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PhD Thesis

Clinical indicators for quality improvement: the case of femur fracture in Portugal

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ABSTRACT

Hip fracture is the most common reason for admission to an acute orthopaedic ward, the majority can be related to osteoporosis and are more frequent above the age of 50 years, in women. Higher mortality and morbidity rates are the major consequences of hip fractures, higher amongst men. With the aging of the population the number of hip fractures tend to increase stretching the available resources.

The objectives of this study are: evaluate the trends of hip fracture incidence in Portugal and identify possible determinants, obtaining a quality measurement before the event and a risk adjustment for the treatment of hip fractures, as well as a characterization of the National Health Service (NHS) in terms of the treatment for this pathology, assessing the quality improvement after the fracture.

Data from the National Hospital Discharge Database was used. Mandatory for all Portuguese public hospitals since 1997, it compiles clinical and demographic information on all discharges. Hospitalizations from 1st January 2000 to 31st December 2008, caused by hip fractures (low energy, patients over 49 years of age) were selected and used as data in all the partial studies. National Authority of Medicines and Health Products (INFARMED) provided the data regarding the osteoporotic medication sales. Population data used to calculate incidence rates was obtained in the Statistics Portugal (INE). Generalized Additive (GAM) and Generalized Linear Models (GLM) were used in the assessment of hip incidence trend. Age-Period-Cohort Models and GAM were used to assess the period and cohort effect. A multilevel Bayesian model was used to obtain a risk adjustment, provide a comparison between providers and obtain a temporal trend on the probability of dying during hospitalization for hip fracture treatment.

During the study period were selected 77,083 hospital admissions (77.4% women) caused by low energy, in patients over 49 years-age, mean age (standard deviation (SD)) at admission was 81.0 (SD 8.5) years old versus 78.0 (SD 10.1) (p-value < 0.0001) for women and men respectively. A turning point in 2003 was identified in the trend of hip fracture incidence in women. This abrupt decrease is compatible with the pattern of bisphosphonates sales. A cohort effect was identified both for men and women, the pattern highlighted changes in risk of hip fracture, on important points in the history of Portugal, statistical significant around 1930.

The probability of dying during a hospitalization to treat hip fractures was associated with individual characteristics', women presented lower probability compared to men, even after adjustment for age, severity, treatment, time to surgery, length of stay, transfers (yes/no), hospital and area characteristics. No hospital effect was identified, hospitals that treat more than 50 hip fractures per year, have the same overall effect on the probability of dying.

The overall probability during the period did not presented changes. However some hospitals presented improvement.

This study provided an extensive analysis on the treatment of hip fractures, during a period of 9 years. The results are innovative and highlight possibilities of improvement as well as valuable information to health authorities.

RESUMO

As fracturas do fémur proximal são a causa mais comum de admissão nos serviços de ortopedia, a sua maioria está relacionada com a osteoporose e são mais frequentes acima da idade de 50 anos, nas mulheres. As elevadas taxas de mortalidade e morbilidade são a maior consequência das fracturas do fémur proximal, apresentando-se mais altas entre os homens. Com o envelhecimento da população o número de fracturas tende a aumentar, acarretando uma elevada utilização dos recursos existentes.

Os objectivos este estudo são: a avaliação da tendência das taxas de incidência de fracturas do fémur proximal em Portugal e a identificação de possíveis determinantes da tendência, obtendo uma medida de qualidade antes da fractura. A obtenção de um ajuste de risco para o tratamento das fracturas, assim como uma caracterização do Serviço Nacional de Saúde (SNS), avaliando a qualidade do tratamento após a fractura.

Os dados da Base de Dados Nacional de Grupos de Diagnóstico Homogéneo relativos a altas hospitalares, contendo informação clínica e demográfica foram usados. As hospitalizações de 1 de janeiro de 2000 a 31 de dezembro de 2008, causadas por fracturas do fémur proximal (baixa energia e pacientes com idade superior a 49 anos) foram selecionadas e usadas nos estudos parciais.

Os dados relativos à venda de medicamentos anti-osteoporóticos foram fornecidos pelo INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde. O Instituto Nacional de Estatística –INE foi a fonte para os dados populacionais que serviram para o cálculo das taxas de incidência. Modelos Aditivos e Lineares Generalizados (GAM e GLM) foram usados para avaliação das tendências da incidência de fracturas. Modelos Idade-Período-Coorte e GAM foram usados para a avaliação da existência de efeitos período e coorte. Um modelo Bayesiano hierárquico foi usado para obter o ajuste de risco, comparar entre hospitais e obter a tendência temporal da probabilidade de morrer durante a hospitalização para tratamento da fractura do fémur proximal.

Durante o período em estudo foram seleccionadas 77,083 admissões hospitalares (77.4% mulheres) com diagnóstico de fractura do fémur proximal, causada por baixa-energia e em doentes com mais de 49 anos de idade, idade média na admissão (desvio padrão DP) foi 81.0 (DP 8.5) versus 78.0 anos (DP 10.1) (valor-p <0.0001) para mulheres e homens respectivamente.

Uma alteração brusca foi identificada na tendência das fracturas nas mulheres, no ano de 2003 compatível com o padrão de vendas de bisfosfonatos. Foi identificado um efeito coorte que reflecte alterações de risco nos principais momentos históricos da história de Portugal, estatisticamente significativo em volta de 1930.

A probabilidade de morrer durante a hospitalização para tratamento da fractura do fémur, proximal está associada com as características individuais dos indivíduos, sendo que as mulheres mesmo depois do ajuste apresentam um valor mais baixo quando comparado com o dos homens. Não foi identificado nenhum efeito do hospital, hospitais que tratam mais de 50 fracturas por ano, têm um efeito semelhante na probabilidade de morrer. A tendência temporal da probabilidade de morrer no hospital, não sofreu alterações durante o período de estudo. No entanto, alguns hospitais mostraram melhorias.

Este é um estudo exaustivo do tratamento de fracturas do fémur proximal, durante um período de 9 anos. Os resultados são inovadores, assinalam possibilidades de melhoria e apresentam informações importantes para as autoridades de saúde.

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CHAPTER I

Introduction

Motivation

The fractures that occur in the proximal part of the femur are also designated hip fractures and can be further classified according to their location; figure 1 is illustrative of the different classification of hip fractures [1]. The majority of hip fractures occur in individuals with fifty or more years-old, mainly due to the reduction of bone mineral density that may lead to osteoporosis [2]. Better conditions of life and healthcare led to an increase of life expectancy in European countries [3], which consequently leads to a higher number of population at risk of sustaining a hip fracture. According to the Statistics Portugal-INE (Instituto Nacional de Estatística), the Portuguese population over the age of 64 suffered an increase of 18.69% from 2001 to 2011 [4].

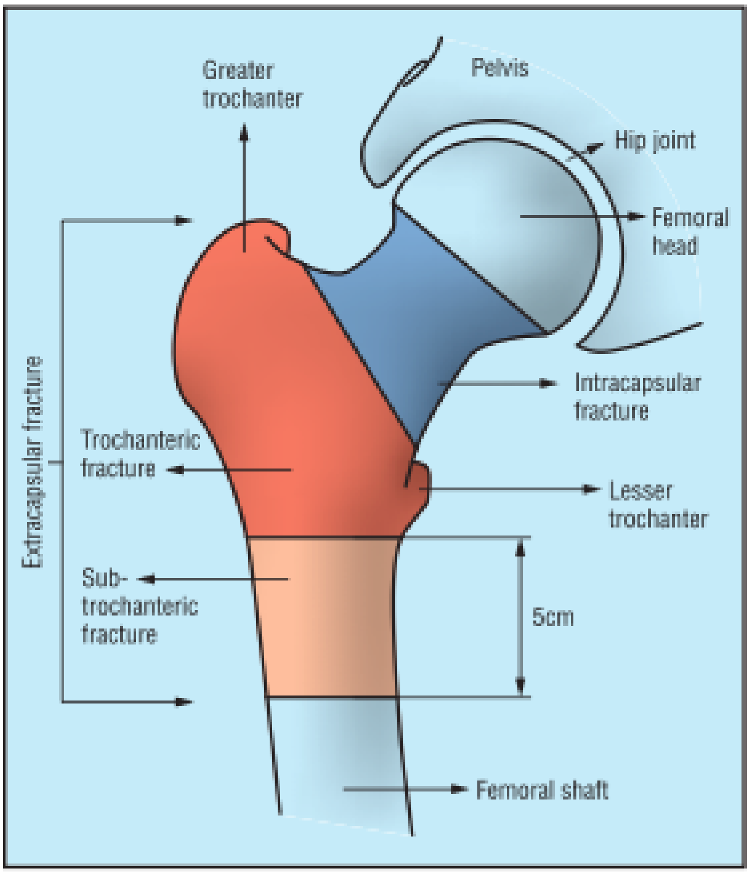

Figure 1: Classification of hip fractures. Reproduced from Parker and Johansen, 2006 [1]

Hip fracture is the most common reason for admission to an acute orthopaedic ward [1] and with the aging of the population the number of hip fractures tend to increase stretching the available resources[5, 6]. In addition, osteoporotic hip fractures present high mortality and morbidity rates [2, 7]. In a period of three years (2000 – 2002) it were treated in hospitals of the National Health System (NHS) 36, 846 cases representing a cost of about 185 hundred thousand Euros. From these patients about 5.6% died while in the hospital [8]. The morbidity and mortality rates after discharge are not easy to assess because the majority of patients recover at home and in Portugal it is not possible to have a database linkage between health databases. However a cohort study conducted in one of the major hospitals in Portugal, during one year, reported at one year follow-up a mortality rate of 23 and 37 per 100 patients in women and men, respectively and that 30% of the patients were in bed confinement [9]. There are studies that report that 80% of women aged 75 years and older preferred death over the loss of independence after the fracture [10].

The interest in quality of health care has been increasing in most health care systems around the world. However, there are countries that still do not assess the quality of care delivered to their citizens [11].

Quality of care can be defined as "the degree to which health services for individuals and populations increase the likelihood of desire health outcomes and are consistent with current professional knowledge" [12] cited by [11]. One way to assess quality of care is through the use of indicators, that can be defined as "measurements tools, screens, or flags that are used as guides to monitor, evaluate, and improve the quality of patient care, clinical support services and organizational function that affect patient outcome" [13] cited by [11]. Clinical indicators can be related to several steps in health care process; therefore there can be structure, process and outcome indicators [11, 14]. Structure indicators are related to the attributes of the material resources and organizational structure. Process indicators are related to the actions in giving and receiving care and finally outcome indicators are related to the description of the effects of care [11, 14]. The outcome of care results from a variety of factors that are not necessarily linked to the quality of care received (e.g. severity of the patient). It is therefore important to adjust the indicators for possible confounders to obtain a fair result.

Clinical indicators should measure areas that contribute with high mortality and morbidity, with high costs in care and that have potential for improvement [15, 16]. Hip fracture is a clinical area that presents all those characteristics.

This study aimed to assess preventive treatment as well as the actual treatment received after a hip fracture.

Preventive treatment, by definition can incorporate a number of different actions that aim to promote and maintain health and prevent disease and disability [17]. Fall prevention, which would be one of the most effective preventive actions [18] is difficult to assess in Portugal, nationwide, because there is not a global strategy or a systematic approach to this preventive measure. Pharmacological treatment is also considered a vehicle to prevent fractures in the elderly, with highest clinical and cost effective results when targeted at those who are at higher risk [18]. These preventive actions would reflect on hip fracture incidence and Portugal would have a measure of preventive treatment for hip fracture.

However, the trend of hip fracture rate can be driven by other factors not directly related to the specific treatment of hip fractures. General health status of the population, life and nutritional conditions, changes in body mass index [18], could serve as confounders to assess the underlying quality of treatment, therefore it is necessary to address the problem from several perspectives to have a better understanding of the indicator.

After the occurrence of the hip fracture, there is established evidence that surgical treatment is better than conservative [19]. Patients with hip fracture are always hospitalized for treatment, even if the treatment received in the hospital will be conservative, which maybe the result of a balance decision of either providers or the patient or family. As mentioned previously the non-existence of database linkage between different health databases in Portugal is a limitation to the outcome measures that can be assessed. In-hospital fatality is available and has been used as outcome measures for hip fracture treatment. The interpretation of the care provided to hip fracture is based on the three-way approach to quality proposed by Donabedian [20, 21], where quality of care should be evaluated using structure, process and outcome indicators, stringed because “good structure increases the likelihood of good process, and good process increases the likelihood of a good outcome” Donabedian (1988). In this perspective better outcomes are a result of both patient characteristics but also procedures and resources associated to providers.

In a previous study, conducted between 2000 and 2002 [8], there were 92 different hospitals with discharges related to the treatment of hip fractures, in figure 2 their location is displayed with a circle proportional to the number of cases treated (it were excluded hospitals with less than 5 cases). In this figure is also displayed the flux of patients from place of residence to the hospitals.

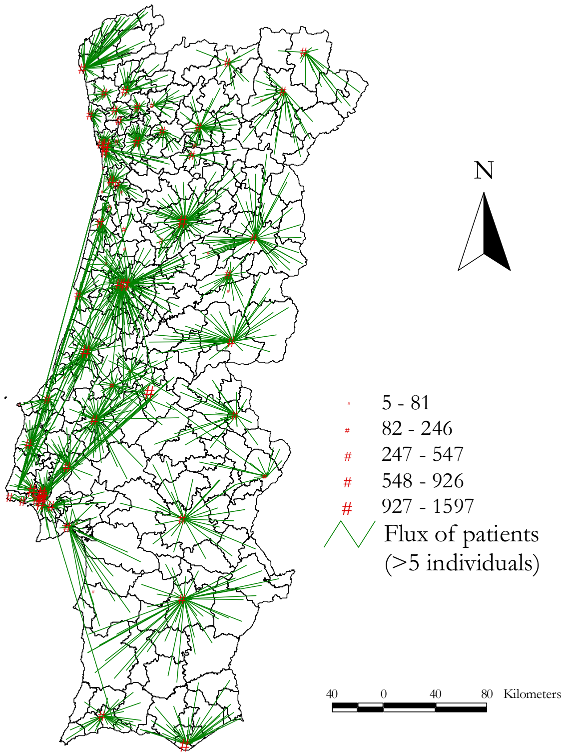

Figure 2: Map of flux of patients with hip fracture: place of residence to hospital of admission, period 2000-2002. Reproduced from Alves, 2005 [8]

Hospitals will differ not only in the amount of patients treated, which can be a measure of their expertise, but also in the resources and actual procedures. Therefore in order to have a feasible indicator for the treatment of hip fracture in Portugal it is important to consider these variations.

Objectives

The main objectives of this work are: evaluate the trends of hip fracture incidence in Portugal and identify possible determinants, obtaining a quality measurement before the event) and a risk adjustment for the treatment of hip fractures, as well as a characterization of the National Health Service (NHS) in terms of the treatment for this pathology, assessing the quality improvement after the fracture.

The following research questions need to be attended:

What is the time trend of hip fracture incidence?

What are possible determinants for such trend?

Interventions?

Cohort effect?

What are the determinants of in-hospital fatality (outcome indicator)?

Economic?

Structure (human and material resources available)?

Patient's medical status?

Procedures?

Are there differences in the quality of hip fracture treatment in Portuguese hospitals?

If the hospitals had the same economical, structural, complexity of patients and preformed the same procedures what would be their fatality experience for patients with hip fractures related hospitalizations?

Are there time trends of in-hospital fatality following a hip fracture?

The strategy will be to divide the focus of the study in two parts. The first part will address the determinants of incidence as a way to achieve the understanding of treatment before the fracture event. The second part will address the determinants of an unfavorable outcome: in-hospital fatality as a way to achieve the understanding of treatment after the fracture event.

Thesis Synopsis

The work presented in this thesis is organized in the following chapters:

Chapter II, state of art, provides a definition of clinical indicators, the importance of risk adjustment and a general overview of the existent indicators for the treatment of hip fractures in several countries. Chapters III to IV present the four scientific articles produced in the context of this thesis.

Chapter III and IV contain the research conducted to address the questions related to the treatment before the fracture event (preventive treatment). First it was conducted a temporal study of hip fracture incidence in Portugal, by sex and age group that revealed an abrupt turning point compatible with pharmacological interventions existent in Portugal. The evolution of medication related to osteoporosis was assess during the same period and the number of bisphosphonates packages sold seem to be plausible explanation for the turning point observed in age standardized incidence rates in women. Chapter III describes this study.

Chapter IV describes the work conducted in order to separate the effect of age, period and cohort in the trend of hip fracture incidence. The study revealed that in fact the year of diagnose had a non-linear effect on hip fracture incidence rates, for women, with a turning point, regardless of age and cohort effect. And identified a cohort effect that presented alterations in all the major moments of the History of Portugal, suggesting a long-term effect on population health of the political and economic actions suffered in the life-time of the patient.

The work developed in order to understand the quality of treatment after the fractures is described in Chapter V and VI. First, and through a systematic review, some macro-economic variables were explored has determinants for in-hospital fatality rates, as described in Chapter V.

In Chapter VI, it is described the adjustment performed as well as the characterization of the SNS regarding the outcome following a hip fracture. The probability of dying while hospitalized, for the treatment of a hip fracture, was manly associated with individual characteristics'. No hospital effect was identified, however some hospitals presented some improvement.

Finally, chapter VII provides a general discussion and conclusions from the work develop in this thesis, and some perspectives for further research work.

After each chapter, a list of the bibliographic references in that chapter is presented.

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CHAPTER II

Clinical Indicators for quality improvement – the case of hip fractures

Clinical Indicators for quality improvement – the case of hip fractures

Introduction

The economic difficulties that our society is facing raise the discussion of quality of care. In health, more than any other field, it is vital to achieve high results, meet high standards, reach the greatest effectiveness and nowadays, more than ever, with the lower costs. In order to assure that the results are met, the assessment measures should be effective. Clinical indicators work as tools to flag situations that potentially need intervention.

Hip fractures implications can be measured at individual or societal level. The effect on a patient can go from loss of previous functional status to a more dramatic outcome of death. However, there are also burdens to society, a surgery to treat a hip fracture is a costly procedure, followed by a rehabilitation that may require specialized help or permanent assistance. Good practices are desirable, the protocols should be followed however the routine producers should be consistently measured and object of systematic analysis, as they may lead to improvement on desirable outcomes and effectiveness of treatment.

Clinical indicators. What are they? And why use them?

Medical care was considered, for a long time, a simple process between the physician and the patient. The treatment process did not seem influenced by external factors, depending only upon biological and psychological variables [1]. With the generalization of health care and the exponential rise of information available the concept of health, itself, suffered alterations and gain a wider amplitude, as is currently viewed as "a state of complete physical, social and mental well-being, and not merely the absence of disease or infirmity", World Health Organization 1946[2]. Therefore, it is recognized that the state of health is influenced not only by health related factors, such as genetic (intrinsic) or promotional aspects (extrinsic), but also by external elements such as economic or social factors [2]. Hence, the process began to be understood as multidimensional, comprising all stakeholders: practitioners, patients and community.

The new paradigm of health and the flow of information led, inevitably, to question the variations in clinical practice [1] and how to measure it. Since the medical care is now considered multidimensional [3, 4], so should be the assessment, and this is the basic idea behind the system-based framework of structure, process and outcome, first proposed by Donabedian [3, 5] for quality of care assessment. This three-way approach sets the entire process of health care divided into parts stringed because “good structure increases the likelihood of good process, and good process increases the likelihood of a good outcome” Donabedian (1988).

The measurement is accomplished through the use of clinical indicators “measurements tools, screens, or flags that are used as guides to monitor, evaluate, and improve the quality of patient care, clinical support services and organizational function that affect patient outcome” [6] cited by [4] that give tangible reflections of health care. Structure indicators are related to the attributes of the material resources and organizational structure. Process indicators are related to the actions in giving and receiving care and finally outcome indicators are related to the description of the effects of care [4, 7].

Clinical relevant indicators are the ones that apply to an health issue that contributes significantly to morbidity or mortality, is associated with high utilization rates or present high treatment costs [8]. Ideally, the health issue should have potential for improvement, however any act of care can have quality assessed, and with the cost constrains it is important to do so, to assure the necessary structural means.

In order to implement indicators, it is necessary very specific criteria and it is important to understand every action under the three aspects of quality of care. A thorough detail provides a better chance to achieve a feasible indicator that truly translates care. Indicators measuring structure quality represent organisational factors where care takes place [3] and can be classified in physical and staff characteristics [9]. The facilities, equipment, economic resources and the organisational structures underlying all these are grouped under the physical characteristics; number and qualification of personnel are under the staff characteristics, however the organisational aspects of these fall into the first group [9]. These aspects do not assure the quality of care but provide an opportunity to receive it.

The real actions of giving and receiving health are represented by process indicators [3] that similar to structure can also be divided into two groups clinical and inter-personal care. In the first category are actions related to the biomedical aspects of healthcare, more technical actions: like activities involved both with diagnosis and treatment, including the information retrieved by clinical history and that obtained by examinations as well as the appropriateness of therapeutic procedures based on such information. In the second category are the aspects related with interactions between patients and care givers [9]. Having these marked differences, indicators from the two categories must have different scientific areas in the background; the knowledge behind the indicators regarding clinical aspects must derive from health sciences, whereas the indicators regarding interpersonal aspects should derive from social/ behavioural sciences [3].

To better obtain a process indicator it is compulsory to look at the strength of the scientific evidence and the cost-effectiveness of the indicator process [8], there are many indicators that follow evidence based guidelines [10]. Scientific evidence may be assessed through published literature or directly through organizations that have that mission, like the Cochrane Collaboration. This organization sets to provide the best evidence for health care [11], trough the preparation, update and promotion of reviews that will help healthcare providers to set guidelines, policy makers to promote indicators, and patients to be a part of the decisions.

Some areas of interest may produce more precise indicators than others, number of hospital beds (structure indicator) is a direct measure in contrast to scales of patient satisfaction (process indicator) [12], however both are important and none should be disregarded.

Finally, outcome measures, which are related to the effect on population and patients health status and can be also divided into two categories: health status and user evaluation [9]. Recovery, restoration of functional status or survival can be considered health status related; Improvement of patients knowledge, changes in patients behaviour or patients satisfactions can be considered a wider class of health status [3] falling into user evaluation category. Whilst it is possible to report the indicators considering a positive approach, the majority of studies published in the literature use the negative side of these standards as measures [13] such as mortality, or fatality rates. Reason for this choice may be related to the objectivity of the measure “death of patient” comparing to others like “satisfaction of patient”. It is easier and less subject to errors to assess the death rather than the restoration of physical status.

The multidimensional core of health and health care should lead stakeholders to the use of several indicators, for all three dimensions. However, these do not invalidate the discussion to set a hierarchy between dimensions. The most sensitive one regards process versus outcome indicators.

Outcome indicator is the ultimate health indicator as it is a reflection of all steps in care [3], including those that are harder to measure, such as technical expertise [14], this however may also be pointed as a negative aspect as it may blind parts that need immediate interventions. Another positive aspect of using outcome measures is the availability of data, at least for the calculation of simple rates. Summing to the negative aspects are the possible lag time between outcomes and interventions, as it may take some years following treatment to develop the outcome [9] as well as the dependency upon other factors such as patient characteristics [10]. Moreover, differences in outcome measures can also be a reflection of differences in measurement, it is therefore important to clearly define cases, outcome and risk factors [14], or even chance, as it may be influenced by number of cases and frequency with which the outcome occurs.

A number of outcome indicators are based on rates, only valid for comparison if based upon a relatively large denominator, overcoming the “Problem of Small Numbers”. This problem is described as the random fluctuation that occurs on rates, by the variation of the numerator in a few cases when the denominator is not sufficient large. This problem may occur when calculating some indicators in small hospitals and aggregation of hospitals or time aggregation may not be a cleaver solutions, because it crashes the possibility of identification of good and bad practices [15]. A solution may be the use of several indicators at a time, namely the use of some that does not take the form of a rate, for instance, Length of Stay (LOS).

Process indicators on the other hand are only valid if they predict the outcome [9, 10], but can instantly be produced following the care, and therefore preventive measures upon bad actions can be immediately taken, instead of waiting for an outcome to be produced. Another positive aspect when using process indicators is the fact that variations in the indicator are more dependent upon differences in care and are easier to interpret [14]. In many cases these indicators are related to actions such as "nutritional status assessed" rather than "hospital specific mortality rate".

Accounting for all these positive and negative aspects and proposed solutions, ideally it is best to include in any assessment system indicators from the three dimensions, as they are complementary and maybe easier to get a correct interpretation of the findings [3].

The use of indicators provides a chance to understand quality in health care, at several levels. Their use is important to use as aim to translate and produce knowledge [14], namely:

- Improve the quality of care of a health care facility;
- Identify poor performers to protect public safety;
- Provide consumer information to facilitate choice of health care provider;
- Inform policymakers at a regional or national level.

In order to meet their goals, indicators should be thoroughly analysed and all possible bias controlled. The first string in the chain: structure is less subject to external influence of other variables; however both process and outcome indicators are disturbed by a variety of variables that have nothing to do with the quality of care received. The severity of the patients treated is one aspect that may affect the final measure and may not lead to linear conclusions, of better care leading to better measure in the indicator; a unit may be performing worse than a similar just because the patients treated there had a more complicated situation, and not because the quality of care was worse. This fact may lead to erroneous conclusions, as the final measure may be biased. The adjustment of the indicators plays, therefore, an important role in the final achievement of fair and reliable measures.

The importance of risk adjustment

The use of indicators to compare efficiency and costs across providers or to compare internally the patient outcome to motivate quality improvement within a provider is to be done carefully. Situations where a better position regarding the result of an indicator represent a better care are not straightforward, since indicators are influenced by other aspects aside from quality of care. Some indicators are more subject to the influence of external factors than other; namely outcome indicators are more sensitive than process indicators to other covariates [16], so the following description is centred on outcome indicators. Outcome measures may be considered a function of quality of care and other covariates, as proposed by Iezzoni, 2003 [17],

Outcomes = ***f*** (intrinsic patients related risk factors, treatment effectiveness, quality of care, random chance)

The purpose of risk adjustment is to remove sources of variation leaving residual differences to reflect the quality of care [18]. Risk adjustments can be performed considering different kinds of risk: clinical outcomes, resources used or patient centred outcomes. The first accounts for outcomes such as death or physical status, the second for costs or length of stay and finally the third account for satisfaction or expectations[19] .

There are some risk-adjustment methods already in use [18, 19] that differ firstly on the risk accounted for, some are focused in costs, others in clinical outcomes, others offer multiple versions for different outcomes [19]. A risk adjustor may predict one outcome but fail to predict another, it is therefore important to choose an adjustor design for the outcome [18, 19].

Risk adjustment may require additional data [8] than the one necessary to calculate the indicator, because the risk of an outcome is, as mentioned before, affected by several patient characteristics, including: demographic characteristics (age, sex, race and ethnicity), clinical factors (such as principal diagnosis and its severity, co-morbid illnesses), socioeconomic factors (such as cultural beliefs and behaviours, economic resources), health related behaviours and activities (such as tobacco use, alcohol consumptions) and attitudes and perceptions (overall health status and quality of life, preferences and expectations for health care services) [18, 20]. Adjusting for all characteristics is considered neither possible nor necessary [19]. The nature of data to be included in the adjustor, whether administrative, clinical or surveys, have a deep influence on the design, e.g, if a large dataset is available than indicators can be empirically developed in opposition to others that are solely based upon clinical judgment [19].

As mentioned, adjusting for all variables is impossible and unnecessary, the choice of what characteristics should be used to adjust is dependent of the outcome, however there are a few that are almost universal. Age is a common variable in the adjustment, since it has almost always an effect, even after adjusting for other variables usually highly correlated like presence of chronic diseases[20]. Age may cause providers to question some forms of treatment and lead to differences in care. Sex is also usually considered in the adjustment, because some studies have reported gender differences namely on cardiovascular interventions: a higher mortality among women but fewer invasive interventions or therapeutic procedures.

Other variables may be a part of the adjustment model namely variables that predict acute clinical stability, translation of immediate risk of death [20]. APACHE – Acute Physiology and Chronic Health Evaluation and its variations is one, among other systems that produces a score to predict outcome of critical illness or injury [21], uses a small number of variables like: arterial oxygenation and respiratory rate.

Principal diagnose as well as the extent and severity of the co-morbidities, defined as the diseases that coexist to the condition of study [21], are important risk adjustors, patients with other coexistent diseases are at higher risk of a negative outcome. Instead of using every disease separately in the adjustment it can be used one of the many co-morbidity index [22], such as Charlson Index [23], that produces a score that reflects the likelihood of mortality and accounts for conditions like dementia, diabetes and myocardial infarction.

Building a risk-adjustment method from the scratch is demanding and very consuming, both time and financially, so the recommendation is to use one of the already developed and validated, as is or change it to fit the goals. The constrains of using a method that does not fit the purposes of the project completely, such as an extra caution in the results interpretation, are compensated with timely results [24]. In both cases it is necessary to combine clinical judgment (using published literature or with the help of experts) with the empirical modelling [24]; involving clinicians in the development brings clinical credibility to the statistical methods.

Clinical indicators in hip fracture treatment

In order to fulfil their objectives clinical indicators should measure areas that contribute with high mortality and morbidity, with heavy costs in care and that have potential for improvement [8, 16]; Hip fracture is a clinical area that presents all these characteristics for that reason many indicator projects have specific indicators for hip fractures.

Individual outcomes may be assessed in many ways for orthopaedic interventions on the hip, both generic, such as quality-of-life measures (SF-36 score, SF-12, EuroQol questionnaire,...), as well as hip-specific such as Harris hip scores (a score ranging a possible of 100, indicating the best possible outcome and assessing pain, function any other areas) or the Oxford hip score (measuring pain and functional and ranging from 12 to 60 points, a higher score translating a greater disability) [25]. These measures may be helpful in the achievement of the standards defined to the indicators.

In Portugal, the entity responsible to regulate Health (ERS – Entidade Reguladora da Saúde) built a system that aims to assess, objectively and consistently, the quality of care. This project, named SINAS [26] (Sistema Nacional de Avaliação em Saúde, National System of Health Assessment) is developed in cooperation with Siemens and the Joint Commission International (JCI- whose focus is on improving the safety of patient care [27]), as the indicators were developed by JCI. For orthopaedic area SINAS establishes 7 indicators:

- Prophylactic antibiotic administration within one hour prior to surgery to patients submitted to total hip arthroplasty (THA) or total knee arthroplasty (TKA);
- Selection of prophylactic antibiotic recommended for specific surgical procedure for THA or TKA;
- Discontinued prophylactic antibiotics within 24 hours after surgery end time for THA or TKA patients;
- Recommended venous thromboembolism prophylaxis for THA or TKA patients;
- THA or TKA patients who received appropriated venous thromboembolism prophylaxis within 24 hours prior to anesthesia start time to 24 hours after anesthesia end time;
- In-hospital mortality for patients surgical treated for hip fracture;
- Revisions to THA or TKA within 30 days after surgery.

This project aims to produce more and better information on the quality of the health system, a continual improvement of health care and empower patients [26], and applies risk adjustment methods.

Internationally, several agencies have been developing indicators for quality improvement, many of which related to hip fracture treatment. Examples of these are: Hip fracture fatality rate by the AHRQ – Agency for Healthcare Research and quality, United States of America, and is defined as the proportion of deaths of all discharged, age >= 18 years with a principal diagnosis code for fracture [28]. This indicator is categorized as an Inpatient Quality Indicator and reflects quality inside hospitals. The agency advices risk adjustments and provides both co-variables and the coefficients to implement the adjustment [29];

The International Quality Indicator Project that establishes its mission in assisting health care organizations in identifying opportunities for improvement in health care [30] and presents indicators for surgical site infections, antibiotic prophylaxis prior procedure, perioperative mortality, unscheduled returns to the operating room, thromboprophylaxis for surgery in hip arthroplasty.

In Denmark the Danish National Indicator Project that aims to "secure mutual grounding and methods for documentation and development of quality in the Danish health care system for the benefit of the patients"[31] has developed and validated a complete set of indicators for hip fractures. Six process indicators:

- Proportion of patients who receive systematic pain assessment at rest and during mobilization using a pain scale;
- Proportion of patients who are mobilized within 24 hours of the operation;
- Proportion of patients whose basis mobility is assessed prior to discharge;
- Proportion of patients where a rehabilitation plan is produced including ADL (Activities of Daily Life) functional level prior to the fracture and an ADL functional level prior to the discharge;
- Proportion of patients where decision has been made regarding medical treatment to prevent future osteoporotic fractures;
- Proportion of patients where decision has been made regarding future fall prevention;

For these indicators the limits in standard of care are above 80% for all and above 90% for the majority. Another seven are available for outcome measurements, for the mortality indicator the project advises an adjustment.

- Proportion of patients who survived at 30 days after admission (standard >= 90%);
- Proportion of patients with an osteosynthesised undislocated medial fracture who are reoperated within 2 years (standard <= 15%);
- Proportion of patients with an osteosynthesised dislocated medial fracture who are reoperated within 2 years (standard <= 30%);
- Proportion of patients with an osteosynthesised subtrochanteric or trochanteric fracture who are reoperated within 2 years (standard <= 5%);
- Proportion of patients with a hemi- or total alloplasty who are reoperated within 2 years (standard <= 10%);
- Proportion of patients who are reoperated due to deep wound infection within 2 years (standard <=2%).

The Canadian Institute for Health Information developed three indicators related to accessibility to surgery and a model to adjust for risk. The indicators differ in the time period between admission and surgery [32]:

- Proportion of patients age 65 and older with surgery within 48 hours of admission to hospital;

- Proportion of patients age 65 and older with surgery on the day of admission or the next day;
- Proportion of patients age 65 and older with surgery on the day of admission, the next day or the day after;

The literature on hip fracture risk and management is used to develop and adjust indicators regarding delay of surgery, nutrition, delirium, patient characteristics, the intervention of interdisciplinary teams or hospital volume [33-39]. As quality is multidimensional any assessment should considered the various aspects involved in the treatment of hip fractures.

Conclusion

The use of indicators has proven to be effective in other areas, in health care the evidence is relatively scarce, perhaps due to considerable variation in the methods used [40]. On a systematic review [40] conducted in Medline and the Cochrane library, for papers published from January 1994 to January 2008, with the search expression of "quality indi*" followed by "hospital care" or "quality improvement" only 21 were included and only one mention the hip/knee as the clinical area to measure [41]. However, hospital measurement needs to be assessed and clinical indicators are the most viable tools for that.

The importance of the indicators concerning hip fractures in hospital performance was recognised, in 2003, when the World Health Organization, launch a project PATH – Performance Assessment Tool for Quality Improvement in Hospitals [42], that developed a set of indicators where 3 concern hip fracture (mortality; readmission, length of stay) [43].

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CHAPTER III

Osteoporotic hip fractures: bisphosphonates sales and observed turning point in trend. A population- based retrospective study

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Osteoporotic hip fractures: bisphosphonates sales and observed turning point in trend. A population- based retrospective study

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Abstract

The aim is to examine the temporal trends of hip fracture incidence in Portugal by sex and age groups, and explore the relation with anti-osteoporotic medication.

From the National Hospital Discharge Database, we selected from 1st January 2000 to 31st December 2008, 77,083 hospital admissions (77.4% women) caused by osteoporotic hip fractures (low energy, patients over 49 years-age), with diagnosis codes 820.x of ICD 9-CM. The 2001 Portuguese population was used as standard to calculate direct age-standardized incidence rates (ASIR) (100,000 inhabitants). Generalized additive and linear models were used to evaluate and quantify temporal trends of age specific rates (AR), by sex.

We identified 2003 as a turning point in the trend of ASIR of hip fractures in women. After 2003, the ASIR in women decreased on average by 10.3 cases/100,000 inhabitants, 95% CI (-15.7 to -4.8), per 100,000 anti-osteoporotic medication packages sold. For women aged 65-69 and 75-79 we identified the same turning point. However, for women aged over 80, the year 2004 marked a change in the trend, from an increase to a decrease. Among the population aged 70-74 a linear decrease of incidence rate (95% CI) was observed in both sexes, higher for women: -28.0% (-36.2 to -19.5) change vs -18.8%, (-32.6 to -2.3)..

The abrupt turning point in the trend of ASIR of hip fractures in women is compatible with an intervention, such as a medication. The trends were different according to gender and age group, but compatible with the pattern of bisphosphonates sales.

Keywords

Bisphosphonates; osteoporosis; hip fractures; anti-osteoporotic medication population studies

Introduction

Identifying and understanding trends of hip fracture incidence is important, not only as a way for planning future medical resources and treating patients but also in planning effective preventive measures [1]. Costs related to hip fractures are not only restricted to hospitalization but also to the long recovery time and assistance that these patients require [2, 3]. Public health interventions can be taken using knowledge gathered from epidemiologic studies using secondary data. These studies can provide valuable information with the use of reliable data on a national basis [4, 5].

The bone quality impairment is associated to aging and elevates the risk of osteoporotic fractures, particularly in post-menopausal women. Furthermore, an excessive pathologic decrease in bone strength can be prevented either by the use of medicaments or by changing activity and nutritional behaviour [6]. Osteoporotic hip fractures are more common among women over the age of 49 years and grows exponentially with aging. With the increase of life expectancy the range of population at risk is considerable, enhancing the need to analyze trends by age groups. In 2008, life expectancy at age 65 in the European Union (27 member states) was 17.2 and 20.7 years for males and females respectively [7]. In Portugal, the same indicator with data from 2009-2011 was 16.9 and 20.2 respectively (last available data) [7, 8]. Moreover, the elderly form the fastest growing age group in most western countries thus aggravating the burden of osteoporosis.

In Portugal there are no national studies addressing the trend of hip fractures. However, internationally several studies have been conducted reporting trends of age-standardized incidence rates of hip fractures [1]. Nevertheless the results are not consensual: increasing, decreasing and stable trends have been reported, which may reflect different stages in the epidemic curve. The results regarding the shape of the trends as well an existing pattern in men have also differ. Studies in Finland [9] and Australia [10, 11] have reported rates of hip fractures compatible with a non-linear trend. However in Finland the decrease pattern was observed in both genders, whereas in Australia only women presented a decreasing pattern. Rates presenting linear decreases have been reported by studies in Belgium [12], Denmark [13], Canada [14], United States [15] for both genders and Spain just for women[16]. Unique causes are impossible to assess, nevertheless studies have pointed out different plausible reasons, according to their results, namely medication for osteoporosis [10, 11, 16] or other interventions [13, 14].

It is important to explore time trends of age-standardized incidence rates of hip fractures although they may hide different underlying trends by age groups thus leading to incorrect conclusions. And since hip fractures affect a wide range of ages, these studies may help uncover unequal patterns and meaningful associations with the preventive procedures undertaken by different countries.

The aim of this work is to examine the temporal trends of hip fracture incidence in Portugal by sex and age group, and explore its relation with anti-osteoporotic medication.

Materials and Methods

Study Area

The study area was Continental Portugal with a population of 10,135,309 inhabitants in 2008. In 2000 there were 3,298,922 inhabitants aged 50 years or over, increasing by 11.9% in 2008 (n= 3,691,104) [8], in contrast with a decrease of -0,6% in the population aged under 50 in the same period.

Data

Population data was the annual official estimates, per sex and 5-year age groups, except for 2001, which was a census year.

We used data from the National Hospital Discharge Register (NHDR). The use of this administrative database is mandatory since 1997 in all Portuguese public hospitals, and compiles information on all discharges such as gender, age, admission and discharge date; first cause of admission (and up to 19 secondary causes) coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM); main diagnosis (and up to 19 secondary diagnoses), also coded according to the ICD9-CM; clinical interventions (up to 20); surgical interventions; hospital providing the care; outcome (deceased, discharge to home, discharge to another hospital); length of stay (LOS) and patient’s place of residence.

In Portugal, access to the national health-care system is free and universal and due to the high costs involved, hip fractures are primarily treated in public hospitals. Therefore hip fractures are highly documented and the NHDR records the total number of admissions with a diagnosis of hip fracture nationwide.

The quality of the NHDR is accessed regularly by both internal (hospitals) and external (ACSS – Central Administration of the National System) auditors [17].

We selected all discharges from 1st January 2000 to 31st December 2008 of individuals aged 50 years or over, with a diagnosis of hip fracture (codes ICD9-CM 820.x) caused by a low or moderate trauma. We excluded cases of bone cancer, readmissions for orthopedic after-care or complications in surgical and medical care (codes ICD9-CM: 170.x, 171.x, V54.x, 996.4), the exclusion expression was applied to all 20 fields containing diagnosis, and represented 0.8% of the cases. To account for misclassification on the diagnosis field other actions were taken, namely revisions were excluded based on procedures codes (81.53 Revision of hip replacement, not otherwise specified) representing a total of 0.08% of the cases. In addition we also excluded cases with length of stay inferior to 5 days, that did not went to a surgery and that were transferred to another hospital, because the first hospitalization could be just to stabilize the patient, these represent 1.1% of the cases.

In Portugal it is not possible to have databases linkage between NHDR and prescriptions so the data on medication was only available for the entire population, and therefore it was not possible to access sales desegregated by sex and age groups, or have the number of patients treated. Data was provided by the National Authority of Medicines and Health Products (INFARMED). We analyzed, on a national level, the number of anti-osteoporotic medication packages sold from 2000 to 2008 through prescriptions made in the National Health System (NHS). We used the total number of anti-osteoporotic medication for the entire population to explain the trend of hip fractures in women, based on our preliminary results that showed no increasing or decreasing trends in ASIR for men. The stable incidence rates of hip fractures among men is compatible with the low prescription of anti-osteoporotic medication for men identified in other countries [12] and information contained in Portuguese national guidelines [18, 19] which focus the prevention of osteoporosis in women. The medications analyzed were those indicated as agents that can act on the inhibition of bone loss or promote directly bone formation [20, 21] with a high evidence level of reducing the risk of a hip fracture: bisphosphonates, calcitonin, hormonal replacement therapy (HRT), Strontium ranelate and Selective Estrogen Receptor Modulators (Reloxifene) as well as vitamin D (recommended to be prescribed in association with the medications mentioned [19]).

We used the Portuguese population from the 2001 census, available from Statistics Portugal (Instituto Nacional de Estatística – INE) as the standard for calculating the direct age-standardized incidence rates (ASIR) per 100,000 inhabitants by gender.

We calculated age-specific rates (AR) by gender, using population counts in the census year of 2001 and official estimates for all the other years. Five-year age groups were used from 50 to 84 years of age and a wider group comprising all patients older than 84.

In addition, we calculated the 95% Confidence Intervals (95% CI) for each rate according to the methods described in Morris and Gardner (2000) [22].

Statistical Analysis

We used Generalized Additive Models (GAMs) to investigate changes in the trends of incidence rates. These models are flexible as they incorporate a non-parametric component that is implemented using spline functions (smoothers) and can reveal possible non-linearities in the effect of the predictors [23]; for this study we were interested in the possible non-linear effect of time in the incidence rates. The GAMs were used in an exploratory manner [24] to identify visually the relationship of time to the mean incidence rate. For the cases where the smooth function of time was statistically significant, we fitted Generalized Linear Models (GLMs) to quantify formally changes in trends. For some models, the smooth non-parametric function was linear so we fitted a GLM with a linear relationship in time. In cases where the smooth function exhibited a turning point, we used piecewise regression with the identified turning points as the cut points, similar to what is described in chapter 12 of Faraway, 2006[24].

We modeled the ASIR as a Gaussian random variable using year as an independent predictor. The GLM results consisted of a linear regression coefficient (the parameter of variable year), in this case the average increase/decrease (depending on the signal of the coefficient) in the rates by an increment of one year. For women, in order to evaluate how sales of anti-osteoporotic medication affect the ASIR, we fitted similar models using the number of packages sold as the independent variable.

We also conducted the analysis on the AR by gender using a GAM followed by a GLM to quantify statistically significant trends. In both cases we assumed that the incidence rates for each age and sex group have a different Poisson distribution, therefore for each group we explored a separate model. Whenever necessary, a negative binomial distribution was used to account for overdispersion [24]. For the AR trend analysis, the natural logarithm of the number of cases was modeled as function of year (nonparametric for GAM) and an offset factor of log (population size of each year). The results of the GLM were expressed as Incidence Rate Ratios (IRR), a relative risk measure representing the factor by which the rate increases/decreases with an increase of a year: a value lower than one represents a decrease in risk between one year and the next (decrease trend), a value higher than one represents an increased risk (increased trend), whereas an IRR equal to one represents an equal risk between two consecutive years (a steady trend). The relative estimated percentage change for each of the periods identified as having a statistically significant trend was calculated by dividing the difference between estimated rates in the final and initial year in the period by the estimated rate in the initial year of the period ([estimated rate final year-estimated rate initial year]/estimated rate initial year). For all measures we calculated the 95% CI.

For the purposes of modeling the age and sex groups separately, the older age groups were aggregated so that the oldest group included patients over 79 years of age. This was done in order to avoid underdispersion.

Statistical analysis was performed using statistical software R version 2.14.1 (Project for Statistical Computing), the mgcv and MASS packages for trend analysis.

A simplistic version of the models implemented is:

1. GAM models for ASIR rate~s(year) and rate~s(number of anti-osteoporotic medication packages sold)
2. GLM model for ASIR rate~year and rate~number of anti-osteoporotic medication packages sold

3. GAM models for AR log(cases)~s(year)+log (population)
4. GLM models for AR log(cases)~year+log (population)

Results

During the study period we identified 77,083 hip fractures, 77.4% in women (mean age (standard deviation (SD)) at admission 81.0 (SD 8.5) years old versus 78.0 (SD 10.1) and (p-value < 0.0001) for women and men respectively. Table 1 shows number of admissions and mean age at admission, according to the year of admission whereas table 2 shows the ASIR and age-specific rates during the period of study.

Table 1 – Summary of statistics of In-patients Characteristics in Portugal (2000-2008).

Variable	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Men									
No. of admissions	1752	1947	1780	1989	1981	1961	2069	1913	2027
Age (Mean; (SD))	77.6 (10.02)	77.4 (10.03)	78.0 (9.92)	77.6 (9.94)	78.4 (10.26)	78.1 (10.20)	78.4 (9.99)	78.2 (10.29)	78.5 (10.14)
Women									
No. of admissions	6086	6537	6295	6814	6820	6820	6892	6569	6831
Age (Mean; (SD))	80.3 (8.59)	80.5 (8.64)	80.9 (8.61)	80.7 (8.72)	81.3 (8.49)	81.2 (8.46)	81.2 (8.47)	81.5 (8.30)	81.8 (8.41)

Table 2 – Age-standardized Incidence Rates (ASIR) and Age-specific Rates (AR) of Hip Fracture per 100,000 inhabitants (95%CI) in Portugal (2000-2008).

Age group	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Men									
ASIR	119.8 (114.2 to 125.4)	130.0 (124.2 to 135.7)	116.4 (111.0 to 121.8)	127.8 (122.2 to 133.5)	123.9 (118.4 to 129.4)	119.2 (114.0 to 124.53)	121.9 (116.6 to 127.2)	110.0 (105.1 to 114.94)	113.4 (108.4 to 118.3)
50 - 54	14.9 (10.8 to 20.0)	17.4 (13.1 to 22.8)	14.5 (10.6 to 19.4)	20.0 (15.3 to 25.6)	16.9 (12.7 to 22.1)	15.2 (11.2 to 20.1)	12.9 (9.3 to 17.5)	14.9 (11.0 to 19.8)	19.3 (14.8 to 24.6)
55 – 59	26.1 (20.2 to 33.1)	25.1 (19.4 to 31.9)	19.6 (14.7 to 25.7)	26.5 (20.8 to 33.3)	25.5 (20.0 to 32.0)	27.4 (21.8 to 34.1)	30.8 (24.8 to 37.7)	28.0 (22.3 to 34.6)	23.2 (14.8 to 29.3)
60 – 64	32.2 (25.5 to 40.2)	40.2 (32.6 to 49.1)	36.1 (28.9 to 44.5)	34.3 (27.3 to 42.5)	39.3 (31.8 to 48.0)	35.0 28.1 to 43.1)	32.1 (25.5 to 39.8)	36.5 (29.6 to 44.7)	35.5 (28.7 to 43.4)
65 -69	70.3 (59.9 to 81.9)	82.9 (71.6 to 95.4)	68.0 (57.9 to 79.5)	65.5 (55.6 to 76.7)	61.3 (51.7 to 72.2)	67.8 (57.7 to 79.3)	66.6 (56.4 to 78.1)	67.7 (57.5 to 79.3)	55.9 (46.6 to 66.5)
70 -74	115.4 (100.6 to 131.9)	142.8 (126.4 to 160.8)	113.5 (99.2 to 129.4)	140.6 (124.7 to 158.0)	112.3 (98.2 to 127.9)	115.4 (101.2 to 131.0)	119.2 (104.8 to 135.0)	101.0 (87.8 to 115.6)	105.1 (91.7 to 119.9)
75 - 79	265.4 (238.8 to 294.1)	259.0 (233.1 to 287.1)	236.4 (211.8 to 263.1)	266.2 (240.3 to 294.2)	239.5 (215.1 to 266.0)	226.9 (203.5 to 252.4)	256.7 (232.0 to 283.3)	198.0 (176.8 to 221.1)	237.8 (214.8 to 262.7)

80 - 84	467.8 (419.3 to 520.4)	502.5 (453.8 to 555.1)	474.3 (428.0 to 524.2)	494.0 (448.0 to 543.4)	480.8 (436.7 to 528.3)	479.6 (436.0 to 526.4)	489.9 (446.4 to 536.5)	465.1 (423.2 to 510.0)	436.0 (396.0 to 479.0)
>84	1042.3 (951.0 to 1140.1)	1101.5 (1008.2 to 1201.3)	1048.1 (957.6 to 1145.0)	1129.2 (1034.7 to 1230.0)	1241.3 (1144.1 to 1344.7)	1108.9 (1019.4 to 1204.3)	1089.0 (1003.0 to 1180.4)	972.4 (893.0 to 1057.0)	1055.7 (974.8 to 1141.5)
Women									
ASIR	336.2 (327.8 to 344.7)	352.9 (344.4 to 361.5)	333.7 (325.4 to 341.9)	356.0 (347.5 to 364.5)	346.5 (338.3 to 354.7)	336.2 (328.3 to 344.2)	329.4 (321.6 to 337.2)	305.3 (297.9 to 312.7)	308.8 (301.5 to 316.2)
50 - 54	14.8 (10.9 to 19.7)	14.5 (10.6 to 19.2)	15.4 (11.4 to 20.2)	18.7 (14.3 to 24.0)	11.7 (8.3 to 15.9)	16.0 (12.0 to 20.8)	13.0 (9.4 to 17.4)	12.6 (9.1 to 16.9)	13.3 (9.7 to 17.7)
55 – 59	30.9 (24.8 to 38.0)	31.4 (25.4 to 38.5)	24.8 (19.5 to 31.1)	33.4 (27.3 to 40.4)	24.7 (19.5 to 30.8)	29.2 (23.5 to 35.7)	25.2 (20.1 to 31.3)	19.1 (14.7 to 24.4)	24.9 (19.8 to 31.0)
60 - 64	54.5 (46.2 to 63.8)	61.7 (52.7 to 71.7)	54.6 (46.2 to 64.0)	59.5 (50.7 to 69.3)	54.7 (46.4 to 64.1)	49.3 (41.5 to 58.1)	58.8 (50.4 to 68.2)	52.1 (44.2 to 60.9)	49.1 (41.6 to 57.6)
65 - 69	122.3 (109.7 to 136.0)	122.8 (110.2 to 136.4)	124.8 (112.1 to 138.6)	133.8 (120.6 to 148.0)	118.1 (105.7 to 131.5)	114.5 (102.2 to 127.8)	113.9 (101.5 to 127.4)	102.7 (90.9 to 115.6)	90.5 (79.4 to 102.6)
70 -74	319.9 (297.9 to 343.1)	333.3 (311.0 to 356.8)	259.4 (239.9 to 280.0)	286.3 (266.0 to 307.8)	277.1 (257.3 to 298.1)	248.5 (229.9 to 268.3)	263.2 (244.0 to 283.4)	232.5 (214.5 to 214.1)	232.1 (214.1 to 251.1)

75 – 79	622.0 (587.5 to 658.0)	636.5 (602.1 to 672.4)	603.8 (570.6 to 638.4)	637.2 (603.5 to 672.4)	600.8 (568.2 to 634.7)	589.0 (557.1 to 622.3)	584.8 (553.3 to 617.7)	529.1 (499.5 to 560.0)	541.5 (511.9 to 572.5)
80 – 84	1122.4 (1063.2 to 1184.0)	1154.4 (1095.7 to 1215.3)	1086.2 (1030.7 to 1143.9)	1154.7 (1099.1 to 1212.3)	1162.6 (1108.2 to 1219.0)	1174.2 (1120.2 to 1230.1)	1108.8 (1057.4 to 1162.0)	1055.4 (1006.0 to 1106.7)	1003.8 (956.2 to 1053.1)
>84	2138.3 (2048.1 to 2231.4)	2323.0 (2229.5 to 2419.5)	2332.1 (2238.5 to 2428.6)	2450.0 (2353.3 to 2549.7)	2465.8 (2370.3 to 2564.3)	2353.0 (2261.8 to 2446.9)	2277.8 (2190.3 to 2368.0)	2157.5 (2073.9 to 2243.6)	2285.3 (2201.1 to 2371.0)

The age groups where the smooth function of time was statistically significant, indicating a statistically significant trend of incidence rates according to time, were 55-59, 65-69, 70-74, 75-79 and over 79 years-old and over in women and 70-74 years-old in men. The following figures 1 and 2 show the statistically significant smooth functions of time by age groups in both sexes and in table 3 we present the results for the age-specific rates using the quantification given by the GLM models.

We identified a linear effect of time in the age groups 55-59 for women and 70-74 for both genders (figures 1 and 2). For the other age groups in women, we identified a point within the period which determines a turn in the trend; these turning points are either increasing to decreasing or an alteration in the velocity of decrease. For women aged 65-69 and 75-79 years, 2003 can be visually identified from figure 1 as the year where a change occurred. For older women aged more than 79, we identified 2004 as the turning point in the trend.

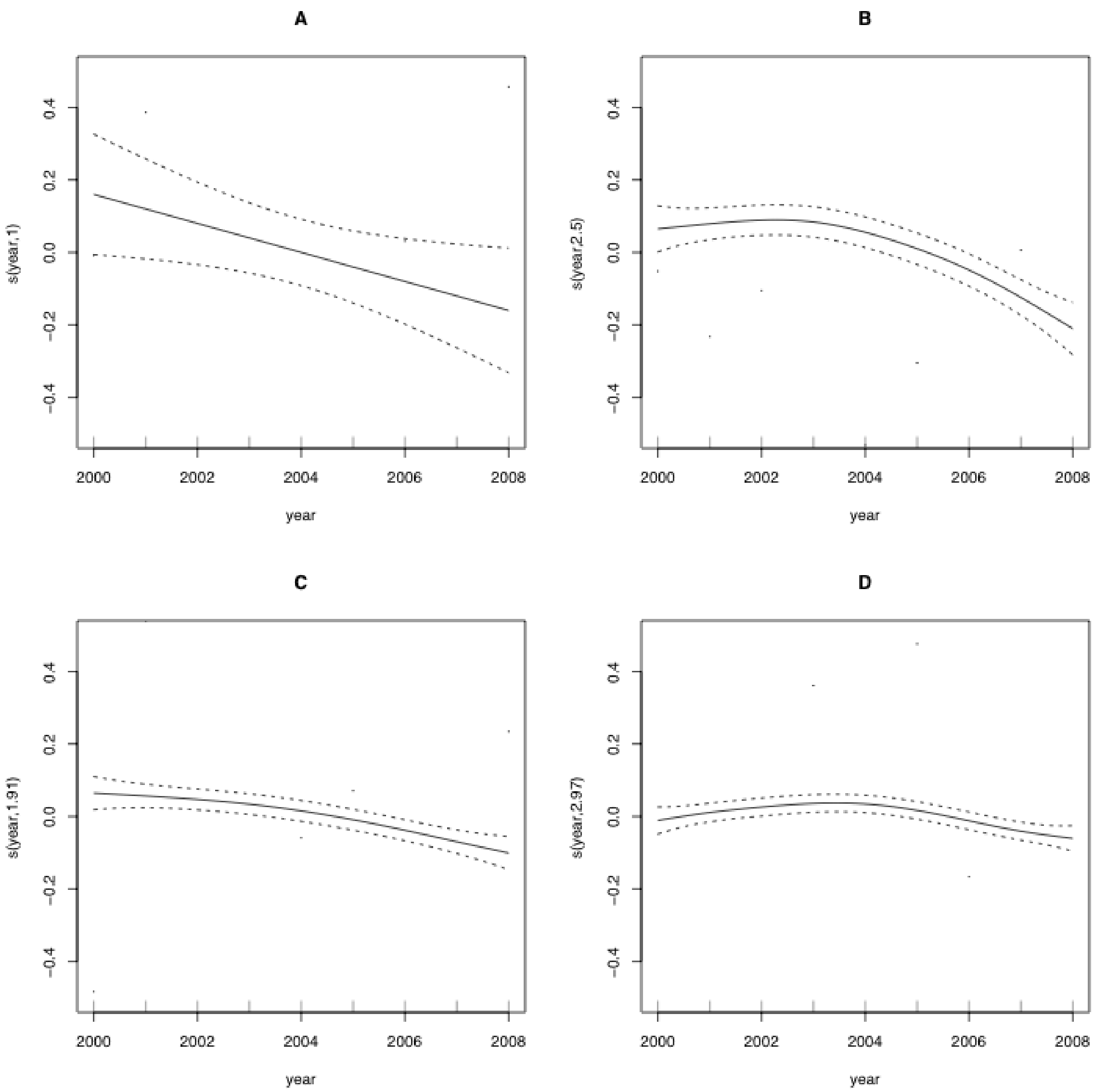

Figure 1 Smooth function of time in AR for women aged: 55-59 years-old (panel A), 65-69 years-old (panel B), 75-79 years-old (panel C) and over 79 years-old (panel D).

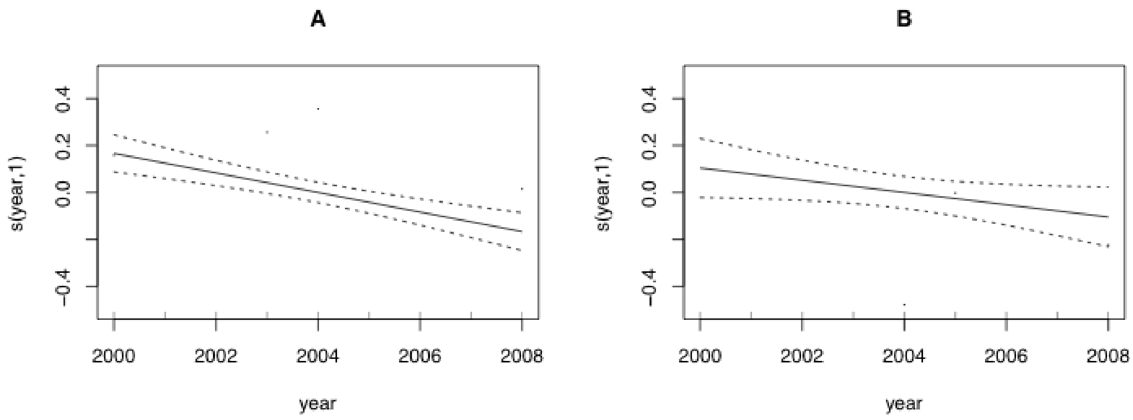

Figure 2 Smooth function of time in AR for women aged 70-74 years-old (panel A) and for men aged 70-74 (panel B)

In figure 3 it can be observed the evolution of anti-osteoporotic medication sales during the period of study. It can clearly be observed that after 2003 the number of biphosphonates packages is the major responsible for the total amount of anti-osteoporotic packages sold.

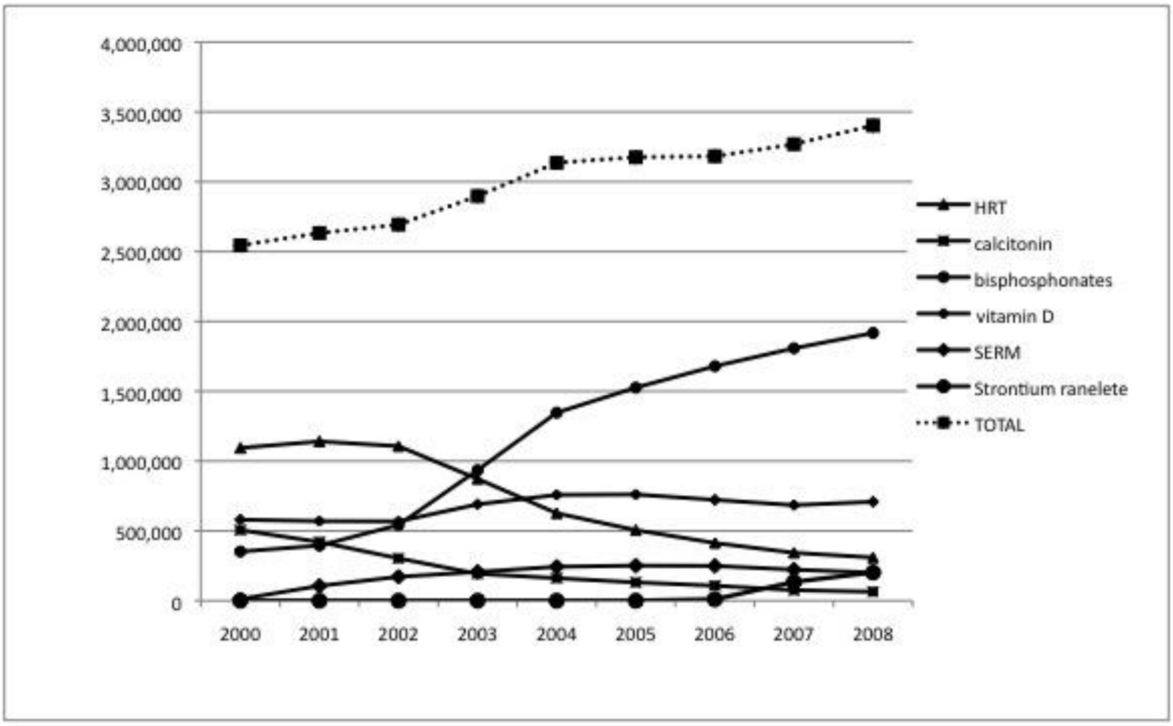

Figure 3 Sales of medication for the prevention of osteoporosis and reduction of fracture risk in Portugal

Analysis of the ASIR by gender revealed a statistically significant effect of time only among women (Figure 4, panel A). This effect is non-linear and the year 2003 was identified as the turning point in the trend.

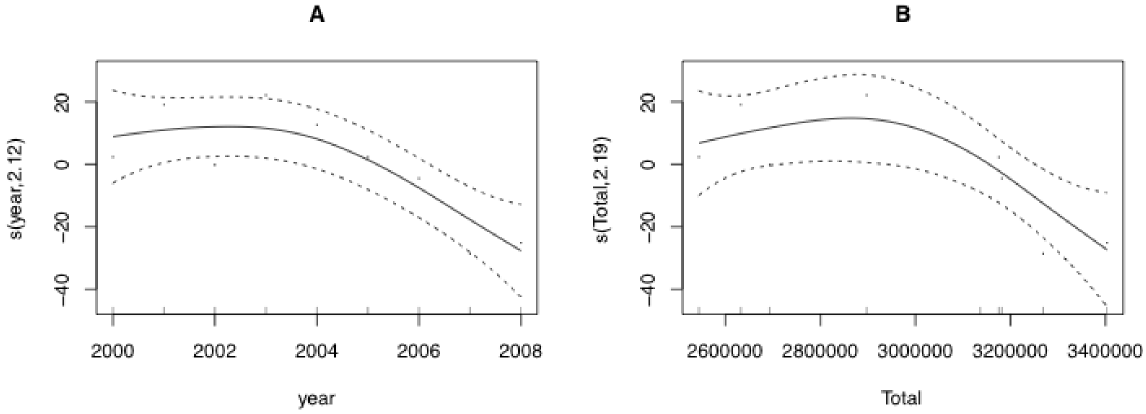

Figure 4 Smooth function of time in Age-standardized Incidence Rates (ASIR) for women (panel A) and of total number of packages for anti-osteoporotic sold in Age-standardized Incidence Rates (ASIR) for women (panel B).

The linear model for the ASIR in women for the period 2000-2003 revealed that for each year, the incidence rate increased on average by 5.1 cases per 100,000 inhabitants with a 95% CI (-1.6 to 11.7). As for the period 2003-2008, the decrease trend was statistically significant with an average decrease of 9.6 cases per 100,000 inhabitants with a 95% CI (-13.4 to -5.7).

The non-linear effect of total number of anti-osteoporotic packages sold in ASIR (figure 4 panel B) is identical to that of time in ASIR (figure 4 panel A) with the same turning point identified in 2003. From 2003 the decrease of 10.2 cases per 100,000 inhabitants with 100,000 packages sold was statistically significant: 95% CI (-15.7 to –4.8).

Table 3 – Incidence Rate Ratios (IRR), Percentage relative change and corresponding 95% CI calculated with GLM

Age-gender group	IRR (95% CI)		% Change (95% CI)	
Men	**Period**		**Period**	
70 -74	2000-2008 0.974 (0.952 to 0.997)		2000-2008 -18.81 (-32.56 to -2.25)	
Women	**Period**		**Period**	
55 - 59	2000-2008 0.961 (0.932 to 0.991)		2000-2008 -27.36 (-43.18 to -7.18)	
65 - 69	2000-2003 1.027 (0.986 to 1.070)	2003-2008 0.937 (0.914 to 0.961)	2000-2003 8.28 (-4.23 to 22.52)	2003-2008 -27.63 (-36.21 to -17.94)
70 -74	2000-2008 0.959 (0.945 to 0.973)		2000-2008 -28.36 (-36.24 to -19.52)	
75 - 79	2000-2003 1.00 (0.980 to 1.020)	2003-2008 0.968 (0.957 to 0.981)	2000-2003 -0.48 (-5.78 to 7.17)	2003-2008 -14.79 (-19.89 to -9.38)
>79	2000-2004 1.013 (1.005 to 1.023)	2004-2008 0.972 (0.963 to 0.980)	2000-2004 5.71 (1.98 to 9.58)	2004-2008 -10.86 (-13.87 to -7.76)

Discussion

In this population-based retrospective study, the year 2003 appeared as a turning point in the time trend of age-standardized incidence rate (ASIR) of hip fracture in women. The observed trend from 2000-2008 with a clear and abrupt decrease change in 2003, is compatible with an intervention on national level. When analysing by sex, the anti-osteoporotic medication packages sold, in each of the years within the study period, had the same impact on the trend of ASIR for women, with the same turning point relating to 2003 sales.

After 2003, with the decrease of HRT, the total number of anti-osteoporotic packages are manly bisphosphonates, suggesting that the massive increase in prescription of these medications was the intervention responsible for the change in the trends of ASIR. The rapidly increase of bisphosphonates sales can be the result of Bone and Joint Decade actions, that raised awareness to prevention, translating in a higher amount of individuals protected and consequently a decrease of incidence rates. However, in Portugal the number of patients treated cannot be assessed, as it is not possible to linkage different health related databases. Furthermore, the results by gender and age group are compatible with this hypothesis. The turning points were only present in women and the change was first observed in the age groups which are the target of these prescriptions in Portugal. Regardless of no causal relationship being able to be attributed is an ecological study, it acknowledges an important aspect that needs further clarification.

The existence of a turning point can be identified visually in other studies [9-11] where the change was attributed to bisphosphonates [10, 11]. However, when the trend is linear and present in both men and women [13-15] questions the extent of bisphosphonates influence were raised [13, 14]. Results similar to ours were observed in a study from Australia [11] and a following study from the same population [10] showed that a decrease in bisphosphonates sales was followed by an increase of hip fracture incidence, underlying the possibility of the trends of hip fracture incidence rates being driven by bisphosphonates.

A change in the trend could be attributed to other factors, however it is unlikely that a change in the demographic and socioeconomic characteristics of the population could occur so promptly that impacted on hip fracture incidence so abruptly has our results pointed out. Other interventions, such as falls prevention campaigns, are usually focused on the elderly age groups (over 80 years old) and were not implemented nationwide in Portugal. Falls prevention actions in Portugal are sparse, conducted locally in some health centers (local impact) and they did not occur simultaneously, therefore it is not likely that such local actions would explain the accentuated turning points in the time trends of ASIR nationwide.

Our study has limitations that in our perspective do not invalidate the results. The relation between the number of bisphosphonates sold and age-standardized incidence rates for women can be questioned because no confounders were used to adjust the effect. In our opinion, the traditional risk factors for osteoporotic hip fractures that could be seen as confounders, such as socioeconomic status or cohort effect, would not have a sudden impact on ASIR, since they do not vary abruptly in time. In our study, the period of 9 years would not be long enough to observe major differences in traditional risk factors at ecological level and even so, they would not have an abrupt impact capable of a turning point in the time trends at national level, we would expect a continuous linear trend like the one obtained on 70-74 age group for both genders.

The strength of our study can be attributed to the data and the statistical methods applied. Our data covers a wide geographic scope, with data containing both hip fractures and medication sales on a national level (excluding the 5% of the population that lives in the autonomous regions), which overmatch local studies. In this paper we analyzed data from several perspectives using flexible models, which to our knowledge have not been used on epidemiological studies of hip fractures. These methods allowed the identification of non-linear effects, complemented with parametric models that allowed the quantification of the decreasing patterns, after the abrupt change. The trends of osteoporotic hip fractures require analysis not only of the age-standardized incidence rates by gender (which can hide unequal patterns by age groups) but also disaggregate analysis by age groups, since the risk increases exponentially with age and the population at risk may require differentiated care.

The incidence rates of hip fractures showed a decreasing trend with a well defined turning point in some age groups. Nevertheless the number of fractures is still raising and with the aging of the population this problem tends to be aggravated, increasing the costs of treatment and rehabilitation of patients. We identified trends of hip fractures at national level and these results may help making better decisions, it is important to have similar studies, in Portugal and other countries, in the following years to help understanding the role of anti-osteoporotic medication on hip fracture incidence, especially with the introduction of strontium ranelate that proved to have a positive impact on some parameters of hip structure, namely bone mineral density [25], but with inconclusive results regarding the decrease of hip fracture risk [26].

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Disclosure Statement

All authors declare no competing interest.

Role of funding source

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CHAPTER IV

Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk

Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk

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Abstract

Purpose:

Healthcare improvements allowed preventive hip fractures measures but also increased life expectancy resulting into more people at risk. The aim is to analyse the effects of age, period and cohort on hip fractures incidence rates by sex, in the 2000-2008 period.

Methods:

We used data from the National Hospital Discharge Database (2000-2008), caused by hip fractures (ICD 9-CM codes 820.x, low energy, patients older than 49). Person-years at risk were calculated using 2001 Portuguese census and official estimates. We fitted an age-period-cohort model (age and period intervals with one year amplitude) that allows the identification of period and cohort effects for all age groups, followed by Generalized Additive Models (GAM) with a negative binomial distribution of the observed incidence rates of hip fractures.

Results:

We found a statistically significant cohort effect in the 77 083 hospital admissions (77.4% women) analyzed. The year 1930 divides the general pattern in women: increasing until 1930, decreasing afterwards. Although not statistically significant, there are risk fluctuations, around 1920 (stable to increasing), 1940 (decreasing to increasing) and 1950 (increasing to decreasing) coincident with political and economic changes in the History of Portugal. In men, the cohort effect presents inflections in the same years, except for 1950. In women the period effect was a decreasing trend after 2004, whereas in men the pattern was random. An exponential like effect was identified in both genders.

Conclusions:

Bone quality reflects a lifetime of exposures; economical/political aspects affecting the population’s health can help understanding the observed cohort effect.

Keywords

Age-period-cohort, hip fractures, osteoporosis, population-based study, time trend

Introduction

Advances in medicine and healthcare led to the development of medications for the prevention of hip fractures [1] but also to the increase of life expectancy; therefore, more people are at risk to sustain hip fractures. These fractures have a negative impact not only at individual level but also at societal level, leading to heavy economic burdens due to immediate treatment and long-term recovery [2].

Hip fracture is a consequence of osteoporosis, a skeletal disorder characterized by compromised bone strength [3]. Bone, a highly metabolic tissue, is constantly in a process of formation/resorption. In the first decades of life the formation is superior to resorption, with roles reversed after the third decade of life [4]. The focus of hip fracture prevention has been in retarding the rate of resorption [5] and in preventing falls, the most common trigger mechanism. Nevertheless, there have been considerations regarding the importance of adequate intrauterine growth in the risk of hip fracture [5, 6].

The common approach to the study of age, period (date of diagnosis) and cohort (date of birth) effects on hip fracture incidence has failed in the understanding of the separated role of the time dimensions. Few studies reported the use of combined analysis to untangle the age-period-cohort (APC) effects [7-9]. The age effect in hip fracture incidence is well described, the risk of fracture increases exponentially in the elderly [10]. However period and cohort effects are more difficult to understand separately and can bias hypothesis formulation.

Interventions such as anti-osteoporosis medication are seen as period effects, which can modify the time trends of incidence rates [11-13]. Cohort effects act differently on generations and can result from changes in wellbeing and quality of health care throughout life [7]. To obtain a reliable explanation for the time trends of hip fracture incidence, the APC dimensions should be addressed using a unique analysis than can provide the separation of the individual effects.

In a previous study we identified a period effect with a turning point in 2003 in the hip fracture incidence rates in women. Following that year an abrupt decrease was observed, compatible with the increased sales of anti-osteoporotic medication packages. In men no pattern was identified [14].

Using a combined approach of estimating APC effects, the aim of this study is to report age, period and cohort effects on hip fracture incidence in Portugal by sex, using national hospitalization data from 2000-2008.

Methods

Data

Data from the National Hospital Discharge Register (NHDR) were selected. The use of this administrative database is mandatory for all Portuguese public hospitals since 1997, and compiles information on all discharges such as gender, age, admission and discharge date; cause of admission and main diagnosis (and up to 19 secondary causes and diagnosis) coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM); among others.

In Portugal, access to the national health-care system is universal and tendentiously free-of-charge, taking into account citizens' social and economic conditions [15].

Due to the high costs involved, hip fractures are primarily treated in public hospitals; therefore the admissions registered in the NHDR represent almost the totality nationwide. The quality of the NHDR is accessed regularly by internal (hospitals) and external (ACSS – Central Administration of the National System) auditors [16].

We selected all discharges from 1 January 2000 to the 31 December 2008 according to the epidemiological indicator of osteoporosis:

- patients aged 50 years or over;
- diagnosis of hip fracture (codes ICD9-CM 820.x);
- caused by a low energy trauma.

We excluded cases of bone cancer, readmissions for orthopaedic after-care or complications in surgical and medical care (codes ICD9-CM: 170.x, 171.x, V54.x and 996.4).

Data were grouped by sex, period of diagnosis (by each calendar year) and age (one year intervals), from 50 to 99 years old. We limited the analysis to 99 years old to avoid statistical instability because from that age on there were few cases and small population.

We used population data from the 2001 Census and the official estimates for the remaining years of the study period [17] to calculate person-years at risk, using the approach described in Carstensen, 2007 [18].

Statistical analysis

We calculated age-specific incidence rates per 100 000 person-years, by sex. Exploratory analysis, prior to statistical modelling, was done using five-year age groups (except for the older age group), from age 50 to 94; the last age group was 95 to 98 years old (due to the algorithm for calculating person-years). We calculated the 95% Confidence Intervals (95% CI) for each incidence rate according to the methods described in Morris and Gardner (2000) [19].

The incidence rates were modelled as functions of A (age), P (period) and C (cohort), using an underlying negative binomial distribution, to correct for overdispersion [20]. A simplistic formulation for the models is:

cases~f(A)+g(P)+h(C)+person-years

where

f, g and h are non-parametric smooth functions (natural splines);

The statistical analysis was developed using the apc.fit implemented on the epi package from software R version 2.15.2 (The R Foundation for Statistical Computing) [21]. The drift parameter, which represents the linear secular trend that cannot be exclusively explained as period or as cohort effect, was extracted using the weighted method.

The problem of separating the APC effects is well described in the literature and several methods have been proposed to overcome the identifiability problem caused by the linear dependency between the three variables (age-period-cohort) [22, 23]. To overcome such problem we used previous knowledge [14] to choose the parameterization: set the cohort function at zero at 1920 (median of birth date for women, the same reference was used for men to allow comparisons) and constrain the period effects to be zero on average with zero slope. Estimates can vary with different parameterizations; however curvature of the effect is invariant. With this approach we could identify whether period had the same effect (decreasing, increasing or stable incidence rates) on all age-groups – the period effect, and/or if all birth cohorts had similar behaviours (decreasing, increasing or stable incidence rates) - the cohort effect.

Following this exploratory analysis, an age, period, cohort analysis was also performed using Generalized Additive Models (GAM). These models are more robust since they allow the identification of non-linear effects of the predictors (age, period and cohort) in the response variable (incidence rate of hip fracture), through spline functions (smoothers) [24]. This approach was implemented using mgcv package of R, where restrictions to overcome the identifiability problem were implemented in GAM algorithm: constraining the smooth functions to have zero mean [25]. This method allows the visualization of the smoother functions in the mean incidence rate of hip fracture for all the effects - age, period and cohort - adjusted for the others. Interpretation of the resulting graphs are: increasing patterns are increasing risk regarding the mean incidence rate, decreasing patterns are decreasing risk regarding the mean incidence rate; if the confidence intervals (CI) contains the zero then the effects are not statistical significant.

Results

During the study period we identified 77 083 hip fractures, 77.4% in women with a mean age of 81.0 years-old (standard deviation (SD) 8.5 years-old), higher than mean age of men (78.0 years-old (SD 10.1)) (p-value < 0.0001). We excluded 208 cases in patients older than 99 years (26 cases in men and 182 cases in women).

Age-specific incidence rates by sex, for each of the period years are listed in table 1. In men, fluctuations in all age groups can be observed, whereas the incidence rates in women presented a more stable decreasing pattern.

Table 1: Age specific crude incidence rates per 100,000 person-years and 95% confidence intervals, by sex, for each of the period years 2000-2008.

Sex	Age-	Period Years								
Men	**groups**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
	50-54	13.6 (9.8 to 18.2)	16.5 (12.4 to 21.6)	14.2 (10.3 to 19.0)	19.6 (15.1 to 25.2)	17.0 (12.7 to 22.2)	15.5 (11.4 to 20.5)	13.4 (9.6 to 18.2)	16.0 (11.8 to 21.2)	19.7 (15.1 to 25.2)
	55-59	22.2 (17.2 to 28.1)	22.0 (17.0 to 28.0)	17.9 (13.4 to 23.5)	25.6 (20.1 to 32.1)	25.9 (20.3 to 32.5)	29.1 (23.1 to 36.3)	34.5 (27.8 to 42.3)	32.7 (26.1 to 40.4)	24.4 (19.00 to 30.8)
	60-64	29.9 (23.7 to 37.3)	47.6 (30.5 to 45.8)	34.4 (27.5 to 42.4)	33.4 (26.6 to 41.4)	39.3 (31.8 to 48.0)	36.3 (29.2 to 44.8)	33.9 (27.0 to 42.1)	39.0 (31.5 to 47.7)	36.3 (29.5 to 44.3)
	65-69	72.1 (61.5 to 84.0)	84.9 (73.4 to 97.8)	68.8 (58.5 to 80.4)	65.9 (55.9 to 77.2)	61.7(52.1 to 72.6)	67.3 (57.3 to 78.7)	65.0 (55.1 to 76.2)	66.1 (56.1 to 77.4)	54.2 (45.2 to 64.5)
	70-74	104.0 (90.6 to 118.8)	131.8 (116.6 to 148.3)	108.2 (94.5 to 123.4)	137.5 (121.9 to 154.5)	113.3 (99.1 to 129.0)	120.4 (105.6 to 136.7)	127.6 (112.2 to 144.5)	110.4 (96.0 to 126.4)	108.4 (94.6 to 123.8)
	75-79	226.1 (203.4 to 250.5)	231.6 (208.4 to 256.7)	220.8 (197.8 to 245.7)	259.4 (234.1 to 286.7)	240.5 (216.0 to 267.1)	237.4 (212.9 to 264.1)	280.7 (253.8 to 309.8)	228.2 (203.7 to 254.8)	251.3 (226.9 to 277.6)
	80-84	346.2 (310.3 to 385.1)	405.3 (365.9 to 447.7)	410.9 (370.8 to 454.1)	463.9 (420.8 to 510.3)	492.8 (447.5 to 541.4)	527.4 (479.4 to 578.9)	583.7 (531.9 to 639.2)	598.5 (544.6 to 656.3)	492.6 (447.4 to 541.2)

	85-89	891.3 (795.3 to 995.8)	896.3 (801.6 to 999.2)	794.9 (707.5 to 890.2)	932.1 (839.2 to 1032.6)	889.4 (800.4 to 985.7)	805.8 (722.6 to 896.1)	783.9 (703.3 to 871.4)	702.5 (627.8 to 783.6)	870.8 (789.1 to 958.7)
	90-94	1398.0 (1173.7 to 1653.0)	1486.0 (1259.1 to 1742.2)	1414.2 (1197.6 to 1658.9)	1166.3 (974.5 to 1385.2)	1632.9 (1409.0 to 1882.6)	1457.1 (1250.4 to 1688.5)	1529.8 (1322.1 to 1761.0)	1397.1 (1203.1 to 1613.8)	1200.6 (1024.9 to 1398.0)
	95-98	2072.3 (1353.7 to 3036.3)	2106.8 (1411.1 to 3025.7)	2382.5 (1668.7 to 3298.4)	1506.2 (974.7 to 2223.4)	2358.3 (1706.7 to 3176.7)	1995.8 (1425.9 to 2717.8)	2269.1 (1684.2 to 2991.6)	1610.0 (1148.9 to 2200.9)	1426.1 (1009.2 to 1957.4)
Women		2000	2001	2002	2003	2004	2005	2006	2007	2008
	50-54	13.6 (10.0 to 18.1)	13.8 (10.1 to 18.3)	15.1 (11.2 to 19.8)	18.4 (14.1 to 23.6)	11.7 (8.3 to 16.0)	16.3 (12.3 to 21.3)	13.4 (9.8 to 18.0)	13.4 (9.7 to 18.0)	13.5 (9.5 to 18.0)
	55-59	27.1 (21.7 to 33.3)	28.5 (23.0 to 34.9)	23.3 (18.3 to 29.2)	32.7 (26.7 to 39.6)	24.9 (19.7 to 31.1)	30.3 (24.5 to 37.1)	27.4 (21.8 to 34.0)	21.6 (16.6 to 27.6)	25.9 (20.6 to 32.1)
	60-64	50.5 (42.8 to 59.1)	57.2 (48.9 to 66.5)	51.6 (43.7 to 60.5)	57.7 (49.2 to 67.2)	54.8 (46.5 to 64.3)	51.4 (43.3 to 60.6)	62.6 (53.6 to 72.7)	55.9 (47.5 to 65.4)	50.4 (42.7 to 59.1)
	65-69	127.0 (113.9 to 141.2)	127.6 (114.5 to 141.8)	127.8 (114.8 to 142.0)	135.4 (122.1 to 149.8)	118.5 (106.1 to 132.0)	112.5 (100.5 to 125.6)	109.8 (97.9 to 122.8)	98.7 (87.4 to 111.1)	86.7 (76.1 to 98.3)

70-74	295.2 (274.9 to 316.6)	311.2 (290.4 to 333.2)	248.9 (230.2 to 268.6)	280.7 (260.8 to 301.8)	279.3 (259.3 to 300.4)	257.7 (238.4 to 278.2)	279.2 (258.9 to 300.7)	250.2 (230.8 to 270.7)	236.4 (218.1 to 255.8)
75-79	532.9 (503.3 to 536.7)	574.1 (543.1 to 606.4)	567.8 (536.6 to 600.3)	622.6 (589.6 to 656.9)	605.3 (572.5 to 639.5)	615.5 (582.2 to 650.3)	634.8 (600.6 to 670.4)	604.1(570.3 to 639.4)	567.8 (536.7 to 600.2)
80-84	823.5 (780.1 to 868.8)	914.2 (867.8 to 962.5)	932.5 (884.9 to 982.1)	1085.6 (1033.4 to 1139.8)	1189.2 (1133.5 to 1246.9)	1294.8 (1235.2 to 1356.4)	1340.0 (1277.9 to 1404.4)	1380.4 (1315.7 to 1447.4)	1133.3 (1079.6 to 1188.9)
85-89	1871.7 (1771.4 to 1976.3)	1983.6 (1882.1 to 2089.2)	1900.5 (1802.9 to 2002.1)	1853.7 (1759.1 to 1952.1)	1687.4 (1599.0 to 1779.5)	1721.2 (1633.6 to 1812. 7)	1683.8 (1598.3 to 1772.8)	1642.4 (1559.6 to 1728.4)	1747.9 (1664.1 to 1834.7)
90-94	2728.5 (2525.2 to 2943.9)	2740.5 (2540.7 to 2952.0)	2736.0 (2540.2 to 2943.0)	2804.0 (2609.6 to 3009.2)	3198.1 (2994.2 to 3412.3)	2929.0 (2737.8 to 3130.1)	2724.4 (2543.7 to 2914.7)	2506.4 (2336.6 to 2685.4)	2524.7 (2357.5 to 2700.7)
95-98	2750.5 (2284.1 to 3284.8)	3481.9 (2972.4 to 4054.3)	3063.3 (2602.9 to 3582.3)	3139.8 (2689.4 to 3644.7)	3325.6 (2877.4 to 3824.2)	2700.0 (2311.6 to 3135.5)	3166.8 (2759.5 to 3617.7)	2618.3 (2261.9 to 3015.2)	3076.6 (2702.7 to 3488.2)

The analysis of the deviance between adjacent lines (table 2, a lower p-value indicates a more suitable model than the previous) indicates that a full APC model is more adequate for women (identifications of both period and cohort effects are statistically significant), whereas in men the trends seem to be explained more accurately using the age-period model.

Table 2 - Comparison between simpler models for men and women, through the comparison of adjacent lines and the p-value from F-test.

	Men			**Women**		
Model	**Residual Deviance (DF- Degrees of Freedom)**	**Deviance difference (DF difference)**	**p-value**	**Residual Deviance (DF)**	**Deviance difference (DF difference)**	**p-value**
Age	687.6 (437)			1385.2 (437)		-
Age+drift	675.2 (436)	12.4 (1)	0.0004	1374.8(436)	10.4 (1)	0.001
Age+Cohort	673.2 (434)	2.0 (2)	0.3422	1313.0 (434)	61.8 (2)	3.6×10^{-4}
Age+Cohort+Period	653.8 (432)	19.4 (2)	6.6×10^{-5}	1237.6 (432)	75.435 (2)	$<2.2\times10^{-16}$
Age+Period	656.6 (436)	-2.7 (2)	0.25439	1299.5 (434)	-61.9 (2)	3.6×10^{-14}
Age+Drift	675.2(436)	-18.7 (2)	8.8×10^{-5}	1374.8 (436)	-74.3 (2)	$<2.2\times10^{-16}$

Figure 1 represents the estimate effect from APC models, using the apc.fit for women and men. Similar age effects for both genders can be observed, plus a similar cohort effect until around 1938/39.

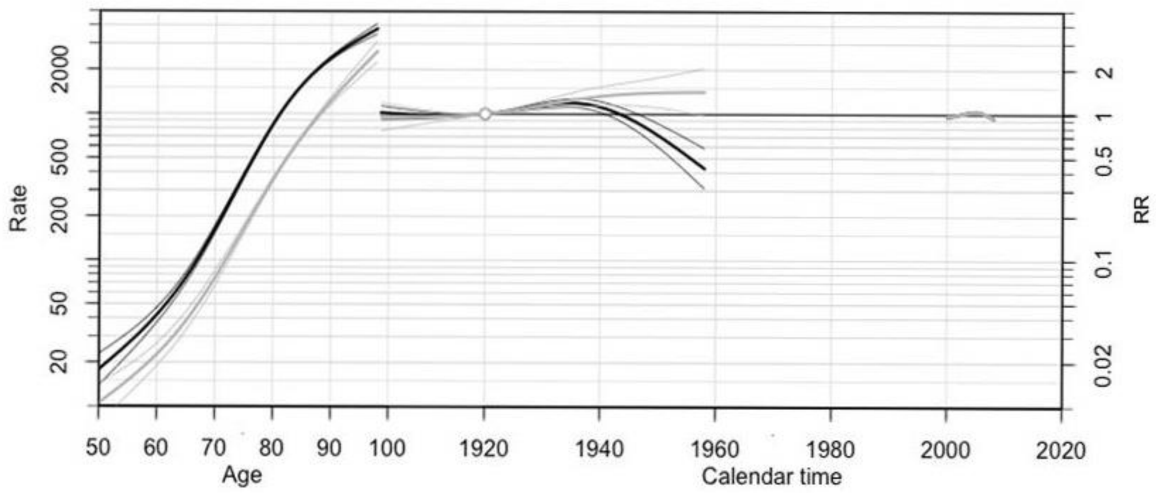

Figure 1: Estimated effects for hip fracture incidence rate using the Age-Period-Cohort model. For each sex (women in black, men light grey) three curves are displayed and can be interpreted as: The left curves are the age-specific incidence rates for 100 000 person-years. The centre curves are the rate ratios relative to the 1920 cohort. The curve on the right side shows residuals ratio rates relative to period effect. Fitted values are plotted with 95% confidence intervals.

Table 3 displays the rate ratios relative to cohort 1920 plotted on the centre graph of figure 1, for both men and women. For the parameterization used, the rate ratio (RR) varies from an estimated decrease risk of 57% in the 1958 birth cohort to an increased risk of 19% in 1934, 1935 and 1936 birth cohorts in women. In men, the estimated RR varies from a decreased risk of 5% in 1904-1910 (although not statistically significant) to an increased risk of 42% in 1956 birth cohorts.

Table 3: Rate ratios of birth cohort and 95% CI relative to 1920, for men and women.

	Men	Women		Men	Women		Men	Women
Cohort	RR (95% CI)		Cohort	RR (95% CI)		Cohort	RR (95% CI)	
1902	0.96 (0.77 to 1.19)	1.02 (0.91 to 1.13)	1920	Reference	Reference	1938	1.3 (1.13 to 1.49)	1.16 (1.08 to 1.26)
1903	0.96 (0.78 to 1.17)	1.01 (0.92 to 1.11)	1921	1.01 (1 to 1.02)	1.01 (1.01 to 1.01)	1939	1.31 (1.14 to 1.51)	1.14 (1.05 to 1.24)
1904	0.95 (0.79 to 1.15)	1 (0.92 to 1.1)	1922	1.02 (1.01 to 1.03)	1.02 (1.01 to 1.03)	1940	1.33 (1.14 to 1.54)	1.12 (1.02 to 1.22)
1905	0.95 (0.8 to 1.13)	1 (0.92 to 1.09)	1923	1.03 (1.01 to 1.05)	1.04 (1.02 to 1.05)	1941	1.34 (1.15 to 1.56)	1.09 (0.99 to 1.19)
1906	0.95 (0.81 to 1.12)	0.99 (0.92 to 1.07)	1924	1.05 (1.02 to 1.08)	1.05 (1.04 to 1.07)	1942	1.35 (1.15 to 1.59)	1.05 (0.95 to 1.16)
1907	0.95 (0.83 to 1.1)	0.99 (0.92 to 1.06)	1925	1.06 (1.03 to 1.1)	1.07 (1.05 to 1.09)	1943	1.36 (1.15 to 1.61)	1.02 (0.91 to 1.13)
1908	0.95 (0.84 to 1.09)	0.98 (0.93 to 1.05)	1926	1.08 (1.03 to 1.12)	1.08 (1.06 to 1.11)	1944	1.37 (1.15 to 1.63)	0.98 (0.87 to 1.09)
1909	0.95 (0.85 to 1.07)	0.98 (0.93 to 1.04)	1927	1.09 (1.04 to 1.15)	1.1 (1.07 to 1.13)	1945	1.38 (1.15 to 1.65)	0.93 (0.83 to 1.06)
1910	0.95 (0.86 to 1.06)	0.98 (0.93 to 1.03)	1928	1.11 (1.05 to 1.18)	1.12 (1.08 to 1.16)	1946	1.38 (1.14 to 1.68)	0.89 (0.78 to 1.02)
1911	0.96 (0.87 to 1.04)	0.97 (0.93 to 1.02)	1929	1.13 (1.06 to 1.21)	1.14 (1.1 to 1.18)	1947	1.39 (1.14 to 1.7)	0.85 (0.73 to 0.98)

1912	0.96 (0.89 to 1.03)	0.97 (0.94 to 1.01)	1930	1.15 (1.07 to 1.24)	1.15 (1.1 to 1.2)	1948	1.4 (1.13 to 1.73)	0.8 (0.69 to 0.94)
1913	0.96 (0.9 to 1.02)	0.97 (0.94 to 1)	1931	1.17 (1.08 to 1.27)	1.17 (1.11 to 1.22)	1949	1.4 (1.12 to 1.75)	0.76 (0.64 to 0.9)
1914	0.96 (0.91 to 1.02)	0.97 (0.95 to 1)	1932	1.19 (1.08 to 1.3)	1.18 (1.12 to 1.24)	1950	1.4 (1.11 to 1.78)	0.72 (0.6 to 0.86)
1915	0.97 (0.93 to 1.01)	0.97 (0.95 to 0.99)	1933	1.21 (1.09 to 1.33)	1.19 (1.12 to 1.25)	1951	1.41 (1.09 to 1.81)	0.67 (0.55 to 0.82)
1916	0.97 (0.94 to 1)	0.98 (0.96 to 0.99)	1934	1.23 (1.1 to 1.37)	1.19 (1.12 to 1.26)	1952	1.41 (1.08 to 1.84)	0.63 (0.51 to 0.79)
1917	0.98 (0.95 to 1)	0.98 (0.97 to 0.99)	1935	1.25 (1.11 to 1.4)	1.19 (1.12 to 1.27)	1953	1.41 (1.06 to 1.87)	0.59 (0.47 to 0.75)
1918	0.98 (0.97 to 1)	0.99 (0.98 to 0.99)	1936	1.26 (1.12 to 1.43)	1.19 (1.11 to 1.27)	1954	1.41 (1.05 to 1.91)	0.56 (0.44 to 0.71)
1919	0.99 (0.98 to 1)	0.99 (0.99 to 1)	1937	1.28 (1.13 to 1.46)	1.18 (1.1 to 1.27)	1955	1.42 (1.03 to 1.94)	0.52 (0.4 to 0.68)
						1956	1.42 (1.01 to 1.98)	0.49 (0.37 to 0.65)
						1957	1.42 (0.99 to 2.02)	0.46 (0.34 to 0.61)
						1958	1.42 (0.98 to 2.06)	0.43 (0.31 to 0.58)

The effect of all parameters, age, period and cohort on hip fractures incidence rates can be observed in figure 2, using a GAM analysis. Age effects are similar for both genders, whereas the period effect is different: a decrease pattern in women after 2004 and a fluctuation pattern in men. The cohort effect, between 1920 and 1940, presents a similar statistically significant pattern in both sexes: increasing risk until 1930 followed by a decreasing risk to about 1940; even though the patterns are not statistically significant after this point both sexes present an increase, which in women is interrupted by another decreasing around 1950.

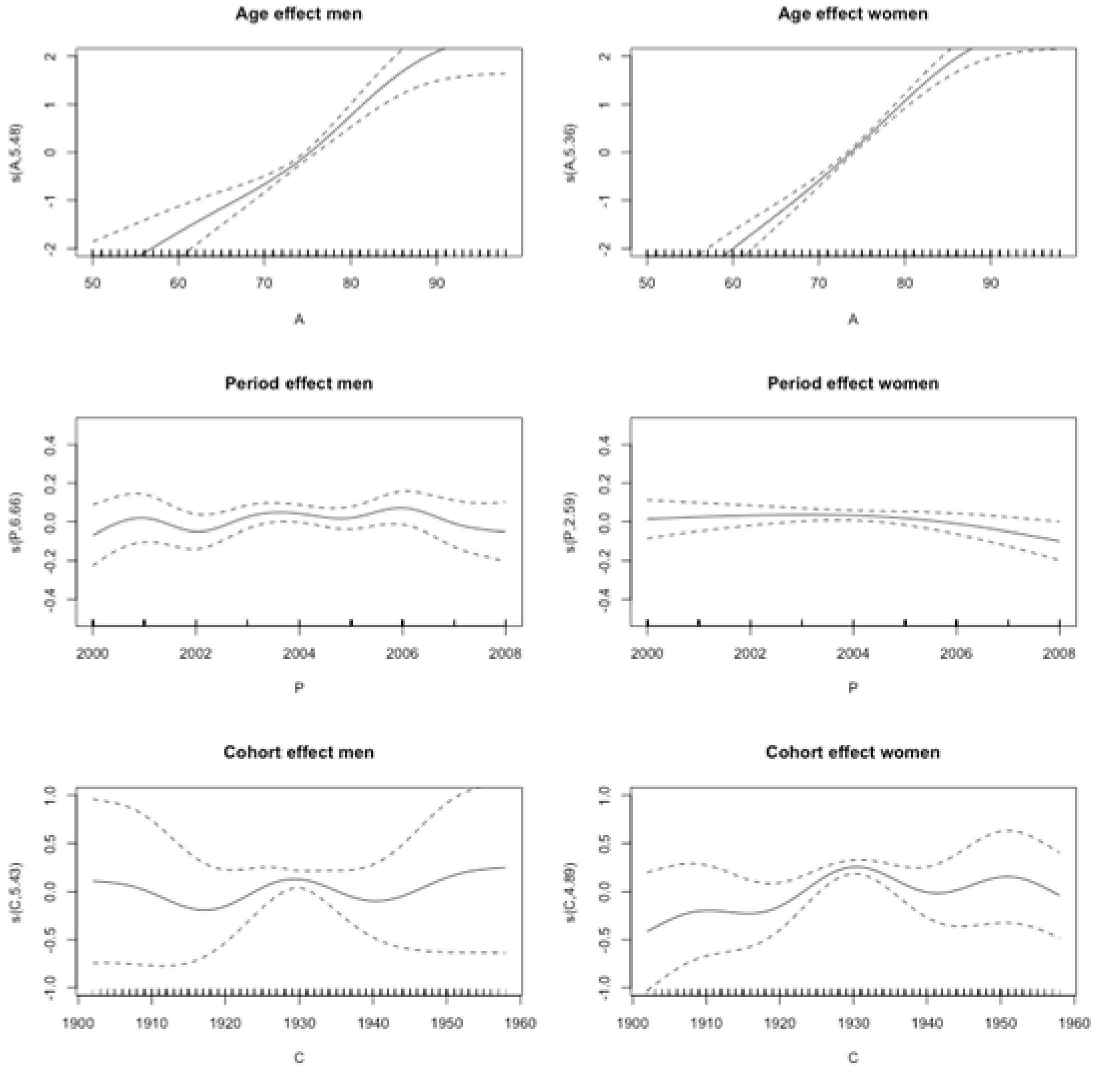

Figure 2: Effect of age, period and cohort on hip fracture incidence rates, 2000-2008, modelled by GAM in women and men, relative to the mean rate.

Some numeric results from GAM models are displayed in table 4.

Table 4 – Results from the GAM models for the hip fracture incidence rates in women and men, 2000-2008.

	Men			Women		
Smooth terms	p-value	R-square (adjusted)	Deviance explained	p-value	R-square (adjusted)	Deviance explained
s(A)	$<2\times10^{-16}$	0.927	98%	$<2\times10^{-16}$	0.968	99.1%
s(P)	0.0009			$2.65*10^{-6}$		
s(C)	2.02×10^{-8}			$<2\times10^{-16}$		

The cohort effect in men and women as well as the historical curve of consumers prices index and chronogram of political and economic changes in Portugal are displayed in Figure 3, to help the discussion of the results.

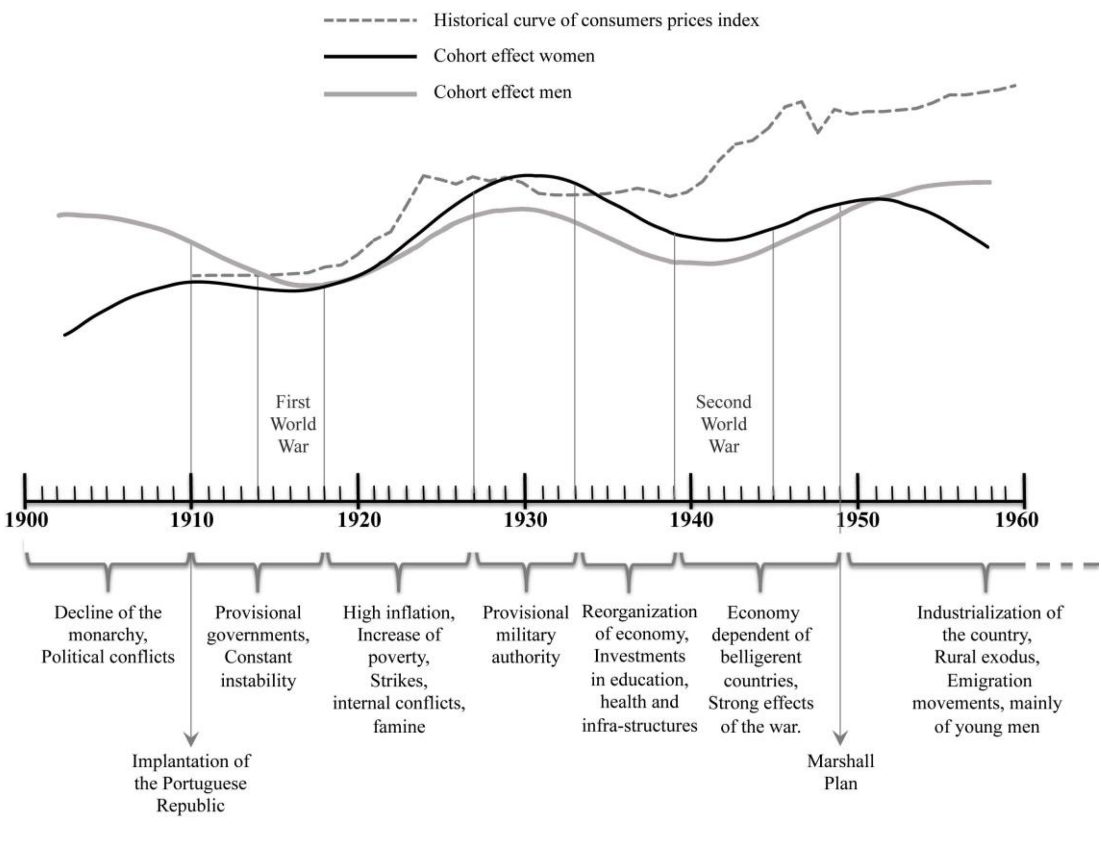

Figure 3: Cohort effect in women and men, historical curve of consumers prices index and chronogram of political and economic changes in Portugal.

Discussion

A cohort effect on hip fracture incidence rates in Portugal was observed, with risk fluctuations in men and women born at times of major political and economic changes: deficient nutritional and health conditions in intrauterine life and childhood could be a plausible explanation for the increased risk in cohorts born in times of deprivation, and similarly investments on health and wellbeing could explain the decreasing in risk in cohorts born in times of political stability. In women, this effect was marked by a tendency of risk increasing until 1930, followed by risk decreasing (Figures 1 and 2). Even though not statistically significant, there were inflections in the risk in 1920 (from stable to increasing), 1940 (from decreasing to increasing), and in 1950 (from increasing to decreasing) (Figure 2). Similar results were observed for men except for 1950, when the decreasing risk trend was not observed. Women in younger cohorts presented lower risk, while for men the estimated risk in younger cohorts was higher (Table 2).

Regardless of an existing cohort effect, there was a period effect in women with a marked turning point in 2004, where the incidence rate decreased. The age effect was similar in both sexes, with an exponential-like age increase, as expected and reported in most of the studies.

The current literature is scarce on studies that analyze the effects of time on the three different scales (age, period and cohort) and comparisons must be carefully interpreted because of differences in methodologies. Nevertheless, in New Zealand [7] and Sweden [8] a similar continuous decrease of risk for younger cohorts was observed, but period effects were opposite, with New Zealand showing a continuous increase and Sweden a continuous decrease. Comparisons between our results and the Swedish are also difficult because there is an overlay of only three calendar years. The age effects were consistent with established knowledge: risk increased exponentially with age. Two other studies attempt to report the time effects separately: one used a methodology that cannot produce comparable results with ours [26] and another uses data from older periods 1968-86 [9].

Hip fractures can be a consequence of balance between formation and resorption in bone tissue through lifetime [4]. Therefore, we can argue that hip fractures are a consequence of lifetime exposure, rather than the result of a short-time exposure. The quality of life in youth can be especially determinant for the quality of bones, and osteoporosis was until few years ago considered a paediatric disease with clinical manifestation in the elderly [27]. Heaney et al (2000) [27] described the bone mass life-line where the maximum bone mass potential achieved by hereditary factors can be altered by several environmental factors. In addition, intrauterine development is determinant in adult bone mass pick [5, 6]; bone growth in uterus demands suitable nutrients supplied via maternal food intake: periods of political and economic changes influence population health, and the twentieth century was replete with major conflicts. In Portugal, internal changes contributed to the global effects of major conflicts.

The first three decades of the twentieth century in Portugal were marked by internal and external causes of instability, with impact on the population quality of life. Portugal was still recovering from the political change from a Monarchy to a Republic (1908-1910) when, in 1914, the First World War (WWI, 1914-1918) was declared with Portugal playing an active part with the Allies. During the war, in 1917 and 1918 there was a food shortage in Portugal and after that the population had to face the Spanish flu (1918 and 1919). The post-WWI period in Portugal was marked by increasing inflation, one of the highest in Europe, aggravated by political instability. Portugal was amongst the poorest and unhealthiest countries in Europe [28]. See figure 2 (cohort effect) for compatible risk alterations in the incidence of hip fractures during these years.

From 1927 to 1933, a new major political change marked the History of the nation; the Republic was replaced by a provisional authority, led by the military, followed by a totalitarian regime that lasted 41 years. In the 1930s, the political stability was achieved, finances and economy were reorganized and investments were made to construct thousands of elementary schools, hospitals, health centres, and infrastructures such as roads, electricity, and sewage. Portugal faced a progressive improvement in the general quality of life; Figure 2 (cohort effect) shows compatible risk alterations, around this period.

The decreasing risk of hip fractures observed in cohorts born in the 1930s turned to another period of risk increasing after 1940. In spite of the neutral part that Portugal played in Second World War (WWII, 1939-1945), there were economic, social and political effects, mainly because Portugal depended on belligerent countries' imports to obtain fuel, industrial primary resources and food. After the WWII, there was a boost in the European economy, with the Marshall Plan (1948-1951); Portugal received the funds in 1949, mostly used to purchase food supplies. In 1952 Portugal implemented the 1st Foment Plan to elevate the living conditions, improve productivity, reduce unemployment [28] and increase the industrialization of the country. At that time Portugal was mainly a rural society and the industrialization started a process of rural exodus. Nevertheless, Portugal was still among the poorest countries in Europe and the isolation of the totalitarian government prevented the country to follow the post-WWII development of the other west European countries. The solution to escape poverty, for many Portuguese, was to emigrate. The 1950s was a period of intense emigration, mainly of young men, especially to France and Germany. Their cash remittances helped not only to improve the wellbeing of their families in Portugal but also the industrialization of the country. Meanwhile the emigrants themselves were living under very poor conditions. This could be a possible explanation for gender risk inequalities for cohorts born after 1950 observed in our results: for men, the risk continued to increase while for women it started to decrease. However, data for a longer period needs to be analysed in future studies, in order to improve the estimates for younger cohorts.

Causal effect in epidemiology has been thoroughly discussed and analysed [29]: observational studies lack the criteria of causality and therefore results are commonly overlooked. It is difficult to attribute causal effects in hip fractures incidence due to the intrinsic nature of bone health, reflecting a lifetime of exposures, however our results stressed a number of aspects that can be seen as indicators of causality. Besides, there was a reasonable match between the cohort effect and historical data of the consumers price index (figure 3, where the historical events were also overlaid) which reflects the standard of living and measures the changing costs of purchasing goods and services, often used as an indicator of life conditions [30]. It is accepted that conditions during the period where bone formation surpasses bone resorption, including intrauterine growth, have impacts on bone health later in life [5, 27]. Hence the similar cohort effect observed in both genders, with changes in each and every single period of time where a major historical event occurs (Figure 2 cohort effect and figure 3), should not be overlooked on the basis of lack of strong association, or of disregarding other causal factors. Nevertheless, we are not postulating causality neither that the cohort effect is a necessary or a sufficient cause [29] in understanding the trends in hip fracture incidence, but it seems an important one to be analyzed in future studies. The simultaneity of risk alterations and historical events back the hypothesis of the importance of nutrient availability during uterine growth as much as conditions during childhood and adolescence.

The inherent limitations of studies using the APC models, that are related to the identifiability problem and invalidate the quantification of the different effects, do not surpass the importance of the obtained results. The strength of our study relies on addressing age, period and cohort effects simultaneously from several methodology perspectives and using nationwide population-based data.

With this study an innovative perspective on the reasons that drive the trends of hip fracture incidence rates is presented, highlighting the considerable differences in the population at risk for sustaining a hip fracture. There was a fluctuation on hip risk in both men and women born at times of major political and economic changes, regardless of period effects, which could be related to the nutritional and health conditions in Portugal at the time.

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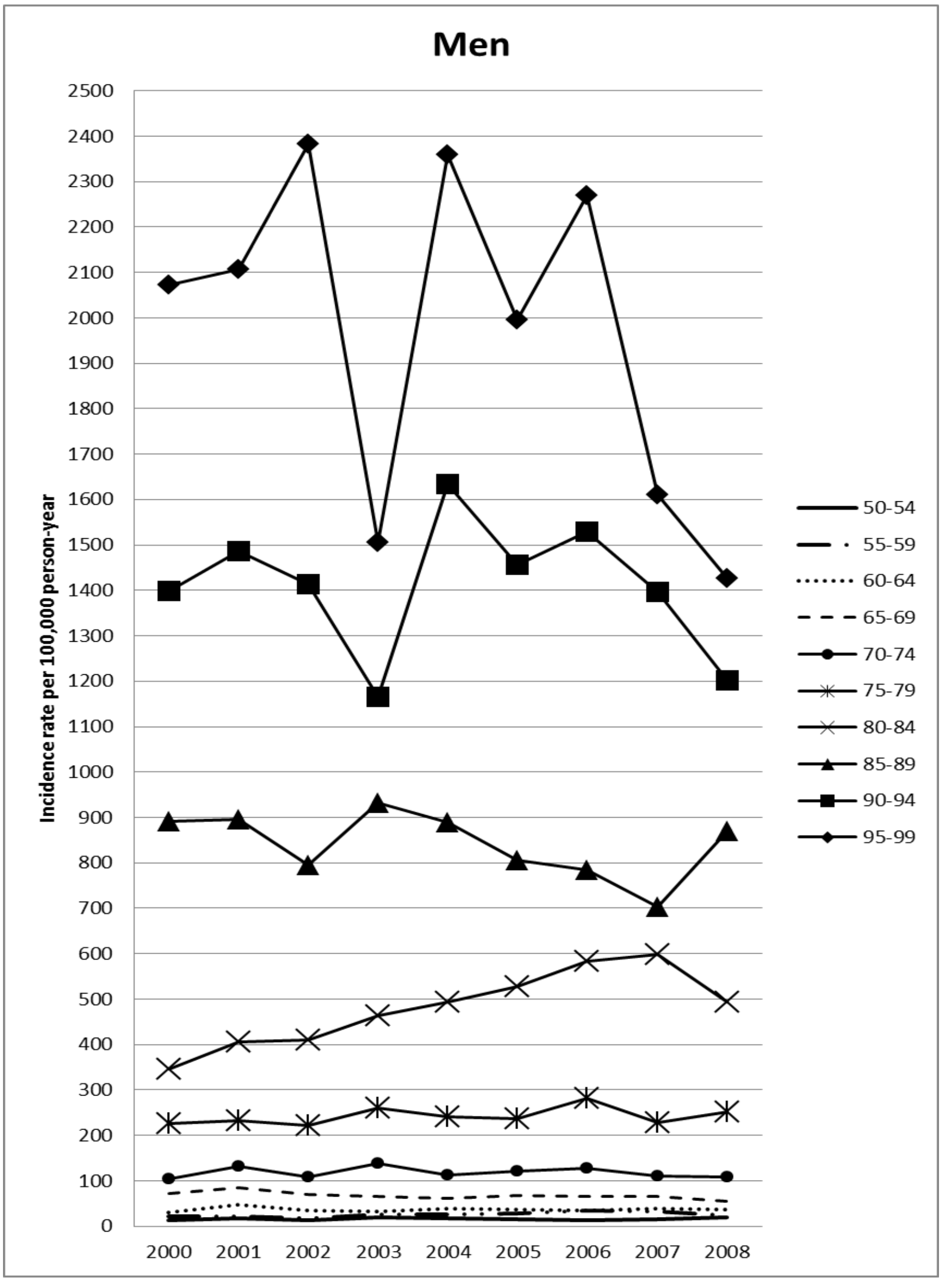
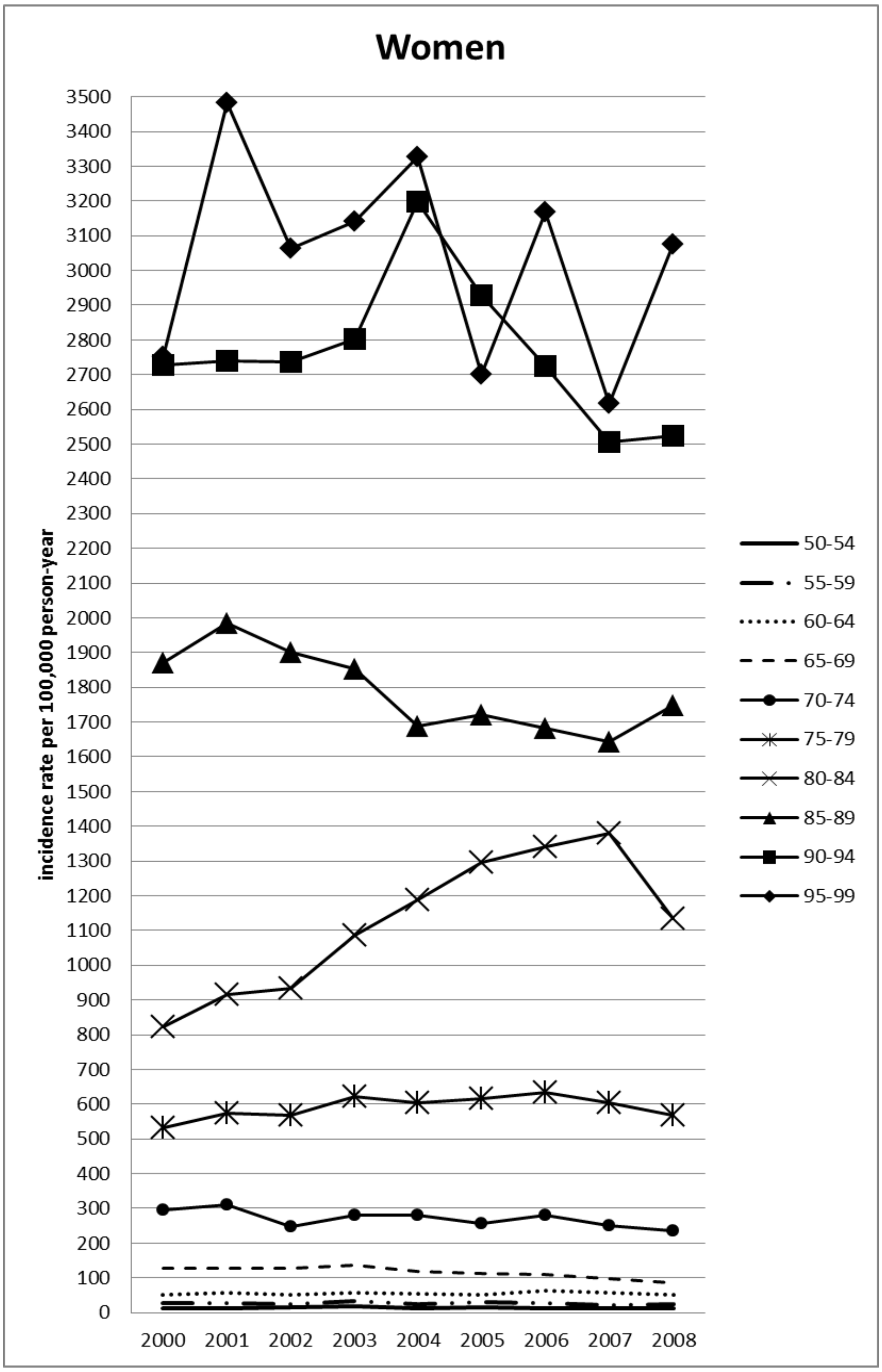
Additional Materials



Additional figure 1: Age specific crude incidence rates per 100,000 person-years, for period 2000-2008 in men.



Additional figure 2: Age specific crude incidence rates per 100,000 person-years, for period 2000-2008 in women.

CHAPTER V

The unaccounted role of macro economic variables: meta-regression to explain in-hospital fatality rates following hip fractures

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The unaccounted role of macro economic variables: meta-regression to explain in-hospital fatality rates following hip fractures

Authors: Sandra Maria Alves, Enrique Goméz-Barrena, Steve Kurtz, Maria de Fátima de Pina

Abstract

Background: Hip fractures have consequences to patients - morbidity and mortality - and to health systems - economic burden of surgical treatment and of recovery. The aim of this study is to assess if macro-economic variables can explain in-hospital fatality rates following hip fracture, in patients aged 50 years-old or more.

Methods: In-hospital fatality rate was obtained through a systematic review conducted on MEDLINE database via PubMed. Studies, published after the year 1999, were included if data for in-hospital fatality rates, following a hip fracture admission (ICD-10 S72.0 – S72.2 or ICD-9CM 820), were available for patients aged 50 years-old or more. Studies of patients with other comorbidities (such as cancer) were excluded. Macro-economic and social variables were retrieved from Organisation for Economic Co-operation and Development (OECD) and Global Health Observatory Data Repository from World Health Organization (WHO). A multiple regression analysis was conducted.

Results: We selected 20 estimates comprising 735,348 hip fractures, from 16 studies, developed in 11 countries. The in-hospital fatality rates (%) ranged from 0.7 in Taiwan to 14.0 in the United Kingdom; 99.9 of the total variability was due to heterogeneity between studies. The density of practicing physicians and of hospital beds explained heterogeneity.

Conclusions: Heterogeneity of in-hospital fatality rates following hip fractures was partly explained by macro-economic variables (including allocation of medical resources) indicating that studies on inequalities of health outcomes should not focus only on individual and hospital characteristics.

Keywords

Hip fractures, in-hospital fatality, Bone decade, osteoporosis, meta-regression, health resources, outcome

Introduction

The importance of bone and joint disorders was formally recognised with the launch of the Bone and Joint Decade (2000-2010) and osteoporosis was identified as one of the five target areas[1].

Patients with a hip fracture are at higher risk of mortality compared with the non-hip fracture population, and this risk is likely to be elevated through long periods after the incident [2, 3]. It is plausible that macro-economic variables, even and national level, can be correlated with mortality after hip fractures, since economic constrains have direct implications on health outcomes; although studies usually focus only on hospital or patients characteristics, to compare fatality between different hospitals [4]. The most common are studies where differences in fatality are assessed through the age, gender and co-morbidities of the patients [5-7]. Studies focusing on operative management for fractures have also been published [5, 8, 9].

Fatality may qualify for the ultimately quality indicator, and mortality tables as well as risk assessment are currently used. However fair assessments should account for several sources of risk, including economical ones.

The aim of this study is to explore how macro-economic variables, at country level, can explain differences between in-hospital fatality rates, following hip fractures, in patients aged 50 years of age or older.

Materials and Methods

Data Collection

Hip fracture data were collected through scientific papers selected by systematic review and macro-economic data were obtained through official websites of international organizations.

Hip fracture fatality data

Data Search

A systematic review was conducted on MEDLINE database via PubMed during October and November of 2010. The search expression, transcribed below, was obtained using analogue combinations of Medical Subject Heading (MeSH) terms: hip fracture and mortality. This query was supplemented by use of search criteria in All Fields, in order to obtain any other paper that might be misclassified in MeSH Terms.

Manual search was conducted using references of selected studies. In order to obtain a full coverage, authors of studies that met the inclusion/exclusion criteria but didn't exhibit in-hospital fatality, were contacted via e-mail in an attempt at gathering more data.

("hip fractures"[MeSH Terms] OR "hip fractures"[All Fields] OR "Femoral Neck Fractures"[MeSH Terms] OR "Femoral Neck Fractures"[All Fields] OR "femur neck"[All Fields]) AND ("hip fractures/mortality"[MeSH Terms] OR "mortality"[MeSH Subheading] OR "mortality"[All Fields])

Study Selection

Studies were selected if they contained in-hospital fatality data, as a result of admissions with hip fracture diagnosis, using the International Classification of Diseases (ICD) codes S72.0 – S72.2 (version 10) or 820.x (9th Revision, Clinical Modification). Only studies published in English, Portuguese or Spanish, from 2000 through 2010 were considered for analysis.

Studies were considered when allowing the extraction of data for age groups ≥50 years. We excluded experimental, case studies and reviews, as well as studies with one of the following characteristics: only patients ≥85; sex-specific; patients with severe pre-existent conditions (such as cancer or renal dysfunctions); comparisons of different surgical interventions; less than 200 fractures; data before 2000 (in order to control for other sources of heterogeneity that could have changed over time).

In-hospital fatality rates, period of data, population, sample size, geographical location, and percentage of women patients were variables extracted from eligible studies.

For each study, macro-economic variables were collected according to geographical location and year of data resulting in one estimate per country in the data modelling, except for Canada. When studies had data from more than one year, with no possibility of disaggregating it into more estimates, macro-economic data were selected for the mid-year of the study period.

Macro-Economic data

The Organization for Economic Co-operation and Development (OECD) [10] and the Global Health Observatory Data Repository from the World Health Organization (WHO) [11] were assessed, through the internet, during July 2011 for macro-economic variables at country level. Whenever possible data from the OECD were used: otherwise, data from WHO were used to fill the gaps. The agreement between the different sources was high.

After exploratory analysis, four variables, from different themes, were selected: 1 - Private expenditure on health as a percentage of total expenditure on health, accounting for the amount of expenditure on activities intended to promote health and prevent disease, cure illness and reduce premature mortality, on nursing care, provision and administration of public health and health programmes. This variable was retrieved from WHO; 2 - Hospital beds, density per 1,000 population, that accounts for “all hospital beds which are regularly maintained and staffed and immediately available for the care of admitted patients" [10]; 3 - Practising physicians density per 1,000 population. OECD was the primary data source for variables 2 and 3 and whenever necessary complemented with WHO data; 4 - GINI Income distribution – Inequality, after taxes and transfers, for the retirement age population >65, retrieved from the OECD. Higher values of the GINI index represent higher inequalities.

The allocation of GINI to each study was made using the country and the year of data, while for all the other variables an arithmetic mean, using values from the five previous years from data allocation, was computed, in order to obtain a more accurate measure as these variables may have a time-lag effect.

Data Analysis

Analysis was conducted using R metafor package software [12], with in-hospital fatality rates (IHR) as the effect. Since IHR is a proportion, the Freeman-Tuckey double arcsine transformed proportion was applied [13]. A weight was applied to each study according to sample size - larger sample sizes contributed more to the analysis.

A random effect model, that allows a different effect for each study [14], was applied to quantify the global heterogeneity between studies. The I2 statistics, presented with 95% Confidence intervals (CI), was used to assess the proportion of total variability due to heterogeneity rather than chance, and may be interpreted as follows: 25%, 50%, 75% indicating low, moderate, and high levels of heterogeneity, respectively [14]. Heterogeneity was also assessed, visually, by the forest plot (where point estimates, CI, and respective weights used as well as a global estimate and CI are displayed) and through the Cochran's Q test p-value [15]. The global effect of in-hospital fatality was computed, using the random effect model.

Potential macro-economic sources of heterogeneity were investigated using a meta-regression mixed-model; residual analysis was performed to identify possible outliers. R2 measure was used to report the proportion of variance explained by the covariates as described in Boresntein, 2009 [14]. Positive coefficients indicate a positive direct relationship, where an increase/decrease in the explanatory variable leads to an increase/decrease on IHR. Negative coefficients on the other hand, represent negative relationships, where the explanatory variables vary in the opposite direction of IHR (increase of explanatory variable leads to decrease in IHR, and vice-versa).

To facilitate the reasoning a few IHR were predicted for values of explanatory variables.

A complete case analysis was performed in the meta-regression models.

Results

An initial search resulted in 1,141 papers. After abstract and full text analysis most were excluded as shown in the flow-chart (figure 1), resulting in a total of 16 studies, which met all inclusion criteria.

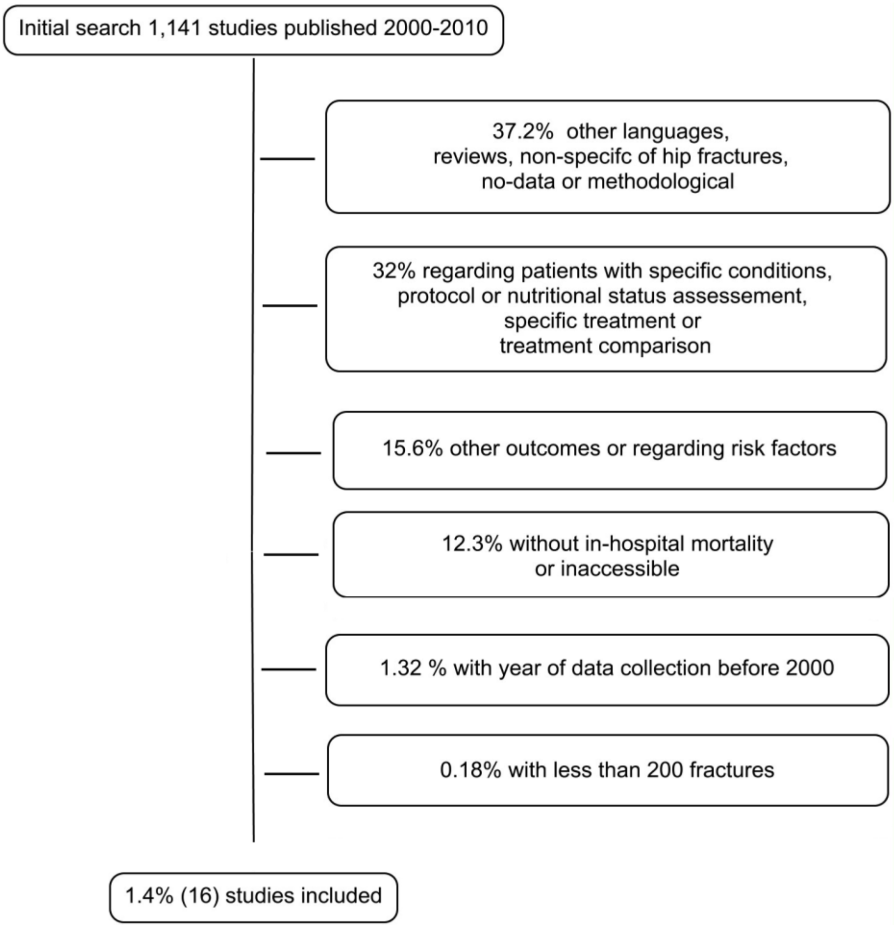

Figure 1. Flow-chart illustrating the selection process.

Papers only mentioning hip fractures but not presenting results were classified has non-specific, whereas recommendations or scale validation papers were classified has no-data or methodological.

Cross-reference search was done but no additional studies were found. The studies eligible led to 20 different point estimates, for different countries or data-periods.

As shown in table 1, studies were conducted in 11 different countries and comprised a total of 735,348 cases of hip fractures.

Table 1. Information regarding included studies.

Study	Data period	Population	Sample Size	Geographical location
Alvarez-Nebreda [16]	2000-2002	All patients hospitalized with an acute hip fracture, aged 65 years or older (ICD-9 CM codes 820.0 to 820.9)	107,718	Spain
Bergeron [17]	1996-2003	All consecutive patients, aged 60 or more operated with an isolated hip fracture (ICD-9 codes 820), caused by falls	906	Canada
Boufous [18]	1999-2000	Patients aged 50 years and over hospitalized with a primary diagnosis of the neck of femur (ICD-9 CM codes 820 or ICD-10 codes S72.0- S72.2)	5,648	Australia (New South Wales)
Cruz [19]	2004-2006	All patients aged 50 and over hospitalized with a proximal femur fracture after a low impact fall	267	Portugal (Caldas da Rainha)
Haaland [20]	2003-2004	Patients aged 50 or over hospitalized with a low-impact hip fracture, excluding pathological fractures due to malignancy or intrinsic bone disease	342	Canada (Ontario)
Hagino [21]	1997-2004	Patients aged 60 and over hospitalized with a hip fracture	290	Japan (Yamanashi)
Hindmarsh [22]	2000-2003	Patients aged 65 or older hospitalized with the principal diagnosis of hip fracture (ICD- 10- AM codes S72.0- S72.2) caused by unintentional falls	16,836	Australia (New South Wales)
Lefaivre [23]	1998-	All patients over the age of 65 hospitalized with an isolated fracture of the	607	Canada

	2001	proximal femur		(Vancouver)
Morosano [24]	2001-2002	Patients aged 50 or over hospitalized with a hip fracture	763	Argentina (Rosario)
Nielsen [25]	2005-2006	All patients hospitalized with only one episode of hip fracture within the period, over 64 years of age	6,266	Denmark
Pereira [26]	2001	Patients aged 60 or over admitted with a femoral neck or intertrochanteric fracture caused by falls, excluding cancer.	246	Brazil (Rio de Janeiro)
Söderqvist [27]	2003	All patients aged 66 or over with a hip fracture, excluding pathologic fractures	1,944	Sweden (Stockholm)
Shao [28]	1996-2002	Patients over 64 years of age, admitted with a hip fracture (codes ICD-9 820) who underwent surgery, excluding pathological fractures	75,482	Taiwan
Vidal [29]	2003-2004	All patients, aged over 59, admitted to hospital, with a main diagnosis of hip fracture (ICD-9 codes 820), excluding cancer, high impact trauma	3,754	Canada (Quebec)
Wu [30]	1998 - 2009	All patients admitted to hospital with a main diagnosis of hip fracture (aged 45 or over) (ICD- 10 codes S72.0, S72.1, S72.2)	551,976	England
Yonezawa [31]	2003-2006	All patients admitted to hospital with a hip fracture, aged over 60	536	Japan (Kanagawa)

In-hospital case fatality rates (IHR) ranged from 0.6% in a study conducted in Taiwan [16] to 14.0% in the United Kingdom [17] and this heterogeneity is displayed in the forest plot (figure 2). In this figure we can also observed the weights attributed to each of the studies. The percentage of total variability due to heterogeneity rather than sampling error (I2) was 99.9% (95% CI 99.84 – 99.96) and the global estimate for in-hospital case fatality rate was 5.6 (95% CI 3.8% - 7.7%). Cochran's Q test p-value was < 0.001 concluding that not all estimates share a common effect.

Only four studies presented data by gender (table 2) so no analysis was conducted separately for each sex. And as expected, all studies reported higher fatality rates for men.

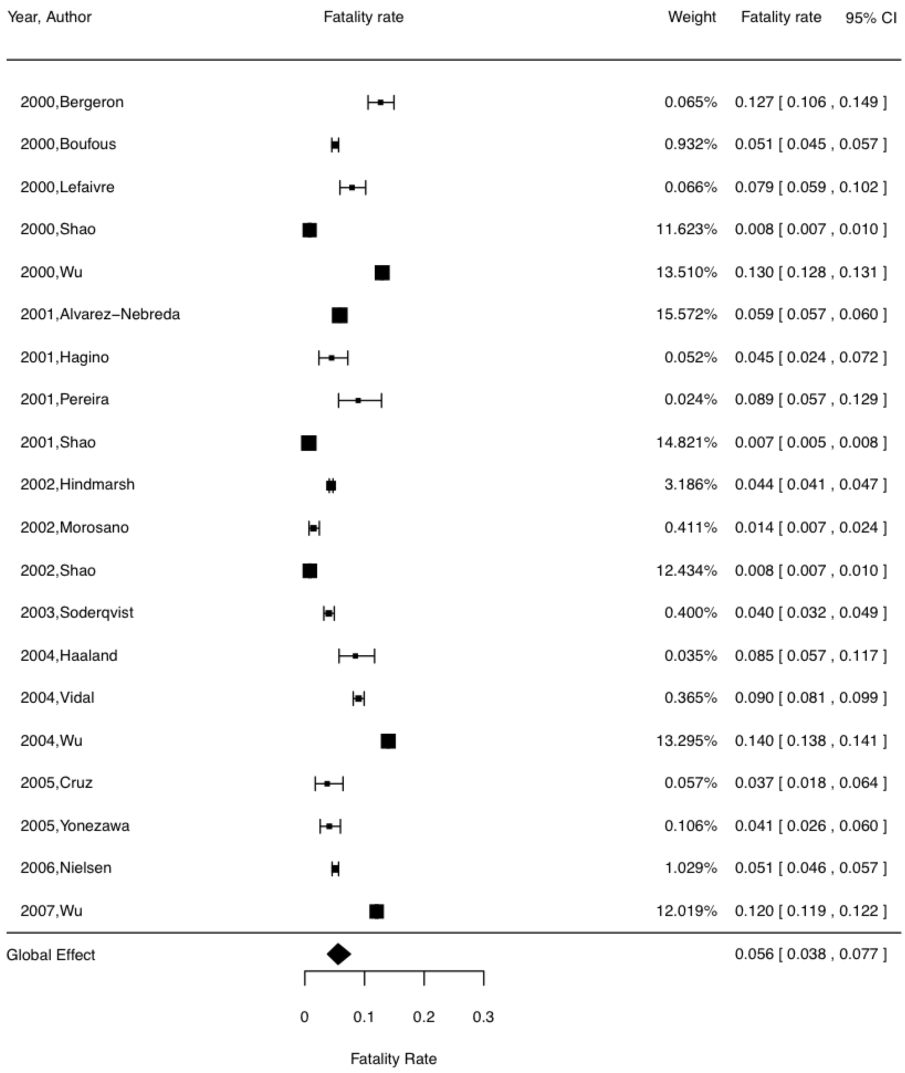

Figure 2. Forest plot with IHR estimates and global effect.

Only 4 studies presented data by gender (table 2) so no analysis was conducted separately for each sex. And as expected, all studies reported higher fatality rates for men.

Table 2. Information regarding IHR and other variables by study.

Study	**Allocated year of data**	**Gender Composition**	**In-hospital fatality rates**		
			Women	Men	Total
Alvarez-Nebreda [16]	2001	Women (74.3%)	4.8%	8.9%	5.9%
Bergeron [17]	2000	NA	NA	NA	12.7%
Boufous [18]	2000	Women (73.4%)	NA	NA	5.1%
Cruz [19]	2005	Women (76%)	NA	NA	3.7%
Haaland [20]	2004	Women (74.9%)	NA	NA	8.5%
Hagino [21]	2001	Women (79.7%)	NA	NA	4.5%
Hindmarsh [22]	2002	Women (74.9%)	3.4%	7.4%	4.4%
Lefaivre [23]	2000	Women (79%)	5.8%	16%	7.9%
Morosano [24]	2002	Women (79.7%)	NA	NA	1.4%
Nielsen [25]	2006	Women (73.8%)	NA	NA	5.1%
Pereira [26]	2001	Women (72.8%)	6.1%	16.4%	8.9%
Söderqvist [27]	2003	Women (74.7%)	NA	NA	4.0%
Shao [28]	2000	Women (61.1%)	NA	NA	0.8%

	2001	Women (59.8%)	NA	NA	0.7%
	2002	Women (61.3%)	NA	NA	0.8%
Vidal [29]	2004	Women (79.8%)	NA	NA	9.0%
Wu [30]	2000	NA	NA	NA	13.0%
	2004	NA	NA	NA	14.0%
	2007	NA	NA	NA	12.0%
Yonezawa [31]	2005	Women (83%)	NA	NA	4.1%

Availability of explanatory variables were: Private expenditure on health as a percentage of total expenditure on health (available for 17 estimates; minimum 15.9 in Sweden [18], maximum 58.2 in Brazil [19], mean 27.4, SD 10.9), Hospital beds density per 1,000 population (available for 15 estimates; minimum 2.7 in Brazil [19], maximum 15.0 in Japan [20], mean 5.3, SD 3.7), Practising physicians density per 1,000 population (available for 17 estimates; minimum 1.3 in Brazil [19], maximum 3.5 in Portugal [21], mean 2.3, SD 0.6) and finally GINI (available for 15 estimates; minimum 0.2 in Denmark [22], maximum 0.328 in Portugal [21], mean 0.28, SD 0.05).

The results from the simple meta-regression models are presented in table 3, whereas the multiple meta-regression model on table 4.

Table 3: Simple meta-regression models

Variable	**Coefficient estimate**	**95% CI**	**P-value**	R^2
Practising physicians density per 1,000 population	-0.08	(-0.13 to -0.03)	<0.01	35.8%
Hospital beds density per 1,000 population	-0.01	(-0.01 to 0.00)	0.21	2.3%
GINI	-0.40	(-1.16 to 0.36)	0.30	0.0%
Private expenditure on health as a percentage of total expenditure on health	-0.00	(-0.00 to 0.00)	0.45	0.0%

Table 4. Multiple meta-regression model.

	Coefficient estimate	**95% CI**	**P-value**	R^2
Intercept	0.53	(0.38 to 0.63)	<0.01	48.7%
Practising physicians density per 1,000 population	-0.08	(-0.12 to -0.03)	<0.01	
Hospital beds density per 1,000 population	-0.01	(-0.02 to -0.00)	0.01	

The predicted (multiple model) In-Hospital Fatality Rate (IHR) for densities of 5.3 for hospital beds and 1.5 for practising physicians is 10.7%. Whereas the predicted IHR for densities of 5.3 for hospital beds and 2.5 for practising physicians is 6.4%.

Predicting from the multiple meta-regression model, considering the densities of 5.3 for hospital beds and 1.5 for practising physicians the prediction for In-Hospital Fatality Rate (IHR) is 10.7%. Whereas values of 5.3 and 2.5 for the densities of hospital beds and practicing physicians, respectively, corresponded to a prediction of 6.4% in IHR.

Discussion

The differences observed on in-hospital fatality rates (IHR), following a hip fracture, could be partly explained by the differences on resources (density of practising physicians and density of hospital beds).

Our results can assist decisions on resource allocation as the economy is facing serious challenges and resources are being carefully managed. A balance between immediate and long-term savings is necessary before decisions are made - investments on health resources, such as number of physicians or hospital beds, have impact on fatality. Our results also highlight the importance of considering other variables, aside from patient or hospital characteristics, in the understanding of in-hospital fatality variability following hip fractures. Outcome measurements such as mortality have been recognised as the ultimate quality measurement of treatment in many conditions. A feasible indicator should be analysed thoroughly, at every possible perspective. All sources of heterogeneity should be adjusted and accounted for.

The reasons for the observed differences in the fatality rates can be the result of a number of different factors related to individual characteristics [3], namely age and sex. The inability of having individual data regarding the health status of the patients at the time of fracture treatment makes it impossibility for meta analytic studies to study both individual and macro variables together. However, the information on the health status of the individuals can be somehow measured by the availability of health resources for the population. In this sense, the results obtained are quite intuitive, higher density of resources leads to less in-hospital fatality. The availability of practising physicians can act on the general health status of the population and, specifically, can also lead to better monitored elderly, which are usually a population with chronic conditions, and subject to the intake of many different medications [23], having a positive effect on mortality; This positive effect can also be the result of a decrease time to surgery [24] due to the availability of physicians and hospital beds.

The study presents some limitations that do not invalidate the results. The use of fatality rates as the effect in meta-analytic studies may be considered inadequate since it may reflect the influence of many other variables. However, the aim of this work was not to produce a global estimate on the IHR, but to model the influence of factors of heterogeneity usually disregarded. The number of possible factors of heterogeneity had to be limited due to a problem that the majority of meta-analytic studies face, the small number of studies selected.

The strengths of our study lies in the innovative methodological approach that is being proposed where part of the heterogeneity in IHR following hip fractures could be explained by macro-economic variables, with impacts on both resource allocation and risk adjustment. The results achieved by the systematic review, conducted in MEDLINE, also provide a valuable insight on the IHR during the Bone and Joint Decade.

Conclusions

Unfavourable outcomes, like in-hospital fatality following a hip fracture can be explained by differences in macro-economic variables, such as allocation of medical resources. The current economic crisis is leading to cuts in public investments in health, in some countries, including Portugal. Studies such as ours are useful not only for the purpose of understanding fatality following hip fractures but also as a public-health indicator identifying the importance of health investments.

Author's contribution

MFP and SMA were responsible for the conception and design of the study; SMA and MFP created the search expression; SMA conducted the search; SMA and MFP defined exclusion criteria and proceed to studies selection; SMA and MFP agreed on macro-economic data; SMA conducted the analysis; SMA, MFP, EGB and SK were involved in the discussion; SMA was responsible for writing the paper; MFP, EGB and SK participated in reviewing the initial and intermediate drafts. MFP made the final revision. All authors read and approved the final manuscript.

Disclosure Statement

All authors declare no competing interest.

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FCT had no role in this manuscript.

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CHAPTER VI

In-hospital fatality following a hip fracture improving opportunities: where should the focus be?

In-hospital fatality following a hip fracture improving opportunities: where should the focus be?

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Abstract

Background: The increase number of elderly is aggravating the demand on health systems caused by hip fractures treatment. Fatality can be used an indicator for quality of treatment. The aims are: obtain a risk adjustment and compare hospital effect on the probability of dying during a hospitalization for hip fracture.

Methods: We used a multilevel (patient/hospital/area) Bayesian approach. The outcome measure was in-hospital fatality; patient level factors were collected from the National Hospital Discharge Register; hospital level factors form the National Hospital Inquiries and area level factors from Statistics Portugal.

Results: Data from 47 hospitals (45 areas) treating 53,684 hospitalizations was used. Variables with significant association with the probability of dying, after adjustment for overall fatality in hospital and orthopedic ward, were (log scale 95% Credible intervals): age (0.07 (0.06 to 0.07)), sex (0.72 less for women (-0.80 to -0.63)), length of stay -0.01 (-0.02 to -0.01), severity (highest versus lowest category (2.50 (2.30 to 2.71))), conservative treatment had a highest increased in probability of dying versus other treatments, except internal fixation. Delay in surgery was not a statistically significant effect, except compared to no surgery category. The overall effect of time in the probability of dying was not statistically significant (-0.02 (-0.06 to 0.00)). However some hospitals did present improvements.

Conclusions: In spite of the difficulty of assessing quality of care, multilevel approach seems a better solution. Our results point that improvements made in the population health status can have positive impacts on improving in-hospital probability of dying.

Keywords

Hip fractures, osteoporosis, treatment outcome, in-hospital fatality, adjustment, population-based study

Introduction

The advances in medicine and the improvement of the general wellbeing led to an increase of life expectancy [1] and consequently to more population at risk of hip fractures with impact on individuals (increase morbidity and mortality - especially in the first three months) and on societies (costs of treatment and recovery [2-4]). Even though a decrease in the trend of hip fracture incidence rate have been reported [5-7], the total number of fractures is increasing, leading to high demand for treatment at orthopedic wards, stretching the resources and compelling changes without compromising outcomes [8].

In-hospital outcomes, such as fatality rates, can be used as reliable indicators to measure and improve quality of care and allowing fair comparisons between providers. Outcome is a function of quality of care and other covariates, namely intrinsic characteristics of patients [9]: therefore, to obtain fair indicators, sources of variation need to be removed through risk adjustment models - residuals reflecting the quality of care. Risk adjustment refers to factors such as delay of surgery, nutrition, delirium, patient characteristics, intervention of interdisciplinary teams and hospital volume [10-13]. Although, adjust for all characteristics [14] may be difficult to achieve reliable results it is necessary to account for different sources of variation. Our study is innovative because we account for different sources of variation within a single model, allowing a holistic view of quality of care.

The aims of this study are: 1- to obtain a risk adjustment for hip fractures in-hospital fatality rate and 2- to compare the probability of in-hospital fatality rate, from 2000 to 2008.

Methods

The study area was Continental Portugal, which had 3,298,922 inhabitants over 49 years old in 2001[15]. The coast area concentrated 70% of the population and the higher density and most specialized hospitals.

Data

We accounted for different sources of variation to obtain an unbiased indicator, and classified the data into 3 hierarchical levels: patients, hospitals and (spatial) areas.

In-hospital fatality was the outcome measure; the list of variables (and sources) used for risk adjustment, by level, is in Table 1.

Table 1- Variables used to adjust for the risk in-hospital fatality, by level, and source.

Level	Variable	Source
Patient	Age (years)	National Hospital Discharge Register (NHDR)
	Sex (men/women)	
	Length of stay (LOS)	
	Transfer (yes/no)	
	Treatment (conservative/internal fixation/without internal fixation/ partial arthroplasty/ total arthroplasty)	
	Time to surgery (zero days/1 day/2 days/>2 days/no-surgery)	
	Severity – Charlson Index (0/1/2/3/>3)	
Hospital	Number of hospitals within a 30 Kilometres radius	-
	Classification (Group 2/4/5)	Official classification for financial proposes [18]
	Volume (number of patients treated for hip fracture)	NHDR
	Proportion of beds in orthopaedic wards from the total number of beds	National Hospital Inquiry (NHI)
	Proportion of orthopaedic medical staff from the total number of medical staff	
	Proportion of patients dead in the hospital from the total number of patients that left the hospital	
	Proportion of patients dead in the orthopaedic ward from the total number of patients that left the	

	orthopaedic ward	
	Number of orthopaedic surgeries (large and medium size)	
Area	Average number of medical consultations in health centres by habitant	Health Statistics- available at National Institute of Statistics (Instituto Nacional de Estatística – INE [17])
	Number of nurses per 1,000 habitants	
	Number of pharmacies per 1,000 habitants	
	Number of resident medical doctors per 1,000 habitants	
	Proportion of private hospitals from the total number of hospital in the area	

All variables from patient level and volume of admissions from hospital level were retrieved from the National Hospital Discharge Register NHDR. The use of this administrative database is mandatory since 1997 in all Portuguese public hospitals, and compiles information such as gender, age, admission and discharge date; causes and diagnosis (up to 20) of admission coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM); clinical and surgical interventions; hospital providing the care; outcome; length of stay (LOS) and the patient place of residence.

In Portugal, access to the national health-care system is universal and tendentiously free-of-charge. Therefore hip fractures are highly documented and the NHDR records the total number of admissions with a diagnosis of hip fracture nationwide. The quality of the NHDR is assessed regularly by both internal (hospitals) and external (ACSS- Central Administration of the National System) auditors [16].

All discharges from 1 January 2000 to 31 December 2008, from individuals aged 50 years or over with diagnose of hip fracture (codes ICD9-CM 820.x), caused by low or moderate trauma, were selected. We excluded cases of bone cancer, readmissions for orthopedic after-care or complications in surgical and medical care (codes ICD9-CM: 170.x, 171.x, V54.x and 996.4).

Co-morbidities, registered in the NHDR, were integrated in the model through the use of the Charlson Index, a co-morbidity index calculated using the scoring system [17] presented in Additional Table 1. The delay to surgery was calculated as the time (days) between admission and surgical treatment.

Variables from hospital level were mainly associated with structure and expertise. We included the official classification of hospitals that uses the average cost of patient, and that classifies the hospitals into 5 different groups (1 to 5, decreasing cost). Hospitals treating hip fractures are classified as one of the groups 2, 4 or 5 [18].

To avoid the small numbers statistical instability, we excluded 26 hospitals (accounting for 1,244 hospitalizations) that treated on average less than 50 fractures by year. During the study period the National Health Service (NHS) was restructured, with the association of some hospitals in Hospital Centres. We excluded admissions in such Hospital Centres (after the restructure), because it was not possible to link the hospitalization with the resources.

Data at hospital level was obtained from the National Hospital Inquiry (NHI), which is annually conducted by the Statistics' Portugal (INE). For reasons of confidentiality, the NHI doesn't explicitly identify the hospitals, although based on some variables (for municipality, size and type of hospital) we were able to identify most of them, except four hospitals in the Lisbon area accounting for 7,365 admissions that were excluded. For the implementation of the statistical model, 47 hospitals from 45 different municipalities (areas) were used. All included areas had at least one hospital that treats hip fractures; however they can differ in terms of number of health equipments and/or performance. Variables were retrieved from INE.

Statistical analysis

A multilevel (hierarchical) statistical model for the binary outcome (dead/survival) was used to obtain a risk adjustment at patient level and that also for comparison between providers.

We used the natural hierarchical structure of the data to model the probability of survival: patients were nested in hospitals that in turn were nested in areas – a three level model. Patients treated in the same hospital may have similar individual characteristics - therefore they are dependent events, and so are hospitals located in the same municipality. Theses facts were taken into account in the statistical model; failing to account for this specificity could have lead to invalid results [19]. Multilevel models allowed simultaneous analysis of the group-level and individual level predictors (correcting for the biases in parameter estimates resulting from dependencies) and decomposition of the outcome at each level [20, 21].

We used a Bayesian approach, using Markov Chain Monte Carlo (MCMC). Prior beliefs about unknown parameters were incorporated in the form of prior distributions and then updated by information in the data to give posterior distributions, which expresses all the uncertainty about each parameter. Posterior distributions were used to calculate point estimates (e.g. mean, median, mode), standard deviations and 95% credible intervals (95%CI) [19].

Suppose that y_{ijk} is the outcome (0 = survival/1 = death) of patient i treated in hospital j in area k and that p_{ijk} is the probability of death during hospitalization for hip fracture. The model used is:

Patient level

$y_{ijk} \sim \text{Bernoulli}(p_{ijk})$

$\text{logit}(p_{ijk})=\text{beta}_0+\text{beta}_1\text{age}_i+\text{beta}_2\text{sex}+\text{alpha}_j\text{year}_i+\text{beta}_3\text{LOS}_i+\text{beta}_4\text{transfer}_i+\text{beta}_5\text{severity}+$

$beta_6 treatment + beta_7 timetosurgery + Psi_{jk}$

where i=1,…,53684 patients, j=1,...,47 hospitals and k=1,…,45 areas.

Note,

$logit(p_{ijk}) = log(p_{ijk}/(1- p_{ijk}))$

Hospital level

$Psi_{jk} = gamma_{0j} + gamma_1 number\_hospitals_j + gamma_2 classification_j + gamma_3 volume_j + gamma_4 beds + gamma_5 medical_j + gamma_6 hosp\_fatal_j + gamma_7 orto\_fatal_j + gamma_8 orto\_surg_j + theta_k$

$\alpha_j \sim N(\nu, \sigma^2)$

$gamma_{0j} \sim N(0, \tau^2)$

Area level

$theta_k = delta_{0k} + delta_1 med\_consul_k + delta_2 nurses_k + delta_3 pharmacies_k + delta_4 doctors_k + delta_5 private_k$

$delta_{0k} \sim N(0, \phi^2)$

All ‘global’ parameters associated with various explanatory variables, namely $beta_m$, $gamma_n$ and $delta_p$ for m=1,..,6, n=1,…,8 and p=1,…,5, were given a Gaussian prior distribution with zero mean and variance 1000. Such Gaussian priors are uninformative in the sense that they effectively express our belief that the parameter can take any positive or negative value with approximately equal probability. For variance parameters σ2, τ2 and ϕ2 and more specifically their inverse, we assumed gamma distributions with mean 100 and variance 20,000. Such a gamma distribution for the inverse of a variance parameter is also uninformative and restricts values to the positive real line.

The model was implemented using WinBUGS software [22] combined with the statistical software R version 2.15.2 (The R Foundation for Statistical Computing) and specifically the R package R2WinBUGS. Using those samples, we calculated the posterior mean as a point estimate for each parameter. 95% Credible Intervals (CI) were obtained by calculating the 2.5% and 97.5% empirical quantiles of the posterior samples. The posterior means can be interpreted as the multiplicative effect on the Odds Ratio (OR) of each explanatory variable. Identification of statistical significant coefficients will be done looking for 95% CI that do not contain zero. Positive credible intervals will have positive effect on OR, increasing the OR. Negative credible intervals will have negative effects on OR, decreasing the OR.

Results

After exclusions, 53,684 hospitalizations were used for fitting the model, from 47 different hospitals in 45 different areas, during the period of 2000-2008 in Portugal. On average, women were older at time of hospitalization (mean 81.0 years (8.5 SD) versus mean 78.1 years (10.1 SD) in men) and accounted for 41, 389 hospitalizations (77.1%). The overall in-hospital fatality rate was higher in men 9.1% compared to women (4.9%) (p-value <0.001). In 5,538 (10.3%) of the hospitalizations the treatment was conservative (no surgery). Characteristics of the patients, disaggregated by outcome, are displayed in table 2.

Table 2: Patient level characteristics at baseline, by outcome.

Variable		Dead	Alive	p-value
Age (Mean (SD))		84.0 (7.8)	80.1 (9.0)	<0.001
Sex (% in sex)	Men	1,115 (9.1%)	11,180 (90.9%)	<0.001
	Women	2,011 (4.9%)	39,378 (95.1%)	
LOS (Mean (SD))		14.6 (13.7)	15.3 (19)	0.038
Transfer (% in transfer)	Yes	250 (5.4%)	4,368 (94.6%)	0.214
	No	2,876 (5.9%)	46,190 (94.1%)	
Severity (% in severity)	0	1,574 (3.8%)	39,526 (96.2%)	<0.001
	1	577 (14%)	3,554 (86%)	
	2	550 (8.3%)	6,507 (91.7%)	
	3	234 (20.4%)	914 (79.6%)	
	>3	191 (27.4%)	507 (72.6%)	
Treatment (% treatment)	Conservative	1,371 (24.8%)	4,167 (75.2%)	<0.001
	Internal fixation	14 (11.1%)	112 (88.9%)	
	Without internal fixation	1,125 (3.5%)	31,239 (96.5%)	
	Partial	527 (4.4%)	11,490 (95.6%)	

	arthroplasty			
	Total arthroplasty	89 (2.4%)	3,550 (97.6%)	
Time to surgery (% Time in surgery)	Zero days	518 (3.7%)	13,481 (96.3%)	<0.001
	1 day	273 (3.5%)	7,517 (96.5%)	
	2 days	176 (4%)	4,244 (96%)	
	> 2 days	788 (3.6%)	21,149 (96.4%)	
	No surgery	1,371 (24.8%)	4,167 (75.2%)	

Hospitals characteristics varied greatly (Additional Figures 1, 2, 3 and 4) and the amount of treated fractures, in the period, ranged from 206 to 3,200 per hospital.

The left panel of Figure 1 plots the in-hospital fatality rate in the nine-years period for each hospital (95% Confidence Intervals). The lowest rate observed was 2.95 per 100 (1.37 to 4.53) and the highest observed was 11.85 (8.91 to 14.79). The central panel in Figure 1 shows, at the logit scale, the hospital effect ($gamma_{0j}$) on the in-hospital probability of dying. Negative estimates represent lower probabilities; positive estimates represent higher probabilities of dying. All 95% CI contained zero so one may argue that none of the effects are significantly different from zero, however some hospitals have a noticeably different effect than most of the others, for instance the negative effect of hospital 11 and the positive effect of hospital 19. Note the difference in the left and centre panels of Figure 1, which is due to the model accounting for patient and area characteristics in the data. The model effectively indicates that the hospital effect in the probability of dying is effectively constant over Portugal if one accounts for individual patient characteristics and the area effect.

Finally, the rightmost panel in Figure 1, shows the effect of time ($alpha_j$) on the probability of dying (p_{ijk}) where we can observe that some hospitals have negative estimates (e.g. hospital 5, 9, 35, 44, 47), indicating a decrease on the probability of dying with time for that hospital..

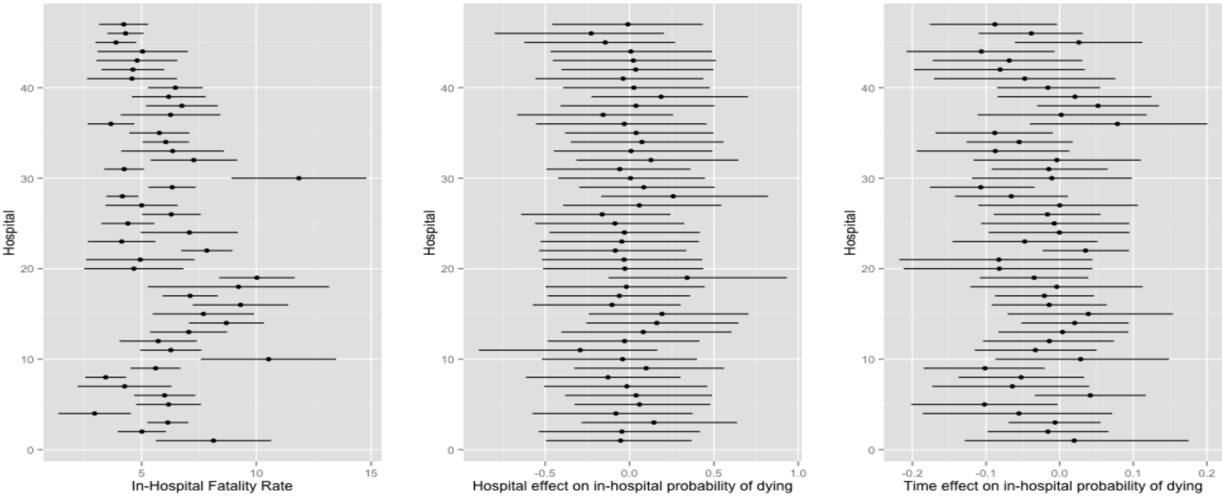

Figure 1: Leftmost plot is the In-hospital fatality crude rates by hospital with 95% Confidence Intervals; Centre plot the Hospital effect on the in-hospital probability of dying with 95% Credible Intervals, estimated from the model; Rightmost plot is the time effect on in-hospital probability of dying with 95% Credible Intervals, estimated from the model.

Table 3 displays estimates and 95% credible intervals for the parameters associated with all explanatory variables in the data.

Table 3: Fixed effect-estimates from the model in log odds scale and variances

Level	Variable		Coefficient	SD	Estimates (95% Credible Intervals)
Patient	(Intercept)		$beta_0$	0.759	-8.090 (-9.683 to -6.558)
	Age		$beta_1$	0.003	0.067 (0.065 to 0.073)
	Sex (% in sex)	Men	$beta_2$		Ref
		Women		0.044	-0.718 (-0.804 to -0.631)
	LOS (Mean (SD))		$beta_3$	0.0018	-0.013 (-0.017 to -0.010)
	Transfer (% in transfer)	Yes	$beta_4$		Ref
		No		0.080	-0.021 (-0.179 to 0.134)
	Severity (% in severity)	0	$beta_5$		Ref
		1		0.059	1.308 (1.191 to 1.423)
		2		0.058	1.061 (0.948 to 1.172)

		3		0.089	2.052 (1.876 to 2.227)
		>3		0.106	2.505 (2.287 to 2.714)
	Treatment (% treatment)	Conservative	$beta_6$		Ref
		Internal fixation		0.340	-0.011 (-0.071 to 0.63)
		Without internal fixation		0.149	-1.263 (-1.539 to -0.969)
		Partial arthroplasty		0.153	-1.066 (-1.347 to -0.764)
		Total arthroplasty		0.185	-1.140 (-1.493 to -0.774)
	Time to surgery (% Time in surgery)	Zero days	$beta_7$		Ref
		1 day		0.081	-0.156 (-0.317 to 0.0003)
		2 days		0.094	-0.016 (-0.202 to 0.166)
		> 2 days		0.065	-0.065 (-0.192 to 0.065)
		No surgery		0.155	1.000 (0.711 to 1.309)
Hospital	Number of hospitals within a 30 Kilometres radius		$gamma_1$	0.021	0.026 (-0.017 to 0.069)
	Classification	2	$gamma_2$		Ref
		4		0.022	-0.032 (-0.461 to 0.407)
		5		0.347	0.188 (-0.543 to 0.839)
	Volume		$gamma_3$	$8\ e^{-4}$	$-3\ e^{-4}$ (-0.002 to 0.001)
	Proportion of beds in orthopaedic wards in the total number of beds		$gamma_4$	0.979	-0.864 (-2.850 to 0.970)
	Proportion of orthopaedic medical staff in the total number of medical staff		$gamma_5$	1.064	0.533 (-1.503 to 2.707)
	Proportion of patients dead in the hospital in the total		$gamma_6$	3.144	7.093 (1.073 to 13.470)

	number of patients that left the hospital				
	Proportion of patients dead in the orthopaedic ward in the total number of patients that left the orthopaedic ward		$gamma_7$	3.606	24.771 (17.620 to 31.740)
	Number of orthopaedic surgeries (large and medium size)		$gamma_8$	$8.322e^{-5}$	$6.291e^{-5}$ ($-1.20e^{-4}$ to $2.156e^{-4}$)
Area	Average number of medical consultations in health centres by habitant		$delta_1$	0.226	0.236 (-0.240 to 0.635)
	Number of nurses per 1,000 habitants		$delta_2$	0.050	$8.213e^{-4}$ (-0.108 to 0.087)
	Number of pharmacies per 1,000 habitants		$delta_3$	1.048	-1.480 (-3.427 to 0.615)
	Number of resident medical doctors per 1,000 habitants		$delta_4$	0.0545	-0.010 (-0.105 to 0.104)
	Proportion of private hospitals in the total number of hospital in the area		$delta_5$	0.381	0.024 (-0.730 to 0.781)
Variances	Between hospitals		tau $gamma_0$	0.044	0.071 (0.015 to 0.177)
	Between areas		tau $delta_0$	0.051	0.081 (0.016 to 0.204)
	Between hospital/time		tau_beta_3	0.002	0.007 (0.004 to 0.011)
	Overall effect of time on the probability of dying		nu	0.018	- 0.027 (-0.062 to 0.008)

The variables at area level presented non-significant results and none of the areas presented a differentiated effect on the probability of dying (additional figure 5).

Discussion

Our results revealed that the differences observed in in-hospital fatality rates can be explained by patient individual characteristics and their underlying health status but also by variables related to the quality of treatment. That is, if hospitals treating patients with the same profile had the possibility to undertake surgery within the same time lag and provide surgical treatment to all patients, they would all have the same impact on the probability of dying. Our results identify that the opportunities to improve in-hospital fatality lie in the improvement of general health status of the individuals and in the increase of surgical treatment.

All providers, after adjustment, had a similar effect on the probability of dying. Nevertheless, we were able to identify some hospitals that improved during the study period. The use of a multilevel model incorporating various sources of variation to adjust the probability of in-hospital fatality allowed a more robust comparison between providers and the identification of the trend of in-hospital fatality by provider, even if no hospital or area effect could be identified.

Our interpretation of the care provided to hip fracture was based on the three-way approach to quality proposed by Donebedian [23, 24], where quality of care should be evaluated using structure, process and outcome indicators, stringed because "good structure increases the likelihood of good process, and good process increases the likelihood of a good outcome" Donabedian (1988). Our model incorporated outcome, process and structure components. After adjustment for patient characteristics and health status, variables related to process such as time to surgery and treatment were still determinant for better outcomes. Our results only showed an increased effect on the probability of dying when comparing no surgery with undertaking surgery on the day of admission (reference). Studies reported that after adjusting for confounding factors, no effect of time to surgery was identified [25]. However, accumulated evidence seems to favour earlier surgery associating it with lower risk of death, lower rates of postoperative complications and reduced length of stay [11, 26]. Patients that are treated conservatively were identified as having higher risk of in-hospital fatality, in agreement with other studies and guidelines [27-29].

Resources were incorporated through variables at hospital level, such as beds or medical staff in orthopedic ward. However, the effect of these variables was not statistically significant. The area level variables were proxy measures of the influence of areas more capable of providing healthcare. However, no significant area effect was identified.

Other procedures that were not measured in this study, like early assessment of patients' nutritional risk, systematic pain assessment during mobilization evaluated in other studies [30] or recommended thromboprophylaxis [27, 29] can have impact on the probability of dying during hospitalization but are unlikely to significantly explain differences between providers, because hospitals seem to have the same effects after adjustment for the measured variables. Nevertheless, assessments regarding other processes and outcome measures could be vital to understanding the improvements observed in some hospitals, during the study period, but no such data were available for our study. The multidimensional nature of healthcare makes the measurement of quality difficult. Improvements in the probability of dying during hospitalizations for hip fractures can be due to a wide variety of factors, directly associated with hospital performance: changes in pre-operative (e.g. with early stabilization of the patient) and in pos-operative treatment (eg. with nutritional assessment and treatment or a multidisciplinary approach to recovery) [23, 24]. Conservative treatment, although identified as a risk factor in the probability of dying, can be related to bad hospital procedures but also to personal choices of patients. The adequate treatment of the very old (nonagenarians and centenarians) is still under discussion [31-33], and families may decide that their relatives should not face the consequences of surgery.

As expected, the effects of age, sex and severity were similar to what other studies described [34]; the gender difference, which prevail after the adjustment for severity index was similar to other studies. The reasons for differences in gender remain unclear even after adjusting for medications [35]; the infection has been pointed as possible cause for the differences [36].

The national scope, incorporating hospitals where 70% of hip fractures were treated in Portugal is one of the strengths of our study. The other strength relies on the appropriate multilevel approach. The common approach to profile providers has been to predict the outcome at individual level, calibrate the process to use it on a different provider, and compare observed and predicted outcome for each provider [37, 38]. The hierarchical approach using patients at level I and hospital at level II, allowed us to predict outcome at individual level and a comparison between providers simultaneously. Limitations are mostly related to data sources; the impossibility of database linkage between different health databases in Portugal prohibits the use of mortality after discharge. The use of administrative databases restrains the possibility of studying different outcomes, such as functional recovery, important because studies have shown that providers may have good performances in one outcome and bad performances on others [39].

After adjusting for confounding factors, hospitals from the National Health System in Portugal do not seem to have a differentiated effect on the probability of dying in patients hospitalized for hip fracture. To improve fatality outcome, health care systems should address the general health of population.

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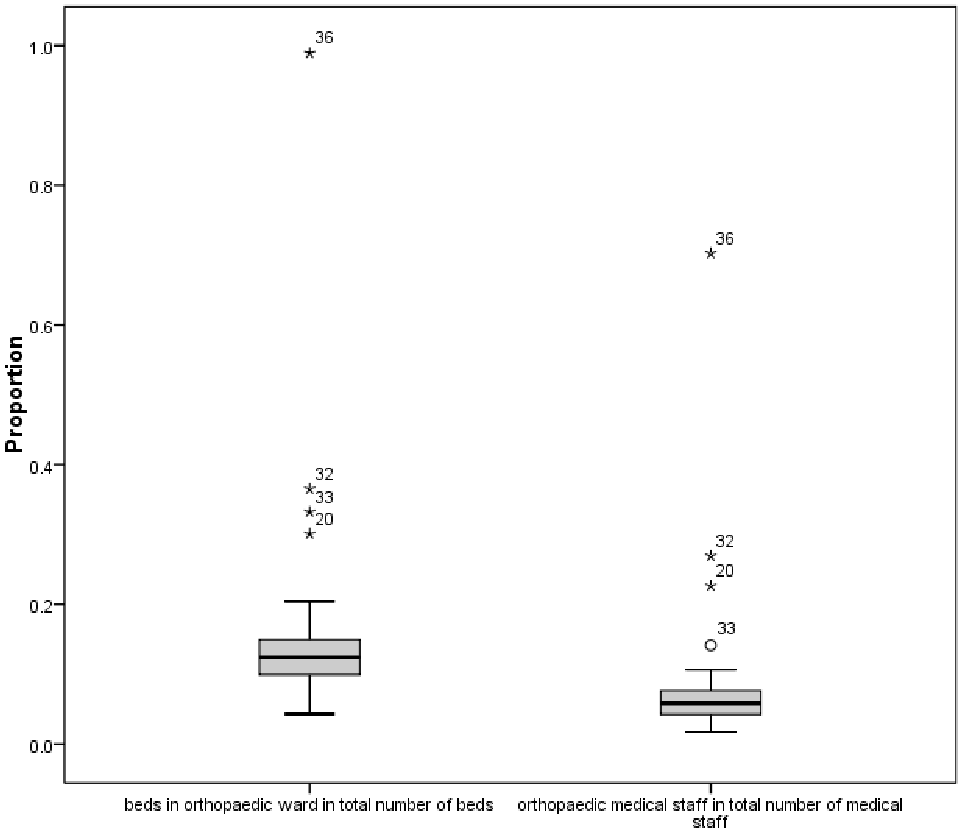
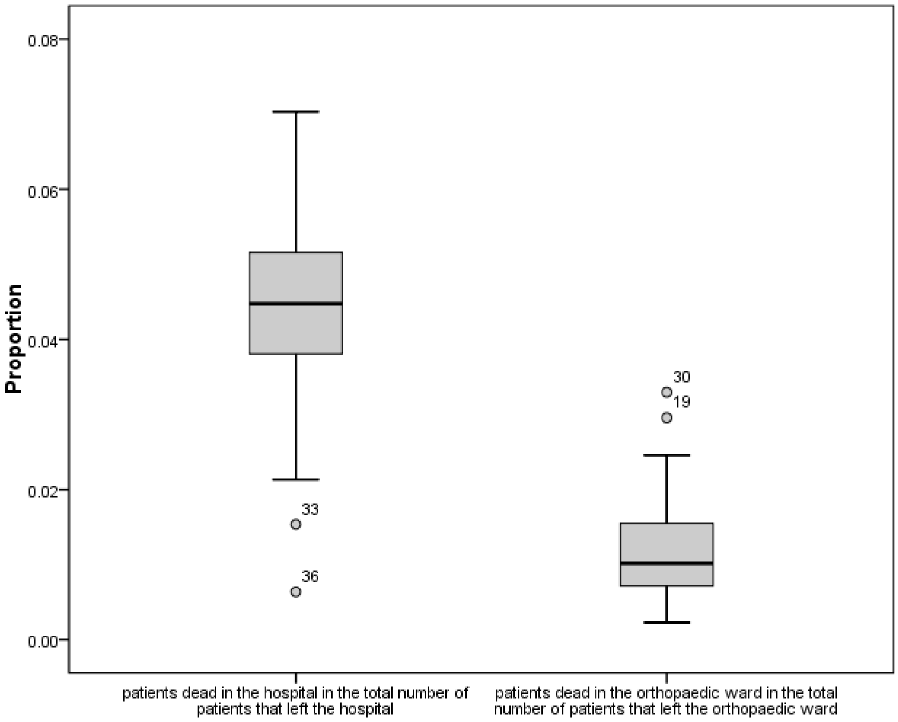
Additional Materials

Additional Table 1- Scoring system to calculate the Charlson Index

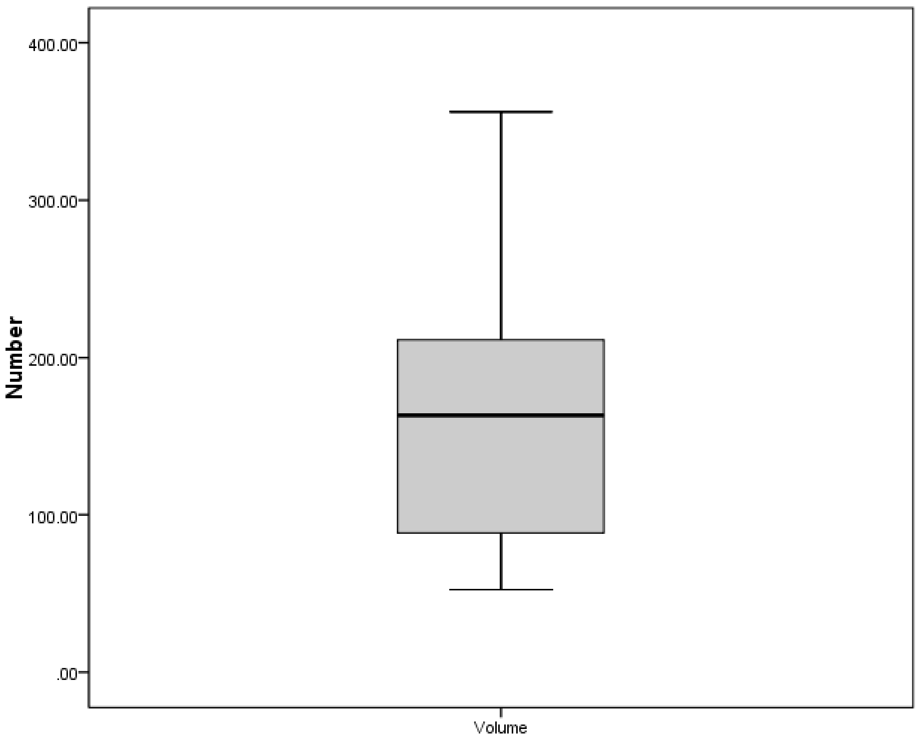
Weights	Conditions	ICD-9 CM codes	Weights	Conditions	ICD-9 CM codes
1	Myocardial infarct	410, 411	2	Hemiplegia	342, 434, 436, 437
	Congestive heart failure	398, 402, 428		Moderate or several renal disease	403, 404, 580-586
	Peripheral vascular disease	440-447		Diabetes	250
	Dementia	290, 291, 194		Any tumor	140-195
	Cerebrovascular disease	430-433, 435		Leukemia	204-208
	Chronic pulmonary disease	491-493		Lymphoma	200, 202, 203
	Connective tissue disease	710, 714, 725	3	Moderate or several liver disease	070, 570, 572
	Ulcer disease	531-534	6	Metastatic solid tumor	196-199
	Mild liver disease	571, 573			



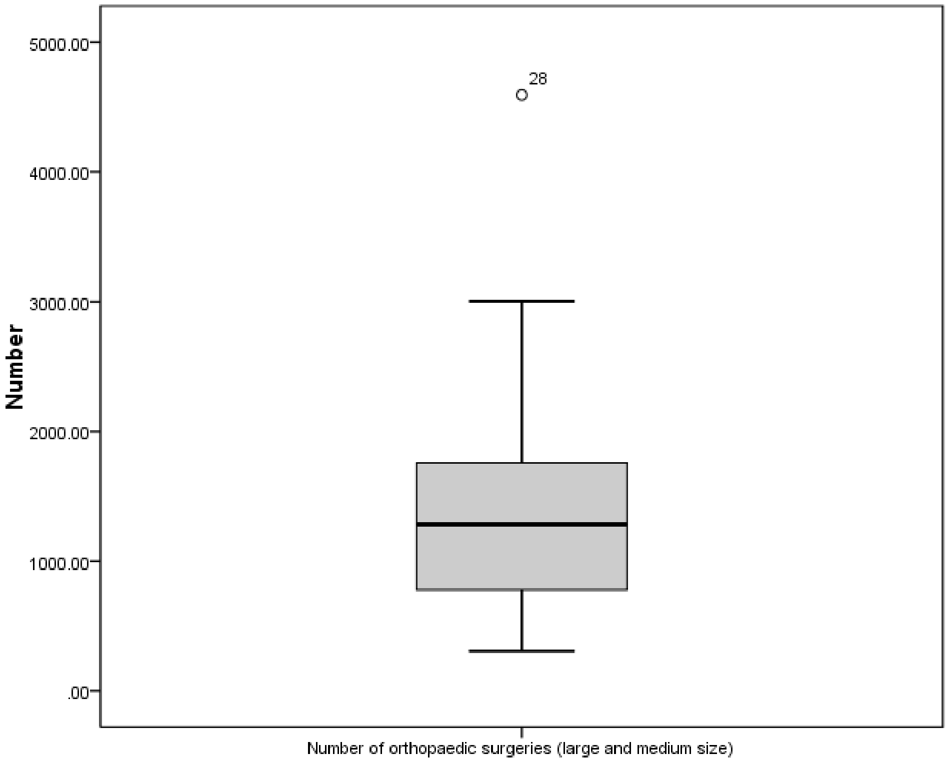
Additional figure 1: Differences in annual averages by hospital of Proportion of beds in orthopaedic ward in total number of beds and Proportion of orthopaedic medical staff in total number of medical staff. Outliers are identified.



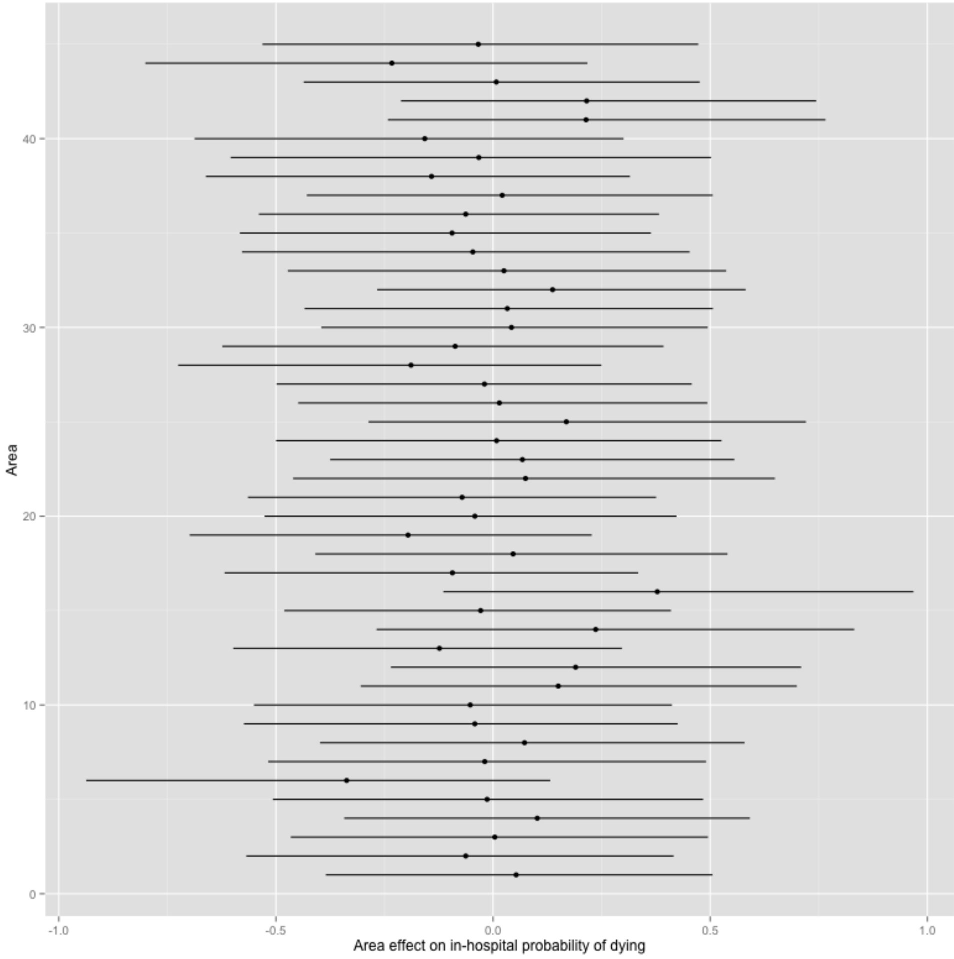
Additional figure 2: Differences in annual averages by hospital of Proportion of patients dead in the hospital in the total number of patients that left the hospital and Proportion of patients dead in the orthopaedic ward in the total number of patients that left the orthopaedic ward. Outliers are identified.



Additional figure 3: Differences in annual averages by hospital of Volume.



Additional figure 4: Differences in annual averages by hospital of Number of orthopaedic surgeries (large and medium size).



Additional figure 5: Area effect on the in-hospital probability of dying with 95% Credible Intervals, estimated from the model

CHAPTER VII

General Discussion, Conclusions and perspectives

In this population-based retrospective study, the year 2003 appeared as a turning point in the time trend of age-standardized incidence rates (ASIR) of hip fracture in women. The observed trend from 2000-2008 with a clear and abrupt decrease change in 2003, is compatible with an intervention on national level. A change in the trend could be attributed to a number of different factors, however it is unlikely that a change in the demographic and socioeconomic characteristics of the population could occur so promptly that impacted on hip fracture incidence so abruptly has the results pointed out.

In order to further investigate the intervention responsible for the prevention of hip fracture, the number of anti-osteoporotic medication packages sold in Portugal, in each year of the study period was analyzed. The results were similar: the same impact on the trend of ASIR for women, with the same turning point relating to 2003 sales. Other interventions, such as falls prevention campaigns, are usually focused on the elderly age groups (over 80 years old) and were not implemented nationwide in Portugal. Falls prevention actions in Portugal are sparse, conducted locally in some health centers (local impact) and they did not occur simultaneously, therefore it is not likely that such local actions would explain the accentuated turning points in the time trends of ASIR nationwide.

After 2003, with the decrease of hormonal replacement therapy, the total number of anti-osteoporotic packages sold were mainly bisphosphonates, suggesting that the massive increase in prescription of these medications was the intervention responsible for the change in the trends of ASIR.

The study allowed the identification of a plausible intervention: the prescription of bisphosphonates. It does not postulate on the effectiveness of the treatment, with the quantification of prevented hip fractures by number of treated patients or the adverse effects of its use. However, it is a measure of quality, in the sense that patients at risk are receiving the attention for hip fracture prevention, with the prescription of the available medication. The rapidly increase of bisphosphonates sales can be the result of the Bone and Joint Decade actions, that raised awareness to prevention, translating in a higher amount of individuals protected and consequently a decrease of incidence rates.

Other authors have reported decreased trends [1-6], however, this study differ from all the others. Some identified linear trends which made the authors question the influence of bisphosphonates [4, 5]. In other studies where turning points in incidence rates were identified and related to the bisphosphonates sales, the identifications was merely visual, with no used of adequate statistical methods [1, 2].

Trends of hip fractures can be driven by interventions or by alterations in risk factors of the individuals. Due to the diversity of proposed factors that are associated with trend of hip fracture, this study analyses the problem through different perspectives. Even after accounting for differences observed in birth cohorts, a decreasing pattern compatible with intervention was identified, in the period of study for women incidence rates. The cohort effect identified risk fluctuations in every year that Portugal suffered political or economic changes, with impact on population.

An increased risk after the beginning of World War I, where the population suffered from a shortage of food supply and faced the Spanish flu, followed by one of the highest inflation seen in Europe. Situation aggravated in Portugal by a serious internal political instability. The next chronologic event in the history of Portugal, around 1930, with a change in the political regime had an influence in the health conditions of the population, already measured by higher birth and lower mortality rates, also reflected on the risk of hip fracture, with a decrease risk of fracture for birth cohorts born in this period. Portugal was totally dependent on importation, when in 1939, World War II begins, leaving the population once again under food restrictions, and the results reflect this with a new increase of risk observed in birth cohorts during this period. The next alteration, with a decrease in the risk is observed in the same period were Portugal receives financial aid through Marshall Plan.

No one, of the scarce number of published paper using a methodology to study the impact of combined age, period and cohort effects reported similar results for cohort effects [7-10], which makes sense, since the quality of bone is a reflection of a life-time balance between formation and resorption occurring in bone tissue with improved results from adequate external conditions [11, 12]. Therefore the results obtained in the Age-Period-Cohort (Chapter 4) are biological and historical plausible, and since the economic, social and political history differs from country to country it is expected that the relation with risk of fractures in the elderly is also different from country to country. On the other hand, the age effect is similar in all studies. Period effect is difficult to compare, because the studies that use the same methodology use different period.

The study of hip fracture incidence rates as an indicator of preventive treatment, proved to be effective. Even after the identification of a cohort effect, there is a decrease in hip fracture rate in women. Regardless of no causal relationship being able to be attributed using ecological studies, the results from chapters 3 and 4, acknowledge important aspects that can be useful in public health. Population at risk of sustaining hip fracture is wide and diverse, any preventive action benefits from the information provided. The results also provide future lines of investigation. The economical constrains that the population is facing might lead to decrease of the number of anti-osteoporotic medication sales, which can result in a possible increase in the trend, hence the importance of continuing the trend analysis. In addition, it would be also important to evaluate the trend of other type of fractures, since prolonged use of bisphosphonates have been associated with atypical femoral fractures as well as osteonecrosis of the jaw and are already being described as negative on other skeleton parts [13].

The results regarding the study of quality of treatment after the fracture, were based on an outcome: in-hospital fatality.

First, possible factors that could explain differences in-hospital fatality rates were explored, in the study presented in chapter 5. The results from a meta-regression analysis showed that the effect of economic variables should be taken into consideration when explaining differences in in-hospital fatality rates observed in published studies. Variables related to allocation of medical resources were identified as having a positive impact on in-hospital fatality rates. Higher number of medical doctors and bed availability leads to a decrease of in-hospital fatality rates. These results are in accordance to the results obtain in the previous chapters, more health resources lead to better fitted population, or to a more prompted response to the treatment, and therefore to a better outcome if the fracture occurs.

The quality framework proposed for the assessment of the quality of treatment, included 3 levels: patients, hospitals and areas. The results identified that the individual characteristics' of the patient (age, sex and severity of health conditions) and some variables related to procedures (time to surgery and treatment) have impact on the probability of dying in the hospital for the treatment of a hip fracture. Better health fitted population can face the treatment with a higher probability of surviving the hospitalization than less fitted population.

In Portugal, hospitals that treat more than 50 hip fractures per year do not present differentiated effect on the probability of the patient dying while hospitalized, after the adjustment for patients, hospital and area characteristics'.The overall probability of dying did not present alteration in the time frame of the study. However, some hospitals presented significant improvements, and others the tendency to an aggravated effect in the study period. Factors that could help understand these changes overtime, such as changes in pre-operative and pos-operative treatment (early stabilization, nutritional assessment and treatment), should be further investigated. However, changes in procedures may difficult to evaluate nationwide, due to lack of available data. No area effect was identified; medical resources from the areas were the hospital is set were not determinant for the outcome.

The methodology applied in chapter 6, was also applied in a study regarding hip fractures to determine the association between timing of surgery and in-hospital mortality, the results did not find evidence that the effect of delayed surgery on mortality was different across hospitals [14]. Hospital and regional differences in outcomes of hip fractures, were reported by a study in Finland [15], their approach also included only providers with more than 50 patients treated yearly. However, the methodological approach was simpler, even if the authors acknowledge the existence and benefit of more complex alternatives [16].

The results from chapter 5 and 6 can be interchangeable, chapter 5 shows that risk adjustment should take resources into consideration, chapter 6, using this knowledge shows that individual characteristics', such as general health condition of the patient acts on the probability of dying. When lacking patient characteristics, such as in meta-analysis, in chapter 5, macro-economic variables that can act on health status of population seems to be a solution to explain a part of the observed variability.

The restructuration that occurred during the period of the study in some hospitals of SNS (National Health System) with some fusions, based on aggregation of resources (human and material) will lead to an important need in the future; the assessment of the implications in the treatment of hip fractures.

Another important global result, was the possible existence of a gender difference in the treatment of hip fractures, both in prevention and in treatment. Usually associated with women, that have higher risk due to the rapid bone loss after the menopause, men seem to be overlooked. The trend of hip fracture incidence rates is decreasing in women; women are usually the target population of anti-osteoporotic medication. However, men tend to have a worse outcome, even after adjustment for health status and treatment. With the increasing life-expectancy of men, osteoporotic fractures in men should be given more attention.

Limitations of these studies are manly associated with data limitation. In spite of being a rich and important font of epidemiological data the National Hospital Discharge Register (NHDR) has some limitations, like the lack of information about the functional recovery of the patient at time of discharge, or more accurate information on surgical procedures, or even in the possibility of tracking the patient between hospitals.

The results and methodology applied in this study were innovative, few published paper identified a marked turning point in the trend of hip fractures, compatible with intervention. No other paper, that showed the plausible effect of the history on the cohort effect of hip fractures trend could be identified. The use of macro-economic variables to explain the variation between in-hospital fatality rates was not identified in no other published work. Finally, the multilevel approach, which is seldom applied to adjust the risk of unfavorable outcomes, showed that given some initial characteristics, acute care may not be as important as primary and preventive care in the treatment of hip fracture.

This study is an extensive research on hip fracture treatment in Portugal, using a global perspective, with quality assessment before and after the fracture event. It allowed not only the general perspective of the treatment given within the study period but also the identification of some aspects that can be addressed in order to obtain improvement: medication, different birth cohort risk, general health of the population, conservative treatment.

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