incidence rates of this major public health issue in Europe. In addition, this study proves the value of general practice databases to estimate and compare incidence of disease, among multiple sources once common procedures are followed.

REFERENCES

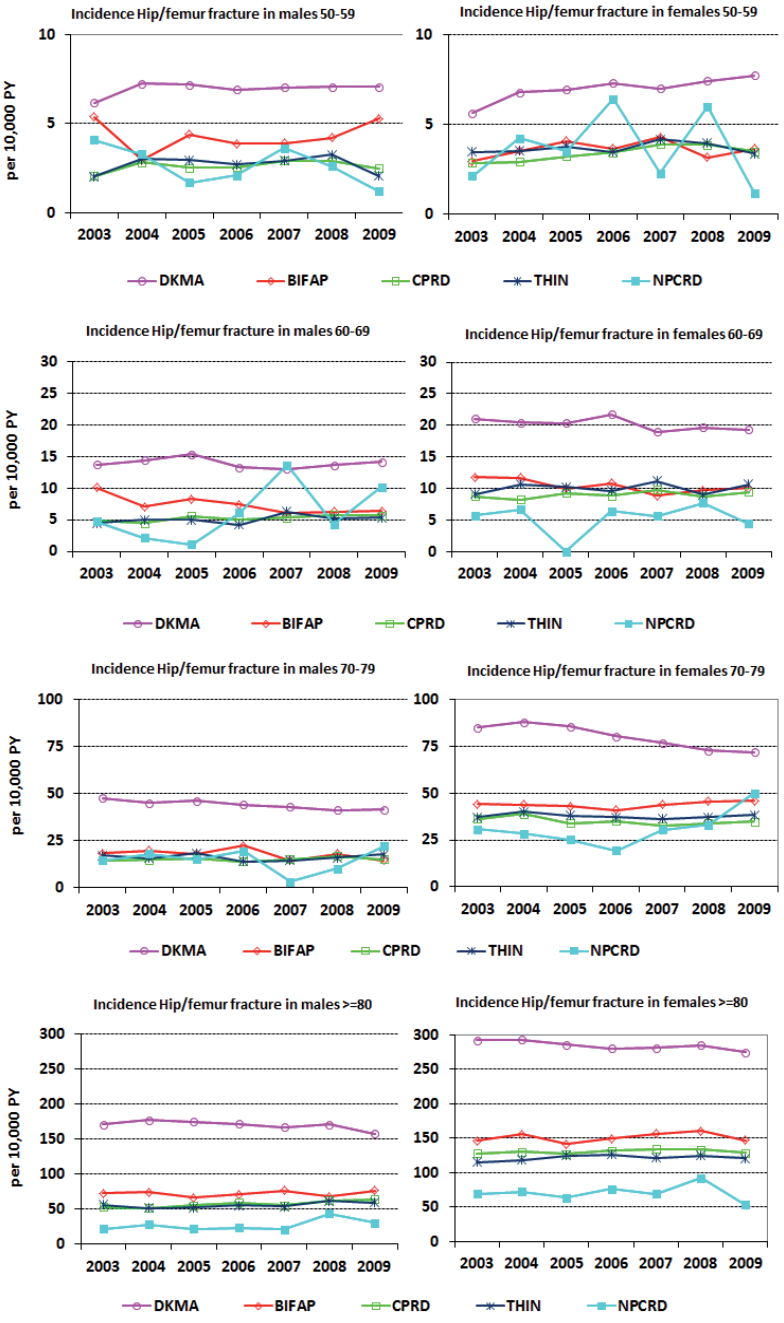
1. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C (2012) A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 23 (9):2239-2256.
2. Osteoporosis in the European Union in 2008: Ten years of progress and ongoing challenges. (2008) International Osteoporosis Foundation http://www.sante.public.lu/publications/maladies-traitements/osteoporose/osteoporosis-eu-2008/osteoporosis-eu-2008.pdf. Accessed 02/10/2012
3. Cummings SR, Melton LJ (2002) Epidemiology and outcomes of osteoporotic fractures. Lancet. 359 (9319):1761-1767.
4. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE, Quine S (2000) Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ. 320 (7231):341-346
5. Polinder S, Meerding WJ, van Baar ME, Toet H, Mulder S, van Beeck EF, Group ER (2005) Cost estimation of injury-related hospital admissions in 10 European countries. J Trauma. 59 (6):1283-1290; discussion 1290-1281
6. Kanis J (2007) Assessment of osteoporosis at the primary health care level. on behalf of the World Health Organization Scientific Group (WHO). http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf. Accessed Nov 2012
7. Mann E, Meyer G, Haastert B, Icks A (2010) Comparison of hip fracture incidence and trends between Germany and Austria 1995-2004: an epidemiological study. BMC Public Health. 10:46.
8. Hernandez JL, Olmos JM, Alonso MA, Gonzalez-Fernandez CR, Martinez J, Pajaron M, Llorca J, Gonzalez-Macias J (2006) Trend in hip fracture epidemiology over a 14-year period in a Spanish population. Osteoporos Int. 17 (3):464-470.
9. Lyritis GP, Rizou S, Galanos A, Makras P Incidence of hip fractures in Greece during a 30-year period: 1977-2007. Osteoporos Int. 2013;24(5):1579-85.
10. Korhonen N, Niemi S, Parkkari J, Sievanen H, Palvanen M, Kannus P (2013) Continuous decline in incidence of hip fracture: nationwide statistics from Finland between 1970 and 2010. Osteoporos Int. 24(5): 1599-1603.
11. Lakatos P, Balogh A, Czerwinski E, Dimai HP, Hans D, Holzer G, Lorenc RS, Palicka V, Obermayer-Pietsch B, Stepan J, Takacs I, Resch H (2011) 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. 6 (1-2):1-12.
12. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, Melton LJ, Cummings SR, Kanis JA (2011) Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporos Int. 22 (5):1277-1288.
13. Abbing-Karahagopian V, Kurz X, de Vries F, van Staa T, Alvarez Y, Hesse U, et al. (2014) Bridging Differences in Outcomes of Pharmacoepidemiological Studies: Design and First Results of the PROTECT Project. Curr Clin Pharmacol. 9(2): 130-138.
14. Balasegaram S, Majeed A, Fitz-Clarence H (2001) Trends in hospital admissions for fractures of the hip and femur in England, 1989-1990 to 1997-1998. J Public Health Med. 23 (1):11-17
15. Lalmohamed A, Welsing PM, Lems WF, Jacobs JW, Kanis JA, Johansson H, de Boer A, de Vries F (2012) Calibration of FRAX (R) 3.1 to the Dutch population with data on the epidemiology of hip fractures. Osteoporos Int. 23 (3):861-869.
16. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 17 (12):1726-1733.
17. Giversen IM (2006) 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. 17 (4):552-564.
18. Wu TY, Jen MH, Bottle A, Liaw CK, Aylin P, Majeed A (2011) Admission rates and in-hospital mortality for hip fractures in England 1998 to 2009: time trends study. J Public Health (Oxf). 33 (2):284-291.
19. Pages-Castella A, Carbonell-Abella C, Aviles FF, Alzamora M, Baena-Diez JM, Laguna DM, Nogues X, Diez-Perez A, Prieto-Alhambra D (2012) "Burden of osteoporotic fractures in primary health care in Catalonia (Spain): a population-based study". BMC Musculoskelet Disord. 13:79.
20. Goettsch WG, de Jong RB, Kramarz P, Herings RM (2007) Developments of the incidence of osteoporosis in The Netherlands: a PHARMO study. Pharmacoepidemiol Drug Saf .16 (2):166-172.
21. Icks A, Haastert B, Wildner M, Becker C, Meyer G (2008) Trend of hip fracture incidence in Germany 1995-2004: a population-based study. Osteoporos Int. 19 (8):1139-1145.
22. Dhanwal DK, Dennison EM, Harvey NC, Cooper C (2011) Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 45 (1):15-22. doi:10.4103/0019-5413.73656
23. Johnell O, Borgstrom F, Jonsson B, Kanis J (2007) Latitude, socioeconomic prosperity, mobile phones and hip fracture risk. Osteoporos Int. 18 (3):333-337.
24. Elffors I, Allander E, Kanis JA, Gullberg B, Johnell O, Dequeker J, Dilsen G, Gennari C, Lopes Vaz AA, Lyritis G, et al. (1994) The variable incidence of hip fracture in southern Europe: the MEDOS Study. Osteoporos Int 4 (5):253-263
25. Fretland S, Kruger O (1998) [Femoral neck fractures in Nord-Trondelag 1988-95. Incidence differences between winter and sommer months]. Tidsskr Nor Laegeforen. 118 (1):34-36
26. Gronskag AB, Forsmo S, Romundstad P, Langhammer A, Schei B (2010) Incidence and seasonal variation in hip fracture incidence among elderly women in Norway. The HUNT Study. Bone. 46 (5):1294-1298.
27. Poole KE, Compston JE (2006) Osteoporosis and its management. BMJ. 333 (7581):1251-1256. 10.1136/bmj.39050.597350.47
28. De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA (1997) Bone density and risk of hip fracture in men and women: cross sectional analysis. BMJ. 315 (7102):221-225
29. Johnell O, Gullberg B, Allander E, Kanis JA (1992) The apparent incidence of hip fracture in Europe: a study of national register sources. MEDOS Study Group. Osteoporos Int. 2 (6):298-302
30. Dolan P, Torgerson DJ (1998) The cost of treating osteoporotic fractures in the United Kingdom female population. Osteoporos Int. 8 (6):611-617
31. Tafuri S, Martinelli D, Balducci MT, Fortunato F, Prato R, Germinario C (2008) Epidemiology of femoral neck fractures in Puglia (Italy): an analysis of existing data. Ig Sanita Pubbl. 64 (5):623-636
32. Nilson F, Moniruzzaman S, Gustavsson J, Andersson R (2012) Trends in hip fracture incidence rates among the elderly in Sweden 1987-2009. J Public Health (Oxf). 35(1):125-131.
33. Adams AL, Shi J, Takayanagi M, Dell RM, Funahashi TT, Jacobsen SJ (2012) Ten-year hip fracture incidence rate trends in a large California population, 1997-2006. Osteoporos Int. 24(1):373-376.
34. Pasco JA, Brennan SL, Henry MJ, Nicholson GC, Sanders KM, Zhang Y, Kotowicz MA (2011) Changes in hip fracture rates in south-eastern Australia spanning the period 1994-2007. J Bone Miner Res. 26 (7):1648-1654.
35. Leslie WD, Sadatsafavi M, Lix LM, Azimaee M, Morin S, Metge CJ, Caetano P (2011) Secular decreases in fracture rates 1986-2006 for Manitoba, Canada: a population-based analysis. Osteoporos Int. 22 (7):2137-2143.
36. Holt G, Smith R, Duncan K, Hutchison JD, Reid D (2009) Changes in population demographics

and the future incidence of hip fracture. Injury. 40 (7):722-726.

37. Greene D, Dell RM (2010) Outcomes of an osteoporosis disease-management program managed by nurse practitioners. J Am Acad Nurse Pract. 22 (6):326-329.
38. PASEO (Physical Activity among SEdentary Older people). (2009) EU Commission, Executive Agency for Health and Counsumers (EAHC). http://www.paseonet.org/the_project.html. Accessed 2012 November
39. Huerta C, Abbing-Karahagopian V, Requena G, Oliva B, Alvarez Y, Gardarsdottir H, Miret M, Schneider C, Gil M, Souverein PC, De Bruin ML, Slattery J, De Groot MC, Hesse U, Rottenkolber M, Schmiedl S, Montero D, Bate A, Ruigomez A, García-Rodríguez LA, Johansson S, de Vries F, Schlienger RG, Reynolds RF, Klungel OH, de Abajo FJ. Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. Pharmacoepidemiol Drug Saf. 2015 Jul 7. doi: 10.1002/pds.3825. [Epub ahead of print]
40. Garcia Rodriguez LA, Ruigomez A (2010) Case validation in research using large databases. Br J Gen Pract. 60 (572):160-161.
41. Evans JG, Seagroatt V, Goldacre MJ (1997) Secular trends in proximal femoral fracture, Oxford record linkage study area and England 1968-86. J Epidemiol Community Health. 51 (4):424-429
42. Schilcher J, Michaelsson K, Aspenberg P (2011) Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 364 (18):1728-1737.

Supplementary Figure 2.3A. Trends over the study period of sex and age-specific IRs (in the population 50 years or older) in five databases with complete data.



Note that the scale used in the y-axis has been accommodated to better observe the trends and vary by age groups

Supplementary Table 2.3A Incidence rates and time trends in the general population in the participating databases of the study.

	2003	2004	2005	2006	2007	2008	2009	Slope (95% CI)	% variation[#]
BIFAP									
No. fractures	1503	1847	1871	1805	1745	1498	1137	-	
Person-years	1397047	1742682	1840894	1776966	1680082	1416105	1091342	-	
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
Standardised 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	3147	3375	3465	3611	3629	3677	3600	-	
Person-years	3640845	3847614	3932917	3972745	3901072	3830411	3640820	-	
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
Standardised 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	2880	3018	3126	3060	3142	3189	3101		
Person-years	3579571	3647552	3643259	3675595	3699299	3713072	3667410		
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
Standardised 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	106545	114024	120932	127565	133824	142231	-		
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	272655	173315	164399	135386	192507	154675	114214		
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
Standardised 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	9316	9568	9477	9291	9180	9296	9113		
Person-years	5207838	5223111	5209669	5210109	5209064	5222891	5207078		
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
Standardised 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	-	-	-	15196	13997	15154	-	-	-
Person-years[$]	-	-	-	10387207	10395597	10415393	-	-	-
IR per 10,000py	-	-	-	14.63	13.46	14.55	-	-	-
Standardized IR	-	-	-	13.39	12.13	12.91	-	-	-

* $p < 0.05$; # % Variation: (Slope/2003 IR)*100

$ Incidence per 10,000 Insured persons BAVARIAN, not enough data to assess time trends

Supplementary Table 2.3B: 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*

3

Understanding findings of pharmacoepidemiological studies: complexity of concomitant exposures

3.1

Understanding inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip fracture

Victoria Abbing-Karahagopian, Patrick C. Souverein, Elise Martin, Consuelo Huerta , Francisco de J. Abajo, Hubert G.M. Leufkens, Gianmario Candore, Yolanda Alvarez, Jim Slattery, Montserrat Miret, Gema Requena, Miguel Gil, Rolf H.H. Groenwold, Robert F. Reynolds, Raymond G. Schlienger, Mark C. H. de Groot, Olaf H. Klungel, Tjeerd P. van Staa, Toine C.G. Egberts, Marie L. De Bruin , Helga Gardarsdottir .

Accepted for publication in an adapted version in Pharmacoepidemiology and Drug Safety. 2015; 25 (suppl 1) doi: 10.1002/pds.3862

ABSTRACT

Background

Results from multiple observational studies on the same exposure-outcome association may be inconsistent due to variations in methodological, clinical and health care system factors. In this study we evaluated the impact of applying a common study protocol and data specifications on the consistency of results from cohort studies on antidepressant (AD) use and the risk of hip/femur fracture in three European primary care databases

Methods

In the 'Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium' (PROTECT) project we conducted separate cohort studies in three European primary care databases (Spanish BIFAP, Dutch Mondriaan and UK THIN) to assess the association between AD (i.e. selective serotonin re-uptake inhibitors [SSRI] and tricyclic antidepressants [TCA]) and hip/femur fracture. The hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using time-dependent multivariable Cox proportional hazard models.

Results

The adjusted HR for SSRI use and hip/femur fracture was higher in Mondriaan (3.27; 95% CI 1.93, 5.53) than BIFAP (1.63; 95% CI 1.45, 1.83) and THIN (1.72; 95% CI 1.59, 1.87. This difference may be partially explained by an interaction between SSRI and age in Mondriaan. The adjusted HR for TCA use and fracture was similar in Mondriaan (1.98; 95% CI 1.00, 3.92), BIFAP (1.28; 95% CI 1.02, 1.60) and THIN (1.32; 95% CI 1.20, 1.46).

Conclusion

Applying common protocol and data specifications on different populations and data produced some variation of results for SSRI use. However, consistently similar methods also enable identification of relevant effect modifiers.

INTRODUCTION

The availability and accessibility of electronic health care databases has greatly increased the number of pharmacoepidemiological studies over the past decades. The potential inconsistency of study findings on the same exposure-outcome association has fueled the debate on the validity and value of observational evidence [1] Reviews and meta-analyses are challenging tools to appraise this evidence [2] and to investigate sources of heterogeneity, which may be both methodological and clinical in nature [3]. The unravelling of these two factors can be difficult.

In the context of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project [4], we selected the example of antidepressant (AD) associated fracture risk to demonstrate the diversity of results. A wide range of pooled relative risk (RR) estimates has been reported for fractures in several meta-analyses [5-9] ranging from 1.01 [10] to 2.40 [11] for selective serotonin re-uptake inhibitors (SSRIs) and 1.21 [10] to 2.40 [12] for tricyclic antidepressants (TCAs) and fractures. Analyses that were restricted to cohort studies show a reduction in the heterogeneity index I^2 from 90% to 51% for studies on SSRI use [9] and from 77% to 30% for studies on TCA use and fractures [6] when compared to the main analysis. The design of the study is only one aspect of the methodological choices that influences results; therefore, the remaining heterogeneity still has to be explained. Other potential methodological factors contributing to heterogeneity are many, including differences in duration of follow-up, exposure (timing, duration and dose) and outcome definitions and the availability of confounders and their adjustment.

The aim of our study was to evaluate the impact of applying a common study protocol and data specifications on the consistency of results from cohort studies on AD (i.e. SSRIs and TCAs) use and the risk of hip/femur fracture in three European primary care databases.

METHODS

Study setting and data sources

This study was conducted within the Framework for Pharmacoepidemiology Studies, a sub-project within PROTECT, which aims to develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiology studies, applicable to different safety issues using different data [13].

A common study protocol [14] and data specification were designed to evaluate the association between AD use and hip/femur fracture using three European primary care databases:

the "Base de datos Informatizada para la investigación Farmacoepidemiologica en Atención Primaria" (BIFAP) [15]; the combined Mondriaan [16] databases of The Netherlands Primary Care Research Database (NPCRD) [17], and the Almere Health Care group (AHC) from the Netherlands; and The Health Improvement Network (THIN) [18] from the United Kingdom (UK). All databases provide general practitioner (GP) generated information [13].

Study cohorts

In this article, we use "PROTECT cohorts" to indicate these three cohorts collectively, and "BIFAP", "Mondriaan" and "THIN" to specify each database from which the cohort is derived.

The PROTECT cohorts included patients 18 years and older, who were enrolled in a GP practice for at least a year and who received one or more prescriptions of a SSRI or TCA during the period from 1 January 2001 to 31 December 2009 (31 December 2008 for Mondriaan-AHC). New user cohorts were identified, including patients with a first AD prescription (start date) during the study period without any AD prescription in the six months preceding the start date. Patients having a hip and/or femur fracture during the year prior to start date were excluded.

Exposure definition

For each patient, all SSRI and TCA prescriptions were identified and treatment episodes were constructed. A treatment episode was defined as a series of subsequent prescriptions, independent of dosage changes or switching between antidepressants. The theoretical duration of each prescription was estimated based on the number of tablets prescribed and the prescribed dosage regimen (BIFAP and THIN). In Mondriaan (NCPRD and AHC), prescription length was set at 90-days (maximum allowed prescription duration in the Netherlands) as information on the dosage regimen was absent. Patients were considered to have discontinued therapy if 30 days or more elapsed between the theoretical end date of an AD prescription and the subsequent AD prescription.

Exposure was further divided into episodes of current, recent and past use. Current use was considered as the treatment episode including additional 30 days after the estimated theoretical end date of the last prescription to account for carry-over effects. Recent use included the period between 1-60 days after current use. Past use included the period following recent use until a new prescription was filled or end of follow up.

Study outcome

Patients were followed from start date until the first hip/femur fracture or until the end of data collection, whichever came first. Hip/femur fractures were identified by International Classification Primary Care (ICPC)-2 codes and string text diagnosis in BIFAP, by ICPC-2

codes in Mondriaan and by Read codes in THIN [14]. Hip/femur fractures were manually reviewed in BIFAP (free text content) but not in Mondriaan and THIN.

Potential confounders

Potential confounders (co-medications, co-morbidities and lifestyle factors) were identified from the literature (Figure 1- footnote). Confounders were measured at baseline and updated whenever patients switched between exposure states. Within the same exposure state confounders were updated every 182 days. The status of co-medication use was defined as use in the prior 182 days and co-morbidities were defined as recorded or not ever before in the patient history. More details on study analyses are available online [14].

Systematic review of published cohort studies

To compare the risk estimates from this study with those reported in the literature, a systematic literature search was performed in PubMed (May 7, 2013). The search (Supplementary Figure 3.1A), included the terms: "Fracture" and ("antidepressant" or "antidepressive agents" or "selective serotonin reuptake inhibitors" or "SSRI") and "Fracture" and ("Tricyclic antidepressant" or "TCA") in the title/abstract of the publications. Subsequently, we searched for terms "cohort", "prospective" and "retrospective". A second search to screen studies identified in reviews/meta-analysis was performed using terms: "review" or "meta-analysis" and "fracture" and ("antidepressants" or "selective serotonin reuptake inhibitors" or "SSRI" or "Tricyclic antidepressant" or "TCA"). Studies were selected according to the following criteria: studies 1) assessing the association of AD use and fracture 2) a cohort design and 3) reporting risk estimates for SSRI and TCAs separately. Our selection criteria yielded seven studies on SSRI use [10, 12, 19-23] and risk of fracture and six studies on TCA use [10, 12, 19, 21-23] and risk of fracture (Supplementary Table 3.1A).

Statistical analyses

The risk of hip/femur fracture was estimated in models with incremental addition of confounders as follows (Figure 1): Model A: age and sex; Model B: well-established risk factors and life style factors added to Model A; Model C: risk factors related to fractures added to Model B; and Model D: a list of co-morbidities/co-medications added to Model C. Information on lifestyle factors was only available in THIN and partly in BIFAP. In addition, models B^-, C^- and D^- were also applied excluding lifestyle factors in all databases. The risks were expressed as hazard ratios (HRs) with 95% confidence intervals (CI) using time dependent Cox proportional hazard models. Past use was considered as the reference group.

Statistical analyses were done using SAS® version 9.2 (THIN and Mondriaan) and STATA version 11 (BIFAP) software. Analyses were performed locally at the institutions of the

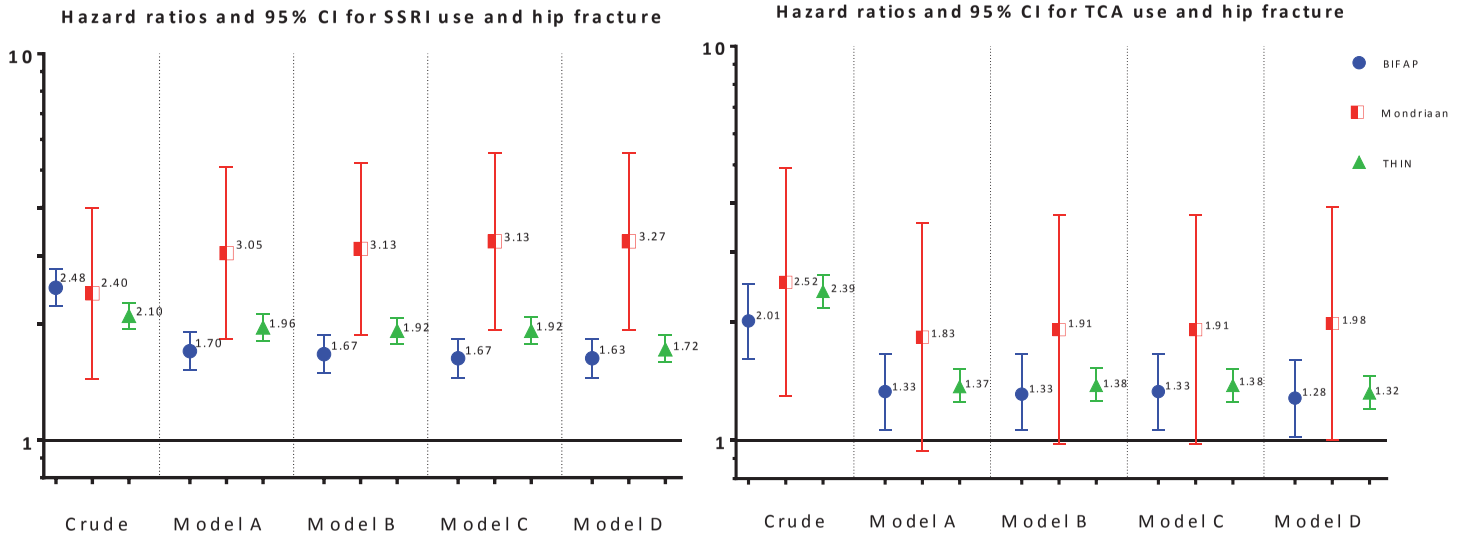


Figure 1: Crude and adjusted hazard ratios for current SSRI and TCA use and hip/fracture in the three PROTECT cohorts

Model A: age and sex; **Model B**: variables in model A and previous fracture, systemic glucocorticoid use and rheumatoid arthritis and lifestyle factors (smoking, alcohol use, and body mass index) ; **Model C:** variables in model B and history of osteoporosis, history of other bone diseases (Paget's disease, osteogenesis imperfect), previous use of bisphosphonate or any of the other bone protecting drugs: raloxifene, Strontium ranelate, Parathyroid hormone, Calcium & vitamin D, Calcitonin, Calcitriol; **Model D**: variables in model C and co-medications: benzodiazepines, antidepressants other that TCAs or SSRIs, antipsychotics/lithium, anti-Parkinson drugs, anticonvulsants, inhaled glucocorticoids, bronchodilators (including beta-2-adrenoceptors agonist and anticholinergics), anti-arrhythmics, sedating antihistamines, antihypertensive drugs (including ACE inhibitors, angiotensin II antagonists, Beta blocking agents, calcium channel blockers, other antihypertensives), diuretics, Estrogen-containing hormone replacement therapy (HRT), Thyroid hormones, anti-thyroid drugs, disease-modifying anti-rheumatic drug (DMARD), thiazolidinediones, other anti-diabetics, metoclopramide, anticoagulants, morphine/opiate, ≥2 prescriptions for a non-steroidal anti-inflammatory drug (NSAIDs), statins, proton pump inhibitors and aromatase inhibitors and co-morbidities: anaemia, seizures, syncope, ischaemic heart disease, cerebrovascular disease, malignant neoplasms, inflammatory bowel disease, obstructive airway disease, liver disease, impaired renal function, mental disorders and dementia and/or Alzheimer.

Models B, C, and D in Mondriaan do not include lifestyle factors: smoking, alcohol use, and body mass index. Models B, C, and D in BIFAP do not include information on alcohol use.

database teams. Results were blinded and submitted centrally to the PROTECT Research Manager. Results were not shared until all analyses were finalized.
Post-hoc sensitivity analyses were conducted aiming at explaining the study results. The first sensitivity analysis evaluated the impact of the 90-days AD prescription length assumption in Mondriaan. In Mondriaan, the crude and adjusted HRs were assessed for 60 and 30-days prescription lengths. The presence of an interaction between the exposure and age was investigated. Finally, non-linearity of age and fracture in the Mondriaan cohort was assessed.

To assess inconsistency among the results a comparison of the HRs was performed between the PROTECT and published cohort studies. The HR ranges for SSRI and TCA use was calculated as the difference between the largest and the smallest HRs. The pooled HRs and 95% CIs were estimated applying a random-effects model (with a priori assumption of between-study heterogeneity). Odds ratios (ORs) reported in published cohort studies and HRs estimated in the PROTECT cohorts were log transformed [24]. Forest plots were generated using Review Manager Software, version 5.2 [25].

RESULTS

There were 252,203, 22,954 and 587,637 new AD users included in the BIFAP, Mondriaan and THIN cohorts, respectively (Table 1). The mean age ranged from 49 to 51 years across cohorts. The BIFAP cohort included 10% more females than the other two cohorts. The proportion of patients using SSRIs at baseline ranged from 53% to 78% and those using TCA ranged from 14% to 32% in the three databases. The median duration of an AD treatment episode was 90 days (range: 1-3278), 176 days (range: 1-2920) and 86 days (range 1-3103) in BIFAP, Mondriaan and THIN, respectively. At baseline, the frequency of confounder variables varied among the cohorts (Table 1).

The crude HRs (95% CI) for current SSRI versus past use were 2.48 (2.22, 2.78), 2.40 (1.44, 4.00) and 2.10 (1.94, 2.27) and for current TCA 2.01 (1.61, 2.50), 2.52 (1.30, 4.92) and 2.39 (2.17, 1.63) in BIFAP, Mondriaan and THIN, respectively (Table 2). For current use of SSRI and TCA compared with past use, age and sex adjusted HRs were about 1.4- to 1.7- times higher in Mondriaan compared with BIFAP and THIN (Figure 1). Adjusting for age (and sex) increased the HR for current use of SSRI in Mondriaan and decreased in BIFAP and THIN. The fully adjusted models yielded a 1.9- to 2.0- times higher HR (3.27, 95% CI [1.93, 5.53]) for SSRI use in Mondriaan (Figure 1) compared with the other two PROTECT cohorts (1.63, 95% CI [1.45, 1.83], and 1.72, 95% CI [1.59, 1.87], in BIFAP and THIN, respectively). Similarly, though with a less pronounced difference than in SSRI users, current use of TCA

Table 1: Baseline characteristics of PROTECT cohorts.

	BIFAP	Mondriaan	THIN
Cohort characteristics	**N=252,203**	**N=22,954**	**N=587,637**
Age (years) mean ± SD	50.9 ± 16.9	48.8 ± 17.2	49.7 ± 18.5
Range	18 – 106	18 – 104	18 – 106
Females N(%)	183,451 (72.7)	14,596 (63.6)	374,551 (63.7)
Users N(%)			
SSRI	195,426 (77.5)	13,817 (60.2)	312610 (53.2)
TCA	35,377 (14.0)	7,585 (33.0)	186,785 (31.8)
SSRI and TCA	21,400 (8.5)	1,552 (6.8)	88,242 (15.0)
AD treatment episode duration in days (median)	90	176	86
range	1-3278	1-2920	1-3104
Hip/femur fracture N(%)	1,535 (0.6)	82 (0.4)	3,756 (0.6)
Previous fractures N(%)	12,584 (5.0)	1,106 (4.8)	109,533 (18.6)
Body mass index (kg/m^2) N(%)			
< 25	35,866 (14.2)	N/A	233,932 (39.8)
≥ 25	80,824 (32.1)		287,988 (49.0)
Missing	135,513 (53.7)		65,717 (11.2)
Smokers N(%)		N/A	
Never	84,165 (33.4)		284,761 (48.5)
Ex	4,089 (1.6)		118,234 (20.1)
Current	39,126 (15.5)		176,340 (30.0)
Missing	124,823 (49.5)		8,302 (1.4)
Alcohol users N(%)	N/A	N/A	420,244 (71.5)
No users			96,732 (16.5)
Missing			70,661 (12.0)
Co-morbidities N(%)			
Rheumatoid arthritis	1,508 (0.6)	0 (0)	9,362 (1.6)
Osteoporosis	13,575 (5.4)	409 (1.8)	14,780 (2.5)
Paget's disease	247 (0.1)	N/A	580 (0.1)
Anaemia	1,8557 (7.4)	1,063 (4.6)	41,091 (7.0)
Epilepsy/seizures	2,324 (0.9)	171 (0.7)	13,350 (2.3)
Syncope	16,261 (6.5)	734 (3.2)	20,965 (3.6)
Ischaemic heart disease	12,145 (4.8)	1,014 (4.4)	40,700 (6.9)
Cerebrovascular disease	9,550 (3.8)	536 (2.3)	23,129 (3.9)
Malignant neoplasms	16,469 (6.5)	1,350(5.9)	47,394 (8.1)
Inflammatory bowel disease	1,116 (0.4)	143 (0.6)	6,630 (1.1)
Obstructive airway disease	6,923 (2.7)	1,164 (5.1)	43,021 (7.3)
Liver disease	4,165 (1.7)	90 (0.4)	4,620 (0.8)
Chronic renal failure	2,304 (0.9)	0 (0.0)	2,827 (0.5)
Mental disorders (other than depression)	5,224 (2.1)	931 (4.1)	14,056 (2.4)
Dementia and/or Alzheimer	2,956 (1.2)	127 (0.6)	3,794 (0.6)
Co-medications N(%)			
Glucocorticoids (oral)	562 (0.2)	1,071 (4.7)	27,901(4.7)

in Mondriaan was associated with a higher risk (HR=1.98, 95% CI [1.00, 3.92]) compared with the risk found in BIFAP (HR=1.28, 95% CI [1.02, 1.60]) and THIN (HR=1.32, 95% CI [1.20, 1.46]). Including lifestyle factors in the analysis in BIFAP and THIN had negligible effect on the risk estimates (Table 2).

Table 1: Baseline characteristics of PROTECT cohorts. (continued)

	BIFAP	Mondriaan	THIN
Cohort characteristics	**N=252,203**	**N=22,954**	**N=587,637**
Bisphosphonate	6,341 (2.5)	369 (1.6)	9,203 (1.6)
Raloxifene	2,222 (0.9)	2 (0.0)	534 (0.1)
Strontium ranelate	322 (0.1)	2 (0.0)	260 (0.0)
Parathyroid hormone	56 (0.0)	1 (0.0)	0 (0.0)
Calcium & vitamin D	10,471 (4.2)	371 (1.6)	1,066 (0.2)
Calcitonin	1,031 (0.4)	0 (0.0)	41 (0.0)
Benzodiazepines	99,805 (39.6)	7,926 (34.5)	96,322 (16.4)
Antidepressants (other than SSRI and TCA)	8,787 (3.5)	768 (3.3)	15,043 (2.6)
Antipsychotics/lithium	13,769 (5.5)	592 (2.6)	29,577 (5.0)
Anti-Parkinson drugs	2,128 (0.8)	150 (0.7)	3,601 (0.6)
Anticonvulsants	10,659 (4.2)	724 (3.2)	16,415 (2.8)
Inhaled glucocorticoids	4,672 (1.9)	923 (4.0)	33,159 (5.6)
Bronchodilators	17,078 (6.8)	2,172 (9.5)	68,774 (11.7)
Anti-arrhythmic	1,523 (0.6)	89 (0.4)	2,926 (0.5)
Sedating antihistamines	2,270 (0.9)	0 (0.0)	2,241 (0.4)
Antihypertensive drugs*	47,569 (18.9)	4,406 (19.2)	134,302 (22.9)
Diuretics	23,276 (9.2)	2,194 (9.6)	77,534 (13.2)
Estrogen-containing hormone replacement therapy	3,968 (2.2)	724 (3.2)	36,450 (6.2)
Thyroid hormones	8,918 (3.5)	682 (3.0)	29,817 (5.1)
Anti-thyroid drugs	515 (0.2)	0 (0.0)	1,090 (0.2)
Disease-modifying anti-rheumatic drug (DMARD)	1,431 (0.6)	240 (1.0)	6,053 (1.0)
Thiazolidinediones	430 (0.2)	37 (0.2)	2,719 (0.5)
Other anti-diabetics	13,637 (5.4)	1,323 (5.8)	27,063 (4.6)
Metoclopramide	6,678 (2.6)	951 (4.1)	15,422 (2.6)
Anticoagulants	6,948 (2.8)	2,475 (10.8)	11,061 (1.9)
Morphine/opiate	17,082 (6.8)	1,983 (8.6)	66,498 (11.3)
non-steroidal anti-inflammatory drugs (≥2 prescriptions)	41,795 (16.6)	2,611 (11.4)	115,864 (19.7)
Statins	23,285 (9.2)	2,071 (9.0)	67,538 (11.5)
Proton pump inhibitors	58,323 (23.1)	3,623 (15.8)	85,968 (14.5)
Aromatase Inhibitors	526 (0.2)	39 (0.2)	1,547 (0.3)

N/A= info not available; SSRI= selective serotonin re-uptake inhibitors; TCA=tricyclic antidepressants; *= Antihypertensive drugs include ACE inhibitors, Angiotensin II antagonist, beta-blocking agents, Calcium channel blockers, and other hypertensive drugs except diuretics.

The range for the adjusted HRs (Figures 2a and 2b) for current SSRI use was larger for the PROTECT studies than for the published studies (1.64 and 1.34, respectively). The range for the adjusted HRs for TCA use was smaller for the PROTECT studies than for the published studies (0.70 and 1.19, respectively).

Adjusting the pre-defined AD prescription length in Mondriaan (Supplementary Table 3.1B) resulted in reduced median AD treatment episode length, from 176 to 134 and 120 days, for the 60 and 30-days prescription durations, respectively. However, there were no notable changes in risk estimates of SSRI and TCA use.

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Crude	Past use	526	409303	1	27	36,421	1	1,751	1,401,610	1
	Recent use *	137	57,617	1.91 (1.58 - 2.30)	7	3,388	2.57 (1.11 - 5.93)	239	134,840	1.42 (1.23 - 1.64)
	Current use *	872	293,268	2.37 (2.12 - 2.65)	48	25,465	2.39 (1.47 - 3.86)	1,766	651,516	2.16 (2.01 - 2.32)
	Type									
	TCA	93	37,135	2.01 (1.61 - 2.50)	13	18,360	2.52 (1.30 - 4.92)	597	199,712	2.39 (2.17 - 1.63)
	SSRI	740	236,974	2.48 (2.22 - 2.78)	35	6,620	2.40 (1.44 - 4.00)	1,118	425,123	2.10 (1.94 - 2.27)
	SSRI +TCA	39	19,159	1.64 (1.18 - 2.27)	0	485	NA	51	26,681	1.52 (1.15 - 2.02)
	Dose (DDD)									
	< 182	795	273,863	2.31 (2.07 - 2.59)	36	12,732	3.59 (2.13 - 6.06)	948	339,283	2.22 (2.03 - 2.43)
	≥ 182 < 365	33	10,857	2.43 (1.71 - 3.45)	1	3,174	0.39 (0.05 - 2.91)	256	124,786	1.62 (1.41 - 1.85)
	≥ 365	44	8,548	4.05 (2.98 - 5.51)	7	5,721	1.60 (0.69 - 3.68)	562	187,447	2.40 (2.18 - 2.64)
	Missing	0	0	0	4	3,838	1.52 (0.50 - 4.57)	0	0	0
	Duration (days)									
	0 - 30	83	58,203	1.44 (1.14 - 1.82)	7	2408	3.75 (1.61 - 8.71)	246	96,757	1.61 (1.32 - 1.97)
	31 - 182	302	105,401	2.04 (1.76 - 2.35)	24	10,077	3.05 (1.73 - 5.38)	600	254,163	1.74 (1.55 - 1.94)
	183 - 365	153	48,300	2.46 (2.06 - 2.95)	8	5,030	1.99 (0.90 - 4.42)	290	108,087	2.05 (1.79 - 2.34)
	> 365	334	81,364	3.21 (2.80 - 3.68)	9	7,950	1.50 (0.70 - 3.19)	639	192,509	2.69 (2.46 - 2.95)

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts (continued)

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Model A	Recent use *	137	57,617	1.71 (1.42 - 2.07)	7	3,388	2.60 (1.12 - 6.01)	239	134,840	1.38 (1.19 - 1.60)
	Current use *	872	293,268	1.63 (1.46 - 1.82)	48	25,465	2.53 (1.56 - 4.09)	1,766	651,516	1.70 (1.59 - 1.60)
	Type									
	TCA	93	37,135	1.33 (1.06 - 1.66)	13	18,360	1.83 (0.94 - 3.56)	597	199,712	1.37 (1.25 - 1.52)
	SSRI	740	236,974	1.70 (1.52 - 1.90)	35	6,620	3.05 (1.83 - 5.09)	1,118	425,123	1.96 (1.81 - 2.12)
	SSRI +TCA	39	19,159	1.37 (0.99 - 1.89)	0	485	NA	51	26,681	1.42 (1.08 - 1.88)
	Dose (DDD)									
	< 182	795	273,863	1.63 (1.46 - 1.82)	36	12,732	3.49 (2.07 - 5.89)	948	339,283	1.78 (1.63 - 1.95)
	≥ 182 < 365	33	10,857	1.39 (0.98 - 1.98)	1	3,174	0.50 (0.07 - 3.73)	256	124,786	1.47 (1.29 - 1.68)
	≥ 365	44	8,548	2.06 (1.51 - 2.80)	7	5,721	2.13 (0.92 - 4.92)	562	187,447	1.73 (1.57 - 1.90)
	Missing	0	0	0	4	3,838	1.35 (0.45 - 4.03)	0	0	0
	Duration (days)									
	0 - 30	83	58,203	1.20 (0.95 - 1.52)	7	2408	3.63 (1.56 - 8.44)	246	96,757	1.61 (1.31 - 1.97)
	31 - 182	302	105,401	1.64 (1.42 - 1.90)	24	10,077	3.14 (1.78 - 5.52)	600	254,163	1.76 (1.57 - 1.96)
	183 - 365	153	48,300	1.73 (1.44 - 2.07)	8	5,030	2.29 (1.03 - 5.06)	290	108,087	1.73 (1.51 - 1.98)
	> 365	334	81,364	1.71 (1.49 - 1.97)	9	7,950	1.59 (0.75 - 3.39)	639	192,509	1.67 (1.53 - 1.84)

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts (continued)

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Model B	Recent use *	137	57,617	1.72 (1.43 - 2.08)	7	3,388	2.63 (1.14 - 6.09)	239	134,840	1.38 (1.19 - 1.60)
	Current use *	872	293,268	1.61 (1.44 - 1.80)	48	25,465	2.61 (1.61 - 4.29)	1,766	651,516	1.69 (1.57 - 1.81)
	Type									
	TCA	93	37,135	1.33 (1.06 - 1.66)	13	18,360	1.91 (0.98 - 3.73)	597	199,712	1.38 (1.26 - 1.53)
	SSRI	740	236,974	1.67 (1.49 - 1.87)	35	6,620	3.13 (1.87 - 5.22)	1,118	425,123	1.92 (1.77 - 2.07)
	SSRI +TCA	39	19,159	1.37 (0.99 - 1.90)	0	485	NA	51	26,681	1.39 (1.05 - 1.84)
	Dose (DDD)									
	< 182	795	273,863	1.60 (1.43 - 1.80)	36	12,732	3.59 (2.13 - 6.07)	948	339,283	1.78 (1.63 - 1.95)
	≥ 182 < 365	33	10,857	1.38 (0.97 - 1.97)	1	3,174	0.52 (0.07 - 3.83)	256	124,786	1.46 (1.27 - 1.66)
	≥ 365	44	8,548	2.06 (1.51 - 2.80)	7	5,721	2.22 (0.96 - 5.15)	562	187,447	1.69 (1.53 - 1.86)
	Missing	0	0	0	4	3,838	1.40 (0.47 - 4.19)	0	0	0
	Duration (days)									
	0 - 30	83	58,203	1.13 (0.89 - 1.43)	7	2408	3.76 (1.62 - 8.75)	246	96,757	1.60 (1.31 - 1.96)
	31 - 182	302	105,401	1.54 (1.33 - 1.79)	24	10,077	3.23 (1.83 - 5.68)	600	254,163	1.76 (1.57 - 1.97)
	183 - 365	153	48,300	1.72 (1.44 - 2.07)	8	5,030	2.36 (1.06 - 5.22)	290	108,087	1.70 (1.49 - 1.95)
	> 365	334	81,364	1.77 (1.54 - 2.03)	9	7,950	1.65 (0.78 - 3.52)	639	192,509	1.66 (1.52 - 1.83)

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts (continued)

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Model C	Past use	526	409303	1	27	36,421	1	1,751	1,401,610	1
	Recent use *	137	57,617	1.72 (1.43 - 2.08)	7	3,388	2.63 (1.14 - 6.09)	239	134,840	1.38 (1.19 - 1.60)
	Current use *	872	293,268	1.61 (1.44 - 1.80)	48	25,465	2.61 (1.61 - 4.29)	1,766	651,516	1.68 (1.57 - 1.81)
	Type									
	TCA	93	37,135	1.33 (1.06 - 1.66)	13	18,360	1.91 (0.98 - 3.73)	597	199,712	1.38 (1.25 - 1.52)
	SSRI	740	236,974	1.67 (1.49 - 1.87)	35	6,620	3.13 (1.87 - 5.22)	1,118	425,123	1.92 (1.78 - 2.08)
	SSRI +TCA	39	19,159	1.36 (0.98 - 1.89)	0	485	NA	51	26,681	1.39 (1.05 - 1.84)
	Dose (DDD)									
	< 182	795	273,863	1.60 (1.43 - 1.79)	36	12,732	3.59 (2.13 - 6.07)	948	339,283	1.78 (1.63 - 1.95)
	≥ 182 < 365	33	10,857	1.38 (0.97 - 1.96)	1	3,174	0.52 (0.07 - 3.83)	256	124,786	1.46 (1.27 - 1.67)
	≥ 365	44	8,548	2.05 (1.50 - 2.79)	7	5,721	2.22 (0.96 - 5.15)	562	187,447	1.69 (1.54 - 1.86)
	Missing	0	0	0	4	3,838	1.40 (0.47 - 4.19)	0	0	0
	Duration (days)									
	0-30	83	58,203	1.13 (0.89 - 1.43)	7	2408	3.76 (1.62 - 8.75)	246	96,757	1.60 (1.31 - 1.96)
	31-182	302	105,401	1.55 (1.33 - 1.80)	24	10,077	3.23 (1.83 - 5.68)	600	254,163	1.76 (1.58 - 1.97)
	183-365	153	48,300	1.72 (1.43 - 2.06)	8	5,030	2.36 (1.06 - 5.22)	290	108,087	1.70 (1.48 - 1.95)
	> 365	334	81,364	1.77 (1.54 - 2.03)	9	7,950	1.65 (0.78 - 3.52)	639	192,509	1.67 (1.52 - 1.83)

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts (continued)

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Model D	Recent use *	137	57,617	1.67 (1.38 - 2.02)	7	3,388	2.59 (1.11 - 6.04)	239	134,840	1.36 (1.17 - 1.57)
	Current use *	872	293,268	1.56 (1.40 - 1.75)	48	25,465	2.71 (1.66 - 4.44)	1,766	651,516	1.54 (1.44- 1.66)
	Type									
	TCA	93	37,135	1.28 (1.02 - 1.60)	13	18,360	1.98 (1.00 - 3.92)	597	199,712	1.32 (1.20 - 1.46)
	SSRI	740	236,974	1.63 (1.45 - 1.83)	35	6,620	3.27 (1.93 - 5.54)	1,118	425,123	1.72 (1.59 - 1.87)
	SSRI +TCA	39	19,159	1.24 (0.90 - 1.72)	0	485	NA	51	26,681	1.22 (0.92 - 1.61)
	Dose (DDD)									
	< 182	795	273,863	1.57 (1.40 - 1.76)	36	12,732	3.81 (2.23 - 6.51)	948	339,283	1.74 (1.59 - 1.90)
	≥ 182 < 365	33	10,857	1.28 (0.90 - 1.82)	1	3,174	0.56 (0.08 - 4.18)	256	124,786	1.32 (1.15 - 1.51)
	≥ 365	44	8,548	1.87 (1.37 - 2.55)	7	5,721	2.35 (1.00 - 5.53)	562	187,447	1.46 (1.32 - 1.61)
	Missing	0	0	0	4	3,838	1.30 (0.44 - 3.88)	0	0	0
	Duration (days)									
	0-30	83	58,203	1.13 (0.89 - 1.43)	7	2408	3.81(1.63 - 8.91)	246	96,757	1.59 (1.30 - 1.94)
	31-182	302	105,401	1.54 (1.32 - 1.78)	24	10,077	3.27 (1.84 - 5.82)	600	254,163	1.74 (1.56 - 1.96)
	183-365	153	48,300	1.64 (1.37 - 1.97)	8	5,030	2.43 (1.09 - 5.44)	290	108,087	1.54 (1.34 - 1.77)
	> 365	334	81,364	1.70 (1.48 - 1.95)	9	7,950	1.78 (0.82 - 3.83)	639	192,509	1.54 (1.40 - 1.70)

Table 2: Crude and multivariate models of HR of SSRI and TCA and hip/femur fracture with incremental adjustment of confounders in the PROTECT cohorts (continued)

Model		BIFAP			Mondriaan			THIN		
		E	PY	HR (95%CI)	E	PY	HR (95%CI)	E	PY	HR (95%CI)
Model D - LS	Recent use *	137	57,617	1.67 (1.38 - 2.02)	7	3,388	2.59 (1.11 - 6.04)	239	134,840	1.36 (1.17 - 1.57)
	Current use *	872	293,268	1.56 (1.40 - 1.75)	48	25,465	2.71 (1.66 - 4.44)	1,766	651,516	1.54 (1.44- 1.66)
	Type									
	TCA	93	37,135	1.28 (1.02 - 1.60)	13	18,360	1.98 (1.00 - 3.92)	597	199,712	1.32 (1.20 - 1.46)
	SSRI	740	236,974	1.63 (1.45 - 1.83)	35	6,620	3.27 (1.93 - 5.54)	1,118	425,123	1.72 (1.59 - 1.87)
	SSRI +TCA	39	19,159	1.24 (0.90 - 1.72)	0	485	NA	51	26,681	1.22 (0.92 - 1.61)
	Dose (DDD)									
	< 182	795	273,863	1.57 (1.40 - 1.76)	36	12,732	3.81 (2.23 - 6.51)	948	339,283	1.74 (1.59 - 1.90)
	≥ 182 < 365	33	10,857	1.28 (0.90 - 1.82)	1	3,174	0.56 (0.08 - 4.18)	256	124,786	1.32 (1.15 - 1.51)
	≥ 365	44	8,548	1.87 (1.37 - 2.55)	7	5,721	2.35 (1.00 - 5.53)	562	187,447	1.46 (1.32 - 1.61)
	Missing	0	0	0	4	3,838	1.30 (0.44 - 3.88)	0	0	0
	Duration (days)									
	0-30	83	58,203	1.13 (0.89 - 1.43)	7	2408	3.81(1.63 - 8.91)	246	96,757	1.59 (1.30 - 1.94)
	31-182	302	105,401	1.54 (1.32 - 1.78)	24	10,077	3.27 (1.84 - 5.82)	600	254,163	1.74 (1.56 - 1.96)
	183-365	153	48,300	1.64 (1.37 - 1.97)	8	5,030	2.43 (1.09 - 5.44)	290	108,087	1.54 (1.34 - 1.77)
	> 365	334	81,364	1.70 (1.48 - 1.95)	9	7,950	1.78 (0.82 - 3.83)	639	192,509	1.54 (1.40 - 1.70)

Model A: age and sex; **Model B**: variables in model A and previous fracture, systemic glucocorticoid use and rheumatoid arthritis and lifestyle factors (smoking, alcohol use, and body mass index). Lifestyle factors were not available for Mondriaan and information on alcohol use was not available in BIFAP.; **Model C:** variables in model B and history of osteoporosis, history of other bone diseases (Paget's disease, osteogenesis imperfect), previous use of bisphosphonate or any of the other bone protecting drugs: raloxifene, Strontium ranelate, Parathyroid hormone, Calcium & vitamin D, Calcitonin, Calcitriol; **Model D**: variables in model C and co-medications: benzodiazepines, antidepressants other that TCAs or SSRIs, antipsychotics/lithium, anti-Parkinson drugs, anticonvulsants, inhaled glucocorticoids, bronchodilators (including Beta-2-adrenoceptors agonist and anticholinergics), anti-arrhythmics, sedating antihistamines, antihypertensive drugs (including ACE inhibitors, angiotensin II antagonists, Beta blocking agents, calcium channel blockers, other antihypertensives), diuretics, Estrogen-containing hormone replacement therapy (HRT), Thyroid hormones, antithyroid drugs, disease-modifying anti-rheumatic drug (DMARD), thiazolidinediones, other antidiabetics, antiemetic (metoclopramide), anticoagulants, morphine/opiate, two or more prescriptions for a non-steroidal anti-inflammatory drug (NSAIDs), statins, proton pump inhibitors and aromatase inhibitors and co-morbidities: anaemia, seizures, syncope, ischaemic heart disease, cerebrovascular disease, malignant neoplasms, inflammatory bowel disease, obstructive airway disease, liver disease, impaired renal function, mental disorders and dementia and/or Alzheimer. **Model D - LS:** variables in model D without lifestyle factors (smoking, alcohol use and body mass index). Model D and Model DS are the same in Mondriaan. *past use as the referent category. Dose: cumulative dose within current exposure categorized into three groups: DDD < 182, ≥182 and < 365 and ≥365 DDD) and duration of use within current exposure categorized into four groups: 0-30 days, 31-182 days, 183-365 days and >365 days. E=events; PY= person years; NA = not applicable

In Mondriaan, there was no interaction between age and TCA use (p=0.85). However, there was an indication of the presence of an interaction between age and SSRI use (p=0.07). Without taking interactions into account, the overall effect of SSRI use on hip fracture was 3.05 (95% CI: 1.83, 5.09). Allowing for an interaction between age and SSRI use in the adjusted model yielded a HR of 1.49 (95% CI: 0.57, 3.93) for subjects aged 50.9 years (mean age in BIFAP -Table 1). There was no interaction between age and exposure in BIFAP (p= 0.51 and p=0.98 for TCA and SSRI, respectively) and THIN (p=0.13 and p=0.21 for TCA and SSRI, respectively).

Additional analyses (results not shown) on non-linearity of age and fracture in Mondriaan showed that the relation between age and the outcome was linear and adding e.g. age squared to the model did not change the effect estimates of SSRI and TCA use.

DISCUSSION

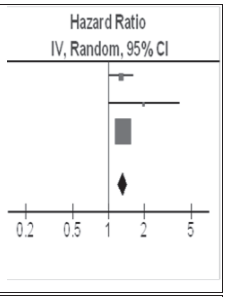
In the three uniformly conducted PROTECT cohort studies, we found that both SSRI and TCA use were associated with an increased risk of hip/femur fracture. These results are consistent with studies previously reporting an association. The HRs for SSRI use were higher in Mondriaan compared with HRs in BIFAP and THIN while the HRs for TCA use were similar in all cohorts. The range between the adjusted HRs for SSRI use was larger among the PROTECT studies (HRs: 3.27 and 1.63) than the range among the published studies (HRs: 2.35 and 1.01). The interpretation of the risk estimates from the fully adjusted models in Mondriaan should be done with caution as the cohort from the Mondriaan databases was a much smaller and a younger cohort compared to the cohorts from the BIFAP and the THIN databases.

Despite harmonizing the study design, protocol and data specifications, we found higher risk estimates for SSRI use in Mondriaan than in BIFAP and THIN. Several sensitivity analyses were conducted to explore the possible reasons for this.

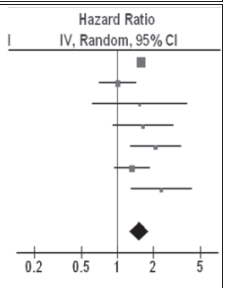
Our assumption that a 90-days AD prescription duration in Mondriaan would result in bias toward an increased risk was not confirmed by changes in risk estimates. The interaction between SSRI exposure and age in Mondriaan (potential higher effect of SSRI among younger patients), though statistically not significant, indicates the possible presence of an age related factor, which was absent in the other two cohorts. This factor cannot be one of the confounding variables we adjusted for in our study. The confounding variables were selected and controlled similarly in the three databases. Lifestyle variables not recorded in Mondriaan and partly recorded in BIFAP did not introduce notable differences in HRs in

2a

Study on SSRI	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95%
BIFAP	0.4886	0.0597	43.1%	1.63 [1.45,1.83]
Mondriaan	1.1848	0.269	7.6%	3.27 [1.93,5.54]
THIN	0.5448	0.0414	49.3%	1.72 [1.59, 1.87)
Total (95% CI)			100%	1.77 [1.51,2.07]
Range of HRs				1.64
Hetrogeniety:Tau^2 = 0.1; Chi^2 = 6.49, df=2 (p=0.04); I^2=69%; 95%CI [10,62]				
Test for overall effect : Z=7.13 (P<0.00001)				

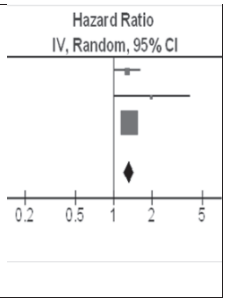


Study on SSRI	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95%
Coupland 2011	0.4574	0.0334	38.0%	1.58 [1.48,1.69]
Diem 2011	0.01	0.1798	15.8%	3.27 [0.71,1.44]
Ensrud 2003	0.4318	0.4642	3.6%	1.54 [0.62, 3.83]
Lewis 2003	0.5008	0.298	7.7%	1.65 [0.92, 2.96]
Richards 2007	0.7419	0.2447	10.4%	2.10 [1.30, 3.39]
Sprangler 2008	0.2852	0.1717	16.7%	1.33 [0.95,1.86]
Ziere 2008	0.8544	0.2943	7.8%	2.35 [1.32, 4.18]
Total (95% CI)			100%	1.52 [1.27,1.82]
Range of HRs				1.34
Hetrogeniety:Tau^2 = 0.2; Chi^2 = 10.29, df=6 (p=0.11); I^2=42%; 95%CI [43,83]				
Test for overall effect : Z=4.58 (P<0.00001)				



2b

Study on TCA	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95%
BIFAP	0.2449	0.1148	15.7%	1.28 [1.02,1.60]
Mondriaan	0.683	0.3485	1.7%	1.98 [1.00,3.92]
THIN	0.2904	0.05	82.6%	1.32 [1.20, 1.46)
Total (95% CI)			100%	1.33 [1.21,1.45]
Range of HRs				0.70
Hetrogeniety:Tau^2 = 0.00; Chi^2 = 1.43, df=2 (p=0.49); I^2=0%; 95%CI [0,100]				
Test for overall effect : Z=6.20 (P<0.00001)				



Study on TCA	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95%
Coupland 2011	0.2311	0.0422	52.8%	1.26 [1.16,1.37]
Diem 2011	0.1906	0.1742	16.9%	1.21 [0.86,1.70]
Ensrud 2003	0.6043	0.2691	8.4%	1.83 [1.08, 3.10]
Lewis 2003	0.8713	0.3226	6.1%	2.39 [1.27, 4.50]
Richards 2007	0.1823	0.275	8.1%	1.20 [0.70, 2.06]
Ziere 2008	0.5247	0.2833	7.7%	1.69 [0.97,2.94]
Total (95% CI)			100%	1.37 [1.16,1.61]
Range of HRs				1.19
Hetrogeniety:Tau^2 = 0.01; Chi^2 = 6.76, df=5 (p=0.24); I^2=26%; 95%CI [0,52]				
Test for overall effect : Z=3.73 (P<0.0002)				

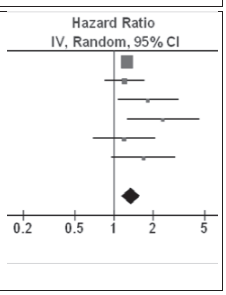


Figure 2 Forest plots of fully adjusted* hazard ratios from PROTECT and published studies on SSRI use (2a) and TCA use (2b) and hip fracture.

SE =standard error; IV=inverse variance; CI= confidence interval; df= degrees of freedom; * HRs are adjusted for all available confounders in the three databases (Model **D** for BIFAP and THIN and Model **D** - excluding lifestyle variables for Mondriaan) for details refer to online appendix. Forest plots were generated using Revman software and 95% CIs for I^2 were (added to the figure) calculated manually applying formula suggested by Higgins et al (2). Range (highest minus lowest) for the HRs (added to the figure) was calculated manually.

BIFAP and THIN (Table 2). Moreover, the list of the adjusted confounders was extensive, limiting the possibility of a substantial influence of residual confounding on our results. Nevertheless, the presence of interaction between age and SSRI exposure in the Mondriaan cohort and the absolute values of the risk estimates especially in the fully adjusted models should be interpreted with caution. The interaction phenomenon should be further tested in larger populations to exclude factors like small sample size effects.

Different coding systems (ICPC-2 codes in BIFAP and Mondriaan and Read codes in THIN) to identify the outcome could have introduced inconsistency. We were also unable to distinguish between hip and femur fractures the proportion of which may defer by age. No linkages to hospital data were done in any of the databases to prevent discrepancies in the level of outcome ascertainment. An extra case ascertainment step, using free text information, was performed in BIFAP as the only divergent step in the study protocol. This step excluded 31.5% of the cases with fractures other than hip/femur. We did not estimate the HRs including these fracture cases or explore the distribution of these over the different exposure states. Despite this additional ascertainment in BIFAP, risk estimates were comparable between BIFAP and THIN.

Health care system/clinical aspects

The higher risk of fracture found among AD users in Mondriaan may be explained by factors other than study methods. In an earlier study [26], we found that the Netherlands has the lowest and most stable prevalence of AD prescribing during the study period compared with Spain and the UK. Moreover, we compared incidence rates of hip/femur fracture during the study period [27] and found in 2008 an incidence of hip/femur fracture per 10,000 person-years of 10.6 in Spain, 7.3 (NPCRD) and 8.9 (AHC) in the Netherlands and 8.7 in the UK. These rates were comparable to rates in other European countries. Furthermore, country level differences in AD prescribing and incidence of hip fracture exist. We also showed that even with the assumption of shorter prescription lengths, the duration of AD use was longer in Mondriaan compared with BIFAP and THIN. However, our results did not show increasing risk by duration of use. The sensitivity analyses showed that the higher risk in Mondriaan is not due to the difference in methods for defining prescription duration.

There are two previously published studies on AD use and fractures conducted in different Dutch databases. These studies (cohort design [19] and case-control design [28]), report higher risk estimates for SSRI use compared results from the published studies selected in our study (but lower than in Mondriaan). Furthermore, a study [29] in the UK Clinical Practice Research Datalink (previously known as General Practice Research Database) reported odds ratios for fracture outcomes ≥43 days after the first prescription of TCA [1.15, 95% CI:1.08; 1.23] and SSRI [1.32, 95% CI: 1.19; 1.48]. These risk estimates, despite

study design differences, are comparable to our results in THIN. Whether this country level difference, specifically the higher risk of fracture among AD users in the Netherlands, is due to specific clinical factors deserves further exploration. Moreover, country level differences in AD prescribing in primary care and health care system in general, especially in Europe, are documented [30]. Although the GP is the gatekeeper of the health care system in Spain, the Netherlands and the UK, differences in accessibility to specialist care might exist.

Our approach of harmonizing study methods allowed us to minimize methodological differences and explain possible non-methodological factors. In pharmacoepidemiology, there are several consorted efforts focusing on the use of different methods and data sources for improving drug safety systems. A recently published study [31] by the Observational Medical Outcomes Partnership (OMOP [32]) is worth contrasting against our study. The OMOP study examined 53 drug and adverse-event associations in nine different databases applying cohort and self-controlled case series designs. In the OMOP study, authors developed a common data model, which was applied to different data sources and subsequently performed a uniform analysis to estimate risks. Although keeping study designs constant, the heterogeneity (I^2 index) remained substantial. Our approach of extensive harmonization, from definitions of variables to analyses step, minimized heterogeneity due to study method differences and allowed to investigate other possible factors introducing heterogeneity.
The common-protocol approach in which data sources are analyzed separately instead of a priori pooling of data sources allows the investigation of additional sources of variability that would otherwise have been lost in the pooling process as in the OMOP study [31].

A limitation of this study is that, regardless of our extensive effort to harmonize the study protocol and data specification document, inherent differences of databases hindering this process could not be avoided. There are differences in coding systems and the level of detailed information on studied outcome, co-morbidities and lifestyle factors. However, we found comparable incidences of fracture and a minimal effect of adjustment of confounders on the HRs compared with the effect of adjusting for age/sex. Differences in the application of statistical analyses using different software packages (SAS and STATA) was harmonized at syntax level excluding the possibility of discrepancies due to differences in programming. Another aspect of using a predefined common protocol is the selection of a fixed set of confounders in multivariable models in PROTECT cohorts regardless of their impact. The impact of this approach on the risk estimates and their confidence intervals needs further investigation. The presence of interaction between age and the exposure should be further investigated in larger databases.

We observed an increased risk of hip/femur fracture in AD users in all three cohorts. Applying similar pharmacoepidemiological study methods to different populations and data

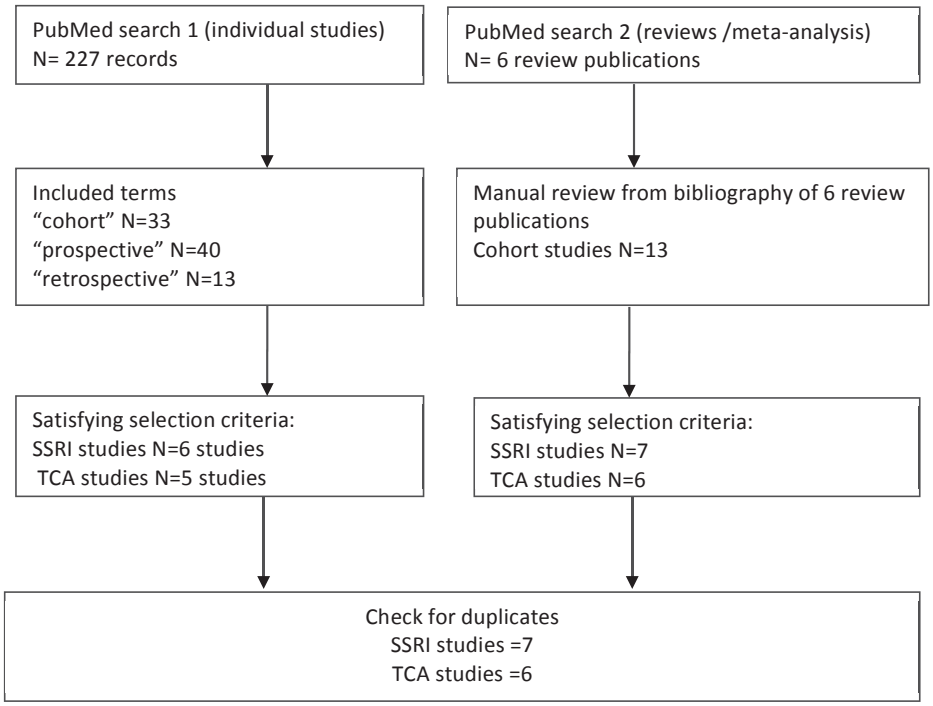
sources resulted in similar risks for TCA use and some variation for SSRI use. Some of these differences may express real (or natural) variance in the exposure-outcome co-occurrences. However, consistently similar methods also enable the identification of relevant possible effect modifiers.

REFERENCES

1. Vandenbroucke JP. Balancing benefits and harms in health care: observational data on harm should complement systematic reviews of benefit. BMJ. 2003; 327: 750.
2. Dobbins M, Cockerill R, Barnsley J. Factors affecting the utilization of systematic reviews. A study of public health decision makers. Int J Technol Assess Health Care. 2001; 17: 203-14.
3. Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ. 1994; 309: 1351-5.
4. PROTECT-EU. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium. http://www.imi-protect.eu/ (cited 10 July, 2014).
5. Wu Q, Bencaz AF, Hentz JG et al. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int. 2012; 23: 365-75.
6. Wu Q, Qu W, Crowell MD et al. Tricyclic antidepressant use and risk of fractures: A meta-analysis of cohort and case-control studies. J Bone Miner Res. 2013; 28: 753-63.
7. Rabenda V, Nicolet D, Beaudart C, et al. Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int. 2012; 24: 121-37.
8. Oderda LH, Young JR, Asche CV et al. Psychotropic-related hip fractures: meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. Ann Pharmacother. 2012; 46: 917-28.
9. Eom CS, Lee HK, Ye S et al. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. J Bone Miner Res. 2012; 27: 1186-95.
10. Diem SJ, Blackwell TL, Stone KL et al. Use of antidepressant medications and risk of fracture in older women. Calcif Tissue Int. 2011; 88: 476-84.
11. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998; 351: 1303-7.
12. Lewis CE, Ewing SK, Taylor BC et al. Predictors of non-spine fracture in elderly men: the MrOS study. J Bone Miner Res. 2007; 22: 211-9.
13. Abbing-Karahagopian V, Kurz X, de Vries F et al. Bridging Differences in Outcomes of Pharmacoepidemiological Studies: Design and First Results of the Protect Project. Curr Clin Pharmacol. 2014; 9: 130-8.
14. ENCePP. The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance. Electronic Register of Studies. http://www.encepp.eu/encepp/viewResource.htm?id=3667 (cited 10 July, 2014).
15. Medicines and Healthcare products Regulatory Agency (MHRA). Addiction to benzodiazepines and codeine: supporting safe use. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123123 (cited 10 July, 2014).
16. Welke KF, Karamlou T, Diggs BS. Databases for assessing the outcomes of the treatment of patients with congenital and paediatric cardiac disease—a comparison of administrative and clinical data. Cardiol Young. 2008; 18 Suppl 2: 137-44.
17. Lader M. Benzodiazepines revisited—will we ever learn? Addiction. 2011; 106: 2086-109.
18. Mercier A, Auger-Aubin I, Lebeau JP et al. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. BMC Fam Pract. 2013; 14: 55.
19. Ziere G, Dieleman JP, van der Cammen TJ et al. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of nonvertebral fractures. J Clin Psychopharmacol. 2008; 28: 411-7.
20. Spangler L, Scholes D, Brunner RL et al. Depressive symptoms, bone loss, and fractures in postmenopausal women. J Gen Intern Med. 2008; 23: 567-74.

21. Richards JB, Papaioannou A, Adachi JD et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007; 167: 188-94.
22. Ensrud KE, Blackwell T, Mangione CM et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med. 2003; 163: 949-57.
23. Coupland C, Dhiman P, Morriss R et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011; 343: d4551.
24. Walter SD, Cook RJ. A comparison of several point estimators of the odds ratio in a single 2 x 2 contingency table. Biometrics. 1991; 47: 795-811.
25. Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.
26. Abbing-Karahagopian, Huerta C, Souverein P et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations and methodological implications. Eur J Clin Pharmacol. 2014; 70: 849-57.
27. Requena G, Abbing-Karahagopian V, Huerta C et al. Trends in incidence rates of hip and femur fracture in five European countries, 2003-2009. A comparison using electronic health care records databases. Calcif Tissue Int. 2014; 94: 580-9. .
28. Verdel BM, Souverein PC, Egberts TC et al. Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. Bone. 2010; 47: 604-9.
29. Hubbard R, Farrington P, Smith C et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol. 2003; 158: 77-84.
30. Paykel ES, Brugha T, Fryers T. Size and burden of depressive disorders in Europe. Eur Neuropsychopharmacol. 2005; 15: 411-23.
31. 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; 178: 645-51
32. Foundation for the National Institutes of Health. Observational Medical Outcomes Partnership. http://omop.fnih.org/ (cited 10 July, 2013)
33. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-60.

Supplementary Figure 3.1A
Systematic review of published cohort studies on antidepressant use and hip fracture.



Supplementary Table 3.1A: Main study characteristics of the PROTECT cohorts and selected published cohort studies

Author (Year) Country	Study population (age in yrs) N=number	Exposure assessment (timing)	Fracture type (validation) N=number of cases	Mean follow-up (yrs)	Adjusted covariates (adjustment timing)
PROTECT cohorts	GP database (18+) BIFAP N=252,203 Mondriaan N=22,912 THIN N=588,850	Prescribing data (time varying, current= TE +30days, recent=1-60 days, past=90 days following current)	Hip/femur (prescribing data) BIFAP N=740 (SSRI), N=93 (TCA) Ascertainment with free text for BIFAP Mondriaan N=35 (SSRI), N=13 (TCA) THIN N=1118 (SSRI), N=597 (TCA)	BIFAP =3.0 Mondriaan=2.9 THIN=3.7	Age/sex/lifestyle factors/established confounders/confounders related to outcome/list of co-medications and co-morbidities. Lifestyle factors not recorded in Mondriaan [GP records] *(time-dependent)*
Coupland et al (2011) UK	Diagnosed with depression (65+) N=60746	GP records (time varying, time since start & stop periods of 1-28, 29-84 & 85+ days)	Limb, ribs, skull, vertebrae, pelvis (GP records) N=1597 (SSRI) N=809 (TCA)	5.0	Age/sex/depression – severity/Townsend deprivation score /smoking/previous falls, co-morbidities & co-medications [GP records]*(baseline)*
Diem et al (2011) US	Community dwelling women (70+) N=8412	Interview, medicine box check (4 cross-sectional moments: use/no use 30 days prior interview)	Hip (interview, radiograph check) N=87[a] (SSRI) N=33[a] (TCA)	10.0	Age/health status/weight/IADLs/ability to rise from a chair/m-MMSE/smoking/ use of alcohol/co-medications/medical history/GDS score/walks for exercise / fracture, falls history/total-hip BMD [interview] *(4 points in time)*
Ensrud et al (2003) US	Community dwelling women (65+) N=8127	Interview (cross-sectional at 2 points in time)	Hip(interview, radiograph check) N=6[a] (SSRI) N=24[a] (TCA)	4.8	Age/BMD/health status/co-morbidity/ co-medication/physical activity/ neuromuscular function/falls/cognitive function/smoking/ depression score [examination & interview] *(2 points in time)*

Supplementary Table 3.1A: Main study characteristics of the PROTECT cohorts and selected published cohort studies (continued)

Author (Year) Country	Study population (age in yrs) N=number	Exposure assessment (timing)	Fracture type (validation) N=number of cases	Mean follow-up (yrs)	Adjusted covariates (adjustment timing)
Lewis et al (2007) US	Community dwelling men (65+) N=5876	Interview (baseline) TCA users 1.7%	Non-spine (tri-annual interview/ radiograph check) N=11[a] (SSRI) N=10[a] (TCA)	4.1	Age/BMD/clinical site/ race-ethnicity/ functional status, anthropometric, cognitive, visual and neuromuscular function, co-medications and co-morbidity [examination & interview] *(baseline)*
Richards et al (2007) CA	Community dwelling (50+) N= 5008	Interview, medicine box check (baseline & at 5 yrs, Current use =baseline)	NS (Self-report, radiograph check) N=17[a] (SSRI) N=13[a] (TCA)	5.0	BMD/height, weight/ smoking/physical activity/falls, previous fractures/vertebral deformities/co-morbidity/co-medication/ mental state, depression score [interview] *(baseline)*
Spangler et al (2008) US	Women (50-79) N=93676	Interview, medicine box check (baseline)	Hip (interview, hospital record check) N=734[a] (SSRI)	7.4	Age/weight-height/ethnicity/years since menopause/physical function/smoking/ CVD/ analgesic or narcotic/previous fracture/Depressive symptoms [interview] *(baseline)*
Ziere et al (2008) NL	Community dwelling (55+) N=7983 TCA users=0.31%	Dispensing data (time varying; current (event date), past	Non-vertebral (GP record) N=18 (SSRI) N=25 (TCA)	8.4	Age/sex/ depression during follow up, disability category, lower-limb disability/ co-medication/co-morbidities [interview, examination, dispensing records]*(baseline and time-dependent)*

a=estimated from published information, GP= general practice, SSRI=selective serotonin reuptake inhibitor, TCA= tricyclic antidepressant, IADL= independent activities of daily living, m-MMSE= Mini-Mental State Examination, GDS= geriatric depression scale, BMD=bone marrow density, NSAID= non-steroidal anti-inflammatory drugs, OCD=obsessive-compulsive disorder; NS= not specified fracture; TE= treatment episode; UK= United Kingdom; US= United States; CA=Canada; NL= the Netherlands

Supplementary Table 3.1B: Crude and age and sex adjusted hazard ratios and 95% confidence intervals for main and sensitivity analyses for Mondriaan cohort

database	Mondriaan								
	Main analysis: Rx length 90 days			Sensitivity analysis: Rx length 60 days			Sensitivity analysis: Rx length 30 days		
AD use	**Crude HR (95% CI)**	**Age/sex adjusted HR (95% CI)**	**Events (person-years exposed)**	**Crude HR (95% CI)**	**Age/sex adjusted HR (95% CI)**	**Events (person-years exposed)**	**Crude HR (95% CI)**	**Age/sex adjusted HR (95% CI)**	**Events (person-years exposed)**
Past	referent	referent	27 (36,421)	referent	referent	31 (38,178)	referent	referent	35 (40,399)
Recent	2.57 (1.11-5.93)	2.60 (1.12-6.01)	7 (3,388)	2.03 (0.89-4.63)	2.04 (0.89-4.66)	7 (3,977)	1.31 (0.58-2.97)	1.27 (0.56-2.87)	7 (5,761)
Current	2.39 (1.47-3.86)	2.53 (1.56-4.09)	48 (25,465)	2.19 (1.37-3.51)	2.33 (1.46-3.72)	44 (23,118)	2.27 (1.43-3.61)	2.42 (1.53-3.85)	40 (19,115)
CA	2.52 (1.30-4.92)	1.83 (0.94-3.56)	13 (6,620)	2.20 (1.10-4.40)	1.59 (0.79-3.18)	11 (5,854)	2.60 (1.31-5.14)	1.86 (0.94-3.68)	11 (4,692)
SRI	2.40 (1.44-4.00)	3.05 (1.83-5.09)	35 (18,360)	2.24 (1.36-3.70)	2.85 (1.73-4.69)	33 (16,858)	2.21 (1.34-3.66)	2.82 (1.71-4.66)	29 (14,120)
SRI & TCA	NA	NA	0 (485)	NA	NA	0 (406)	NA	NA	0 (303)

AD= antidepressants; HR= hazard ratio; CI= confidence interval; Rx= prescription TCA= tricyclic antidepressants

3.2

Concomitant medication use and its implications on the hazard pattern in pharmacoepidemiological studies: example of antidepressants, benzodiazepines and fracture risk

Victoria Abbing-Karahagopian, Patrick C. Souverein, Joke C. Korevaar, Hubert G.M. Leufkens, Toine C.G. Egberts, Helga Gardarsdottir and Marie L. De Bruin.

Epidemiology, Biostatistics and Public Health. 2015; 12 (3): e11273-1

ABSTRACT

Background

Antidepressants and benzodiazepines are often co-prescribed and both associated with an increased fracture risk, albeit with distinctive hazard patterns. Timing of initiation of one with respect to the other and duration of use may influence the combined fracture hazard.

Objectives

To describe patterns of concomitant use of benzodiazepine and antidepressants in terms of timing of initiation and duration and to illustrate the potential impact of various scenarios of timing of co-use on hip fracture hazard.

Methods

Patients initiating antidepressant therapy (2002-2009) were identified from the Netherlands Primary Care Research Database. Concomitant benzodiazepine use was assessed according to the start time of benzodiazepine with respect to antidepressant therapy start. Duration of concomitant use was estimated relative to the length of antidepressant treatment episode.

Results

Among 16,087 incident antidepressant users, 39.0% used benzodiazepines concomitantly during their first antidepressant treatment episode. The time of initiation of benzodiazepine use was variable (64.4% starting before, 13.7% simultaneous and 21.9% after antidepressants). Duration of concomitant use in the three groups varied.

Conclusions

Co-prescribed medications with a common adverse event may not only require accounting for concomitant use, but also the timing of start and duration of use as the overall hazard may vary accordingly.

BACKGROUND

Poly-pharmacy is often unavoidable in daily clinical practice, but may be associated with additional risks of adverse events. Several examples of frequently combined medications with the same adverse event have been described: aspirin and clopidogrel and the risk of bleeding [1] anti-rheumatic agents and methotrexate and the risk of hepatotoxicity [2] and angiotensin converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drug (NSAID) use and renal impairment [3]. When hazard patterns of drug-adverse event vary over time, the risk of an adverse event may differ at the initiation of a therapy compared to during continuous use or even after termination of therapy. Timing of start of concomitant medication use may hence modify the combined effect.

Electronic health care databases are often used for observational research on adverse effects of medications [4, 5]. The availability of longitudinally recorded data allows for a detailed characterization of both the exposure to medication and the outcome of interest. In more recent drug-adverse event studies, we observe elaborated definitions of the main exposure of interest but rarely of the concomitant medication use as a confounding or effect modifying factor. It is important to account for concomitant medication use in more detail, as two medications may be associated with the same adverse event, albeit with different hazard patterns over time.

To elaborate this, we portray the example of concomitant use of benzodiazepines among antidepressant users and the hazard for fracture as the common adverse event. Concomitant use of antidepressants and benzodiazepines is proven to be effective to treat the acute phase of depression [6] and hence are often co-prescribed in routine clinical practice [7]. The use of antidepressants [8-14] and benzodiazepines [15-20] have both been associated with an increased risk of fractures. The hazard patterns for fracture have been reported to be different for these two classes of medications. Studies have reported high risk of fracture for antidepressant use (both selective serotonin re-uptake inhibitors and tricyclic antidepressants) starting three to six months after continuous use followed by a lower but persistent risk up until in the fourth to fifth year of continuous use [9,12, 11]. In contrast, fracture risk is highest immediately after initiation of benzodiazepine use and there is a marked decrease in the risk upon continuous use as reported in various studies [18, 20, 22]. Accordingly, fracture hazard for antidepressant use is high long after initiation of therapy with bone mineral density alteration as the potential mechanism of action, whereas the more acute risk for fracture associated with benzodiazepine use is thought to be related to an increased risk of falls. Assuming at least an additive effect of concomitant use and the approximate patterns of fracture hazard for antidepressant and benzodiazepine use roughly derived from risk estimates reported in previous studies as noted above, different timings of

benzodiazepine use start may modify the combined risk for fracture. This is shown in Figure 1, where different scenarios of combined risk patterns for concomitant use are depicted. Scenario 1A represents the situation where patients use antidepressants but do not use benzodiazepines and hence bear the potential risk pattern associated with antidepressant use only. Further, scenarios 1B, 1C and 1D represent situations where patients start using benzodiazepine concomitantly before, simultaneous and after the initiation of antidepressant use, respectively. As shown, the coexisting and/or overlapping risk patterns, assuming at least an additive effect, for these three groups are different.

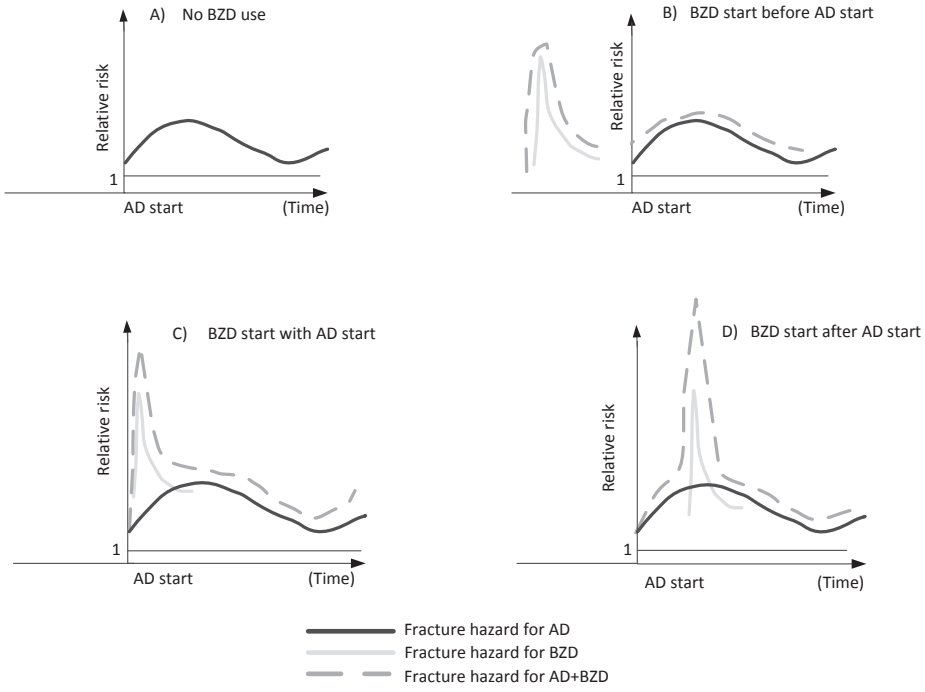


Figure 1: Four scenarios of timing of benzodiazepine initiation among new antidepressant users and their respective hazard functions for hip fracture over time
AD=antidepressants
BZD=benzodiazepine

The aim of this study was to estimate concomitant use of benzodiazepine among antidepressant users and characterize the timing of benzodiazepine start with respect to antidepressant therapy start and the duration of concomitant use. Secondly, we aimed to illustrate scenarios of timing of initiation and duration of concomitant benzodiazepine use among

antidepressant users and discuss potential scenarios and implications on the estimation of the combined hazard for hip fracture.

METHODS

Setting

Data were obtained from the Netherlands Primary Care Research Database (NPCRD) [23], a database from general practices that register data on morbidity, drug prescriptions and referrals in electronic medical records on a continuous basis. The NPCRD includes more than 350,000 patients registered at 85 practices. Prescription data are classified according to Anatomical Therapeutic and Chemical (ATC) [24] classification and morbidity is coded using the International Classification of Primary Care (ICPC) [25].

Study population

All patients with a first prescription for an antidepressant drug (ATC N06A) enrolled in practices, which are registered in the database between 2002 and 2009 were identified. The date of the first antidepressant prescription was considered to be the start date. Patients aged 18 years and older at the time of the start date with at least one year of enrollment history in NPCRD and at least 90 days of follow-up available were eligible for inclusion. We included only new users, defined as patients who had their first AD prescription (start date) during the study period without any AD prescription in the year preceding the start date.

Definition of antidepressant use

For each patient starting an antidepressant, all prescriptions for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MOAIs) were identified. Treatment episodes were constructed according to the method previously applied by Gardarsdottir et al. [26]. In short, a treatment episode comprised a series of subsequent antidepressant prescriptions, irrespective of switching between different types of antidepressant and changes in dose regimen. As prescribing records in NCPRD did not provide information on the dosing regimen, the prescription length for each antidepressant was considered to be 90 days, consistent with the maximally allowed dispensing duration in the Netherlands. In case a subsequent antidepressant prescription with the same drug was collected before the theoretical end date of a previous antidepressant prescription, the number of overlapping days was added to the theoretical end date of the subsequent antidepressant prescription. If a subsequent prescription was another antidepressant, the patient was considered to have switched therapy and any remaining days from the previous type of antidepressant were disregarded.

A new treatment episode was assumed when an interval of 30 days or more occurred between the theoretical end date of a prescription and the next prescription for the same patient. For all patients, only the first treatment episode was assessed.

Concomitant use of benzodiazepines

Among patients with a first episode of antidepressant use, all prescriptions for benzodiazepines (ATC codes N05BA), benzodiazepine derivatives (ATC N05CD) and benzodiazepine related drugs (ATC N05CF) were identified.
As information on the dosing regimen for benzodiazepine was not available, the length of a benzodiazepine prescription was assumed to be 30 days, based on the common prescribing practice for benzodiazepines in the Netherlands. To assess concomitant us of benzodiazepines ('co-use') during the first episode of antidepressant use, we calculated the number of days that benzodiazepines were used within this period. If a benzodiazepine prescription was issued prior to the start of antidepressants or the theoretical end date of a prescription was after the end date of the antidepressant treatment episode, only the days within the antidepressant episode were taken into account.

Using a fixed duration of 30 days for a benzodiazepine prescription can inflate the number of days use in case the prescriptions were e.g. issued on a weekly basis or were used in a higher frequency. Therefore, we created a rule that the number of days of co-use could not be larger than the difference between the last theoretical end date of a benzodiazepine prescription and the start of benzodiazepine/start of the antidepressant treatment episode, whichever came last. As an antidepressant episode can potentially last for years, we applied the above mentioned rule taking into account clusters of benzodiazepine use, where a difference of 182 days between the end date of one benzodiazepine prescription and a subsequent one marked a new cluster. This prevented a scenario where intensive co-use at the beginning and at the end of an antidepressant episode would overestimate the number of days of co-use. Concomitant use of benzodiazepines within the first antidepressant episode was further defined in two dimensions: First, we assessed the timing of benzodiazepine start with respect to the start of the antidepressant treatment episode (T=0). Three subgroups of patients were identified according to the timing of concomitant benzodiazepine start: 1) patients who start using benzodiazepines before, 2) those who start using benzodiazepine simultaneously (on the same day) and who have no benzodiazepine prescription in the 182 prior to the start day and 3) patients who start using benzodiazepine after the start of the antidepressant treatment episode.
Second, the duration of concomitant use in days was plotted relative to the length of the antidepressant treatment episode in days.

Data Analysis

The cohort of new antidepressant users was described for sex, age, major indications (footnote Table 1), length of antidepressant treatment episode and type of antidepressant use. Mean, median and standard deviation were calculated. The frequency of concomitant use of benzodiazepine was determined according to the definitions described above. Results were stratified by timing of benzodiazepine start. Duration of concomitant benzodiazepine use was compared with respect to antidepressant treatment episode length. Data analyses were performed using SPSS for Windows 20.0 (SPSS Inc, Chicago, IL).

Table 1 Characteristics of antidepressant therapy initiators

Antidepressant therapy initiators **N=16,087**	**N**	**%**
Female	10,207	63.4
Mean age (standard deviation)	50	(18)
Indication of use		
Depression	5713	35.5
Anxiety	1775	11.0
Sleeping disorder	382	2.4
Unspecified	473	2.9
Other	5226	32.4
Unknown	2518	15.7
Antidepressant episode duration in days		
Mean (Standard deviation)	295	(345)
Median	166	
Minimum	90	
Maximum	2920	
25^{th} percentile	90	
25^{th} percentile	344	
3 month	5480	34.1
>3-6 months	3295	20.5
6-12 months	3608	22.4
>12 months	3704	23.0
Only selective serotonin re-uptake inhibitors use	8714	54.2
Only tricyclic antidepressants use	5386	33.5
Only other antidepressant use	1987	12.3

Depression: depression and related disorders (ICPC code P76, P03)
Anxiety: anxiety and related disorders (ICPC codes: P01, P74)
Sleeping disorder (ICPC code: P06)
Unspecified: no diagnosis determined by the general practitioner
Unknown: missing data.

RESULTS

A total of 16,087 patients initiated antidepressant treatment between 2002 and 2009 (Table 1). The majority (63.0%) was female and the mean age was 50 years (SD 18) at the start of antidepressant treatment. The most frequently recorded indications were depression/depression related disorders (35.5%), followed by anxiety/anxiety related disorders (11.0%). The range of the antidepressant episode lengths was wide (between 90 and 2920 days) and the mean and median were 295 and 166 days, respectively. About one third (34.0%) of the patients had the minimum antidepressant treatment length (3 months), corresponding to a single antidepressant prescription. The majority of the patients were SSRI users (54.2%) and only one third of the patients were TCA users.

More than one third (39.0%) of the new antidepressant users were concomitant users of benzodiazepines (Figure 2) at least once during their antidepressant treatment episode. The majority (64.4%) of these patients initiated benzodiazepine use before antidepressant therapy start. In total 21.9% of concomitant users started using benzodiazepine after initiation of antidepressant therapy, and 13.7% started the use of benzodiazepines and antidepressants simultaneously.

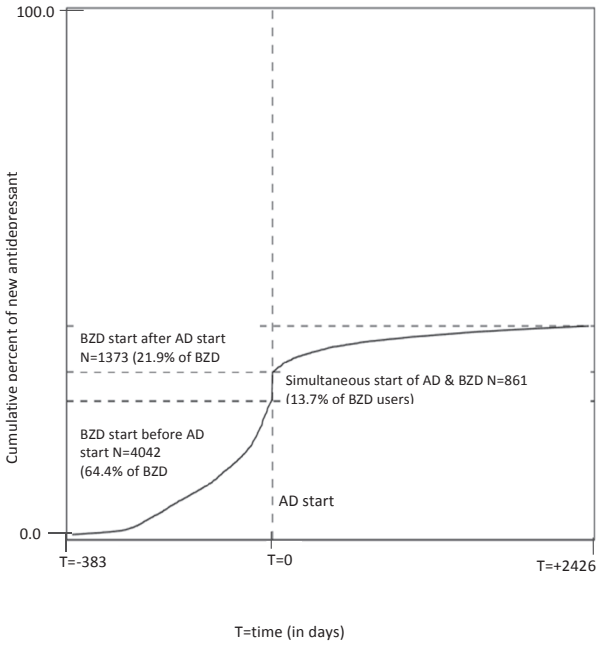


Figure 2: Distribution of concomitant benzodiazepine use among new antidepressant users, according to timing of benzodiazepine start with respect to antidepressant treatment episode start (T=0)

Figure 3 shows the duration of the concomitant benzodiazepine use versus total antidepressant treatment episode length overall, as well as for those who start benzodiazepine use before, simultaneous and after antidepressant treatment initiation separately. Figure 3A shows regular periods of 30, 60 and 90 days of benzodiazepine co-use during the antidepressant treatment episode in addition to some other lengths of periods of concomitant

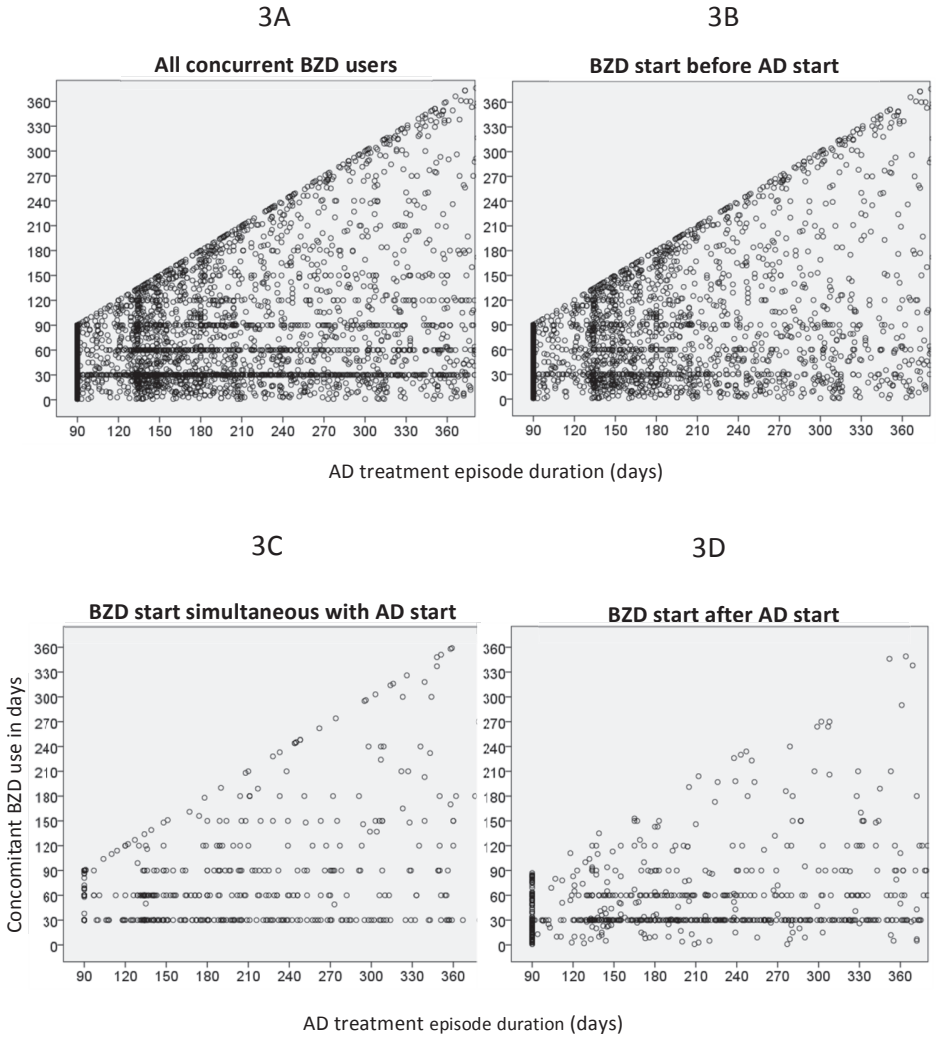


Figure 3: Distribution of duration of concomitant use of benzodiazepine with respect to the duration of antidepressant treatment episode: overall (3A) and in three different patient groups in terms of timing of benzodiazepine start (3B-3D)

AD= antidepressants

BZD=benzodiazepines

benzodiazepine use. Figures 3B and 3C indicate relative long duration of concomitant use of benzodiazepine among the subgroups of antidepressant users who start using benzodiazepine before and simultaneous compared with the duration of concomitant use for those who start using benzodiazepine after antidepressant initiation (figure 3D) which was relatively shorter. Comparing the scatter plot of prescriptions in figures 3B, 3C and 3D, we notice more density of prescriptions clustered in a diagonal line indicating a positive correlation between the length of co-use and the length of antidepressant treatment episode in figure 3B and to a lesser extent in figure 3C compared to figure 3D. This indicates a more regular benzodiazepine co-prescribing at intervals of 30, 60 and 90 days during antidepressant treatment episode in figure 3D which does indicates a less relative increase of co-use duration compared to figures 3B and 3C.

DISCUSSION

In our study population of incident antidepressant users, 39% of patients were concomitant benzodiazepine users. This is in line with the proportion of co-use reported in several recent studies on psychotropic poly-pharmacy from Canada (49.3%) [27], Japan (36.7%) [7] and the Netherlands (40.1%) [28]. Among the concomitant users, timing of start of benzodiazepine use varied. The majority of concomitant users (64.4%) started using benzodiazepines before the start of the antidepressant therapy. Moreover, 13.9% of concomitant users initiated benzodiazepine use on the same day as the antidepressant start day. The duration of concomitant use varied also among these patient groups with different timing of benzodiazepine start. In general, the duration of concomitant use was longer for patients who started using benzodiazepine before and simultaneous to antidepressant therapy start compared with patients who started using benzodiazepine after antidepressant treatment initiation. The highest fracture risk of concomitant co-use is expected when a benzodiazepine is initiated 3 to 6 months after start of antidepressant therapy (figure 1D). Approximately 10% of our study population falls in this category (figure 2). We are not aware of any publications describing the concomitant use of benzodiazepines among antidepressant initiators in this level of detail with respect to timing and duration of co-use.

Antidepressants and benzodiazepines are widely used medications and are prescribed for a broad range of indications. Despite the wide range of indications for prescribing antidepressants [29], the most frequently recorded indications are depression-/related indications and anxiety-/related indications [30, 31]. Patients diagnosed with depression or anxiety related morbidities are advised to continue using antidepressants for at least a year to prevent relapse [32]. On the other hand, benzodiazepines are advised to be prescribed for shorter periods [33-35] as they may be highly addictive [36] and may have higher chance for misuse

and associated risks such as falls especially in elderly [37, 38]. Long-term use of benzodiazepines has been reported to be problematic in several studies [36, 39, 40]. Concomitant use of antidepressants and benzodiazepines is proven to be effective to treat the acute phase of depression (6). Considering guidelines for prescribing and reports of utilization studies of both medications and the prevalence of their co-prescription [41], a more detailed characterization of the dynamics of concomitant use when evaluating a common adverse event is imperative. The main motive for this, as shown in scenarios 1B, 1C and 1D, is the combined hazard patterns, which may be different for different timing of benzodiazepine start.

Studies on the association of antidepressants and fractures have, almost always, considered benzodiazepine use as confounding to the main exposure and subsequently adjusted for. This is irrespective of study type (case-control or cohort or other), source of data used (survey or electronic health care database) and/or definition of the confounder variable. However, previous association studies have not corrected for timing of start of the confounder with respect to the main exposure. A literature search showed eight cohort studies [10, 13, 42-47] on antidepressant use and fracture risk. Five of those studies used interview generated information on medication use. Because of the relative simplicity of these medication data, advanced assessment of co-prescription is not possible. Of the three studies [13, 45, 47] that have used electronic health care databases, only two included benzodiazepine use as a potential confounder. Coupland et al used a simple adjustment for use of hypnotics/anxiolytics at baseline [45]. Abbing et al took into account timing of co-use, by adding benzodiazepine exposure to the multivariate model as a time-dependent covariate [13, 45, 47]. However, duration of benzodiazepine use was not taken into account simultaneously. This implies that the hazard is assumed constant over time, hence neglecting the specific hazard functions for benzodiazepine-induced fracture risk as depicted in figure 1. In our present study, we found that more than half of the concomitant users started benzodiazepines more than 2 weeks before antidepressant initiation (figure 2). For those patients, concomitant benzodiazepine should in fact no longer be regarded a potential confounder, as the hazard of fracture has already disappeared (figure 1B).

The recent multi-country study from our group [13, 45, 47] showed different risk estimates for fracture per country, despite applying common methods for defining antidepressant use as the main exposure and benzodiazepine use as co-medication. Considering different scenarios of hazard patterns and magnitudes of concomitant use discussed in figure 1 hypothesize that residual confounding because of insufficient adjustment of timing and duration of co-use may have played a role. The three cohorts might have different distributions of patients with respect to timing of benzodiazepine start (more prevalent users in cohorts where the risk estimate is lower – acute risk of benzodiazepine absent) and hence different magnitudes of overall risk found in their study. Specifically, when antidepressant

treatment start is the T0 – exposure window of interest, the cohort with higher risk estimate in our previous study may have a larger patient group with scenarios in figures 1C and 1D as more relevant compared to the cohorts with lower risk estimates where figure 1B may be more relevant.

Our study has some limitations. First, information on the prescribed dose was not available in the database and assumptions on prescription length for antidepressant and benzodiazepine had to be made. However, the assumed prescription lengths were based on the common prescribing practices in the Netherlands. Second, patients starting with benzodiazepine use after the initiation of antidepressant therapy can, by definition, not have duration of concomitant benzodiazepine use that is equal to the duration of antidepressant use. This may introduce bias when comparing the duration of concomitant use between the subgroups based on timing of benzodiazepine start (before starters / simultaneous starters / after starters). Third, the combined hazard scenarios depicted in figure 1 were simplified for illustration purposes and were not based on empirical data, hence ignoring aspects like dose and possible drug-drug interaction. In addition, we were not able to test whether our hypothesis on a fluctuating cumulative fracture hazard function associated with combined antidepressant and benzodiazepine use is true. A general limitation for such studies can be the unavailability of patient compliance information which may differ not randomly in the three groups. Future studies, which include fracture endpoints, are needed to fill this knowledge gap.

Conclusion

The frequency of concomitant benzodiazepine use among antidepressant users is considerable and the timing of concomitant benzodiazepine start is highly variable. When studying a common adverse event associated with medications that are often co-prescribed, as in the example of antidepressants, benzodiazepines and hip fracture, it is important to take into account not only the presence of concomitant medication use, but also the timing of start and duration of co-use as the overall hazard may vary accordingly.

REFERENCES:

1. Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med. 2009;150(6):379-86.
2. Castrejon I, Gibson KA, Pincus T. Efficacy and safety of methotrexate in combination with other non-biologic disease-modifying antirheumatic drugs (DMARDs) in treatment of rheumatoid arthritis. Bull Hosp Jt Dis. 2013;71 Suppl 1:S20-8.
3. Thomas MC. Diuretics, ACE inhibitors and NSAIDs—the triple whammy. Med J Aust. 2000;172(4):184-5.
4. Blake KV, Devries CS, Arlett P, Kurz X, Fitt H. Increasing scientific standards, independence and transparency in post-authorisation studies: the role of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Pharmacoepidemiol Drug Saf. 2012;21(7):690-6.
5. Hennessy S. Use of health care databases in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. 2006;98(3):311-3.
6. Kanba S. Although antidepressants and anxiolytics are frequently used together to treat depression in the acute phase, how effective is the concomitant use of these drugs? J Psychiatry Neurosci. 2004;29(6):485.
7. Onishi Y, Hinotsu S, Furukawa TA, Kawakami K. Psychotropic prescription patterns among patients diagnosed with depressive disorder based on claims database in Japan. Clin Drug Investig. 2013;33(8):597-605.
8. Ray WA, Griffin MR, Malcolm E. Cyclic antidepressants and the risk of hip fracture. Arch Intern Med. 1991;151(4):754-6.
9. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998;351(9112):1303-7.
10. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med. 2003;163(8):949-57.
11. Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. J Clin Psychopharmacol. 2008;28(4):384-91.
12. van den Brand MW, Pouwels S, Samson MM, van Staa TP, Thio B, Cooper C, et al. Use of antidepressants and the risk of fracture of the hip or femur. Osteoporos Int. 2009;20(10):1705-13.
13. Ziere G, Dieleman JP, van der Cammen TJ, Hofman A, Pols HA, Stricker BH. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of non-vertebral fractures. J Clin Psychopharmacol. 2008;28(4):411-7.
14. Verdel BM, Souverein PC, Egberts TC, van Staa TP, Leufkens HG, de Vries F. Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. Bone. 2010;47(3):604-9.
15. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. Jama. 1989;262(23):3303-7.
16. 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;155(16):1801-7.
17. 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;158(6):892-8.
18. 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;164(14):1567-72.
19. Chang CM, Wu EC, Chang IS, Lin KM. Benzodiazepine and risk of hip fractures in older

people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry. 2008;16(8):686-92.
20. 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;19(12):1248-55.
21. 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;158(1):77-84.
22. 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;66(2):276-82.
23. LINH. Netherlands Institute for health services research. 1992 [cited 2013 april]; Available from: http://www.linh.nl/
24. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. 1996 [cited 2013 April]; Available from: http://www.whocc.no/atc_ddd_index/
25. Lamberts H., Wood M. ICPC. International Classification of Primary Care. Oxford: Oxford University Press; 1987.
26. 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;63(4):422-7.
27. Sanyal C, Asbridge M, Kisely S, Sketris I, Andreou P. The utilization of antidepressants and benzodiazepines among people with major depression in Canada. Can J Psychiatry. 2011;56(11):667-76.
28. van Geffen EC, Gardarsdottir H, van Hulten R, van Dijk L, Egberts AC, Heerdink ER. Initiation of antidepressant therapy: do patients follow the GP's prescription? Br J Gen Pract. 2009;59(559):81-7.
29. Mercier A, Auger-Aubin I, Lebeau JP, Schuers M, Boulet P, Hermil JL, et al. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: an analysis of guidelines and systematic reviews. BMC Fam Pract. 2013;14:55.
30. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. J Affect Disord. 2007;98(1-2):109-15.
31. Abbing-Karahagopian V. Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo FJ, Leufkens HGM, Slattery J, Alvarez Y, Miret M, Gil M, Oliva B, Hesse U, Requena G, de Vries F, Rottenkolber M, Schmiedl S, Reynolds R, Schlienger RG, de Groot MCH, Klungel OH, van Staa TP, van Dijk L, Egberts ACG, Gardarsdottir H, & De Bruin ML. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations and methodological implications. Eur J Clin Pharmacol 2014.70: 849-57.
32. Patten SB, Kennedy SH, Lam RW, O'Donovan C, Filteau MJ, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. I. Classification, burden and principles of management. J Affect Disord. 2009;117 Suppl 1:S5-14.
33. Trimbos Institute. Guidelines for benzodiazepines. version 2008 [cited 2013 November]; Available from: http://www.ggzrichtlijnen.nl/index.php?pagina=/richtlijn/item/pagina.php&id=573&richtlijn_id=59
34. Medicines and Healthcare products Regulatory Agency (MHRA). Addiction to benzodiazepines and codeine: supporting safe use. [cited 2013 November]; Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123123
35. Danish Health and Medicines Authority. Effective effort against the excessive use of benzodiazepines in denmark. [cited 2013 November]; Available from: http://sundhedsstyrelsen.dk/en/medicines/consumption-analyses/effective-effort-against-the-excessive-use-of-benzodiazepines-in-denmark?sc_site=website

36. Lader M. Benzodiazepines revisited—will we ever learn? Addiction. 2011;106(12):2086-109.
37. Berdot S, Bertrand M, Dartigues JF, 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;9:30.
38. 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.
39. Willems IA, Gorgels WJ, Oude Voshaar RC, Mulder J, Lucassen PL. Tolerance to benzodiazepines among long-term users in primary care. Fam Pract. 2013;30(4):404-10.
40. Kollen BJ, van der Veen WJ, Groenhof F, Donker GA, van der Meer K. Discontinuation of reimbursement of benzodiazepines in the Netherlands: does it make a difference? BMC Fam Pract. 2012;13:111.
41. Lenze EJ, Mulsant BH, Shear MK, Houck P, Reynolds IC. Anxiety symptoms in elderly patients with depression: what is the best approach to treatment? Drugs Aging. 2002;19(10):753-60.
42. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, et al. Predictors of non-spine fracture in elderly men: the MrOS study. J Bone Miner Res. 2007;22(2):211-9.
43. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007;167(2):188-94.
44. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, et al. Depressive symptoms, bone loss, and fractures in postmenopausal women. J Gen Intern Med. 2008;23(5):567-74.
45. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.
46. Diem SJ, Blackwell TL, Stone KL, Cauley JA, Hillier TA, Haney EM, et al. Use of antidepressant medications and risk of fracture in older women. Calcif Tissue Int. 2011;88(6):476-84.
47. Souverein PC, Abbing-Karahagopian V et al. Inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip fracture. PDS Supplement 2015 Accepted.

3.3

Concomitant users of antidepressants and benzodiazepines: does different timing of initiation modify the risk of osteoporotic fracture?

Victoria Abbing-Karahagopian, Patrick C. Souverein, Toine C.G Egberts, Hubert G.M. Leufkens, and Marie L. De Bruin.

ABSTARCT

Background

To determine whether the risk of osteoporotic fracture is modified by differences in patterns of concomitant exposure to antidepressants and benzodiazepines.

Methods

A case-control study was conducted to evaluate the risk of osteoporotic fracture with associated with the duration of either single or concomitant exposure to antidepressants and/or benzodiazepines. Cases were 18-years and older with a first admission for an osteoporotic fracture (1991-2002) matched up to four controls from the Dutch PHARMO-RLS. Duration of exposure to antidepressants and/or benzodiazepines was classified in eleven categories of which six concomitant categories.

Results

9,943 cases and 36,359 controls were included. Adjusted odds ratio (OR_{adj}) for single benzodiazepine users was 1.32; whereas for single antidepressant users the range was 1.38-1.88. Among concomitant exposures, risk estimates varied with duration of use. The OR_{adj} for the six categories of concomitant users were highest among short-term those benzodiazepine users rather than long-term benzodiazepine users (range: 2.87 – 4.18 vs. 1.78 – 2.01, respectively).

Conclusion

Different patterns of concomitant use of antidepressants and benzodiazepines, with exposure definitions accounting for biological mechanisms and hazard patterns of the individual medications, may modify the risk of osteoporotic fracture. Sufficient evidence on such findings in larger and different populations should support more tailored co-prescribing policies.

BACKGROUND

Observational studies have often reported varying risk estimates on the same exposure-outcome association. Concomitant exposure to medications and their association with a common outcome has rarely been evaluated in pharmacoepidemiological studies. Exposure to one drug is usually considered as the main exposure of interest and exposure to the other concomitantly used drug(s) is adjusted for (simple or time-dependent presence or absence adjustment) as a confounder. In an approach like this, the possibility of identification of effect modifiers will be absent. As such, differences in effect estimates from studies would tend to be explained by some of the methodological differences like study design or choices of confounders or population characteristics.

A clinical example where different risk estimates have been reported is the association between exposure to psychotropic medication (more specifically, antidepressants and benzodiazepines) and fracture risk. In several reviews [1-7], differences in study results have been discussed in terms of, among others, differences in selection and control for confounding, estimation of exposure and its duration and confounding by indication. This drug-adverse event pair has therefore been selected for in depth methodological study in the PROTECT project [8]. One of the aims of PROTECT was to develop a methodological framework for pharmacoepidemiology studies to be applied in different databases and to investigate discrepancies in the results.

Antidepressants and benzodiazepines are often co-prescribed to treat depression, especially in the first phase [9]. In a previous study, we have shown different dynamics of concomitant use of these two medications [10]. Hazard patterns for fracture have shown to be different for antidepressant and benzodiazepine users. Benzodiazepines are associated with especially an acute risk [11], whereas the fracture risk of antidepressants increases with duration of use [12]. The mechanism for fracture due to benzodiazepine use is explained through relaxation of muscles, sedation and falls [13, 14]. This risk is especially increased during the first weeks of use, and less pronounced after prolonged use. The mechanism of fracture due to antidepressant use, in addition to sedation and falls, is explained through negative effects on bone mineral density (BMD) i.e. the risk increases with longer durations of use [15, 16]. As a consequence, users of both antidepressants and benzodiazepines may have a complex overall hazard pattern for fracture, which may be dependent on the differences in duration of use of both drugs [10]. So far, studies have primarily focused on quantification of the fracture risk with either one of the drug classes.
Therefore, this study aimed to estimate the risk of osteoporotic fracture associated with both antidepressants and benzodiazepines, taking into account differences in patterns of concomitant use. More specifically, in a single model we differentiated the risk estimates

according to different duration of concomitant use according to time since start of each medication class separately. Secondly, we have also applied a less advanced model (where one of the drug classes was analysed as the primary exposure), which is already applied for the same data in a previous publication for direct comparison.

METHODS

Setting

Data for this study were obtained from the Dutch PHARMO Record Linkage System (PHARMO RLS), which is a large, dynamic, patient oriented data network designed to be used for pharmacoepidemiology and outcome studies (www.pharmo.nl). Data of inhabitants from (almost one quarter of the total Dutch population) both rural and urban areas are in this database which has shown to be representative of the Dutch population [17, 18]. Longitudinal data in the PHARMO RLS consist of, among other data, drug dispensing records from community (outpatient) pharmacies. The PHARMO database also contains hospital discharge records including information on primary and secondary diagnosis, procedures, admission and discharge dates. The pharmacy records consist of data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, and the prescribed dosing instructions. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification (http://www.whocc.no/atc_ddd_index). The diagnoses are coded according to the International Classification of Diseases, 9th Revisions, Clinical Modification (ICD-9-CM).

Study design and study population

A case-control study was conducted using data from the period from 1 January 1991 to 31 December 2002, as used previously by Verdel et al. [19]. Cases were defined as patients 18 years and older with a first admission of osteoporotic fracture (including fractures of the hip/femur (ICD-9 819-821), radius/ulna (ICD-9 813), humerus (ICD-9 812) vertebra (ICD-9 805-806), rib (ICD-9 807) or clavicle (ICD-9 810)). The index date was the date of hospitalization for an osteoporotic fracture. Up to four controls with no history of fracture during the study period were matched on year of birth, sex, and geographic area. The index date for the controls was the same as the index date of the matched case. Both the cases and controls were eligible for inclusion if they had at least 365 days of history in the PHARMO database prior to the index date.

Exposure definition antidepressants and benzodiazepines

For all patients all prescriptions for antidepressants and benzodiazepines before the index date were identified. The assessed antidepressants included selective serotonin reuptake in-

hibitors (SSRIs, ATC code: N06AB), serotonin–norepinephrine reuptake inhibitors (SNRIs, ATC code N06AX), tricyclic antidepressants (TCAs, ATC code N06AA), or monoamine oxidase inhibitors (MAOIs, ATC code N06AF/AG). The benzodiazepine group included both benzodiazepines and benzodiazepine-related drugs (ATC codes: N05BA, N05CD, and N05CF).

A patient was considered a current user of an antidepressant or benzodiazepine if the index date fell between the start date and theoretical end date of a prescription. The theoretical end date of a prescription was calculated from the date of dispensing, the number of units dispensed and the prescribed dosage. If the end date of the last prescription was before index date, drug exposure was classified as past use. Duration of current use was assessed by looking back from the current use prescription and identifying the initial start date of treatment while allowing for a 30 day gap between the end date of a previous prescription and a new prescription.

For patients that used an antidepressant and/or a benzodiazepine, current use was further classified in eleven mutually exclusive categories according to the duration of antidepressant and/or benzodiazepine use before the index date and compared to individuals who never used antidepressants or benzodiazepines during the observed time period before the index date (Table 2). The duration of current antidepressant use was categorized as either less than 9 months, between 9 months and 36 months or more than 36 months elapse up to the index date. The duration of current benzodiazepine use was categorized as either less than 28 days or more than 28 days elapse between the start date of the first benzodiazepine prescription and the index date. These categorizations were based on previous studies reporting a bimodal hazard curve for fracture over 5 years of continuous use of SSRIs [12] and a more acute risk during the first months of use of benzodiazepine [20-22]. Specifically, the cut-off points for timing of start for antidepressants (first peak of hazard at 6 months which drops after 12 months [12] (our first cut-off point: 9 months) and second less steep peak which drops after three years of continuous use [12] (our second cut-off point: 36 months) were based on the hypothesized a longer term effect (BMD) as described in van den Brand et al. The 28-days exposure categorization for benzodiazepines, a more acute effect (falls), was based on studies describing high acute risk during the first month of use [20-22].

Potential confounding factors

Information on the following medication use anytime within six months before the index date was determined for the cases and controls: anti-psychotic drugs (excluding lithium), lithium, antiParkinson drugs, anticonvulsants, oral and inhaled glucocorticoids, hormone replacement therapy, disease-modifying anti-rheumatic drugs (DMARDs), anti-arrhythmics, thiazide diuretics, beta-blockers, drug for diabetes, morphine/opiates, non-steroidal

anti-inflammatory drug (NSAIDs) and thyroid hormones. Hospitalization records were assessed for a history of hospitalization before the index date for cardiovascular disease, malignant neoplasm, inflammatory bowel disease, rheumatoid disease, musculoskeletal disease, obstructive airway disease, impaired renal function, mental disorder or cerebrovascular disease.

Data Analyses

Conditional logistic regression was used to estimate the risk of osteoporotic fractures among antidepressant and/or benzodiazepine users and expressed as odds ratios (ORs) and 95% confidence intervals (CIs). For the primary analyses (Model 1) the eleven categories of current use defined according to the duration of the medication concerned were compared against no use (reference). For the secondary analyses, duration of current use of either antidepressants (Model 2) or benzodiazepines (Model 3) was modeled as the main exposure, while the current use of other class was modeled as a covariate. Stepwise backward elimination based on Likelihood Ratios with significance level of 0.20 for the exclusion of covariates from the final model was considered. Data were analyzed using SPSS version 21 (SPPS Inc. Chicago, Illinois, USA).

RESULTS

We included 9,943 patients with an osteoporotic fracture, who were matched to 36,359 controls. The mean age of the cases was 67.8 years (SD 19.3 years) and 66% were females. Remaining characteristics of the cases and the controls are shown in Table 1. In general, the cases had more co-morbidities and a higher prevalence of medication use. The most frequent co-morbidities in both cases and controls were obstructive airway and cardiovascular diseases. The most frequently used medications were NSAIDs and beta-blocking agents.

The distribution of cases and controls according to duration of use of antidepressants and/or benzodiazepines is given in Table 2. 15.5 % of the study population used either antidepressants or benzodiazepines, or both. Around 4% were single users of antidepressants, 13.2% were single users of benzodiazepines and only 1.7% was concomitant users. Overall, use of benzodiazepines on the index date was almost three times higher (17.8% of cases vs. 6.6% of cases) than antidepressant use. Most antidepressant use started less than 9 months before the index date, whereas only very few patients used antidepressants longer than 3 years. Most benzodiazepine use started more than 28 days before the index date (15% of cases) compared to use started 28 days or less before the index date (2.7% of cases).
In the primary analysis (Model 1), the adjusted ORs (OR_{adj}) ranged from 1.32 to 4.18 among the 11 exposure groups (see Table 3). The highest OR_{adj} (range 2.87 to 4.18) were observed

Table 1: Characteristics of case and control patients

	Cases N=9943		Controls N=36359	
	n	**%**	**n**	**%**
Age				
18-39	1182	11.9	4299	11.8
40-59	1644	16.5	6221	17.1
60-79	3808	38.3	14259	39.2
80+	3309	33.3	11580	31.8
Mean and standard deviation (SD)	67.8	(±19.3)	67.4	(±19.1)
Sex (female)	6561	66.0	23818	65.5
Previous hospitalization				
Cancer	490	4.9	1343	3.7
Cardiovascular disease	1630	16.4	4505	12.4
Cerebrovascular disease	360	3.6	699	1.9
Inflammatory bowel disease	305	3.1	705	1.9
Obstructive airway disease	3231	32.5	8751	24.1
Mental disorders	35	0.4	56	0.2
Musculoskeletal disease	956	9.6	2704	7.4
Medication use				
Main exposure[1]				
Antidepressant drugs	651	6.5	1188	3.3
Benzodiazepines	1772	17.8	4337	11.9
Co-medication[2]				
Anti-arrhythmic drugs	139	1.4	410	1.1
Anti-diabetic drugs	963	9.7	2640	7.3
Antiepileptic drugs	304	3.1	514	1.4
Anti-Parkinson drugs	251	2.5	402	1.1
Antipsychotic drugs	460	4.6	898	2.5
Beta-blocking agents	1281	12.9	5107	14.0
DMARDs*	158	1.6	284	0.8
Hormone replacement therapy	236	2.4	937	2.6
Inhaled corticosteroids	844	8.5	2548	7.0
Lithium	22	0.2	51	0.1
NSAIDs**	2513	25.3	6532	18.0
Opioids	364	3.7	560	1.5
Oral glucocorticoids	616	6.2	1496	4.1
Thiazide diuretics	907	9.1	3251	8.9
Thyroid hormones	83	0.8	227	0.6

* DMARDs: Disease Modifying Anti-Rheumatic Drugs

** NSAIDs: Non-Steroid Anti-Inflammatory Drugs

1) Current use on the index date

2) Use within a six-month period prior to the index date

Table 2. Distribution of cases and controls over exposure categories

Cases N (%) /Controls N (%)

Exposure		BZD		
		No current use	**Current ≤28 days**	**Current >28 days**
AD	No current use	7831 (78.8%) / 31311 (86.1%)	243 (2.4%) / 683 (1.9%)	1218 (12.2%) / 3177 (8.7%)
	Current ≤9 months	186 (1.9%) / 350 (1.0%)	19 (0.2%) / 19 (0.1%)	131 (1.3%) / 192 (0.5%)
	Current 9-36 months	123 (1.2%) / 294 (0.8%)	13 (0.1%) / 12 (0.0%)	107 (1.1%) / 186 (0.5%)
	Current >36 months	31 (0.3%) / 67 (0.2%)	2 (0.0%) / 3 (0.0%)	39 (0.4%) / 65 (0.2%)

BZD: benzodiazepine
AD: antidepressant

Table 3. Adjusted odds ratios estimating the relative risk of osteoporotic fracture according to duration of current antidepressant and benzodiazepine exposure.

Primary exposure*		BZD			
Model 1		**No current use**	**Current ≤28 days**	**Current >28 days**	**Model 2****
AD	No current use	Reference	1.32 (1.13-1.54)	1.32 (1.23-1.43)	Reference
	Current ≤9 months	1.87 (1.55-2.25)	3.24 (1.68-6.25)	2.01 (1.59-2.54)	1.75 (1.51-2.02)
	Current 9-36 months	1.38 (1.11-1.72)	4.18 (1.86-9.37)	1.89 (1.47-2.43)	1.45 (1.23-1.71)
	Current >36 months	1.88 (1.20-2.93)	2.87 (0.45-18.4)	1.78 (1.18-2.70)	1.59 (1.17-2.15)
	Model 3***	Reference	1.38 (1.19-1.59)	1.30 (1.21-1.40)	

BZD: benzodiazepine; AD: antidepressant
* Model 1: current use of benzodiazepines and/or antidepressants in 11 mutually exclusive categories according to the duration of use, which are compared to no use of benzodiazepines or antidepressants (reference category).
** Model 2: Antidepressant use as primary exposure, adjusted for current benzodiazepine use (yes/no) and other confounders.
*** Model 3: Benzodiazepine use as primary exposure, adjusted for current antidepressant use (yes/no) and other confounders.

among antidepressant users starting their benzodiazepine use shortly (≤ 28 days) before the fracture date, irrespective of duration of antidepressant use. Among individuals that did not use antidepressants, benzodiazepine use was associated with a 1.3-fold increased risk of osteoporotic fracture, regardless the duration of benzodiazepine use.

In Figure 1, the risk estimates form Table 3 are displayed according to categories of benzodiazepine use to provide more insight in the effect of duration antidepressant use of across these strata. Use of antidepressants without concomitant use of benzodiazepines was associated with an increased risk of osteoporotic fractures, which was highest in the first 9 months of use, than somewhat lower in the period between 9 and 36 months of use, increasing again after 3 years of use (Figure 1, left panel). A similar pattern of duration of antidepressant use was observed in Model 2, where antidepressant use was analyzed as the main exposure adjusting for benzodiazepine use in a multivariable model (Figure 1, right panel). However,

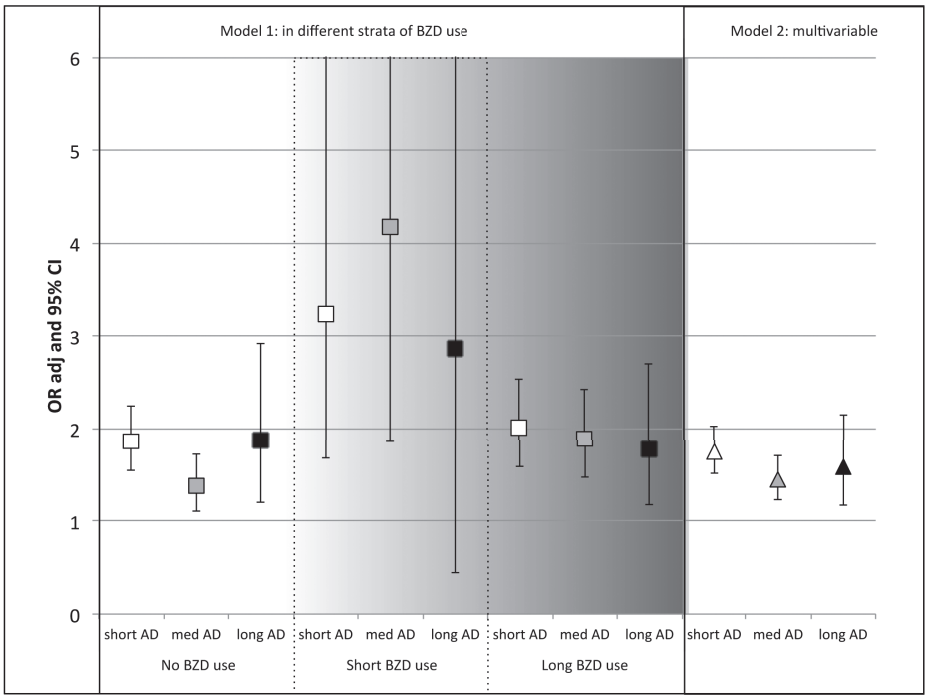


Figure 1. Dose response effects of duration of antidepressant use and osteoporotic fracture risk, taking into account co-use of benzodiazepines.

Model 1: Mutually exclusive categories taking into account duration of use of antidepressant and benzodiazepines simultaneously. Model 2: Duration of antidepressant use is main exposure, adjusted for current benzodiazepine use with multivariable logistic regression.

'Short AD' ≤ 9 months, 'med AD' 9 to < 36 months and 'long AD' >36 months elapse since initiation of antidepressant therapy.

'Short BZD' ≤ 28 days and 'Long BZD' >28 days elapse since initiation of benzodiazepine therapy.

among users of benzodiazepines no lower risk estimates were observed for 9 to 36 months of antidepressant use (Figure 1, second and third panel).

In Figure 2, the risk estimates form Table 3 are displayed according to categories of antidepressant use to provide more insight in the effect of duration benzodiazepines use of across these strata. Fracture risk associated with benzodiazepine use was highest among patients who used antidepressants concomitantly. Among them, higher adjusted risk estimates were observed for patients that started benzodiazepines shortly before the index date, irrespective of the duration of antidepressant use (Figure 2, Model 1). In model 3, where benzodiazepines were modeled as the main exposure multivariable adjusted for concomitant antidepressant use, only a marginally higher risk was observed among short-term users of benzodiazepines, compared to those who started benzodiazepine more than 28 days before the index date.

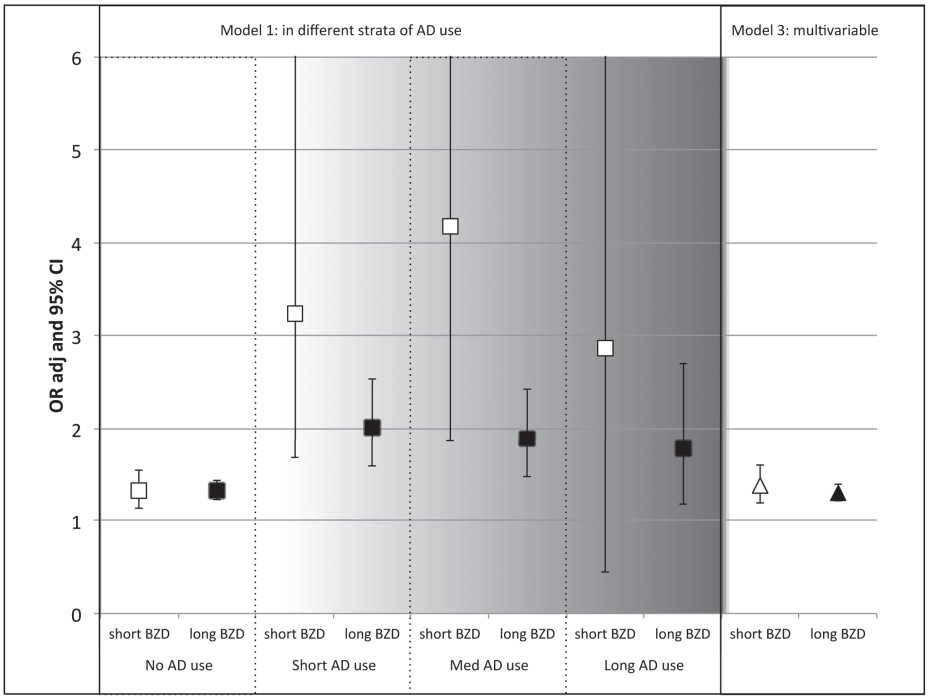


Figure 2. Dose response effects of duration of benzodiazepine use and osteoporotic fracture risk, taking into account co-use of antidepressants.

Model 1: Mutually exclusive categories taking into account duration of use of antidepressant and benzodiazepines simultaneously. Model 3: Duration of benzodiazepine use is main exposure, adjusted for current antidepressant use with multivariable logistic regression.

'Short AD' ≤ 9 months, 'med AD' 9 to < 36 months and 'long AD' >36 months elapse since initiation of antidepressant therapy.

'Short BZD' ≤ 28 days and 'Long BZD' >28 days elapse since initiation of benzodiazepine therapy.

DISCUSSION

We found consistently increased risks for osteoporotic fractures among patients using antidepressants and/or benzodiazepines. The magnitude of the risk estimates varied, however, with duration of single or concomitant use of antidepressants and benzodiazepines (range of OR_{adj} 1.78 to 4.18). Among single users of antidepressants, the risk first decreased before increasing again, as the duration of use increased. Antidepressant users, who also used benzodiazepines, first had an increased then a decreased risk as the duration of benzodiazepine use increased. Among single users of benzodiazepines, the risk was constant with the duration of use. Benzodiazepine users who also used antidepressants, had first an increased and then a decreased risk as the duration of antidepressants increased. As such, among con-

comitant users, the highest risks were observed among short-term benzodiazepine starters compared to those who used benzodiazepines for a longer period.

From previously reported fracture studies we expected the combined hazard of antidepressants and benzodiazepines to be the highest among those with short-term use of both classes. This hypothesis could be partially confirmed. We did find that concomitant use was associated with higher risks than either class alone. We also found that among antidepressant users short-term benzodiazepine use was associated with higher risks than long-term use. In contrast to our expectations, the highest risk was observed among concomitant users with short-term benzodiazepine use and between 9 and 36 months antidepressant use. Power was however low, as reflected in the wide confidence intervals, prohibiting us to draw firm conclusions on true differences in risk estimates between the strata.

As far as we know, we are the first to simultaneously model duration of use effects on fracture risk of benzodiazepines and antidepressants. The duration effects of the two classes individually, however, have been studied before and we can compare our findings in this sense.
With respect to effect of duration of antidepressant use, first a decrease then an increase in OR_{adj} (1.75, 1.45 and 1.59, Model 2). Firstly, we compare these results with those reported in one of the PROTECT studies on the same association analyzed in three different databases using a common protocol [23]. In this PROTECT study, the effect of duration on the risk estimates were distinctively clear in one database (Mondriaan from the Netherlands) where a significant increased risk in the first 6 months of use was seen which decreased afterwards. However, this effect of the duration was not seen in the other two databases (Bifap from Spain and CPRD from the UK).
Secondly, comparing in terms of hazard pattern, our findings are in line with the patterns described for fracture risk among continuous users of SSRI and TCA in the study by van den Brand et al. [12]. In contrast, Hubbard et al. have shown the effect of new starters on the risk of fracture and have reported a sharp decrease from high risk in the first 14-days followed by lower risks in 15-42 and >42 days from the fracture among SSRI and TCA users. The result of Hubbard et al, are not in line with the hazard pattern found in our study and also those described in van den Brand et al where the peak reaches at 6 months and 3 months and the lowest risks are at 9 months and 1 year (and another at 2.5 years) among continuous users of SSRIs and TCAs, respectively. Liu et al. have shown higher risks among new-current users (start <30 days before the fracture) compared to the risk among continuous current users (start >31 days before) both among SSRI and TCA users. The 30-day contrast between new user and continuous current user in the study of Liu et al. is further distinguished in our study taking into account the duration of therapeutic advice for antidepressant use especially for treating depression (treatment duration at least 9 months).

Our study distinguishes between relatively newer initiators and those who have started use for a longer time (>36 months). As depression is the most frequent recorded indication for prescribing antidepressants in most European countries [24], exposure characterization in our study is also in line with the clinical guidelines for prescribing antidepressants. Shorter periods of exposure defined for new users (as in Liu et al. and Hubbard et al.) or longer period for continuous users without accounting for timing of start of use (as in most previous studies) would not show risk pattern fluctuations clearly.

As to comparing our results with studies on benzodiazepines as primary exposure, we did not find notable differences among patient groups who only used benzodiazepines with different timing of initiation from the fracture date (≤28 days OR_{adj} 1.38 and >28 days 1.30; Model 3). Our results are not in line with those reported by a similar PROTECT study [25]. The PROTECT study reported highest risk in the first 30 days of use which decreased with increasing duration of use. However, this duration effect was only seen in one of the databases (Mondriaan from the Netherlands) while such a pattern could not be shown in the other two databases (Bifap from Spain and CPRD from the UK).

Our results are also in contrast to other previous studies, which have found more pronounced higher acute risks in the beginning of exposure, which decreases with continuous use. The only previous study, which has defined exposure according to the start date of use of benzodiazepines, has classified exposure into 7 categories during the first year of initiating use [11]. This study reports decreasing risks in the first two months as the start date increases from the fracture date (the highest being in the group who have started use within 14 days before the fracture date). Unfortunately, we could not apply such an extensive classification as we had considered concomitant use of two drugs, which would have made expanded classification into smaller periods of exposure impossible due to small numbers. Comparison with other studies is difficult where different durations of current exposure [26-28] or reference exposure of 14-days and less [29] is considered.

The two PROTECT studies [23, 25] which have applied common methods to study the association between antidepressant use and fracture and between benzodiazepine use and fracture by applying two different designs (cohort and case-control) have shown that apart from the adjustment for basic confounders such as age and sex, adjustment for several other covariates especially general practice, life style or socio-economic status related factors does not alter the risk estimate greatly. Consequently, when the choice of the confounder may be debated as a contributing factor for different study results on the same association, the interaction term as complex combinations of two medications is often missed. Based on our findings, we may argue that some of the differences in the risk estimates among different studies may be due to different prevalence of the complex concomitant exposure patterns

in the study populations. As we have shown, these differences in exposure definition may be especially variable among concomitant users with different dynamics of initiation of one medication with respect to the other and from the outcome of interest. Hence, relevant confounders, in this case exposure to concomitant medication, should be tested as an effect modifier.

Timing of start of concomitant medication as an effect modifier for a common outcome, as shown in our study, may also be important in other exposure adverse events commonly associated in pharmacoepidemiology studies. Examples may be many naming two would be: antihypertensive use and falls [30] (with possible concomitant exposure to benzodiazepine or antidepressants) and gastrointestinal effects of cox-2 inhibitors and concomitant use of non-steroidal anti-inflammatory drugs (NSAID) use [31].

Such findings in risk differences due to different exposure patterns of two medications can very useful in personalizing of co-prescribing policies by taking into account current and history of medication use of the patient with an aim to minimize the risk of certain adverse events common for both medications.

Strengths and limitations

To our knowledge, this study is unique in mapping osteoporotic fracture risk estimates for concomitant use of antidepressants and benzodiazepines according to timing of initiation of use of individual drug class from the fracture date. Detailed exposure definition and distinction between the concomitantly used medications is one of the strengths of the study. Another aspect is that the database used includes hospital discharge information, which is absent in the other Dutch databases against which we have compared our findings. This study has also limitations. Despite the fact that our study population was not small, the expanded definition of the exposure has created small numbers of cases and controls in each category (11 categories). This has also prevented further splitting of SSRI and TCA antidepressant, which have shown different risk estimates and patterns in the literature. Defining extensive exposure categories has also created the challenge of dealing with multiplicity. The issue of multiplicity is extensively discussed in clinical trials [32, 33] but to a lesser extent in the context of observational epidemiological studies. There are emerging statistical suggestions to deal with the problem of multiplicity (too many exposures variables or exposure categories modelled) in observational studies [34]. However, with the relatively small dataset that we have used, correcting for multiplicity would not have been possible.

Conclusion

Our study has not only shown that different patterns of concomitant use of antidepressant and benzodiazepine drugs increases the risk of osteoporotic fractures but also has demon-

strated that timing of initiation of one drug with respect to the other and fracture date is an effect modifier. The modifying effect showed higher risk of fracture in the initial period of concomitant use (the first 28-days of benzodiazepine initiation concomitant with the use of antidepressants regardless of the timing of start of the latter).

Elucidating differences in risk estimates of fractures, among concomitant users of antidepressants and benzodiazepines, through exposure definitions which account for the proposed biological mechanisms and hazard patterns of the individual medications helps to identify important effect modifiers and related risk patterns for different types of concomitant users. Sufficient evidence on such findings in larger and different populations should support more tailored co-prescribing policies and avoid identified high risk periods for specific patient groups.

REFERENCE

1. Wu Q, Qu W, Crowell MD, Hentz JG, Frey KA. Tricyclic antidepressant use and risk of fractures: A meta-analysis of cohort and case-control studies. J Bone Miner Res. 2013;28(4):753-63.
2. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int. 2012;23(1):365-75.
3. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007;30(2):171-84.
4. Rabenda V, Nicolet D, Beaudart C, Bruyere O, Reginster JY. Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int. 2012;24(1):121-37.
5. Oderda LH, Young JR, Asche CV, Pepper GA. Psychotropic-related hip fractures: meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. Ann Pharmacother. 2012;46(7-8):917-28.
6. 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;27(5):1186-95.
7. 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.25(1):105-20.
8. Abbing-Karahagopian V, Kurz X, de Vries F et al. Bridging Differences in Outcomes of Pharmacoepidemiological Studies: Design and First Results of the Protect Project. Curr Clin Pharmacol. 2014; 9: 130-8.
9. Kanba S. Although antidepressants and anxiolytics are frequently used together to treat depression in the acute phase, how effective is the concomitant use of these drugs? J Psychiatry Neurosci. 2004;29(6):485.
10. Abbing-Karahagopian V, Souverein PC, Korevaar JC, Leufkens HGM, Egberts TCG, Gardarsdottir H, De Bruin ML Concomitant medication use and its implications on the hazard pattern in pharmacoepidemiological studies: example of antidepressants, benzodiazepines and fracture risk. Epidemiol Biostat Pub Health. 2015, Vol 12 (3) e11273 – 1-10
11. 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;19(12):1248-55.
12. van den Brand MW, Pouwels S, Samson MM, van Staa TP, Thio B, Cooper C, et al. Use of antidepressants and the risk of fracture of the hip or femur. Osteoporos Int. 2009;20(10):1705-13.
13. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc. 2002;50(10):1629-37.
14. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. Osteoporos Int. 2006;17(6):807-16.
15. Mussolino ME, Jonas BS, Looker AC. Depression and bone mineral density in young adults: results from NHANES III. Psychosom Med. 2004;66(4):533-7.
16. Wong SY, Lau EM, Lynn H, Leung PC, Woo J, Cummings SR, et al. Depression and bone mineral density: is there a relationship in elderly Asian men? Results from Mr. Os (Hong Kong). Osteoporos Int. 2005;16(6):610-5.
17. Overbeek JA, Zhao Z, van Herk-Sukel MP, Barber BL, Gao S, Herings RM. Costs of hospital events in patients with metastatic colorectal cancer. J Med Econ. 2011;14(5):656-61.
18. Houweling PL, Molag ML, van Boekel RL, Verbrugge SJ, van Haelst IM, Hollmann MW. ['Postoperative pain treatment' practice guideline revised]. Ned Tijdschr Geneeskd. 2013;157(49):A7005.
19. Verdel BM, Souverein PC, Egberts TC, van Staa TP, Leufkens HG, de Vries F. Use of antidepres-

sant drugs and risk of osteoporotic and non-osteoporotic fractures. Bone. 2010;47(3):604-9.
20. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. JAMA. 1989;262(23):3303-7.
21. 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;158(6):892-8.
22. 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.
23. Souverein PC, Abbing-Karahagopian V, Martin E, Huerta C , de Abajo F, Leufkens HGM , et al. Understanding inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip/femur fractures PDS suppl (in press). 2015.
24. Abbing-Karahagopian V. Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo FJ, Leufkens HGM, Slattery J, Alvarez Y, Miret M, Gil M, Oliva B, Hesse U, Requena G, de Vries F, Rottenkolber M, Schmiedl S, Reynolds R, Schlienger RG, de Groot MCH, Klungel OH, van Staa TP, van Dijk L, Egberts ACG, Gardarsdottir H, & De Bruin ML. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations and methodological implications. Eur J Clin Pharmacol. 2014.70: 849-57.
25. Requena G, Huerta C, Gardarsdottir H, Logie J, Gonzalez-Gonzalez R, Abbing-Karahagopian V, et al. Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies across databases from the PROTECT-EU project. Pharmacoepidemiol Drug Saf. 2015.
26. 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;158(1):77-84.
27. Ziere G, Dieleman JP, van der Cammen TJ, Hofman A, Pols HA, Stricker BH. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of non-vertebral fractures. J Clin Psychopharmacol. 2008;28(4):411-7.
28. Diem SJ, Blackwell TL, Stone KL, Cauley JA, Hillier TA, Haney EM, et al. Use of antidepressant medications and risk of fracture in older women. Calcif Tissue Int. 2011;88(6):476-84.
29. 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;66(2):276-82.
30. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA. 2014;174(4):588-95.
31. Laine L. Gastrointestinal effects of NSAIDs and coxibs. J Pain Symptom Manage. 2003;25(2 Suppl):S32-40.
32. Phillips A, Fletcher C, Atkinson G, Channon E, Douiri A, Jaki T, et al. Multiplicity: discussion points from the Statisticians in the Pharmaceutical Industry multiplicity expert group. Pharmaceutical Statistics. 2013;12(5):255-9.
33. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. Statistics Med. 2014;33(4):693-713.
34. Patel CJ, Ioannidis JP. Placing epidemiological results in the context of multiplicity and typical correlations of exposures. J Epidemiol Comm Health. 2014;68(11):1096-100.

4

General discussion

Discrepancies between the findings of pharmacoepidemiological studies on the same drug exposure-health outcome relation have challenged the process and validity of evidence based benefit-risk evaluations. In an effort to understand the sources of variability among such findings, we have taken the association between antidepressant and/or benzodiazepine use and hip fracture for in-depth assessment. This was also one of the associations selected by the researchers from work-package 2 of the IMI-PROTECT project [1, 2], but our analyses were broader. This drug-adverse event combination was evaluated in multiple databases as exposure, as health outcome and as their association in terms of relative risk. In all the studies in this thesis, databases from the following five European countries have been used for this evaluation:

1. The Bavarian Claims Database from Germany
2. The BIFAP (The database for pharmacoepidemiology studies in primary care) from Spain
3. The Danish National Databases from Denmark
4. The Clinical Practice Research DataLink (CPRD) and The Health Improvement Network (THIN) from the UK
5. The Mondriaan databases (Mondriaan-NPCRD and Mondriaan-AHC), the PHARMO-RLS database from The Netherlands.

The characteristics of the above listed databases are described in detail in chapter 1.2, except for the Dutch PHARMO-RLS [3] database, which was described in chapter 3.3.

Electronic healthcare databases, such as those listed above, are used for estimating the prevalence and incidence of drug use and drug use patters, that of health outcomes, as well as for evaluating drug-health outcome associations. Many factors should be considered to be able to comprehend the sources of variability in the findings from different studies. The three main factors are the study design, data used to characterise the exposure, outcome and other relevant variables and the applied data analyses. In addition, healthcare system, population and sociocultural aspects may differ in different studies. These factors, summarized in Table 1, may furthermore change over time. Time related factors can for example be the availability, cost and clinical positioning of the medications, as well as the cultural aspects related to health, disease and/or its treatment in certain populations. All these challenge the interpretation of differences between study findings in medication use patterns, frequency estimates of health outcomes and their risk across populations.

Appreciating the nature and the mixture of factors causing the variability in findings of previous studies (Table 1), we have applied the following two approaches to understand this

Table 1: Examples of possible sources of variability in the findings of the studies using the eight European healthcare databases in this thesis

Sources/factors of variability	Features
Study design	Various observational study designs
	Cross-sectional/prospective/retrospective, case-control/ cohort/case-only designs and their variations
	Definition of exposure, outcome and other relevant variables
	Risk and reference time windows
Data/Database	
Setting	Primary care, pharmacy, claims
Nature	Prescriptions (issued, despised), diagnosis, medical / prescription history, patient/prescriber information
Coding system in the database	Drug exposure: ATC (4), BNF (5)
	Event outcome: ICD (6), READ (7), ICPC (8)
Unit of time data recorded and/or uploaded	Daily, quarterly
Historical data available in the database	Duration before the study period (patient history)
Variability in denominator information	Dynamic population, datasets extracted at different times in a year
Data analyses	Different statistical tests
	Intricate differences in similar study designs
	Potential confounding and/or effect modifying factors
Healthcare/prescribing guidelines	Drug exposure: Prescribing practices
	Event outcome: Diagnostic guidelines
Actual prescribing and utilization	Differing culture of prescribing /medication use
Reimbursement practices	Affects medication utilization
Population characteristics	Age, sex, health and lifestyle differences

variability with respect to the prevalence of antidepressant and benzodiazepine prescribing, the incidence of hip fracture and their association:

I. Harmonisation of study methods using different databases to evaluate the reduction in variability in the results (in chapters 2.1, 2.2, 2.3 and 3.1)
II. Assessment of the dynamics, the complexity and the duration of concomitant exposure to antidepressants and benzodiazepines to understand its impact on the risk of hip fracture (in chapters 3.2 and 3.3)

In this general discussion we will discuss the application of these two approaches, our findings as well as their clinical meaning (section III). We conclude with some recommendations based on our interpretation of these findings.

I. Harmonisation of observational study methods: an illusion or a painstaking process?

The design, conduct, analysis and reporting of randomised clinical trials (RCTs) – by many still considered the paradigm of clinical research- is highly standardized. The ICH (*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*) is an ultimate effort to safeguard people through standards of good clinical practice (GCP), for the development and registration of new pharmaceuticals [9]. Its primary objective is to increase the efficiency of safe and standardised conduct of clinical trials and avoid unnecessary testing of medications. In addition to registering and reporting of clinical trial data [The EU [10] and the US [11] registers]; the CONSORT-*Consolidated Standards Of Reporting Trials* [12] recommendations guide the appropriate reporting of these trial results. Appropriately executed, registered and reported trials should limit the necessity to repeat a trial. Highly regulated processes for clinical trials (conduct and registration) have formed extensive standard operating procedures (SOPs), which can be followed to assure maximum validity and transparency.

Observational studies are intended to reflect the real-world situation in contrast to the more artificial situation of the RCT. This increases the external validity but inherently puts pressure on internal validity. The methodology and the data used for observational studies are much more variable than that of RCTs. Despite the challenges of this kinesis, diversity and scale of the factors introducing variability in results and the current guidelines for reporting study protocols and results. For observational studies guidelines for reporting also exist (*STrengthening the Reporting of OBservational studies in Epidemiology*- STROBE [13]) and recently registers have been established for posting study protocols as well as results (*The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*-ENCePP [14]). Nevertheless, registration of observational study protocols and results are optional in most cases. In contrast, RCT registration is compulsory by regulatory agencies and major journals. A lingering question remains whether further harmonisation and transparency of design, conduct, analyses and reporting of observational studies would contribute to a better understanding and possibly even partly solve variability observed between study results of the same exposure-outcome association.

The harmonisation process applied in our studies (chapters 2.1, 2.2, 2.3 and 3.1) has entailed a long and a gradual progression. It has involved persistently moving towards specifying yet additional details in the study protocols and definitions of variables of interest, in a consensus process, among a large group of researchers from the individual database centres and partners in the IMI-PROTECT consortium. High level definitions in the study protocol were still open to different interpretations when different researchers, even at the same centre (i.e. using the same database), attempted to discuss their understanding of the defined

exposure or outcome variable. Therefore, our effort was to collectively agree and define, specify, sketch and record every single element in the study protocol in a data specification document (also referred by others as statistical analysis plan - SAP) in this harmonisation process. Figure 1 shows the different levels of details on the reported study methods, taking exposure definition as a generic example. Moving from the study protocol level to the study analyses application level, details specific to the data type (prescriptions issued/or dispensed, diagnoses, prescriptions/or procedures claimed etc.) and the structure (such as linkage steps needed to connect different types of data within a single database, the specific prescription needed to be linked to the specific diagnosis or claim etc.) would be clarified and recorded. In this thesis, when we refer to harmonisation of the study methods, we indicate an attempt to harmonise until the data specification document level (Figure 1). The last level (application of the statistical analyses) was not part of the harmonisation process and was done locally at each database centre blinded for the ongoing activities in the other centres. In addition, quality control of data management and analyses was performed in a decentralized manner i.e. internal quality assurance process planned and executed at each database center according to process deemed appropriate by the centre. No external quality assurance was applied on the final protocols and analyses by a third party organisation.

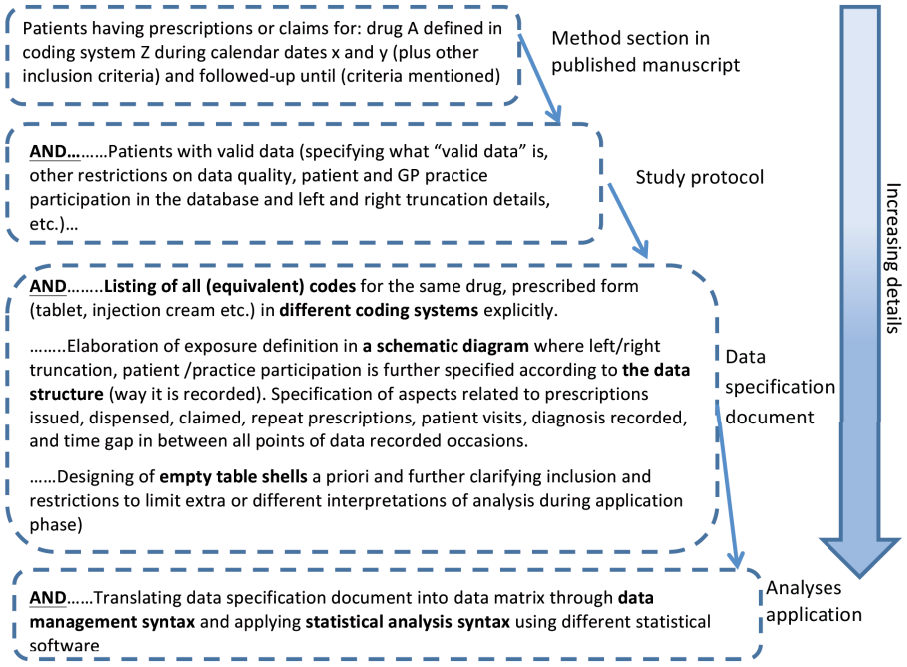


Figure 1: Illustration of different levels of information details present in observational study methods taking exposure description as a generic example.

The rationale for the common study protocol approach was the following: if there are too many sources and levels of variability (whether population, data or study methods related), harmonising study methods should at least reduce the total variability and contribute to understanding of sources of variability other than the study methods. Moreover, if a common study protocol is applied, a direct comparison of the estimates of medication use (or a health outcome) would also be possible. This would then avoid the limitations of cross-population comparisons with estimates made according to totally different definitions. For example, it was shown that different definitions of prevalence of medication use applied in the same population would lead to clearly different prevalence estimates of statin use in the same Dutch population [15]. In addition to common definitions, we have applied age and sex standardisation using the European Union population in 2008 as a standard in the studies (chapters 2.1, 2.2 and 2.3) in order to overcome differences in population distributions in terms of age and sex and support cross comparison of the results. As antidepressants and benzodiazepines are used for various indications we have also uniformly estimated the distribution of indications for prescribing among these populations as well as the number of prescriptions issued for each patient (chapter 2.1 and 2.2).

The application of the harmonised protocols has made it possible to make some direct inferences on and explanations of the sources of variability in the results. In chapter 2.1, the variability in the observed prevalence rates of SSRI and TCA prescribing in different countries could be explained in terms of: database type (only primary vs. primary and secondary care data); differences in prescribing habits or culture especially when age and sex stratification were applied (general practitioners vs. specialists, higher prescribing in 20-60 years old patient groups in the UK and a relatively lower prescribing in the Netherlands). Similarities between the countries could also be directly seen such as in the indications for which the prescriptions were issued (mainly depression and anxiety related disorders in all the countries). Such differences or similarities would not have been possible to detect if different definitions of medication use were compared across countries. Similarly, in chapter 2.2, we could explain differences in the prescribing rates of anxiolytics and hypnotics in terms of prescribing habits [16, 17], patient perception and behavior [18] as similarly reported in the literature. However, beyond the confirmation of the prescribing rates in the individual countries compared with literature findings, we could see specific differences between countries. In general, the distribution of the various indications for prescribing benzodiazepines, as a single drug group, showed comparable proportions in all the databases (anxiety and sleeping disorder being major indications). However, classifying prescribing rates categorized as anxiolytics, hypnotics and other benzodiazepine related drugs (zopiclone, zolpidem and zaleplon), we could see differences among the countries. These major differences in prescribing habits need further examination of indications for prescribing. National guidelines in the individual countries cannot be pointed as a source of

variability in the results as they are in general similar. So, our study could show the distinct features when different populations are compared using a common definition.

The study in chapter 2.3 showed generally comparable incidence rates in all the countries. Moreover, the study generated a first-hand finding of a decreasing trend in the incidence rates of fracture in Denmark which was absent in the other countries. This study gave us the indication that a health outcome as fracture, which is usually estimated using hospital admission or discharge data, can also be properly estimated using different general practice databases. Our results have reinforced that when the health outcome studied has a clear clinical diagnosis (such as fracture) and leads almost always to a hospital admission, dichotomous classification of this outcome does not suffer greatly from misclassification. Recording of such outcomes are already harmonised in the clinical setting (i.e. recorded in electronic healthcare databases), better than outcomes with complex diagnostic procedures and the recording of them in such databases.

In chapter 3.1 we have applied the cohort study design, defined in a common study protocol and a data specification document, across three different databases (THIN, BIFAP and Mondriaan) to study the association between antidepressant use and hip/femur fracture. We have observed variability in the risk estimates of these three databases. This counter-intuitive finding at first sight (actual results further discussed below in section III 'Clinical findings from the Application of the Harmonised Protocols'), needs an appropriate understanding of the results in the context of the harmonisation process applied. Therefore, due to the maximum harmonisation possible in the protocol and the data specification document we could further analyse the differences in the observed hazard ratios in these uniformly conducted cohort studies in terms of: the exposure definition, the availability of different confounding information in the databases and the presence of effect modification. The harmonisation of the exposure variable (defined as SSRI and TCA use) could not be achieved equally across the three cohorts. Due to the absence of information on dosage regimen in the Mondriaan databases we had to assume a fixed duration for each prescription length (90-days). In the other two databases prescription length was estimated based on the prescribed or the dispensed amount and the dosage regimen of the medication allowing 30-days gap in between consecutive prescriptions within a treatment episode. This divergent aspect of the exposure definition indicated the limitations of the harmonisation process (due to different levels of data availability). However, as we had a centralised process of protocol harmonisation we could further probe, via the individual database holders into the data and apply sensitivity analyses to gain more insight in the sources of variability in the results. As such, a sensitivity analysis was performed to see the impact of this divergent exposure definition (prescription duration) on the calculated hazards ratios. We found no influence of this assumption on the estimated risk. Furthermore, we excluded the impact of

differences in the availability of confounding information in the three databases on the risk estimates. This was done by adopting an incremental approach in the fitted models for adjusting for the confounders that were present in all of the databases. Subsequently, a gradual addition of confounder variables which were present only in one or two databases was done. Therefore, we could compare adjusted hazards ratios adjusted for the same confounding variables. In fact, except for two major confounders (age and sex), further adjustment for the other and especially lifestyle related confounders had very little impact on the hazard ratios. We could conclude that confounding factors could not explain the variability in the risk estimates. This conclusion can challenge a prevalent discussion on the lack of recorded information on confounders [19] in databases. Further, we tested for the presence of an effect modification due to age in all three cohorts. This analysis showed the presence of an interaction only between SSRI use and age in the Mondriaan cohort and not in the other two cohorts. This pointed out an age related factor (potentially higher effects of SSRI among younger patients) only in the Mondriaan cohort.

To contrast our process of harmonisation, it is important to discuss the common data model (CDM) approach used in several initiatives such as – OMOP [20], EU-ADR [21] and Mini-sentinel [22]. In a CDM approach [23], a common data model and vocabulary is generated which is needed to conduct research in multiple databases. The ultimate aim is to gain efficiency and power and detect safety signals in a timely manner. The CDM approach involves primarily retaining patient level information at the site of the databases where the researchers have the task of translating this patient-level data into aggregate common data model and send to a central research site to be analysed as a primary input from the respective database. The general principles of patient privacy, study methods and reporting transparency are integral parts of this process. The most obvious difference between the CDM approach and that of ours is the centralised way of harmonising the protocol while applying the analyses in decentralized settings of the databases in our approach. In contrast, the CDM performs a decentralized aggregation of patient-level information at the individual databases before the application of centralized analyses (Figure 2). The CDM method has been proven to be efficient and to decrease the heterogeneity of disease estimates from different databases [24]. Apart from the differences in the process of these two approaches, our adopted approach did not aim at achieving efficiency and statistical power as the CDM approach does. Our main goal was to have more insight in the variability of the results. Particularly, as would occur when different research groups would separately perform studies on the same research question.

Studies applying the CDM approach, like the one by Madigan et al. [25] have tested large numbers of drug-adverse event relationships (53 pairs) in several databases (10 different databases) using a common study design (cohort or self-controlled case series). These

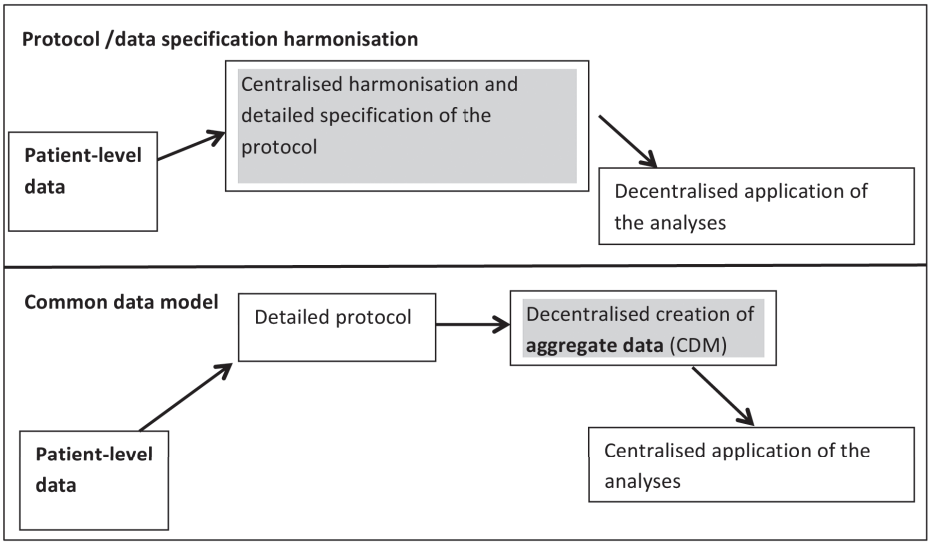


Figure 2: Schematic diagram of high level process differences between the protocol harmonisation applied in this thesis and the common data model approaches.
CDM=common data model

studies have reported promising uses of the CDM approach in terms of concordance rate (before and after standardization process) [24] and percentages of heterogeneity found in drug-adverse event associations in common [25] and different [26] study designs. We have not utilized these measures of heterogeneity, as our purpose was more to understand rather than quantify variability in the results. Moreover, an attempt to quantify heterogeneity or variability of risk estimates in our three cohorts for example would have generated no robust estimates.

The application of harmonised protocols in multiple databases was a unique experience, which has provided a good insight in the conduct of observational studies when large and different electronic healthcare databases are used. Despite our extensive and meticulous efforts to harmonise study methods across different databases, we could not achieve complete harmonisation due to several intrinsic and practical barriers especially related to the databases. However, harmonisation of the protocols provided a useful insight into the sources of variability and opportunity for direct cross-country comparisons especially in the estimation of the prevalence and incidence rates of medication use and health outcome. Such an insight would not have been possible with the use of CDM, which feeds into the analyses already aggregated data. We are confident that for such studies (prevalence/incidence estimations) a more harmonised approach would be as important as the efficiency and the statistical power gained by applying the CDM approach. However, harmonisation

of study protocols for drug-adverse event association studies are more challenging and may require much more time and resources than the CDM approach, in addition to limitations to degree of harmonisation possible as discussed above.

Our inference from the harmonisation process is that it is an illusion to expect full harmonisation of observational studies and to make the organisation of study conduct similar to clinical trials. Hence, focusing on inclusion of more details in the study protocols and making them transparent would be an essential step towards full comprehension of the applied methods. Currently, published study protocols contain insufficient details on the data specification definitions. Furthermore, public posting of the application of the data specification document in actual analyses with appropriate accompanying explanatory documents may be very useful in increasing the validity and transparency of the applied study methods. The STROBE guidelines may be further crystallised to include such details on data specification and analyses applied. Increased transparency on study methods and conduct details of observational studies will also be valuable for the application of quality control processes. In addition to quality assurance at the side of research organization, there can be room for some quick quality check procedures by the database owners, or journal editors. Such additional quality checks would be possible when enough details are reported and electronic healthcare databases are used for these studies in contrast to earlier observational studies based on survey results.

II. Complexity of concomitant exposure and its relevance in risk estimation

In studying a drug-adverse event association, the usual approach is defining the main exposure and the outcome of interest and then to adjust in the data analyses for the possible confounders. However, medication prescribing or use, in real-world situations, is complicated. Polypharmacy and co-prescribing is a usual practice especially in psychiatric care [27-31]. This introduces a challenge for accounting for the additional risk due to the concomitant exposure. This is because the hazard curve of the common risk for the two medications may be very different and the depending on the concomitant use pattern, the overall risk may differ among patients. In chapters 3.2 and 3.3 we have applied the second approach to understand the variability in the risk estimates: assessing the complexity of concomitant use of antidepressants and benzodiazepines in terms of initiation of therapy and duration of use. We have discussed and analysed the different patterns of this concomitant exposure in terms of its impact on fracture risk. In chapter 3.2 we have identified a cohort of incident antidepressant users in the Mondriaan-NPCRD database. We found almost 40% of the incident users also using benzodiazepines i.e. concomitant users. This confirmed the polypharmacy reported in several studies and added important evidence that concomitant use of these two drugs is also prevalent in primary care, as it was already reported in secondary care [27, 28, 31]. In this study, we have further characterized concomitant use among these

patients in terms of duration of use with respect to the start of antidepressant therapy. Our results showed different patterns of concomitant use among this cohort. Specifically, the data showed longer concomitant use in patients who have started using benzodiazepines before and simultaneous to start of antidepressant therapy, compared with patients who have started using benzodiazepines after antidepressant treatment initiation. With graphical depictions of concomitant use patterns we could argue that different risks for different patterns of use could be expected. We could test then this line of reasoning in chapter 3.3.

In chapter 3.3, we have applied the case-control design among antidepressant users in the Dutch PHARMO-RLS database to study the risk of osteoporotic fracture. This study showed the concomitant use of antidepressants and benzodiazepines has variable durations in accordance to our findings in chapter 3.2. The adjusted odds ratios for fracture varied with the duration of single or concomitant use (range 1.78 to 4.18). Among single users of antidepressants, the risk first decreased before increasing again, as the duration of use increased. Among single users of benzodiazepines, the risk was constant with the duration of use. However, among the concomitant users the risks were different in those who used benzodiazepines on a short vs. long term. This was also true for concomitant users with short, median and long durations of antidepressant use. As such, among concomitant users, the highest risks for fracture were observed among short-term benzodiazepine users compared to those who used benzodiazepines for a longer period. In this study we treated concomitant exposure as a complex exposure rather than a variable in an exposure-confounder-outcome model, as often used in association studies. We could see the presence of effect modification through different durations of concomitant use. The modifying effect showed higher risk of fracture in the initial period of concomitant use (the first 28-days of benzodiazepine initiation, concomitant with the use of antidepressants regardless of the timing of start of the latter). We had based the definition of concomitant exposure duration on the estimated risk patterns of individual exposures published in previous literature. By doing so, we could include one important dimension of exposure (duration), which showed to be an effect modifier. To gain more insight in the concomitant use of antidepressants and benzodiazepines studies with exposure definitions including both medications should be considered. In our study we had only looked at the effect of duration. However, effect of dose is not less important especially in concomitant use. Defining exposure to two concurrently used medications as a complex exposure in larger and different populations are needed to further confirm our results and handle issues of sufficient statistical power needed to split the effect of duration of the concomitant exposure.

Placing the complexity of concomitant exposure into context to attempt explaining the variability found in the fracture risk estimates in the three uniformly conducted cohort studies, is enticing. The presence of age as an effect modifier in the Dutch Mondriaan cohort (which

generated higher risk estimates compared to the other cohorts) may raise a question: Is the observed effect modification of age a proxy for different concomitant exposure durations that we observed in another Dutch database (PHARMO database)? Is this phenomenon (concomitant use pattern) specific to the Dutch population which is absent in the other populations like in Spain and the UK? Is the variability in the observed risks in the studies of this same drug-adverse event association due to an important effect modifier, and can be absent or present in different populations? Furthermore, we found the lowest rates of antidepressant and benzodiazepine use in the Dutch population in our studies. The characterisation of concomitant exposure to these two medications may indicate an additional difference between the populations, which has to be further investigated for proper inferences.

We should keep in mind however, that there were limitations of data availability (absence of data on the prescribed dose in the Dutch Mondriaan database) indicating again the limitations of the process of harmonisation. Nevertheless, when study protocol specifications and in this case concomitant exposure definitions are made public (with explicit reporting of these limitations) study results can be further replicated in different databases trying to overcome the relevant limitations. Our findings of different risk estimates for fracture based on the concomitant exposure is very intriguing and a similar approach for defining concomitant use can be adopted for example: to study the risk of fracture among concomitant use of antihypertensive medications [32] and benzodiazepines. It is important to detect the presence of effect modification in such studies. Stratified analyses or marginal structural models [33] are applied methods to detect important effect modifiers. However, complex concomitant exposure definitions, based on the individual medication hazard curves as we have done in our studies, may provide more insight into the patterns of concomitant use as a combined exposure. Detecting a relevant effect modification may be more important especially when different low relative risks are reported on the same drug-adverse event association and many variables are fitted in different models [34]. An attempt to understand the variability among the reported low relative risks, with short a range, can be very challenging. More in-depth investigation on the impact of concomitant exposures on the risk estimates in different databases taking into account differences in database size, and relevant data availability is the way forward for the observational studies. Understanding the effect modification underlying concomitant medication use should help design better study protocols giving more importance to etiological aspects than simple cause and effect studies. Current benefit-risk evaluations require the input of more nuanced observations on the drug-adverse event effects and less hierarchical approach for casual effects of the determinants of an outcome. For such a prognostic approach for designing observational pharmacoepidemiological studies drug safety and effectiveness protocols requires a paradigm shift among the researchers.

III. Clinical Findings from the Application of the Harmonised Protocols

In this section, we attempt to assess the clinical value of our findings. We describe the results of the individual studies conducted using harmonised protocols. Specifically, we report the prevalence of antidepressant and benzodiazepine prescribing and the incidence of hip/femur fracture in five European countries. We also present findings from uniformly conducted cohort studies on the risk of fracture among antidepressant users using three databases from Europe.

Antidepressant and benzodiazepine use in Europe

Drug utilisation studies on antidepressants and benzodiazepines, in the early 1980s and -90s, were most often cross-sectional surveys or consisted of aggregate country data on drug expenditure or sales volume [35-37]. The increasing availability of electronic healthcare databases has provided the opportunity for more detailed assessments of medication use in a particular setting and comparisons across regions and countries using patient-level data. Yet, heterogeneity of measures used to quantify utilisation reported in the literature has remained to be large. Although the use of individual patient information brings us a step closer in assessing drug consumption in actual clinical practice, as long as definitions and measures of consumption are not common among studies a valid comparison is simply not possible. Relatively few studies have done cross-country comparisons of antidepressant [38-42] or benzodiazepine [43-47] use. This is in contrast to huge numbers of studies performed in single populations defined according to specific or narrow indications or age groups. These highly selective populations often do not reflect the country/general population profile and have intrinsic differences, which can be due to a large variety of factors summarized in Table 1. So applying common measures of antidepressant use or prescribing (synonymously used as distinction between the two was out of scope for this thesis) showed relatively stable trends over the study period from 2001 to 2009 (chapter 2.1). In addition, prescribing rates were highest in the United Kingdom and lowest in the Netherlands. Stratification of antidepressants according to drug class (defined as selective serotonin reuptake inhibitors-SSRIs or tricyclic antidepressants-TCAs) showed a slight increase in SSRI use over the study period in all countries in contrast to TCA use, which showed a decrease. This phenomenon confirms the earlier studies indicating increase in SSRI use at the cost of TCA use in most European countries [39, 48]. In general, prescribing rates for SSRIs were higher than those for TCAs in all countries except in Germany. This was one of the distinctive features we could see in the prescribing of antidepressants in Germany indicative of higher use of TCAs compared to other countries. Despite the previously reported [49] gradual increase in SSRI prescribing in Germany among children, our study showed a clear contrast between the higher use of TCA in Germany compared to the other countries. Further age and sex-standardisation of the prescribing data showed higher prescribing in women compared with men and increasing prevalence with increase in age. This phenomenon was in agreement

with previous studies [44, 50, 51]. In addition, we found higher prescribing rates in age groups 20 to 60 years in the UK especially among females compared to the other countries. This finding suggests the need for further in-depth study on the use of antidepressants in the UK with further description of the patients in this wide adult age group. Finally, the prescribing rates estimated for the same country but in different databases (CPRD and THIN from the UK and Mondriaan-NPCRD and Mondriaan-AHC from the Netherlands) showed similar results confirming the generalisability of the findings at country level.

In chapter 2.2 we have seen notable differences in the prevalence of benzodiazepine prescribing and/ or dispensing in the respective countries. Particularly, the age and sex-standardised prevalence rates showed an increasing trend in Spain, a decrease in Denmark, Germany and one of the databases in the Netherlands (Mondriaan-AHC) and a stable trend in the UK and in the Mondriaan-NPCRD databases. There were two consistent features of benzodiazepine use, which confirmed the findings of the previous studies: a higher prevalence of benzodiazepine use in women and a steady increase in use with increase in age [52-55]. Looking at the trends over the 9-year study period in different age groups, we saw a decreasing trend in use among elderly (chapter 2.2) in all databases except in the Spanish BIFAP. In the BIFAP database, the prevalence in different age groups showed a steady increase, in contrast to our findings in the other databases however, consistent with previous studies [56, 57]. Further stratification of benzodiazepine prescribing in terms of anxiolytics and hypnotics showed completely different patterns of prescribing. Anxiolytics were prescribed more in Spain, Germany and in Mondriaan_AHC database while hypnotics were more used in the UK and in Denmark. These results were in line with the literature when we compare country specific situations [43-45, 47, 56-59].

Hip/femur fractures in Europe

In chapter 2.3 we could directly compare two aspects of hip/femur fracture across the relevant databases and populations: age and sex-standardised incidence rates and trends over the 9-year study period. The age and sex standardised incidence rates in Denmark were twice as high as the rates observed in the UK, the Netherlands, and Spain. In line with previous literature, the incidence of hip/femur fracture was higher among females than in males [60-62] in all countries with an exponential increase with age regardless of sex [63]. Moreover, we did not see a clear north-south gradient in the incidence of hip/femur fracture as reported by previous studies [64, 65] except for the clearly higher incidence rates in Denmark. However, we had just one southern country (Spain) to make such a comparison. The rates in the two databases in the Netherlands showed lot of fluctuations across the 9-year period and were remarkably lower than those reported by the Dutch NCPRD and national hospital discharge [66]. The fluctuations were likely due to the limited power of the Dutch databases (smaller) compared to the relatively larger databases from the other

countries (chapter 1.2). An explanation for the lower rates from the Netherlands during the study period may be the fact that the recording of fractures in the primary healthcare records (using ICPC codes [8]) by the general practitioners has been actively promoted only in 2010-2011. Before this date, significant under-recording of fractures in the general practice (GP) databases could have occurred. Finally, a close examination of the trends in the incidence rates over time showed a steady decrease only in Denmark. The rates were rather stable over time in the other databases. In general, the findings of hip/femur fracture in primary healthcare databases that we have used were in line with the findings in other databases form the same countries. The incidence rate in Denmark in our studies has not only confirmed the result from earlier studies [67] in the country but also has shown the contrast in the incidence rates with the other countries (almost two times higher rates in Denmark than in other countries).

Antidepressant use and the risk of hip/femur fracture

When the results from different pharmacoepidemiological studies on the same association are compared, or evaluated in a meta-analysis for example, listing of high-level differences in study methods (such as cohort, case-control or case-only design differences) [68] is one of the first explanation of the main culprits for variability. In chapter 3.1 we have applied the cohort study design, defined in a common study protocol and a data specification document, across three different databases (THIN, BIFAP and Mondriaan) to study the association between antidepressant use and hip/femur fracture. In these cohorts, antidepressant use (stratified as SSRIs and TCAs) was considered as the main exposure of interest. The use of benzodiazepines and various other exposures (relevant co-medications, comorbidities and lifestyle factors) were adjusted as time-varying confounders. Results of these three cohort studies showed increased risks for hip/femur fracture consistent with the previous studies [69, 70]. However, there were some differences in the observed hazard ratios among these uniformly conducted studies. The hazard ratio for SSRI use was higher in the Mondriaan databases compared with the hazard ratios in BIFAP and THIN while the hazard ratios for TCA use were similar in all three cohorts. The fully adjusted hazard ratio for SSRI use in Mondriaan was about 2 times higher (3.27) compared with the hazard ratios in BIFAP and THIN cohorts (1.63 and 1.72, respectively). The higher hazard ratio in the MONDIRAAN database compared with those observed in BIFAP and THIN was also seen for TCA use however; the difference was less pronounced. We have also observed a wider range for the adjusted hazard ratios for SSRI use than the range reported for the risk of fracture and SSRI use by several cohort studies in the literature [69, 71].

Final considerations and Recommendations for the Future

Harmonisation of the study protocols of the studies reported in this thesis has contributed to the understanding of the variability in the results of pharmacoepidemiological stud-

ies, albeit only to certain extent. Factors other than the study methods are to be sought for further explanation of the variability in the results from different studies on the same drug-adverse event association. The harmonisation of the study methods across different databases can only be performed partially. This is due to the inherent differences between databases used. Therefore, as a compensation of limitations to full harmonisation, additional transparency on the details of the study protocols and data specification documents should enhance the understanding and contextualizing of study results. Abiding by the STROBE [13] guidelines for reporting the minimum essential elements of a study protocol (for example in ENCePP) can be fortified by extra details. Details can be provided with respect to exposure, outcome and confounder definitions and also further specifications on the steps implemented in population selection, data management and analyses syntax application. When this information is made public, the replication or further analyses of the research question can be performed in the same and other databases. A replication in the same database would be comparable to quality control procedures well adopted in the clinical trials and experimental studies. A commendable feature is the support for more transparency of study methods by liberating authors from the total word count restrictions in peer –reviewed journals for the study methods sections. This is a new and encouraging feature, already applied by a few journals, such as the Journal of National Cancer Institute [72]. Such transparency would surely contribute to more structured internal (i.e. research organization) and external (i.e. for example the journal or database owners) quality control mechanism in observational studies.

Moreover, we have observed that treating the main exposure as a single major exposure of interest, in a drug-adverse event association study, without accounting for the variability of a simultaneously related exposure to a another medication overlooks the presence of a potential effect modifier. Such co-medications which are also strongly related to the outcome of interest and are often co-prescribed should be analysed as one complex multi-dimensional concomitant exposure variable. Not accounting for this complexity may miss the identification of specific co-exposure scenarios where the risk of outcome differs and may particularly be high for certain "type" of concomitant users. When such an understanding of the differences in risk estimates exists, appropriate adaptation of prescribing guidelines could then aim at minimising the risk for certain patients. A way forward to achieve this is to treat medication use and its effects as a prognostic question rather than uni-causal safety question and miss detecting important effect modifications is not taken into account.

Based on our findings we consider the importance of drug utilisation studies focusing on complex concomitant exposure patterns. Furthermore, reporting of detailed definitions of the applied study methods cannot be stressed enough. Drug utilisation studies would add important insight into the evaluation of the complex exposures and their potential impact

on the health outcome studied. Hence, appropriately defined and conducted drug utilisation studies may become an integral part of development of study protocols for observational pharmacoepidemiological studies on drug-adverse event associations. Appropriate characterisation of drug utilisation in terms of prescribing behaviour and trends, duration and indications of use; would serve as a ground-work for appropriate definitions of such prevalent concomitant exposures. A thorough understanding of this would feed into more detailed exposure definitions based on actual practice rather than theoretical guidelines in a country.

REFERENCES

1. PROTECT-EU. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium [cited 2013 July]. Available from: http://www.imi-protect.eu/.
2. 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. 2014;9(2):130-8.
3. the PHARMO Institute Available from: http://www.pharmo.nl/.
4. World Health Organisation. the Anatomical Therapeutic Chemical (ATC) classification system [updated 2015 July 13]. Available from: http://www.whocc.no/atc/structure_and_principles/.
5. BNF. British National Formulary [updated 2015 July 13]. Available from: http://www.bnf.org/bnf/index.htm.
6. World Health Organisation. International Classification of Diseases [cited 2015 July 13]. Available from: http://www.who.int/classifications/icd/en/.
7. READ coding system [cited 2015 July 13]. Available from: http://systems.hscic.gov.uk/data/uktc/readcodes.
8. International Classification of Primary Care, Version 2-Plus Source Information [cited 2015 July 13]. Available from: http://www.nlm.nih.gov/research/umls/sourcereleasedocs/current/ICPC2P/.
9. Herbst R, Multier AM. [Pathological structures of the placenta examined under the electron microscope. 1st observations of villi of aborted human ova]. Gynecologie et obstetrique. 1971;70(4):369-76.
10. Sinz V, Herbst M, Ursinus K, Kuhn I, Elze P. [Extra- and intracellular electrolyte changes in heart surgery operations]. Zentralblatt fur Chirurgie. 1971;96(22):725-33.
11. The U.S. National Institues of Health. Clinicaltrials.gve: Registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Available from: https://www.clinicaltrials.gov/ct2/about-site/background.
12. CONSORT Group. Consolidated Standards of Reporting Trials Available from: http://www.consort-statement.org/.
13. STROBE Group. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE). Available from: http://www.strobe-statement.org/.
14. European Medicines Agency. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®). Available from: http://www.encepp.eu/.
15. Mantel-Teeuwisse AK, Klungel OH, Verschuren WM, Porsius A, de Boer A. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. J Clin Epidemiol. 2001;54(11):1181-6.
16. Pharoah PD, Melzer D. Variation in prescribing of hypnotics, anxiolytics and antidepressants between 61 general practices. The British journal of general practice: Br J Gen Pract. 1995;45(400):595-9.
17. van der Waals FW, Mohrs J, Foets M. Sex differences among recipients of benzodiazepines in Dutch general practice. BMJj. 1993;307(6900):363-6.
18. 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;45(2):153-63.
19. In: Gliklich RE, Dreyer NA, editors. Registries for Evaluating Patient Outcomes: A User's Guide. AHRQ Methods for Effective Health Care. 2nd ed. Rockville (MD)2010.
20. Foundation for the National Institutes of Health. Observational Medical Outcomes Partnership [cited 2013 July]. Available from: http://omop.fnih.org/.

21. Patadia VK, Coloma P, Schuemie MJ, Herings R, Gini R, Mazzaglia G, et al. Using real-world healthcare data for pharmacovigilance signal detection - the experience of the EU-ADR project. Expert Rev Clin Pharmacol. 2015;8(1):95-102.
22. Platt R, Carnahan RM, Brown JS, Chrischilles E, Curtis LH, Hennessy S, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:1-8.
23. Reisinger SJ, Ryan PB, O'Hara DJ, Powell GE, Painter JL, Pattishall EN, et al. Development and evaluation of a common data model enabling active drug safety surveillance using disparate healthcare databases. J Am Med Inform Assoc. 2010;17(6):652-62.
24. Voss EA, Ma Q, Ryan PB. The impact of standardizing the definition of visits on the consistency of multi-database observational health research. BMC Med Res Methodol. 2015;15:13.
25. 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;178(4):645-51.
26. Madigan D, Ryan PB, Schuemie M. Does design matter? Systematic evaluation of the impact of analytical choices on effect estimates in observational studies. Ther Adv Drug Saf 2013;4(2):53-62.
27. Chakos MH, Glick ID, Miller AL, Hamner MB, Miller DD, Patel JK, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. Psych Serv. 2006;57(8):1094-101.
28. Barbui C, Nose M, Mazzi MA, Thornicroft G, Schene A, Becker T, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. Int Clin Psychopharmacol. 2006;21(6):355-62.
29. Gadit AA. Polypharmacy practice in psychiatry. J Coll Phys Surg Pak. 2005;15(8):451-3.
30. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. Curr Med Chem. 2004;11(3):313-27.
31. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. Pharmacoepidemiol Drug Saf. 2003;12(1):41-8.
32. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174(4):588-95.
33. Chiba Y, Azuma K, Okumura J. Marginal structural models for estimating effect modification. Ann Epidemiol. 2009;19(5):298-303.
34. Lunt M, Solomon D, Rothman K, Glynn R, Hyrich K, Symmons DP, et al. Different methods of balancing covariates leading to different effect estimates in the presence of effect modification. Am J Epidemiol. 2009;169(7):909-17.
35. Williams P, Bellantuono C, Fiorio R, Tansella M. Psychotropic drug use in Italy: national trends and regional differences. Psychol Med. 1986;16(4):841-50.
36. Barbui C, Campomori A, D'Avanzo B, Negri E, Garattini S. Antidepressant drug use in Italy since the introduction of SSRIs: national trends, regional differences and impact on suicide rates. Soc Psychiatry Psychiatr Epidemiol. 1999;34(3):152-6.
37. Arpino C, Da Cas R, Donini G, Pasquini P, Raschetti R, Traversa G. Use and misuse of antidepressant drugs in a random sample of the population of Rome, Italy. Acta Psychiat Scand. 1995;92(1):7-9.
38. Alonso MP, de Abajo FJ, Martinez JJ, Montero D, Martin-Serrano G, Madurga M. [Evolution of antidepressive drug consumption in Spain. The impact of selective serotonin re-uptake inhibitors]. Medicina Clinica. 1997;108(5):161-6.
39. Bauer M, Monz BU, Montejo AL, Quail D, Dantchev N, Demyttenaere K, et al. Prescribing patterns of antidepressants in Europe: results from the Factors Influencing Depression

Endpoints Research (FINDER) study. Eur Psychiatry. 2008;23(1):66-73.
40. Bowers L, Callaghan P, Clark N, Evers C. Comparisons of psychotropic drug prescribing patterns in acute psychiatric wards across Europe. Eur J Clin Pharmacol. 2004;60(1):29-35.
41. Lidell E, Luepker R, Baigi A, Lagiou A, Hildingh C. Medication usage among young adult women: a comparison between Sweden, the USA, and Greece. Nurs Health Sci. 2008;10(1):4-10.
42. Zito JM, Tobi H, de Jong-van den Berg LT, Fegert JM, Safer DJ, Janhsen K, et al. Antidepressant prevalence for youths: a multi-national comparison. Pharmacoepidemiol Drug Saf. 2006;15(11):793-8.
43. 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 Aff Dis. 2008;110(1-2):84-93.
44. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. Journal Clin Psychiatry. 2002;63(9):817-25.
45. van Hulten R, Isacson D, Bakker A, Leufkens HG. Comparing patterns of long-term benzodiazepine use between a Dutch and a Swedish community. Pharmacoepidemiol Drug Saf. 2003;12(1):49-53.
46. Patten SB, Wang JL, Williams JV, Lavorato DH, Beck CA, Bulloch AG. Frequency of antidepressant use in relation to recent and past major depressive episodes. Can J Psychiatry. 2010;55(8):532-5.
47. Zito JM, Safer DJ, de Jong-van den Berg LT, Janhsen K, Fegert JM, Gardner JF, et al. A three-country comparison of psychotropic medication prevalence in youth. Child Adolesc Psychiatry Ment Health. 2008;2(1):26.
48. Rosholm JU, Andersen M, Gram LF. Are there differences in the use of selective serotonin reuptake inhibitors and tricyclic antidepressants? A prescription database study. Eur J Clin Pharmacol. 2001;56(12):923-9.
49. Hoffmann F, Glaeske G, Petermann F, Bachmann CJ. Outpatient treatment in German adolescents with depression: an analysis of nationwide health insurance data. Pharmacoepidemiol Drug Saf. 2012;21(9):972-9.
50. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. J Affect Disord. 2007;98(1-2):109-15.
51. Poluzzi E, Motola D, Silvani C, De Ponti F, Vaccheri A, Montanaro N. Prescriptions of antidepressants in primary care in Italy: pattern of use after admission of selective serotonin reuptake inhibitors for reimbursement. Eur J Clin Pharmacol. 2004;59(11):825-31.
52. van Hulten R, Leufkens HG, Bakker A. Usage patterns of benzodiazepines in a Dutch community: a 10-year follow-up. Pharm World Sci. 1998;20(2):78-82.
53. Ohayon MM, Caulet M, Priest RG, Guilleminault C. Psychotropic medication consumption patterns in the UK general population. J Clin Epidemiol. 1998;51(3):273-83.
54. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck GA. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. Int Clin Psychopharmacol. 2007;22(5):292-8.
55. 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;18(7):572-8.
56. Spanish Agency for Medicines and Medical Devices (AEMPS). Uso de Benzodiacepinas en España (1992-2006) Available from: http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/ansioliticos_hipnoticos.pdf.
57. 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 Publ. 2004;78(3):379-87.
58. Linden M, Lecrubier Y, Bellantuono C, Benkert O, Kisely S, Simon G. The prescribing of psychotropic drugs by primary care physicians: an international collaborative study. J Clin Psychopharmacol. 1999;19(2):132-40.
59. Danish Health and Medicines Authority. Effective effort against the excessive use of benzodiazepines in Denmark. Available from: http://80.160.70.136/en/topics/statistics,-prices-and-reimbursement/statistics-and-analyses/analyses/consumption-analyses/effective-effort-against-the-excessive-u—in-denmark.
60. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.
61. Johnell O, Gullberg B, Allander E, Kanis JA, Group MS. The apparent incidence of hip fracture in Europe: a study of national register sources. Osteoporos Int. 1992;2(6):298-302.
62. Dolan P, Torgerson DJ. The cost of treating osteoporotic fractures in the United Kingdom female population. Osteoporos Int. 1998;8(6):611-7.
63. Poole KE, Compston JE. Osteoporosis and its management. BMJ. 2006;333(7581):1251-6.
64. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthopaed. 2011;45(1):15-22.
65. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239-56.
66. The National Public Health Compass (in Dutch). Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/bewegingsstelsel-en-bindweefsel/heupfractuur/omvang/#reference_4461.
67. 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.
68. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
69. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int. 2012;23(1):365-75.
70. Wu Q, Qu W, Crowell MD, Hentz JG, Frey KA. Tricyclic antidepressant use and risk of fractures: A meta-analysis of cohort and case-control studies. J Bone Miner Res. 2013;28(4):753-63.
71. 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;27(5):1186-95.
72. Journal of National Cancer Institute Available from: http://www.oxfordjournals.org/our_journals/jnci/for_authors/ms_prep.html.

5

Summary & Samenvatting

SUMMARY

Introduction and aim of this thesis

The use of EHR and the availability of data from EHRs has increased the feasibility of conducting pharmacoepidemiology studies and expedited timelines needed for conducting observational studies thus rapidly increasing the rate and amount of research related output. With more available studies, also the number of contradictory findings has increased. We even know several examples of different findings and conclusions for the same drug-adverse event association studied in the same database. Moreover, observational studies have increasingly reported low relative risks (between 1 and 2). The potential public health impact of these safety events may, despite the reported low relative risks, be high. Moreover, the interpretation of the variability among these low relative risks becomes very challenging. The evaluations of bias and understanding of sources of the variability in the reported results has become a crucial need especially in benefit-risk evaluations where evidence-based data has to be collated. Accordingly, there are many systematic and collective efforts in consortia examining this broad theme with the application of different approaches. Several studies in this thesis are part of such a multi-partner European consortium called IMI-PROTECT project. ***Chapter 1.1*** provides a general introduction to the theme and discusses the context of IMI-PROTECT. In this introductory chapter the rationale and the overarching aim of this thesis are described. In short, the aim of this thesis is to understand the variability in findings of pharmacoepidemiological studies resulting from different choices in study methods. In an effort to understand this variability specifically in studies on the same drug-adverse event; we have taken the case of antidepressant and/or benzodiazepine use and hip fracture for an in-depth assessment. This association was also one of the selected drug-adverse events by the researchers from the work-package 2 of the IMI-PROTECT project, but our analyses in the studies of this thesis were broader.

Variability of medication use and health outcomes in Europe: application of harmonised methods

The general objectives and the first results of the work-package 2 of the IMI-PROTECT project are discussed in ***chapter 1.2***. In this chapter we have first presented the rationale for the need to systematically study the impact of methodological choices on the results of the observational studies. This was done by presenting several examples in the literature when discrepant results have been reported on the same drug-adverse event associations even when the same database is used. Therefore, we have shortlisted six drug and adverse event combinations and identified seven European databases where methodological studies could be performed. The drug-adverse event combinations were chosen given their public health importance, prevalence of drug use, the seriousness and acute or chronic characteristics of the health events. In these criteria for selection, which were agreed upon in a consensus

process, the final selected drug-adverse pairs were made sure to represent enough variety in terms of several factors such as event-seriousness, regulatory context, ascertainment feasibility in the databases. The selected six drug-adverse event pairs were 1) inhaled long-acting beta-2 agonists and acute myocardial infarction; 2) antimicrobials and acute liver injury; 3 and 4) antidepressants and/or benzodiazepines and hip fracture; 5) anticonvulsants (approved for treatment of epilepsy) and suicide/suicide attempts; 6) calcium channel blockers and malignancies. These associations were to be tested in the databases available through the partners in the IMI-PROTECT consortium from five European countries. The available databases were 1) The Bavarian Claims Database from Germany; 2) The BIFAP (The database for pharmacoepidemiology studies in primary care) from Spain; 3) The Danish National Databases from Denmark; 4) The Clinical Practice Research DataLink (CPRD) and The Health Improvement Network (THIN) from the UK and 5) The Mondriaan databases (Mondriaan-NPCRD and Mondriaan-AHC) from The Netherlands. Further in this chapter we have described the literature and the epidemiology of the events in detail. The databases were described in terms of their scope, type of information included and repressiveness to the general population. These detailed descriptions made the setting where several studies were to be performed. In the following chapters in this thesis we discuss studies on antidepressant and/or benzodiazepine use and hip fractures more thoroughly and use this as an instrument to explore variability in-depth.

In ***chapter 2.1*** we have studied the prescribing/use of antidepressants in the seven primary care databases from five European countries (Denmark, Germany, The Netherlands, Spain and United Kingdom) that were part of the IMI-PROTECT consortium. To describe the prevalence and trends of prescribing, we have applied a common methodology for quantification. The rationale for this harmonised approach was simple: as previous drug utilization studies have used a variety of data types and methods to quantify the prevalence of drug use, cross-country comparisons are almost an impossible challenge. Furthermore, using the databases under IMI-PROTECT, which provide patient level information, would contrast the enormous literature on drug utilisation based on aggregate data. Therefore, we have developed a common study protocol and data specification document, where the prevalence of antidepressant prescribing was evaluated using the same time fame and criteria for calculating the numerators and denominators using these diverse databases. In this study, antidepressant use was defined as selective serotonin reuptake inhibitors-SSRIs or tricyclic antidepressants-TCAs during the period between 2001 and 2009. To exclude possible variability introduced by differences in sex and age distribution of populations represented by the different databases we have applied direct standardization using the distribution of the Eurostat population (27 countries) in 2008. In addition, we described use in terms of number of prescriptions, and indications for which SSRIs and TCAs were prescribed harmonising definitions across the different database structures and coding

systems. The age- and sex-standardised prevalence of antidepressant use was lowest in the two Dutch (391 and 429 users per 10,000 person-years) and highest in the two UK (913 and 936 users per 10,000 person-years) populations in 2008. The prevalence in the Danish, German, and Spanish populations was 637, 618, and 644 users per 10,000 person-years, respectively. Prescribing rates in 20- to 60-year-old patients in the two UK populations were higher compared to the other populations. SSRIs were prescribed more often than TCAs in all except in the German population, where TCA use was higher than SSRI use. In majority of the countries we observed an increasing trend of antidepressant prescribing over time. Having applied a uniform method to calculate the prevalence, variability in the results could be evaluated and explained in the light of differences in the database characteristics and/or clinical aspects related to antidepressant use. In addition to confirming the feasibility of applying common study methods, cross-country comparisons and understanding possible sources of variability would not have been possible when results would be based on different methodologies.

In ***chapter 2.2*** we quantified the prevalence of benzodiazepine use in seven primary care databases from the same five European countries as in chapter 2.1 (Denmark, Germany, The Netherlands, Spain and United Kingdom). We have again applied a common protocol for defining benzodiazepine use, which was categorised as anxiolytics and hypnotics. In order to adjust for differences in age and sex distribution between the databases, we standardised the prevalence rates using the Eurostat (27 countries) population in 2008. We calculated yearly prevalence rates and further described "use" in terms of number of prescriptions, recorded indications and trends throughout the study period (2001-2009). We found remarkable differences in the prevalence rates of benzodiazepine use, which are not attributable to differences in age or sex distribution in their respective populations. Crude prevalence rates of benzodiazepine prescribing ranged from 570 to 1700 per 10,000 person-years over the study period. Standardisation by age and sex did not substantially change the differences. Standardised prevalence rates increased in the Spanish (+13%) and United Kingdom databases (+2% and +8%) over the study period, while they decreased in the Dutch databases (-4% and -22%), the German (-12%) and Danish (-26%) database. Prevalence of anxiolytics use outweighed that of hypnotics in the Spanish, Dutch and the German databases, but the reverse was shown in the United Kingdom and Danish databases. Prevalence rates showed consistent increase with age and were two-fold higher in women than in men in all the databases. A median of 18% of users received 10 or more prescriptions in 2008. Due to the application of a common study protocol it was possible to interpret differences found in the different countries in terms of both clinical and prescribing habits. Although differences in the prevalence of disorders for which benzodiazepines are prescribed among the countries could not be ruled out, our study indicated that some of the differences may be attributed to various prescribing habits of the physicians in the primary care. This study also confirmed

the feasibility of applying common study protocols in databases from different countries which are administratively and electronically arranged in a different ways.

The quantification of the occurrence of a health outcome using a common study protocol in different databases was done in ***chapter 2.3***. The incidence of hip/femur fracture was calculated using the same seven primary health care databases from five European countries as in chapter 2.1 and 2.2 (Denmark, Germany, the Netherlands, Spain and the United Kingdom). Age and sex standardization was applied, using Eurostat (27 countries) population in 2008, to exclude differences across the different databases. Yearly incidence rates (IR) were calculated and stratified by age (< 50 and ≥ 50 years old). The incidence rate ratios (IRRs) and their 95 % confidence intervals (95 % CIs) were calculated to assess the effect of sex on different age groups in each database. Analysis was also applied to investigate the presence of a trend in the incidence rates over the study period (2001-2009). As a pioneer study quantifying the incidence of hip/fracture applying harmonised definitions across databases, we found the following three main features: 1) the incidence rate of hip/femur fracture was two times higher in Denmark (52 per 10,000 person-years in ≥50 years old) as compared to the United Kingdom, the Netherlands, and Spain (range 15-25 per 10,000 person-years in ≥50 years old), while the rate in Germany was in between (30 per 10,000 person-years in ≥50 years old). 2) Incidence rates in females were twice as high as in males in all countries and they increased with age (exponentially) irrespective of sex. 3) A significant decreasing trend in the incidence rates was detected only in Denmark and there was no meaningful trend in the other countries throughout the study period. Our results confirmed the strong relationship of fracture outcome with age and sex as reported in the previous studies. In addition to providing incidence rates across different countries comparable to the literature our study showed that it is feasible to quantify the occurrence of a health outcome recorded in hospitals using primary care databases, in contrast to the previous studies which have mainly used hospital admission or discharge data.

We have taken the application of common study protocols in observational studies using different databases from IMI-PROTECT a step further in ***chapter 3.1*** by studying the association between antidepressant use and hip/fracture. In this study we have applied a cohort study design and harmonised definitions of exposure to antidepressants, adjustment for co-medications and co-morbidities and the outcome specification in three different databases from the Netherlands, Spain and the United Kingdom. Three incident user cohorts were identified from the Dutch Mondriaan, Spanish BIFAP and the United Kingdom THIN databases. Incident antidepressant user cohorts were stratified as selective serotonin re-uptake inhibitors (SSRI) and tricyclic antidepressants (TCA) users by defining use in terms of treatment episodes which were defined according to the prescribed or dispensed prescriptions and calculated length of prescriptions. In the three uniformly conducted IMI-

PROTECT cohort studies, we found that both SSRI and TCA use were associated with an increased risk of hip/femur fracture. However, there were some differences between the adjusted hazard ratios (HR and 95 % confidence intervals - CI) among the three cohorts. This difference was specifically for SSRI use and hip/femur fracture which was higher in Mondriaan (HR=3.27; 95 % CI 1.93, 5.53) than in BIFAP (HR=1.63; 95 % CI 1.45, 1.83) and in THIN (HR=1.72; 95 % CI 1.59, 1.87). This difference was partially explained by an effect modification by age in SSRI users in Mondriaan. The variability in hazard ratios was less pronounced among TCA users. The adjusted HR for TCA use and fracture risk was 1.98; 95 % CI 1.00, 3.92 in Mondriaan 1.28; 95 % CI 1.02, 1.60 in BIFAP and 1.32; 95 % CI 1.20, 1.46 in THIN. Applying common protocol and data specifications in different populations and data has made it possible to compare the hazard ratios and further explore sources of variability in the observed risks. Consistent application of harmonised methods has also enabled the identification of relevant effect modifiers (different risk estimates in different groups varying by age) important in the evaluation of this drug-adverse event association.

Complexity of concomitant exposure to medications

In ***chapter 3.2*** we have taken a closer look at the concomitant use of antidepressants and benzodiazepines in a cohort of patients in the Netherlands Primary Care Research Database (NPCRD). The rationale for the need to explore the details of the dynamics of concomitant use of these medications was that these two medication groups are frequently co-prescribed. Moreover, antidepressant and benzodiazepine use have been both associated with fractures in observational pharmacoepidemiological studies. However, in all previous studies one of these two medication groups is considered as the main exposure of interest, while adjusting for the exposure to the other. Nevertheless, as these two medications are related to the same outcome, the timing of start and the duration of use of each may impact the overall risk for fracture. In this study, we have identified a cohort of antidepressant users and further described the exposure in terms of treatment episodes based on consecutive prescriptions. Subsequently, we have defined the start of benzodiazepine use with respect to the antidepressant treatment episode start. In our defined cohort of antidepressant use we found 40% of the patients use also benzodiazepines concomitantly. Moreover, concomitant use was very different regarding the timing of start of benzodiazepines with respect to start of antidepressants. Specifically, we found that the majority (64.4%) of concomitant users are already benzodiazepine users before starting antidepressant treatment therapy. We have found that the timing of benzodiazepine start was highly variable with respect to antidepressant therapy start. In this study we have further discussed, with the use of schematic diagrams the possible scenarios of timing of start of benzodiazepines with respect to antidepressant start and possible overall fracture risk patterns. Our conclusion was that when a common outcome is associated with two medications used concurrently, it is important to take into account not only the presence (exposed/not exposed) of concomitant

use but also the timing of start of one with respect to the other as the overall hazard may differ accordingly.

In ***chapter 3.3*** we could further test the association between concomitant use of antidepressants and benzodiazepines and osteoporotic fractures in a case-control study. The study was done using PHARMO-RLS, a Dutch pharmacy database with linked hospital records. We have identified all patients (18 years and older) with a first hospital admission for an osteoporotic fracture. We have matched these cases with up to four control patients (no history of fracture) during the study period (1991-2002) on date of birth, sex and geographic area. Concomitant exposure to these two medications was defined according to the proposed biological mechanisms and hazard patterns reported for each medication in the literature. Analyses of risk estimates (odds ratios) was done in different models to show differences in these effect measures when conventional approach (antidepressant as main exposure of interest and benzodiazepine use as a confounding variable and vice versa) is applied vs. a more complex way of differentiating concomitant exposure (defined based on to the duration of each exposure regarding the start of one with respect to the other) would result to. Results of this study showed not only increased risks of osteoporotic fracture among all patients (single and concomitant users) but also that there are different patterns of concomitant use of antidepressant and benzodiazepine drugs. In addition, it was shown that the timing of initiation of one drug with respect to the other and fracture date modifies the risk of fracture. Specifically, we found high risk among concomitant users where the risk of fracture was particularly high in the initial period of concomitant use (the first 28-days of benzodiazepine initiation concomitant to the use of antidepressants regardless of the timing of start of the latter). We concluded the study by advocating the replication of our findings in different and larger populations to overcome the statistical limitations of extensive exposure definitions. We further stressed the importance of such complex exposure definitions in identifying special risk periods which would definitely be useful in adjusting co-prescribing guidelines.

General discussion and conclusion

Finally ***chapter 4*** discusses the findings of the studies included in this thesis from a broader perspective. In this chapter the contribution of harmonisation of study methods to understand the variability among the results of studies on antidepressant and benzodiazepine use and hip fracture and their association are discussed in more detail. In addition to the clinical findings, we discussed issues and challenges related to the necessity of increased harmonisation and transparency in such observational studies. We compare and contrast the context and regulations related to standardisation processes and transparency of study methods in clinical trials vs. observational studies. We discussed issues related to the reported details on study methods and the granularity of the details on the application of

the study methods reported in 1) peer reviewed publications, 2) publically registered study protocols and 3) data specification documents and data analyses steps needed to conduct a study, respectively. We argued that these documents/steps include increasing level of details in the stated order, respectively. We also made clear that even publically registered study protocols of observational studies, which lack the obligatory context of clinical trials, lack certain granularities which hinder quality checks or reproduction of the results. Lack of complete comprehension of the details on the application of definitions of exposure, outcome and important covariates in a certain study, makes the understanding of sources of variability in the results - a complicated exercise as it is - becomes even more challenging.
Furthermore, we discussed how treating an exposure mono-dimensionally as main vs. secondary (confounding) exposures may overlook the presence of important effect modifiers when quantifying a drug-adverse event association. We argued, based on our finding of effect modification in fracture risk among antidepressant and benzodiazepine users that when two medications are often co-prescribed and the dynamics of concomitant use are not accounted for in the definition of this "complex" exposure we may miss identifying specific co-exposure scenarios where the risk of the outcome differs and may particularly be high for certain "type" of concomitant users. We propose a way forward to tackle the complexity of such concomitant exposures by treating medication use and its effects as a prognostic question rather than uni-causal safety question. To achieve this, we need robust drug utilisation studies where these exposures are well dissected, explored and understood. Such drug utilisation studies should serve as a ground work for a better designing of association studies in pharmacoepidemiological research.

SAMENVATTING

Introductie en doelstelling van het proefschrift

Observationeel epidemiologisch onderzoek gebruikt steeds complexere methoden en databronnen. Naast de cross-sectionele analyses en de op interview-gebaseerde gegevens, worden meer geavanceerde analyses uit de elektronische medische dossiers (EMD) gebruikt. Dit fenomeen heeft in de afgelopen decennia geleid tot een toename van observationele studies en een toename in het aantal publicaties hiervan. Het grotere aantal beschikbare studies heeft geleid tot een aantal tegenstrijdige resultaten; er zijn verschillende voorbeelden van analyses gebruikmakend van dezelfde database met tegenovergestelde conclusies. Daarnaast is er een trend waarneembaar van het rapporteren van lage (maar variabele) relatieve risico's (tussen 1 en 2) op het ontstaan van een bepaalde bijwerking. Omdat de mogelijke gevolgen voor de volksgezondheid van deze bijwerkingen, ondanks de lage relatieve risico's, toch hoog kunnen zijn, is de interpretatie van deze verschillen een belangrijke uitdaging. Het begrijpen van de oorzaken van de variatie in de gerapporteerde resultaten speelt daarin een belangrijke rol, met name wanneer de onderzoeksresultaten gebruikt worden voor de beoordeling van de baten-risico balans van een geneesmiddel. Verschillende internationale initiatieven zijn actief om variaties in resultaten te verklaren aan de hand van methodologische verschillen in observationeel onderzoek. Dit proefschrift is een onderdeel van een dergelijk Europees project genaamd IMI-PROTECT.

Hoofdstuk 1.1 geeft een algemene introductie op het thema en beschrijft de context van het IMI-PROTECT project. Dit inleidende hoofdstuk omvat de achtergrond en het overkoepelende doel van dit proefschrift: het begrijpen van de variatie in de resultaten van farmacoepidemiologische-studies als gevolg van verschillende keuzes in studieopzet. Om dit inzichtelijk te maken nemen wij de associatie tussen het gebruik van antidepressiva en benzodiazepines in relatie tot het optreden van fracturen als casus en bespreken wij methodologische aspecten en hun gevolgen op de onderzoeksresultaten.

Variatie in geneesmiddelgebruik en gezondheids-uitkomsten in Europa: de toepassing van geharmoniseerde methoden

Hoofdstuk 1.2 beschrijft de algemene doelstellingen en de eerste resultaten van het IMI-PROTECT-project. In dit hoofdstuk wordt de noodzaak van het systematisch bestuderen van de impact van methodologische keuzes op de resultaten van de observationele studies besproken. Dit wordt gedaan aan de hand van voorbeelden uit de literatuur, waarbij tegenstrijdige resultaten zijn gerapporteerd over dezelfde combinatie van een geneesmiddel-bijwerking associatie, soms zelfs bij gebruik van dezelfde databank. Een lijst van zes geneesmiddel-bijwerking combinaties is opgesteld en zeven Europese databanken zijn geïdentificeerd, waarin methodologische studies konden worden uitgevoerd. De geneesmiddel-bijwerking combinaties zijn gekozen vanwege hun relevantie voor de volksgezondheid, intensiteit van

het geneesmiddelgebruik, ernst van de bijwerking en/of de acute of chronische gevolgen van de bijwerking. De criteria voor de selectie van de geneesmiddel-bijwerking combinaties zijn overeengekomen binnen het IMI-PROTECT consortium door middel van een consensus proces. De geselecteerde zes geneesmiddel-bijwerking combinaties zijn 1) geïnhaleerde langwerkende bèta-2 mimetica en acuut myocardinfarct; 2) antibiotica en acute leverbeschadiging; 3 en 4) antidepressiva en/of benzodiazepines en heupfractuur; 5) anti-epileptica en suïcide en/of suïcidaliteit; 6) calciumantagonisten en kanker. Deze combinaties zijn bestudeerd in de databanken uit vijf Europese landen, beschikbaar gesteld door partners in het IMI-PROTECT consortium. De beschikbare databanken waren 1) de databank van de Kassenärztliche Vereinigung Bayerns, verder aangeduid als de 'Bavarian Claims Database' uit Duitsland; 2) BIFAP (Base de datos para la Investigacion Farmacoepidemiologica en Atencion Primaria) uit Spanje; 3) de Deense nationale databanken; 4) De Clinical Practice Research DataLink (CPRD) en The Health Improvement Network (THIN) uit het Verenigd Koninkrijk en 5) de Mondriaan databanken (Mondriaan-NPCRD en Mondriaan-AHC) uit Nederland. Verder worden in dit hoofdstuk de literatuur en de epidemiologie van de gezondheidsuitkomsten in detail beschreven. Ook is de omvang, het soort informatie, en de representativiteit van elke databank ten opzichte van de landelijke bevolking beschreven.

In ***hoofdstuk 2.1*** is het gebruik van antidepressiva in de zeven eerstelijnszorg databanken uit vijf Europese landen (Denemarken, Duitsland, Nederland, Spanje en het Verenigd Koninkrijk) in het IMI-PROTECT consortium bestudeerd. Om de prevalentie van het gebruik en trends hierin te onderzoeken en kwantificeren, is een geharmoniseerde methodologie toegepast. De reden voor deze geharmoniseerde aanpak was eenvoudig: voorgaande studies naar het geneesmiddelgebruik, hebben verschillende soorten data en methoden gebruikt om de prevalentie te kwantificeren, waardoor vergelijkingen tussen landen bijna onmogelijk werd. Bovendien beschikken de databanken binnen IMI-PROTECT, over informatie op patiëntniveau, terwijl een groot aantal van de voorgaande studies gebaseerd was op geaggregeerde data. Vervolgens zijn een gemeenschappelijk studieprotocol en data-specificatiedocument opgesteld, om zo de analyses te kunnen harmoniseren over de verschillende databanken. Het gebruik van antidepressiva werd gedefinieerd als het gebruik van selectieve serotonine heropname remmers (SSRI's) of tricyclische antidepressiva (TCA's) in de periode 2001 tot 2009. Om mogelijke variabiliteit, geïntroduceerd door verschillen in geslacht en leeftijdsopbouw van de bevolkingen in de bestudeerde landen uit te sluiten, is directe standaardisatie toegepast volgens de distributie van de bevolking van Eurostat (27 landen) in 2008. Daarnaast, is het gebruik in termen van het aantal voorschriften en diagnoses voor SSRI's en TCA's, op een geharmoniseerde manier beschreven. De leeftijd- en geslachtgestandaardiseerde prevalentie (in 2008) was het laagst in de twee Nederlandse databanken (391 en 429 gebruikers per 10.000 persoonsjaren) en het hoogst in de twee Britse (913 en 936 gebruikers per 10.000 persoonsjaren). De prevalentie was respectievelijk 637, 618, en

644 gebruikers per 10.000 persoonsjaren in de Deense, Duitse en Spaanse populaties. Het gebruik van antidepressiva in de patiëntengroepen tussen 20 en 60 jaar oud in de twee Britse populaties was hoger in vergelijking met de andere populaties. SSRI's werden vaker voorgeschreven dan TCA's in alle landen, behalve in de Duitse populatie, waar TCA-gebruik hoger was dan SSRI-gebruik. In het merendeel van de landen was een stijgende trend van antidepressiva-gebruik in de studieperiode waarneembaar. Het toepassen van geharmoniseerde methoden om de prevalentie te berekenen heeft het mogelijk gemaakt om de variatie in de resultaten te evalueren aan de hand van zowel de technische verschillen tussen de databanken als ook de klinische aspecten van het antidepressiva-gebruik. Verder heeft deze studie niet alleen vergelijkingen tussen landen kunnen maken, maar ook de mogelijke oorzaken van variatie in de resultaten kunnen verklaren. Dit was niet mogelijk geweest bij het gebruik van verschillende methodieken.

In ***hoofdstuk 2.2*** is de prevalentie van benzodiazepine-gebruik in de zelfde zeven eerstelijns gezondheidszorg databanken uit vijf Europese landen (Denemarken, Duitsland, Nederland, Spanje en het Verenigd Koninkrijk) gekwantificeerd. Ook hier is een geharmoniseerd protocol gebruikt. Benzodiazepine-gebruik werd in deze studie onderverdeeld in gebruik van anxiolytica en van hypnotica. Om te corrigeren voor de verschillen in leeftijd en geslacht van de populaties is standaardisatie toegepast volgens de Eurostat (27 landen) bevolking in 2008. Jaar-prevalenties zijn berekend en het gebruik (uitgedrukt in aantal recepten), geregistreerde indicaties en de trends gedurende de onderzoeksperiode (2001-2009) zijn beschreven. In deze studie zijn opmerkelijke verschillen in de prevalentie van benzodiazepine-gebruik gevonden, die niet veroorzaakt werden door verschillen in leeftijd en geslacht tussen de populaties. De ongecorrigeerde prevalentie van benzodiazepine-gebruik varieerde tussen 570 en 1700 gebruikers per 10.000 persoonsjaren over de studieperiode. Standaardisatie voor leeftijd en geslacht resulteerde niet in wezenlijke verschillen benzodiazepine-gebruik tussen de landen. Over de jaren steeg de gestandaardiseerde prevalentie in de Spaanse databank (+ 13%) en de databanken van het Verenigd Koninkrijk (+ 2% en + 8%), terwijl de gestandaardiseerde prevalentie daalde in de Duitse (- 12%), Deense (-26%) en twee Nederlandse (-4% en -22%) databanken. Een hogere prevalentie van het gebruik van anxiolytica ten opzichte van hypnotica werd geobserveerd in de Spaanse, Nederlandse en Duitse databanken, maar het tegenovergestelde werd gevonden in de databanken uit het Verenigd Koninkrijk en Denemarken. Er was een consistente stijging in gebruik van benzodiazepines te zien met de leeftijd. Daarnaast was het gebruik van benzodiazepines in alle databanken twee keer hoger bij vrouwen dan bij mannen. Gemiddeld heeft 18% van de gebruikers van alle landen 10 of meer voorschriften voor benzodiazepines ontvangen gedurende 2008. Door de toepassing van een geharmoniseerd onderzoeksprotocol was het mogelijk om de verschillen tussen landen aan de hand van, zowel klinische factoren, als voorschrijfgewoonten te verklaren. Hoewel de geobserveerde variatie in de prevalentie als

gevolg van verschillen in de onderliggende aandoeningen waarvoor benzodiazepines worden voorgeschreven in de landen niet kon worden uitgesloten, heeft ons onderzoek laten zien dat sommige verschillen mogelijk het gevolg zijn van verschillen in voorschrijfgedrag van de artsen in de eerste lijn. Deze studie heeft ook de haalbaarheid van het toepassen van geharmoniseerde studieprotocollen in de databanken uit verschillende landen bevestigd, ondanks technische verschillen tussen de databanken.

Hoofdstuk 2.3 beschrijft de kwantificering van het optreden van een gezondheidsuitkomst waarbij een geharmoniseerd onderzoeksprotocol in verschillende databanken is gebruikt. De incidentie van heup/femur fracturen is bepaald in zeven databanken van de eerstelijns gezondheidzorg in vijf Europese landen (Denemarken, Duitsland, Nederland, Spanje en het Verenigd Koninkrijk). Standaardisatie voor leeftijd en geslacht werd toegepast, met behulp van Eurostat (27 landen) bevolking in 2008, om verschillen tussen landen te elimineren. Jaarlijkse incidentiecijfers werden berekend en gestratificeerd naar leeftijd (patiënten jonger dan 50 jaar en patiënten van 50 jaar en ouder). We hebben gekeken of het geslacht van invloed is op de incidentiecijfers in de verschillende leeftijdsgroepen. Daarnaast zijn trends in de incidentie in de periode 2001 en 2009 onderzocht. Onze hoofdbevindingen van de geharmoniseerde analyses waren: 1) de incidentie van heup/femur fracturen bij patiënten van 50 jaar en ouder was twee keer hoger in Denemarken (52 gevallen per 10.000 persoonsjaren) dan in het Verenigd Koninkrijk, Nederland en Spanje (15 tot 25 gevallen per 10.000 persoonsjaren), terwijl de incidentie in Duitsland daartussenin lag (30 gevallen per 10.000 persoonsjaren). 2) De incidentie bij vrouwen was twee keer zo hoog als bij mannen in alle landen en de incidentie nam bij beide seksen exponentieel toe met de leeftijd. 3) Een significant dalende trend over de tijd in de incidentie werd enkel in Denemarken geobserveerd en er werd geen noemenswaardige trend in de andere landen gezien. Deze resultaten hebben de sterke associatie tussen fracturen en leeftijd en geslacht zoals beschreven in eerdere studies bevestigd. Naast het beschrijven van up-to-date incidentiecijfers van fracturen in verschillende landen, heeft onze studie ook aangetoond dat het mogelijk is om gezondheidsuitkomsten waarvan bekend was dat die goed gemeten kunnen worden in ziekenhuizen, zoals fracturen, ook bestudeerd kunnen worden in databanken van de eerstelijnszorg.

De toepassing van een geharmoniseerd studieprotocol hebben wij verder uitgewerkt in een studie naar het verband tussen antidepressiva gebruik en heup/femur fracturen in databanken van IMI-PROTECT. In de cohortstudies beschreven in ***hoofdstuk 3.1*** is hebben wij een geharmoniseerde definitie van de blootstelling aan antidepressiva en bepaling van de uitkomst (fracturen) toegepast en alle analyses op dezelfde manier gecorrigeerd voor co-medicatie en co-morbiditeit. Drie cohorten van nieuwe antidepressiva-gebruikers werden geïdentificeerd in de Nederlandse Mondriaan, Spaanse BIFAP en Britse THIN databanken.

Nieuwe gebruikers van antidepressiva werden gestratificeerd op basis van klasse antidepressivum; gebruikers van selectieve serotonine-heropnameremmers en/of tricyclische antidepressiva. Gebruiksduur werd berekend op basis van verstrekte voorschriften per patiënt en de geplande duur van de recepten. De drie uniform gedefinieerde cohorten in de IMI-PROTECT databanken toonden aan dat zowel het SSRI- als TCA-gebruik waren geassocieerd met een verhoogd risico op heup/femurfracturen. Toch vonden wij enkele opmerkelijke verschillen in de (gecorrigeerde) hazard ratios (HRs) tussen de drie cohorten. De associatie tussen SSRI-gebruik en heup/femurfracturen was beduidend hoger in de Mondriaan databank (HR = 3,27; 95% CI 1,93-5,53), vergeleken met BIFAP (HR = 1,63; 95% CI 1,45-1,83) en THIN (HR = 1,72; 95% CI 1,59-1,87). Dit verschil was deels te verklaren door effectmodificatie als gevolg van het leeftijdsverschil in SSRI-gebruikers in de Mondriaan databank. De variatie in berekende risico's was minder sterk te zien bij TCA-gebruikers. De gecorrigeerde HRs voor TCA-gebruik en het risico op fracturen was 1,98; (95% CI 1,00-3.92) in Mondriaan; 1,28; (95% CI 1,02-1,60) in BIFAP en 1,32; (95% CI 1,20-1,46) in de THIN databank. De geharmoniseerde analyses hebben ons tevens in staat gesteld om de berekende risico's tussen de cohorten te kunnen vergelijken. Daardoor kon de variatie in de resultaten verder worden verklaard aan de hand van technische verschillen in databasestructuur en/of klinische verschillen. Consequente toepassing van geharmoniseerde methoden bij de evaluatie van deze geneesmiddel-bijwerking associatie, maakt de identificatie van relevante effectmodificaties van risico's mogelijk.

Complexiteit van gelijktijdige blootstelling aan meerdere geneesmiddelen

In ***hoofdstuk 3.2*** is het gelijktijdig gebruik van antidepressiva en benzodiazepines in een cohort van patiënten in 'the Netherlands Primary Care Research Database' (NPCRD) onderzocht. De reden om de details van de dynamiek van simultane blootstelling aan deze geneesmiddelen te onderzoeken, was dat deze twee groepen geneesmiddelen vaak gelijktijdig worden voorgeschreven. Daarnaast zijn antidepressiva- en benzodiazepine-gebruik beide geassocieerd met een verhoogd risico op fracturen. In alle eerdere gepubliceerde farmacoepidemiologische studies wordt één van beide medicaties beschouwd als de hoofdblootstelling en de andere als secundaire blootstelling en als zodanig geanalyseerd. Wanneer deze twee geneesmiddelen met betrekking tot dezelfde uitkomst worden onderzocht, kan echter het tijdstip van start en duur van de blootstelling van elk het gezamenlijke risico op fracturen beïnvloeden. In deze studie is een cohort van antidepressiva-gebruikers geïdentificeerd en het gelijktijdig gebruik van benzodiazepines beschreven. Dit werd gedaan door te kijken naar het moment van starten van benzodiazepine-gebruik ten opzichte van de start van het antidepressiva-gebruik, alsmede de duur van het gelijktijdig gebruik van beide geneesmiddel-groepen. In ons cohort van antidepressiva-gebruikers gebruikte 40% van de patiënten ook gelijktijdig benzodiazepines. Het gelijktijdig gebruik was echter wel afhankelijk van de timing van de start van het benzodiazepine gebruik. Namelijk, het me-

rendeel (64,4%) van de gelijktijdige gebruikers waren al benzodiazepinegebruikers voordat de therapie met een antidepressivum werd geïnitieerd. Deze studie heeft verder laten zien dat de start van benzodiazepine-gebruik zeer variabel was tussen antidepressiva-gebruikers. In deze studie is verder aan de hand van diagrammen van de mogelijke scenario's van het starten van benzodiazepines gebruik ten opzichte van antidepressiva gebruik, de mogelijke invloed op het gezamenlijke risico op een fractuur bediscussieerd. Onze studie concludeert dat het belangrijk is om niet alleen rekening te houden met de aanwezigheid (blootgesteld ja/nee) van gelijktijdig gebruik maar ook het tijdstip van de start van het ene middel ten opzichte van het andere middel, wanneer een uitkomst is geassocieerd met twee verschillende geneesmiddelen die gelijktijdig worden gebruikt

Hoofdstuk 3.3 toetst de associatie tussen gelijktijdig gebruik van antidepressiva en benzodiazepines en osteoporotische fracturen in een patiënt-controle onderzoek. Voor deze studie zijn data van PHARMO-RLS (databank met gegevens uit Nederlandse apotheken gekoppeld aan ziekenhuisgegevens) gebruikt. In deze databank zijn alle patiënten (18 jaar en ouder) met een eerste osteoporotische fractuur geïdentificeerd in de periode 1991 tot 2002. Deze patiënten zijn gepaard met maximaal vier controlepatiënten (geen voorgeschiedenis van fracturen) en gematcht op leeftijd, geslacht en geografisch gebied. Gelijktijdige blootstelling aan antidepressiva en benzodiazepines is gedefinieerd en ingedeeld op basis van eerder beschreven biologische mechanismen en risicopatronen voor elk geneesmiddel. Fractuurrisico's (odds ratio) werden berekend en het model van de door ons voorgestelde multidimensionale blootstellingsmaat werd vergeleken met eerder toegepaste modellen met een conventionele benadering (antidepressiva als hoofdblootstelling en benzodiazepine gebruik als secundaire blootstelling en omgekeerd). De resultaten van deze studie toonden niet alleen verhoogde risico's op osteoporotische fracturen bij alle patiënten (monotherapie en gelijktijdig gebruik van beide geneesmiddelen), maar ook verschillen in de risico's van verschillende 'soorten' van gelijktijdig gebruik. Bovendien werd in deze studie aangetoond dat het tijdstip van starten van het ene geneesmiddel ten opzichte van het andere middel, de hoogte van risico op fractuur beïnvloedt. Zo zagen wij een hoog risico bij 'gelijktijdige gebruikers' en in het bijzonder in de beginperiode van gelijktijdig gebruik (de eerste 28 dagen van benzodiazepine gebruik gelijktijdig met het gebruik van antidepressiva ongeacht het tijdstip van starten van antidepressiva). Wij pleiten er in onze studie voor dat onze bevindingen gerepliceerd worden in andere en grotere populaties. Verder wordt het belang van dergelijke complexe blootstellingsdefinities om bepaalde risicoperiodes te identificeren benadrukt, hetgeen nuttig kan zijn voor het aanpassen van de richtlijnen van gelijktijdig voorschrijven van geneesmiddelen.

Algemene discussie en conclusie

Tot slot worden in **hoofdstuk 4** de bevindingen van de studies in dit proefschrift vanuit een breder perspectief belicht. In dit hoofdstuk wordt de bijdrage van de harmonisatie van onderzoeksmethoden om de variatie van de resultaten in antidepressiva- en benzodiazepine-gebruik en heupfractuur-studies te begrijpen in meer detail besproken. Behalve de klinische bevindingen worden ook de uitdagingen van meer harmonisatie en transparantie in dergelijke observationele studies uitgelicht. Daarnaast worden de context en regelgeving van standaardisatie-processen en transparantie-verplichtingen in klinische trials versus observationele studies vergeleken. Ook de mate van gerapporteerde details met betrekking tot onderzoeksmethoden en informatie over de toepassing van de studiemethoden in databanken op niveau van 1) peer-reviewed publicaties, 2) publiekelijk geregistreerde studieprotocollen en 3) statistische methoden en de toepassing ervan worden in dit hoofdstuk besproken. Er wordt vastgesteld dat deze documenten/niveaus in de genoemde volgorde in toenemende mate details rapporteren.

Zelfs in de gepubliceerde onderzoeksprotocollen van observationele studies in publieke registers ontbreken nog verschillende essentiële details over de onderzoeksmethoden. Dit komt mede doordat de verplichte context van de klinische studies ontbreekt voor observationele studies. Dit kan de interpretatie van de resultaten van observationele onderzoeken belemmeren. Gebrek aan details over definities van de blootstelling, gezondheidsuitkomsten en verdere methode-gerelateerde informatie maakt het begrijpen van de mogelijke oorzaken van de variatie in de resultaten - een ingewikkelde oefening op zich - een nog grotere uitdaging. Bovendien stellen wij dat wanneer blootstelling uni-dimensionaal wordt gedefinieerd (primaire versus secundaire blootstelling), belangrijke risicomodificatie kan worden gemist, bij het kwantificeren van een geneesmiddel-bijwerking associatie. Wij stellen voor om de complexiteit en details van gelijktijdige blootstelling in beschouwing te nemen en de blootstelling niet als een uni-causaal veiligheidsvraagstuk maar als een prognostische vraagstelling te benaderen. Om dit te bereiken zijn robuuste studies naar het geneesmiddelgebruik cruciaal, zodat de opzet en methodiek van de associatiestudies in farmacoepidemiologisch onderzoek beter kunnen worden gedefinieerd.

Appendices

Acknowledgements

“մէկ ձեռքը ծափ չի տար”

The above proverb means: “One hand will not clap”. It is indisputably true when it comes to working on a PhD. In fact to finish up a PhD track, in addition to the personal drive and skills, one would need sufficient causes to be present as described in causal pies by Rothman back in 1976. In these, the three necessary causal factors (without which there would be no causal effect) would be:

Factor 1: Research opportunity, which is in line with the interest and skills of the person having the desire to walk the PhD path

Factor 2: Scientific guidance and advice from an established team

Factor 3**:** Mental and physical support from the social environment

Therefore, I am thankful for all who contributed to these factors on my PhD path.

It all started with an appointment just to discuss possibilities of an AIO (a Dutch acronym for PhD candidate employment) function at the department of Pharmacoepidemiology & Clinical Pharmacology. In Armenian phonetically “այո” (aio) means “yes”. This was the check for the first factor for which I am thankful to Prof. Olaf Klungel, Prof. Bert Leufkens and Prof. Ton de Boer. Dear Olaf, from the first time we met to discuss a “possible” and a “big” project where the official sign off by EMA was yet to come, I knew this was the right place for me: the European project PROTECT. This was one of the first EU-IMI projects and the first one for the department to manage a huge part of it. I am grateful that I was part of it. Thank you for the trust and your guidance during all these years.

When the context is there, it is just the beginning. Without the coaching, advice, and sometimes being thrown into the deep there would be no achievements. I am deeply thankful for having all those from my promotors and co-promotors. Promotors: Prof. Bert Leufkens and Prof. Toine Egberts. Dear Bert, your “helicopter view” has been very valuable. Every time when a detail is discussed you manage to inspire people to broaden their own visual field without losing eye on the detail. This constant *zooming in* and *zooming out* approach that you teach and preach and apply it yourself so masterly, is a school for teaching on its own. I am very lucky to have had a peek view of that. Dear Toine you were actively involved in my track when the boat needed a captain. I cannot thank you enough for all what you did to lead, to avoid storms and to focus on the right direction. This boat ended up on safe shores mainly because of your assistance, guidance and personal encouragement. You have been fundamental in defining scopes within and outside PROTECT studies, for shaping the clinical and methodological aspects of the studies, and last but not least extending a hand to relieve me of my frustration and to accept that the track is going to be longer. Like a mantra I had to repeat your words “Every track is different” throughout the years. As professional as you are, you never miss a moment to give support on personal level when it is much

needed. I am very grateful for all that. Co-promotors: Dr. Marieke de Bruin and Prof. Tjeerd van Staa. Dear Marieke, I am happy that you accepted to be my adviser with the realisation of the risks of taking up the role halfway in a track. A brave action! Without your continuous support and our Amsterdam meetings at the IJsbreker this track would not have been completed. Your skilled comments, eye for the details and questions on the real meaning of the findings have been very valuable for the studies in this thesis. Thank you! Dear Tjeerd, you were more involved in the beginning of the track. We had several brainstorming and scope defining sessions together which have been very valuable. You had many ideas which we could not implement. Nevertheless they were not less useful learning moments for me. I hope future opportunities will be created.

My sincere gratitude and appreciation goes for the members of the review committee and the time they provided for reviewing this thesis. The experts in the review committee were: Prof. dr A. de Boer, Prof. dr M.L. Bouvy, Dr X. Kurz, Prof. dr R.J. van Marum and Prof. dr R.H. Vander Stichele.

The PROTECT project was led by the department of Pharmacoepidemiology & Clinical Pharmacology at Utrecht University. So, there were many people involved without whom large part of the thesis would not have been possible. Dear Olaf, you were at the front seat of project leadership. I admire your knowledge, skills and resilience which were needed to take up the responsibility of work-package 2, a huge and challenging part. The closing of the consortium was so brilliantly done in London at EMA (February 2015). Chapeau! Dr. Robert Reynold (from Pfizer) the project co-lead with Olaf who guided the work smoothly into its deliverables. Dear Robert, it is always a pleasure to meet and connect with you. You are an excellent scientific reviewer and very pleasant person to work with. I hope in the future these occasions will still come. Project management was done by Ines Teixidor Dal Pont. Dear Ines your skills of managing this multi-partner project were excellent. Thank you! Dr. Patrick Souverein. Dear Patrick, what can I say? You are not only the "data coach", you often call yourself, but also the one person who wears many hats at the same time. Without you no AIO would be able to find his way in a short time. Thank you! Dr. Rolf Groenwold. Dear Rolf, your knowledge on methods fascinates me. The few times we have sat together to solve a statistical problem, I appreciated even more your skills in explaining rather complicated formulas in a simplified manner. You are a true teacher! Dr. Mark de Groot and his counterpart as a co-lead Dr. Raymond Schlinger (Novartis) are gratefully acknowledged for their input, leading the working groups and reviewing the manuscripts. I am thankful for Dr. Helga Gardarsdottir for taking over the antidepressant working group leadership, so that I could have more time for manuscript writing. PROTECT has been an amazing learning experience for many. The secretarial support at the department by Ineke Dinzey, Anja Elbertse and Suzanne de Visser are kindly acknowledged.

Being part of a huge consortium gives the opportunity to work with many people. The only limitation is that when an acknowledgment is to be done, completeness of the list can be at risk. Hence, I will mention names with 95% confidence interval of being complete. A priori apologies if I miss some names unintentionally.

I will start with the Spanish group. Dear Prof. Francisco de Abajo, your guidance and your proactive team of professionals enabled easy communication lines with the Utrecht group. A big factor for success in PROTECT. I thank you for your scientific input and also making such extensive scientific collaborations a great learning experience. Dear Dr. Consuelo Huerta, I thank you for your big contribution to PROTECT and for the nice collaboration. You were, the "benzodiazepine group" lead, and I was the "antidepressant group" lead. I have enjoyed our cooperation. Dr. Gemma Requena, we were the two PhD candidates in PROTECT who went through similar situations. You finished and started to work and I had to do it in the opposite sequence. I am glad I am still in touch with you. Also from the Spanish group were Ana Rigomez, Miguel Gil, Luisa Ibanez and Elisa Martin to name only few. Thank you all! I thank prof. Joerg Hasford, from Germany, for his continuous reviews and advice on the manuscripts. I also thank Dr. Marietta Rottenkolber and Dr. Sven Schmiedl. Dear Sven, you were a valuable addition to the team as a clinician! danke schön! The Danish databases were led, by an extremely capable statistical scientist Ulrik Hesse. The UK databases were represented by scientists from the industry and at EMA namely Dr. John Loggie, Dr. Montserat Miret and Dr. Yolanda Alvarez. Thank you all for your contributions in the studies.

My first introduction to the Utrecht University was during my Master thesis project. I was given the opportunity to work on the WHISTLER project by Prof. Bert Brunekreef. Dear Bert, thank you for allowing me to work and learn from you and your great team at IRAS.

Then there is the social support. The list of the names can get longer here. In addition to those who have contributed to the studies scientifically, I had the luck to also know other people in the department and outside for which I am grateful. All the (ex-)AIOs from the Went building to the David de Wied building in Utrecht (Dr. Laurette, Corinne, Dr. Martin, Joris, Hamid, Ali, Yasser, Yared, Alfi, Fariba, Dr. Niels, Dr. Jamal, Dr. Sanni, Dr. Arief, Dr. Heshu, Dr. Grace, Dr. Francisco, Dr. Talitha, Dr. Suzanne and all those with whom I could laugh, exchange jokes, opinions, frustrations and joys, I am thankful. Dear Dr. Sulmaz, you are an admirable person with a big and strong heart. You deserve the best.
Friends, near and across borders, especially those who I met on PhD path and shared a lot (Danijela Stojanovic you are a special one!) hope to see you all in the future.

I am lucky to have two great paranimfs, Renate Udo and Dr. Joelle Hoebert. Thank you for not only accepting to stand by me on the important day to come, but also until that date during the preparations of this thesis. I feel lucky and I am thankful! Dear Renate, I am looking forward to your thesis defence.

Friends and family come always at last but are not less appreciated. For all the missed opportunities to come together for a drink and sharing experiences, and enjoy each other, I thank you for your understanding and support. I have a long list to catch up which I will do with great pleasure. All the opera dates, concert dates, "ouderavonden", "burenborrels" or just "friends together" gatherings I am looking forward to them. Thank you all for your patience. The greatest support tangible and intangible support was from my family.

Հեռու եւ մոտիկ հարազատներս, հորքոյրներ՝ Նորա եւ Թագուհի: Ցուսամ շուտով կը տեսնուինք:
Պապա (†) ճաճ Աստուած հոգիդ լուսաւորէ: Քու ցանցած հունտդ հիմա ես կը քաղեմ, յիշատակդ վառ: Մամա ճաճ, դուն մեր տունին որհնութիւնն ես: Աստուած ձեզի մեր գլխէն պակաս չընէ: Վահան ճաճ, մէ՛կ հատիկ եղբայրս: Քու ուրախութիւնդ իմս է, իմս ալ՝ քուկդ: Շատ կը սիրեմ ձեզ:

Chère Francine, merci pour le courage, l'optimisme et l'amour que tu donnes à notre petite famille.

Mijn twee oogappels: Armèn en Anoush. Zonder jullie heeft het leven geen betekenis. Ik ben dankbaar voor jullie steun en liefde. Ik ben nog meer dankbaar om te zien met welke waarden jullie in het leven aan het opgroeien zijn. Ik ben een trotse moeder!
Jean-Marc hokis, er zijn geen woorden voor de onvoorwaardelijke liefde waartoe jij in staat bent om te geven. Jij bent mijn alles!

List of co-authors

Francisco J de Abajo
BIFAP Research Unit (Spanish Agency for Medicines and Medical Devices)
University of Alcalá, Madrid, Spain.

Marie L De Bruin
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Medicines Evaluation Board, the Netherlands

Toine CG Egberts
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands

Helga Gardarsdottir
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands

Rolf HH Groenwold
Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands

Mark CH de Groot
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands
University Medical Center Utrecht, Utrecht, the Netherlands

Joerg Hasford
Ludwig-Maximilians-Universität-München

Consuelo Huerta
BIFAP Research Unit (Spanish Agency for Medicines and Medical Devices)

Olaf H Klungel
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands

Xavier Kurz
European Medicines Agency

Hubert GM Leufkens
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Medicines Evaluation Board, the Netherlands

Gemma Requena
OXON Epi Madrid, Spain

Patrick C Souverein
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands

Tjeerd P van Staa
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester, the United Kingdom

Frank de Vries
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
Maastricht University Medical Centre, the Netherlands

All co-authors of work-package 2 of IMI-PROTECT
(Framework for pharmacoepidemiology studies)*:
Y. Alvarez, G. Candore, J. Durand, J. Slattery (European Medicines Agency); J. Hasford, M. Rottenkolber (Ludwig-Maximilians-Universität-München); S. Schmiedl (Witten University); F. de Abajo Iglesias, M. Gil, C. Huerta Alvarez, B. Oliva, G. Requena (Agencia Espanola de Medicamentos y Productos Sanitarios); R. Brauer, G. Downey, M. Feudjo-Tepie, M. Schoonen (Amgen NV); S. Johansson (AstraZeneca); J. Robinson, M. Schuerch, I. Tatt (Roche); L.A. Garcia, A. Ruigomez (Fundación Centro Español de Investigación

Farmacoepidemiológica); J. Campbell, A. Gallagher, E. Ng, T. van Staa (General Practice Research Database); O. Demol (Genzyme); K. Davis, J. Logie, J. Pimenta, (GlaxoSmithKline Research and Development LTD); L. Bensouda-Grimaldi (L.A. Sante Epidemiologie Evaluation Recherche); U. Hesse, P. F. Rønn (Lægemiddelstyrelsen (Danish Medicines Agency); M. Miret (Merck KGaA); J. Fortuny, P. Primatesta, E. Rivero, R. Schlienger (Novartis); A. Bate, N. Gatto, R. Reynolds (Pfizer); E. Ballarin, P. Ferrer, L. Ibañez, J.R. Laporte, M. Sabaté (Fundació Institut Català de Farmacologia); V. Abbing-Karahagopian, S. Ali, D. de Bakker, S. Belitser, A. de Boer, M.L. De Bruin, A.C.G. Egberts, L. van Dijk, H. Gardarsdottir, R. Groenwold, M. De Groot, A. Hoes, O. Klungel, B. Leufkens, W. Pestman, K. Roes, P. Souverein, F. Rutten, J. Uddin, R. van den Ham, E. Voogd, F. de Vries (Universiteit Utrecht).

*The complete list of WP-2 members. Some names are a repetition to the above list of co-authors.

List of publications

PUBLICATIONS INCLUDED IN THIS THESIS

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. 2014;9(2):130-8.

Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo F, Leufkens HG, Slattery J, et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. Eur J Clin Pharmacol. 2014;70(7):849-57.

Huerta C, **Abbing-Karahagopian V,** Requena G, Oliva B, Alvarez Y, Gardarsdottir H, et al. Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. Pharmacoepidemiol Drug Saf. 2015; Jul 7. doi: 10.1002/pds.3825. [Epub ahead of print]

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; 94(6):580-9.

Abbing-Karahagopian V, Souverein PC, Korevaar JC, Leufkens HGM, Egberts TCG, Gardarsdottir H, De Bruin ML Concomitant medication use and its implications on the hazard pattern in pharmacoepidemiological studies: example of antidepressants, benzodiazepines and fracture risk. Epidemiology Biostatistics and Public Health. 2015, 12; (3), e 12731-1

*Souverein PC, *__Abbing-Karahagopian V,__ Martin E, Huerta C, de Abajo FJ, Leufkens HGM, Candore G, Alvarez Y, Slattery J, Miret M, Requena G, Gil M, Groenwold RHH, Reynolds R, Schlienger RG, Logie JW , de Groot MCH, Klungel OH, van Staa TP, Egberts ACG, De Bruin ML, Gardarsdottir H. Understanding inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip/femur fractures. Pharmacoepidemiol Drug Saf. 2015; 25, Suppl 1 DOI:10.1002/pds.3862 #

*Equal contribution of co-authors
Only part of the content included in this thesis

RELATED PUBLICATIONS NOT INCLUDED IN THIS THESIS

Requena G, Huerta C, Gardarsdottir H, Logie J, Gonzalez-Gonzalez R, **Abbing-Karahagopian V,** Miret M, Schneider C, Souverein PC, Webb D, Afonso A, Boudiaf N, Martin E, Oliva B, Alvarez A, De Groot MC, Bate A, Johansson S, Schlienger R, Reynolds R, Klungel OH, de Abajo FJ. Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies across databases from the PROTECT-EU project. Pharmacoepidemiol Drug Saf. 2015; Jun 23. doi: 10.1002/pds.3816. [Epub ahead of print]

OTHER PUBLICATIONS

Abbing-Karahagopian V, van der Gugten AC, van der Ent CK, Uiterwaal C, de Jongh M, Oldenwening M, Brunekreef B and Gehring U. Effect of endotoxin and allergens on neonatal lung function and infancy respiratory symptoms and eczema. Pediatr Allergy Immunol. 2012;23(5):448-55.

About the author

Victoria Karahagopian was born in Beirut on April 9, 1971. She grew up and finished elementary and secondary schools during the civil war (1974-1991). She sat for the Baccalaureate examinations at the time when the Ministry of Education re-established the official exams, for the first time after the war, despite the fact that not all schools could manage to cover the complete program. She passed the exams being among the 6% in her class earning her Baccalaureate in Science Expérimentale. During the periods of cessez-le-feu, she has actively organised Armenian cultural events in the local student and later literary clubs. She has performed recitation of poetry of well-known Armenian poets at various official occasions. She was also an active scout (Scouts du Liban) for years reaching the cheftaine level. She was admitted to the Faculty of Health Sciences at the American University of Beirut to study Environmental Health Sciences in 1991. After earning her Bachelor of Sciences degree, she received a complete tuition funding to continue her Master's degree (a Master of Public Health - MPH). After graduation she worked at the same university (department of Biochemistry) in research (on Wilson's disease) and later at the Ministry of Public Health. At the Ministry of Health, she was part of a team developing the national post-war rehabilitation plan for the Central Laboratory of the Ministry. Her contribution was specifically in the development of the rehabilitation program for the Microbiology Laboratory services of the country. In 1998 she moved to academia to combine research and teaching at the Faculty of Health Sciences at the Balamand University, where she worked until 2002 when she moved to the Netherlands following her heart.

In the Netherlands, she earned her certificate for Dutch language after taking the state exams (program II academic level) in May 2003. She worked as a freelancer/volunteer for projects with the International Office of RIVM (Bilthoven) and International Projects office at NSPOH (Amsterdam) from 2004 to 2005. She started her second Master education (Epidemiology) at the Maastricht University in 2006. She was given the opportunity to do her Master thesis at the IRAS (Institute for Risk Assessment Sciences) at the Utrecht University. She graduated in 2009. In 2009 (October), she joined the Faculty of Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University as a PhD candidate. Her PhD was mainly within the EU-IMI funded project: PROTECT. In 2014 (February), she moved to work at Novartis Vaccines as an epidemiologist. Currently, Novartis Vaccine has become GSK Vaccines where she still works.

Victoria lives in Amsterdam and is married to Jean-Marc Abbing. They have two children: Armèn Henri (2003) and Anoush Aline (2006).